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INHIBITION OF BARORECEPTOR AND CHEMORECEPTOR REFLEXES ON HEART RATE BY AFFERENTS FROM THE LUNGS

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SUMMARY

1. Brief stimuli were delivered to the carotid baroreceptors or chemoreceptors in dogs anaesthetized with chloralose and paralysed with D-tubocurarine. Baroreceptor stimulation was achieved by forceful retrograde injection of 2–5 ml of air-equilibrated saline into the external carotid artery after first clamping the common carotid artery. Chemoreceptor stimulation was achieved by rapid retrograde injections of 0·2–0·5 ml of warmed CO_2-equilibrated saline into the external carotid artery. Observations were made during periods of temporary cessation of artificial ventilation.

2. When the volume of the lungs was not changing, prompt decreases in heart rate were evoked by chemoreceptor or baroreceptor stimuli except when these were delivered during the inspiratory phase of breathing (as judged from the records of phrenic nerve activity).

3. No changes in heart rate were evoked when these stimuli were timed to occur during expansion of the lungs in response to a rapid increase in intratracheal pressure (6–10 mmHg in 1–2 sec). Decreases in heart rate were evoked when the stimuli occurred during slower inflations of the lungs.

4. Both stimuli regained their effectiveness on heart rate with time after inflations of the lung when the lungs were held inflated. Both stimuli evoked large decreases in heart rate when delivered during deflations of the lung.

5. The effects of lung inflation on the effectiveness of both cardiodepressor reflexes were abolished by surgical denervation of the lungs.

INTRODUCTION

Koepchen, Wagner & Lux (1961) and Haymet & McCloskey (1975) showed that brief stimuli to the baroreceptors of the carotid sinus reflexly evoke bradycardia when delivered in the expiratory phase of the respiratory cycle, but have little or no effect if given during inspiration. Similarly, the chemoreceptors of the carotid body reflexly evoke bradycardia when they are stimulated in the expiratory, but not in the inspiratory, phase of the respiratory cycle. This respiratory modulation of baroreceptor and chemoreceptor reflexes is not entirely caused through activation, during inspiration, of slowly adapting mechanoreceptors in the lungs and thorax, as both reflexes can be evoked during the apnoea of the Hering–Breuer inflation reflex and during maintained inflation in periods of apnoea following hyperventilation, in the absence of central inspiratory drive activity. Also, it has been shown in experiments

using paralysed dogs, that the cycling of central respiratory neurones is sufficient to impose this modulation of both baroreceptor and chemoreceptor reflexes on heart rate (Davidson, Goldner & McCloskey, 1976).

Anrep, Pascual & Rossler (1936*a*, *b*) concluded that the mechanisms responsible for sinus arrhythmia include a central one and a reflex one arising from the activation of mechanoreceptors in the lungs. Daly & Scott (1958) described the cardiovascular responses to stimulation of the carotid arterial chemoreceptors and showed that the primary response of bradycardia was not seen when breathing increased in response to the stimulation, but was seen when ventilation was controlled. They concluded that the activation of mechanoreceptors in the lungs could mask the primary reflex response.

A central neural respiratory modulation of baroreceptor and chemoreceptor reflexes on heart rate has been demonstrated (Davidson *et al.* 1976). The present study was undertaken to see if afferents from the lungs also modulate the baroreceptor and chemoreceptor reflexes. Part of this work has been briefly reported (Gandevia, McCloskey & Potter, 1977).

METHODS

Experiments were performed on twelve dogs of both sexes, weighing 9–19 kg. The animals were anaesthetized with intravenous thiopentone (Pentothal, Abbott, 25 mg/kg), followed by intravenous chloralose (α-chloralose, British Drug Houses, 80 mg/kg). In each dog the trachea was cannulated low in the neck and nylon cannulae were inserted with their tips facing towards the heart into the lingual and external carotid arteries on both sides. The tips of these cannulae were positioned close to each other and in close communication with the carotid sinus. A nylon cannula was inserted in a femoral vein for administration of anaesthetic or drugs. Rectal temperature was maintained at 37–39 °C.

Arterial pressure was measured from either a lingual or external carotid artery, using a Statham P23 AC transducer, and was recorded on one channel of a Grass polygraph pen recorder. Intratracheal pressure, as an indicator of air flow, was measured through a wide (2 mm i.d.) catheter inserted into the trachea, using a Statham transducer and recorded on the polygraph. The same catheter and transducer were used to measure intratracheal pressure in paralysed animals. The electrocardiogram and the beat-by-beat heart rate (Grass 7P4 cardiotachometer, triggered from the e.c.g.) were also recorded.

In paralysed animals respiratory activity was recorded from the central end of the cut and de-sheathed phrenic nerve through platinum electrodes, and this phrenic neural discharge was integrated using a Grass 7P 3B preamplifier ('leaky' integrator; time constant 0·05 sec). To produce paralysis intravenous D-tubocurarine (1–2 mg/kg) was given slowly until all respiratory movements ceased: the animals were then ventilated on pure oxygen with a Starling 'Ideal' pump, usually adjusted so that some phrenic nerve activity remained. Observations on chemoreceptor and baroreceptor reflexes were made during periods when the pump was temporarily stopped.

In eight dogs the lungs were denervated after a control series of observations had been made. This was done on the right-hand side by opening the chest through the fourth intercostal space and cutting the pulmonary vagus close to the hilum of the lung. On the left-hand side the vagus was cut in the neck, the right vagus being left intact. Evidence of successful pulmonary denervation was the abolition of the Hering–Breuer inflation reflex. Resting heart rates were little altered after pulmonary denervation.

Brief baroreceptor and chemoreceptor stimuli were given as described by Haymet & McCloskey (1975). The chemoreceptor stimuli were provided by sudden retrograde injections into the external carotid artery of small volumes (0·2–0·5 ml.) of warmed saline equilibrated with CO_2. Injections of similar small volumes of saline equilibrated with air were always without reflex effect. Baroreceptor stimuli were delivered by sudden retrograde injections of 2–5 ml of air-equilibrated saline into the external carotid artery, after first clamping the common carotid

artery below the carotid sinus. Stimuli were delivered during the inspiratory or expiratory phases of breathing (as judged from the record of phrenic nerve activity), or during the inflation of the lungs and at various times after inflation while the lungs were maintained in the inflated state by positive pressure of 8–10 mmHg. The lungs were inflated by an experimenter blowing into a tube attached to the tracheal cannula. Stimuli were also delivered during deflation of the lungs from this pressure (see also Results, section 3).

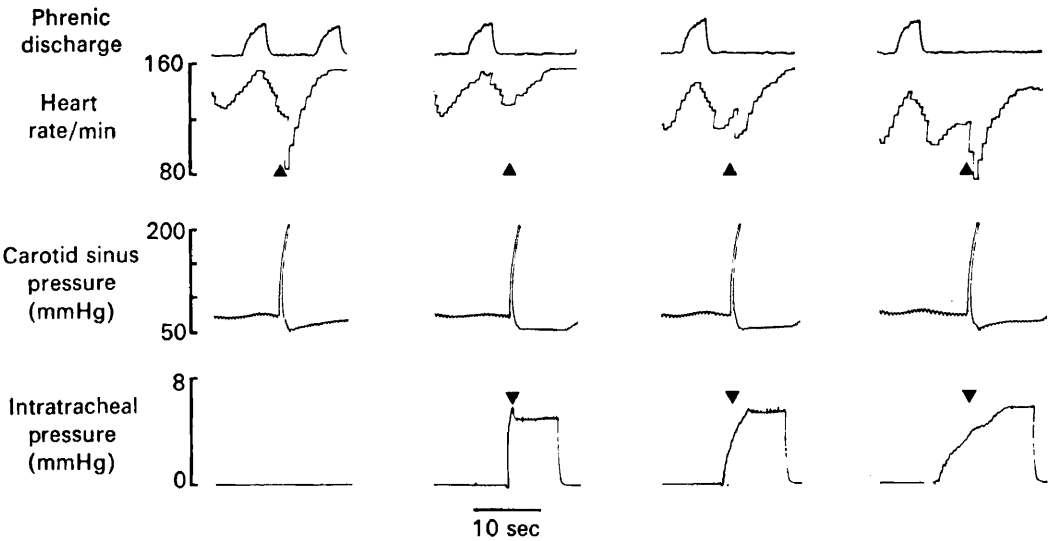

Fig. 1. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Integrated phrenic nerve activity, heart rate, carotid sinus blood pressure and intratracheal pressure, recorded during a period of temporary cessation of artificial ventilation, are shown. The effects of baroreceptor stimuli (pulses of intracarotid pressure at markers) on heart rate can be seen. A control baroreceptor stimulus given in the expiratory phase of breathing evokes a prompt bradycardia (panel at left). A stimulus given during an increase in intratracheal pressure of 6 mmHg in 1–2 sec evokes little or no bradycardia (second panel). A stimulus given during a slower rise in intratracheal pressure (2–5 sec) evokes a slight bradycardia (third panel). A stimulus given during even slower rises in intratracheal pressure (10–15 sec) evokes a prompt bradycardia similar to the control response (fourth panel). (In this and following figures the heart rate trace is triggered beat-by-beat by the e.c.g. and refers to the beat preceding its registration: i.e. it lags behind the heart rate change by one beat.)

RESULTS

1. *Central modulation of reflex responsiveness*

In all these experiments the findings of Koepchen *et al.* (1961) and Haymet & McCloskey (1975) were confirmed in spontaneously breathing dogs: brief baroreceptor or chemoreceptor stimuli evoked little or no reflex bradycardia when delivered during inspiration, but did evoke prompt and marked bradycardia when given in expiration. In paralysed dogs the findings of Davidson *et al.* (1976) were confirmed: in periods when ventilation was temporarily stopped, baroreceptor and chemoreceptor stimuli again evoked no reflex bradycardia when delivered in the inspiratory phase of the neural respiratory cycle, as judged from the phrenic nerve recordings, but evoked a prompt bradycardia when delivered in the expiratory phase of the cycle (see Figs. 6 and 7).

2. *Effects of stimuli timed with respect to air flow into the lungs*

(*a*) *Fast ramps.* Rapid inflations of the lungs were achieved by an experimenter blowing into a tube connected to the tracheal cannula. Inflations in which the tracheal pressure was raised from atmospheric pressure by 6–10 mmHg in 1–2 sec were delivered during the expiratory phase of breathing. Chemoreceptor or baroreceptor stimuli delivered during these ramps of pressure evoked no reflex bradycardia. There was no evidence of inspiratory activity in the phrenic electroneurograms during these ramps of pressure. The process of lung inflation, in the absence of evidence of central inspiratory activity, was therefore shown to be sufficient to block both reflexes (see Figs. 1, 2, 3, 4, 6 and 7).

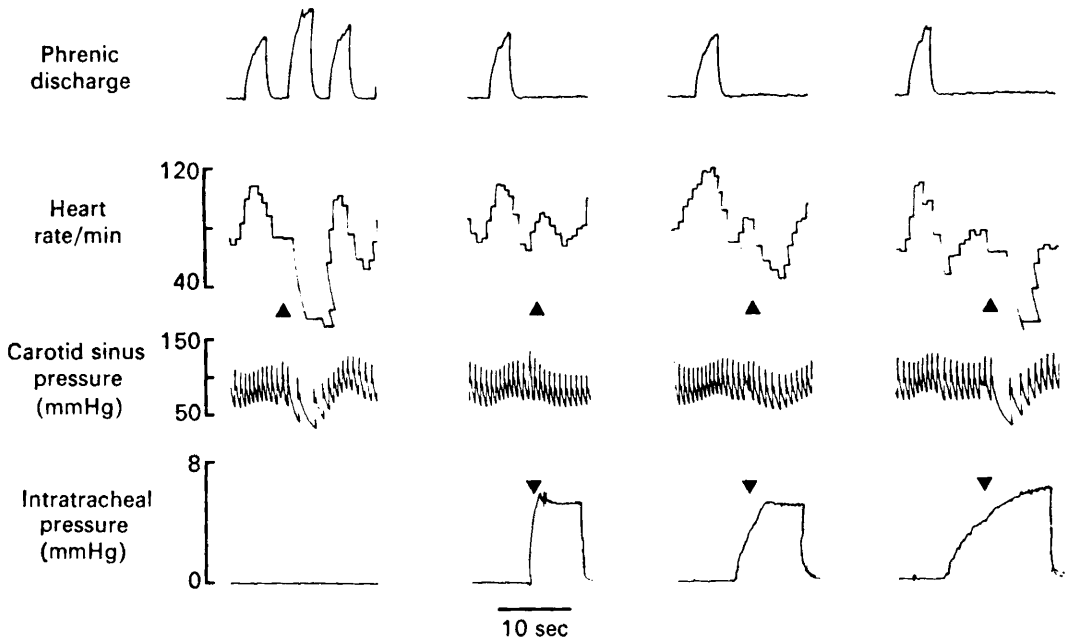

Fig. 2. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Integrated phrenic nerve activity, heart rate, carotid sinus blood pressure and intratracheal pressure, recorded during a period of temporary cessation of artificial ventilation, are shown. The effects of chemoreceptor stimuli (intracarotid injections of CO_2-saline at markers) on heart rate can be seen. A control chemoreceptor stimulus given in the expiratory phase of breathing evokes a prompt bradycardia (panel at left). A stimulus given during an increase in intratracheal pressure of 6 mmHg in 1–2 sec evokes little or no bradycardia (second panel). A stimulus given during a slower rise in intratracheal pressure (2–5 sec) evokes a slight bradycardia (third panel). A stimulus given during even slower rises in intratracheal pressure (10–15 sec) evokes a prompt bradycardia similar to the control response (fourth panel).

(*b*) *Slow ramps.* The effects of slower ramps of tracheal pressure were also tested. Pressure was raised again by 6–10 mmHg, commencing during the expiratory phase of breathing, but inflations were made more slowly so that the inflations proceeded for 2–15 sec. Again there was no evidence of inspiratory activity in the phrenic electroneurograms during the inflations. Chemoreceptor and baroreceptor stimuli were delivered during these inflations: most commonly the stimuli were given at

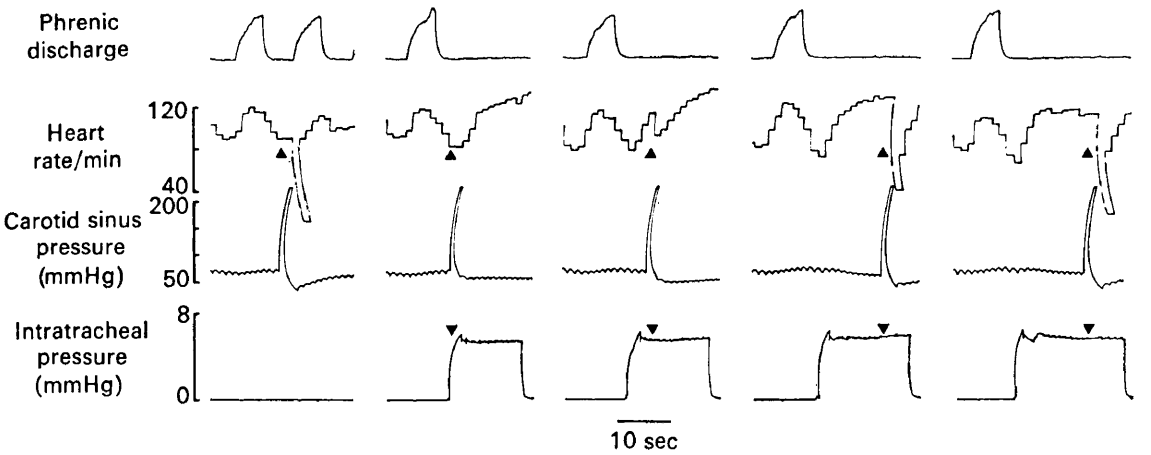

Fig. 3. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Integrated phrenic activity, heart rate, carotid sinus blood pressure and intratracheal pressure, recorded during a period of temporary cessation of artificial ventilation, are shown. The effects of baroreceptor stimuli (pulses of intracarotid pressure at markers) on heart rate can be seen. A control baroreceptor stimulus given in the expiratory phase of breathing evokes a prompt and large bradycardia (panel at right). A stimulus given during an increase in intratracheal pressure of 6 mmHg in 1–2 sec evokes little or no bradycardia (second panel). Stimuli given after the increase in intratracheal pressure, but while the lungs remain inflated, regain their effectiveness with time (three panels at right).

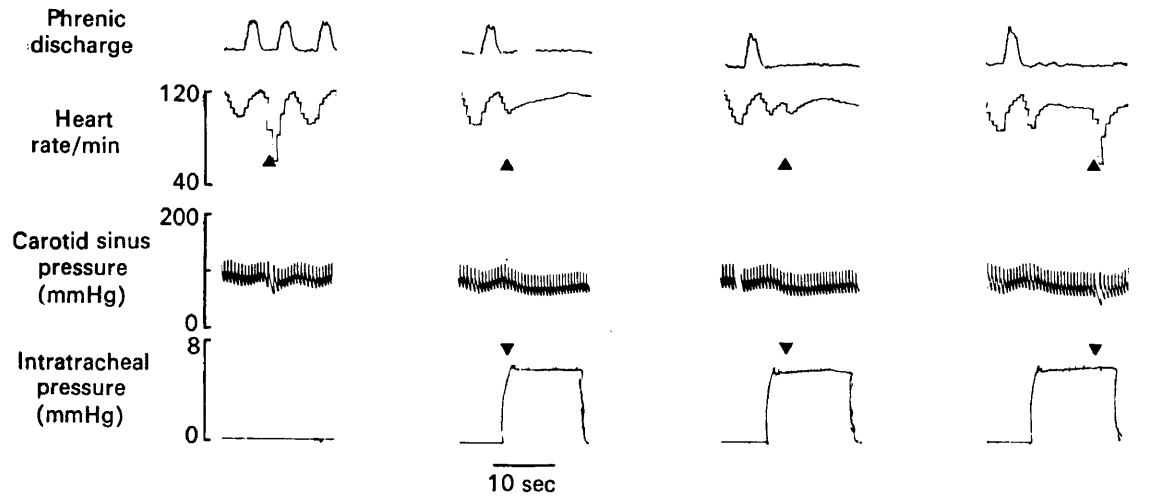

Fig. 4. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Integrated phrenic activity, heart rate, carotid sinus B.P. and intratracheal pressure, recorded during a period of temporary cessation of artificial ventilation, are shown. The effects of chemoreceptor stimuli (intracarotid injections of CO_2-saline at markers) on heart rate can be seen. A control chemoreceptor stimulus given in the expiratory phase of breathing evokes a prompt and large bradycardia (panel at left). A stimulus given during an increase in intratracheal pressure of 6 mmHg in 1–2 sec evokes little or no bradycardia (second panel). Stimuli given after the increase in intratracheal pressure, but while the lungs remain inflated, regain their effectiveness with time (two panels at right).

about the mid-point of the ramp of pressure. In all tests the effectiveness of both stimuli was clearly related to the rate of air flow into the lungs: for slow ramps of pressure (taking about 10 sec to reach peak) the reflexes were as prompt and as complete as in the control conditions (i.e. as in the expiratory phase, without inflation); for ramps of intermediate duration (taking 3–6 sec to reach peak), the reflexes were prompt, but typically evoked a smaller bradycardia than in the control conditions (see Figs. 1 and 2).

(*c*) *Responses evoked after fast ramps.* In these experiments fast ramps of pressure were applied as described in section 2(*b*) above, and the tracheal pressure was then held constant at the top of the ramp (6–10 mmHg). Chemoreceptor and baroreceptor stimuli were delivered at various times *after* the ramp. Graded responses were observed in all tests, related to the delay between attainment of the peak of pressure and delivery of the stimulus. Stimuli usually evoked a slight bradycardia as soon as 1 sec after air flow into the lungs was completed. By 5–15 sec after the inflow of air, baroreceptor and chemoreceptor stimuli again evoked the full reflex bradycardia (see Figs. 3, 4, 6 and 7).

Thus, the phenomenon observed by Haymet & McCloskey (1975) in unparalysed dogs was confirmed here in paralysed animals: during prolonged periods of inflation (Hering–Breuer inflation apnoea) both baroreceptor and chemoreceptor stimuli still evoked prompt bradycardia. Haymet & McCloskey took this as evidence that tonically active mechanoreceptors in the lungs and thorax excited by inflation were not sufficient by themselves to block the baroreceptor and chemoreceptor reflexes.

3. *Effects of stimuli given during air flow out of the lungs*

In all experiments in which inflating ramps were tested, the peak inflation pressure was maintained until chemoreceptor and baroreceptor reflex responsiveness was fully restored, and then the tracheal cannula was opened to the air and the lungs rapidly deflated. Chemoreceptor and baroreceptor stimuli given during these rapid deflations usually evoked a prompt and large bradycardia (see Figs. 6 and 7). Commonly, however, deflation evoked an inspiratory effort and the stimuli, which then fell within the inspiratory phase of breathing, were then ineffective.

In four animals the effects of larger deflations were tested. A pneumothorax was formed on each side of the chest so that each lung could be seen. A narrow, cuffed, endotracheal tube was then tied into the trachea and advanced until its tip lay in the right main bronchus. With the cuff deflated both lungs were ventilated through this tube. When the cuff was inflated, only the right lung opened through the tube and the volume of the left lung remained unchanged. That this was so could be confirmed by direct inspection of each lung. The left lung could then be inflated to 10–20 mmHg and maintained at this pressure while the right lung was inflated and deflated independently. Chemoreceptor and baroreceptor stimuli delivered during a fast inflating ramp of the right lung alone, or of both lungs together (10–20 mmHg in 1–2 sec) evoked no reflex bradycardia. However, the stimuli regained their effectiveness about 5–15 sec after the ramp of pressure. The right lung was then rapidly deflated by suction applied to the endotracheal tube, so that it collapsed from its grossly inflated state to close to its residual volume within about 1 sec. This deflation did not, however, evoke an inspiratory effort presumably because of a Hering–Breuer

inflation reflex originating in the still-inflated left lung. Respiratory efforts re-commenced when the left lung was allowed to deflate. In all four animals an indication that reflexes originating in the right lung were intact was obtained on evoking a Hering–Breuer inflation reflex by inflating the right lung while the left lung remained collapsed.

Chemoreceptor and baroreceptor stimuli were delivered by an experimenter watching the right lung and were timed to occur as the lung was close to complete collapse. They evoked their usual prompt and marked reductions in heart rate (see Fig. 5).

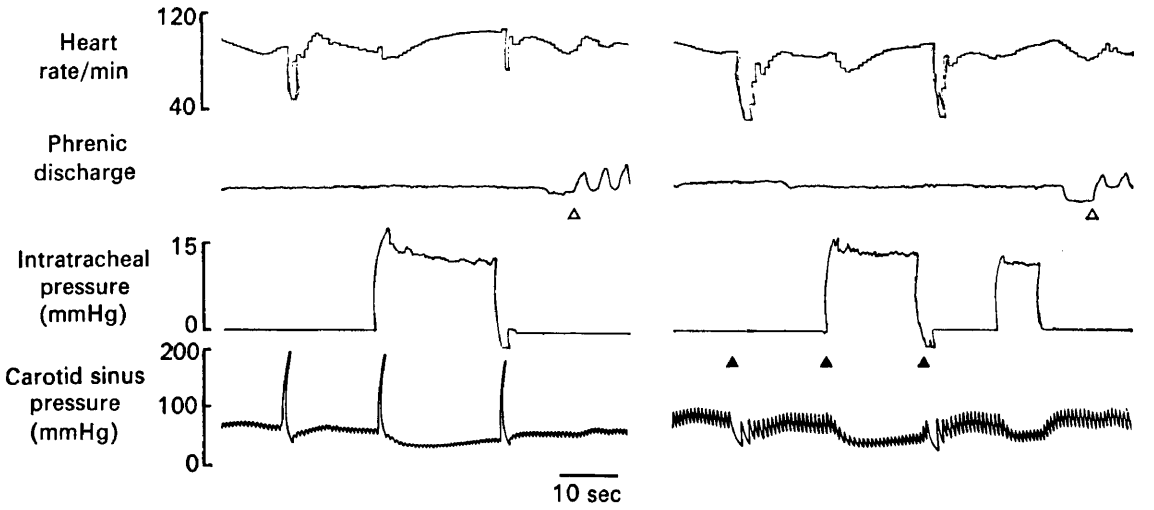

Fig. 5. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Heart rate, integrated phrenic activity, intratracheal pressure (delivered to right lung only) and carotid sinus B.P., recorded during two periods of temporary cessation of artificial ventilation, are shown. The effects of baroreceptor stimuli (pulses of intracarotid pressure: left panel) and chemoreceptor stimuli (intracarotid injections of CO_2-saline at markers: right panel) on heart rate can be seen. In each panel the left lung remains hyperinflated from the start of the record to the marker (open triangle) under the phrenic record. Baroreceptor and chemoreceptor stimuli evoke prompt and large bradycardia before, but not during, a pressure rise inflating the right lung. Both stimuli remain effective during a rapid deflation of the right lung. Inflation and deflation of the right lung, unaccompanied by stimuli, cause little change in heart rate (intratracheal pressure changes at far right).

4. *Effects of denervation of the lungs*

After pulmonary denervation, brief stimuli to the arterial baroreceptors or chemoreceptors evoked a prompt bradycardia when delivered during air flow into the lungs, as well as during maintained inflations or during air flow out of the lungs (see Figs. 6 and 7). That is, the inhibition of the reflexes which could be caused during air flow into the lungs of animals with intact vagi could no longer be observed when the pulmonary vagi were cut.

Figs. 6 and 7 illustrate all the phenomena associated with respiratory modulation of reflex effectiveness: the activity of the central inspiratory neurones in the absence of lung expansion can block the reflexes and the movement of the lungs into an expanded state in the absence of central inspiratory activity can also block them. The reflexes are not blocked during maintained static inflation, nor during deflation. The effects of lung expansion are not seen when the lungs are denervated.

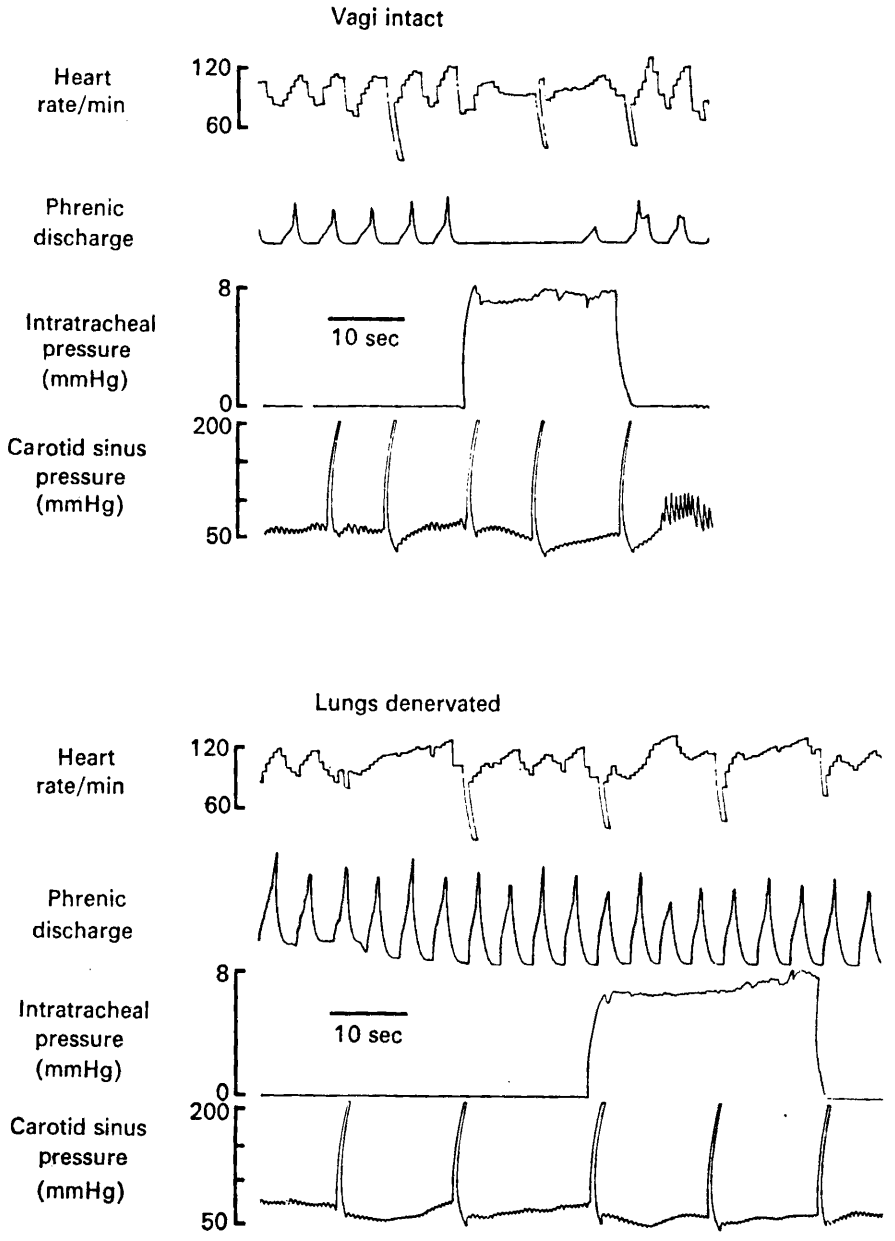

Fig. 6. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Upper and lower panels show heart rate, integrated phrenic activity, intratracheal pressure and carotid sinus blood pressure, recorded during periods of temporary cessation of artificial ventilation. The effects of baroreceptor stimuli (pulses of intracarotid pressure) on heart rate are seen. When the vagi are intact, (upper panel) baroreceptor stimuli evoke bradycardia except when delivered during periods of inspiration (first of the stimuli shown) or while the lungs are expanding in response to a rise in intratracheal pressure (third stimulus). After denervation of the lungs (lower panel), the stimuli remain ineffective during periods of central inspiratory activity (first stimulus), but now evoke a large bradycardia when delivered while the lungs are expanding in response to a rise in intratracheal pressure.

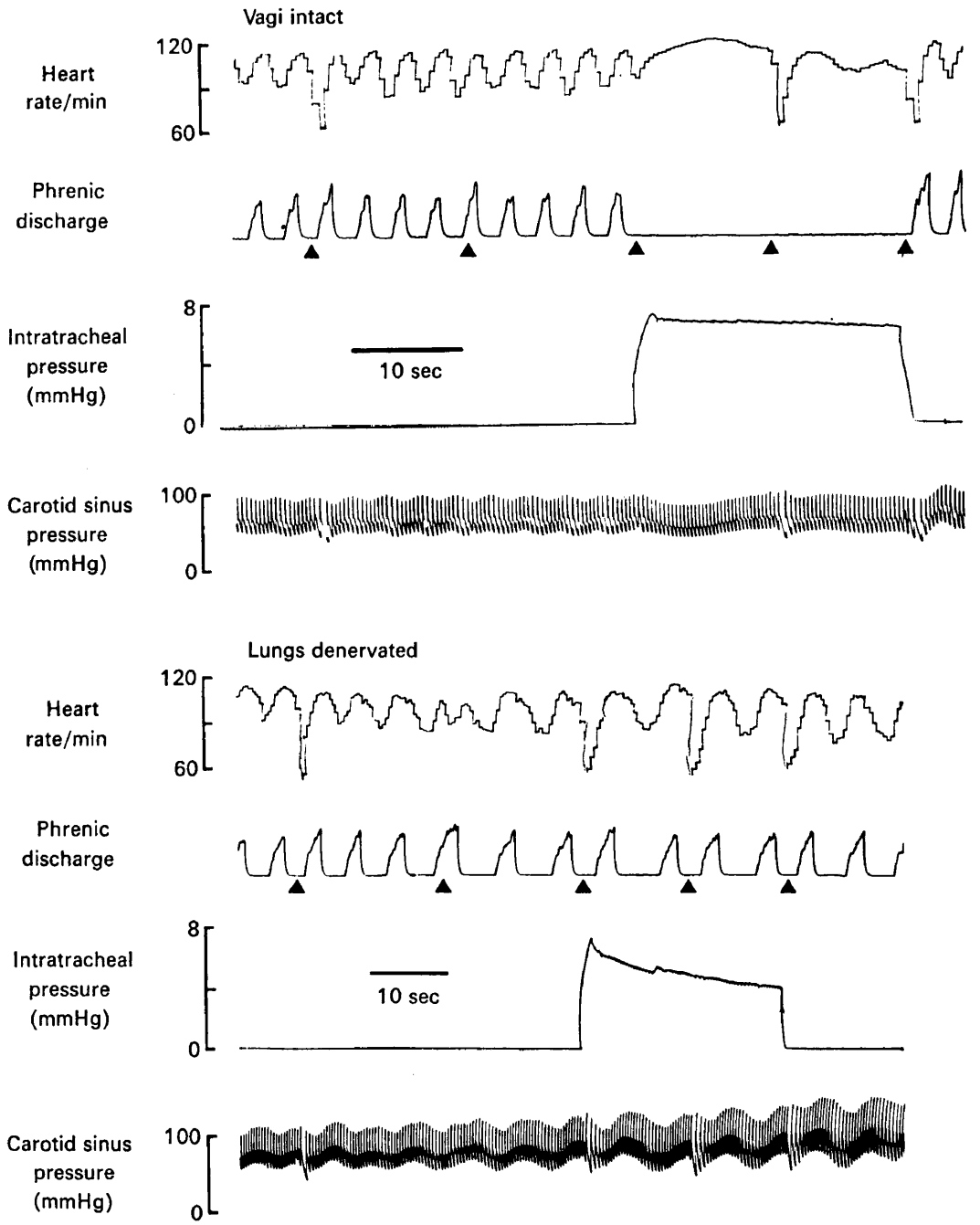

Fig. 7. Dog, anaesthetized with chloralose and paralysed with D-tubocurarine. Upper and lower panels show heart rate, integrated phrenic activity, intratracheal pressure and carotid sinus blood pressure, recorded during periods of temporary cessation of artificial ventilation. The effects of chemoreceptor stimuli (intracarotid injections of CO_2-saline at markers) on heart rate are seen. When the vagi are intact (upper panel), chemoreceptor stimuli evoke bradycardia except when delivered during periods of inspiration (second of the stimuli shown) or while the lungs are expanding in response to a rise in intratracheal pressure (third stimulus). After denervation of the lungs (lower panel), the stimuli remain ineffective during periods of central inspiratory activity (second stimulus), but now evoke a large bradycardia when delivered while the lungs are expanding in response to a rise in intratracheal pressure.

DISCUSSION

Koepchen *et al.* (1961) and Haymet & McCloskey (1975) have shown that during inspiration, baroreceptor and chemoreceptor effects on the heart rate are blocked. In experiments on paralysed animals Davidson *et al.* (1976) showed that the activity of neural inspiratory mechanisms, as indicated by phrenic nerve activity, were alone sufficient to block these reflexes. The present study confirms and extends the work of Koepchen *et al.* (1961), Haymet & McCloskey (1975) and Davidson *et al.* (1976). Here we have confirmed that the presence of central inspiratory drive activity without movement of the lungs is sufficient to block these reflexes, and have found as well that lung expansion without central inspiratory drive activity also blocks both reflexes. In the intact animal it is likely that both mechanisms act together. This would serve to assure the effectiveness of the block.

The inhibition of both reflexes caused by expansion of the lungs is attributable to the excitation of receptors in the lungs because it is abolished by denervation of the lungs. The sensory elements involved are sensitive to the rate of expansion of the lung and the effectiveness of the inhibition which they cause is dependent on this rate of inflation. The inhibitory effect occurs when air flows into, but not out of, the lungs. It becomes gradually less potent with time as the lungs are held in the inflated state. In our present studies the experimental animals were paralysed and ventilated on oxygen prior to the periods of stoppage of the pump during which our observations were made. The levels of alveolar or arterial carbon dioxide tension were not monitored in these animals, and it is conceivable that they may have been elevated in order to maintain central inspiratory drive. The failure of maintained pulmonary inflation to block vagally mediated changes in heart rate is unlikely, however, to be due to this possible coincidence of raised oxygen and carbon dioxide tensions. Haymet & McCloskey (1975) and Davidson *et al.* (1976) reported similar effects in animals spontaneously breathing air.

A recent brief report by Lopes & Palmer (1976) suggested that the bradycardia evoked by electrical stimulation of the carotid sinus nerve could be attenuated by central inspiratory drive activity or by sustained inflation of the lungs. These authors gave no indication of the magnitude of the pressures used to achieve sustained inflations, however, and it is likely (cf. Anrep *et al.* 1936*a*) that these considerably exceeded the pressures used here (for example, their Fig. 1*c* shows a lung inflation that caused sufficient obstruction of venous return to reduce arterial pressure by approximately 60 mmHg within 10 sec).

The identity of the intrapulmonary receptor type or types responsible for the inhibition of both cardiodepressor reflexes is not revealed by our experiments. If a single receptor type were responsible, it should possess the following properties to account for our findings: a sensitivity to the rate of lung inflation but no response to deflation, and a significant degree of adaptation during maintained inflation. The pulmonary stretch receptors come closest to meeting these requirements. They discharge in response to inflation but not deflation, are sensitive to the rate of lung inflation, and adapt slowly at a fixed lung volume (e.g. Paintal, 1973; Widdicombe, 1974). The property which is difficult to fit with our findings is the adaptation to a maintained inflation. The degree of adaptation of pulmonary stretch receptors is not

great. It can be seen, for example, in our Figs. 3, 4, 6 and 7 that maintained lung inflations sufficient to cause a Hering–Breuer apnoea (as judged from the phrenic electroneurogram) did not block the cardiodepressor reflexes. This was also the experience of Haymet & McCloskey (1975) and Davidson *et al.* (1976). Because the Hering–Breuer apnoea was maintained it can be concluded that appreciable activity of the pulmonary stretch receptors was continuing. However, the inhibition of the cardiodepressor reflexes did not continue. This observation suggests that the discharges of the pulmonary stretch receptors are not, in an unmodified form, responsible for inhibiting the baroreceptor and chemoreceptor reflexes on heart rate. However, central neurones which relay the phasic but not the tonic elements of stretch receptor inputs, i.e. which differentiate, mathematically, the stretch receptor input with respect to time, could provide the basis for the inhibition of cardiodepressor reflexes. In this respect the Rβ neurones (Baumgarten & Kanzow, 1958), found in the vicinity of the nucleus of the tractus solitarius, are of interest. These neurones discharge in phase with phrenic motoneurones and are stimulated also by lung inflation. Thus they are active in circumstances in which the mechanisms causing vagal bradycardia are refractory, and thus may be associated with this phenomenon. While many investigators report no marked adaptation of the response of Rβ neurones to sustained lung inflation, such adaptation is apparently frequently seen (Berger & Mitchell, 1977; K. M. Spyer and R. M. McAllen, personal communication) so that this aspect of their behaviour also correlates well with the conditions associated with vagal refractoriness.

Another intrapulmonary receptor type possibly concerned in the effects described is the 'fast-adapting' receptor (Knowlton & Larrabee, 1946), the so-called 'lung-irritant' receptor. Lung-irritant receptors discharge in a roughly rate-sensitive way to lung inflations, particularly to large inflations, and adapt rapidly so that they have little or no activity during maintained inflations (Paintal, 1973; Widdicombe, 1974; Sampson & Vidruk, 1975). These properties could enable these receptors to be responsible for our findings. However, the lung-irritant receptors are also sensitive to deflations of the lung, and it has been seen in our Figs. 5, 6 and 7 that both cardiodepressor reflexes can be readily evoked during lung deflations. It is true, however, that the lung-irritant receptors are not particularly sensitive to deflations from moderate expansions to functional residual capacity, as tested in some of our experiments (Figs. 6 and 7) (Widdicombe, 1974; Sampson & Vidruk, 1975). It might, therefore, be claimed that the lung irritant receptors could still account for our findings. Experiments of the type shown in our Fig. 5 are therefore most important. In these experiments, very large deflations (from large expansions to volumes close to residual volume) were tested. Such large deflations are known to excite lung irritant receptors powerfully (Widdicombe, 1974; Sampson & Vidruk, 1975). They did not, however, inhibit the baroreceptor and chemoreceptor reflexes on heart rate. It therefore appears unlikely that lung irritant receptors are responsible for the effects we have described. It could still be argued that the lung irritant receptors are responsible, but only during inflations, because their effects during deflations are in some way modified by other information about the direction of lung movement. We cannot rule out this possibility altogether, but we do note that in experiments of the type shown in Fig. 5, the pulmonary stretch receptors of the non-moving lung were

signalling to the central nervous system that the lungs were *in*flated, and were doing so sufficiently strongly to prevent an inspiratory effort when the moving lung collapsed. It is unlikely, therefore, that lung irritant receptors are 'gated' by pulmonary stretch receptor activity in such a way as to enable them to be responsible for the inhibition of cardio-depressor reflexes we have described.

The modulation of cardiovascular reflexes by central and peripheral respiratory mechanisms is likely to require consideration in many situations. Reflex bradycardia can be fully evoked only when inspiratory efforts and lung movements are absent. Cardiac slowing, which is a sign of a foetus distressed by hypoxia, is thus likely to be most marked when there are no foetal respiratory movements. Similarly, other reflexes which cause bradycardia are likely to do so most effectively when breathing is stopped: this is shown, for example, for oculo-cardiac and diving reflex bradycardia, in the following paper (Gandevia, McCloskey & Potter, 1978). Sinus arrhythmia is likely to become marked in situations where reflex bradycardia is evoked, but breathing continues (e.g. Levy, Degeest & Zieske, 1966; Schweitzer, 1937). Where reflex stimuli arise which would normally evoke a bradycardia, but breathing is at the same time increased, the bradycardia may be partly masked or even completely blocked. Thus, sustained stimulation of the carotid arterial chemoreceptors evokes a ventilatory response that can prevent the 'primary' response of reflex bradycardia from being seen (Daly & Scott, 1958). Similarly, the hyperpnoea of exercise may block the tendency of any rise in arterial pressure to evoke a bradycardia through the baroreceptor reflex; this mechanism might account for the so-called 'resetting' of the baroreceptor-cardiodepressor reflex in exercise (Streatfeild, Davidson & McCloskey, 1977).

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REFLEX BRADYCARDIA OCCURRING IN RESPONSE TO DIVING, NASOPHARYNGEAL STIMULATION AND OCULAR PRESSURE, AND ITS MODIFICATION BY RESPIRATION AND SWALLOWING

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SUMMARY

1. Digital pressure applied to the eyes evokes reflex bradycardia in human subjects and anaesthetized dogs. The bradycardia is most pronounced when breathing stops.

2. In the dog oculo-cardiac reflex bradycardia is mediated by vagal stimulation and by sympathetic withdrawal.

3. Oculo-cardiac reflex bradycardia in the dog is reduced by central neural inspiratory activity and by the excitation of pulmonary afferents by inflation of the lungs. In human subjects it is reduced when inspiratory efforts are made against a closed glottis.

4. Nasopharyngeal stimulation with water evokes reflex bradycardia in the anaesthetized dog. This bradycardia is reduced by central neural inspiratory activity and by the excitation of pulmonary afferents by inflation of the lungs.

5. Bradycardia occurs in normal human subjects during immersion of the face in water ('diving'). This bradycardia is reduced when inspiratory efforts are made against a closed glottis.

6. Swallowing evokes transient tachycardia in human subjects. During diving or the application of ocular pressure, swallowing reduces the reflex bradycardia which these evoke.

INTRODUCTION

Brief stimuli delivered to the carotid chemoreceptors and baroreceptors evoke prompt reflex bradycardia when they are timed to occur in the expiratory phase of the respiratory cycle, but have little or no effect on heart rate when given during inspiration. (Koepchen, Wagner & Lux, 1961; Haymet & McCloskey, 1975). The bradycardia evoked in these reflexes is mediated mainly by the vagus nerves, although withdrawal of cardiac sympathetic tone can also be involved and is similarly modulated by the respiratory cycle (Davis, McCloskey & Potter, 1977). The respiratory modulation of these reflexes is attributable to two mechanisms: there is an inhibitory effect on the reflexes arising from activity of inspiratory neurones in the central nervous system (Koepchen *et al.* 1961; Davidson, Goldner & McCloskey, 1976), and there is a further inhibitory effect arising from the excitation of intrapulmonary receptors during air flow into the lungs (Gandevia, McCloskey & Potter, 1978). Presumably both inhibitory mechanisms usually operate together.

In the present study we have investigated other stimuli known to evoke bradycardia, and have looked for modulations of reflex effectiveness attributable to central and peripheral reflex respiratory mechanisms. The reflexes studied here were the oculo-cardiac reflex (Aschner, 1908), the diving reflex (Andersen, 1966) and a reflex arising from naso-pharyngeal stimulation (cf. Angell James & Daly, 1972), in experiments on normal awake human subjects and anaesthetized dogs. We also report observations on the changes in heart rate which accompany swallowing in man, and discuss these in the light of our other findings.

METHODS

Animal experiments. Experiments were performed on eighteen adult dogs of both sexes, weighing 9–19 kg. Eleven of these animals were also used in the study of chemoreceptor and baroreceptor reflexes described in the preceding paper (Gandevia *et al.* 1978). The animals were anaesthetized with intravenous chloralose (α-chloralose: British Drug Houses; 80 mg/kg). In each dog the trachea was cannulated low in the neck. A nylon cannula was inserted in a femoral vein for administration of anaesthetic or drugs. Rectal temperature was maintained at 37–39 °C.

Arterial blood pressure was measured through a cannula in a lingual artery using a Statham P23AC transducer, and was recorded on one channel of a Grass polygraph pen recorder. The electrocardiogram and the beat by beat heart rate (Grass 7P4 cardiotachometer, triggered from the e.c.g.) were recorded. Respiratory activity was measured according to the requirements of the particular experiment. In some animals an indication of tracheal air flow was obtained by measuring the pressure at the tip of a wide (2 mm i.d.) catheter inserted into the trachea, using Statham transducer. Alternatively, respiratory activity was measured by a bag-in-box method similar to that described by Donald & Christie (1949) in which the animal inspired through a valve from a bag enclosed in an airtight box into which expired air was led; pressure in the box, which was related to the tidal volume of the breath taken, was measured using a Grass PT5A volumetric pressure transducer. In paralysed animals, respiratory activity was recorded from the central end of the cut and de-sheathed phrenic nerve using platinum electrodes. This phrenic neural discharge was integrated using a Grass 7P3B preamplifier ('leaky' integrator; time constant 0·05 sec).

Two reflexes were tested in anaesthetized dogs, the oculo-cardiac reflex and the reflex elicited by nasopharyngeal stimulation. The oculo-cardiac reflex was elicited by an experimenter placing the thumbs on the closed eyelids of the animal and pressing. No measurement of the pressure used was made, but similar pressures were applied to awake human subjects in other experiments (see below) without causing great discomfort. Nasopharyngeal stimulation was achieved by a method similar to that described by Angell James & Daly (1972). A cuffed, endotracheal tube was inserted into the trachea pointing rostrally and advanced until its tip lay in the nasopharynx. The tube was then tied firmly into the trachea, and the cuff was inflated. Tap water at room temperature was led into this tube when nasopharyngeal stimulation was required, and was collected through a rubber glove tied over the muzzle as it flowed out of the nose and mouth. The rate of flow of water was usually 1 l./min.

Human experiments. Experiments were performed on eight healthy subjects of both sexes, including the three authors. Electrocardiograms were measured from conventional limb leads, and beat by beat heart rate was obtained using a Grass 7P4 cardiotachometer triggered from the e.c.g. Both were recorded on the polygraph. For both diving reflex and oculo-cardiac reflex studies subjects were usually seated. Diving reflexes were elicited by the subject's immersing the nose and mouth in a small bowl of cold water. Oculo-cardiac reflexes were elicited by an experimenter placing the thumbs on the subject's closed eyelids and pressing. The pressure was firm, but subjects were instructed to tell the experimenter as soon as any discomfort occurred; all the results reported here were obtained in experiments in which the subjects reported no discomfort.

In the diving experiments the subjects, of course, stopped breathing while their faces were immersed. In the experiments on the oculo-cardiac reflex subjects were instructed to stop breathing while the eye pressure was applied (see Results). Although we noted no consistent differences between reflexes elicited with the breath held in inspiration and those in which it was

held in expiration, we usually asked our subjects to commence breath-holding at the normal end-expiratory point. In the course of a 'dive' or of application of eyeball pressure during a breath-hold, subjects performed one of two simple manoeuvres in response to an instruction from an experimenter. The subjects were required either to swallow or to make a single inspiratory effort against a closed glottis ('false breath'). Swallowing was used in these experiments because it had been found that resting subjects breathing normally increase their heart rates by 10–30 beats/min for a few beats on each occasion they swallow (Fig. 1; see also Miller & Sherrington, 1916).

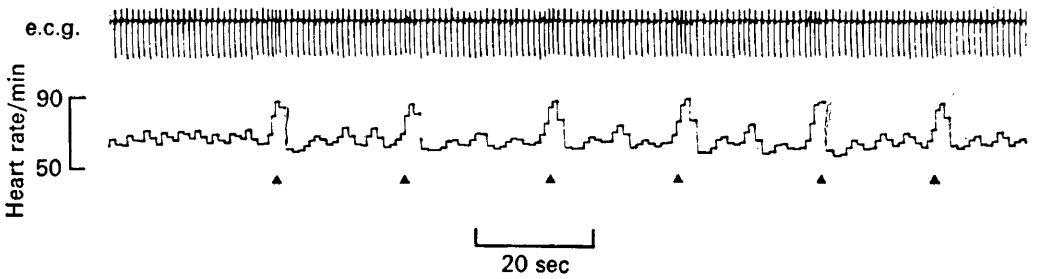

Fig. 1. Effects of swallowing on heart rate. Records show e.c.g. and heart rate of a normal resting human subject. The subject swallows on six occasions, marked by filled triangles.

RESULTS

Oculo-cardiac reflex

Animal experiments. The typical response to the application of pressure to the eyes in the anaesthetized dog was a bradycardia. In some dogs this was considerable, in others it was slight, but in all there was an enhancement of respiratory sinus arrhythmia accompanying the bradycardia. In about twelve of eighteen dogs tested, there was also some reduction in the rate and depth of breathing during the application of pressure.

In order to test the effectiveness of the oculo-cardiac reflex during periods in which an animal was not breathing, Hering–Breuer inflation reflexes were evoked by occluding the trachea at the end of normal inspirations. When the lungs were thus held inflated the animal made no attempt to breathe for many seconds, during which time the effectiveness of the reflex could be tested. Typically, there was a slight increase in heart rate during a control trial of lung inflation alone. This was probably attributable to the slight fall in blood pressure which occurred during the period of positive intrathoracic pressure. When pressure was applied to the eyes during Hering–Breuer inflation apnoea, however, the bradycardia which was evoked was large, and was always larger than the bradycardia evoked by similar pressure applied during normal breathing. If both eyeball pressure and lung inflation were maintained for long enough, the animal would ultimately make an inspiratory effort. Whether such an inspiratory effort was permitted to draw air into the lungs (Fig. 2) or not (Fig. 4), it was accompanied by a sudden and marked reduction in the bradycardia which then returned as the inspiratory effort concluded. Responses of this type are shown in Fig. 2; similar responses were obtained in all dogs in which oculo-cardiac reflexes could be evoked (fourteen of eighteen dogs).

The oculo-cardiac reflex bradycardia was mediated mainly by the vagus nerves. This was shown in six dogs in which previously marked bradycardia was all but

abolished following vagotomy or administration of atropine (1–2 mg/kg). In all six, however, slight bradycardia was still evoked by eyeball pressure, and this was attributable to withdrawal of sympathetic neural tone, as it was no longer evoked after administration of propranolol (1 mg/kg). In three of the six animals in which bradycardia due to sympathetic withdrawal could be demonstrated, there was a greater response elicited when eyeball pressure was applied during the expiratory

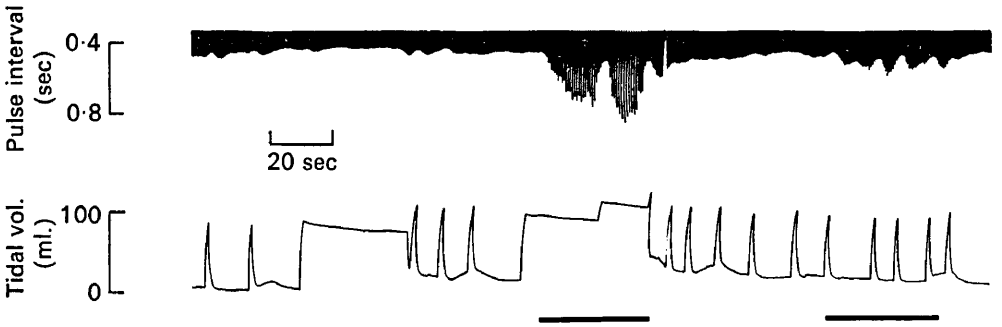

Fig. 2. Dog, anaesthetized with chloralose. Records show pulse interval and tidal volume (measured by bag-in-box method, inspiration upwards). Marker bars at bottom of figure show periods during which digital pressure was applied to the eyes. On two occasions the tidal volume record shows inspiratory apnoea, achieved by occluding the expiratory line. Inspiratory apnoea or ocular pressure alone evoke little change in heart rate. When ocular pressure is applied during a period of inspiratory apnoea, there is marked bradycardia; note that this bradycardia is transiently reduced when the inspiratory apnoea is interrupted by a breath.

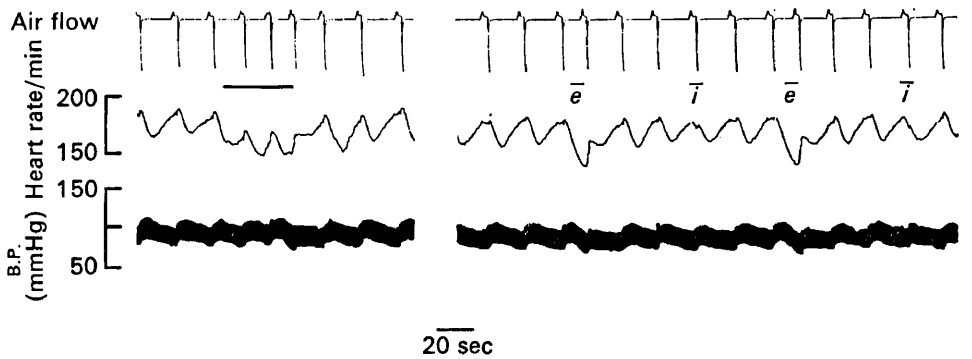

Fig. 3. Dog, anaesthetized with chloralose; bilateral vagotomy. Records show tracheal air flow (inspiration upwards), heart rate and arterial blood pressure. Marker bars below the air flow record show periods in which pressure was applied to both eyes. In the panel at the left the bradycardia in response to sustained ocular pressure is seen. In the panel at the right the bradycardia evoked by ocular pressure applied only during the expiratory phase of breathing (*e*) is compared with that evoked by similar pressure applied only during inspiration (*i*).

phase of breathing than when it was applied during inspiration. This effect is shown in Fig. 3, and is similar to respiratory modulation of sympathetic responses to chemoreceptor and baroreceptor stimuli described by Davis *et al.* (1977).

In seven dogs more elaborate experiments were performed in order to elucidate the respiratory mechanisms responsible for reducing oculo-cardiac bradycardia whenever an inspiration occurred (e.g. Fig. 2). These animals were paralysed with D-tubo-

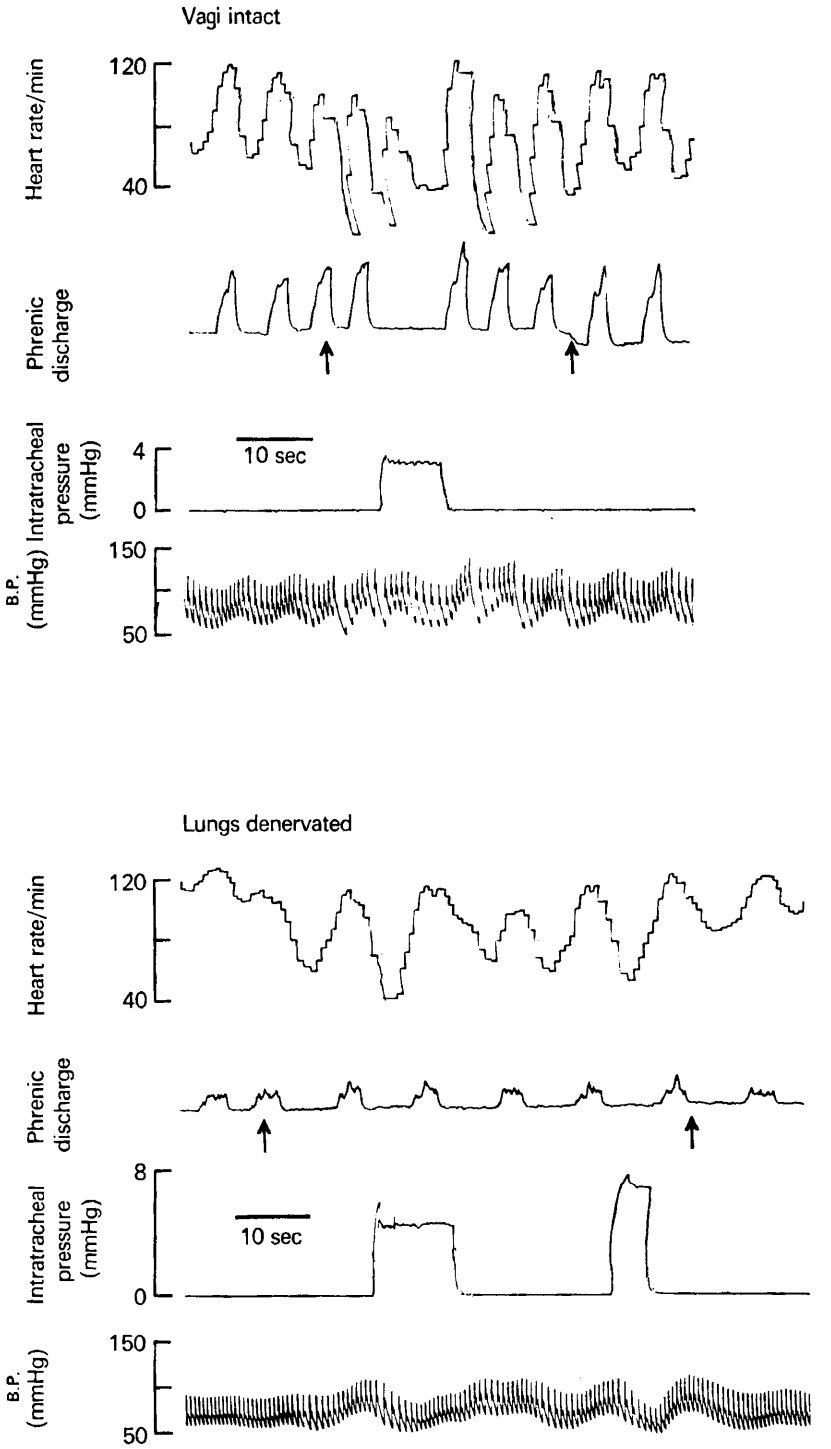

Fig. 4. Dog, anaesthetized with chloralose, paralysed with D-tubocurarine. Records of heart rate, integrated phrenic neural activity, intratracheal pressure and arterial B.P., obtained during periods of temporary cessation of artificial ventilation, are shown. Ocular pressure was applied between the arrows. In the upper panel the response to ocular pressure is seen: there is a pronounced bradycardia which is reduced on each occasion that inspiratory (phrenic) activity occurs. The bradycardia is also reduced as the lungs are inflated, but returns while the inflation is maintained. In the lower panel the response to ocular pressure is seen after surgical denervation of the lungs; bradycardia is again evoked but reduced on each occasion that inspiratory activity occurs. The bradycardia is no longer reduced by lung inflation, nor does inflation inhibit inspiration as it did before pulmonary denervation.

curarine (1–2 mg/kg) and artificially ventilated on oxygen with a Starling 'Ideal' pump. From time to time the pump was stopped and experiments on the oculo-cardiac reflex were performed. Respiratory activity in the paralysed animals was indicated by the integrated phrenic electroneurogram. When pressure was applied to the eyes in these animals, oculo-cardiac reflex bradycardia occurred. With each

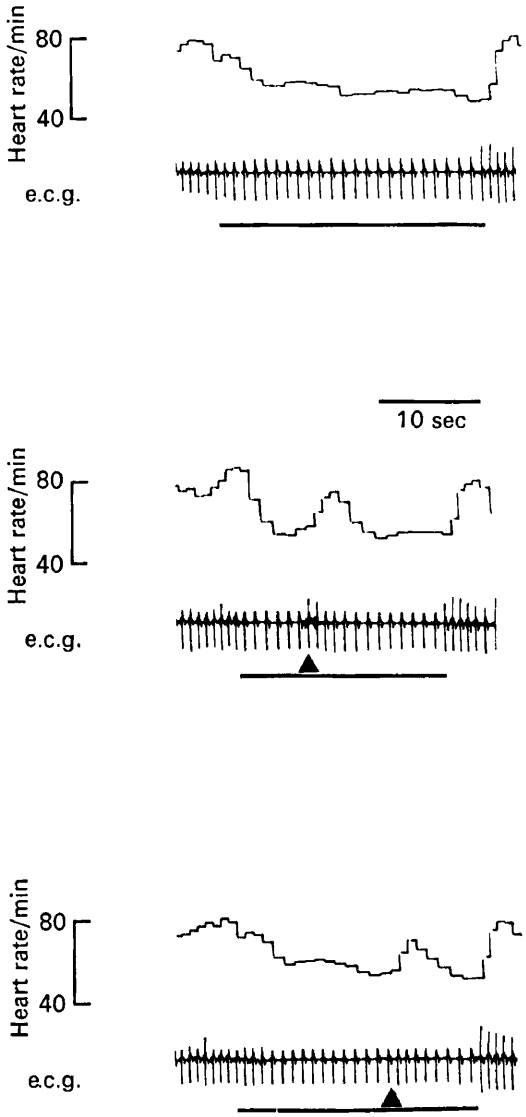

Fig. 5. Records show the heart rate and e.c.g. from a normal human subject during three periods of voluntary apnoea in which bilateral ocular pressure was applied (marker bars). The upper panel shows a control response. The middle panel shows the effect of the subject taking a 'false breath' (see text) at the filled triangle. The lower panel shows the effect of the subject swallowing at the filled triangle.

inspiratory effort indicated by the phrenic electroneurogram, the bradycardia was reduced, but it returned when the effort concluded. When the lungs were inflated within 1–2 sec to a pressure of 4–8 mmHg by an experimenter blowing into a tube connected to the tracheal cannula, this again reduced the oculo-cardiac reflex

bradycardia. The bradycardia returned within a few seconds of the air flow into the lung even when the lung inflation was maintained. Such inflations were associated with a silencing of the activity in the phrenic nerve, presumably because of the Hering–Breuer inflation reflex. In all seven dogs the lungs were then surgically denervated by cutting the left vagus nerve in the neck, and the right pulmonary vagus through a thoracic incision at the level of the fourth rib (Gandevia *et al.* 1978); this procedure denervated the lungs, but maintained cardiac vagal innervation on

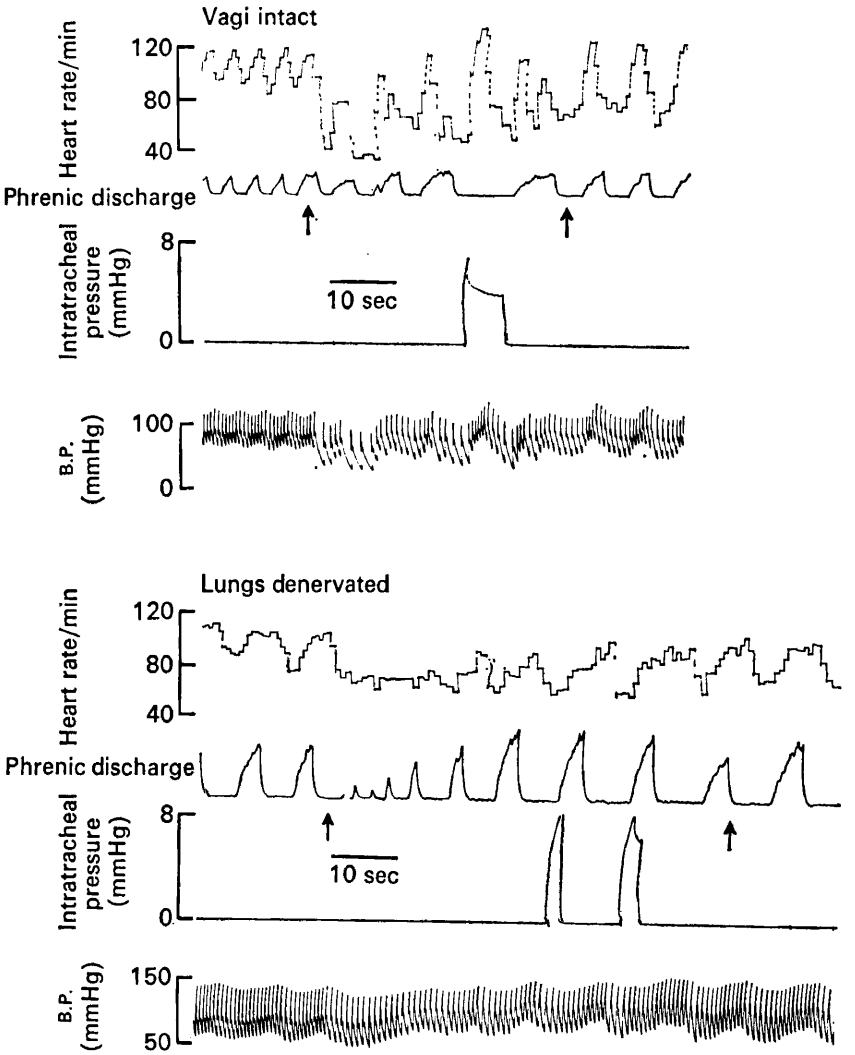

Fig. 6. Dog, anaesthetized with chloralose, paralysed with D-tubocurarine. Records of heart rate, integrated phrenic neural activity, intratracheal pressure and arterial blood pressure, obtained during periods of temporary cessation of artificial ventilation, are shown. Nasopharyngeal stimulation was applied between the arrows. In the upper panel the response to nasopharyngeal stimulation is seen: there is a pronounced bradycardia which is reduced on each occasion that inspiratory (phrenic) activity occurs. The bradycardia is also reduced as the lungs are inflated but returns while the inflation is maintained. In the lower panel the response to nasopharyngeal stimulation is seen after surgical denervation of the lungs; bradycardia is again evoked but reduced on each occasion that inspiratory activity occurs. The bradycardia is no longer reduced by lung inflation.

the right side. Repeating the initial experiment after pulmonary denervation showed that oculo-cardiac reflex bradycardia still occurred and was still reduced with each inspiratory effort, but was no longer reduced by lung inflation. A complete set of findings from a typical experiment are shown in Fig. 4.

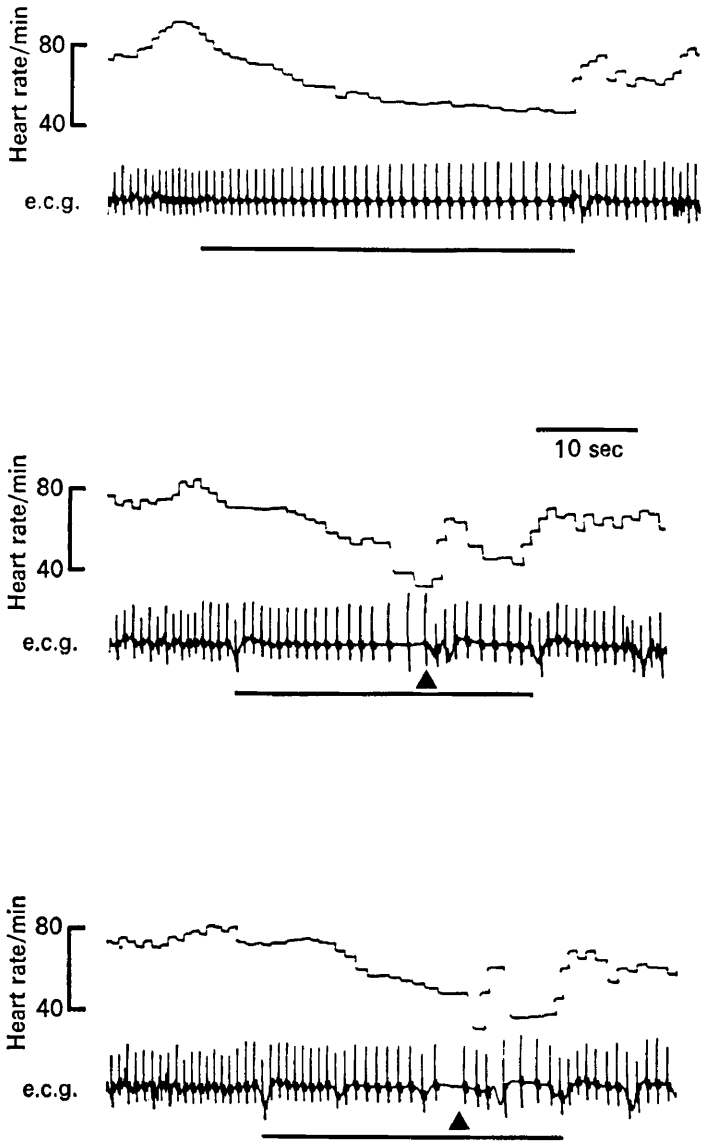

Fig. 7. Records show the heart rate and e.c.g. from a normal human subject during three periods of voluntary apnoea in which the face and mouth were immersed in water (marker bars). The upper panel shows a control response. The middle panel shows the effect of the subject taking a 'false breath' at the filled triangle. The lower panel shows the effect of the subject swallowing at the filled triangle.

Human experiments. Oculo-cardiac reflex bradycardia was evoked on many occasions in each of eight normal volunteer subjects. The bradycardia was easier to demonstrate and was more marked during breath holding. This finding is consistent with the observations in the dog, reported above (e.g. Fig. 2). We found no consistent

difference in the magnitude of the bradycardia evoked when breath-holding was performed in the inspiratory or expiratory position.

The oculo-cardiac reflex bradycardia was reduced whenever a subject took a breath, despite the continued application of pressure to the eyes. The bradycardia was also reduced if the subject made a 'false breath', or it the subject swallowed. Fig. 5 shows results from a typical subject.

Nasopharyngeal stimulation

Experiments similar to those on the oculo-cardiac reflex described above were performed in ten dogs. The passage of cold water through the nasopharynx was associated with a pronounced bradycardia which was reduced with each inspiratory effort, and enhanced in periods of Hering–Breuer inflation apnoea.

Seven of the dogs were paralysed with D-tubocurarine, artificially ventilated on oxygen, and then tested with nasopharyngeal stimulation in periods during which the pump was temporarily stopped. In these animals nasopharyngeal stimulation evoked a prompt reflex bradycardia which was reduced on each occasion that the phrenic electroneurogram indicated inspiratory activity. The bradycardia was also reduced by the inflation of the lungs (to 4–8 mmHg within 1–2 sec), although the bradycardia returned despite maintained static inflation of the lungs (see Fig. 6). Inflation of the lungs in this way was associated with silencing of the phrenic electroneurogram, presumably because of a Hering–Breuer inflation apnoea. Denervation of the lungs abolished the effects of lung inflation.

Diving

Eight normal volunteer subjects participated in many 'dives' in which they immersed the nose and mouth in a bowl of cold water. Each dive was associated with a reflex bradycardia, and we found no consistent differences in the responses to dives in which the breath was held in inspiration and those in which the breath was held in expiration. Most subjects normally swallow at the moment of immersing the face in water and find it most difficult to prevent themselves from doing this (Ebbecke, 1943). Diving bradycardia came on more slowly in dives which commenced with a swallow and was reduced whenever a subject took a 'false breath', or swallowed. Fig. 7 shows results from one subject.

DISCUSSION

It is known that stimulation of the carotid chemoreceptors or baroreceptors can evoke reflex bradycardia, but that such reflex effects are wholly or partly blocked during the inspiratory phase of breathing by central neural inspiratory mechanisms (Koepchen *et al.* 1961; Davidson *et al.* 1976) and by the central actions of sensory nerves from the lungs (Gandevia *et al.* 1978). In the present study we examined reflex bradycardia evoked by other stimuli and found that it, too, could be reduced by central neural inspiratory activity or by the actions of sensory nerves from the lungs. The central and reflex effects of breathing upon mechanisms which slow the heart appear, therefore, to be generally effective and not to be specifically confined to baroreceptor and chemoreceptor reflexes. It may be, however, that the reflexes we have examined here act by augmenting either the baroreceptor or chemoreceptor

reflexes, so that the generality of the effect may be only apparent. It has been suggested, for instance, that diving bradycardia occurs through a facilitation of arterial chemoreceptor reflexes (e.g. Jones & Purves, 1970; Daly, Elsner & Angell James, 1977) or of baroreceptor reflexes (Andersen & Blix, 1974).

The mechanisms by which the respiratory modifications of reflex bradycardia act were considered fully in the preceding paper (Gandevia *et al.* 1978), and the analysis offered there requires no elaboration in the light of the present results. The most clear-cut experiments were those performed in paralysed dogs (see Figs. 4 and 6), in which it was shown that bradycardia was reduced during the discharge of central inspiratory neurones unaccompanied by any movement of the lungs, or during air flow *into* (but not *out of*) the lungs in the absence of central inspiratory drive activity. Denervation of the lungs established that the effects of air flow were mediated by sensory nerves from the lungs, and the observation that the reduction in bradycardia was not sustained during a static inflation suggests that the intrapulmonary receptors responsible had a considerable phasic sensitivity.

The oculo-cardiac reflex was first described by Aschner (1908) and Dagnini (1908) and is evoked by pressure on the eyeball or traction on the extrinsic muscles of the eyes. It has its afferent limb in the trigeminal nerve and efferent limbs in the vagus and (as shown here) sympathetic nerves. The reflex is of obscure significance and was used here because it provides a mechanism for evoking bradycardia which is not apparently dependent upon arterial baroreceptor or chemoreceptor reflexes. The reflex is sometimes used by the physician attempting to terminate supraventricular tachycardia and our observations suggest that the manoeuvre will be more likely to succeed if the patient is asked to hold his breath while it is performed. Aserinsky & De Bias (1963) reported that oculo-cardiac reflex bradycardia is suppressed by artificial ventilation, a finding which we would attribute to the phasic activity of intrapulmonary receptors. As severe bradycardia or even cardiac arrest attributable to the oculo-cardiac reflex can occur during ophthalmic surgery (Katz & Bigger, 1970), a precaution suggested by these observations would be for anaesthetists to increase the frequency of lung inflations during surgical manipulations of the eye.

The reflexes elicited by diving in man and by nasopharyngeal stimulation in the dog are similar (Angell James & Daly, 1972). It is known that diving bradycardia in man (Daly & Angell James, 1975) and in the duck (Andersen, 1963) is reduced when a breath is taken, even if the inspired gas does not alter the blood gas tensions. Our experiments suggest that the reduction is brought about by both central inspiratory and phasic pulmonary afferent mechanisms. Recent studies by Bamford & Jones (1976) in the duck lead also to this conclusion. In the episodes of diving and oculo-cardiac reflex bradycardia in which 'false breaths' were taken (Figs. 5 and 7), both mechanisms could have been operating, although the pulmonary distortion was presumably much less than would have occurred during a normal breath. As with the oculo-cardiac reflex, there are known to be hazards in surgical procedures from cardiac arrhythmias attributable to reflexes from nasopharyngeal and endotracheal stimulation (Katz & Bigger, 1970), and again the present findings suggest that more frequent lung inflations imposed during such procedures should give some protection.

Swallowing was a manoeuvre which was used in an attempt to activate central respiratory neurones without causing an accompanying distortion of the lungs. It is

known that many medullary neurones which discharge in association with inspiration also discharge at the commencement of a swallow (Hukuhara & Okada, 1956; Sumi, 1963). The same neurones discharge when a stimulus known to induce swallowing is presented in a paralysed animal (Sumi, 1963). These inspiratory neuronal discharges may be associated with the very slight inspiratory effort ('Schluckatmung') which is a characteristic early event in swallowing (Doty, 1968). The association of tachycardia with swallowing was observed by Miller & Sherrington (1916) and has been demonstrated here (Fig. 1). Central inspiratory neural activity accompanies swallowing, and we have shown here that similar activity reduces bradycardia. It follows, as was shown in Figs. 5 and 7, that swallowing reduces oculo-cardiac or diving reflex bradycardia. Attempts were also made, in many experiments on three domestic ducks, to look at the effects of swallowing on diving bradycardia in these diving animals but they could not be induced to swallow while diving.

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Breathing and control of heart rate

The advice to "take frequent deep breaths" given to someone close to fainting evidently has physiological justification. Recent work on the mechanisms of bradycardia has shown that the various reflexes that evoke it operate only during the expiratory phase of breathing,[1] while inspiration may increase the heart rate.

This new knowledge has important applications in the management of bradycardia and, more important, tachycardia. The heart is slowed when a rise in arterial pressure stimulates the baroreceptors of the carotid sinus, or when a fall in arterial oxygen tension stimulates the chemoreceptors of the carotid bodies. Slowing is evoked also through more complex reflexes during nasopharyngeal stimulation or when pressure is applied to the eyeballs (the oculocardiac reflex) or the face is immersed in water (the diving reflex). These reflexes, however, have little or no effect on heart rate during the inspiratory phase of breathing but are confined to the period of expiratory air flow and the pause between breaths.[1] The effect holds true whether the bradycardia is brought about by vagal excitation or by sympathetic withdrawal.[2]

The action of inspiration in inhibiting reflex bradycardia is sometimes produced by the activity of inspiratory neurones in the respiratory centres even when the thorax and lungs do not move (since it occurs, for example, when an inspiratory effort is made against a closed glottis[1 3]). The inhibition may be produced equally well, however, by stimulation of intrapulmonary stretch receptors during lung inflations, even when such inflations are imposed at a time when the inspiratory centres are silent.[3] Usually both inhibitory mechanisms occur together during inspiration, so that the inspiratory block of reflex bradycardia is doubly assured.[4 7]

These new findings provide explanations for several well-known phenomena. Sinus arrhythmia occurs because an otherwise steady source of vagal tone is intermittently interrupted by the inhibitory effects of successive inspirations, so that vagal impulses flow towards the heart and slow it only during expiration. More frequent and more powerful interruption of vagal tone could be expected during hyperventilation and would help to account for the accompanying tachycardia. Furthermore, as heart rate and the respiratory cycle appear to be related in the fetus in the same way as in the adult,[8] and as hypoxia is commonly associated with a cessation of fetal respiratory movements,[9] the cardiac slowing that is such a prominent sign of hypoxic distress in the fetus can now be more readily understood.

Clinically, the most important application of our better understanding of the reflex basis of bradycardia is in procedures used for terminating bouts of supraventricular tachycardia. Since breathing inhibits the reflexes that evoke bradycardia all attempts to increase vagal tone—whether by carotid sinus massage, pressure on the eyes, or applying water to the face—should be attempted while the patient voluntarily holds his breath.[1] The obligatory holding of the breath when the face is completely immersed gives the method a physiological advantage over carotid sinus massage or eye pressure[10] unless the patient voluntarily holds his breath during those procedures. Ideally, breath holding should occur in the end-expiratory phase. But as reflex inhibition from intrapulmonary receptors is phasic, and lasts only a few seconds when the lungs are held inflated,[3] breath holding in the inspiratory position should carry no great disadvantage.

On the other hand, where bradycardia becomes excessive, as in simple vasovagal faints or during manipulations in ophthalmic and nasopharyngeal surgery,[11] it should be preventable by voluntarily increased breathing or by increasing the frequency and amplitude of imposed lung inflations. Even the glass of water given to someone who feels faint makes good physiological sense, for swallowing is known to be associated with intense bursts of firing in central inspiratory neurones, and this central inspiratory activity inhibits vagal excitation and relieves bradycardia.[1]

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CARDIORESPIRATORY HOMEOSTASIS

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"The importance of the nervous system, which communicates with the external world on the one hand, and causes internal organs to function and establish the milieu intérieur *in which they live."*
Claude Bernard ('Cahier Rouge')

The cardiovascular and respiratory systems co-operate to deliver oxygen from the atmosphere to metabolizing tissues, and carbon dioxide from those tissues to the atmosphere. Clearly, there would be little point in the respiratory system increasing its delivery of oxygen if the cardiovascular system could not carry that oxygen to the tissues, nor is the cardiovascular system continuing its normal rate of transport if the respiratory system were temporarily to stop, or to be prevented from, delivering oxygen. Much of the co-operation which prevents such mis-matching occurs under the guidance of the central nervous system.

It is known from experiments on anaesthetized animals that the 'primary' reflex responses to stimulation of the peripheral arterial chemoreceptors are increased pulmonary ventilation, bradycardia and systemic vasoconstriction (Bernthal, Greene & Revzin, 1951; Daly & Scott, 1958; Salisbury, Galletti, Lewin & Rieben, 1959; Daly & Hazzeldine, 1963; Downing, Remensnyder & Mitchell, 1962; Daly, Hazzeldine & Ungar, 1967; Daly, 1972).

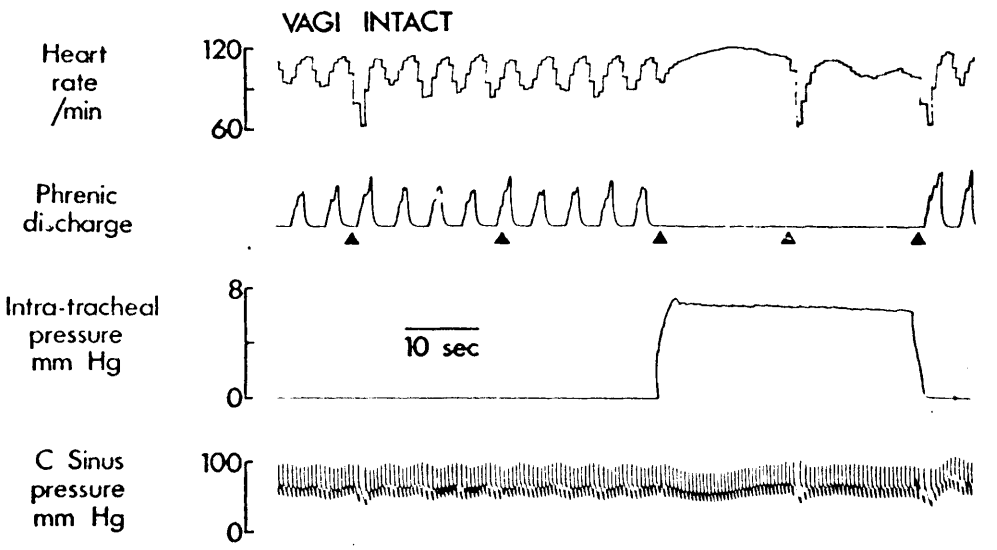

Fig. 1. Records from a dog, anaesthetized with chloralose and paralyzed with D-tubocurarine, showing heart rate (beat-by-beat, triggered from e.c.g.), 'integrated' phrenic nerve activity, intratracheal pressure, and blood pressure measured in the region of the carotid sinus. The effects of brief, selective stimuli to the arterial chemoreceptors (intracarotid injections of CO_2-saline at markers) on heart rate are seen. Chemoreceptor stimuli evoke bradycardia when the lungs are motionless only when central inspiratory activity (judged from the phrenic neurogram) is absent (first stimulus). The stimuli fail to evoke bradycardia when central inspiratory is present even when the lungs are motionless (2nd stimulus), or when the lungs are expanding in the absence of central inspiratory activity (3rd stimulus).

[From Gandevia, McCloskey & Potter, 1978a: reproduced with permission of *The Journal of Physiology*].

Often, these primary cardiovascular responses are not seen because they are obscured by responses in the opposite direction that are secondary to the increase in breathing: thus, tachycardia and vasodilatation often accompany systemic hypoxia.

The basis of this phenomenon is illustrated in Fig. 1. When brief, selective stimuli are delivered to the carotid body chemoreceptors in an anaesthetized and paralyzed dog they evoke reflex bradycardia when given in the expiratory phase of the respiratory cycle, but have little or no effect on heart rate when given in inspiration. This is so even when the paralyzed experimental animal is motionless. This indicates that the inhibitory effect of inspiration can be attributed to the cyclical activity of central inspiratory neurones: in Fig. 1 this central activity is reflected by the recorded discharge in the phrenic nerve. However, when the central inspiratory neurones are silent, inflation of the lungs is also able to inhibit the heart-slowing reflex: this is also seen in Fig. 1. It appears, therefore, that there are both central and peripheral mechanisms which ensure that the heart rate will accelerate during the inspiratory phase of breathing and that it will be possible to slow the heart only in the absence of inspiratory activity (Koepchen, Wagner & Lux, 1961; Haymet & McCloskey, 1975; Gandevia, McCloskey & Potter, 1978a, b). It is important to note that the influences of inspiration are both central *and* peripheral. This means that one cannot rely on controlling only one of these influences if one wishes to remove changes due to inspiration. Thus, artificially ventilating the lungs at a constant rate so as to keep constant the peripheral mechanical accompaniment of inspiration will leave central inspiratory neurones free to change their activity, and so inspiratory influences may still come into play.

Respiratory influences on cardiovascular responses have physiological significance in the conservation of oxygen. When there is hypoxia the arterial chemoreceptors are stimulated and pulmonary ventilation is reflexly increased: the deeper and more frequent inspirations then effectively block any reflex bradycardia evoked through the chemoreceptors and the heart rate increases. A similar situation seems to hold for peripheral arteriolar tone — the larger inspirations block the primary chemoreceptor reflex of vasoconstriction (Daly & Scott, 1962, 1963; Daly & Robinson, 1968; Daly, 1972). This means that when oxygen is scarce breathing is stimulated and, importantly, the cardiovascular system is enabled to increase its oxygen delivery through tachycardia and peripheral vasodilatation. The cardiovascular responses are suited to the respiratory ones.

If, on the other hand, hypoxia develops when breathing cannot increase — as, for example, in an individual diving under water — inspiratory inhibition of the primary chemoreceptor reflexes of

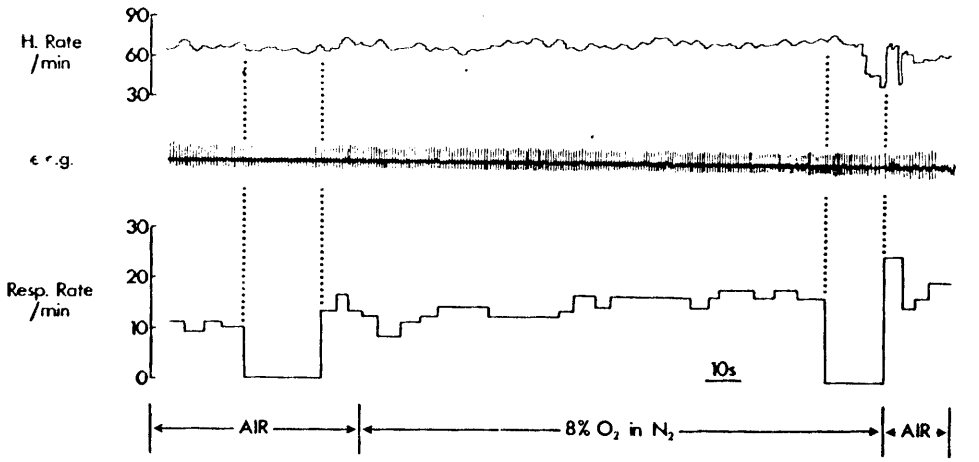

Fig. 2. Records from a normal human subject showing heart rate (beat-by-beat), e.c.g., and respiratory rate. The records commence with the subject breathing room air and the respiratory rate falls to zero through a period of voluntary breath-holding: during this period heart rate is little changed. The subject then breathes an hypoxic gas mixture and both the respiratory rate and the heart rate increase. On the second occasion the respiratory rate falls to zero the subject again voluntarily holds his breath: this time the subject is hypoxic and the heart rate slows considerably. See text for discussion.
[E.K. Potter & D.J. McCloskey, previously unpublished data; see also Gross, Whipp, Davidson, Koval & Wasserman, 1976].

bradycardia and vasoconstriction will not occur. Thus the heart will slow, thereby reducing its work and its oxygen consumption, and peripheral blood flow will decrease. Again the cardiovascular responses are suited to the respiratory ones, and again the total response is appropriate to oxygen conservation.

These mechanisms can be seen at work with respect to heart rate in Fig. 2. There, the heart rate is seen to be fairly constant throughout a period of voluntary breath-holding in a normal subject. When the same subject starts to breathe an hypoxic gas mixture, breathing is stimulated and the heart rate gradually rises. Presumably, also, there is widespread peripheral vasodilatation. These responses can be understood in the light of the mechanisms described above. When the subject, who is now hypoxic, again voluntarily holds his breath there is a pronounced bradycardia. Presuming that responses similar to those seen in anaesthetized animals occur (e.g. see Daly, 1972), there is also peripheral vasoconstriction. It is of interest to contrast, in Fig. 2, the state immediately before the second (hypoxic) breath-hold with that during it. Before the cessation of breathing the appropriate cardiovascular response to oxygen lack is a tachycardia and vasodilatation to match the increased ventilation. Once breathing has stopped, however, no more oxygen is delivered by the respiratory system and the appropriate cardiovascular response is bradycardia and vasoconstriction. In both states oxygen supply and conservation are well served, and in both states cardiovascular and respiratory responses are in step.

The co-operation of cardiovascular and respiratory systems in this way is achieved principally by the neural consequences of inspiratory activity. Inspiration is the active phase of breathing and it is an oxygen-delivering process; by its central and reflex accompaniments it is related to the appropriate cardiovascular responses of tachycardia and vasodilatation. Expiration, the usually passive phase of breathing, is not associated with oxygen delivery; it permits the oxygen-conserving cardiovascular responses of bradycardia and vasoconstriction.

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SCIENCE

Proprioceptive Illusions Induced by Muscle Vibration: Contribution by Muscle Spindles to Perception?

Guy M. Goodwin, D. Ian McCloskey and Peter B.C. Matthews

Proprioceptive Illusions Induced by Muscle Vibration: Contribution by Muscle Spindles to Perception?

Abstract. *When vibration of 100 hertz was applied to the tendon of the biceps or the triceps muscle, the subject made a systematic misjudgment of the angle at the elbow. During contraction the error could be as much as 40 degrees. The subject thought that the elbow was in the position that it would have assumed if the vibrated muscle had been stretched.*

The mechanisms underlying kinesthesia or "position sense" have long been debated. Sherrington (*1*) attributed position sense solely to the central perception of the discharges from the appropriate proprioceptive end organs. Others (*2*), following Helmholtz, have argued that the sensory centers are informed by recurrent pathways of the dispatch of commands from the higher motor centers, and that this of itself can lead to changes in the perception of position. Both mechanisms are now usually accepted as being capable of paying a part. Sherrington (*1*) produced the first evidence that muscle spindles are sensory end organs and suggested that they should be included among the mechanoreceptors that contribute to kinesthesia. Since the arrival of the electronic era it has been shown that the muscle spindle afferents do indeed signal the mechanical state of the muscle, but there has been a parallel accumulation of evidence against the spindle discharges having any access to conscious sensation. Instead, the spindle has been seen as reserved for the subconscious control of movement, notably by the cerebellum. The various receptors in joints have accordingly been allocated the sole responsibility for providing the peripheral contribution to kinesthesia.

The evidence for this view has been firmly based on human studies. First, the regional anesthetization of a finger joint produces a gross loss of awareness of the position of the finger when it is moved passively, even though the muscle spindles in the relevant muscles may be presumed to be behaving normally (*2*, *3*). Second, the passive stretching of a muscle in the conscious subject by pulling upon the exposed tendon fails to produce any clear proprioceptive sensation (*4*). Thus the muscle spindle has appeared to be excluded from contributing to sensation. Until recently, this view was supported by the inability of electrophysiologists to discover a cortical representation of spindle afferents by the recording of an evoked potential in response to stimulation of a muscle nerve at an appropriate strength. However, with refinements in technique such projections have now been amply demonstrated in both cat and monkey (*5*). The following proprioceptive illusion, which may be produced in the normal human subject, suggests that under suitable circumstances spindle afferent discharges can contribute to perception.

The illusion has been produced as follows. The blindfolded subject sat with his upper arms lying parallel and horizontal on a support. His forearms were free to move in the vertical plane. A light wooden splint was tied to each forearm and connected via a string to a potentiometer to allow recording of the angle at the elbow. The recording arrangement was nonlinear, but gave a reproducible reading that was accurate to within 2°; this was adequate for the present experiments. One arm was designated as the experimental arm. The spindles in either its biceps or its triceps muscle were then excited by manually applying a physiotherapy vibrator to the appropriate tendon (Pifco vibrator; frequency of vibration, 100 hz; amplitude of movement, of the order of 0.5 mm when loaded). The other arm was designated as the tracking arm, and the subject was asked to keep it aligned with the vibrated arm. The tracking arm thus was an objective indication of the subject's estimate of the position of the vibrated arm. The subject was told to maintain the position of the vibrated arm against gravity, but was asked not to oppose any movement which tended to take place when the arm was vibrated or moved by the experimenter. Essentially similar results were found when the arm commenced moving reflexly from a position of complete rest against a stop.

Figure 1 shows the typical effect of vibrating the biceps muscle. Shortly after the vibration began, the vibrated arm started to move into flexion under the influence of the tonic vibration reflex. This phenomena is now well known and is attributed to the excitation of the spindle primary endings by the vibration; this excitation is believed to lead to a stretch reflex type of response, although there may well also be contributions from higher centers (*6*). The initial part of the reflex movement was not perceived by the subject, but when movement of some 10° had occurred the subject became aware of the motion and began to move his tracking arm also. But the tracking arm moved more slowly than the vibrated arm so that the misalignment between them increased progressively.

After the vibrated arm had moved through about 40°, its movement was gently arrested without the subject's knowledge. As a result of the reflex movement itself, a long string was gently pulled tight; one end of the string was attached to the splint and the other was fixed. The subject then had a strong sensation that his arm was being moved in the opposite direction to that in which it had just been

moving (that is, that the movement was changing from flexion to extension). This did not surprise him, as he had no knowledge of what was actually happening; and in some trials the experimenter did indeed forcibly extend the vibrated arm. The movement of the tracking arm (Fig. 1) provides an objective measure of the extent of the subjective sensation of the reversal of movement. At the end of the period of vibration, there was an error of more than 40° in the alignment of the subject's forearms, although the subject believed that he was successfully managing to keep them parallel. At the end of the period of vibration he immediately became aware of his error and made the appropriate correction.

Figure 2 illustrates the analogous experiment on the triceps muscle. In this case the tonic vibration reflex induces an extension rather than a flexion, and the illusion is the mirror image of that when the biceps muscle is vibrated. But in principle what happened was the same. First, the subject moved his tracking arm with a lag. Second, when the vibration-induced movement was checked the tracking arm reversed its direction of motion; indeed, it soon overshot its initial position.

Such reactions have been observed in more than 20 subjects, many of whom were initially new to this kind of experiment. The illusions are so clear-cut that they could still regularly be reproduced in experienced subjects, even though subjects knew that they were suffering form a delusion. The effects might, however, vary in size in successive repetitions of the experiment and were not always as great as those illustrated. Nonetheless, the reversal of the tracking movement when the reflex movement was resisted was a consistent feature. In one subject, vibration regularly failed to elicit a reflex contraction. This subject felt that his arm moved in the opposite direction to that in which the reflex would have taken it, just as if the reflex had been arrested from the very beginning. Several other subjects had a similar sensation when the vibration was turned on and before any appreciable reflex movement had occurred. These findings help dispel the objection that the main results were essentially dependent upon the subject's voluntarily changing his motor commands the moment he perceived that his vibrated arm was beginning to move.

Passive movements imposed on the subjects by the experimenter could of course be tracked with a much higher degree of accuracy. This is illustrated in Fig. 3. The subjects did not experience any significant local cues, from pressure or other sensations, that the movement had been resisted; local cues were minimized by the movement being stopped gradually rather than abruptly. Cues were further eliminated in a few control experiments by applying the resisting force to the hand

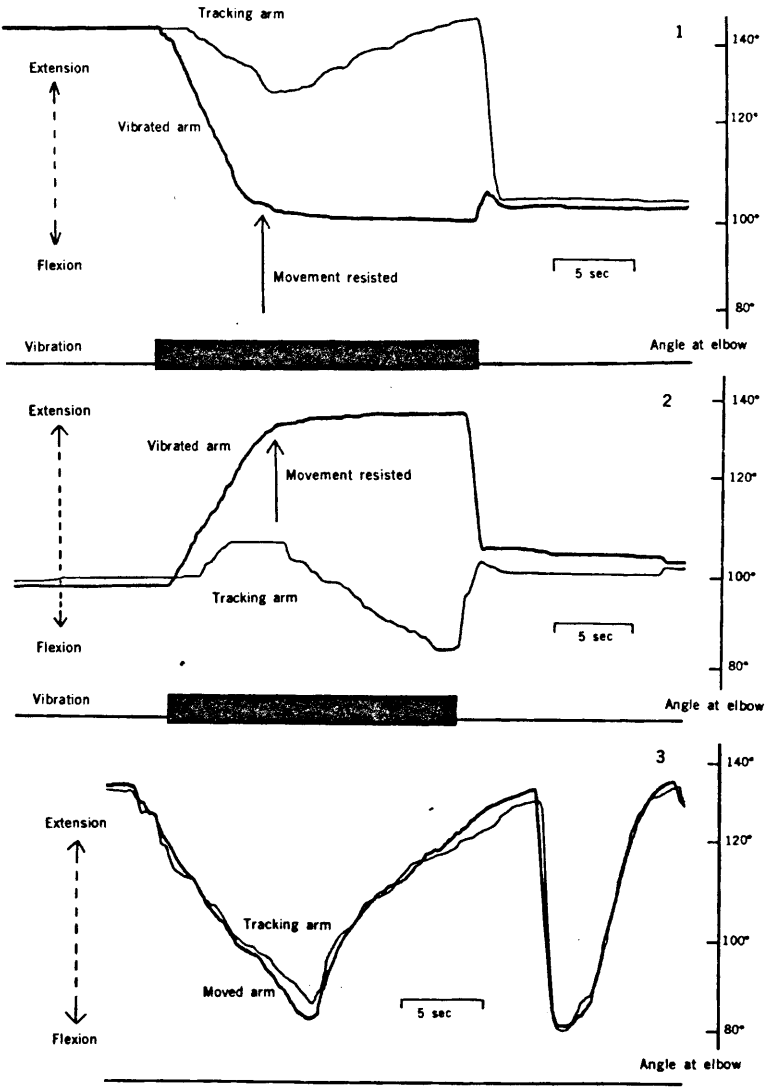

Fig. 1. The effect of vibrating the tendon of the right biceps muscle so as to produce a tonic vibration reflex, which moved the arm into flexion. The blindfolded subject used the left arm to track what he believed to be the position of the vibrated right arm. From the arrow onward, any appreciable further flexion of the vibrated arm was prevented because the movement gradually pulled taut a long string that was attached to a splint on the arm and fixed at its far end. Fig. 2. The effect of vibrating the tendon of the right triceps muscle so as to produce a tonic vibration reflex, which moved the arm into extension. The blindfolded subject used the left arm to track what he believed to be the position of the vibrated right arm. From the arrow onward, any appreciable further extension of the vibrated arm was prevented as in the experiment in Fig. 1. Fig. 3. The accuracy of tracking of passively imposed movements. The right arm was moved by the experimenter, and the subject was asked to track it with his left arm. Same subject (still blindfolded) was used as in Figs. 1 and 2. The experimenter held a splint on the subject's arm and not the arm itself.

after it had been made insentient; this was done by inflating a pressure cuff around the wrist and occluding the circulation for the appropriate time. We have also observed, but not measured, similar illusions concerning motion at the knee and ankle joints, although these illusions have not been nearly as well developed as those for the elbow. Others have found that at these sites, vibration may induce misjudgments of a few degrees in estimates of the steady position of the joint (*7*).

The illusions of position can be attributed to the excitation of intramuscular receptors rather than of extramuscular receptors, since the effects were not obtained when the vibrator was applied directly over the elbow joint or to regions of skin overlying bone. Nor did such nonspecific application of vibration distort position sense, since the subjects did not then make systematic tracking errors when the vibrated arm was moved by the experimenter. Thus the widespread excitation of Pacinian corpuscles, which must undoubtedly have occurred, seems to have produced merely a sensation of vibration itself and cannot be held responsible for the illusory sensations of limb position. Of the intramuscular receptors, the muscle spindle primary endings may reasonably be held responsible, for these are far more powerfully excited by vibration than are any of the other muscle receptors (*8*). However, both the Golgi tendon organs and the spindle secondary endings do show some sensitivity to vibration, and so it is impossible to say whether or not they contributed to the development of the present illusions; all three types of proprioceptors have been believed to be denied access to consciousness.

The findings are compatible with the idea that during muscle contraction, the spindle primary discharges that are set up by the vibration are interpreted by the higher neural centers as if they were due to excitation of the spindles by stretching the muscle; the increased discharges would then indicate that the vibrated muscle was longer than it actually was and would so produce a corresponding error in the central judgment of the angle at the elbow. In addition, the illusion induced by vibration may be as much one of velocity of movement as of position per se. This may perhaps be why the reversed motion of the tracking arm continued for so long after the reflex movement was arrested (Figs. 1 and 2); the volume of driven spindle discharge may be presumed to have risen to a plateau soon after the reflex movement was impeded. Be that as it may, the present illusion appears sufficient to throw serious doubt on the current view that muscle afferent firing is without influence on perception. The perceived position of a limb may thus be attributed to the compounding of three kinds of signals: afferent from joint receptors, efferent from motor centers, and afferent from muscle spindles.

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The persistence of appreciable kinesthesia after paralysing joint afferents but preserving muscle afferents

Until about 10 years ago it was widely but uncritically believed that the discharges from muscle afferents contribute to kinesthesia or 'position sense'. Sherrington[12] asserted in 1900 that they did so, and though his opinion appears to have been without experimental support it nonetheless gained widespread acceptance. However, in 1960 by refining and extending the observations originally made a century earlier by Helmholtz, Brindley and Merton[1] established that the discharges from muscle spindles in the extrinsic eye muscles are without influence on the conscious perception of the direction in which the eyes are pointing. At about the same time, less rigorous experiments on moving joints after locally paralysing the joint afferents were taken to show that the stretching of limb muscles was also without sensory action[2,4,9–11]. However, we recently found that muscle vibration may induce an illusion of movement just as if the vibration-induced increase in muscle afferent firing had been perceived[5,6]. This led us to re-investigate the sensory effects of moving joints when the joint afferents have been paralysed, but while the afferents to some of the muscles acting at the joint have been spared; this can readily be done for various joints of the hand because the bellies of the long muscles which act on the fingers lie in the forearm. We have found that an appreciable awareness of movement can then persist, which argues that muscle receptors do contribute to kinesthesia and that the commonsense classical view has been too hastily discarded.

In 7 subjects the index finger was ring-blocked by injecting 2–3 ml of 2% lignocaine around its base. This produced a complete clinical anaesthesia of the finger to light touch, heavy touch, pin-prick and squeezing; thus, the afferent fibres to both of the interphalangeal joints may be presumed to have been paralysed. Nevertheless, an awareness of passive movement persisted at both joints. When the experimenter manipulated the anaesthetized joints the subject could correctly state, first whether or not the finger was being moved, second whether it was being moved into flexion or extension, and third whether it was being held at full extension or full flexion. The subject succeeded in all this when he was consciously relaxing the muscles acting on the finger, but he found it a great deal easier to say what was happening when he was allowed to voluntarily tense the muscles concerned. No systematic study was made of the threshold for the detection of movement or the accuracy with which static positions of the finger could be recognised, but for both there was a deterioration in performance from the normal. The anaesthetized finger was particularly bad at detecting slowly applied movements and this probably explains why in broadly similar experiments Provins[11] was sometimes able to move the metacarpophalangeal joint throughout its physiological range without the subject being aware of the displacement; Provins used an angular velocity of 0.6°/sec. At the proximal interphalangeal joint, we have found that subjects readily detect movements of 10–20° when these are applied at 5–10°/sec, but they have the greatest difficulty in detecting the movement or fail altogether when the velocity is reduced to below 1°/sec; this occurred irrespective of whether or not the subjects were tensing their muscles. The stretches

were applied with a servo-controlled solenoid[8].

In 9 subjects the whole hand was made anaesthetic by anoxia and its intrinsic muscles paralysed. Sometimes this was done by occluding the circulation at the wrist by inflating a child's sphygmomanometer cuff just above the wrist and waiting the appropriate time. Alternatively, a more rapid paralysis was achieved by first inflating a cuff round the upper arm and then, when the whole arm was anaesthetic, the usual cuff was inflated at the wrist and the upper cuff removed. The upper cuff appeared to be the more efficient at producing circulatory occlusion, probably because at this site the blood vessels are not partly protected from the pressure by surrounding bone. Once the upper cuff was removed the forearm rapidly recovered.

The completeness of the anoxic anaesthesia was established by the same criteria as before. In addition, the joint afferents supplying the metacarpophalangeal joints could be directly demonstrated to be paralysed by the inability of the subject to detect lateral movements at these joints. Lateral movements may be expected also to excite the proprioceptors in the intrinsic muscles of the hand; however, these too will have been paralysed by the anoxia. In contrast, the subjects could still detect flexion–extension movements both at the metacarpophalangeal joints and at the interphalangeal joints, though less well than normally. The subjects could readily tell which finger was being moved. Interestingly, however, they could not distinguish between movements at different joints of the same finger; this is to be expected since the forearm muscles on whose proprioceptors the subjects may then be presumed to have been relying act similarly on all the joints of a single finger. Again, movements were more readily detected when the relevant forearm muscles were lightly tensed. This parallels the observation that in spastic patients with hands rendered insentient by anoxia the appreciation of imposed movements of the fingers is 'strikingly preserved'[3].

For both types of anaesthesia every subject asserted that he knew what was happening to a finger in the usual sort of way by 'feeling it move', and that he was not relying upon subsidiary clues such as any transmission of movement to unanaesthetised regions of skin. This has been the experience of all the present authors as well as of completely naive subjects. It has been suggested that in the present circumstances the movement of the fingers is detected solely because the bellies of the long flexor muscles 'nudge the top edge of the cuff, where the skin is not anaesthetic, and give a clue to the movement'[9]. This was excluded for the present experiments by obtaining the same results when, after complete anaesthesia of the hand had been achieved, the cuff round the wrist was replaced by a cuff round the upper arm; the muscles of the forearm then remained functional for 10 min or more while the hand remained anaesthetic.

Particular stress has previously been laid on an apparent complete absence of position sense at the interphalangeal joint of the thumb after rendering the hand anoxic[9,10]. We found that some of our subjects were then unable to detect movements of this joint of as much as 90° when the muscles acting upon it were relaxed. But all our subjects were able to detect movements of below 90° when either the flexor or the extensor muscles were lightly tensed. Moreover, both for thumb and fingers the

subject could detect when a voluntary movement in either direction was manually obstructed by the experimenter. Left unimpeded the obstructed movement would have been about 90°; possibly the previous report of inability to detect obstruction to movement in similar circumstances depended upon the movements then tested being rather smaller[9,10]. The big toe has also been reported to lack position sense when anaesthetized[2]. However, the matter was tested only for relatively slow movements (2°/sec) and with the relevant muscles relaxed; it was actually then believed on indirect evidence that muscle contraction would have restored some kinesthesia.

We take the above findings as evidence that signals from muscle receptors can influence consciousness and do contribute to the subjective awareness of limb position; in other words we are re-iterating the classical view that muscle receptors contribute to kinesthesia together with joint receptors. The present experiments do nothing to show which of the various mechanoreceptors in muscle are responsible. The earlier experiments with vibration suggest that the spindle primary endings make a significant contribution in this respect, but we have no evidence to show whether or not their action is an exclusive one; *a priori*, there seems to be no good reason why they should be especially singled out. The favourable effect of tensing the relevant muscles may possibly be attributable to the co-activation of fusimotor neurones along with the α motoneurones and so increasing the sensitivity of the spindle afferent endings; the sensitivity of the tendon organs, however, might be increased by the direct effect of the extrafusal contraction. The failure of some subjects to detect movement of the thumb when it was lying relaxed may perhaps be related to the observation that anoxia of the hand has been found to interfere with the stretch reflex of the long flexor muscle of the thumb, even though the muscle itself has not been interfered with[7]. Apparently, widespread peripheral anaesthesia can interfere with proprioceptive action, possibly by removing a normal source of central facilitation whether of fusimotor neurones or of synapses acted upon by the proprioceptive afferents themselves.

In summary, it is concluded that muscle afferents can contribute to kinesthesia because kinesthetic sensations can still be evoked by moving joints with their attached muscles after the joint and cutaneous afferents have been inactivated.

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THE CONTRIBUTION OF MUSCLE AFFERENTS TO KINÆSTHESIA SHOWN BY VIBRATION INDUCED ILLUSIONS OF MOVEMENT AND BY THE EFFECTS OF PARALYSING JOINT AFFERENTS

BY

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UNDER most conditions we are consciously aware of the position of the various parts of our limbs relative to each other and whether they are moving or still. This awareness has been given, among others, the names of "kinæsthesia" and "position sense." These two terms are usually treated as synonymous and both taken to cover all aspects of the awareness, whether static or dynamic. This practice will be continued here except that the term "kinæsthesia" will be preferred when there is an element of movement involved, and "position sense" when movement is largely absent. For the first half of the present century it was widely but uncritically thought that signals from receptors in both muscles and joints contributed to the full range of kinæsthetic sensations, and no distinction was made between them. Sherrington (1900, 1918) gave this view the whole weight of his authority, although he had no very definite evidence on which to base an opinion. Paradoxically, he then proceeded by his detailed analysis of the reflex actions of the muscle afferents to help to open the way for the alternative view, namely that signals from muscle receptors are reserved for the subconscious control of movement and quite fail to penetrate consciousness. This latter view came into prominence in the 1950s with the inability at that time of various workers to detect an evoked potential on the cortical surface on stimulating group I muscle afferents, though they could readily do so on stimulating cutaneous afferents (Mountcastle, Covian and Harrison, 1952; McIntyre, 1953, 1962). With refinements in technique, however, such projections were later amply demonstrated in both cat and monkey (for example: Oscarsson and Rosén, 1963; Phillips, Powell and Wiesendanger, 1971; *see* review in Matthews, 1972), so this particular argument soon ceased to apply. But by that time, other reasons had been adduced for the view that the main muscle afferents do not contribute to consciousness. To begin with, the development of the hypothesis of the servo control of movement through the fusimotor pathway led to the feeling that the cortex had no need to "know"

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precisely what was happening at the lower levels of the motor control system; moreover, it was suggested that a conscious awareness of the spindle afferent discharge would merely confuse the issue, since the spindle discharge was seen as the misalignment signal between the desired and the actual length of a muscle rather than as a signal which was meaningful in itself. This view was forcefully put by Merton when he stated (1964)

"until the underlying incompatibility of these two notions is felt one cannot properly appreciate the character of the problems that face us in this field";

the two notions were that muscle spindles could be held responsible first for the stretch reflex and second for position sense. More conservative neurophysiological opinion, without necessarily accepting the servo hypothesis, agreed that the signals from muscle afferents were too complex to be used in position sense (Mountcastle and Powell, 1959; Mountcastle and Darian-Smith, 1968).

The whole issue became complicated by the tendency to equate the problem of the role of the spindles in somatic muscles with the role of the spindles in the extrinsic eye muscles; these latter can in some respects be studied more readily because there are no joint receptors to bother about, and their study has led to important conceptual advances. A century ago, Helmholtz (*see* 1925) adduced cogent evidence that the subjective awareness of the direction of the gaze depends not upon proprioceptive discharges from the extraocular muscles, but is

"simply the result of the effort of will involved in trying to alter the adjustment of the eyes."

His most forceful argument was that

"in those cases where certain muscles have suddenly been paralysed, when the patient tries to turn his eye in a direction in which it is powerless to move any longer, apparent motions are seen."

This, he felt, showed that

"our judgement as to the direction of the visual axis is formed as if the will had produced its normal effects . . . and since no change has taken place in the positions of the images on the retina of the paralysed eye, we get the impression as if the objects shared the supposed movements of the eye."

Sherrington (1900, 1918) thought that Helmholtz's arguments were invalid, but later workers have generally failed to feel the force of Sherrington's objections and have preferred to side with Helmholtz. This was particularly so because workers on lower animals subsequently found that surgically rotating the eye (swell fish) or the head (insects) would cause the animal to perform repeated circling movements; these were thought to have as their proper purpose the maintenance of the stability of the world as seen by the animal, but with inversion of the visual image the movements had precisely the opposite effect and so the movements were kept going indefinitely. Sperry (1950) introduced the term "corollary discharge" for the neural activity which he suggested might underlie his own behavioural findings on fish; he did so in the following words:

"Thus any excitation pattern that normally results in a movement that will cause a displacement of the visual image on the retina may have a corollary discharge into the visual centres to compensate for the displacement."

It may be noted that in these experiments on lower animals corollary discharges would have originated from somatic motor centres as well as from oculomotor centres since the movements were of the whole body and not just of the eyes. In the new terminology, Helmholtz's observations in man which had originally been attributed to a "sensation of innervation" were now ascribed to a "corollary discharge" from oculomotor centres to sensory centres.

Von Holst (1954) used yet another terminology for the same phenomena and talked of a subtractive interaction between an "efference copy" and a returning afferent signal and suggested that "the difference can either influence the movement itself, or, for instance, ascend to a higher centre and produce a perception." In 1960, Brindley and Merton repeated and refined Helmholtz's observations and so established to general satisfaction that the eye lacks position sense. Particularly cogent observations were made on observing the effects of preventing the eye from moving by holding it with forceps. When vision was occluded, movement was believed to have taken place as intended. When vision was preserved, the visual world appeared to move in the direction of the intended movement. Related effects were found when a movement was imposed on the eye by the experimenter. With vision occluded, the subject was unaware that movement had occurred as already noted by Irvine and Ludvigh (1936), whereas with vision preserved the world rather than the eye was felt to move. All this was taken to show that the position of the eye was judged on the basis of corollary discharges rather than on the basis of peripheral afferent discharges. Thus for the last decade it seems to have been universally accepted that the eye is without position sense and that the very numerous muscle spindles in human extraocular muscles cannot influence consciousness. This naturally led to the feeling that the discharges from spindles in somatic muscles may also fail to penetrate to the conscious level. Ironically, however, the recent unanimity over the eye has turned out to rest upon an insecure foundation and very recent work by Skavenski (1971), published after the present experiments were completed, has entirely reopened the question of the role of the extraocular spindles. By improving the sensory testing procedures Skavenski succeeded in demonstrating an awareness of eye position which appeared to depend upon inflow signals from the muscle afferents rather than from visual information or corollary discharges. His two trained subjects could reliably detect whether, and in which direction, their eyeballs were displaced by the experimenter when vision was occluded and the conjunctivæ were anæsthetized; the displacements were about 10 degrees in extent and were applied via a stalk mounted on a close-fitting contact lens. Moreover, when asked to do so, Skavenski's subjects were largely successful in maintaining the direction of their gaze in spite of the eye being acted upon by a force which would otherwise have produced a displacement of some 5 degrees; again visual and other non-proprioceptive sources of information were excluded as providing the basis for the correction. Skavenski suggested that in the previous basically similar experiments weak proprioceptive sensations might have passed unnoticed because the subjects were untrained and were under "some degree of discomfort or duress." Skavenski's findings, however, in no way interfere with the conventional view that corollary discharges must be postulated in order to explain the stability of the visual world in the face of self-induced movement; but his results do raise the question as to how far corollary discharges contribute to the position sense of the eye, meaning by this the ability of the subject to recognize the direction of the gaze independently of visual clues. In the past these two functionally different roles for corollary discharges do not appear to have been distinguished as would now appear essential.

In the 1950s and 1960s experimental evidence progressively supported the view that somatic spindles resembled extraocular spindles in being without sensory action. At the same time, however, it became apparent that in another respect extraocular spindles differed from somatic spindles in that they were unable to elicit a stretch reflex, be it monosynaptic or polysynaptic in its mediation (Whitteridge, 1960; Keller and Robinson, 1971). The first direct evidence against a sensory action

for somatic muscle afferents was provided by Browne, Lee and Ring (1954) who anæsthetized the metatarsophalangeal joint of the big toe in man by infiltrating it with procaine and found that the subject then became largely unaware of whether or not his toe was being moved when the muscles were relaxed. The procaine would, of course, have paralysed the joint and cutaneous afferents without influencing those from the appropriate muscles, since these lie far away. Thus these results were taken by some to show that muscle receptors made no contribution to position sense, though the authors themselves actually thought on indirect evidence that the muscle receptors provided an important contribution when the muscles acting at the joint were tensed; they did not report, however, any experiments on the anæsthetized toe to support this view.

Provins (1958) later performed similar experiments on the metacarpophalangeal joint of the index finger and found that an equally gross impairment of position sense was produced irrespective of whether or not the muscles acting at the joint were tensed, though the interference with kinæsthesia does not appear to have been as great as that previously described for the toe. It passed generally unnoticed, however, that Provins tested position sense only with a single slow velocity of angular movement (0·6 degree/sec), so that his findings could not properly be generalized to rapid movements. A few years later, Butt, Davies and Merton (Merton, 1964, 1970) made the whole hand anæsthetic by inflating a pressure cuff around the wrist and waiting the appropriate time to render it anoxic. It was stated that the top joint of the thumb then became "quite insensitive to passive movements of whatever range or rapidity," and though the experiments were never written up in full this claim was naturally given much weight by subsequent reviewers (cf. Phillips, 1969).

In previous similar experiments, however, Chambers and Gilliatt (1954) found that in spastic patients the appreciation of passive movements of the fingers was "strikingly preserved" after making the hand insentient and concluded that this showed the "state of contraction of resting muscles is of considerable importance in the perception of movement and posture." In normal subjects, Chambers and Gilliatt found that although making the hand anoxic produced a severe impairment of postural sensation in the fingers yet the loss was not complete; Merton agreed with the finding, but he felt free to disregard it for he believed that it depended merely upon clues to the occurrence of movement derived from the bellies of the long finger flexors nudging against the top end of the pressure cuff where the skin was not anæsthetic. In 1967, Gelfan and Carter fortified what had by then become the orthodox view by pulling upon various tendons exposed via a skin incision in the awake human subject. This failed to produce any "awareness of muscle stretching," though it did produce various sensations, including pain, localized to the site of the skin incision and tendon grasping. It may be questioned, however, whether the condition of their experiments were really suitable for the detection of relatively unobtrusive sensory signals. Their subjects appear to have been experimented upon as a prelude to surgery performed for therapeutic reasons, and in a certain number of subjects over and above the 9 reported upon the tests had to be discontinued "because of undue apprehension, complaints of pain, or with whom communication was unreliable because of language problems." Moreover, they would appear to have concentrated upon asking their subjects whether they experienced "any sensation referable to the muscles" rather than to the relevant joints.

All this human work was supported by animal experimentation performed over about the same period of time and which showed that repetitive electrical stimulation of group I muscle afferents with an implanted electrode appeared to be without action on the functioning of the higher cortical levels in the awake animals. First, group I volleys failed to desynchronize the EEG in the way that cutaneous afferent volleys so readily do (Giaquinto, Pompeiano and Swett, 1963). Secondly, it has so far proved impossible to condition a cat to respond by pressing a bar to group I stimulation (Swett and Bourassa, 1967). Thus it became the physiological orthodoxy of the 1960s that muscle receptors have no part to play in kinæsthesia (*see* for example: Rose and Mountcastle, 1959; Matthews, 1964; Mountcastle and Darian-Smith, 1967; Merton, 1970; Phillips, 1969). Some felt that joint receptors should be held entirely responsible for position sense, while others argued

that corollary discharges (sense of effort) also played an important part, as they do for the eye (Merton, 1964, 1970). However, as indicated above, the rejection of a role for muscle afferents was less soundly based than at first sight appeared, and not all workers accepted the conventional line. For example, Paillard and Brouchon (1968) did not do so when they showed that the position of the arm was more accurately perceived when it was actively moved into a new position by the subject himself than when it was passively moved into the same position by the experimenter; they suggested that this might be partly due to a conscious awareness of the differences between the spindle discharges in the two conditions.

The present paper describes experiments which argue that the common-sense classical view has been too hastily discarded and that receptors in somatic muscles do contribute to kinæsthesia. The results fall into three parts. First, there is a description of the distortion of position sense which may be induced by muscle vibration and which we have found it convenient to study at the elbow on vibrating either the biceps or the triceps muscle. The distortion is most simply attributed to the vibration-induced discharges of muscle receptors being interpreted by the higher centres as if they were due to muscle stretch, the sensation being referred to the joint as if it were moving in the appropriate direction. The muscle spindle primary endings seem likely to be chiefly responsible for these are far more powerfully excited by vibration than are the other two main receptors of muscle (spindle secondaries, tendon organs; Brown, Engberg and Matthews, 1967). This conclusion prompted us to reinvestigate the sensory effects of moving joints when the joint afferents have been paralysed, but while the afferents to some or all of the muscles acting at the joint have been spared. The findings are described in the second part of the paper and show that a measure of position sense may persist after the afferents to the joints of the finger or of the thumb have been inactivated. At the same time, as described in the third part of the paper, we were able to make certain observations on the role of any corollary discharges from motor centres to sensory centres when a limb is moved. These appear to have a different function from those of eye muscles, but one which cannot be neglected once kinæsthesia is held to be partly attributable to the discharges of muscle afferents. Three preliminary notes have already been published (Goodwin, McCloskey and Matthews, 1972*a*, *b*, c).

METHODS

A remarkable feature of the present experiments has been the simplicity of the techniques which have been adequate to display the qualitative features of the responses we have studied. Almost everything that we have noted could profitably be studied in a more quantitative manner, but to have done so in the first instance would have risked obscuring general principles in a mass of detail.

All experiments were performed on normal human subjects. Each of the authors has been the subject for virtually every type of experiment presently described. In addition, some 30 other subjects of either sex have been recruited for one or other type of experiment; some were physiologists, some were technicians, and some were students. This large number of subjects was employed partly because every new experimental procedure was tried out on, among others, a subject who had no previous experience of the experiments. Thus all our experiments have been performed on a range of subjects who varied from the experienced and possibly biased to the completely naïve.

The vibration studies were performed on each of the two main muscles acting at the elbow, that is the biceps brachii and the triceps brachii. The vibration was applied to the skin immediately over their tendons at a point just above the elbow. Vibration of biceps probably also affected brachialis, but this is immaterial since the actions of the two muscles are so similar. Two different vibrators have been used with similar results. In most experiments a Pifco Physiotherapy Vibratory Massager (Model No. 1556) was used. This has a vibrating plastic head of 3·5 cm diameter driven by an electric motor. It vibrates at 100 Hz with a maximum peak-to-peak amplitude of movement of about 2 mm; when it was applied to the subject's arm the movement was reduced to about 0·5 mm. The Pifco vibrator was applied to the subject's arm simply by being firmly pressed by the experimenter on to the skin overlying the requisite tendon. In the later experiments we frequently used the vibrator that has been developed in the Department of Clinical Neurophysiology of Uppsala University (TVR vibrator V1A). This consists of a small d.c. motor with an eccentric load which can be strapped to the arm with broad rubber bands thus ensuring a constant pressure of application; a minor disadvantage was that the vibration tended to be transmitted along the rubber bands and so could affect the antagonistic muscle as well as the one intended. This vibrator was also used to produce a frequency of vibration of around 100 Hz with an amplitude of movement of about 0·5 mm.

Measurements of the angle at the elbow-joint were made by recording the potential produced by a potentiometer which was rotated by movement at the elbow. The subject was seated with his upper arms resting on a horizontal support and his forearms free to move in the vertical plane. The axis of the potentiometer was aligned with the axis of the elbow and a rod attached to its spindle. The rod was attached to the subject's wrist by flexible rubber bands and so was constrained to follow the movement of the forearm, but with enough "give" in the system to overcome minor changes in the axis of rotation of the elbow. Permanent records were taken with an Ultraviolet Recorder (S.E. Laboratories, type 3000) and were accurate to about 3 degrees, though the scale was slightly non-linear. Unfortunately, all the records required very heavy retouching for photographic reproduction. In addition, the experimenter, who could, of course, see what was happening, would periodically question the subject on the nature of his sensations and note the answers.

RESULTS

A. Illusions Induced by Vibration

Tracking of a vibrated arm.—A simple way of demonstrating the distortion of position sense which may be produced by vibration is to use one arm to indicate the illusory position of the other. In our original experiments, which lend themselves to ready repetition, this was done as follows. The blindfolded subject sits at a table with his upper arms resting horizontally upon it and with his forearms free to move in the vertical plane and in full supination. One arm is then designated as the "experimental arm" to which vibration will be applied. The other arm is designated as the "tracking arm" and the subject is asked to keep it aligned with the experimental arm so as to provide an objective indication of his subjective estimate of the position of the vibrated arm. Initially, the forearms are held with the elbows slightly short of full extension; this entails the subject contracting his flexor muscles to counteract gravity. He is instructed to avoid voluntarily moving the experimental arm and told that if he should find it moving of its own accord or being displaced by the experimenter then he should make no attempt to oppose the motion but should use the "tracking arm" to show the experimenter what he feels to be happening. Fig. 1 illustrates a qualitatively typical example of how he then behaves on applying vibration to the

tendon of the biceps muscle; not all subjects, however, showed such large responses. Shortly after the vibration began the vibrated arm started to move into flexion under the influence of the tonic vibration reflex. This phenomenon is now well known since its independent description in 1966 by Hagbarth and Eklund and by De Gail, Lance and Neilson and is attributed to the excitation of the spindle primary endings by the vibration leading to a stretch reflex type of response, though there is still some uncertainty about the detailed mechanism. The initial part of the reflex movement was not perceived by the subject so that he kept the tracking arm still even though the vibrated arm was moving. After an error of a few degrees had developed he became aware of the motion and began to move his tracking arm also, but to begin with the tracking arm moved more slowly than the vibrated arm so that the misalignment between them increased progressively; in some subjects, however, once the tracking arm began to move it lagged no further. If at any point during the movement the blindfold was removed the subject would invariably express surprise at the position in which he had put himself. Likewise when the vibration was stopped during the course of tracking the subject would immediately realign his arms with tolerable accuracy. Although he was instructed to do this by moving only the tracking arm, some subjects tended to move the vibrated arm also.

Fig. 1 also shows the remarkable effect of interfering with the progress of the tonic vibration reflex by arresting the movement without the subject's knowledge. This was brought about by the reflex movement itself gently pulling tight a long string after the vibrated arm had moved through about 60 degrees; one end of the string was attached to a splint

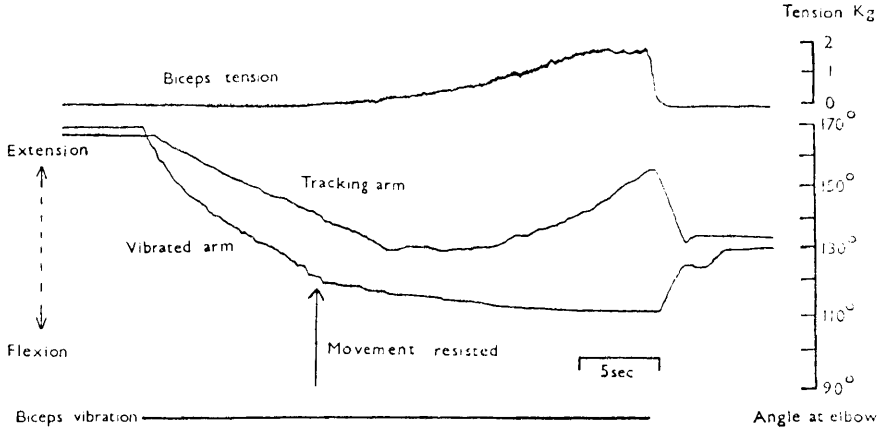


FIG. 1.—The effect of vibrating the tendon of the right biceps muscle so as to produce a tonic vibration reflex which moves the arm into flexion. The left arm is used to track the subjectively apparent position of the vibrated right arm. From the arrow onwards any appreciable further flexion of the vibrated arm was prevented by the movement gradually pulling taut a long string which was attached to a splint on the arm and fixed at its far end to an isometric myograph. The top trace shows the resultant recording of tension. The tension calibration in this and all subsequent records applies to the force developed at the wrist. When the arm was fully extended the angle at the elbow was 180 degrees. This and all subsequent records have been retouched. It may be noted that even in the absence of vibration the subject was not completely accurate in aligning his arms; this was typical.

or to a wrist-band on the subject's arm and the other end was fixed. The subject then developed a strong sensation that his arm was being moved in the opposite direction to that in which it had just been moving (i.e. that the movement was changing from flexion to extension); this did not surprise him as he had no knowledge of what was actually happening, and in some trials the experimenter did indeed forcibly extend the vibrated arm. Fig. 1 demonstrates the extent of the sensation of the reversal of movement and its continuation after the reflexly elicited contractile tension had reached a plateau. At the end of the period of vibration the subject had an error of over 40 degrees in the alignment of his forearms, though he still believed that he was successfully managing to keep them parallel. If the reflex contraction of biceps was made isometric from the start then the tracking arm was moved into extension from the very beginning.

Not all subjects, however, would allow such large errors to develop and would stop moving the tracking arm after a smaller displacement. When questioned, they would sometimes state that they could still feel it moving into extension but knew that it could not really be doing so, and so did not continue to track it. Others would keep the arm still and express themselves satisfied with the match. Yet others would move the tracking arm backwards and forwards and say that they could not decide what was happening; possibly they were confused because they were receiving incompatible evidence from different sources and were sometimes responding to one and sometimes to another. When in fig. 1 the vibration was stopped the subject immediately became aware of his error and made the appropriate correction. The magnitude of the misjudgement that a subject may make of the position of his arm during vibration

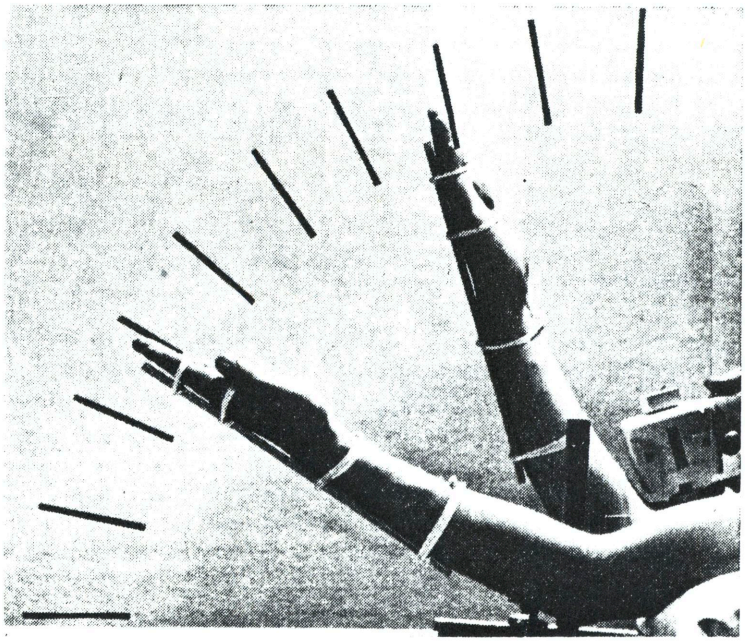


FIG. 2.—Posed photograph to illustrate the magnitude of the difference in position of the vibrated and the tracking arm that can occur while the subject believes he is managing to keep them aligned. The photograph shows the position of the arms as they were at the end of the period of vibration in fig. 1. The scale is marked in tens of degrees.

is emphasized in fig. 2 which shows the position reached at the end of fig. 1 after the reflex movement had been arrested.

In two subjects, vibration regularly failed to elicit a reflex contraction and each felt that his arm moved in the opposite direction to that in which the reflex would have taken it, just as if the reflex had been arrested from the very beginning. Several other subjects had a similar sensation when the vibration was turned on, and before any appreciable reflex movement had occurred, but, any such initial apparent movement preceding and in opposition to the real movement was usually too transitory to be tracked.

Fig. 3 illustrates the analogous experiment on the triceps muscle. In this case the tonic vibration reflex induces an extension rather than a flexion and so the illusion is the mirror image of that just described on vibrating biceps. But in principle the sequence of events was just the same.

First, the movement was tracked with a lag. Secondly, when the vibration-induced movement was checked the tracking arm reversed its direction of motion. On vibrating triceps the arm was in our standard tracking position with the biceps resisting gravity as in fig. 2 and the triceps initially relaxed. The same results were obtained on vibrating triceps while it itself was being made to resist a steady pull by loading the arm at the wrist with 500 g wt by suspending a weight over a pulley. The greater rapidity of the reflex movement in fig. 3 in comparison with that of fig. 1 is probably because the movement of fig. 3 was being assisted by gravity rather than opposed by it. One or two of our subjects spontaneously commented that at the very beginning of vibration of the triceps there was a feeling of the whole arm being elevated at the shoulder as well as the more usual feeling of flexion at the elbow. This presumably occurred because the long head of triceps arises from the scapula, so that afferent activity arising from this component of triceps might be expected to be

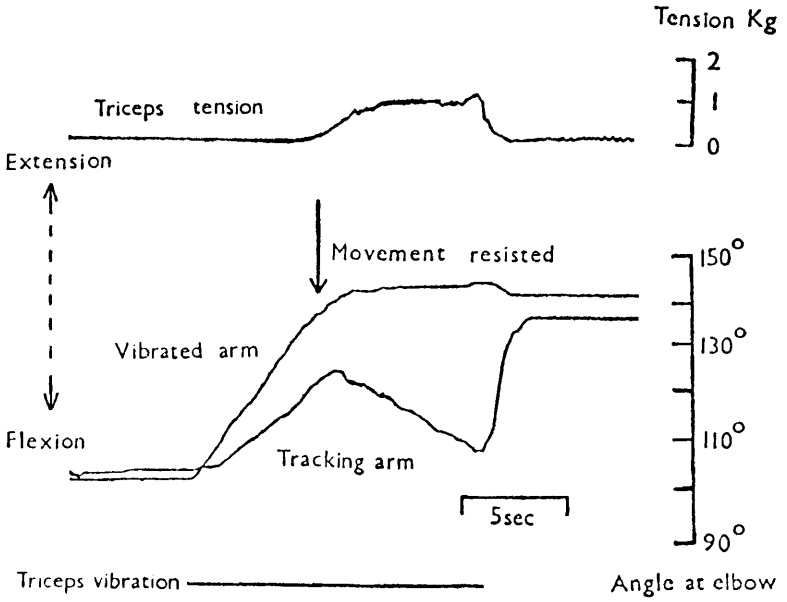


FIG. 3.—The effect of vibrating the tendon of the right triceps muscle so as to produce a tonic vibration reflex which moves the arm into extension. The left arm is used to track the subjectively apparent position of the vibrated right arm. From the arrow onwards any appreciable further extension of the vibrated arm was prevented by the movement gradually pulling a string taut which was fixed at its far end to a myograph.

referred to both joints. Biceps, of course, is a supinator as well as a flexor of the elbow but we did not come across any examples of subjects reporting any feeling of pronation on vibrating biceps.

A degree of uncertainty in the interpretation of the above experiments arises from the slightly contradictory nature of the instructions given to the subject. On the one hand, he was told to hold his arm still initially. On the other hand, he was told not to interfere with any reflex movement that he should find occurring spontaneously. Thus it is possible that the moment he perceives that the arm is moving the subject alters his voluntary motor discharges in some way and with it any corollary discharges from motor centres to sensory centres; it might, therefore, be suggested that the illusory sensations result from a change in voluntarily elicited corollary discharges rather than to the direct effect of the vibration-induced afferent input itself.

This objection was circumvented in control experiments in which the subject started with his arm resting passively against a stop, and so avoiding the need for any initial voluntary contraction. He was then told that the vibration might induce an involuntary reflex contraction and that if it did so he was to let the reflex proceed without voluntary interference. This gave the same results as before, in that the subject failed to perceive the initial part of the reflex movement and that he reversed the motion of the tracking arm when the reflex was obstructed. But now a new complication arose, namely that the subject inevitably became aware at the very beginning of the reflex movement that it must be taking place because he felt his arm ceasing to make contact with the supporting stop on which it initially lay; this was so even though the arm itself did not touch the stop but only did so through a splint which moved with the arm.

This difficulty was overcome in three further control experiments in which the subject's hand was made insentient by anoxia and in which the hand rather than the arm made contact with the stop. Thus he was deprived of any cutaneous clues as to when the arm started to move. The same results were still obtained. One such case is illustrated in fig. 4.

Evidence that vibration acts through exciting intramuscular receptors.—Passive movements imposed on the subjects by the experimenter could, of course, be tracked with a much higher degree of accuracy than were reflexly induced movements of similar velocity. This was equally true when the experimenter moved the subject's arm while the joint was being vibrated, thus excluding the possibility that the failure to detect the reflex contraction arose merely from a non-specific desensitization of the joint afferents, or of their central pathways, as a result of the vibration. This is illustrated in fig. 5. It is notable, however, that the subject's ability to follow a change in position was appreciably better than his ability to reproduce the absolute position of the passively moved arm; this was usual both in the presence and absence of joint vibration. The subjects did not experience any significant local cues from pressure, etc., to guide them in the passive tracking, for similarly good performance was obtained when the hand was made insentient by anoxia and the experimenter applied the force required to move the arm to the hand rather than to a splint running along the arm. Likewise, the illusion of reversal of motion on arresting the reflex movement persisted when the resisting force was applied to the hand after it had been made insentient, as already illustrated in fig. 4.

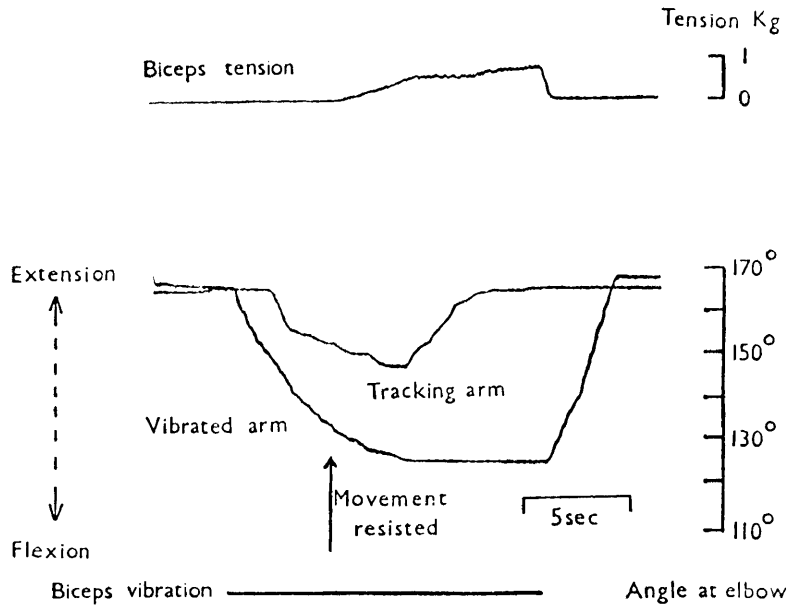


FIG. 4.—Typical tracking errors like those already illustrated but now occurring in the absence of any preceding voluntary contraction and in the absence of peripheral cues from the hand as to the forces applied to the limb. The right arm was initially supported by the hand lying upon a sandbag so that the subject did not have to exert a voluntary effort to maintain its position. The right biceps was then vibrated so as to produce the usual tonic vibration reflex. As before, after the limb had traversed a certain distance its movement was arrested by the pulling tight of a string which was applied to the hand. In this case, however, the hand had been made insentient by a prolonged period of anoxia so the subject had no cutaneous clues as to when his arm started and stopped moving. The termination of the tracking movement before the end of the vibration is probably due to the tracking arm then being nearly fully extended.

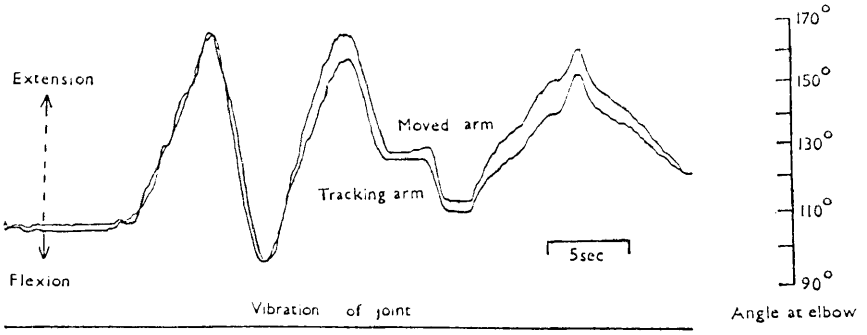


FIG. 5.—The tracking of movements which were passively imposed on the subject during vibration of the elbow-joint but not of the muscles. The right arm was moved by the experimenter and the subject was asked to track it with his left arm. The experimenter held a splint on the subject's arm and not the arm itself. Same subjects as figs. 1 and 2. The Pifco vibrator was pushed against the lateral side of the elbow throughout.

The illusions may be attributed to the excitation of intramuscular receptors rather than of extramuscular receptors, since there was no sign of them when the vibrator was applied directly over the elbow-joint or to regions of skin overlying bone. The possibility of the illusions being mediated by joint receptors was further eliminated by finding them for the thumb after its joint afferents had been inactivated by making the whole hand anoxic. Vibrating the tendon of flexor pollicis longus in the region of the thenar eminence then gave rise to a sensation of extension of the thumb, and vibrating the tendons of extensor pollicis longus and brevis at the base of the thumb gave a sensation of flexion, without in either case eliciting any obvious reflex contraction or producing a sensation of the hand itself being vibrated. Again, the apparent movement was in the direction of stretching of the particular muscles which were being vibrated, just as seen on vibrating biceps and triceps when movement was obstructed. It should be noted, however, that applying vibration to the same regions of the normally sentient hand usually failed to produce a clear-cut illusion of the thumb moving in any particular direction. This is probably because the vibration spreads through the hand to excite receptors in muscles with opposing functions.

In all cases studied the vibration-elicited afferent discharges induced, directly or indirectly, the illusion that the vibrated muscle was more stretched than it actually was. As will be discussed later the illusion seems to be primarily one of a continuing movement rather than one of the limb taking up more or less rapidly a new position. The muscle spindle primary endings may be suspected to be chiefly responsible, since they are far more powerfully excited by vibration than are any of the other muscle receptors (Brown, Engberg and Matthews, 1967). However, both the Golgi tendon organs and the spindle secondary endings do show some sensitivity to vibration and so it is impossible to say whether or not they were contributing to the development of the illusions.

Illusions in the absence of muscle contraction.—The experiments described so far are all compatible with the view that the vibration-induced muscle afferent discharges were perceived by the sensorium and treated as if they were due to stretch of the vibrated muscle. At the time we first performed the vibration experiments this suggestion appeared to be heresy, and so we attempted to reconcile our findings with the orthodox view by laying stress on the fact that the illusions had been observed during centrally induced muscle contraction (Goodwin, McCloskey and Matthews, 1972*a*) for there would not then necessarily be any conflict with the view that passive stretch of a non-contracting muscle did not elicit a sensation. However, we have now repeatedly observed illusions of movement when the vibrated muscle was not contracting.

The first situation which we studied systematically was that in which the triceps muscle was used to develop a constant extension force against a stop, and the flaccid biceps then vibrated.

The subject was given an oscilloscopic display of the tension that he was producing and asked to keep the tension constant in spite of the vibration of the muscle which was antagonistic to the contracting one; during the biceps vibration the subject had to try harder to maintain the triceps

contraction, presumably because he then had to overcome an inhibition of the triceps motoneurons by the Ia discharges from its antagonist. As before, the subject was asked to use his other arm to track any movement that occurred of the vibrated arm. The pull of the arm was resisted by a string connected to a myograph and so it did not appear implausible to the subject that his arm might indeed be allowed to move; he was, of course, unable to see his arms.

The strength of the triceps pull was usually below half of the maximum value that the subject could exert, but the precise value was immaterial and similar results were obtained with widely different tensions. Fig. 6 illustrates that an illusory sensation of movement still occurs under these conditions and that on vibrating biceps the arm was felt to extend as if the biceps were being stretched. The same result in principle was obtained in the converse experiment of vibrating the triceps muscle while the biceps was voluntarily contracting. The arm was then felt to flex as if the triceps was being stretched.

The vibrated muscle was found not to develop any significant tonic vibration reflex under these circumstances in which its antagonist was being voluntarily driven to produce an appreciable proportion of its maximum tension. Presumably the reflex was inhibited by a combination of descending motor activity and reflexes from the contracting muscle. The absence of contraction was judged by the simple procedure

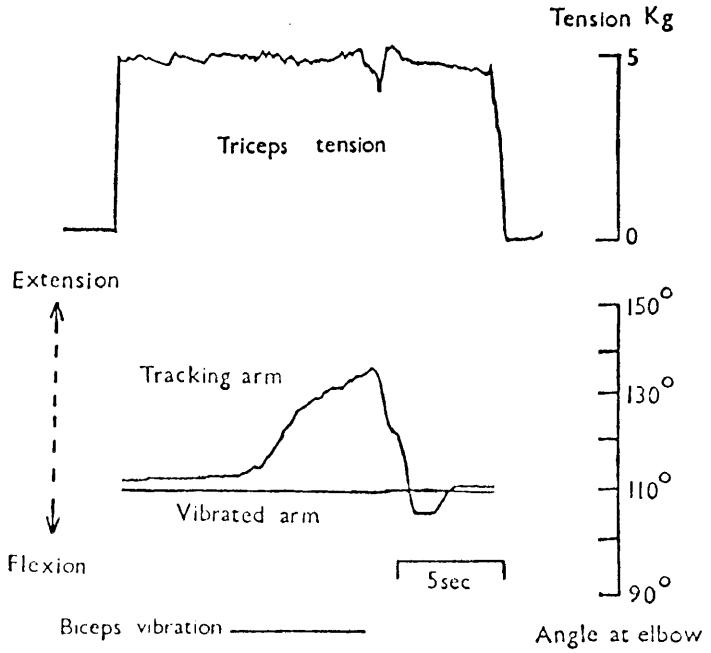


FIG. 6.—The tracking of the illusory sensation of movement which was induced by vibrating a muscle that was relaxed while its antagonist was forcibly contracting isometrically. The right arm was used to produce a constant force in the direction of extension by contraction of the triceps muscle. The biceps was then quite flaccid. The vibration was applied to the right biceps and the left arm used to track the resulting illusion of movement of the right arm. The subject was given a visual display of the tension he was producing and was asked to maintain the same tension throughout, in spite of the disturbing effect of the vibration.

of palpating the vibrated muscle which was found to remain quite flaccid. The efficacy of palpation as a method of detecting weak contractions was established by asking the subject to make voluntary contractions of a variety of strengths. This showed that a contraction developing only 2 per cent of the maximum tension that either muscle could produce could be readily detected by palpation, and also by seeing the muscle become bunched up.

The above experiment, however, does not entirely eliminate the possibility that the occurrence of a muscle contraction is a prerequisite for muscle afferents to be able to influence perception. The vibrated muscle itself was not contracting but its antagonist had been deliberately made to contract rather forcibly. It seems possible that a higher centre that is supposed to require a contraction in order to be able to come into action might view the elbow-joint as a whole, and be influenced by whether or not a contraction is occurring in any of the muscles acting at the joint and is unconcerned by whether it happens to be in flexors or extensors. This was made unlikely by the response of some subjects in the standard original experiment of tracking the reflex movement when the hand was initially lying on a stop. Some subjects then reported a movement in the direction of extension of the vibrated muscle, that is in the opposite direction to any subsequent reflex movement, before the hand began to move and while all the muscle may be presumed to have been relaxed. Moreover, as already mentioned, two subjects never developed a reflex contraction but still had illusions of movement.

The irrelevance of muscle contraction as a prerequisite for the illusory sensations was more systematically demonstrated by placing the subject's arms in the horizontal plane so that movements at the elbow were no longer influenced by gravity.

The upper arm lay horizontal on boards at chest level and the forearms were supported in slings, which were hung from the ceiling by cords. The elbows could then move freely and the arms had little or no tendency to come to rest in any particular position. Any such slight tendency could, if required, be resisted by the experimenter gently pulling upon the sling so as to hold the elbow in any desired position; alternatively, a slight balancing force could be provided by a light weight acting via a pulley. Thus the subject could allow his arms to lie quite relaxed. As before, the development of a contraction on vibration could be detected by palpation, but in addition even a very weak contraction would signal its occurrence by causing a movement of the forearm with its sling. A force of 0·1 kg wt was sufficient to displace the relaxed arm, whereas either the biceps or the triceps can develop a force of over 10 kg wt (expressed as a force at the wrist) so that we should have been able to detect contractions of only 1 per cent of the maximal value provided that they were maintained for long enough to produce a visible movement.

We also endeavoured to check on the absence of contraction by recording the electromyogram of the biceps or triceps with surface leads. Unfortunately, the vibration induced various artefacts, probably mostly due to movement of the electrodes, and so electromyography proved to be a much less sensitive method of detecting a small contraction than did the two simpler methods. Thus we did not employ it systematically to see whether or not the vibrated muscle was contracting for we had no confidence in our ability to detect small contractions. Under these conditions and using the Uppsala vibrator it proved readily possible by lowering the

driving voltage to produce a vibration which did not elicit any reflex contraction, but which still produced sensations of movement (lowering the voltage here decreases both the frequency and the amplitude of the vibration). The sensation was again one of the elbow moving in the direction that it would have if the vibrated muscle had been stretched, as had been previously seen in some subjects in the vertical tracking position before the development of the reflex; the absence of a reflex producing a genuine movement in the opposite direction allowed the illusory movement to be experienced far more vividly than it was when it was abruptly cut short by the real movement. In the horizontal position the illusion could continue for a minute or more (*see later*). The illusion was observed for both biceps and triceps, and was so clear cut that we did not deem it worth altering our recording arrangements so as to be able to make quantitative measurements on asking the subject to track the illusory movements with his other arm; however, we regularly asked the subject to track the movements so that we could have a further indication that they were indeed experiencing illusory movements. The best results were obtained when the elbow was put in such a position that the vibrated muscle was near its physiological maximum length, for it was then easiest to adjust the vibrator so as to produce vivid sensations without eliciting a reflex contraction. Thus it may be concluded that there is no need for there to be a maintained muscle contraction in order for vibration to be able to produce maintained proprioceptive illusions.

Effects of varying the state of contraction.—It should next be emphasized that although the illusion can be produced in the absence of muscle contraction it

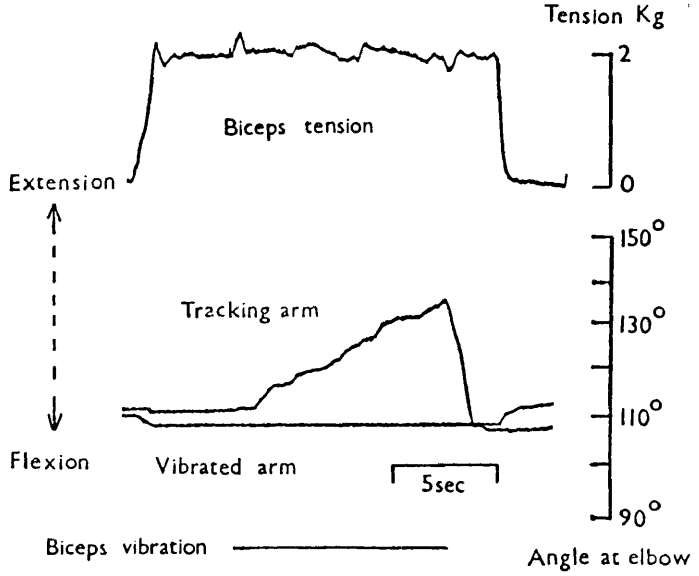


FIG. 7.—The production of the usual illusory sensation on vibrating a muscle which was already contracting voluntarily and whose activity was voluntarily modulated so as to maintain the same tension throughout. The right arm was used to produce a constant isometric force in the direction of flexion by contraction of the biceps. The vibration was then applied to the biceps and the subject asked to use his other arm to track the resulting illusion of movement.

develops perfectly clearly during muscle contraction. Its occurrence on development of tension under isometric conditions after arresting the movement induced by the tonic vibration reflex has already been amply illustrated. Fig. 7 demonstrates the occurrence of the illusion when vibration is applied to a muscle which is making a voluntary isometric contraction that is maintained at a constant strength by visual feedback. As usual the subject felt that the vibrated muscle was being extended. To begin with, contraction was entirely voluntarily initiated; but as the vibration took effect so some of the contraction may have been produced by the tonic vibration reflex with the subject correspondingly reducing his voluntarily maintained central drive. Under isometric conditions there did not appear to be any particular interference between moderate muscle contractions and the development of the illusion of a movement in the direction of extension of the vibrated muscle. Under isotonic conditions, the occurrence of a contraction appeared to interfere with the illusion, but this was probably merely because the genuine reflexly elicited shortening of the vibrated muscle counteracted the illusory sensation of its being stretched. Indeed, in a few cases the difference between the velocity of movement of the vibrated arm and that of the tracking arm seemed to be very much the same during the initial shortening phase of isotonic tracking as it was in the subsequent isometric phase, when the movement was obstructed in experiments such as those of figs. 1 to 4. But the experiments were not performed in a suitable way to put this impression on a firm quantitative basis, and many subjects did not show tracking movements at as constant a velocity as those illustrated. Moreover, it should be noted that the muscle spindle afferents are likely to be less responsive to the vibration while the muscle is shortening than they are when the muscles are isometric; thus the total amount of afferent excitation is likely to be different in the two cases.

There was nothing crucial about the particular tensions employed to demonstrate the effects, for both under isometric and under isotonic conditions the illusion of the vibrated muscle being extended was well developed for a range of tensions, provided that these were only of moderate extent. But a sufficiently strong voluntary contraction was found to abolish the illusion. This could be shown either isotonically by loading the arm with weights by a pulley and asking the subject to maintain the position of his arm, or isometrically as in fig. 7.

For example, in one particular case one of our trained subjects was instructed to perform the standard isotonic tracking experiment while holding up a weight of 6 kg. On vibrating his biceps tendon he then made no movement at all of either of his arms and, moreover, spontaneously expressed surprise that the turning on of the vibrator had failed to produce the usual sensation of movement to which he had become accustomed. Similar results have been obtained on vibrating the contracting triceps, but when biceps was vibrated while triceps was contracting as in fig. 6 the illusion persisted however strong the contraction.

It seems likely that this absence of an effect on vibrating a strongly contracting muscle is due to a voluntarily induced fusimotor firing activating the spindle afferents so powerfully that they are already firing at around 100/sec and so are not appreciably further excited by vibration at 100 Hz (similar considerations would apply if the tendon organ were to be responsible for the illusion so this particular observation

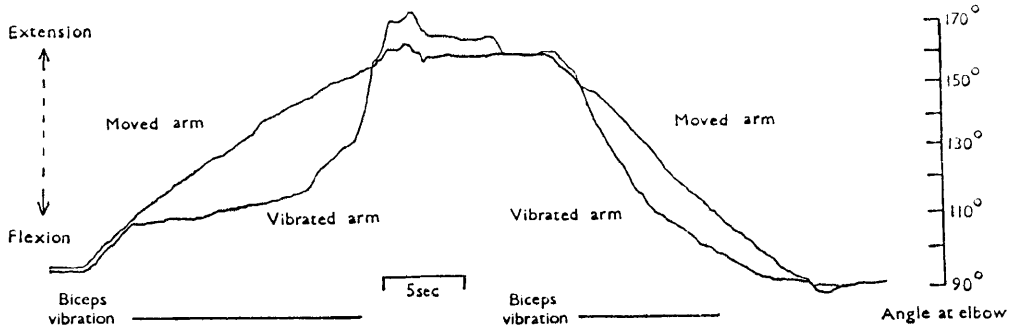


FIG. 8.—The effect of vibration applied to an arm that the subject was using to make a voluntary movement. The left arm was moved by the experimenter to provide a reference and the subject was asked to track it with his right arm. During the periods indicated vibration was applied to the biceps of the right arm which was the one which was being moved voluntarily. This caused the subject to position the vibrated arm so that it was unduly flexed with regard to the reference arm, that is so that its vibrated muscle was unduly short. This occurred irrespective of whether the vibrated arm was being moved into flexion or extension, although the effect was more dramatic when the arm was being moved into extension. The arm was moving in the vertical plane with the upper arm lying horizontal so that the biceps muscle will have been contracting throughout.

does not of itself discriminate between them and spindles as the causative receptor). Incidentally, the absence of an illusory sensation under these conditions provides a further control that the effect depended upon intramuscular receptors since only these should have been so markedly affected by the strength of the contraction. Distant pacinian corpuscles, for example, would presumably be powerfully excited by the vibration irrespective of whether the muscle was contracting and at what strength.

Distortion of position sense during voluntary movement of vibrated limb.—So far described have been a distortion of kinæsthesia occurring in the following conditions: in the absence of contraction, during steady isometric contraction of the vibrated muscle or of its antagonist, and during reflex movement under isotonic conditions. The following experiment shows that the illusion occurs equally during a slow voluntary movement. The experimenter moved one arm, the reference arm, backwards and forwards at a slow constant velocity. The subject was asked to follow it with his other arm, the experimental arm, in the usual way as in the previous experiments (figs. 1 to 3). In this case, however, the arm which was doing the tracking was vibrated. As shown in fig. 8, during the vibration the experimental arm came out of alignment with the arm it was meant to be following, and as usual it appeared to the subject that the vibrated muscle was longer than it actually was.

This effect was most obvious when the vibrated muscle (biceps in this case) was gradually reducing the strength of its contraction and letting the elbow extend, but was also seen when the biceps was shortening. The asymmetry of fig. 8 was the usual state of affairs including when the arm was loaded with a weight over a pulley so that biceps was necessarily contracting at all positions of the elbow and the triceps relaxed. When the same experiment was performed during rapid movements the subject found it very hard to move his vibrated arm in conjunction with the reference arm. This seemed to be due more to an interference with motor action rather than to interference with position sense, and all subjects expressed dissatisfaction with their performance

at tracking under these conditions. The most notable finding was that in comparison with the moved arm the amplitude of voluntary excursion of the vibrated arm was grossly reduced, and this occurred mainly through a failure of the vibrated muscle to relax to the normal extent. For example, when biceps was vibrated extension was markedly incomplete but flexion of the vibrated arm took place to somewhere around the correct final value. When the vibrated arm was moved in a series of suddenly applied steps, rather than continuously, the tracking arm was usually consistently misplaced in the direction of stretch of the vibrated muscle. Sometimes, however, a subject managed to achieve moderately accurate tracking over part of the range in spite of the vibration. This was usually when the movement was such as to allow the vibrated muscle to shorten, and may thus be related to the ability of the subjects to make moderately accurate fast movements in the shortening direction, as just noted.

In slow tracking movements like that illustrated in fig. 8 the subjects were invariably thrown into error by the vibration even though they were convinced that they were managing successfully to maintain their arms in alignment in spite of the vibration. Thus during slow movement there would undoubtedly appear to be a vibration-induced distortion of position sense over and above any reflex interference with normal motor control.

Measurement of latency of illusion.—The greater clarity of the illusory sensations in the absence of contraction in the horizontal position enabled us to establish an upper limit for the latency of the development of the illusory sensation.

One arm was vibrated in the usual way while in his other hand the subject held a push-button with which he was asked to give a signal the moment he was certain that he was feeling a movement. This required him to distinguish between an awareness of movement itself and an awareness simply that the vibrator had been turned on. He was asked to set his threshold for the detection of movement at a fairly high level, as if he were going to be punished for any incorrect positive answers. The time of onset of the vibration and the subject's response were recorded on moving paper from which the "reaction time" could be determined to within 50 msec. Nine out of the 11 subjects studied in this way signalled that they experienced a sensation of movement in 0·30 to 0·65 sec after the vibration started, and 5 of them stated that they became aware of the movement as soon as they felt the vibrator had been turned on. (The 2 remaining subjects had weak illusions and reaction times of just over 1 sec.) Measured under similar conditions the reaction time to simply being aware that the vibrator had been turned on was 0·15 to 0·30 sec and may have depended upon auditory clues as well as upon awareness of the vibratory sensation itself.

The above figures apply to the median values of the latencies obtained in a number of trials for each subject. The latency measured in this way seems unlikely to give a true indication of the minimum time required for the subject to perceive the illusory sensation, but may rather reflect the requirement for the subject to discriminate between the occurrence of vibration, which must have excited many kinds of receptor, and the occurrence of a sensation of movement, which seems likely to have depended upon the excitation of just one kind of receptor, namely the spindle primary ending. Moreover, the illusory movement probably had to build itself up to a finite size before the subject was certain enough of its existence for him to be prepared to give a positive answer. Our suspicion is that under more favourable conditions the excitation of the receptor responsible for the illusory movement would lead to a response at appreciably shorter times than those presently measured, and that there need be no particular slowness in the development of the sensation

itself. This view is supported by the finding that brief bursts of vibration of 0·1 to 0·2 sec duration were experienced as producing a movement, although the subject could only report that a movement had occurred well after the vibration had stopped. The latency needed to start tracking a vibration-induced sense of movement was usually somewhat longer than that required simply to signal its occurrence. This is probably merely due to the greater complexity of the tracking task which involves an assessment of the velocity of the apparent movement of the vibrated arm and its reproduction by the motor system.

How far is the illusion one of a false movement and how far one of a false position?—To introspective analysis, the awareness that a limb is moving and the awareness of its absolute position seem to be readily separable sensations. But in most practical situations the sensations tend to be intertwined, for any movement must lead to a new position, and a new position can only be achieved by movement. The extent to which movement signalling and positional signalling are separate entities in the internal language of the nervous system remains to be unravelled by future work. Things do not necessarily work in the common-sense way. For example, in the visual world it is possible to experience a continuing movement of viewed objects without the development of any change in their apparent position. This happens in the so-called "waterfall illusion" which occurs when the gaze is transferred to a static field of view after being fixed on a moving object such as a waterfall. Its existence suggests that there are separate central mechanisms concerned with signalling movement and with signalling absolute position (McKay, 1970), although, of course, the individual photoreceptors are not specialized in any such way. For kinæsthetic sensation it would be the simplest for the physiologist if its different subdivisions were subserved by functionally distinct receptors, rapidly adapting ones for signalling movement and slowly adapting ones for signalling position, but the spindle primary ending, with which we are currently particularly concerned, cannot be meaningfully said to signal either movement or velocity for it responds to both stimuli, and its frequency of discharge at any time depends upon their combination. What the central nervous system makes of the mixed signal depends entirely upon how it goes about its internal business. If an analysing centre is restricted to observing the instantaneous value of the spindle primary discharge it can do nothing to separate the length and velocity components of the stimulus. But if it is endowed with a certain amount of memory, or if it is given access to information from other types of receptor which differ from the spindle primary in their relative sensitivity to length and velocity stimuli, then in theory the centre should be capable of disentangling the relative values of the two. Thus if vibration be supposed to be having its main kinæsthetic effects by exciting the spindle primary endings then the nature of the kinæsthetic sensation evoked by vibration will depend upon the behaviour of the central decoding mechanisms. In point of fact, it looks as if the false messages induced by vibration are to some extent taken to mean both that the muscle is in the act of being stretched at a constant velocity, and also it is in the state of being significantly more extended than it actually is.

False velocity sensations: The first reason for thinking that the vibration-induced discharges are interpreted as partly due to a false velocity of movement is that this is what some subjects report when they are asked what they are primarily experiencing in the tracking experiments. Moreover, even when they have brought their tracking arm to a constant position while the vibration is continuing some subjects may state that they can still feel the vibrated arm moving, but they know that it would be wrong to move their tracking arm any further as the arms would then be misaligned. This seems to be because they are receiving alternative clues about the position of the two arms other than from the receptors which are excited by vibration, and at some point they prefer to accept the evidence from the alternative sources and refuse to follow the apparent movement any further. Alternatively, others may state that they have "lost" the position of the vibrated arm and move the tracking arm backwards and forwards to try and find it. Or again, after tracking for some distance they may become aware that they are no longer properly aligned and return the tracking arm somewhat, though rarely as far as its correct position, and then start tracking the velocity signal once more.

A simple example of preferring non-vibration clues occurs when the subject moves his tracking arm into an extreme position at a time when the vibrated arm is being held by the experimenter somewhere in the middle of its range (*see* fig. 4). If the experimenter restores the tracking arm to the correct alignment at a time when the subject is refusing to move it further then the subject is once more prepared to follow the false movement. Again, as illustrated in fig. 9, if the subject

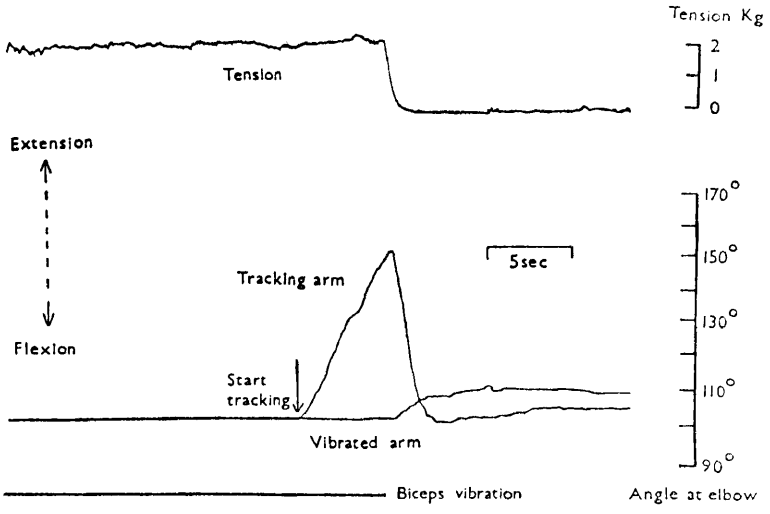


FIG. 9.—The persistence of the illusion of movement for a very prolonged period. The right biceps was vibrated in the usual way under isometric conditions after initially moving freely, while the left arm was initially held in alignment with it by the experimenter. After the vibration had been continued for a full minute, when the reflexly induced tension had been constant for over 20 sec, the experimenter released the subject's left arm and asked him to track any continuing movement that he was still experiencing of his vibrated arm. The velocity of the resulting tracking movement was then very similar to that seen at the beginning of the period of vibration in other trials with the same subject.

was prevented from tracking for a full minute after the vibration was turned on he still felt that his arm was moving at the end of the minute. If the vibration had induced a sensation simply that the arm was in a certain position, albeit normally achieved with a certain lag, then the subject might have been expected to move his arm smartly to the new position which was indicated by the particular frequency of vibration being employed. Instead he made a tracking movement of very much the same velocity as he did when he was asked to track from the very beginning of a period of vibration.

Though we have not studied the matter systematically we have the impression that the velocity of the falsely perceived movement increases both with the frequency and with the amplitude of the vibration. Immediately after the end of a period of vibration there was often a sensation lasting a second or so that the arm had reversed its direction of motion, even when there was no overt movement occurring either during the vibration or on its cessation, but the illusion was too transitory for us to be able to make any effective observations upon it.

False sensation of position: But equally, during vibration many of the subjects seemed systematically to mis-estimate the angle of their elbow, independent of any false sensation of its moving. This was shown first by the fact that numerous subjects accepted without question that they had managed to keep their arms aligned in the standard tracking procedure, and felt that there was no question of their having moved into a false position merely because they had been following a velocity signal. They claimed that they knew the position of their vibrated arm, and on being shown their error said that it was just that the perceived position did not correspond with the one that the arm was actually in.

A way of testing the sensation of position somewhat independently of the sensation of velocity was achieved by asking the subject to use a finger of the normal arm to point to the perceived position of a finger of the vibrated arm.

The subject was blindfolded and arranged in the usual position with his arms free to move in the vertical plane. A Perspex screen was placed between the two arms and marked out in degrees at the elbow (*see* fig. 2). One arm, designated as the reference arm, was moved by the experimenter to a certain position and the tip of its index finger placed against the screen and then held there by the experimenter so that the subject did not have to make any particular muscular effort to maintain its position. The subject's other arm was designated as the indicator arm and used to indicate his perception of the position of the reference arm. Initially both arms lay horizontally on the table. Ten seconds after the reference arm had been moved into position the subject was asked to bring his indicator arm into alignment with the reference arm and then to place it against the screen with the tips of the index fingers of the two hands in direct opposition. He was allowed to take as long over this as he felt was required and there was no question of his having to move into the final position in a single action. When the subject had made his decision the experimenter noted the result on the scale and both arms were returned to the horizontal. First, this procedure was repeated ten times in the absence of vibration, to the same final position, to determine the subject's normal accuracy. Secondly, a further 10 trials were made under the same conditions but with the biceps of the reference arm being vibrated continuously; the vibration was maintained for the whole period including while the reference arm was resting horizontally. Thirdly, the control series of 10 trials without vibration was repeated. This showed that during vibration the subject perceived his reference arm to be up to 15 degrees more fully extended than he did in the absence of vibration. For example, in one particular case when the reference arm was moved so that the angle at the elbow was 130 degrees the arm was indicated to be 8 degrees more extended during

vibration than in its absence and this was statistically significant (mean error of 20 trials without vibration $+8{\cdot}0° \pm 0{\cdot}53$ S.E. of mean, the + indicating that the error was in the direction of extension; mean error of 10 trials during vibration $+16{\cdot}0° \pm 0{\cdot}70$; $P < 0{\cdot}01$ by the t test). Similarly significant results were obtained for 5 other subjects with the final position of the elbow 40 degrees to 60 degrees short of full extension.

A difficulty about the finger pointing test performed in the particular way described above is that the initial and final positions of the subject's reference arm were always the same and so the suspicion arises that the subject might be making a standard movement of the indicator arm, or bringing it to a standard final position, irrespective

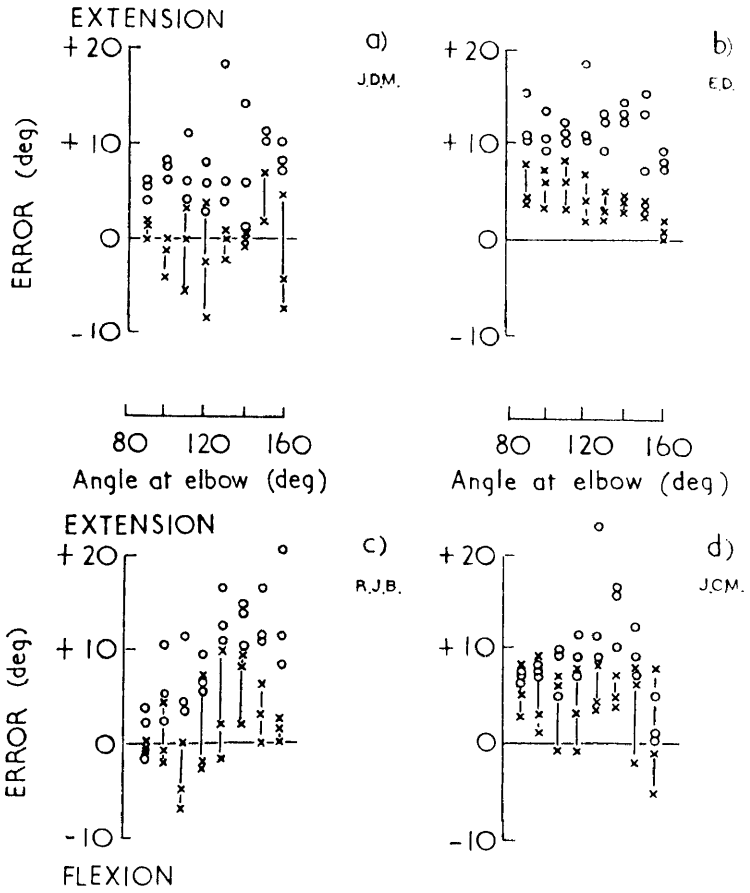


FIG. 10.—Vibration-induced errors in position sense demonstrated by "finger pointing." Each of the four scatter diagrams shows results from a separate subject. The subject was seated as in fig. 2 and one of his arms was passively moved by the experimenter into a certain position where it was held by the experimenter without the need for the subject to exert himself. Ten seconds later the subject was asked to bring his other arm into alignment with the moved arm so as to indicate its subjective position. The abscissa shows the position of the passively moved arm (full extension = 180 degrees). The ordinate shows the extent and direction of any error in alignment. Each of the 8 final positions were tested three times without vibration (x) and three times during continuous vibration of the biceps of the arm which was passively moved by the experimenter (o). Further description in text.

of any clues that he might be receiving from his reference arm. To obviate these difficulties the accuracy of finger pointing to a number of different positions was tested in the following way.

Eight positions were chosen at 10-degree intervals from 90 degrees to 160 degrees angle at the elbow. These were arranged in random order and the subject's reference arm moved from one to the other without returning to the horizontal in between. A period of 10 sec was allowed from the time the indicator arm was aligned with the reference arm before the reference arm was moved on to its next position; during this time neither the subject nor the experimenter corrected the position of the indicator arm, however great any error. After each position had been tested both arms were returned to the horizontal and left there for 10 sec so that the subject could re-calibrate his sense of their position. The series of 8 positions was then re-tested as before, but in a different order, and then after a further 10 sec re-calibration the same positions were tested for a third time in yet another order. After a further re-calibration the whole procedure was repeated with each point tested a further three times in precisely the same order as before, but during continuous vibration of the biceps of the reference arm. Fig. 10 shows the results obtained for four separate subjects. Subject JDM (a) showed some of the largest deviations that we observed between the responses obtained in the presence and absence of vibration, while subject JCM (d) showed some of the smallest differences. During biceps vibration JDM indicated that on average, throughout the range tested, he felt his arm to be 8·3 degrees more extended that it was in the absence of vibration; this value differs significantly from zero (S.E. of mean, 1·0 $P<0·01$ on t test). These figures were determined by taking the difference between the values of each pair of the 23 corresponding points obtained in the presence and absence of vibration (24 points for the other subjects); normally each of the 8 positions studied was tested three times both with and without vibration, each time from a different preceding position. When all 23 points of each kind were lumped together the mean deviation induced in subject JDM by the vibration was still, of course, 8·3 degrees in the direction of extension but the variability was slightly greater than when corresponding points were compared. (S.E. of mean 1·1 instead of 1·0); however, the deviation was still highly significant. The statistics for the other 3 subjects were as follows: ED, vibration-induced deviation $+7·3°\pm0·66$ the + indicating extension (or $\pm0·69$ for lumped points); RJB, mean deviation $+7·7°\pm0·94$ (or $\pm$ 1·4); JCM, mean deviation $+5·0\pm0·86$ (or $\pm$ 1·2); all these mean deviations differ significantly from zero on the t test ($P<0·01$) irrespective of which measure of standard error was employed. Similar results were obtained for the 4 other subjects who were tested in this way.

It may be concluded that vibration induces a small but significant distortion of the sense of absolute position as well as inducing an illusion of movement. However, this conclusion could usefully be fortified by studying the matter under a wider range of conditions for it is by no means easy to devise good measures of "position sense" which are independent of sensations of movement and independent of the accuracy of the motor machinery and the ability to monitor its performance.

Another notable feature of experiments of the kind illustrated in fig. 10 was the inaccuracy with which many subjects reproduced the position of one arm by indicating it with that of the other, thus suggesting that the absolute sense of position in the absence of visual calibration is rather bad. For example, some subjects made errors of up to 15 degrees while remaining convinced that they were performing adequately (cf. also fig. 5). The errors were not only random errors scattered either side of the correct position, but also tended to be systematically biased one way or the other, usually in the direction of undue extension of the elbow. Sometimes the bias increased progressively during the course of an experiment throughout which the subject was blindfolded and given no opportunity to re-calibrate himself. We have made no attempt to quantify these deficiencies in the normal accuracy of position sense though we have noted their regular occurrence including in our standard tracking situation. They are already well known and are at present being investigated to sort out the multifarious contributory factors, such as the length of time the reference arm

is maintained in position and whether it is moved there passively by the experimenter or actively by the volition of the subject (Paillard and Brouchon, 1968; Brouchon and Hay, 1970). These inaccuracies in the absolute sense of position contrast with the accuracy with which movement away from a predetermined position can be detected; a movement at the elbow of 1–2 degrees can be reliably detected provided the velocity of movement is about 0·1 degree/sec (Cleghorn and Darcus, 1952; Laidlaw and Hamilton, 1937).

As long recognized, such a difference "argues for existence of a sensation of movement *per se* as an elemental product of muscular sense, and not as a judgement based on comparison of discrete sensations of position" (Sherrington, 1900, p. 1017). This does not prove, however, that position and velocity are signalled by different peripheral receptors. It might merely be that the relevant receptor which signals position is moderately rapidly adapting and has an appreciable dynamic sensitivity over and above its positional sensitivity. Such behaviour is shown by the Ruffini joint endings (Skoglund, 1956). If the threshold be supposed to represent an absolute change in receptor discharge this would lead the dynamic threshold to be lower than the static threshold when both are expressed as degrees of displacement. Moreover, it should be noted that the central awareness of the absolute position of a limb could in theory be based on the integration, in the mathematical sense, of velocity signals derived from a rapidly adapting receptor without involving slowly adapting receptors, though in practice the latter seem likely to take an important part.

Tracking of involuntary post-contraction movements.—It has been known to many generations of schoolboys that the arm may raise itself apparently spontaneously when one lets it lie by one's side immediately after producing a powerful isometric contraction of the relevant muscles, such as by pushing against a wall while standing. The phenomenon has been studied by various physiologists with general agreement that the effect is indeed a physiological one and does not depend upon auto-suggestion, that it exists in the majority of subjects, and that it may be found for virtually any somatic muscle after a period of intense isometric contraction, though it appears to be particularly well shown for the deltoid (for example: Forbes, Baird and Hopkins, 1926; Allen and O'Donoghue, 1928; Zigler, 1944; Fessard and Tournay, 1951). But no proper explanation is available as to the genesis of the phenomenon. The electromyographic activity during the contraction is identical with that of a voluntary contraction with the same time course, thus dispelling the early idea that the effect might depend upon some unusual kind of muscle contraction which was not fully under the control of the CNS. Moreover, the contraction can readily be overridden voluntarily. Indeed, the phenomenon usually only occurs when the relevant muscle is relaxed and the subject pays it the minimum of attention, as well as avoiding any gross overt muscular action elsewhere in the body. Forbes, Baird and Hopkins (1926) showed electromyographically that the contraction fails to take place if the muscle is initially prevented from shortening, but that it can persist for a while under isometric conditions if an obstruction is encountered after an appreciable movement has already taken place. In view of earlier suggestions that muscle afferents may perhaps play some part in the genesis of the phenomenon, and because of the superficial similarity of the post-contraction movement with that of the tonic vibration reflex it seemed of interest to see whether or not the post-contraction movement was also associated with aberrations of position sense. This was tested by asking the subject to track the movements with his other arm.

Our first tracking experiments were performed with the deltoid muscle by asking the subject to push against a wall for 30–60 sec and then to put his arm by his side and let any involuntary

movement occur without interference. After he was accustomed to the occurrence of the phenomenon he was asked to use his other arm to track his perception of the extent of the involuntary movement; his eyes were meanwhile closed. To simple inspection by the experimenter, the tracking was then performed perfectly well without any obvious lag in the detection of the involuntary movement, thus showing that the subject remained fully aware of the position of his arm in spite of his motor system acting without his bidding. Moreover, when the moving arm was obstructed after moving through 20–30 degrees the subjects all denied any sensation of a reversal of movement; nor did they signal one with their tracking arm, although they all did so when elbow movement induced by the tonic vibration reflex was obstructed.

In addition, we studied the post-contraction movement of the biceps muscle in 5 subjects using the standard tracking procedure with graphic recording as described earlier (figs. 1–4). The conditioning contraction of biceps was an isometric contraction of about two-thirds of the maximal value maintained for about 30 sec and made with the elbow nearly fully extended. The involuntary movement of biceps did not, however, occur as readily as did that of the deltoid, and to obtain satisfactory movements we had to instruct our subjects that a movement might be expected and that if they should feel one starting they should allow it to proceed. They then produced post-contraction movements which they assured us were involuntary, but perhaps not so convincingly so as those seen for the deltoid. These elbow movements induced by the slow contraction of biceps were effectively tracked, and there was no tendency for the tracking movement to reverse when the involuntarily moving arm was halted. Thus unlike the situation for the slow movements induced by the tonic vibration reflex the accuracy of position sense appears to be preserved during a post-contraction movement. This supports the idea that the aberrations seen during the vibration reflex are likely to be due to the abnormal afferent signals set up by the vibration itself, rather than due to a central misinterpretation of, or an abnormality of, any corollary discharges which may occur during the movements. But the argument is a weak one since the central mechanisms responsible for the two types of involuntary contraction are probably quite different, and the above view rests primarily on the experiments described earlier in which vibration induced proprioceptive sensations without eliciting a muscle contraction.

B. Persistence of Appreciable Kinæsthesia after Paralysis of Joint Afferents

The preceding findings with vibration led us to question the current orthodoxy that the discharges of muscle afferents are without effect on perception. It thus seemed important to repeat some of the experiments on which the currently conventional view was based. This has shown that appreciable kinæsthesia may persist after paralysing joint afferents, but while preserving the afferents to some of the muscles acting at the joint studied. Such a differential action on the two kinds of afferent can be readily achieved for various joints of the hand because the bellies of the long muscles which act on the fingers and thumb lie in the forearm. Thus the injection of local anæsthetic into a finger or the making of the whole hand insentient by anoxia should abolish the position sense of the digits if this were to depend solely upon the joint afferents. But in fact we find that it fails to do so. There is, however, a considerable reduction in the delicacy of position sense so we are in no way arguing that the joint afferents do not contribute importantly to position sense, merely that their peripheral contribution is not an exclusive one.

Paralysis by local anæsthetic.—In 8 subjects the index finger was ring-blocked by injecting 2–3 ml of 2 per cent lignocaine around its base. The efficacy of the anæsthesia was improved by occluding the circulation to the hand for 10–15 min

after the injection, so as to allow time for the lignocaine to act without its being swept away by the blood stream; this made it unnecessary to inject adrenaline with the lignocaine. The circulation was re-established for the experiment proper. The lignocaine produced a complete clinical anæsthesia of the finger to light touch, heavy touch, pin-prick and squeezing. The anæsthesia extended to the very base of the finger and persisted for some 15 min after re-establishing the circulation. Thus the afferent fibres to both of the interphalangeal joints may be presumed to have been paralysed. None the less, an awareness of passive movement persisted at both joints. When the experimenter manipulated the anæsthetized joints the subject could correctly state, first whether or not the finger was being moved, secondly whether it was being moved into flexion or extension, and thirdly whether it was being held at full extension or full flexion. In the last case, however, we failed to establish how far the subject really had an effective awareness of position *per se*, and how far he was relying upon his memory of the history of the displacement. The subjects succeeded in making the various judgements when the muscles acting on the finger were consciously relaxed, but they found it a great deal easier to say what was happening when they were allowed voluntarily to tense either the flexor or the extensor muscles acting on the joint. Every subject stated that he knew what was happening to his finger in the usual sort of way by "feeling it move," and that he was not relying upon subsidiary clues such as any slight deformation of unanæsthetized regions of skin.

No systematic study was made of the threshold for the detection of movement or the accuracy with which statically maintained positions of the finger could be recognized, but for both there was a considerable deterioration in performance from the normal. The anæsthetized finger was particularly bad at detecting slowly applied movements. At the proximal interphalangeal joint, our subjects could readily detect movement of 10–20 degrees when these were applied at 5–10 degrees/sec, but they had the greatest difficulty in detecting the movement or failed altogether when the velocity was reduced to below 1 degree/sec (cf. Provins, 1958); this occurred irrespective of whether or not the subjects were tensing their muscles. The stretches were applied with a servo-controlled solenoid which had been developed for stretching cat muscles (Matthews, 1962). The finger was held still by a padded retort clamp which was firmly applied to the proximal phalanx in a region where it was anæsthetic.

Paralysis by anoxia.—In 10 subjects the whole hand was made anæsthetic and its intrinsic muscles paralysed by occluding the circulation. Sometimes this was done by inflating a child's sphygmomanometer cuff just above the wrist and waiting the appropriate time; the point of using a child's cuff is that it is narrower than an adult's and so produces relatively less effect on the forearm muscles. Alternatively, a more rapid paralysis was achieved by first inflating a cuff round the upper arm and then, when the whole arm was anæsthetic, the usual narrow cuff was inflated round the wrist and the upper cuff removed. The upper cuff appeared to be the more efficient at producing circulatory occlusion, probably because at the wrist the blood vessels are partly protected from the pressure by surrounding bone. However, the paralysis

produced by the upper cuff may have been partly due to local pressure on the nerve as well as to general anoxia of the limb, since there was sometimes a temporary partial recovery of sensation in the hand on shifting the cuff from elbow to wrist; a further period of waiting then produced complete failure of nervous action in the hand. With the rapid method, the required total period of anoxia was usually about one hour. Once the upper cuff was removed the forearm rapidly recovered its cutaneous sensibility and the strength of its muscles. No differences were found between the experiments performed with the two methods of producing an anoxic paralysis of the hand.

The completeness of the anæsthesia produced by the anoxia was established using the same clinically standard stimuli as were used for testing the lignocaine anæsthesia. In addition, the afferents that supply the metacarpophalangeal joints themselves could be directly demonstrated to be paralysed by the inability of the subjects to detect lateral movements at these joints. Lateral movements do not affect the long muscles in the forearm and so must normally be signalled by some combination of the activity of joint afferents and of the proprioceptors in the intrinsic muscles of the hand. In the anoxic hand all these will have been paralysed, and so the inability to detect lateral movements provides an internal control that the desired anæsthesia had indeed been achieved. None the less, the subjects could still detect flexion-extension movements both at the metacarpophalangeal joints and at the interphalangeal joints of the fingers, though appreciably less well than normally. Again, movements were more readily detected when the relevant forearm muscles were lightly tensed. It has been suggested that in the present circumstances the movement of the fingers is detected solely because the bellies of the long flexor muscles "nudge the top edge of the cuff, where the skin is not anæsthetic, and give a clue to the movement" (Merton, 1964). This was excluded for the present experiments by obtaining our usual results when, after complete anæsthesia of the hand had been achieved, the cuff round the wrist was replaced by a cuff round the upper arm. The muscles of the forearm then remained functional for ten minutes or more while the hand remained anæsthetic; during this period the perception of movement of the fingers was retained.

The subjects could readily tell which finger of the anoxic hand was being moved by the experimenter. Interestingly, however, they could not distinguish between movement at the metacarpophalangeal joint and the proximal interphalangeal joint of the same finger when the finger was near full extension. This is to be expected since the forearm muscles on whose proprioceptors the subjects may then be presumed to have been relying act similarly on both joints of the same finger, whether flexion or extension. It is the intrinsic muscles, which were then paralysed, which act upon them differently. As a corollary, subjects with an anoxic hand were found to be unable to detect an extension of one joint (say the metacarpophalangeal) combined with a flexion of the other (i.e. the proximal interphalangeal) of such relative magnitudes that the extensor tendons on the back of the hand did not move appreciably; similar sized movements of either joint alone could be detected.

Another interesting finding was an inability to detect movement in the anoxic hand at the distal interphalangeal joint of the middle finger while the other two joints of this finger were fully flexed and all three joints of each of the two adjacent fingers were fully extended; movement at this joint could be detected when the middle finger was extended. As is well known to anatomists (cf. Gray, 1967), it is impossible voluntarily to move the terminal interphalangeal joint of the normal finger when it is put in this position because the terminal portions of both flexor and extensor tendons are then slack so that contraction of their muscles no longer influences the joint. Thus an inability to detect movement at this joint when the anoxic hand is put into this slightly unusual posture supports the idea that muscle receptors were responsible for the detection of a similar movement when the joints of the finger were all extended.

Particular stress has previously been laid on an alleged complete absence of position sense at the interphalangeal joint of the thumb after rendering the hand anoxic (Merton, 1964, 1970). We found that some of our subjects were indeed unable to detect movements of this joint of as much as 90 degrees when the muscles acting upon it were relaxed. Others, however, had no difficulty in doing so. But all our subjects were readily able to detect movements of below 90 degrees when either the flexor or the extensor muscles were lightly tensed, just as with the fingers. Judging from an aside this also seems to have been Merton's experience (1964, p. 398), but he again attributed the awareness of the movement to clues derived from "changes in pressure on the skin" at some distant site which was unanæsthetized. Our subjects had little doubt that they were not relying upon such subsidiary clues and if any such occurred they reported upon them separately, and said that the sensation was quite different from that of feeling a digit move. The failure of some subjects to detect movement of the anoxic thumb when it was lying relaxed seems likely to be related to the finding that anæsthesia of the thumb greatly diminishes the reflex response of its long flexor muscle to stretching, even though the muscle itself has not been interfered with (Marsden, Merton and Morton, 1971, 1972). This might be due to the elimination of a normal central facilitation, by cutaneous or joint afferents, of the reflex actions of the muscle afferents, and might equally affect their sensory actions. Alternatively, peripheral anæsthesia might lead to a diminution of tonic fusimotor firing by removing a normal source of reflex facilitation and thereby reduce the sensitivity of both primary and secondary spindle endings to stretching.

C. Corollary Discharges and Kinæsthetic Sensations

In previous experiments on subjects with anoxic hands the subjects were said to have the experience that an attempt to move the thumb was always successfully accomplished irrespective of whether or not it was obstructed by the experimenter. Thus it was stated "if the movement is restrained by holding the thumb the subject believes he has moved it just the same" (Merton, 1964, p. 394). In so far as this belief in the success of the movement was based on a subjective "awareness" of the position of the thumb the experiment fitted in with the idea that corollary discharges from motor to sensory centres ("sense of effort") produce a kinæsthetic sensation but that muscle afferents do not. However, our repetition of virtually the same experiment gave us completely different results. Our subjects with hands made

insentient by anoxia could readily detect for both the fingers and the thumb when the course of a large movement was manually obstructed by the experimenter. This was so irrespective of whether the movement was into flexion or extension. Left unimpeded the movement which was obstructed would have been about 90 degrees. The obstruction was sometimes applied at the very beginning of the movement, and sometimes about half-way along its course. The counterforce required to stop the subject becoming aware of the obstruction by a movement of the whole of the arm was produced by the experimenter holding the subject's insentient hand. Since obstruction to movement must alter the pattern of muscle afferent firing we take the ability of our subjects to detect an obstruction as further evidence that muscle afferents can indeed produce a sensory action; in the present case, however, there is no internal evidence to show whether this is a direct action, or an indirect one produced by an alteration in the pattern of motor firing accompanied by a change in any corollary discharges. It seems likely that the previous report of the inability to detect an obstruction to movement of the thumb in similar circumstances depended upon the movements then tested being rather smaller (apparently only about 20 degrees, Merton, 1970). When our subjects were attempting small movements of the terminal phalanx of the thumb they were barely aware that they were succeeding in doing so even when they were unobstructed unless they were allowed to watch the movement. Thus we were not surprised that when blindfolded they could not then reliably detect an obstruction.

Movement without sensation.—The above findings led us to question the suggested role of corollary discharges in producing a conscious perception of movement of a limb and to inquire into the subjective sensation on attempting a movement when the muscle itself is paralysed so that no movement can occur. The findings demonstrated the inability of any corollary discharges that there may be to produce a sensation of movement when they are acting on their own without the help of afferent feedback. In 7 subjects we studied the time course of the paralysis of movements of the index finger on making the whole arm anoxic by a pressure cuff placed just above the elbow. The hand lay on a support to which it was strapped. The interphalangeal joints of the index finger were fixed in full extension by strapping and the metacarpophalangeal joint was partly flexed under the action of gravity and a light spring; the other fingers were slightly flexed. As the arm became anoxic the subject was asked periodically to lift up his index finger as far as it would go into extension. Immediately afterwards he was asked to mimic the movement with his other, unaffected, index finger so as to provide an objective measure of his sensation of the extent of the movement. The monitoring hand lay in the same position as the experimental hand. The movements of both fingers were recorded via potentiometers which were connected to strapping on the fingers by string. Fig. 11 demonstrates the result and shows that during the progressive paralysis the subject regularly underestimated the extent of the movement. He thus systematically believed that he was weaker than he actually was. Moreover, he entirely failed to perceive the last two real movements that he succeeded in making before his muscles gave out.

Thus the subject cannot have relied upon any corollary discharges for his recognition of the occurrence of a movement. If he had done so, he should have continued to signal the occurrence of a movement after he had stopped being able to make one, instead of the other way round. The illustrated result is typical of all experiments; in some of them, moreover, the period in which a movement was made but not perceived lasted for appreciably longer. After we had completed the above type of experiment we discovered that similar findings had already been described by Laszlo (1966), but were not then illustrated.

The records on the right of fig. 11 were taken after the forearm had been allowed to recover from the anoxia, but the hand had been kept insentient by applying a cuff

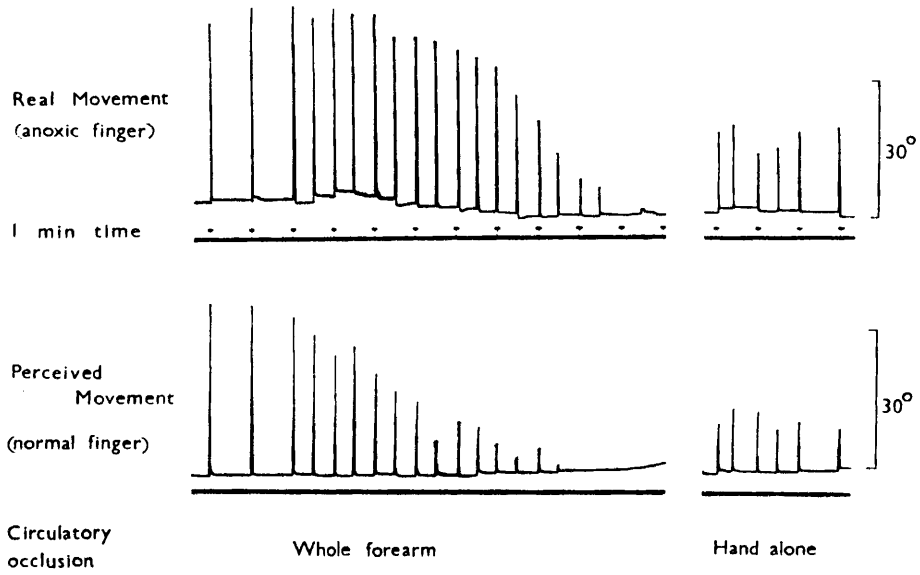


FIG. 11.—Records demonstrating that on progressive paralysis of a limb the perception of movement may be more severely impaired than the actual ability to move. This makes it unlikely that the perception of movement can depend primarily upon any corollary discharges from the motor centres to the sensory centres. The top trace shows the movements at the metacarpophalangeal joint of the index finger of one hand at a time when the circulation to the arm was occluded; the interphalangeal joints were fixed in full extension by strapping. Periodically, the subject was asked to raise his finger to full extension and then to lower it again; in between the finger lay partly flexed under the action of gravity and a light spring. Immediately afterwards he was asked to make an equivalent movement with the index finger of his other hand, thus providing an objective measure of his perception of the extent of the movement which was being paralysed. In the first part of the record the circulation to the whole of the forearm and hand was occluded by a pressure cuff above the elbow. This eventually led to a complete paralysis of all the muscles involved, and to a complete loss of sensation. Even when he was paralysed the subject still continued to attempt the movement at half-minute intervals. In the second part of the record the pressure cuff had been shifted to the wrist so that the hand remained anæsthetized, but the muscles of the forearm had been able to recover. The upper cuff was inflated for 13 mins before the beginning of the records shown. There was an interval of 14 mins between the two sets of records. The recordings were made by connecting the fingers to freely moving potentiometers. The subject could not see either his hands or the recordings.

to the wrist. They demonstrate that muscle afferents can inform the subject that he is able to move, even though his joint afferents remain non-functional. This is in line with all that has been said earlier, namely that the discharges of muscle afferents can influence consciousness. In the experiments of fig. 11 the subject moderately underestimated the movement, when he was relying on muscle afferents alone. In other experiments this effect was much more marked and the subject might believe that he was achieving only some 20 per cent of the movement that he was actually making. It may be noted that to produce finger extension in the normal state the subject would have been contracting his interossei as well as his forearm muscles, so with his hand insentient he was deprived of feedback from some muscle afferents as well as from the joint afferents. This is perhaps why with the hand insentient the subject found it a matter of some difficulty to move the finger. He had to try very hard to succeed at all and was not able to move it throughout its normal range. It felt rather as if the finger were stuck in glue. If the paralysis of the whole forearm was not commenced until after the hand has been made anæsthetic by a wrist cuff, the perception of movement is again lost in advance of the actual paralysis of the movement itself. In our way of thinking, the subject's failure to recognize the full extent of their residual strength may be attributed to their afferent fibres being paralysed slightly in advance of the motor fibres, as also suggested by Laszlo (1966).

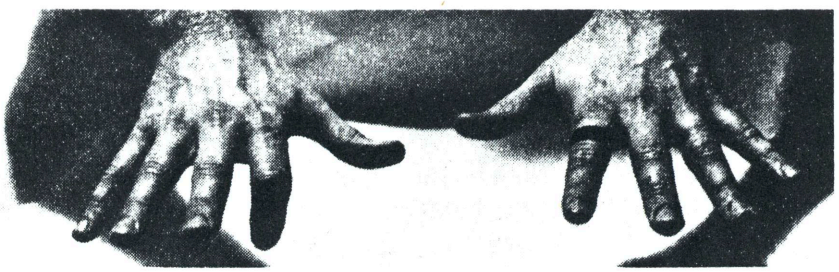
It might be suggested that when the paralysis was complete the subjects did not pay proper attention to their corollary discharges as an indication of movement because they had already learnt, on the basis of afferent feedback received during the course of the progressive paralysis, that the movement was paralysed so that they therefore no longer expected to be able to move. This was excluded by asking some of our subjects to keep quite still until the paralysis could be presumed to be complete. When asked to move the affected fingers or thumb they replied, after trying to move, that they could not do so and that there was no sensation of movement with even the hardest attempt. The present authors have all experienced this awareness of an inability to move the moment that one tries to do so; indeed, on the first attempt one is considerably surprised that one does not succeed. Rather similarly it has been variously reported to us that when a conscious human subject is paralysed with curare, or has a complete local anæsthetic block of his lower lumbar nerve roots, then he is fully aware that he cannot move even when he cannot see his paralysed limbs. Thus Dr. M. I. M. Noble of the Charing Cross Hospital, who has had personal experience, wrote to us: "There is a clear perception of inability to move during complete paralysis with curare. If asked to move a finger, you know that you cannot." Again, Campbell (1970) in reply to a question at a symposium as to how he felt when curarized said, "I did not know what my inspiratory centre was doing; I felt no rhythmic or continuous sensation of any sort in my chest or my head. The only sensation I experienced on attempting voluntary movement of the limbs was surprise that nothing happened." Thus the sensory centres for the limbs would appear superficially to receive quite different information from that received by the centres for the eyes, since for the latter corollary discharges are usually held to be

responsible for the sensation of movement (cf. Brindley and Merton, 1960). But there may be more similarities than might at first sight appear for in one standard textbook it is stated for the eye that "complete paralysis of the muscles by curare is accompanied by a conscious sensation of limitation in movements of the eyes with no illusory movement of the environment" (Cogan, 1969, citing Siebeck, 1954).

Phantom limbs.—The above conclusion contradicts classical neurological thought which, largely on the basis of the behaviour of phantom limbs, has long held that corollary discharges, though not so called, can cause sensations of movement of the limbs. For example, this view is to be found in Gowers and Taylor's textbook of 1899 where it is argued that "our knowledge of active states of the muscle is due, at least in some measure, to the effect on consciousness of the activity of the nerve-structures causing the movement" since among other things "after amputation of a limb, a person who makes an effort to move the lost part seems to feel as if he did move it." At first sight the argument seems impeccable; but in fact serious flaws have since become apparent, though they do not appear to have been widely appreciated. To begin with, it is necessary to distinguish between two kinds of movement of the phantom limb. First, when the part of the body bearing the stump of the limb is moved, then the phantom limb moves with it, but the phantom does not alter the relative positions of its various parts. This is an invariable experience and allows the phantom to be pushed through a solid obstacle. Secondly, a proportion of subjects experiencing a phantom limb can produce a movement at a phantom joint and change the relative position of the imaginary parts by willing the movement to occur. The repertoire of such phantom movements is usually, however, extremely limited and they cannot apparently be finely graded; nor can a phantom joint normally be moved throughout the whole of its range.

The occurrence of simple displacement of the whole of the phantom is irrelevant for debating the possible existence of corollary discharges, since the phantom is merely required to keep station with the body image. This requires no change in the neural representation of the phantom itself and thus no new signals related to the phantom. But in the face of the apparent impossibility of any afferent feedback from the moving parts, the ability to alter the angle of a phantom joint might appear to establish the existence of corollary discharges, for there would appear to be no alternative way in which the sensory centres could be informed that the subject had made the requisite effort of will to move the phantom. However, in reviewing the field in 1941 Riddoch suggested that "preservation of postural sensibility in the stump" was a prerequisite for the ability to make internal movements of the phantom. A few years later, Henderson and Smyth (1948) published the findings on some 300 cases of phantom limb which they studied meticulously over a period of four years in the seclusion of a prisoner-of-war camp. They found that internal movements of the phantom were invariably associated with contraction of some of the muscles in the stump. Moreover, if the contraction could be abolished, as by cutting nerves supplying the stump, then the ability to move the phantom was lost. They concluded that "appreciation of willed movement depends on afferent impulses from muscles which normally move the part." No doubt, after an amputation the afferent discharge on attempting a movement is only a fraction of what would normally be present, but there seems no objection to accepting it as sufficient to produce a change in the neural representation of the position of the phantom. Thus, on its own, the ability to move a phantom limb can no longer be taken as sufficient to prove the existence of corollary discharges from motor to sensory centres.

A further observation supporting the idea that any corollary discharges are ineffective at inducing a sensation of movement was made in the course of anæsthetizing the finger in the experiments described above. When the subject suddenly extended all the fingers of the affected hand from a position of full flexion he felt that the anæsthetized finger had lagged behind and failed to extend itself



Perceived movement (normal finger) | Real movement (anæsthetized finger)

FIG. 12.—Another example of the paralysis of local afferents preventing the central perception of the full extent of a voluntary movement. This would not occur if the subject relied for this primarily upon "corollary discharges." The index finger of the left hand (marked with circle) had been ring-blocked by the injection of lignocaine at its base. The subject was asked suddenly to extend all the digits of the affected hand starting from a position of flexion, and then immediately afterwards to put the fingers of his other hand in the position into which he felt he had moved the affected hand. His position was then voluntarily frozen and photographed. The insentient finger was felt to have failed to extend itself fully, though it actually succeeded in doing so.

as fully as the others, although it actually succeeded in doing so. This is illustrated in fig. 12 in which the normal hand is used to mimic the perceived position of the hand with the anæsthetized finger. As was regularly observed under these conditions the subject felt that the anæsthetized finger remained partly flexed, particularly at the proximal interphalangeal joint. Thus once again a reduction of peripheral feedback leads to an underestimate of the extent of a muscular act. In this case, we cannot distinguish between the relative importance of paralysis of joint afferents and the inevitable concomitant paralysis of the afferent fibres from the distal portions of the lumbrical and interosseous muscles, though we suspect the latter to be the important effect.

Sensorimotor interactions.—In spite of the above findings, other considerations suggest that corollary discharges may play a part in perception when they are suitably combined with feedback signals from the peripheral afferents. If this were not the case then on the basis of the evidence of the first part of this paper any increase of spindle afferent firing induced by fusimotor action would be expected to give rise to an illusory sensation of the limb being moved so as to stretch the muscle in question, whereas this does not appear to happen. Nor is there an illusory sensation of reversal of movement when a moving limb is brought to a halt by coming up against an obstruction—yet all the main mechanoreceptors of muscle may then be presumed to increase their discharges to above the value pre-existing before the limb began to move. The absence of an illusion under such circumstances would be explained if the sensorium had been informed by corollary discharges that the limb was being set in motion and that the fusimotor discharge to it was being increased. The sensorium would then be in a position to judge whether an absolute extension of a contracting muscle was taking place rather than a halting of movement,

depending upon whether the afferent firing increased inappropriately relatively to the fusimotor and alpha motor firing. It might be suggested, however, that signals from joint receptors or even skin receptors are relied upon exclusively for knowledge about the progress of a movement, though this would entail at least a partial reversion to the view that muscle afferents do not influence kinæsthesia. That this is not so is shown by experiments in which the hand has been made insentient by anoxia, since this eliminates all cues about what is happening except those from muscle receptors and, if they exist, those from corollary motor discharges. This thus provides a more precise situation for introspective analysis. As already mentioned, movements obstructed in this situation are correctly perceived to have been obstructed and are not felt to have been reversed. Moreover, when an insentient digit is used isometrically to produce a range of pressures against a rigid obstacle there is no sensation of the object moving. Yet, on the basis of direct human single fibre recording, increases in the strength of voluntary contraction are known to be accompanied by an increase in the firing of both spindle endings and of tendon organ afferents (Vallbo, 1970*a*, *b*, 1971). This again suggests that any increase in peripheral afferent firing is interpreted by the sensorium in the light of what it knows the motor centres to be doing; if the returning afferent discharge is that to be expected on the basis of the performance of the intended motor act it is recognized as such and not interpreted as being due to an externally applied stimulus. This might perhaps be brought about by a simple subtractive interaction between corollary discharges and afferent discharges after they have been put into the same sort of numerical symbolic form, or in von Holst's (1954) terminology by the cancellation of an "efference copy" by a peripherally originating "re-afferent" signal. Such a view, however, has been suggested to be too simple a way of looking at things (McKay, 1970). For the moment it seems safer to restrict oneself to the less precise generalization that corollary discharges may well provide the information which would allow changes in peripheral afferent firing to be evaluated in the light of what is being attempted.

Discussion

The main conclusion of this paper is a qualitative one, namely that muscle receptors do contribute to "position sense." The arguments for this view are marshalled in the summary and do not merit present repetition. In historical perspective there is nothing very startling about the conclusion, for it merely represents a reversion to the classical view which held sway almost universally for the first half of the present century and which was never discarded in many clinical circles. For about the last twenty years in physiological circles, however, the classical view has been believed to have been rendered untenable by various experiments which have been reviewed in the introduction. But for the reasons there indicated none of these experiments were sufficiently comprehensive to have excluded a sensory action of the muscle receptors, and our repetition of some of them with comparatively trivial modifications of experimental detail have produced evidence that muscle receptors do contribute to kinæsthesia. The earlier experiment which still demands repetition, but which

we have not been in a position to undertake, is the study of the sensory action of pulling upon exposed tendons in the conscious human subject; at the same time it would be interesting to observe the effect of applying vibration directly to a tendon. It would also be valuable to make a systematic study of patients in whom a diseased joint has been replaced by an artificial one, as is now so commonly done for the hip. The qualitative clinical impression, which we have confirmed by talking to patients ourselves, is that there is no obvious impairment of their ability to control the angle of the artificial joint although some deficit might have been expected if the joint had been largely deprived of position sense; nor does the patient feel that he is unaware of the position which the joint has taken up at any time. Mr. J. Charnley, Director of Hip Surgery at the Wrightington Hospital, Wigan, wrote to us that he had long believed in the importance of muscle receptors "as a result of the perfection of balance of patients with both hips replaced by artificial hip-joints where there is not the slightest evidence of ataxia or Rombergism" on standard testing. However, clinical observation seems unlikely to be able to bring the matter to a close since in spite of the usual replacement of both the head of the femur and much of the acetabulum a certain number of joint receptors must be left behind, such as those near the acetabular margin and in adjoining fascial planes. In the cat, section of all the macroscopically visible nerves to the knee-joint produces no detectable change in the accuracy with which the animal can use the limb in locomotion (Lindström and Norsell, 1971); again, however, a certain number of joint afferents may have been preserved by virtue of running in muscle nerves.

It may next be noted that the elbow-joint, which is the joint at which for reasons of convenience we have chiefly studied the vibratory illusions, would not appear to be in any way peculiar. We have made restricted observations of the occurrence of similar illusions for the thumb, for the fingers, for the knee and for the ankle. Very recently, there have been two independent studies of the effect of vibration on position sense at the knee and at the ankle (respectively, G. Eklund, Uppsala; A. W. Monster, Philadelphia—personal communications, 1971). In both cases the observations appear to have been largely restricted to an estimate of the subjective position of the joint when the action of vibration had reached an equilibrium, and the vibration-induced deviations were only 1–2 degrees. These findings would appear to relate to the action of vibration on the absolute sense of position rather than upon inducing a sensation of movement, and are thus comparable to our finger-pointing test. This would partly explain why the deviations at these other joints are so much smaller than those we have observed during the tracking of a perceived movement of the elbow. In addition, we suspect that the elbow is a more favourable site for demonstrating the illusory effects of vibration, for we ourselves have found them easier to elicit here. This is perhaps because the elbow is moved by muscles which are relatively circumscribed and which have short tendons; both factors would favour the transmission of vibration to all the spindle endings of the relevant muscle irrespective of whether they lay near its origin or its insertion. In addition, in the upper arm all the muscles with the same function are closely grouped

together. But the velocity illusion is not restricted to the elbow and a very pronounced such illusion may be produced by simultaneously applying vibrators to both Achilles tendons of the standing subject with his eyes shut. As already described (Eklund, 1969) this procedure causes the subject to fall over backwards. We find additionally that if he is held so as to prevent him from doing so, then he feels that he is being strongly pushed forwards so that he believes his body comes to incline forwards though it does not do so in reality. As with the elbow, this is the sensation to be expected if the vibrated muscle, now the triceps suræ, were taken to be being dynamically stretched. It should be noted, incidentally, that we are unable to confirm the earliest description of a kinæsthetic illusion induced by vibration. In describing the tonic vibration reflex it was originally stated in passing that "even though no visible movements are induced, the subject may also have the illusion that during vibration a gradual change of position occurs, corresponding to the movement which should have occurred if the contraction had not been 'isometric' " (Hagbarth and Eklund, 1966). As has been amply illustrated, our experience has been precisely the opposite.

It should also be mentioned that the human tongue has been implied to be an organ that lacks position sense in spite of Cooper's (1953) demonstration that it possesses muscle spindles (Merton, 1964). However, bilaterally infiltrating the inferior alveolar and lingual nerves does not prevent the subject exercising reasonable motor control over the tongue and recognizing the direction in which it is moved by the experimenter, although there is a widespread anæsthesia of its enveloping mucous membranes (Weddell *et al.*, 1940; Adatia and Gehring, 1971). The retention of an ability to do all this may reasonably be attributed to the preservation of the spindle afferents which are believed to travel in the hypoglossal nerves along with the motor fibres. Adatia and Gehring suggested that Carleton's (1938) finding that position sense was abolished in 4 out of 8 subjects by the repeated surface application of 5 or 10 per cent cocaine may have been due to the strong cocaine diffusing into the main bulk of the tongue itself; Carleton omitted to state whether or not the motor fibres to the tongue were affected by her procedure.

The next question is whether each one of the main muscle receptors can influence conscious perception or whether it is the prerogative of only some of them. The illusions induced by vibration seem likely to be largely the responsibility of the primary ending on two counts. First, the primary endings are far more powerfully excited by vibration than are the other muscle receptors. Secondly, the primary endings are normally so sensitive to dynamic stimuli that an abnormally high activity on their part might be expected, if perceived, to give rise to an illusion which is primarily one of an abnormal velocity of movement rather than one of an abnormal joint position. Abnormally increased firing of spindle secondary endings or of tendon organs would not seem likely to lead to such a result, since these do not normally respond especially briskly to dynamic stimuli; thus there is no particular reason why the centres which are entrusted with interpreting their discharges should take them to mean that the muscle was in the act of being stretched dynamically, rather

than simply unduly long (secondary ending) or under an unduly high tension (tendon organ). But it seems possible that some or all of the vibration-induced distortion of the sense of absolute position may have been due to a slight vibratory excitation of the secondary endings, rather than to the central interpretation of the abnormal primary discharges as partly due to a false length of the muscle and partly due to a false velocity of stretching. Tendon organs seem unlikely to be responsible for the presently described vibration-induced illusions since these were found irrespective of whether the muscle was relaxed or contracting, while the sensitivity of tendon organs to vibration increases markedly with increased muscle tension. The same findings exclude any suggestion that the illusions might be attributed to appropriately located joint receptors being sensitized by muscle contraction. A kinæsthetic role for the primary ending is further favoured by the finding that after paralysis of the joint afferents rapid movements are readily detected while slow movements are not; this is to be expected if the responsible peripheral receptor is chiefly sensitive to dynamic stimuli.

We tried unsuccessfully to confirm that an illusion of movement could be produced by activity in group Ia afferents by exciting them electrically rather than via their end-organs. For this a cathode was placed over the popliteal fossa and the stimulus adjusted so that a single shock elicited an H reflex but no M response from the triceps suræ on recording electromyographically with surface leads. The same stimulus was then applied at 50–100/sec when it usually elicited a tonic vibration reflex as already described (De Gail, Lance and Neilson, 1966; Lang and Vallbo, 1967). But it produced too much discomfort in the way of tingling and shooting sensations down the leg and foot for our subjects to be able to decide whether they were also experiencing a kinæsthetic sensation referable to the ankle.

However, once it is granted that any one of the muscle receptors can influence consciousness, in this case the spindle primary ending, then there is no obvious reason for denying such a privilege to the other two main mechanoreceptors, namely the Golgi tendon organ and the spindle secondary ending. All three have now been shown to project to the cortex (*see* references in Matthews, 1972). Indeed, the present demonstration that muscle afferents can influence perception puts a new significance upon their cortical representation. Hitherto, in view of their supposed lack of sensory action, such projections have of necessity been ascribed the sole function of contributing to motor co-ordination, such as by producing a direct servo-controlling type of regulation of pyramidal discharges in the face of external obstructions to movement (cf. Phillips, 1969). Without in any way excluding such possibilities it may now be suggested that the muscle afferents have the definitive role of assisting the cortical elaboration of a "body image," with the various parts of the body arranged in a definite but variable spatial relationship to each other.

From all that has been said it is clear that the terms "kinæsthesia" and "position sense" are umbrella terms covering sensations which can to some extent be subdivided by introspective analysis, and which depend upon the discharges of a variety of receptors as well as probably also upon corollary discharges from motor areas. All the following would now appear to be respectable candidates for contributing to kinæsthesia: the Golgi and the Ruffini endings of joints, the primary and secondary

spindle endings, and the tendon organs. It seems desirable to develop methods for subdividing position sense into components, but it is not easy to see how this might be achieved in the intact subject. Indeed, even the testing of kinæsthesia as a whole often makes demands upon the efficiency of the memory and the accuracy of motor control, as in the tests employed by Cohen (1958). In standard clinical practice, the testing of "position sense" by asking the patient to state whether a digit is being moved or is held still, and whether it has been moved up or down would appear to depend primarily upon an ability to perceive movement, rather than upon an ability to detect absolute position *per se*. In the terminology that we prefer this is to say that the clinician more usually tests "kinæsthesia" rather than true "position sense." Sometimes position sense is tested by asking the subject himself to move one arm and then to touch one of its fingers with a finger of the other hand; depending upon precisely how it is performed this procedure may test the ability to reproduce a standard motor command rather than testing position sense itself.

This leads on to the problem as to how the information provided by a variety of different receptors is compounded by the CNS to produce a unitary picture of limb position. Moreover, the sensation seems to be one that is referred to the whole limb with its joints, irrespective of whether the excited receptors happen to lie in muscles or in joints. The simplest mechanism for the mixing of signals would be for some higher centre to take a weighted mean of all the various signals of the same kind. But the confusion into which some of our subjects were thrown by vibration suggests that they could to some extent perceive independently the signals from different receptors, say for example spindle receptors and joint receptors, so that when the signals were incompatible the subjects were perplexed as to which of them should be accepted as valid; this was certainly so when they were presented with a conflict between cutaneous signals and the vibration-induced proprioceptive signals. However, the size of the positional errors that most subjects were prepared to accept when they were primarily following a vibration-induced sensation of movement suggests that joint receptors are relatively inaccurate at providing an awareness of absolute position. This is in line with the considerable inaccuracy with which the absolute position of one limb can be reproduced by that of the other, provided that the subject is prevented from making the match by gauging the extent of the movement required to achieve the desired position (Paillard and Brouchon, 1968; *see also* present results). It may be noted that the total number of afferent fibres to a joint is relatively small in comparison with the number of afferent fibres to the muscles that act upon the joint. For example, in the cat the knee-joint is supplied by fewer than 400 medullated fibres whereas on a conservative estimate there are some 4,000 medullated afferent fibres devoted to supplying the quadriceps, hamstring and sartorius muscles (figures from Skoglund, 1956; Sherrington, 1894). This suggests that the delicacy of position sense could be appreciably improved by the utilization of signals from muscle afferents along with those from joint afferents; but this should not be taken to imply that all the receptors convey the same type of information. A related question is whether joint receptors contribute to the estimate

of the velocity of a movement, or whether they just signal its occurrence and leave it to the spindle endings to provide a quantitative measure of the speed. In other words, would the quantity of primary firing that we induced by vibration have produced a yet greater sensation of movement if it had been combined with the appropriate joint signals? The occasional observation that the difference in velocity between the vibrated arm and the tracking arm was approximately the same whether or not the vibrated arm was moving suggests that joint receptors may perhaps have little part to play. Any number of related questions remain for future study.

The most intriguing questions, however, relate to the mode of interaction between corollary discharges and afferent signals. The acceptance of the view that muscle afferents do contribute to kinæsthesia immediately makes it necessary to postulate the existence of corollary discharges because a given muscle afferent signal has no absolute meaning in itself, but only in relation to the degree of motor activity. Spindle firing depends upon fusimotor firing as well as upon stretch, and tendon organ firing depends primarily upon the intensity of muscle contraction. The failure, during muscle paralysis, of attempts to move to elicit a sensation of movement argues that corollary discharges cannot act on their own but only in combination with afferent feedback. Moreover, corollary discharges would appear to be shown to have a quite different kind of action from that of afferent signals, and there now seems little likelihood that they can be allocated the role of producing a proprioceptive sensation *per se*. They could, for example, interact with the afferent input at some low level and thus determine what is transmitted to the sensorium. The failure of corollary discharges to produce a sensation on their own might then conceivably be because they act by inhibition to sculpture the pattern of impulses transmitted to the next higher level; but, any firm statement is impossible since in our experiments the system might be so disorganized by deafferentation that it simply refuses to work at all.

However, even though they are not perceived by themselves corollary discharges should not be held to be unimportant for perception. Irrespective of theory, introspection shows that apart from a knowledge of the actual events themselves one quickly becomes aware when a disparity arises between what one expects and what actually happens. This suggests that one's consciousness is indeed informed of mismatch signals generated in lower order control loops when something goes wrong. Information on the failure of execution of a movement could be provided by a centre which computed the mismatch signal between the actual returning afferent signals and those which would be expected on the basis of the proper execution of the planned movement. These latter could be estimated on the basis of corollary discharges, the initial situation of the body, and knowledge of the nature of the external world derived from previously attempting similar movements. Thus, an unexpected obstruction to movement has the opportunity to demonstrate its existence by leading to an increase in the firing of both spindles and tendon organs above that which would otherwise occur. The ratio between these two signals, moreover, could provide a guide as to the nature of the obstruction, for example whether it is

rigid or elastic; similar mechanisms may underlie many simple sensorimotor discriminations such as the ability to gauge the consistency of a cheese by squeezing it. Be that as it may, the essential point is that it would be of little value for the highest sensory centres to receive raw signals directly from the muscle afferents, because what these mean depends entirely upon what the relevant muscle is being told to do by the motor system. Thus one now appears driven to accept that the central kinæsthetic mechanisms are yet more complicated than has hitherto been supposed, for they must synthesize a coherent picture out of a number of diverse signals rather than simply mirroring what is happening to the joint receptors. The problem can no longer be sidestepped by comfortably supposing that the complex signals from the muscle afferents are without action on perception.

Summary

(1) The introduction reviews certain evidence which has accumulated over the last twenty years and which has been taken to suggest that muscle afferents do not influence consciousness. It is pointed out that the experiments on which this view was based were not sufficiently comprehensive to have proved the point. The present results suggest that the common-sense classical view that muscle afferents do contribute to kinæsthesia has been too hastily discarded.

(2) Vibration of the tendon of the biceps or the triceps muscle at 100 Hz by pushing a physiotherapy vibrator on to the overlying skin is shown to produce an illusion of movement at the elbow in the direction which would occur if the vibrated muscle was being stretched. This has been found under the following conditions: with the arm lying horizontally with its muscles relaxed, with the vibrated muscle contracting isometrically under the influence of the tonic vibration reflex, with the vibrated muscle voluntarily contracting so as to produce a constant isometric tension, with the vibrated muscle relaxed and its antagonist being voluntarily contracted to produce a constant isometric tension. All these could be demonstrated objectively by asking the blindfolded subject to use his other arm to track the perceived position of the vibrated arm. When the vibrated muscle was allowed to shorten under the influence of the tonic vibration reflex, or when the subject was using it to make a slow voluntary movement, he again indicated that the vibrated muscle was more stretched than it actually was. The illusory sensation appeared to be primarily one of the occurrence of movement, i.e. that the joint was rotating at a constant angular velocity; but there also appeared to be a distortion of the absolute sense of position, for among other things in finger-pointing tests the subject aimed as if the vibrated muscle was longer than it actually was.

(3) Various controls showed that these illusions induced by vibration could be attributed to the excitation of intramuscular receptors. Of these the primary ending of the muscle spindles seems the most likely to be responsible, since it is by far the most sensitive to vibration. Thus its vibration-induced discharges appear to reach consciousness and to be treated by the sensorium as if they were due to muscle stretch, and thus to indicate movement at the relevant joint.

(4) This led us to reinvestigate the kinæsthetic effects of moving a finger when its joint afferents had been paralysed, but whilst the afferents to some of the muscles acting upon the finger had been spared. This was achieved either by ring-blocking a finger with lignocaine or by making the whole hand anoxic by occluding its circulation. In both cases the subject could still tell when a finger was being moved, particularly if the muscles acting upon it were lightly tensed. Passive movements of the thumb were also usually detected when the hand was insentient, provided the movement was a large one. The sensations were referred to the moving digit itself and control experiments made it very unlikely that they could have arisen from the accidental excitation of receptors in distant areas of unanæsthetized skin. All this is taken to show that muscle afferents do contribute to kinæsthesia, but does nothing to show which ones among them do so.

(5) The obstruction of a voluntary movement of a digit with anæsthetized joints was readily detected by the subject provided that the attempted movement was sufficiently large. This is not now surprising, since obstruction must change the pattern of muscle afferent firing. Previous experiments, however, suggested that such an obstruction was not detected and that the subject believed that he had still achieved the movement. This fitted in with the idea that a sensation of movement may be produced by "corollary discharges" despatched from somatic motor areas to sensory areas at the same time as motor commands are despatched to lower centres; this is thought to occur for the oculomotor system. But on making the whole arm anoxic, thus paralysing all the muscles which move the finger as well as the joints, the subject lost his sensation of the occurrence of a movement a little before his ability to make a movement. This is probably because the afferent fibres are affected before the motor fibres, and it shows that acting on their own any corollary discharges from somatic motor areas are unable to induce a sensation of movement. There seems, however, to be no tendency to experience illusions of movement under conditions in which spindle firing may be presumed to be increasing as a result of fusimotor activity. This suggests that corollary discharges do exist and serve to modify the kinæsthetic actions of muscle afferent signals in the light of what the motor system is attempting.

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27. The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents.
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POSITION SENSE AFTER SURGICAL DISCONNEXION OF THE CEREBRAL HEMISPHERES IN MAN

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SURGICAL disconnexion of the cerebral hemispheres in experimental animals and in man has shown that the neocortical commissures are needed for the interhemispheric transfer of learning and memory and also for the interhemispheric integration of many sensory and motor functions involving left and right sides of the body (Sperry, 1966–1967; Sperry, Gazzaniga and Bogen, 1969).

While bimanual motor co-ordination is not grossly abnormal in split-brain monkeys (Mark and Sperry, 1968) or men (Sperry, 1966–1967), some functions dependent in part upon perceived proprioceptive information are abnormal. Blindfolded human split-brain patients cannot, for example, mimic with one hand a posture imposed by an experimenter upon the fingers and hand of the other side (Sperry *et al.*, 1969). Some such patients have been reported to be unable even to mimic with one limb the gross postural configuration imposed on the corresponding opposite limb (Norrsell, 1970). Nor, in another task with some dependence on perceived proprioceptive input, can blindfolded split-brain patients select with one hand from an array of different objects the one which matches an object held in the other hand (Sperry, 1967).

These, and related deficits might be explained if proprioceptive afferent information from one side of the body is normally delivered solely to the contralateral hemisphere, with the neocortical commissures serving to distribute the projected signals to both hemispheres. It is known that proprioceptive afferents from joint receptors project principally, and perhaps exclusively, to the somatosensory area I of the contralateral cerebral cortex (e.g. Mountcastle and Darian-Smith, 1968). Recently it has been shown that afferents from receptors in muscle also contribute to the perception of limb position (Goodwin, McCloskey and Matthews, 1972*a*, *b*, *c*), and it is known that these afferents project to area 3a of the contralateral sensorimotor cortex (Oscarsson and Rosén, 1963; Phillips, Powell and Wiesendanger, 1971).

In the present study tests for both joint and muscle sense were used in split-brain subjects, and showed that apparently normal perception of both joint and muscle proprioceptive stimuli given on either side of the body was achieved by each of the divided hemispheres.

METHODS

Subjects—Tests were performed during March 1972 on three patients of Drs. P. J. Vogel and J. E. Bogen (N. G., L. B., R. Y.). As part of treatment for severe epileptic seizures uncontrolled by medication, these patients had undergone some years previously surgical division of the fore-brain commissures including the entire corpus callosum and the anterior commissure. The hippocampal commissure was presumed to have been divided along with the corpus callosum, and the massa intermedia was also divided where it was seen to be present (Bogen and Vogel, 1962, 1963; Bogen, Fisher and Vogel, 1965; Bogen, Sperry and Vogel, 1969).

N. G. has been living a basically normal life as a housewife since her operation in 1963 when she was aged 30. Preoperatively she had radiological evidence of a 2 cm calcification in the central part of the Rolandic fissure of the right hemisphere, and EEG signs of abnormality in the posterior temporal lobe of the left hemisphere. Generalized or temporal lobe seizures had commenced when she was 18 years old. She is right-handed. A fuller case report is given by Bogen, Fisher and Vogel (1965).

L. B. had his operation in 196[illegible] at 13 years of age, following a history of seizures since he was aged 3. There were no radiological or other signs of brain damage up to the time of his operation. He is right-handed.

R. Y., as explained below, gave no positive results in the present tests, but was of interest because he was the subject of a report by Norrsell (1970) regarding his inability to match gross arm postures of one side with the other. His operation was six and a half years prior to the tests described. Preoperatively he had signs of neurological impairment in bilateral sensory and motor cerebral systems.

Testing Procedures

Position sense was tested in three ways. The first was a simple test of elbow-joint position in which presumably signals from both muscle and joint receptors are involved; the second was a specific test of muscle sense at the elbow-joint; and the third was a specific test of joint sense in the finger. In each type of test a proprioceptive stimulus was applied to the arm or fingers of one side of the body and the blindfolded subject was required to indicate his perception of the stimulus with the other side of the body. Alternatively, a subject could be asked to describe in words the nature of the stimuli given on either side: in particular, this gave an indication of perception by the dominant hemisphere, which is responsible for speech, of stimuli given on the non-dominant side.

In the first type of test, the subject sat with his elbows resting before him on a table, leaving his forearms free to move in a vertical plane. One of his arms was moved by an experimenter through a wide range of angles at the elbow-joint, and the subject was asked to give an objective estimate of the position of the moved arm by aligning his other arm with it. Both forearms were connected via strings to potentiometers to allow recording of the angle at the elbow.

In the second type of experiment muscle vibration was used as a specific test of "muscle sense." Recent experiments have shown that vibration of the tendon of a muscle causes an illusion that the vibrated muscle is being stretched—an illusion which has been attributed to excitation of the primary afferents of muscle spindles in the vibrated muscle (Goodwin *et al.*, 1972*a*, *c*). In this test the blindfolded subject again sat with elbows supported and forearms free to move before him, and was instructed as before to indicate the position he believed the experimental arm to be in by aligning the other arm with it. From time to time in the course of a tracking task of the type already described above, vibration was applied to the tendon of the biceps or triceps muscle of the experimental arm with a small physiotherapy vibrator (Portable Massager: Hitachi Ltd.) oscillating at 100 Hz. During vibration the experimental arm was restrained from moving by the experimenter gently grasping the wrist.

In the third type of experiment "joint sense" was specifically tested. As movements of a joint will excite both joint receptors and receptors in the muscles which operate about the joint most proprioceptive testing procedures will not distinguish between the two. This has been thought to

present no problem in the past because muscles were believed to be insentient, but has become one now that they have been shown to be sentient (Goodwin *et al.*, 1972*a*, *b*, *c*). There is, fortunately, a convenient anatomical oddity which allows a joint to be tested for sensation originating solely in the joint receptors. If all the fingers of the hand are extended, and then the middle finger is maximally flexed at the first interphalangeal joint, no voluntary movement is possible at the terminal interphalangeal joint of that finger. This is because the flexor and extensor muscles which normally move the joint are held at lengths unsuitable for action because of their other attachments to the fixed, extended ring-finger (Gray, 1958). The joint is thus freed from effective muscular attachment in this posture, and if the finger is anæsthetized, loses position sense, which can be restored by extending the finger so as to allow the joint again to pull on flexor and extensor tendons (Goodwin *et al.*, 1972*b*, *c*).

Results

The two subjects N. G. and L. B. showed no apparent abnormalities in any of the tests. Both could align either arm with the experimentally moved opposite arm, and their accuracy in this was comparable with that achieved by normal subjects (Goodwin *et al.*, 1972*c*) (*see* figs. 1 and 2). Both could reliably detect an illusion of movement when either one of the muscles operating at the elbow-joint was vibrated, and could indicate this by moving the indicator arm in the appropriate direction—that is, in the direction the arm would move if the vibrated muscle were lengthening. This response is the same as that described by Goodwin *et al.* (1972*a*, *c*) for over 30 normal subjects. Both subjects here gave the response for vibration applied to either arm (*see* figs. 1 and 2).

On the test of joint sense both subjects could reliably detect movements imposed on the terminal interphalangeal joint of the middle finger held so as to dissociate the joint from muscular action as described. They could register their detection of these movements applied on either side by moving a finger of the opposite hand in the same direction at a comparable angular velocity. Displacements of as little as 5–10 degrees were reliably detected: the slowest movements imposed in this test were of the order of 5–10 degrees per second.

In all three tests, both subjects were able to describe accurately and reliably in words stimuli applied on either side of the body.

The third subject, R. Y., did not perform normally in any of the tests. The observation of Norrsell (1970) that a split-brain subject is unable to mimic with one arm the posture imposed on the other was made on this man, and was confirmed here. In all three tests of the present study there was great difficulty in holding this subject to the required task; for example, he would appear for some seconds to be aligning his indicator arm tolerably well with the moved arm in the test of elbow-joint position, but would then move both arms about at random. It is of interest that despite his failure to perform normally in the proprioceptive tasks he is capable of good motor co-ordination of both arms and hands. He can, for example, while engaged in conversation and without obvious visual attention, remove cigarettes from one pocket with one hand, and matches from another pocket with the other hand, and then go through the whole pattern of bilateral co-operative movements involved in lighting the cigarette.

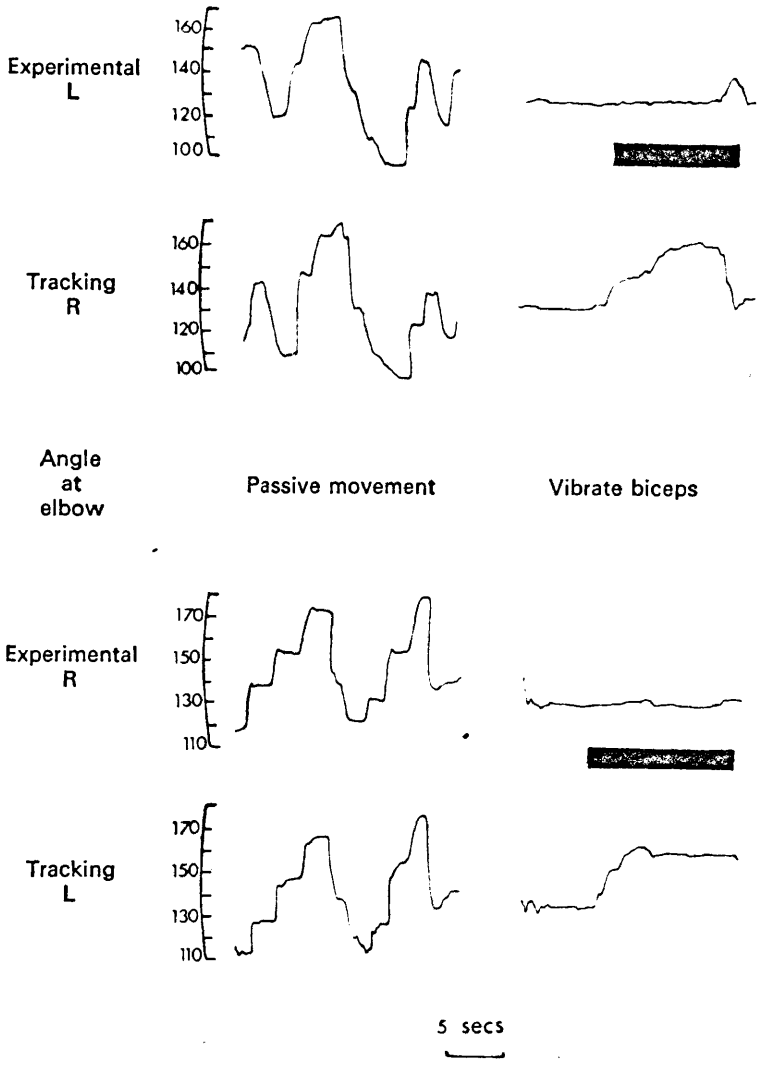

FIG. 1.—Subject N. G. Testing position sense, and "muscle sense," at the elbow-joint. The experimental arm is moved by the experimenter, or gently restrained from moving while the tendon of the biceps muscle is vibrated with a physiotherapy vibrator oscillating at 100 Hz. The blindfolded subject tries to keep the tracking arm in alignment with the experimental arm, so giving an objective estimate of the perceived position of the experimental arm. The angle at the elbow-joint is indicated: full extension is designated 180 degrees. The top of the figure shows the left elbow-joint tested, and the bottom of the figure shows the right tested. During passive movements of either joint by the experimenter, the subject can successfully align the tracking arm with the moved arm. During vibration of the tendon of the biceps of the experimental arm (the heavy marker bar indicates the duration of the vibration), the subject indicates that the elbow-joint is perceived to be extending by moving the tracking arm into extension throughout the period of vibration.

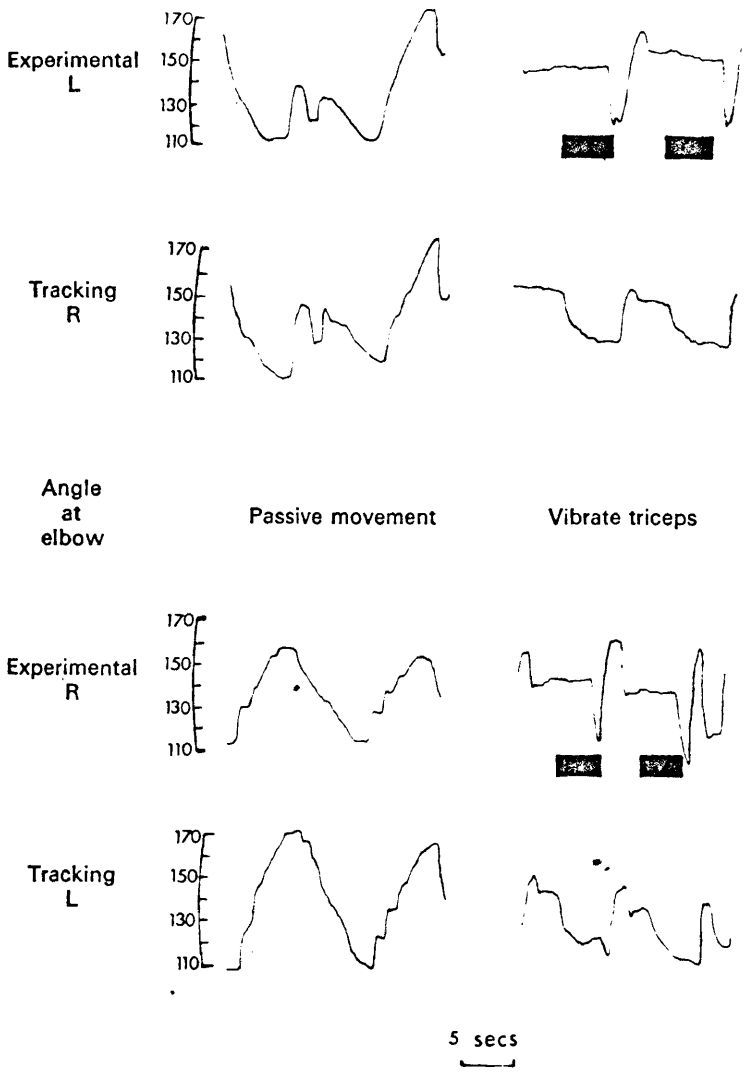

FIG. 2.—Subject L. B. Testing position sense, and "muscle sense," at the elbow-joint. The experimental arm is moved by the experimenter, or gently restrained from moving while the tendon of the triceps muscle is vibrated at 100 Hz. The blindfolded subject tries to keep the tracking arm in alignment with the experimental arm, so giving an objective estimate of the perceived position of the experimental arm. The angle at the elbow-joint is indicated: full extension is designated 180 degrees. The top of the figure shows the left elbow-joint tested, and the bottom of the figure shows the right tested. During passive movements of either joint by the experimenter, the subject can successfully align the tracking arm with the moved arm. During two periods of vibration of the tendon of the triceps of each arm tested (the heavy marker bar indicates the duration of the vibration), the subject indicates that the elbow-joint is perceived to be flexing by moving the tracking arm into flexion throughout the period of vibration; rapid movements of readjustment are made with both arms at the conclusion of each period of vibration.

Discussion

The testing procedures introduced in this study differ from the conventional clinical and physiological methods for testing position sense. The recent experiments of Goodwin *et al.* (1972*a*, *b*, *c*) have shown that position sense in man depends upon afferent information originating in both joints and muscles, and can no longer be regarded as dependent upon joint receptors alone. Thus, it has been necessary to devise separate tests for muscle sense and for joint sense. Unfortunately these two could not be tested here at the same joint, because the vibration, used in testing muscle sensation, spreads widely in the hand and affects antagonist muscles as well as the tested muscles, thus confusing the results; joint sense, as explained, can be tested only in the finger. It is possible, as noted by Goodwin *et al.* (1972*c*), that intramuscular receptors may provide separate lines of information to signal position and movement. The test of muscle sense used here gave predominantly a sensation of illusory *movement*, as was noted by Goodwin *et al.* (1972*a*, *c*), and as was reported in the verbal descriptions given by the subjects here.

These present experiments show that proprioceptive afferent signals from either arm or hand, whether originating in joint or muscle, were delivered to both hemispheres in two of the split-brain patients tested. As the third patient tested is known to have considerable brain damage other than his surgical lesion, it is reasonable to conclude that these two patients show more reliably the effects of dividing the neocortical commissures.

The anatomical implications of the present results are either that the proprioceptive afferents from joint and muscle have both ipsilateral and crossed projections to the cerebral hemispheres, or that commissural connexions at a level "lower" than the callosal are important for the bilateral distribution of unilateral signals.

Bilateral projection of the ascending afferents seems unlikely because there is no anatomical evidence for bilateral representation of proprioceptive afferents in somatosensory areas I or II (Mountcastle and Darian-Smith, 1968). Moreover, gross abnormalities of the sense of movement and the sense of position in the opposite extremities occur upon removal of the postcentral gyrus in man (Penfield and Rasmussen, 1950), and in the monkey (Ettlinger and Kalsbeck, 1962). This suggests that proprioceptive afferents capable of subserving normal kinæsthesia do not project from the affected contralateral limbs to the normal ipsilateral cortex.

Commissural connexions at levels below the neocortical commissures seem more likely to have been the mechanisms responsible for the normal behaviour of the two subjects tested here. Because their surgery had been done some years before the present tests, it is possible that they had learned in the intervening years to use pathways normally of secondary importance. Jones and Powell (1968), however, in anatomical studies in the monkey were unable to find corticocallosal connexions of hand and foot areas, although such connexions were found between areas of representation of more proximal parts, so that an anatomical demonstration of complete higher transfer pathways is lacking.

In so far as these same patients have some abnormalities of left–right integration and performance involving posture-matching, stereognosis, and even motor co-ordination, it now seems that their deficits are of functions other than the bilateral distribution of proprioceptive afferent signals. It is possible that simple movements at single joints could be bilaterally "represented" cortically, with analysis or transfer across the mid-line at a subcortical level, while postures of hand or limb, which involve complex perceptions of the relation of the parts to one another and to the "body image," might be non-transferable across the mid-line if the neocortical commissures are divided. Alternatively, as the tests employed here were only partly quantitative, it could be that some deficits could occur as a result of the compounding of several small errors in qualitatively normal sensory processes.

Summary

Surgical division of the neocortical commissures in man produces abnormalities of some sensory and motor functions involving left and right sides of the body. Some of these functions have a dependence upon proprioceptive afferent input, and it seemed possible that division of the commissures prevents normal distribution of unilateral signals to both hemispheres. The experiments described here show that in two split-brain patients simple proprioceptive information given in the arm or hand of one side was apparently normally distributed to both hemispheres.

Proprioceptive testing is discussed in view of the recent reports that intramuscular receptors can contribute to position sense. The tests employed and described here were a test of movement and position at the elbow-joint, a specific test of muscular kinæsthetic sense at the elbow-joint, and a specific test of joint sense in the terminal interphalangeal joint of the middle finger.

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Position sense following surgical removal of joints in man

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Until very recently it was widely believed by physiologists that muscles are insentient. This view had experimental support from two lines of investigation. In 1960, Brindley and Merton[1] had extended and refined the observations made a century before by Helmholtz and, like Helmholtz, had concluded that signals from stretch receptors in the extrinsic muscles of the eye have no influence upon the conscious perception of the direction of the gaze. At about the same time other experiments, in which joints were moved while the joints themselves and their overlying skin were selectively anaesthetised, were taken to show that stretch receptors in limb muscles also give no consciously perceived signals[2,3,7–9]. Both these lines of experimentation have very recently been re-examined and have produced the contrary evidence that both limb and eye muscles can provide perceived signals[4,5,10].

In their study of limb muscles, Goodwin *et al.*[4,5] anaesthetised the skin and joints of a finger or of the whole hand while leaving the principal flexor and extensor muscles of the fingers unaffected. Their blindfolded subjects were then able to detect when the affected joints were moved. This indicated that discharges from receptors in the muscles were perceived. However, these subjects did not have normal position sense as quite gross displacements were required to evoke kinesthetic sensations. This may have been because muscle receptors subserve merely crude proprioception. Alternatively, widespread peripheral anaesthesia may have removed a normal source of central facilitation of synapses acted upon by the proprioceptive muscle afferents, or of fusimotor neurones. In support of this alternative view is the observation that anoxia of the hand can interfere with the stretch reflex of the long flexor muscle of the thumb, even though the muscle itself has not been interfered with[6].

It is difficult to devise an experiment in which joint afferents can be selectively anaesthetised without causing an accompanying widespread cutaneous anaesthesia. There are, however, certain surgical procedures carried out in man in which whole joints are removed, sometimes being replaced by prostheses. After these procedures there is usually no cutaneous anaesthesia. Surgeons have long known that apparently normal function and position sense remain post-operatively, and this clinical experience was noted, with respect to the hip-joint, by Goodwin *et al.*[5].

We have looked, in 6 patients, at position sense in joints in which surgical

removal of the bony joint had been carried out. Two patients had prosthetic replacements of the metacarpophalangeal joints of all the fingers on both hands, of the type described by Swanson[11,12]. In this surgery each metacarpal head had been entirely removed, the joint capsule cut, released and removed, the synovia resected as far as possible, and the base of each proximal phalanx completely drilled out: simple flexible silicone rubber implants replaced the joints. Three patients had undergone Keller's operation[13] on the metatarsophalangeal joint of the great toe. This operation involved removal of the proximal two-thirds of the proximal phalanx and a portion of the metatarsal head following division and removal of the joint capsule. One further patient had undergone a variation of Keller's operation in which similar surgery was done on the second toe following, in addition, disconnexion of the intrinsic foot muscles from the toe.

All of the joints tested showed normal position sense for flexion or extension. Simple clinical testing procedures were used. The finger or toe to be tested was grasped lightly by its sides and gently moved, and the patients, with vision excluded, were required to state the direction of the imposed movement as soon as they knew it. Care was taken to avoid giving accessory cutaneous clues. In order to gain some quantitative assessment of the kinesthetic sensations, movements were imposed manually at measured angular velocities and the angular displacements detected were noted. All patients could reliably detect movements of 10° when these were applied at 2–3°/sec or faster, and could do this whether or not they were tensing their muscles. This kinesthetic sensitivity contrasts with the poor[4,5] or even apparently absent[2,3,7–9] sensitivity at joints made anaesthetic together with their overlying skin.

It is possible that, despite our precautions, cutaneous signals from the site where the finger or toe was grasped, or from slight stretching of the skin overlying the tested joints, aided subjects in detecting displacements. Alternatively, it is possible that the intact cutaneous afferents here enabled a normal central facilitation of fusimotor neurones or of synapses acted upon by muscle afferents.

Our observations suggest that good kinesthetic sensation remains in the absence of joint receptors. These experiments are, however, open to the criticism that some joint receptors may have remained intact even after extensive disruptive surgery, or may have regenerated post-operatively. We concede that this could be so. However, we can report that we tested some of our subjects as little as 1 week after surgery, before regeneration could have occurred, and found normal position sense. Also, in the patient who had undergone the metatarsophalangeal joint resection of the second toe, we found that normal kinesthetic sensation for flexion and extension remained 1 week post-operatively, although the patient could not detect gross displacements of the same joint from side to side. Since the intrinsic muscles of the foot which would usually be stretched by such lateral movements were disconnected from the moved toe, this observation provides evidence that neither cutaneous receptors nor any remaining joint receptors contributed to perception in this patient.

These observations are reported so as to set before physiologists what has been known to some surgeons for some time, and are relevant to the current re-assessment of the role played by intramuscular receptors in kinesthesia. In no way do they

weaken the conclusion of Goodwin *et al.*[5] that muscle afferents are likely to provide a major contribution to normal position sense.

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DIFFERENCES BETWEEN THE SENSES OF MOVEMENT AND POSITION SHOWN BY THE EFFECTS OF LOADING AND VIBRATION OF MUSCLES IN MAN

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SUMMARY

Recent experiments have shown that if a muscle is vibrated at 100 Hz with a physiotherapy vibrator, then the joint about which that muscle operates is perceived to be moving as if the vibrated muscle were lengthening. Also, the position of the joint at any moment is perceived to be as if the vibrated muscle were stretched. Here, these distortions of sensation were investigated further at the elbow joint. The velocity of the illusory movement induced by vibration is slowed in proportion to the load borne by tensing the vibrated muscle, and at any load the velocity is slower if the muscle is fatigued. The error of position is increased by loading the vibrated muscle. Vibration of lower frequency but greater amplitude can induce errors of position without inducing illusions of movement. It is argued that separate lines of information can arise in muscle to signal positions and movements.

INTRODUCTION

Recent experiments have shown that signals from receptors in muscle can contribute to position sense or kinaesthesia. These experiments were of two types. First, it was shown that appreciable kinaesthesia persists in joints of the fingers and thumb after the joints themselves are anaesthetized, but the afferents from the remote flexor and extensor muscles which move those joints are preserved[6,9]. Second, kinaesthetic illusions arising from the stimulation of intramuscular receptors by vibration were described[7–9].

Which intramuscular receptors serve position sense is not known. From their experiments using muscle vibration Goodwin *et al.*[7–9] argued that the muscle spindle primary afferents are involved. They used a small physiotherapy vibrator oscillating at

100 Hz, applied to the skin overlying muscle tendons, and produced in their subjects proprioceptive illusions in the joints at which the vibrated muscles operate. These were principally illusions of *movement*, the illusory movement being in a direction as if the vibrated muscle were being stretched. Because similar vibration is known from animal experiments to be a powerful stimulus to the primary endings of the muscle spindles[2], and because muscle vibration in man causes an involuntary tonic reflex contraction generally attributed to excitation of the spindle primaries[4,10], Goodwin *et al.* suggested that the vibration-induced illusions of movement they described were due to excitation of these endings. However, primary afferents discharge in the course of normal voluntary muscular activity[15] and no proprioceptive illusions result. Thus, Goodwin *et al.* were led to postulate further that only those discharges from the spindle primaries that are inappropriate for the intended muscular contraction are perceived. In support of this view they reported that the illusion of extension of the elbow joint which usually occurred when the biceps brachii was vibrated could be abolished if the vibration was applied while the biceps was contracting isometrically to exert a large tension. The discharge rate of the muscle spindle primaries is increased when a muscle exerts an increased tension[15], and this increased discharge is appropriate for the intended contraction. Vibration presumably will have little effect on the frequency of firing if this is already high[13]. Thus, vibration of a muscle which is sustaining an increased tension will not cause as much inappropriate discharge of the spindle primary endings as will vibration of an unloaded muscle.

While the predominant effect of vibration is to produce an illusion of *movement* such as would occur if the vibrated muscle were lengthening continuously, there is also an illusion of false *position* associated with vibration. A joint is perceived to be in a position it would take up if the vibrated muscle were stretched[8,9]. It is possible that illusions of false positions arise from the mathematical integration of signals of velocity. Alternatively, separate lines of information on movement and position may originate in muscle. Goodwin *et al.* recognised these two possibilities, but could not distinguish between them.

The present study extends the approach of Goodwin *et al.*[6–9]. The distortions of position sense produced in normal human subjects by loading and by vibration are more completely described. Vibration of muscles with a physiotherapy massager at 100 Hz, as described by Goodwin *et al.*, was used here. In some experiments a grosser form of vibration with greater amplitude and lower frequency was also used in an attempt to activate a greater variety of intramuscular receptor types. The results indicate that separate lines of information for movement and for position exist.

METHODS

Experiments were done on normal male and female subjects. None was aware of the various hypotheses being tested.

Two separate types of experiment were done: one was concerned principally with sensations of movement, the other with the sense of position.

Movement

During vibration of the biceps brachii there occurs an illusion that the elbow joint is moving into extension[7–9]. In the present experiments subjects were asked to give an objective measure of the angular velocity of this illusory movement in the following way. They were blindfolded, and sat with their elbows resting on a support before them and their forearms free to move in a vertical plane. The tendon of the biceps of one arm, designated the experimental arm, was vibrated, and that arm was gently restrained by the experimenter from flexing under the involuntary tonic vibration reflex. The subject was instructed to attend to the velocity of the illusory movement, and then to duplicate this velocity with a voluntary movement of the opposite arm, designated the indicator arm. Subjects were given a short period of training (about 5–10 min) to accustom themselves to the sensations produced by vibration, and to the paradoxical situation in which illusions of movement were experienced of a joint known to be still.

The subjects were required to indicate the angular velocity of the illusory movement during progressive loading of the vibrated biceps. For this, the elbows of both arms were flexed to about 40° from full extension, and loads were added to a bucket suspended over a pulley and supported from a band around the wrist of the experimental arm. Loads were added in increments of 3 lb. The subjects were required to support the loads for no longer than 30 sec at a time, and recovery periods were allowed between observations so as to prevent fatigue in the tested muscle. At the conclusion of these observations the effects of fatiguing the tested muscle were observed. For this, the subjects were required to support a heavy weight (say, 18 lb) in the load bucket for some minutes until they judged that the biceps was considerably fatigued. Then, a series of observations on the velocity of the vibration-induced illusory movement was made while the muscle was unloaded in steps of 3 lb, but without recovery periods in between, so that a state of fatigue was maintained in the test muscle.

For all the above experiments a string was attached to the wrist of the indicator arm and passed to a light lever which turned a potentiometer. This enabled recording of movement at the elbow joint. Vibration was applied with a 'Vibratory Massager' (Pifco Ltd.), oscillating at 100 Hz, with an amplitude of about 1 mm.

Position

Position sense was tested at the elbow joint. Subjects again were blindfolded and sat with their elbows supported before them on a table, and with their forearms free to move in a vertical plane. A perspex screen, marked out in degrees at the elbow, was placed between the arms. One arm, designated the experimental arm, was moved by the experimenter so that the tip of its index finger came to a chosen position on the screen. Ten seconds later the subject was instructed to touch his fingertips together, whereupon he would move his indicator arm by flexing its elbow, and attempt to touch the tips of his index fingers together. Subjects were allowed to take as long over this alignment as they pleased, and there was no question of their having to move into the final position in a single action. The elbow angle chosen by the subject for the

indicator arm was noted. Both fingertips were marked with a fine lengthwise line to allow accurate positioning by the experimenter and noting of the chosen angle against the screen. Usually both arms lay horizontally on the table between trials. Subjects were told that a range of positions for testing would be used between about 20° and 60° into flexion from this horizontal rest position: in fact, only one central position, usually 40°–50° from the rest position, was tested. This central position was chosen to avoid certain accessory clues available nearer full flexion or extension (*e.g.* the weight of the arm, or the distances moved to return both arms to the rest position). Moreover, it was not possible to apply the vibrator to the biceps tendon of an excessively flexed arm. Subjects were not disturbed if successive positions tested were apparently different, because they expected a range of positions to be used.

Each experiment involved a variety of interventions. These were: (1) loading of the experimental arm with weights suspended over a pulley, as described for the movement tests; (2) vibration of the tendon of the biceps of the experimental arm at 100 Hz with the physiotherapy vibrator, also described above; (3) vibration of the tendon of biceps on the experimental side with a padded plunger on a jig-saw attachment of an ordinary workshop electric drill; and (4) combinations of loading and vibration. After a control trial, each intervention under test was used in turn, and then the whole series was repeated until 10 trials of each type were completed.

The vibration with the jig-saw was of a greater amplitude and a lower frequency than that with the physiotherapy massager. The amplitude of the jig-saw's vibration was about 1.5 cm, although when held by the experimenter so as to vibrate the muscle only part of this excursion (perhaps 0.5 cm) was made in contact with the muscle. Thus it delivered more a series of small blows to the muscle tendon than a pure sinusoidal deformation. The frequency of the jig-saw could be varied from 48 Hz to about 2–3 Hz by adjusting the power supplied to it through a variable voltage power supply.

When loads were used the subject lifted the load (either 12 or 15 lb) from the rest position to the point to which the experimenter guided his hand, and held it there until the trial was over: on return to the rest position the arm was unloaded. Vibration was applied to the tendon of the biceps just before the experimental arm was guided to the screen, and remained throughout the trial. At the conclusion of all trials the experimenter guided the experimental arm back to the rest position and the subject was instructed to flex the indicator arm slightly before resting it: this procedure helped obscure any differences in alignment that may have become apparent to a subject detecting differences in the distances travelled by the two arms in returning to the rest position.

RESULTS

Movement

(a) Loading. Fourteen subjects were tested in experiments in which they were required to match the angular velocity of vibration-induced illusory movements. All were able to perceive the illusions, but 5 of them were unable to do this reliably on

every application of vibration. The results reported, therefore, are those obtained on the 9 subjects who had no difficulty in perceiving the illusions in the paradoxical situation of the experiment in which the joint was known to be still.

In all 9 subjects, loading the experimental arm caused the illusory movement to be slowed (see Fig. 1). For all 9 subjects the correlation coefficients between velocity and load showed highly significant negative correlations ($P < 0.001$ by Student's t-test). There was, however, a wide variation between subjects, in the velocities perceived and in the slopes of the velocity–load relationships. Straight lines were fitted for the data from each subject by the least squares method. Perceived angular velocities for unloaded muscle ranged from 7 to 30°/sec, the slopes of the velocity–load lines ranged from —0.45 to —3.1°/sec/lb.

(b) Fatigue. The method used to produce muscular fatigue was simple but depended upon the subjects' own assessments of the extent of the fatigue. Consequently, some subjects were tested in a greatly fatigued state, and some were considerably less fatigued. Moreover, observations were made while the fatiguing process continued. Thus, there was considerable scatter in the observations.

In 6 of the 9 subjects, however, fatigue caused a significant slowing of the

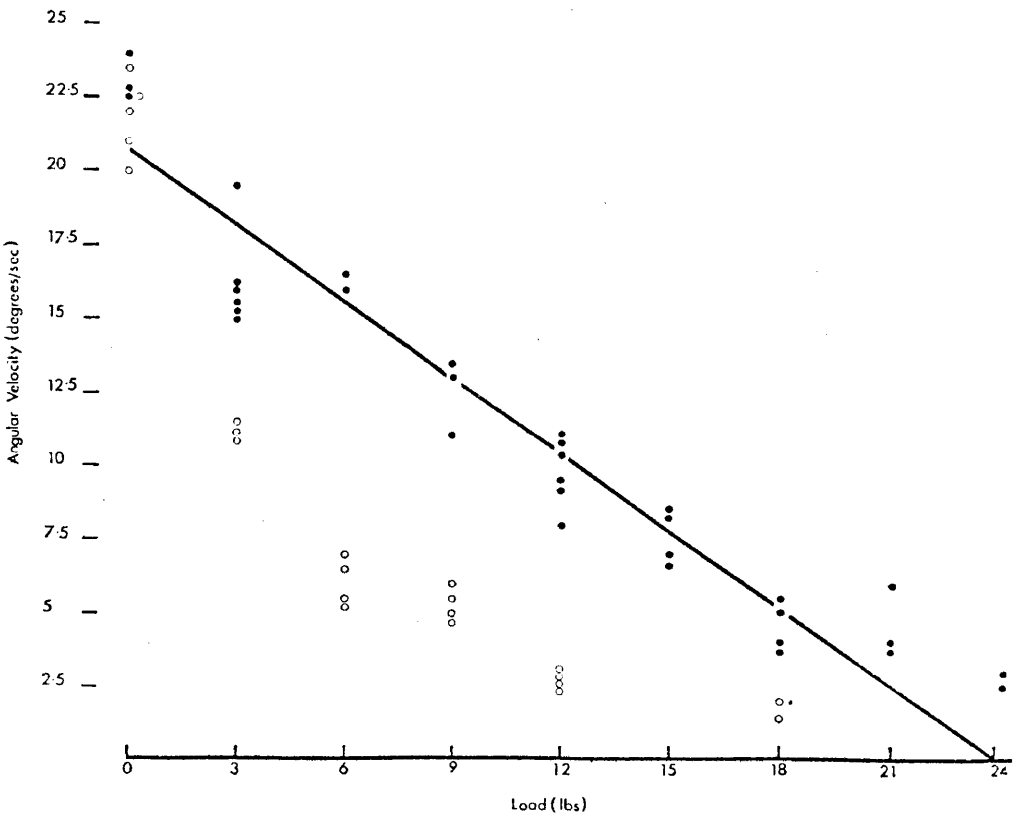

Fig. 1. The angular velocity of the illusory movement of the elbow joint into extension, induced by vibration of biceps brachii at 100 Hz, is plotted against the load at the wrist borne by tensing biceps. The closed circles show the control points, and the line drawn is the line of best fit drawn by the least squares method. The open circles are points obtained when biceps was fatigued through a prolonged period of weight-bearing.

angular velocity of the illusory movements at all added loads. The test of significance was simply that all the points collected during loading in fatigue fell below a line displaced two standard errors of the estimate below the line of best fit drawn through the previously collected velocity–load points (95% of points in the unfatigued velocity–load category would be expected to fall above this line). Fig. 1 shows the results obtained in one subject. Although it appears from Fig. 1 that during fatigue the velocity–load points themselves fall upon a straight line of negative slope, this was not so in all subjects, possibly because of the changing state of fatigue throughout the experiment.

Position

Twenty subjects were used in these experiments. All were normal young adults. Not all the manoeuvres were tried on all subjects. There was considerable variation in the accuracy of these subjects in judging the elbow angle required to bring their fingertips together in the tests described. The positions chosen by different subjects when no intervention was used ranged from 7.5° too flexed, to 7° too extended (means of 10 trials). Consequently, the effects of loading and vibration are described with reference to the control position in each subject individually.

(a) Loading. Loading a muscle causes a subject to believe that the joint is in the position it would take up if the loaded muscle were extended. The results of loading the biceps in 15 subjects are shown in Table I. Similar effects were produced in 5 subjects upon loading triceps, except that this caused subjects to believe the arm to be too flexed rather than too extended as with biceps loading.

There was no apparent difference in the effects produced by loading when the subject was required to support a load throughout a series of observations so as to cause progressive fatigue in the loaded muscle, and when he supported the load only during a trial, resting between trials. This is shown for one subject in Fig. 2. Five other subjects gave similar results.

(b) Vibration at 100 Hz. Vibration with a physiotherapy massaging device at 100 Hz caused subjects to believe that a vibrated muscle was more extended than it was. The results for subjects in whom biceps was vibrated are shown in Table I. Similarly significant errors in the opposite direction were found in 4 subjects in whom the triceps was vibrated.

In further trials on 10 subjects different durations of vibration were used. These subjects were required to attempt to approximate their fingertips in separate trials at 5 or 10 sec after the experimental arm had been positioned and the vibration begun. In all 10 subjects the vibration produced significant errors of the kind described above. In none of the subjects was there a significant difference between the error made after 5 sec vibration and that made after 10 sec vibration.

(c) Loading and vibration (100 Hz). When the biceps was both loaded and vibrated a subject believed that the arm was more extended than it was. Moreover, the errors induced by loading and vibrating together were greater than those induced by vibration alone (see Table I).

There was one notable exception to this. One subject had a particularly strong

TABLE I

POSITION SENSE AT THE RIGHT ELBOW JOINT, TESTED AT 50° FROM FULL EXTENSION

Positions are shown for the elbow angles chosen for the indicator arm in attempted matches. Angles are shown in degrees (± standard error of mean for 10 trials) of error from a true match. Errors in extension are shown as positive, errors in flexion are negative. Angular velocity (mean of 5 trials) of illusion of movement induced by vibration is shown for some subjects. Significance levels come from *t*-tests. n.s. = not significant. Note that one subject, marked with an asterisk, gave results different from the others (see text).

Subject	*Control (°)*	*Load biceps (°)*	*Load vs. control (P <)*	*Vibrate biceps at 100 Hz (°)*	*Vibration vs. control (P <)*	*Angular velocity (°/sec)*	*Vibration + load (°)*	*Vibration + load vs. vibration (P <)*
C.G.	−0.8 ± 0.30	+1.6 ± 0.56	0.01	+6.0 ± 1.02	0.001	2.5	+ 4.9 ± 1.17	n.s.
P.E.	−4.5 ± 0.50	+0.9 ± 0.60	0.001	+0.9 ± 0.37	0.001	1.5	+ 7.7 ± 0.87	0.001
I.N.	−0.1 ± 0.60	+6.6 ± 1.15	0.001	+8.8 ± 0.89	0.001	6.5	+12.9 ± 0.54	0.001
P.C.	−0.4 ± 0.51	+4.3 ± 0.14	0.001	+3.1 ± 1.30	0.01	3.0	+10.9 ± 0.91	0.001
M.S.	−3.3 ± 0.44	+1.6 ± 0.50	0.001	−1.0 ± 0.46	0.01	8.5	+ 3.6 ± 0.37	0.001
J.C.	−7.5 ± 0.67	+0.3 ± 0.67	0.001	+6.4 ± 0.68	0.001	12.5	+11.9 ± 0.34	0.001
E.M.	−3.8 ± 0.67	+5.0 ± 1.22	0.001	+5.2 ± 1.41	0.001	10.0	+ 7.8 ± 1.26	n.s.
R.M.	+0.7 ± 0.46	+1.9 ± 0.72	n.s.	+3.3 ± 0.90	0.01	4.0	+ 6.6 ± 0.56	0.01
A.L.	−5.4 ± 0.63	+0.6 ± 0.40	0.001	+4.3 ± 0.51	0.001	22.5	+ 4.7 ± 1.03	n.s.
J.M.	−2.7 ± 0.47	+0.5 ± 0.22	0.001	+4.8 ± 0.78	0.001	35.0	+ 3.7 ± 0.65	n.s.
I.C.	−2.7 ± 0.64	+0.7 ± 0.52	n.s.	+0.2 ± 0.55	n.s.	1.0	+ 7.0 ± 0.48	0.001
R.H.	+2.3 ± 0.72	+5.3 ± 0.32	0.001	+2.1 ± 0.45	n.s.	—	+ 5.8 ± 0.37	0.001
M.P.	+1.9 ± 0.72	+3.4 ± 0.89	n.s.	+4.0 ± 0.78	0.05	—	+ 7.9 ± 0.41	0.001
R.B.	0.0 ± 0.64	+1.4 ± 0.92	n.s.	+3.2 ± 0.32	0.001	—	+ 5.8 ± 0.24	0.001
M.J.*	+1.2 ± 0.64	+3.4 ± 0.98	n.s.	+23.6 ± 1.54	0.001	18.5	+ 6.1 ± 0.98	0.001

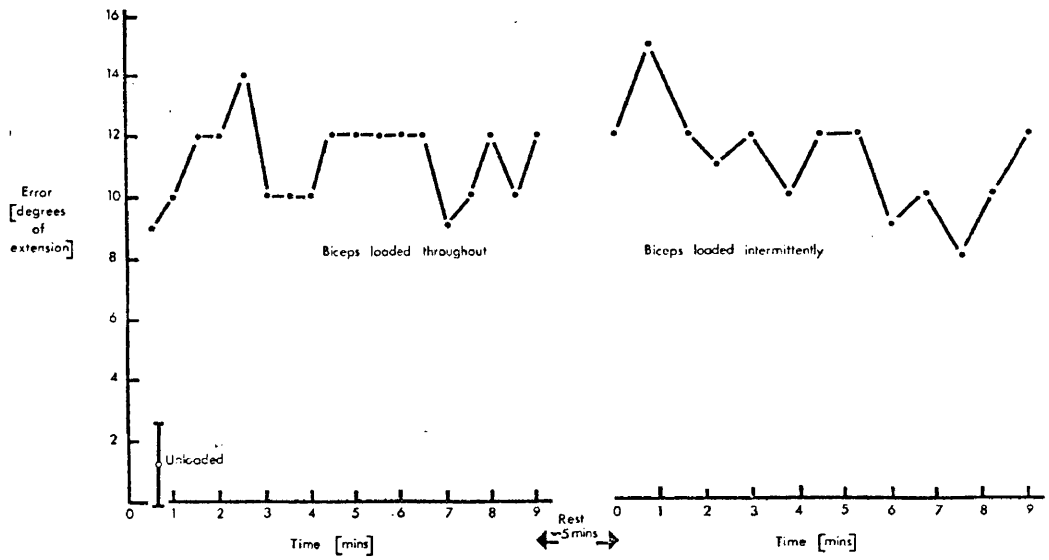

Fig. 2. The error of the estimate of position of the partly flexed elbow joint, in degrees of extension, is plotted against time. On the left of the figure the estimates were made while the biceps of the experimental arm was tensed throughout to support a load of 12 lb applied at the wrist: this caused subjective fatigue, and the subject could not support the load beyond the period shown. On the right of the figure the estimates were made, after an intervening rest period, over a period similar to that used in the first series, but in this series the subject supported the load only intermittently and rested between estimates. At bottom left is shown the subject's control estimate of the position of the unloaded elbow joint (mean of 10 trials $\pm$ 2 S.E.M.).

illusion of movement in response to vibration at 100 Hz. This subject continued to experience this illusion undiminished when the finger of the experimental arm was placed against the perspex screen, although other subjects found the movement illusion much less intrusive once the experimental arm was so evidently anchored. This single subject, marked with an asterisk in Table I, made significantly smaller errors of position when the vibrated arm was both loaded and vibrated, than when it was simply vibrated.

(d) Lower frequency vibration. Vibration with the jig-saw, like vibration with the physiotherapy massager, caused subjects to believe that their elbows were positioned such that the vibrated muscle, whether biceps or triceps, was stretched.

Usually, the jig-saw vibrator, with a frequency of oscillation only half that of the physiotherapy vibrator, caused illusions of movement. These were detected by a procedure similar to the movement tests described above. A subject was asked to keep forearms aligned and then the biceps of the experimental arm was vibrated but restrained from moving. An illusion was shown to be present when the subject moved the indicator arm into extension. By varying the voltage supply to the jig-saw it was possible to slow the frequency of its oscillation. This was done in a series of steps, until application of the slowed vibration no longer caused an illusion of movement. The criterion for this was that the subject did not move the indicator arm into extension on 10 successive trials of vibration.

When a muscle was vibrated at a frequency at which no illusion of movement

TABLE II

POSITION SENSE AT THE RIGHT ELBOW JOINT, TESTED AT 50° FROM FULL EXTENSION

Positions are shown for the elbow angles chosen for the indicator arm in attempted matches. Angles are shown in degrees (± standard error of mean for 10 trials) of error from true match. Errors in extension are shown as positive, errors in flexion are negative. The frequency of jig-saw vibration just low enough to cause no perceived illusion of movement is shown. Significance levels were obtained by *t*-tests. n.s. = not significant.

Subject	*Control (°)*	*Biceps vibration at 100 Hz (°)*	*Biceps vibration with jig-saw (°)*	*Frequency of jig-saw (Hz)*	*Jig-saw vs. control (P <)*	*Jig-saw vs. vibration at 100 Hz (P <)*	*Jig-saw vibration + load (°)*	*(Jig-saw + load) vs. jig-saw (P <)*
P.E.	+1.1 ± 0.62	+ 4.1 ± 0.64	+ 6.9 ± 0.80	35	0.001	0.01	+ 4.2 ± 0.81	0.05
I.C.	—2.7 ± 0.64	+ 0.2 ± 0.55	+ 6.7 ± 0.83	35	0.001	0.001	+ 7.0 ± 0.48	n.s.
M.P.	+0.9 ± 0.68	+ 3.8 ± 0.62	+11.7 ± 0.64	30	0.001	0.001	+ 5.4 ± 0.51	0.001
R.B.	0.0 ± 0.64	+ 3.2 ± 0.32	+11.4 ± 1.20	30	0.001	0.001	+ 5.8 ± 0.69	0.001
R.H.	+2.3 ± 0.72	+ 2.1 ± 0.45	+10.1 ± 1.17	35	0.001	0.001	+ 6.2 ± 0.72	0.01
S.G.	+7.0 ± 0.90	+ 8.9 ± 0.74	+12.0 ± 0.84	25	0.001	0.01	+13.2 ± 0.84	n.s.
M.S.	—4.0 ± 0.76	— 0.7 ± 0.60	+ 2.2 ± 0.56	30	0.001	0.001	+ 1.8 ± 0.64	n.s.
J.R.	+2.2 ± 0.67	+ 7.0 ± 0.98	+ 5.4 ± 1.24	20	n.s.	n.s.	—	—
J.M.	—3.2 ± 0.52	+ 1.6 ± 0.68	+ 9.7 ± 0.83	30	0.001	0.001	+ 4.6 ± 0.72	0.001
I.N.	—1.2 ± 0.42	+ 5.6 ± 0.76	+16.1 ± 0.83	35	0.001	0.001	+11.0 ± 0.88	0.001
T.H.	+3.4 ± 1.04	+14.8 ± 0.75	+12.7 ± 0.97	30	0.001	n.s.	+11.2 ± 0.76	n.s.

was perceived, subjects believed that the joint was in a position such as it would take up if the vibrated muscle were stretched. This was true for vibration of biceps or triceps. Moreover, the error of position made during this low-frequency vibration was usually greater than the error made by the same subject when 100 Hz vibration was used (see Table II). Alternatively, the lower frequency jig-saw vibration could be chosen to give a movement illusion of a velocity comparable to that induced by the 100 Hz physiotherapy vibrator: when this was done the error of position made greatly exceeded the error induced by the 100 Hz vibration. This alternative method was sometimes difficult to use because the movement illusions induced by the jig-saw vibration, even at the maximum frequency attainable with it (48 Hz), were slower than those induced by the 100 Hz physiotherapy vibrator.

(e) Lower frequency vibration plus loading. It has been described above that vibration at 100 Hz causes subjects to make greater errors of position when it is applied to a loaded muscle than when it is applied to an unloaded muscle. A similar effect was not usually found when lower frequency vibration, which caused no movement illusions, was used. Loading either reduced the errors of position, or had no significant effect upon them (see Table II).

DISCUSSION

The present experiments support and extend the work of Goodwin *et al.*[6–9] on the contribution of intramuscular receptors to position sense, or kinaesthesia.

Goodwin *et al.* described illusions of movement induced by vibration of muscles at 100 Hz. The experiments described here provide evidence that the illusions of position, also described by Goodwin *et al.*, do not simply result from mathematical integration by the central nervous system of discharges signalling movement. First, illusory movements induced by vibration are usually too fast for their simple integration to result in position errors of the size of those found here. Second, there is no demonstrable difference in the errors of position which result from applying vibration to a muscle for 5 and 10 sec. Third, loading a muscle slows the illusory movement but increases the vibration-induced error of position. And, fourth, a lower frequency of vibration with increased amplitude can be chosen which will give no perceived illusions of movement, although it will still cause errors of position.

It follows from the considerations above that signals of position can arise which exist apart from any which arise from integration of velocity signals — that is, that separate lines of information are available for signalling position and movement. It remains possible that some integration of movement signals is also sometimes used in the final computation of position, although its influence was over-ridden here. This is, for example, suggested by the exceptional result found in the one subject in whom loading a muscle reduced the position error induced by vibration. Apart from this, in the conditions of the present study, integrations of movement signals were less effective than separate signals more specifically concerning position.

By asking subjects to match the angular velocity of vibration-induced illusory movements, it was possible in this study to avoid a problem experienced by Goodwin

et al.[9]. They observed the effects of muscle vibration in subjects given specifically a position matching task. Thus, many of their subjects became confused, and hesitated, when they followed a movement illusion into a position which other signals indicated was false. In contrast, subjects in this study were prepared, and in fact expected, to misalign their arms when matching the illusory movement in one with a real movement of the other. While this made it easier to observe properties of the illusory movements, some subjects had difficulty perceiving the illusions reliably enough to do this form of test. All, however, did perceive illusions in most trials. Such difficulty is not unexpected in subjects meeting stimuli given in an unusual way: for example, many untrained subjects have difficulty in making reliable observations on visual after-images. It is not surprising that a wide range of velocity–load relations were found in the different subjects. The mechanical state of the vibrated muscle, the amplitude of vibration actually transmitted through the muscle, and the state of fusimotor facilitation are all factors likely to vary widely from subject to subject.

Loading a muscle reduced the angular velocity of the illusory movement induced by vibration. This fits well with the observations of Goodwin *et al.*[9] that in a heavily loaded muscle the illusion may be abolished. Further, as pointed out by Goodwin *et al.*, this provides evidence that intramuscular receptors are responsible for the illusory sensations, since only these should have been so markedly affected by the strength of contraction. It also supports their idea that one perceives only that part of the discharge of the intramuscular receptors which would not usually be present at a given level of contraction. This idea is explained more fully above in the Introduction. They noted, however, that 'similar considerations would apply if the tendon organ were to be responsible for the illusion so this particular observation does not of itself discriminate them and spindles as the causative receptor'. Since there is no reason to expect changes in overall tendon organ activation during the increased efforts required in fatigue, the significant changes in the movement illusion seen in fatigue suggest that tendon organs are not the receptors responsible for the illusion.

Cohen[3] showed that muscular loading led to greater than usual errors in reproducing positions of the shoulder joint, but these errors were not of a systematic nature. Here, loading was shown to cause subjects to believe that the joint has moved in the direction of loading. This might be caused by the discharge of stretch or tension receptors within the loaded muscle. However, such discharges, being 'appropriate' for the contractions performed, would not, on the arguments outlined above, be expected to contribute to position sense. In favour of this is the observation that progressive fatigue of a loaded muscle does not systematically alter the estimate of the position of its joint (Fig. 2), although it is likely that the discharge from muscle spindles would increase throughout the fatigue. Other intramuscular stretch or tension receptors may be involved, or it might be that a consistent error is made by the nervous system in computing the appropriateness of spindle discharge at any load. Another possibility is that the errors arise when muscles pull upon joint receptors so as to alter their discharge rates at any given position: it is known from animal experiments that muscular action can produce such effects[12,14].

Vibration at 100 Hz with a physiotherapy massager produces position errors,

as described by Goodwin *et al.*[8,9]. Similar effects have been described by Eklund[5] at the knee joint. In all but one subject, vibration applied to a loaded muscle caused significantly larger errors of position than it did with an unloaded muscle. It is not clear, however, why the errors of position induced by vibration should be increased by loading. Possibly the vibration is transmitted better mechanically through a contracted muscle; or perhaps it is more effective in this state upon a second type of receptor, not responsible for the illusions of movement.

Lower frequency vibration, although producing no movement illusions, was quite effective in producing errors of position. This is further evidence that position is not indicated by the integration of movement signals. This gross form of interference has had no equivalent in animal studies. The experiments of Bianconi and Van der Meulen[1] showed that transverse vibration of a muscle belly in the cat excited both muscle spindle primary and secondary endings. The jig-saw vibration was used here in an attempt to excite a greater variety of intramuscular receptor types, and it is probable that both muscle spindle primary and secondary endings were excited here, together with tendon organ receptors, and other receptors within the muscle, tendons or joints. Any of these receptors might have been responsible for the position errors which persisted when no movement illusions were perceived. If the important difference in the present experiments was that the vibration at 100 Hz selectively excited muscle spindle primary afferents, whereas the grosser vibration excited both spindle primaries and secondaries, then the following observation may be relevant. Jansen and Matthews[11] have pointed out that 'while the primary ending signals both the length and rate of change of length of the muscle, the secondary ending signals mainly length with a sensitivity not very different from that of the primary ending. Thus the difference in the frequency of discharge of the two kinds of ending approximately signals the rate of change of length of the muscle'.

It appears from the present study that subjective judgements of the static positions of joints and judgements of movements of joints can use different lines of information. It is suggested that the term 'position sense' be reserved for the static judgements, and 'kinaesthesia' for the dynamic ones, and that the two terms should not be regarded as synonymous.

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Estimation of Weights and Tensions and Apparent Involvement of a "Sense of Effort"

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Normal subjects judged weights and tensions in situations where movement was restricted. Weights supported by fatigued muscles felt heavier than when supported before fatigue. In other experiments vibration of muscles at 100 Hz was used. This acts, presumably through activation of the primary endings of the muscle spindles, to produce a reflex contraction of the vibrated muscle, or reflexly to inhibit contraction in an antagonist of the vibrated muscle. Such vibration was used here to disturb the usual relationship of command to achieved tension. Many subjects were guided in their estimates of forces by the effort of contraction rather than by the actual tension produced. In other experiments, subjects were asked to distinguish effort from tension during vibration, and were able to modify either so as to keep the other constant. It is concluded that a "sense of effort" exists, and is separate from a peripheral sense of tension.

INTRODUCTION

Three mechanisms are usually proposed to account for our capacity to estimate the weights of lifted objects. First, the pressure of an object on the skin may be signalled by cutaneous mechanoreceptors; second, receptors within the contracting muscles, or in tendons or joints, may signal the forces exerted in the task, and, third, some entirely centrifugal mechanism may give an estimate of the effort required to support the object. Of these mechanisms, only the cutaneous contribution is not disputed.

For many years it was widely held that there exists a "muscular sense" (18) by which one perceives positions, movements and tensions which is largely subserved by intramuscular receptors. Later, however, several ex-

[1] This work was supported by a grant from the Van Cleef Foundation. Dr. Goodwin is located at the University of Washington.

perimenters reported that their subjects were unable to detect passive displacements of joints in which the joints themselves were anesthetized and the muscles which moved them left unaffected (3, 14, 15, 17). Others reported that their subjects were unable to perceive stretching of muscles caused by pulling on exposed tendons (5). Thus, it became generally believed that the specialized mechanoreceptors in muscles are denied access to consciousness, and that muscles are insentient.

A radically different alternative to the idea of a muscular sense based on information from afferents is that of a centrifugal mechanism which relies on outgoing or motor discharges. The debate between protagonists of these two opposed theories was hotly pursued for the latter half of the nineteenth century. Reviews such as that by Lewes (12) show that the objections on either side were often quite broadly philosophical and that this was thought to be the appropriate level at which to argue. This philosophical approach continued for some time. Sherrington wrote in 1900 (18): "Since Hume, it has been admitted that the perceived results of our volition are the outward ends obtained, and not the inward action of the neuromuscular machinery." And, later still, Granit (8) has written that "to postulate such sensations in a normal subject with normal limbs means to abstain from chances of progress and prefer a 'dead end' of research to a 'live wire.'" Yet, Helmholtz's (10) statement proposing a "sensation of innervation" follows a logical progression from empirical observation to the theory he felt necessary to explain these observations. This theory proposes that a "sensation of innervation" exists by which we perceive the direction in which we move our eyes, a proposal which was repeated with little elaboration after the experiments of Brindley and Merton (2). Similar proposals for a centrifugal movement sense involving the eyes were made by Sperry (20), who spoke of "corollary discharge" from motor to sensory areas, and by von Holst (11), who used the term "efference copy"; in either case, it is not clear to what extent the particular observations made demand an explanation in terms of a centrifugal perceptual mechanism, rather than in terms of positive feedback in a stabilizing postural reflex but they are usually taken as so doing. These centrifugal mechanisms all dealt with movements, specifically eye movements.

Arguing that similar mechanisms existed for limb and eye movement sensations, Merton (13, 14) reintroduced the term "sense of effort" in a somewhat confusing context to describe sensations of movement said to arise when elements of descending command signals, whether directed to eye or limb muscles, gained access to consciousness. Earlier writers (e.g. 22) clearly used the general term "sense of effort" to apply to very different sorts of "effort," such as those of muscular contraction, judgment, and attention. Furthermore, acceptance of the proposition that muscles are in-

sentient necessarily required that the sense of effort of muscle movement described by Merton be a purely centrifugal mechanism.

The present work is an attempt to reevaluate the role of muscle afferents and a sense of effort in the estimation of weights and tensions. This was felt to be necessary in the light of the experiments of Goodwin, McCloskey and Matthews (6) which showed first that muscle receptors do contribute to the perception of limb position and movement, and second that the simplest notion of the centrifugal "sense of effort," as proposed by Merton, is also incorrect.

METHODS

Thirty-two normal young adult male and female subjects participated in some or all of the following experiments. None was familiar with the various hypotheses being tested.

Weight Matching. The first two experiments involved simple weight matching tasks. In the first of these, subjects sat with their elbows, flexed at right angles, resting on a padded table before them. Inextensible strings ran at right angles from padded bands around their wrists, over low friction pulleys, to support two light buckets of equal weight (1 lb or 0.45 kg). The subjects were not blindfolded but the buckets were obscured from their sight by the table. One of the buckets was loaded with a reference weight, usually 3 or 9 lb (1.36 or 4.09 kg). Between lifts an experimenter added or subtracted weights from the other bucket, according to the subject's instructions. The subject then made further lifts, and commanded further changes until satisfied that the two buckets contained equal weights. Usually alternate complete matching trials with a light and a heavy reference weight were performed until ten matches of each were chosen and noted. The weights in the indicator bucket could be altered in increments of 1 lb (0.45 kg) : the starting weights presented in this bucket were either too light, too heavy, or correct, on equal numbers of occasions. Various loading patterns were adopted at random by the experimenter, so that sometimes weights were altered 1 lb at a time, and at other times 2 or 3 lb (0.91 or 1.36 kg) would be added or subtracted, sometimes "overshooting" the reference weight. Subjects were assured that their instructions would always be obeyed but were warned that this would not exclude possible "overshoots." Subjects were allowed two trials on each loading, of up to 5 sec each, bearing both reference and indicator weights simultaneously. To minimize the amount of movement made by the weight-bearing arms, either the buckets were lowered from supports until their weight was taken by the arms, or they were lifted by the arms until they were just free of the supports; either method allowed a little movement, usually about 2 cm at the wrists (angular movement of about 5° at the elbow). Usually both arms were

unloaded between trials. The effects of fatiguing the weight-bearing biceps upon the performance of this task were observed in separate experiments.

In the second weight-matching task, subjects supported weights by flexion of the index fingers. In these tests they sat with both forearms resting flat on a table before them. Each hand gripped a thin vertical metal rod. The index finger of each hand was held flexed at the first interphalangeal joint by a 2.5 cm piece of stiff rubber tubing which was pushed onto the end of the finger. Tied around this rubber tubing, at the level of the terminal interphalangeal joint, an inextensible string ran over a pulley as before to support a light bucket which the subject could not see. Flexion of the index fingers, in a trigger-pulling action, supported weights in a matching task. Movement was minimized to about 0.5 cm at the finger tip (angular movement of about 5°). Identical matching procedures to those described above were used. In this type of experiment it was possible to fatigue the muscles by having them bear a weight for a time, and then to maintain this fatigued state by inflating a sphygmomanometer cuff above the elbow to 300 mm Hg (13). Matching tasks could thus be performed while the reference side was either normal or fatigued. A state of fatigue was held in this way for no longer than 3–4 min before recovery was allowed. The whole process could be repeated to obtain more data points. The control performance for these experiments was determined while the blood pressure cuff was inflated for similar periods above muscles not previously fatigued.

Matching of Isometric Forces. This experiment was similar to the first weight matching task, except that subjects were positioned so that contraction of their biceps brachialis muscles caused them to pull isometrically against strain gauges rather than to support weights. The tension exerted in the reference arm was in this case displayed to the subject on one beam of an oscilloscope. The tension in the other, indicator, arm was recorded, but not shown to the subject. In each experiment, subjects were asked to align the tension record of the reference arm with an adjustable target beam on the oscilloscope (usually representing 2, 3, or 5 kg), and simultaneously to contract the indicator arm so as to "make both arms the same." The respect in which they were to be "made the same" was not specified. This was the actual, and only, request made, and was purposely not elaborated upon. Both arms thus exerted a tension, which subjects were asked to hold for approximately 5–10 sec. Some 10–20 similar trials were done with rest periods (15–45 sec) between. Having established the normal performance of subjects in this task, the experiment was repeated, but throughout each trial vibration was applied either to the contracting muscle (biceps) or to its antagonist (triceps). A small physiotherapy vibrator ("Vibratory Massager": Pifco Ltd), oscillating at 100 Hz with an amplitude of 0.5–1 mm, was pressed onto the skin over the tendon for this purpose. Such vibration is known to cause a slowly developing involuntary reflex contraction

of the vibrated muscle: this effect is now well known, and is usually attributed to the excitation of muscle spindle primary endings by vibration (4, 9). Vibration of the antagonist of a contracting muscle leads to no detectable contraction in the vibrated muscle, but there is an involuntary loss of force achieved by the contracting muscle. This effect can probably be attributed to the excitation of spindle primary endings in the vibrated antagonist which will cause disynaptic reciprocal inhibition of the motoneurons of the contracting muscle. The loss of force can be overcome by an increase of voluntary effort (7). This use of vibration makes possible the investigation of situations in which a tension is achieved with less than usual effort (when the contracting muscle is vibrated), or with more than usual effort (when the antagonist is vibrated).

Distinction between Effort and Tension. It will be shown that all of the above types of experiments suggested that subjects have, and place great reliance upon, a "sense of effort." It was necessary, therefore, when looking for a contribution from intramuscular receptors, to devise a test in which the tension developed by a muscle could be changed by the experimenter without the subject modifying his effort. A variation of the last described experiment above was found suitable for this purpose. Each subject was seated exactly as before, but with only one elbow on the table and flexed to enable him to pull isometrically against the strain gauge. No feedback was given to the subject here, however, and vision was excluded. The wrist and hand of this arm which pulled against the strain gauge, were made insentient by inflating a pressure cuff around the wrist until anesthesia, as judged by usual clinical criteria, was achieved. The subjects were blindfolded. In three of the 12 subjects the skin over the tip of the elbow of the experimental arm was anesthetized by injecting local anesthetic. Subjects were asked to exert a moderately strong pull against the strain gauge, which in practice was between 1 and 5 kg wt. Vibration was applied to the tendon of either the contracting biceps or its antagonist triceps, but was not started until a steady contraction was established, and was stopped before the contraction ended. Subjects were asked to maintain either a constant effort ("Keep your effort constant," or, "Don't change your effort"), or a constant tension ("Keep the tension in the cable constant"), throughout the period of contraction including the period of vibration. No instructions more elaborate than these were given to the subjects. No prior training was given, nor were subjects told the precise nature of the tasks required until ready to start the first trial.

RESULTS

Weight Matching. Most subjects expressed surprise at the subjective difficulty of matching weights with certainty. This difficulty was reflected

in the scatter of matching weights chosen (Fig. 2). All of the subjects felt that they would be more accurate if allowed to move the supported weights. This was tested in the following way. Eight subjects each made ten matching trials of a heavy and a light reference weight supported by biceps in the way described with a minimum of movement, except that, in this series, the correct weight was never presented on the indicator side initially. The scatter of matching was similar to that shown in Fig. 2. After a satisfactory matching weight had been chosen in each trial, the subjects were allowed to move the arms supporting the weights as they pleased, and then to make further adjustments if they thought it necessary to match the weights. In 65 of the 160 trials the subjects chose to make further adjustments, all but one of which made their estimate closer to the reference weight, although 28 choices corrected in this way were still incorrect, and a further 40 choices that were initially incorrect were not further adjusted. It, therefore, seems that precision is gained if movement is permitted. This effect was not studied further.

When a muscle is fatigued, the subjective efforts required to lift weights with it are increased. If a subject is guided by his effort in judging a weight, fatigue of the muscle bearing the weight should make it feel heavier. That this is so was shown here in two ways. First, subjects were required to bear a reference weight of 9 lb (4.09 kg) continuously until considerably fatigued (8–16 min). Throughout this period they chose weights for the other arm, which was rested between loadings, to match the constant weight in the fatiguing arm. The weights chosen gradually increased, as shown in Fig. 1, which could indicate that the subjects relied upon an estimate of their effort in preference to any contrary information from skin, muscle, or elsewhere, assuming such to be available. There may be alternative information to that given by the effort of contraction, since some subjects (four of the nine tested) would occasionally choose a weight that was nearly correct during a series of trials in which they were consistently choosing weights well in excess of the correct value. This interpretation is supported by the experiments in which an attempt was made specifically to dissociate estimates of effort and tension (see below).

In a second type of experiment the reliance on a knowledge of effort was shown in a slightly different way, which was designed to minimize the adaptation of receptors consequent upon prolonged mechanical stimulation. Fatigue of the muscles bearing the reference weights was produced for those muscles which maintain flexion of the index fingers. Fatigue was again induced by prolonged weight bearing (usually 18 lb supported for up to 2 min) but was maintained by temporary ischemia as described in the Methods section. This procedure allowed recovery of the receptors that may have adapted over the period of sustained contraction. Figure 2 shows the

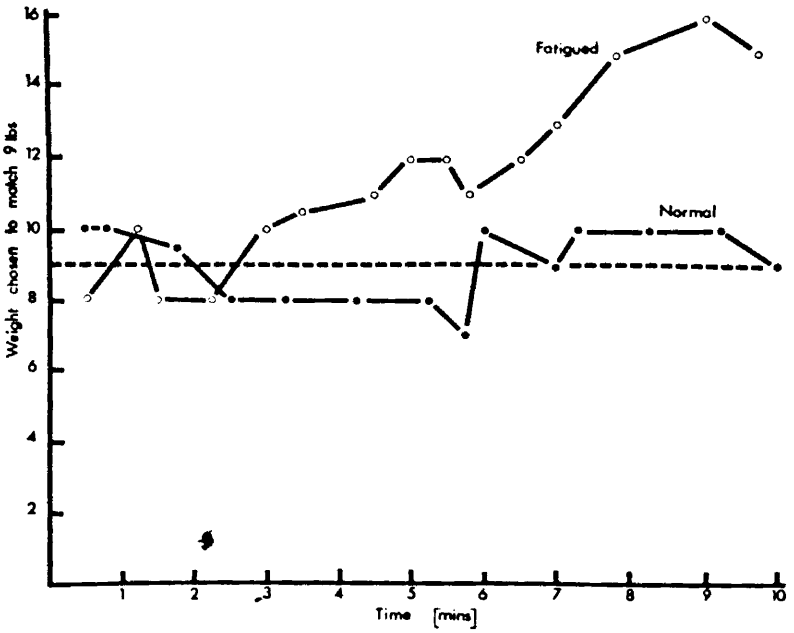

FIG. 1. A subject was given a weight of 9 lb (4.09 kg) to support by contraction of the biceps brachialis muscles of one arm and, in a series of trials, chose apparently equal weights supported in the same way with the other arm. When the reference arm was rested between trials, the subject consistently chose weights close to the reference weight to match it (closed circles). When the reference arm supported its weight continuously, it became fatigued, and heavier weights than the reference weight were chosen to match it (open circles).

results of experiments on eight subjects. It can be seen that matching weights were again chosen in excess of the reference weight when the reference weight was supported by fatigued muscles, i.e., when the subjects exerted an increased effort. The mean weights chosen to match both 3 lb and 9 lb (1.36 and 4.09 kg) in the fatigued state were significantly different from the means of the weights chosen when there was no fatigue ($p < 0.001$ by t test). Again subjects seemed to rely upon their sense of effort in judging the weight of supported objects.

Tension Matching. It seemed possible that the subjects in the experiments with fatigue might have been relying for knowledge of the magnitude of their efforts, not upon a simple centrifugal "sense of effort," but in part upon the afferent discharge from muscle spindle afferents. Muscle spindle afferents are more active when effort is increased to exert greater tensions (21), and they may be presumed to increase their discharge correspondingly during the increased efforts made in fatigue. To test this, 15 subjects were asked to perform the matching tasks in which both arms pulled against strain gauges, the one to a reference tension which the subject could see displayed, and the other in such a way as to "make both arms the same." In this task subjects were inaccurate, and the mean tension chosen

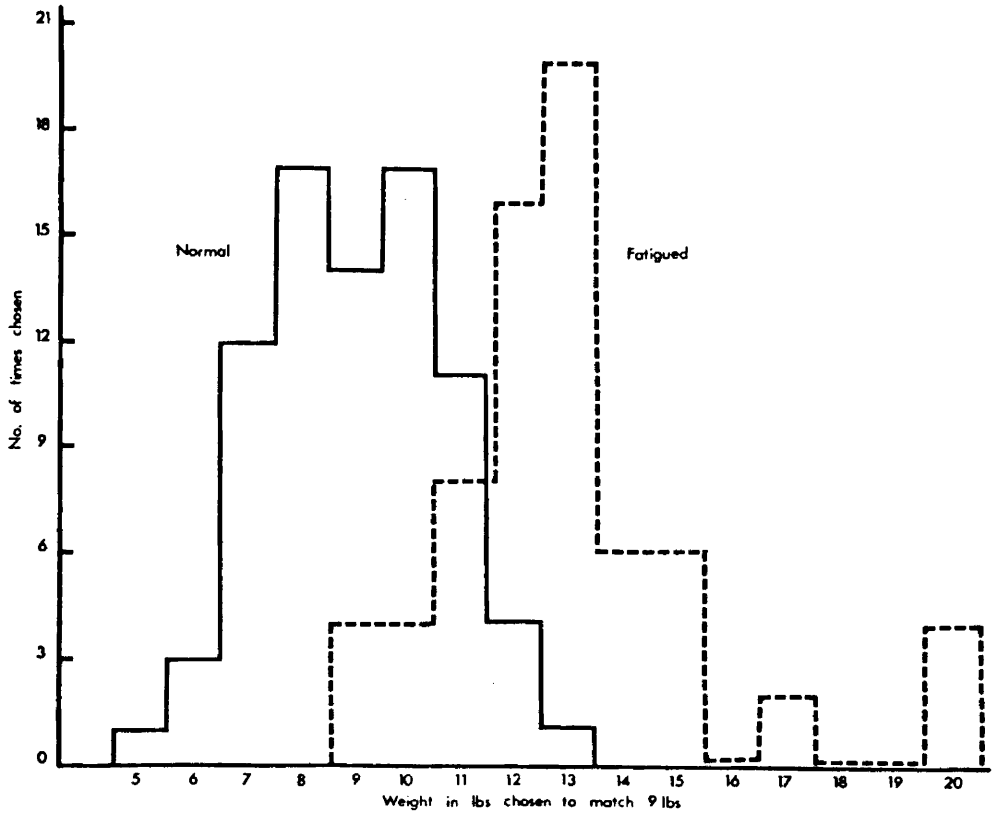

FIG. 2. Pooled data from eight subjects matching weights borne by normal or fatigued finger flexors. The weights chosen to match 9 lb (4.09 kg), and the frequency of each choice, are shown for the two conditions.

in the indicator arm was often as much as 25% different from that in the reference arm. In any individual, however, this error was consistent, and the tension did not vary in time by more than about 10% of the mean matching value chosen. The subjects were next tested in similar tasks performed while either the contracting biceps or its antagonist, triceps, of the reference arm was vibrated continuously. Nine of the 15 subjects consistently chose different matching tensions in the indicator arm in these tasks. They produced tensions smaller than those in the control series when matching a reference arm in which biceps was being vibrated; they chose larger than control tensions when matching a reference arm in which triceps was being vibrated. In either case they made these choices on every occasion, and the tensions chosen departed from the control by 25%, or more. The other subjects made similar errors on some occasions. It appears from these results that many subjects chose to "make both arms the same" with respect to the effort put into contracting them. Moreover, it suggests that effort is perceived separately from spindle discharge.

Distinction between Tension and Effort. The experiments described so far were taken to indicate that there exists a "sense of effort." In testing

for the presence of a muscular sense capable of detecting tensions, the problem became one of eliminating both cutaneous signals and the influences of this sense of effort, as alternative sources of information. This was done, as described in the Methods, by applying and removing vibration within a period of sustained muscular contraction. The active arm was anesthetized at the wrist so as to eliminate relevant cutaneous signals. When asked to maintain a constant effort, the tension produced by these subjects rose above its preexisting level during vibration of the contracting biceps. In contrast, vibration of triceps considerably reduced the tension achieved. In either case the tension quickly returned to the preexisting level at the end of the period of vibration. Figure 3 illustrates these responses. In our subjects, vibration led to changes in tension of at least 25% of the control in these maneuvers, and these changes occurred in all trials.

When asked to maintain a constant tension in the cable during vibration, all subjects were able to achieve this with an accuracy of 20% or better. When the contracting biceps was vibrated the tension produced began to rise, but the subject could then readjust it to maintain its control level; at the conclusion of vibration a slight fall of tension occurred, and then was corrected. A similar pattern was seen when triceps was vibrated during a contraction of biceps, except that there was a fall of tension which was corrected at the start of vibration, and a rise of tension which was corrected at the conclusion of vibration. Figure 3 also illustrates these responses. In these trials, five subjects occasionally failed successfully to adjust their ef-

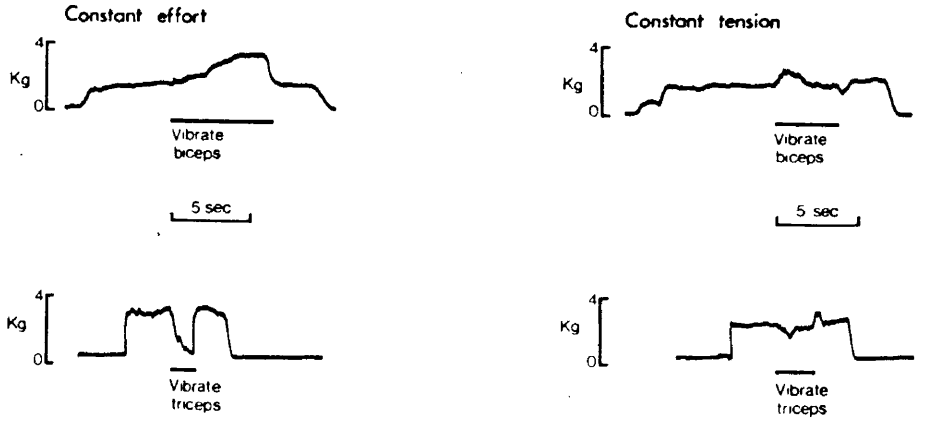

FIG. 3. A subject exerted a force against a strain gauge, by contracting his biceps brachialis muscles: the wrist through which he exerted the force, and the tip of his supporting elbow, were anesthetized (see text), and vision was excluded. He was asked to keep either his effort (traces at left), or the tension he exerted (traces at right), constant. Vibration at 100 Hz of the contracting muscle or of its antagonist (triceps) was applied where shown. The records of tension achieved show that vibration led to considerable changes when the subject was asked to keep his effort constant. When he was asked to keep tension constant, he was able to adjust his effort so as to do so.

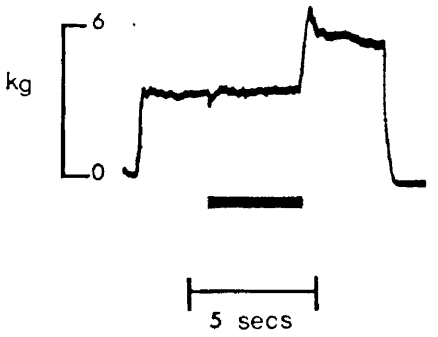

FIG. 4. A subject tested in the same way as shown in Fig. 3, was asked to maintain a constant tension by contracting biceps while its antagonist, triceps, was vibrated during the marked period. He successfully adjusted his efforts and kept tension constant throughout the vibration. He made no adjustment at the conclusion of vibration, yet stated, "That time I got the end part right." See comments in text.

forts, so that tension rose or fell as if they had been asked to maintain a constant effort: such behavior occurred in no more than one trial in four for any of these subjects.

All subjects were able to maintain tensions constant to within 20% of the mean for up to 20 sec in the absence of vibration, even when they were expecting it, or in the presence of vibration applied to the side of the elbow joint. In these control experiments it proved immaterial whether the instructions were to maintain a constant effort or a constant tension.

In our experiments, the subjects registered their detection of tension changes in a muscle by adjusting their efforts so as to cancel them. Some subjects, however, sometimes neglected to readjust their effort at the conclusion of a period of vibration. In the trial recorded in Fig. 4 a subject who previously and subsequently produced adjustments of the type shown in Fig. 3, adjusted his effort at the start but not the finish of the vibration. He was pleased with this performance, and remarked, "That time I got the end part right." Three others behaved similarly, each on one occasion, and volunteered that they, too, were happy with their aberrant performances. It is noted that such behavior would be consistent with a subject having switched from attending to a signal of intramuscular tension to one from his sense of effort during the course of vibration.

DISCUSSION

The experiments described here indicate that a sense of effort is important in the estimation of weights supported by active muscle contraction. This explains most economically why subjects systematically overestimated the weights of objects that they were required to support with fatigued muscles. It is subjectively obvious that under these conditions there is an increased sense of the effort of muscle contraction, but it would not neces-

sarily follow that this increased effort leads to overestimates of the weights of lifted objects. In fact it seems to do so. Attempts have been made, first to reduce the involvement of adaptation of mechanoreceptors during fatiguing contraction, and second, specifically to exclude the involvment of muscle spindle primary afferents in this sense of effort. To this end, it was shown that the effects of fatigue on weight estimation are the same irrespective of whether the estimate is made during a period of fatiguing contraction, or at a later time over which the state of fatigue is maintained by occluding the circulation to the fatigued muscles. Moreover, when changes in the required effort for contraction are induced by reflex inhibition or excitation, rather than by fatigue, most subjects then match forces as if they pay more attention to the effort of contraction than to the actual tension produced. It is assumed here that weight matching and force matching are very similar tasks as presented to subjects in these experiments. This follows from the restrictions made on the movements allowed the subjects during weight estimation. Subjects were asked in the first instance to match weights since this is an unambiguous instruction. The evident dominance of the sense of effort prompted a further examination of the ability of subjects to estimate isometric tensions, and the effects of vibration on such estimates. The behavior of those subjects who showed consistent errors during vibration does not suggest a simple involvement of the muscle spindle primary endings in these effects. The nature of the sense of effort that we have been talking about thus far must remain uncertain. The important point is that subjects behave as if the subjective effort of muscle contraction or some variable proportional to it strongly influences the estimation of the weights of lifted objects. Whether this sense of effort should be regarded as simply a centrifugal mechanism or as involving some inherent comparison of outflow with afferent information remains an open question. This reflects our generally primitive understanding of the various aspects of the sensations we have of movement, tension, effort, and fatigue.

Paradoxically, intramuscular tension, or rather a change in intramuscular tension, seems to be correctly estimated under some conditions. This was suggested by the success of subjects in adjusting their efforts during vibration so as to hold tension constant. On a number of occasions, subjects appeared to switch from judgments of weights and tensions which were dominated by the effort of contraction to estimations which were not so influenced. These instances were sufficiently frequent to suggest that they represented a systematic phenomenon, but were, unfortunately, hard to pin down. Our results are similar to those of Bernhardt (1) who found that discrimination between weights was possible, although of poor accuracy, when the muscular contraction was caused by direct faradization of nerve trunks or muscles. Waller (22), however, pointed out that Bernhardt's

results might have been accounted for by touch alone. This objection could not have applied to our study, because cutaneous sensation from the hand and wrist was eliminated as a source of information. In addition, in three of our subjects any further possible contribution from the skin over the elbow was eliminated by local anesthesia, although simple testing revealed that subjects could not distinguish widely different forces applied to this area normally. It is possible that, in changing the tension which a subject exerted against the gauge, there were changes in muscles elsewhere involved in a supportive role, and that subjects relied upon some extramuscular manifestation of these in making their corrections. This possibility cannot be excluded, although the accuracy of the corrections achieved seems unlikely to have been possible through the use of such distant and diffuse signals. Whether changes in tension, rather than the absolute levels of tension, were detected in our study, has not been resolved. This question may, however, be relevant in considering why movements allow greater precision of weight estimation.

It might be suggested that subjects corrected tension changes not by sensing tension at all, but instead by sensing the illusions of movement and position which vibration causes (6). This is unlikely; the kinesthetic illusions correspond to stretching or lengthening of the vibrated muscles, so that voluntary correction of these would require increased contraction of the vibrated muscles. The corrections made by subjects in these tension detection studies required the opposite response.

We do not know which peripheral receptors are responsible, either solely or in part, for the conscious appreciation of tension. Joint receptors alter their discharges in response to muscular contraction (16, 19), and so might contribute to this perception in some way, despite the more customary emphasis on their possible role in position sense. A more direct signal of tension could be provided to the sensorium by intramuscular receptors. The experiments using vibration here as a stimulus to the primary endings of the muscle spindles suggest that they are not involved. The receptors which, by their responsiveness and situation in muscles, seem most likely to be responsible are the Golgi tendon organs.

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MUSCULAR AND CUTANEOUS MECHANISMS IN THE ESTIMATION OF THE WEIGHTS OF GRASPED OBJECTS

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(*Received* 22 *October* 1973)

Abstract—Subjects matched the weights of beakers supported in a grasp between fingers and thumb of each hand. Wide beakers felt light, and narrow beakers felt heavy. When increased inward force was used to close the grasping digits upon the beakers, as when elastic bands opposed closure of the grasp, or when the grasped object was slippery, the beakers felt light. These illusions occurred whether or not muscular forces along the line of action of the weight

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INTRODUCTION

MULLER and SCHUMANN [2] noted that a blindfolded subject was influenced in his estimation of the weight of any lifted object, in a series of lifts, by the weight of the object lifted immediately before it. They proposed that a subject prepares himself to lift each object with a muscular force just previously found sufficient to lift the preceding object. Thus, if the object comes up quickly and easily using this force, it is perceived as light when compared with the object before it. If the opposite is found, it is perceived to be heavier than the object before it. It is also known that if a subject is not blindfolded, and lifts two objects of equal weight but of different sizes, then the larger of the two will be perceived as the less heavy. This is the so-called size-weight illusion [e.g. 1, 5], and again is usually explained in terms of the perception of a departure of real from "expected", or "prepared for", weight.

The experiments to be described here deal with the perception of the weights of objects grasped by their sides between two fingers on the one side and the thumb on the other side. This form of grip is commonly used in one's daily activities (as, for example, when one lifts a drinking glass from a table). Both muscular and cutaneous mechanisms are shown here to be involved in the judgements of weights of objects lifted in this way. The size-weight illusion, and other related illusions, are shown to be associated with such judgements.

METHODS

Twenty-eight normal young adults participated in the study. None was familiar with the hypotheses being tested.

In all the experiments, subjects grasped plastic beakers between two fingers and a thumb, the skin of the finger and thumb pulps engaging the beakers, and the plane of the palm of the hand vertical. Always, beakers were presented simultaneously to each hand. The beakers were opaque, and empty. From the base of each beaker a fine string ran to support a light bucket (100 g) suspended beneath. Weights could be added to these buckets as required (Fig. 1).

Subjects were seated at a table, on which both elbows rested, and their forearms were extended before them, also resting on the table as far as the wrists; the hands projected from the end of the table. The beakers to be lifted were arranged so as to lie at the fingertips. The subjects were not blindfolded, and could see the beakers but not the buckets and weights suspended beneath.

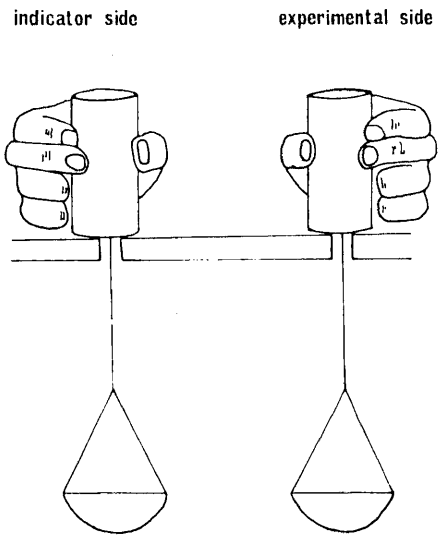

FIG. 1. Experimental set-up. A subject grasps a beaker by its sides between two fingers and the thumb of each hand. A light bucket is suspended from a fine string beneath each beaker. On the "experimental side" a reference weight is suspended, and the subject commands changes in the weights suspended on the other side, the "indicator side", until the weights on both sides are apparently equal. The weight on the indicator side is recorded as an objective estimate of the apparent weight supported on the experimental side.

All experiments took the form of matching tasks. To one hand, the "experimental" or "reference" hand, a beaker with a known load (200 or 500 g) was presented. The beaker presented to the other hand, the "indicator" hand, might be heavier or lighter than this reference weight, or it might be the same. Subjects were required to grasp and support both beakers, and then to release them and instruct the experimenter to add or subtract weights on the indicator side. The process was repeated until both beakers were of apparently equal weight. The subjects were told that their instructions would always be obeyed regarding the direction of loading or unloading, and were warned that the experimenter could, however, choose to overshoot the target. Weights were added or subtracted in multiples of 25 g. The starting weight on the indicator side was too light, too heavy and correct on equal numbers of occasions. The weight chosen on the indicator side was noted as an objective indication of the perceived weight on the experimental side.

In each experiment, heavy and light weights were presented in alternate trials on the experimental side, and trials of each experimental procedure alternated with control trials. Trials were continued until 10 matches in each category were made. The results are presented descriptively below, with numerical examples: all results, however, were analysed statistically and statements that one treatment differed from another are to be taken to mean that the means of the matching weights chosen were significantly different from each other by t-test at $P < 0{\cdot}01$ or better. All stated results were obtained in 10 or more subjects, unless otherwise indicated.

Several manoeuvres were tried on the experimental hand in various trials. Wider or narrower beakers were used on this side; or, beakers were made slippery with petroleum jelly on this side, so as to require a greater inward force to hold them; or, a wire frame was used, to which elastic bands could be attached and connected so as to pull outwards upon the grasping fingers and thumbs.

For the purposes of analysis, a restriction was sometimes placed upon subjects so as to eliminate any muscular effort in the line of action of the suspended weights. For this, both forearms lay flat on a table as before, but the fingers and thumb of each hand were extended across a slightly raised bar (Fig. 2). Thus, muscular effort could be used to close the grasp on the beaker, but not directly to support it. The beaker was supported by the frictional forces between it and the grasping digits. The beakers were matched as before, except that they were lifted simultaneously by the experimenter to the subjects' grasp in each trial.

In several experiments anaesthesia of the grasping fingers and thumb of the experimental side was achieved by ring-block injection of 2 per cent lignocaine at the base of the digits. In other experiments a sphygmomanometer cuff was inflated above the elbow of the experimental arm: these experiments are further described below.

In a quite separate series of observations, a Grass force transducer was set into the side of a beaker in such a way that the inward force under the grasping thumb of a subject could be measured. Unseen weights were

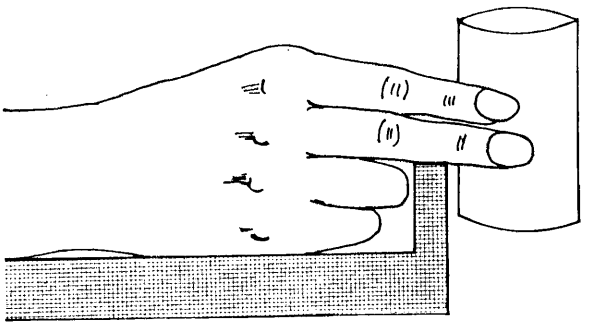

FIG. 2. Diagram shows how a supporting bar was used in some experiments. The fingers and thumb of the grasping hand rested on a support. While the arm and hand lay flat on the table, and these digits rested upon the support, no muscular effort along the line of action of the weight of the grasped beaker could be used to support the beaker.

again attached to the base of this beaker, and subjects made lifts in sequence indicating on each lift whether they judged the weight to be heavier or lighter than the preceding weight, or the same as it. The inward force under the thumb was recorded on each trial on a Grass Polygraph pen recorder.

RESULTS

Matching tasks

Subjects could usually match the weights of beakers to within ± 50 g in control trials. Sometimes a constant error of 25–50 g was made, possibly due to handedness, in which case subjects matched within ± 50 g of this weight. All experimental comparisons were made of the experimental procedure against the chosen control level.

(a) *Width of object.* The control matching trials were usually made with beakers each of 4 cm dia. In some experiments the reference hand was presented with a beaker 8 cm in dia., to be matched by weights in the 4 cm beaker in the indicator hand. Subjects chose lighter weights in the indicator beaker than they had chosen when beakers of equal size were matched. (See Table 1.)

If the reference object was only 0·5 cm in diameter, heavier than control weights were chosen on the indicator side. (See Table 1.)

This is the size–weight illusion: wide objects feel light, narrow ones feel heavy. This illusion was demonstrated when the subjects lifted the grasped objects freely, and when a restriction on direct muscular action was applied through the use of a supporting bar as described.

(b) *Variations of inward force.* The inward forces required in the grasp of the reference hand were altered in two ways. First, a light frame was suspended over the reference hand, and elastic bands were led from this frame to the bases of the grasping digits. In order to close upon the reference object these fingers and thumb had first to exert an inward force of 1 kg; to grasp the object, the inward force required would have been greater than this. When this was done, lighter than control weights were chosen to match it on the indicator side. (See Table 2.)

In another type of experiment, the beaker on the reference side was made slippery with a coating of petroleum jelly, so that it had to be squeezed hard to prevent it slipping from the grasp. Here again, lighter than control weights were chosen for the match performed by the indicator side. (See Table2.)

Thus, a new illusion is described: an increase of inward force causes grasped objects to

Table 1. Mean ± S.E. (10 trials) of grasped weights chosen in the indicator hand to match a weight of 500 g grasped in the experimental hand

Freely lifted Subject	Control	Wide	Narrow
C.R.	480 ± 8·16	330 ± 9·36*	575 ± 11·18*
I.N.	525 ± 11·18	310 ± 12·47*	545 ± 10·67
R.M.	515 ± 7·63	410 ± 14·52*	635 ± 13·01*
I.S.	510 ± 6·71	300 ± 10·54*	635 ± 10·67*
T.C.	465 ± 6·66	375 ± 8·03*	555 ± 11·66*
P.C.	480 ± 7·50	325 ± 8·33*	550 ± 10·54*
E.M.	455 ± 11·66	280 ± 20·00*	545 ± 8·03*
M.J.	565 ± 7·63	430 ± 11·05*	655 ± 11·66*
M.P.	490 ± 9·16	300 ± 8·97*	605 ± 13·84*
R.B.	580 ± 8·97	322 ± 11.45*	665 ± 10·00*
Across restricting bar			
C.R.	465 ± 14·35	305 ± 22·35*	620 ± 16·35*
I.N.	535 ± 32·15	300 ± 15·30*	500 ± 24·60
R.M.	505 ± 20·00	485 ± 14·52	665 ± 11·18*
I.S.	495 ± 9·84	320 ± 12·47*	605 ± 13·01*
T.C.	440 ± 14·52	305 ± 19·24*	525 ± 11·66*
P.C.	500 ± 11·66	295 ± 32·00*	595 ± 13·84*
A.L.	580 ± 11·18	405 ± 8·16*	645 ± 9·36*
M.S.	495 ± 26·75	315 ± 14·04*	685 ± 10·54*
S.B.	515 ± 22·35	305 ± 17·65*	620 ± 13·01*
J.R.	470 ± 11·45	310 ± 13·84*	585 ± 12·47*

In the control series the two hands grasped beakers of equal diameter (4 cm). Data for trials in which the experimental hand grasped a wide beaker (8 cm), or a narrow beaker (0·5 cm), are given. In the upper series of experiments the beakers were lifted freely: in the lower series, the beakers were supported across a restricting bar (see text). Where the experimental trials were highly significantly different from the control ($P < 0{\cdot}001$ by t-test), they are marked by an asterisk (*).

feel lighter. This illusion was seen both when the grasped objects were lifted freely, and when direct muscular action was restricted through the use of a supporting bar.

(c) *Anaesthesia.* Subjects were required to indicate, by matching, the apparent weights of objects grasped between fingers and thumb made anaesthetic on the reference side by ring-block injections of 2 per cent lignocaine.

When the grasped objects were lifted freely in this way, subjects could successfully match the weights. Typically, they did this with some increase in the scatter of matching weights chosen, but there was never a significant difference noted between the means of the group of trials made using anaesthetic digits, and the means of control trials.

However, when subjects were prevented, by a supporting bar, from using any muscular forces in the line of action of the grasped weight, anaesthesia of the fingers and thumb made them extremely inaccurate. Usually they remarked that they were aware that they were supporting an object only because they could see that they were doing so, and that they "felt" no weight. Typically they were satisfied that any weight presented on the indicator side up to about 150–250 g was as good a match as they could achieve, and they accepted any weights in this range on first presentation without asking for alterations. Heavier weights presented to the indicator hand were always rejected as unsatisfactory.

(d) *Vascular occlusion.* The results presented above were taken to show that cutaneous sensation is important in the judgement of the weights of lifted objects, and that it is the

Table 2. Mean ± S.E. (10 trials) of grasped weights chosen in the indicator hand to match a weight of 500 g grasped in the experimental hand

Subject	Control	Elastic	Slippery
Freely lifted			
A.L.	565 ± 10·67	420 ± 8·16*	290 ± 14·52*
J.R.	495 ± 16·99	395 ± 7·63*	315 ± 10·67*
P.C.	475 ± 11·18	260 ± 31·44*	280 ± 15·27*
P.E.	435 ± 8·16	375 ± 8·33*	300 ± 14·90*
S.B.	445 ± 13·85	300 ± 7·45*	275 ± 8·33*
M.J.	550 ± 12·91	435 ± 10·67*	405 ± 8·97*
I.N.	570 ± 13·33	450 ± 10·54*	440 ± 12·47*
M.S.	495 ± 16·99	325 ± 11·18*	310 ± 10·00*
R.C.	425 ± 11·45	160 ± 7·63*	205 ± 10·40*
E.F.	440 ± 9·27	325 ± 8·33*	275 ± 7·45*
Across restricting bar			
A.L.	585 ± 13·33	405 ± 10·67*	315 ± 13·42*
J.R.	470 ± 11·45	355 ± 8·97*	295 ± 8·97*
P.C.	510 ± 12·91	225 ± 11·66*	315 ± 16·99*
P.E.	460 ± 8·16	335 ± 8·03*	305 ± 13·01*
S.B.	505 ± 7·63	295 ± 10·67*	295 ± 12·47*
E.M.	470 ± 11·18	300 ± 13·01*	320 ± 9·74*
M.P.	515 ± 12·47	415 ± 6·66*	305 ± 11·05*
C.R.	470 ± 9·36	365 ± 8·33*	380 ± 7·50*
J.C.	500 ± 7·63	380 ± 10·54*	335 ± 11·45*
P.R.	505 ± 26·35	295 ± 14·04*	275 ± 19·24*

In the control series the two hands grasped beakers similarly. Data for trials in which the experimental hand closed its grasp while restricted by elastic forces, and in which it grasped a slippery beaker, are given. In the upper series of experiments the beakers were lifted freely: in the lower series, they were supported across a restricting bar (see text). Where the experimental trials were highly significantly different from the control ($P < 0·001$ by t-test), they are marked by an asterisk (*).

Table 3. Mean ± S.E. (10 trials) of grasped weights chosen in the indicator hand to match a weight of 500 g grasped in the experimental hand

Subject	Control	Venous occlusion	Venous and arterial occlusion
I.N.	525 ± 8·33	320 ± 7·26*	535 ± 10·67
J.C.	515 ± 8·49	360 ± 9·27*	530 ± 8·33
A.L.	560 ± 10·67	375 ± 7·45*	565 ± 8·16
M.J.	535 ± 7·63	420 ± 8·16*	620 ± 11·05*
P.E.	440 ± 6·66	320 ± 7·86*	520 ± 7·86*
M.S.	485 ± 8·49	340 ± 10·57*	555 ± 8·97*
I.D.	540 ± 9·72	280 ± 14·93*	560 ± 13·14*
S.B.	490 ± 10·67	370 ± 7·26*	535 ± 8·49*
M.V.	525 ± 9·27	520 ± 11·76	505 ± 12·46
J.R.	485 ± 14·52	465 ± 7·63	515 ± 20·00

In the control series the two hands grasped beakers similarly. Data for trials in which the experimental hand was engorged with blood through having a venous occlusion applied above the elbow, and for trials in which venous and arterial occlusion was applied, are given. The beakers were lifted freely. Where the experimental trials were highly significantly different from the control ($P < 0·001$ by t-test), they are marked by an asterisk (*).

basis of judgements made when muscular forces are prevented from acting along the line of action of the suspended weights (see Discussion). The question thus arose: what is the nature of the cutaneous sensation? Introspection suggests that shearing forces, which stretch the skin on the upward facing surface of the finger-tip while relaxing the skin on the lower surface, may be important.

In order to test this suggestion, vascular engorgement of the digits was used in an attempt to alter the shearing properties of the finger-tips. A sphygmomanometer cuff was inflated above the elbow of the reference arm to a pressure of 60–70 mm Hg. This allows arterial blood to enter the arm, but obstructs venous drainage. Eight of ten subjects who matched weights during this manoeuvre chose lighter weights with the indicator side than they had done in control trials (see Table 3). The remaining two chose weights not significantly different from the controls.

To provide another control, the same subjects performed matching trials while the cuff on the reference arm was inflated to 300 mm Hg. In these trials the arms did not become engorged since both arterial and venous flows were obstructed. Five of the eight subjects referred to above chose heavier matching weights than in their uncuffed control trials (see Table 3). All other subjects chose weights not significantly different from the controls.

Inward forces

In a separate study, subjects lifted grasped beakers in sequence and estimated their weights in relation to the preceding weight in the series. During each lift, the *inward* force under the grasping thumb was recorded.

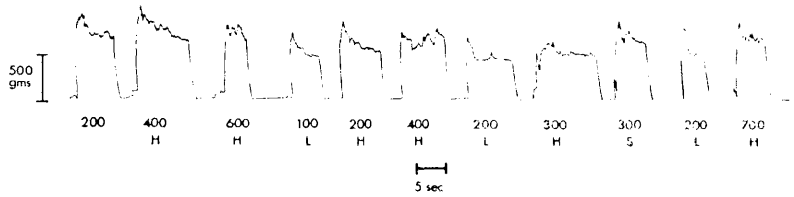

FIG. 3. Record of the inward forces exerted by the thumb of a subject lifting a series of grasped weights. The numbers under each elevation of the record refer to the weight of the grasped object in gms. The letter under each weight designated refers to the subject's estimation of the weight of the object lifted in relation to the weight lifted immediately before it in the series (H—heavier, L—lighter, S—same).

In these experiments, subjects produced widely varying inward forces. Even when the same weight was lifted repeatedly, different inward forces were chosen for the grasp. Typically, subjects gradually reduced the initially chosen inward force during the period of weight-bearing. No constant relationship of the size of the inward force to the magnitude of the preceding weight or to the width of the lifted object, was observed. Despite the widely varying forces chosen in individual trials, larger inward forces were more often exerted for heavier than for lighter weights. Subjects could reliably state (correct at least 9 estimates in 10), whether a weight was heavier or lighter than its precursor, or whether it was the same, when the weights supported were altered in multiples of 100 g between 0 and 800 g. This was so whether the weights were supported across a restricting bar (as described above), or not. A characteristic record showing the inward forces exerted in a sequence of lifts is shown in Fig. 3.

DISCUSSION

When we lift objects in our daily activities, we probably choose more often than not to grip them in the form of grasp investigated here, or in some closely related variant of it. Introspection assures us that we can estimate the weights of lifted objects grasped in this way. The present study was concerned with the physiological and psychological mechanisms underlying this ability.

The grasp itself is complex. Muscular forces act along the line of action of the weight to support the object: the muscles involved are largely those responsible for lateral movements of the wrist. Other muscular forces act at right angles to this line, to close the grasping digits upon the object: these muscles are principally the flexors of the fingers and thumb. The skin of the digits engaging the object is subject to an inward pressure which depends upon the inward muscular force, and to a shearing or distoring force due to the pull of the surface of the object *across* the skin. These cutaneous deformations are not independent, since greater inward pressures reduce the amount of shearing distortion possible: this presumably occurs because greater inward forces drive the grasped objects against less easily deformable deeper structures in the finger or thumb.

The present experiments were designed to enable analysis of the grasp in terms of these variables. The use of a supporting bar to prevent muscular forces from acting along the line of action of the weight aided this analysis. It might seem that such a bar would be insufficient to achieve this reliably, and that further restrictions would be required. This was not the experience here, where subjects showed no inclination to move the wrist laterally (so as to lift the object), when the arm and hand were supported across the bar. That the bar achieved its purpose is indicated by the very different results obtained with and without it during digital anaesthesia. Also, while there can be little doubt that different pressures exerted by the grasping digits upon the bar could have provided accessory cutaneous clues in the tasks, the strong illusions caused by object width and varying inward force were clearly sufficient to over-ride such alternatives.

Either muscular or cutaneous signals are sufficient to allow estimation of the weight of the grasped object. The importance of the muscular mechanism is shown by the retention of subjects' capabilities to estimate weights despite cutaneous anaesthesia, except when muscular action was prevented from directly supporting the weight. The observations here permit only the conclusion that signals generated in conjunction with muscular activity form the basis of the estimations, and do not indicate the site of origin of such signals (whether in the active muscles, the tendons, the joints, or within the central nervous system itself). A cutaneous mechanism can act alone as the basis of the weight estimation, as is shown by the experiments using a supporting bar. With both muscular and cutaneous mechanisms eliminated, by use of supporting bar and anaesthesia together, subjects were unable to estimate weights. Shearing forces which deform the skin of the finger and thumb pulps appear to provide the pattern of cutaneous stimuli involved. When the shearing properties of the digits were altered here by vascular engorgement, errors in estimation were made.

The size–weight illusion was observed in the free grasp, and in the grasp eliminating muscular support. A further illusory effect relating to the size of the inward force exerted in the grasp was observed: simply stated, greater inward force causes grasped objects to feel apparently lighter. An explanation suggested for the size–weight illusion might be extended to cover all these illusions. It is said [e.g. 4, 5], that, through visual or kinesthetic cues, and

on the basis of experience, larger objects are *expected* to be heavy, and smaller ones to be light. When physiological mechanisms provide information on the actual weight of the object, these signals are not themselves always as important in the perception of the weight as is any discrepancy between expected and signalled weight. It could be that not only the size of the object, but also the magnitude of the inward force used to grasp it, set the expectation of what its weight will be. Alternatively, it might be that afferent kinesthetic signals interact within the central nervous system with signals concerning weight or tension, so as to produce illusory sensations.

The great variability of inward forces chosen to grasp objects was noted above. Payne and Davis [3] had similar experience in rather different weight lifting tasks. For the cutaneous signals regarding shearing forces to be meaningful to the central nervous system, some central correction might be expected to be required to allow for the size of the inward forces employed in the grasp. This is because firmer grasps reduce the deformability of the skin by shearing forces. It is surprising therefore, that increased inward forces had similar effects upon perception whether the finger and thumb pulps were compressed, and so rendered less easy to deform by shearing forces, as in grasping slippery objects, or not, as in the grasp against elastic restraints. Apparently the illusory effects in play here were able to over-ride finer musculo-cutaneous imbalances.

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Résumé—Les sujets devaient apparier les poids de gobelets empoignés entre le pouce et les doigts de chaque main. Les larges gobelets étaient perçus légers et les gobelets étroits étaient perçus lourds. Quand la tâche réclamait l'augmentation de la force pour assurer la préhension des doigts sur les gobelets, par exemple en utilisant des bandes élastiques s'opposant à la préhension ou lorsque l'objet saisi était rendu glissant, les gobelets apparaissaient légers. Ces illusions se manifestaient, que les forces musculaires dans la ligne d'action du poids s'exercent ou non dans la préhension. On soutient que des mécanismes musculaires et cutanés sont impliqués dans les estimations de poids des objets saisis.

Zusammenfassung—Versuchspersonen hatten das Gewicht von Bechern zu vergleichen, die zwischen Fingern und Daumen jeder Hand gefaßt waren. Breite Becher wurden als leicht empfunden, enge Becher als schwer. Wenn der Becher mit stärkerem Kraftaufwand der greifenden Finger gepackt wurde, wie es durch elastische Bänder, die dem Fingerschluß entgegenwirken, erreicht wird, oder wenn das gegriffene Objekt glitschig war, wurden die Becher als leicht empfunden. Diese Illusionen traten auf, gleichgültig ob die Muskelkräfte in der Aktionsrichtung des Gewichtes beim Greifen eingesetzt wurden oder nicht. Es wurde diskutiert, ob beim Schätzen von Gewichten ergriffener Objekte muskuläre und Haut-Mechanismen involviert sind.

32. Muscular and cutaneous mechanisms in the estimation of the weights of grasped objects.
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SHORT COMMUNICATION

THE EFFECTS OF PRE-EXISTING LOADS UPON DETECTION OF EXTERNALLY APPLIED RESISTANCES TO BREATHING IN MAN

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SUMMARY

1. It was confirmed that normal subjects can detect an increase in airways resistance of 1·2 $cmH_2O\ l^{-1}\ s$ when this is presented during a sequence of otherwise unresisted breaths.

2. In contrast when such subjects meet the same resistance presented unexpectedly during a sequence of breaths against a larger resistance (2·5 $cmH_2O\ l^{-1}\ s$), they commonly fail to detect it, indicating that they believe no external resistance remains.

3. Subjects breathing continuously against a given external resistance frequently during the course of the study indicate that they believe that a decrease in resistance has been made.

Key words: airways resistance, perception, breathlessness, normal subjects.

Normal subjects can reliably detect an added airways resistance of 1^{-1}·5 $cmH_2O\ l^{-1}\ s$, when this is presented during a sequence of otherwise unloaded breaths (Bennett, Jayson, Rubenstein & Campbell, 1962; Wiley & Zechman, 1966: Aitken, 1969; Noble, Eisele, Trenchard & Guz, 1970). In the present study, subjects were asked to detect a resistance of this magnitude presented during sequences of breaths against larger resistances, as well as during sequences of unresisted breaths.

METHODS

Sixteen normal young adult male and female volunteers participated in this study. None was familiar with the hypotheses being tested. Each subject was seated during the experiment, was blindfolded and wore a noseclip, and breathed through a mouthpiece attached to a short wide tube mounted before him. In this tube there were three openings to room air; one was as wide as the tube itself (2·2 cm), and, together with the mouthpiece, presented no measurable

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resistance to airflow; the others were of smaller diameters, and constituted resistances of 1·2 and 2·5 $cmH_2O\ l^{-1}\ s$ to a steady flow of $1\ l\ s^{-1}$. The resistances of these airways were designated '0', '1' and '2', respectively. At any time two of these three openings could be simply occluded by the experimenter, so that the subject inspired and expired through the remaining opening. This system is similar to that described by Bennett *et al.* (1962). Before each experiment commenced, the subject was given a period of about 5 min to become accustomed to the alternative airways: during this time each airway was used many times while the experimenter told the subject the number designating the airway in use. During the experiment itself soft music was played to the subject through headphones to obscure soft hissing sounds generated by the external resistances. Experimental sequences of twenty to thirty breaths were used, during which time the subject was asked to write down, at the conclusion of each complete breath, the number corresponding to the resistance against which he believed he was breathing. At each breath the correct designation of the resistance in use was written against the subject's record by an observer. External loads were changed only at end-expiration. Between experimental sequences the subject breathed through the airway which offered no resistance, and was not required to write or to concentrate. Subjects took between twelve and twenty breaths/min.

RESULTS

Three subjects were excluded from the study as unsatisfactory. These three registered perception of a resistance in 10%, or more, of breaths in initial sequences of only unloaded breaths. The remaining thirteen subjects indicated perception of a resistance in 1·4% of unloaded breaths, and none of them individually gave such false-positive indications in more than 3% of unloaded breaths.

When resistance 1 was presented during a sequence of unloaded breaths, it was detected in 94% of presentations (range: 88–100%, for individual subjects). It was correctly nominated as resistance 1 in 72% of these detections, and was thought to be resistance 2 in the remainder.

In contrast, when resistance 1 was presented during a sequence of breaths against resistance 2, it was detected (nominated as resistance 1) in only 12% of all presentations (range: 5–22%, for individual subjects). On all other presentations it was incorrectly called resistance 0.

When resistance 2 was presented during a sequence of unloaded breaths, it was always detected by all subjects, and was nominated correctly in 92% of these detections. When resistance 0 was presented during a sequence of breaths against resistance 2, it was correctly indicated in 97% of presentations (range: 92–100%, for individual subjects), and was called resistance 1 in all other presentations.

In addition to these random, unexpected, single-breath presentations of altered resistance, all thirteen satisfactory subjects were also given longer sequences on each resistance. Very few false-positive detections were indicated during sequences of unloaded breaths (see above). However, in sequences of loaded breaths it was not uncommon for subjects to 'change down' in their estimates. Thus, a long sequence against resistance 1 would, after between five and twenty breaths, be indicated as against resistance 0; and similarly a sequence against resistance 2 would, in time, be indicated as resistance 1, or occasionally, as resistance 0. All subjects made errors of this kind.

DISCUSSION

This study has shown that while normal subjects can reliably detect an airways resistance of 1·2 $cmH_2O\,l^{-1}\,s$ when it is presented during a sequence of unobstructed breaths, they commonly fail to detect it when it is presented during a sequence of breaths against a larger resistance. Also, subjects breathing continuously against a resistance often indicate that they believe it to be diminishing.

Wiley & Zechman (1966) showed that although the absolute value of the threshold for detection of added resistances increases as the background resistance increases, the threshold expressed as a percentage change in resistance is constant. This was not so here, where resistances were both added and subtracted. This can be illustrated as follows. One might assume a resistance of the respiratory system and mouthpiece of, say, 4 $cmH_2O\,l^{-1}\,s$. Then the reliably detected step from '0' to '1' represented a 30% resistance change, and from '0' to '2' a 63% change. From these results when loads were added rather than removed it might have been expected that the change from '2' to '1', only a 20% change of resistance, would not be detected. Instead it was usually interpreted as if it was almost twice as big a change. Moreover, the change from '2' to '0' was only rarely interpreted as a change from '2' to '1'.

It is possible that the receptors responsible for detection of added respiratory loads adapt during a series of breaths against a larger resistance and so discharge less when a smaller resistance is unexpectedly substituted than they would if the same resistance were met unexpectedly during otherwise unobstructed breathing. There is no consensus amongst workers in this field regarding the receptors responsible for the conscious detection of added respiratory loads. If a number of receptor types are involved in the conscious detection of loads then all must adapt in the manner proposed to account for the present findings.

An alternative proposal would be that it is adaptation of central neural mechanisms rather than of peripheral receptors which occurs, and is responsible for the current findings. Either proposed mechanism involving adaptation would account for the apparent decreases in resistance signalled by subjects breathing against a continuing steady load. Neither is entirely satisfactory in accounting for those many occasions when subjects failed to detect a test resistance presented during a sequence of breaths against a larger resistance. Had significant adaptation been occurring before the substitution of small resistance for larger resistance, these subjects would presumably have indicated an apparent decrease in resistance before the substitution was made. Yet the results reported here are from sequences where the correct indication was made for the breath immediately preceding the resistance change, and so provide an argument against adaptation as a mechanism. It was the practice in these experiments to halt any sequence in which an apparent 'change down' was indicated during breathing against an unchanging resistance.

A further explanation can be offered which draws a parallel between the perception of load in breathing and judgements of the weights of lifted objects. An illusion well known to psychologists is the so-called size–weight illusion. If large and small objects of equal weight are lifted, the larger always feels lighter (e.g. Woodworth, 1921). The explanation offered is this: one believes from visual or kinesthetic clues, and on the basis of experience, that the large object will be heavy. When it is not, one is struck, not so much by its absolute weight, which is presumably signalled by the various sensory mechanisms involved, but by the departure of real from unexpected weight. A similar argument explains why the small object feels heavy.

Applying this reasoning to breathing, one might suppose that during a sequence of unloaded breaths a subject comes to expect that each successive breath will be unresisted, thus when a resistance is met and correctly signalled, it is perceived to be a resistance because its signalled magnitude departs from what was expected. However, when a subject breathes a sequence of breaths against a larger resistance, his expectation becomes that each successive breath will be resisted similarly. When instead a smaller resistance is met and correctly signalled, he is struck, not by the real (signalled) magnitude of the smaller resistance, but by the departure of real from expected size of resistance. Thus he underestimates the size of the resistance, and may even believe it to be absent, as here.

In studies by Kellogg, Mead, Leith & Konno (quoted by Sears, 1971), a servo-controlled respirator was used to assist breathing in subjects, who, in time, became 'unaware of the assistance, and breathing seemed free and natural' (R. H. Kellogg, personal communication). When the assistance was unexpectedly removed, 'the next breaths, which were normally loaded by the normal resistance and elastance of the respiratory system, seemed like remarkably hard work'. Clearly, similar mechanisms could be involved in that situation and in the experiments presented here.

Clinicians are familiar with the patient who suffers chronic airways obstruction, and who is considerably less breathless than another who has an acute episode of airways obstruction producing similar changes in airways resistance. The present results may well be relevant to an understanding of the different respiratory sensations in such patients.

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Corollary motor discharges and kinaesthesia

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It is claimed that when the oculomotor muscles are paralysed, apparent motions of the external world are seen when attempts are made to turn the eyes[1,3,5]. This phenomenon was explained by Helmholtz[3] as follows: 'our judgement as to the direction of the visual axis is formed as if the will had produced its normal effects — and since no change has taken place in the positions of the images on the retina of the paralysed eye, we get the impression as if the objects shared the supposed movements of the eye'. The perception of sensory signals deriving from the motor command to the oculomotor muscles was called by Helmholtz a 'sensation of innervation'. Similar proposals for a centrifugal movement sense involving the eyes were made by Sperry[11], who spoke of 'corollary discharges' from motor to sensory areas, and by von Holst[4], who used the term 'efference copy'.

Brindley and Merton[1] found that oculomotor paralysis was not necessary to demonstrate effects attributable to corollary discharges. They simply anaesthetised the conjunctival sacs and then held the eyeballs with forceps, restraining them from moving when their subject made active attempts to turn the eyes. 'Apparent movements of external objects in the direction of the attempted movement were seen'.

In all of the observations on the role of corollary discharges in the perception of eye movement, the corollary discharges are perceived in relation to the retinal image (*i.e.* the position of objects in the external world). When Brindley and Merton repeated the experiment described above in a subject whose corneae were occluded the results were less striking. They reported that their subject 'could not tell whether the eyes were held or not', but that, whether they were held or not, 'he regularly had the impression that he succeeded in moving them'. Whether this 'impression' of success amounted to a positive feeling of movement is not clear. The most convincing experiments establishing corollary discharges as sources of perceived sensation of eye movement seem to us, therefore, to be those in which the corollary discharges were interpreted against the afferent signals set up by retinal images.

Merton[9] investigated the role of corollary discharges in the perception of movements made at the terminal joint of the thumb. The joint and skin of the thumb were selectively anaesthetised with an anoxic nerve block which left the flexor and extensor muscles of the joint unaffected. Merton claimed that his subjects perceived

the active movements they attempted at the joint and believed the movements had been achieved, whether or not they were resisted externally. This was taken as establishing the role of corollary discharges in perceived sensations of limb movements. When the same experiments were later repeated[2], however, it was found that external resistances could be detected in such circumstances. Therefore a more direct test of the role of corollary discharges in kinaesthesia became necessary. This was done in the study by Goodwin *et al.*[2] in which all the muscles of the forearm and hand were paralysed by inflating an occluding cuff above the elbow and waiting for an appropriate time. They wrote of their subjects: 'when asked to move the affected fingers or thumb they replied, after trying to move, that they could not do so and that there was no sensation of movement with even the hardest attempt'. They quoted similar experiments by Laszlo[6] supporting this finding, and concluded that corollary discharges are ineffective at inducing sensations of movement.

It seemed possible that the experiments of Goodwin *et al.*[2] and Laszlo[6] failed to show a contribution to kinaesthesia by corollary discharges because the studies were carried out in a situation of peripheral anaesthesia in which there would have been no afferent input against which to 'measure' or 'weigh' the corollary discharges. That is, the situation may have been similar to the experiment of Brindley and Merton[1] described above, in which eye movements were attempted and sometimes obstructed while vision was excluded. Therefore, the following simple experiments were performed to make the test for a contribution by corollary discharge to movement sensation in limb muscles more similar to the most convincing of the experiments on corollary discharges and oculomotor muscles. The methods used aimed at producing afferent inputs against which the subject could interpret any corollary discharges.

Paralysis of the forearm muscles of one arm was produced in 7 normal subjects. Retrograde intravenous injection of 3–5 mg of D-tubocurarine, diluted in 30–50 ml of physiological saline, was given into a superficial vein near the wrist, after first inflating a sphygmomanometer cuff above the elbow to 300 mm Hg[12]. This method caused paralysis of the finger extensors in all subjects, although some active movement remained in the flexors of 4 of the subjects. The paralysis was achieved within 5–10 min of injection, and all observations were made in the succeeding 5 min before any signs of anoxic anaesthesia were evident below the cuff. Both authors acted as subjects. The other subjects were uninformed as to the hypotheses being tested. Ethical considerations regarding informed consent required us to advise the subjects that a paralysant was to be injected — they were all led to believe, however, that it was not certain whether paralysis or simply weakness would be caused. No subjects experienced systemic symptoms, apart from mild transient diplopia, on removal of the cuff at the conclusion of the experiment.

Our subjects were first asked, with vision excluded, to make attempts to move the paralysed but unanaesthetised digits. All were aware that they could not do so, and were unanimous in their denials of any sensations of movement accompanying their attempts. When movements were achieved by muscle groups which were weakened but not paralysed they were perceived with apparently normal accuracy. Passive (imposed) movements of paralysed joints were accurately perceived.

We next proceeded to provide our subjects with cutaneous sensations consistent with successfully achieved movements. They were asked, again with vision excluded, to place both hands before them and to attempt simultaneously to extend (or flex) both index, or middle fingers. As the unparalysed finger moved it brushed against a rough surface (bristles of a paint brush, or rough string). This normal movement also drew, by means of string acting around a pulley, a similar rough surface across the immobile paralysed finger. Both fingers were thus presented simultaneously with similar cutaneous stimuli moving across them in the same direction, at the time when the subject attempted to move them. Our subjects remained unanimous in their denial that any sensation of movement of the paralysed finger accompanied the attempts to move it.

We took 3 of our subjects one step further. Instead of excluding vision, we allowed the subjects to see during the experiment just described. A mirror was placed between the hands, however, so as to obscure the paralysed hand. What the subject could see was the normal hand moving normally, and the image of the normal hand in place of the paralysed hand. When the subject attempted to move both fingers, he 'saw' both move, and felt cutaneous stimuli in both consistent with their having moved together. Two subjects, including one of the authors (D.I. McC.), were adamant that the paralysed finger did not move and that there was no sensation of movement associated with the attempt to move it. The third subject was now prepared to believe that the paralysed finger had moved. He denied, however, that he felt it move in the same way that the normal finger moved. Whenever he closed his eyes, confining himself to possible input from corollary discharges and cutaneous signals consistent with movement, he again became certain that the finger had not moved. One has only to position one's hands around a mirror as we have described, and then to move the finger of one hand while viewing it and its image, to experience the great force of the visual illusion so created. We believe our subject did not perceive corollary motor discharges as movement, but 'saw' his finger move, felt an appropriate cutaneous signal, and conclude it must have moved. 'It was as if it had been passively moved', he said.

We conclude that corollary motor discharges are not in themselves sufficient to cause perceived sensations of movement of muscles other than eye muscles. It seems that eye muscles and limb muscles differ regarding the existence of a contribution to kinaesthesia from corollary motor discharges. Even this conclusion, however, may prove unsatisfactory, as it has been claimed that the apparent movements of the external world, which accompany attempts to move paralysed eye muscles, are seen only when paralysis is incomplete, and not when it is complete[10].

Our experiments do not exclude the possibility that corollary discharges interact with afferent signals, especially those originating in muscles, before allowing those afferent signals access to consciousness[2,7]. Nor do we deny that corollary discharges may themselves provide perceived signals used in weight and tension estimations[8]. Indeed, we note that our subjects consistently volunteered that sensations of 'heaviness' were associated with attempts to move paralysed or grossly weakened muscles.

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Perceived heaviness of lifted objects and effects of sensory inputs from related, non-lifting parts

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In judging the weight of an object by lifting it, one is guided more by the effort put into the muscular contraction than by the muscular tension produced. The guiding sensation, a 'sense of effort', is an efferent, or centrifugal, phenomenon — it arises from, or together with, the command signals travelling from higher centres towards the muscles[3].

Recordings made in conscious monkeys show that some pyramidal tract neurones of the motor cortex discharge in association with stereotyped movements of the upper limb. The activity of many of these neurones has been shown to increase during anaesthesia of the hand on the active side[2]. It is clear that the cortical motor command is modified during such peripheral anaesthesia. Therefore, we were interested to see the effects of peripheral anaesthesia on the perceived heaviness of objects lifted by normal human subjects. We also investigated the effects upon perceived heaviness when subjects were given an augmented peripheral sensory input by having them grasp an object in the hand during muscular activity in the upper arm.

We have used a simple weight-matching task in which subjects estimated the weights of objects lifted and supported by contraction of the muscles of the upper arm which flex the elbow. Subjects sat with their elbows resting on the table and flexed at right angles. Inextensible strings ran at right angles from bands around their wrists, over low friction pulleys, to support light buckets of equal weight (approx. 100 g). The subjects were not blindfolded, but the buckets were hidden from their sight by the table. The loaded buckets were lifted simultaneously and supported for 3–10 sec at a time; between lifts they were supported on strings fixed to the edge of the table. The bucket to be supported by the left arm was always loaded with a 2 kg reference weight. Between lifts an experimenter altered the weights in the bucket supported on the right side according to the subjects' instructions. The subjects then made further lifts and commanded further changes until satisfied that the two buckets contained equal weights: the weight in the right hand bucket then gave an objective indication of the perceived weight on the left side. In the control and each of the test conditions the subjects made 10 such matches. Subjects were assured that their load-

TABLE I

Perceived heaviness of 2000 g weights (mean ± S.E.M. of 10 estimations) lifted using flexors of the elbow in 4 test situations. The hand on the side which lifted 2000 g was either anaesthetized or unanaesthetized, and either involved or not in a firm active grasp.

Subject	*Unanaesthetized*		*Anaesthetized*		*Significance levels (t-test, < %)*		
	Control (g) (C)	*Grasp (g) (G)*	*Control (g) (A)*	*Grasp (g) (AG)*	*C vs. G*	*C vs. A*	*A vs. AG*
F.S.	1990 ± 59	1540 ± 60	2330 ± 82	2280 ± 80	0.1	0.5	n.s.
M.P.	1910 ± 64	1430 ± 47	2840 ± 50	2670 ± 96	0.1	0.1	n.s.
M.F.	1770 ± 33	1440 ± 78	2360 ± 81	2390 ± 60	0.5	0.1	n.s.
G.O.	2000 ± 21	1620 ± 36	2150 ± 52	2100 ± 75	0.1	2	n.s.
N.D.	1670 ± 63	1350 ± 50	1820 ± 57	1790 ± 69	0.1	n.s.	n.s.
J.P.	1640 ± 54	1340 ± 45	1920 ± 55	1900 ± 49	0.1	0.5	n.s.
P.Y.	1830 ± 47	1690 ± 64	2180 ± 88	2180 ± 53	n.s.	0.5	n.s.

ing instructions would always be obeyed but were warned that this would not exclude possible 'overshoots'.

Weight-matching was performed in 4 situations: (i) control — in which the unanaesthetized hand on the reference (left) side held, without grasping firmly, a folded piece of wide rubber tubing; (ii) unanaesthetized grasp — in which the unanaesthetized hand on the reference side grasped the same tubing firmly, with about the same strength as a firm handshake, during the period of weight-bearing; (iii) anaesthetized — in which the hand on the reference side was made anaesthetic from the wrist down by inflating a cuff which occluded the blood supply[1] and (iv) anaesthetized grasp — in which the same anaesthetized hand grasped the rubber tubing firmly as before.

The results from 7 subjects who were investigated in all 4 test situations are shown in Table I. They show the following effects: (i) weights lifted by the flexors of the elbow appeared lighter than in the control situation when the hand on the lifting side was engaged in a grasp, although the lifting muscles themselves did not participate in the grasp; (ii) weights lifted by the same muscles appeared heavier than in the control situation when the hand on the lifting side was anaesthetized, although the anaesthesia did not involve the lifting muscles; (iii) the lightening effect of the grasp was no longer demonstrable when the grasp was performed with an anaesthetized hand. Significant lightening effects of grasping with a sentient hand, and significant increases in perceived heaviness during anaesthesia, were observed in a further 5 subjects.

We interpret these results as follows. There is a sensory input arising in the hand, which can be enhanced by grasping and removed by anaesthesia, and which facilitates the command signals to the flexors of the elbow. Consequently, the command required to lift a weight with these muscles is reduced during a grasp, and increased during peripheral anaesthesia. The experiments on monkeys, cited above[2], give some support to this interpretation. As the perception of heaviness arises from

the command to lift, as a 'sense of effort'[3], a weight appears lighter than usual during a grasp, and heavier than usual during anaesthesia of the hand. It appears that the facilitatory sensory input involved arises predominantly in the hand, rather than in the forearm muscles responsible for grasping, because the lightening effect of the grasp was no longer seen during anaesthesia when the grasp would have excited only sensory nerves in the forearm.

The muscles of the upper arm which flex the elbow are rarely used in situations in which the hand is not also active. It is perhaps not surprising, therefore, that the participation of the hand facilitates their normal operation. It may well be, that in order to achieve certain common cooperative motor performances, the central nervous system often relies to some extent upon facilitation of the activity of one component of a total performance by another.

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JOINT SENSE, MUSCLE SENSE, AND THEIR COMBINATION AS POSITION SENSE, MEASURED AT THE DISTAL INTERPHALANGEAL JOINT OF THE MIDDLE FINGER

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SUMMARY

1. An anatomical peculiarity allows the hand to be positioned so that the terminal phalanx of the middle finger cannot be moved by voluntary effort. When positioned in this way only joint and cutaneous mechanisms subserve position sense. By altering the position of the hand the muscles are again engaged and able to move the finger. Moving the joint then also excites muscular afferents.

2. The position sense of twelve subjects was assessed with and without engagement of the muscles at the joint. Three tests were used in which either angular displacement, angular velocity or duration of displacement were held constant.

3. When muscular attachment was restored, performance in all tests was greatly enhanced. As engagement of the muscles caused little change in the 'stiffness' of the joint, it is unlikely that the improved performance resulted from increased discharges from the joint receptors. Cutaneous mechanisms are unlikely to mediate this improvement as they are likely to have been unaffected by engagement of muscles. It is concluded that intramuscular receptors are partly responsible for normal position sense.

4. In seven of the twelve subjects the test finger was anaesthetized to isolate the contribution of intramuscular receptors. This muscle sense was variable. In some subjects it provided accurate kinaesthetic information but in others the information was crude. If with the test finger anaesthetized subjects exerted voluntary tension with the muscles that move the joint, the muscle sense was improved.

INTRODUCTION

Active and passive movements of joints excite sensory nerves in the joints themselves and in the muscles operating about the joints. It has been widely held that the discharges of the muscle afferents do not impinge on consciousness (e.g. Mountcastle & Powell, 1959; Mountcastle & Darian-Smith, 1968; Gelfan & Carter, 1967; Merton, 1964, 1970). Classical psychophysical studies of position sense (Goldschieder, 1889; Laidlaw & Hamilton 1937; Brown, Lee & Ring, 1954; Provins, 1958) have, therefore, been thought to demonstrate the properties of perceived joint sense.

The assumption that the discharges of muscle afferents do not influence the highest levels of the nervous system has recently been confounded. The demonstration of a previously elusive projection of muscle afferents to the cerebral cortex (Oscarsson & Rosén, 1963; Phillips, Powell & Wiesendanger, 1971) was closely followed by experiments in normal human subjects which showed that sensory information arising in muscles can be perceived (Goodwin, McCloskey & Matthews, 1972*a*, *b*, *c*; Skavenski, 1972; Eklund, 1972; McCloskey, 1973; Cross & McCloskey, 1973; Matthews & Simmonds, 1974; Lackner, 1975). Position sense need not, therefore, be simply joint sense; it may be compounded from both joint and muscle sensations.

In the experiments we report here that we have attempted to study joint sense alone and muscle sense alone, and the position sense which results from the combined operation of both. We have studied the distal interphalangeal joint of the middle finger, because at this joint an anatomical peculiarity permits the hand to be positioned so as to disengage the muscles from the joint, or be re-positioned so that the muscles are again engaged.

METHODS

A major part of the present study quantitates and compares the perception of passive movements of different velocities and duration at the distal interphalangeal joint of the middle finger when muscles are engaged, and when they are not engaged to the joint. The kinaesthetic sensitivity of the joint was tested again when the skin and joint of the middle finger had been anaesthetized.

Subjects. Experiments were performed on twelve healthy male and female subjects aged 19–33 years. Both authors, and one other physiologist, acted as subjects. The remaining nine subjects were technicians or students, and were not aware of the hypotheses being tested. All subjects attended on four occasions when 'joint' sense, and joint plus muscle sense were tested (see below); seven of the twelve attended on a fifth occasion when muscle sense was tested alone during digital anaesthesia.

Positioning of the hand. If the index, ring and little fingers are extended and held extended, and then the middle finger alone is flexed maximally at the proximal interphalangeal joint, the terminal phalanx of that finger cannot be moved by voluntary

effort, irrespective of the angle of the metacarpophalangeal joint. Flexion and extension of the distal interphalangeal joint are impossible because the long muscles which move it are held at inappropriate lengths (Gray, 1973). In this position, the joint is freed from effective muscular attachment. If anaesthetized in this position, the joint loses all position sense, but regains it when the adjacent fingers are aligned with the test finger, restoring effective muscular attachment (Goodwin *et al.* 1972*c*; confirmed here).

We immobilized the hand in two positions, as shown in Pl. 1. In one position (Pl. 1*B*) all fingers were extended except the middle finger, which was flexed at the metacarpophalangeal and proximal interphalangeal joint. The finger fitted through a hole in a board and was clamped at the proximal interphalangeal joint. With their hands thus positioned all subjects were unable to move the terminal phalanx of the middle finger. In the other position (Pl. 1*C*) both the proximal and distal interphalangeal joints were restrained in the fully flexed position in all fingers but the middle one. The middle finger was fully flexed at the proximal interphalangeal joint and slightly flexed at the distal joint. All subjects could now flex and relax the distal interphalangeal joint, but could not actively extend the joint (Gray, 1973). In both positions the angle of the distal interphalangeal joint of the middle finger was set at 30–40° from full extension for testing: this approximates the resting angle of the joint in both postures. Testing was not carried out with the joint initially set further into flexion or extension because skin stretching could sometimes occur in such positions and provide accessory clues for detection of joint displacements.

The immobilizing devices (Pl. 1) which held the hand in the postures were adjusted so that imposed displacements of the terminal phalanx caused movement only about the distal interphalangeal joint of the middle finger. Once an appropriate positioning of the hand was achieved, the immobilizing device was clamped to the table at which the subject sat.

Attachment to finger displacer and calibration. A 17 mm length of hypodermic needle (external diameter 2 mm) was glued to the nail of the middle finger (Ciba Geigy: Fast-set Araldite). The forked ends of a brass rod were fitted into the hollow tube to complete a stirrup arrangement (Pl. 1*A*). The distal end of the rod was coupled to an electromagnetic vibrator driven by a ramp generator (Advanced Dynamic Industries: Vibrator AV-50 and oscillator/amplifier N-300). There were thus two mechanical joints with axes in the same plane between the vibrator and the finger-nail: between the hollow tube on the finger-nail and the rod, and between the rod and the vibrator (Pl. 1*A*, *a* and *b*). This arrangement minimized torsional forces on the finger-nail during movement. As the nail-bed is sensitive to pressure, merely coupling the finger displacer to the finger-nail in this way introduced some accessory clues about any movements imposed by the rod on the finger. These clues were minimized by placing a paper clip tightly across the finger and finger-nail so as to depress the nail in the region of the cuticle, proximal to the coupling of the displacer to the nail. If, during an experiment, a subject reported in response to our questions that cutaneous sensations or pressure on the nail-bed were providing the basis for his detection of movements, either a new paper clip was applied, or movable parts of the immobilizing board were adjusted, and the whole experiment was re-started.

The position of the finger was recorded by displaying the output of a position transducer (Schaevitz: GPM-101) coupled to the displacing rod, on a rectilinear chart recorder (Hewlett-Packard: 7402A). Angular calibration was achieved by using a fine mark on the tip of the finger and a large protractor placed directly under the subject's hand, with its centre directly below the axis of movement of the distal interphalangeal joint. The joint was then displaced 5° and 10° in both flexion and extension. Over the range tested ($\pm$ 10°), a linear relation existed between angular displacement and displacement of the rod. Depending on the calibration of flexion

and extension and on the variable output of the ramp generator for flexion and extension, the calculated angular velocities for flexion and extension were often slightly different at any particular setting of the ramp generator.

Testing and scoring procedures. Three basic tests of position sense were used, first with the muscles disengaged then with muscles engaged. Test *A* involved moving the distal interphalangeal joint through 10° at velocities from 1 to 10°/sec. In Test *B*, the joint was displaced for 1·2 sec at velocities from 1 to 10°/sec. At any particular velocity (Tests *A* and *B*) the subject received in random order ten movements into flexion and ten into extension from the initial angle. In Test *C* the joint was displaced through 2·5°, 5°, 7·5° and 10° from the initial angle at approximately 8°/sec. Subjects received twenty movements altogether (ten into flexion and ten into extension) at each angular displacement. The magnitude and direction of the displacements in Test *C* were randomly chosen and subjects received groups of twenty such movements. After each set of twenty movements, in all tests, subjects were allowed to rest for 2–5 min.

For the twelve subjects, Tests *A*, *B* and *C* without the muscles engaged required three experimental sessions (about 2 hr each), while repetition of the tests with the muscles engaged required only one such session. In tests in which the angular velocities were varied, six of the subjects (randomly selected for each test) were moved in steps of decreasing angular velocity and six subjects in steps of increasing velocity. When the tests were repeated with the muscles engaged and able to flex the joint, subjects were instructed to relax the hand and to exert no tension.

Subjects were asked to respond verbally 'in' (flexion) or 'out' (extension) when they were certain that they knew in which direction their finger had been moved. The term 'detection' is used to indicate correct nomination of direction. To score a point, the subject had to state correctly the direction of movement, either while the movement was taking place or within 3 sec of the finger reaching its new position. The finger was returned to its initial position (30–40° in flexion) immediately after a correct detection or after it had remained at the new position for 3 sec. After being reset to its initial position the finger was not moved for a variable period of 5–10 sec. Subjects received no score for stating incorrectly the direction of movement or for detecting the re-set to the starting position. Our instructions ensured that the overall frequency of false detections was less than 1·5 % (false detections per hundred finger displacements) for tests in which the muscles were not engaged and less than 0·3 % for tests in which the muscles were engaged. The highest rate of false detections by any subject in any test was 5 %.

Presentation of data. Examples of the data acquired from individual subjects (J.R., I.M.) for tests involving 10° displacements are shown in Text-fig. 1. Scores for displacements into flexion and extension are distinguished. To compare the results of the twelve subjects with and without engagement of the muscles (in tests involving 10° displacements and displacements for 1·2 sec) the data from each subject were plotted on the same graph, without distinction between flexion and extension scores, as in Text-figs. 2*A* and 3*A*. To quantitate the performance of the population (Text-figs, 2*B* and 3*B* at bottom) the data were arbitrarily divided into groups of angular velocity, 1·0–1·9°/sec, 2·0–2·9°/sec etc.; some subjects appear more than once in some categories, and do not appear in others. In the studies of 'joint' sensation, not all subjects were moved in the faster range of angular velocities: the best score achieved at the highest velocity used was assumed to be the score in higher velocity brackets for these subjects. Such assumed 'scores' were used to calculate averages. As scores generally improved as the angular velocity increased, this assumption slightly underestimated the accuracy of joint sensation of the population at velocities above 8°/sec. In tests of position sense with the muscles engaged, once a subject had achieved a perfect score (for movements both in flexion and in extension) he was not

usually moved at higher velocities; it was assumed that at higher velocities his score would still have been maximal. This assumption was validated by moving some subjects at higher velocities. Statements in the Results refer to the raw data, and not to data obtained by extrapolation in the above manner.

Anaesthesia. In some experiments fingers were anaesthetized by digital nerve block, using 3–4 ml. lignocaine 2 %, without adrenaline, injected about 1 cm distal to the base of the finger. This produced complete digital anaesthesia as judged by loss of pain, pressure and touch sensation. We maintained the anaesthesia for periods up to 1 hr by placing a wide rubber band around the base of the finger sufficiently tightly to impair venous, but not arterial flow. After removal of the rubber band there was slow recovery of sensation. In subjects anaesthetized in this way the usual ethical requirements of informed consent were fulfilled.

RESULTS

Position sense of the joint isolated from muscle attachment

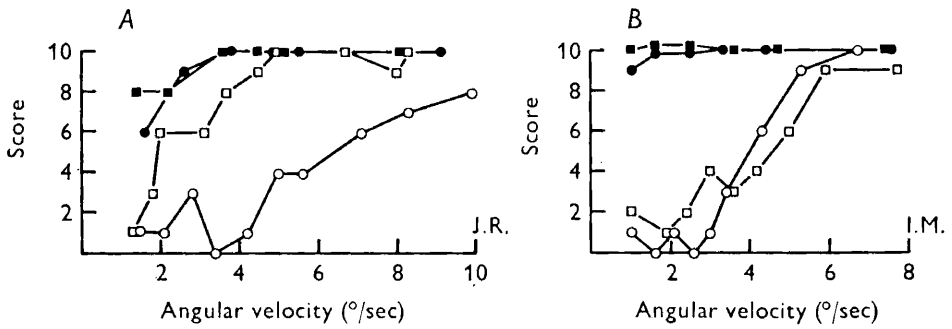
When the hand was positioned so that the distal interphalangeal joint of the middle finger could not be moved voluntarily by the subject, detection of imposed movements relied upon sensory information from receptors in and around the joint, and perhaps to some extent from receptors in the overlying skin. Text-figs. 2, 3 and 4 show the results obtained in twelve subjects in the principal tests (Tests *A*, *B* and *C* described above) when only these sensory mechanisms were available to the subjects. The contribution to position sense from joint receptors could provide no greater acuity than is shown in these results.

Results for Test *A* (10° displacements) from two individual subjects are shown in Text-fig. 1. In these subjects, scores for detections of flexion and extension movements are shown separately. When the joint alone was responsible for the detections, it can be seen that one of the subjects (Text-fig. 1*A*) was better at detecting flexion than extension, while the other detected both with about equal accuracy. Several subjects showed unequal accuracy of detection of flexion and extension movements, although the discrepancy in other subjects was never as marked as that illustrated in Text-fig. 1. Some of these subjects were better at detecting flexion, some extension: in the group of twelve subjects we investigated there was no significant bias towards detection of movement in one or other direction. In other figures we have not, therefore, distinguished the direction of movement.

For 10° displacements (Test *A*: Text-fig. 2) one subject (A.B.) achieved the maximum score at 4·1°/sec. By the highest velocity range (9·0–9·9°/sec) four of the twelve subjects had still not achieved a faultless score. A score of eight or more out of ten was obtained by eleven of the twelve subjects at angular velocities in the range 6·0–7·9°/sec. In this test the absolute displacement of the joint was always the same: the improved performance at

higher angular velocities indicates that the receptors responsible for detection were sensitive to movement (as well as displacement, see below).

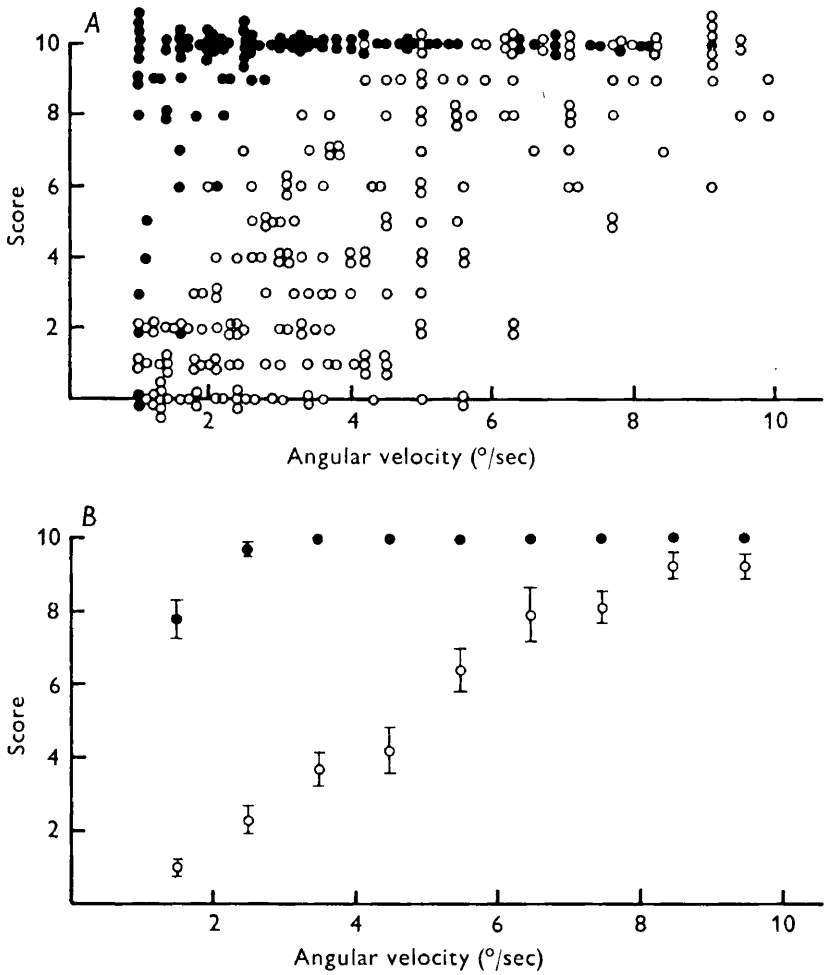
When the duration of displacement was limited to 1·2 sec (Test *B*; Text-fig. 3), one subject (N.D.) recorded a maximum score at 4·5°/sec. Even at angular velocities exceeding 9·0°/sec, two subjects failed to achieve faultless scores. A score of eight or more out of ten was obtained by



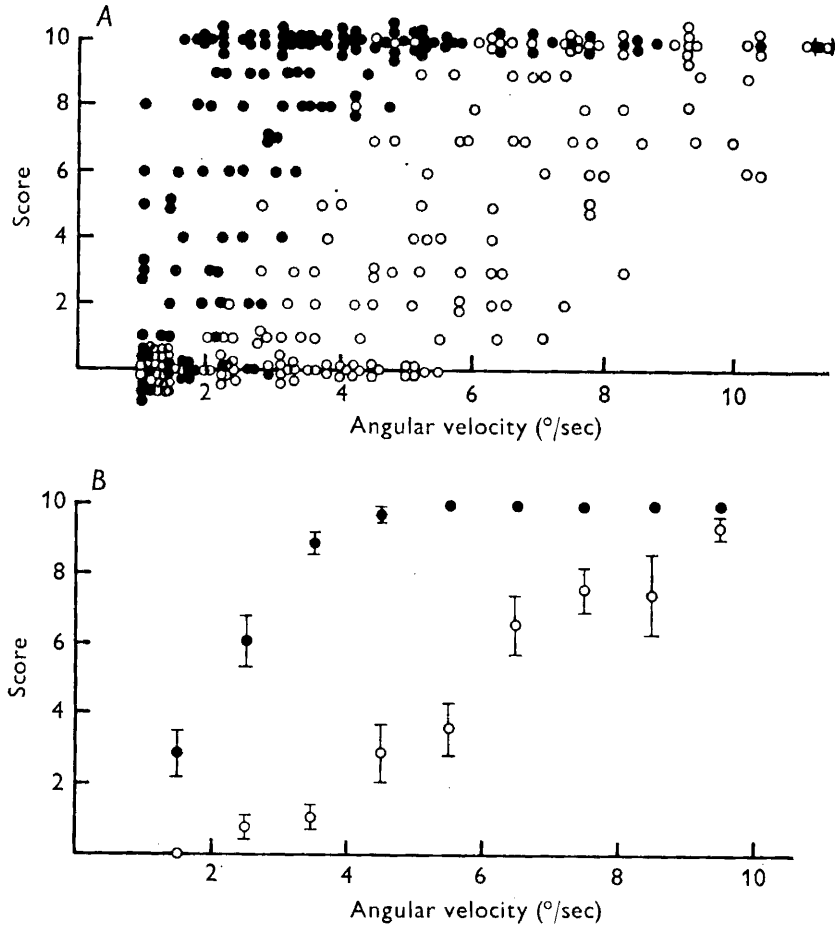
Text-fig. 1. This shows the results of the test using 10° displacements (Test *A*) in two subjects, with muscles disengaged from the joint (open symbols) and with muscles engaged at the joint (filled symbols). Scores out of ten trials for movements into flexion and into extension are represented by square and circular symbols respectively. When joint mechanisms alone were involved, in one subject (*A*), scores for movements into flexion were higher than those for movements into extension. This discrepancy in the detection of movements of different directions was not present in the results of the other subject shown (*B*), nor was it a common feature in the detection of movements by other subjects. In both subjects scoring was higher when the muscles were engaged.

ten of the twelve subjects within the velocity range 7·0–8·9°/sec. In this test, by maintaining the duration of displacement constant, both velocity and displacement signals from receptors would have been expected to increase with increasing velocities of angular displacement.

In the third test of position sense, the angular velocity of displacement was held constant (Test *C*; Text-fig. 4) and the joint was displaced at approximately 8°/sec (mean 8·4; range 7·1–10·4°/sec) in random order through 2·5°, 5·0°, 7·5° and 10°. Both flexion and extension movements were tested. No subject scored more than five out of ten when the displacements were 2·5°, but ten of the twelve subjects scored eight or more out of ten for displacements of 7·5°. In this test the angular velocity of displacement was constant: the improved performances at greater displacements indicate that the receptors responsible for detection are sensitive to displacement (as well as velocity, see above). A population of slowly



Text-fig. 2. This presents in two forms the results from the twelve subjects for Test *A*, involving displacements of 10° at various angular velocities, when the muscles were not engaged (open circles) and when the muscles were engaged (filled circles). No distinction is made between scores obtained for movements into flexion and movements into extension. *A*, data from the twelve individual subjects are plotted together. *B*, scores from individual subjects in the range of angular velocity 1·0–1·9, 2·0–2·9°/sec, etc., and some extrapolated scores in the higher velocity categories have been averaged and the mean score (± S.E. of mean) is plotted for each category. Procedures used to estimate the mean performance of the population are described in the Methods. Both presentations of data show that the acuity of position sense was enhanced by engagement of muscles at the joint. For the full proprioceptive machinery (filled circles) and for joint mechanisms alone (open circles) detection improved as the angular velocity increased, although the angular displacement remained constant.

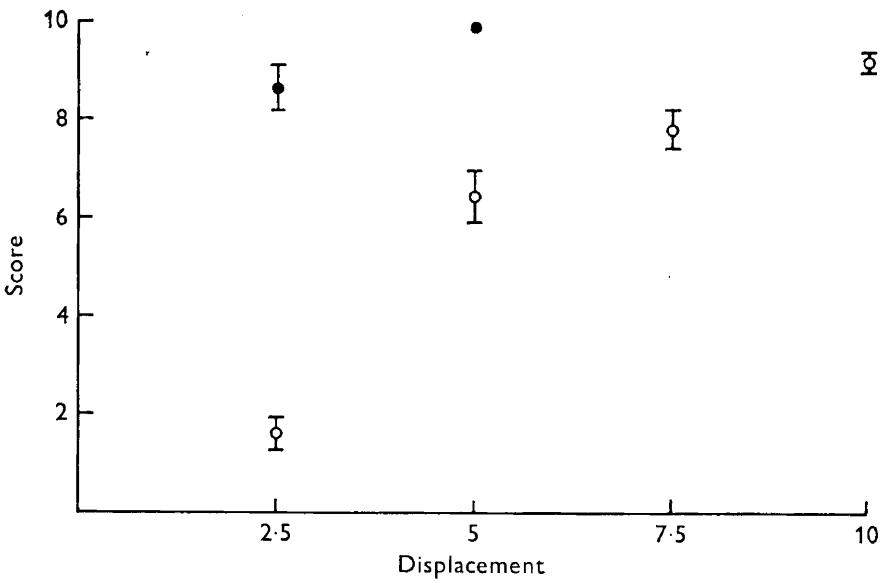


Text-fig. 3. This presents in two forms the results of twelve subjects for Test *B*, involving displacements for 1·2 sec at various angular velocities, when the muscles were not engaged (open circles) and when the muscles were engaged (filled circles). No distinction is made between scores obtained for movements into flexion and into extension. *A*, data from the twelve individual subjects are plotted together. *B*, scores from individual subjects in ranges of angular velocity 1·0–1·9, 2·0–2·9°/sec etc, and some extrapolated scores in the higher velocity categories have been averaged and the mean score (± S.E. of mean) is plotted for each category. Procedures used to estimate the mean performance of the population are described in the Methods. Both presentations of the data show that the acuity of position sense was enhanced by engagement of muscles at the joint. For the full proprioceptive machinery (filled circles) and for joint mechanisms alone (open circles) detection improved as the angular velocity and displacement increased, the duration of displacements remaining constant.

adapting joint receptors, sensitive to both positions and velocity, has been described in animals (Boyd & Roberts, 1953; Skoglund, 1956).

Position sense of the joint with muscular attachment restored

When the hand was immobilized in a position which allowed flexors to move the terminal phalanx of the middle finger (Pl.1*C*), imposed movements of the joint could have excited both joint and muscle receptors. The



Text-fig. 4. This presents the results from twelve subjects for Test *C*, involving displacements of 2·5°, 5°, 7·5° and 10° into both flexion and extension at an angular velocity of about 8°/sec, when the muscles were not engaged (open circles) and when the muscles were engaged (filled circles). Results are shown as the mean score (± S.E. of mean) for each angular displacement. The acuity of position sense was enhanced by engagement of muscles at the joint. With the muscles engaged it was not necessary to move subjects through 7·5° and 10° as eleven of the twelve subjects scored ten for movements of 5° (into flexion and into extension: see text). For the full proprioceptive machinery (filled circles) and for joint mechanisms alone (open circles) detection improved as the angular displacement increased although the angular velocity of movements remained constant.

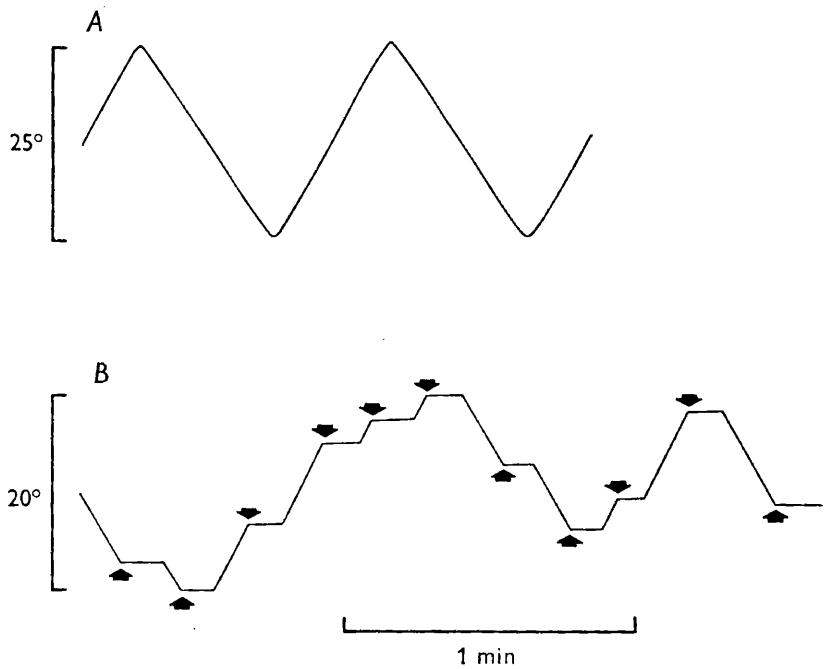
three proprioceptive tests were repeated with angular displacement, duration of displacement and angular velocity held constant (Tests *A*, *B* and *C*), and the results are shown in Text-figs. 2, 3 and 4 respectively.

For 10° displacements (Text-fig. 2), three subjects achieved perfect scores at the slowest velocities tested (*ca.* 1°/sec). All subjects detected all displacements at angular velocities exceeding 2·9°/sec.

With movements of 1·2 sec duration (Text-fig. 3), three subjects had

achieved perfect scores in the range 1·0–1·9°/sec. In the 3·0–3·9°/sec range all subjects had scored eight out of ten or better. All displacements for 1·2 sec were detected at angular velocities exceeding 4·9°/sec.

Angular displacements of 2·5° and 5° at the constant velocity of about 8°/sec (mean 7·5; range 6·3–9·6°/sec) were faultlessly detected by five of



Text-fig. 5. This shows an angular position recording, from a subject: *A*, first positioned so that the muscles were not engaged; and *B*, then so that the muscles were engaged. The points at which the subject stated correctly the direction of movement are indicated by arrows. After any detection there was a pause of several seconds before another movement was started. Movements were at a velocity of about 1°/sec and started from the same initial angle in the two positions. When the muscles were not engaged the subject did not detect any movements, although the distal interphalangeal joint was moved through sweeps of 25°. When muscular attachment was restored to the joint the subject made eleven detections of movement within an angular range of 20°.

the twelve subjects (Text-fig. 4). Of the twelve subjects, eleven scored eight or more out of ten when displaced 2·5° and these subjects detected all displacements of 5°. The subject (F.S.) who failed to detect one 5° displacement correctly detected all displacements (ten in flexion, ten in extension) when displaced 7·5°.

As was found in the tests of joint sense alone, complete position sense was improved by increasing either the extent or velocity of a movement. However, when the full proprioceptive machinery was available, in all

tests, at all ranges of angular velocity and displacement, the subjects' abilities to detect movements were greatly improved.

The enhancement of performance by the addition of muscular mechanism was highlighted in one uninformed subject who was tested with the muscles disengaged immediately before being tested with the muscular attachment restored. He was instructed to state the direction of movement which he was sure had occurred, and he was told that after detecting a movement there would be a short pause of several seconds before another movement was started. From the same starting point (30° into flexion) his finger was moved at about 1°/sec through sweeps of 25°. He failed to detect the direction of these movements (Text-fig. 5) and afterwards stated that he did not even realize that his finger had been moved. This procedure was repeated less than 5 min later when his hand was re-positioned so that voluntary movement of the terminal phalanx was possible. He was tested, however, with the hand quite relaxed. Some displacements of less than 2·5° were detected. Eleven detections of movement were made in that part of the record shown in Text-fig. 5, while the finger was moved through a slightly smaller angular range (20°).

Tension developed during movements when muscles were engaged and not engaged to the joint

Preliminary testing using the hand positions but *not* the immobilizing devices often suggested that engagement of muscles to the distal interphalangeal joint greatly increased the resistance to movement. We measured the resistance met during joint movement by attaching a force transducer (Grass FT03) midway along the finger-nail and using it to move the terminal phalanx of the finger. The tension developed during movements was recorded in six of the twelve subjects, positioned in the immobilizing devices, for 10° displacements into flexion and into extension when muscles were engaged and not engaged to the joint. These measurements indicated the resistance to movement of the joint in the two conditions. Table 1 shows that in four of the six subjects engagement of muscles was surprisingly associated with a decrease in the tension developed during 10° displacements into both flexion and extension. Possibly, slight changes in the tension of the skin around the joint accounted for this. In the remaining two subjects, tension was increased with muscular engagement. There was no apparent correlation between tension and the improvement in performance.

When the hand was immobilized so that flexor muscles were able to move the terminal phalanx, the heaviest weights that the six subjects could lift (using a flexion movement) were also recorded (Table 1). This weight indicated the maximal tension that could be exerted by the flexor

muscles on the distal interphalangeal joint. Subjects all lifted weights which were in excess (by at least forty times) of the tensions recorded during passive movements.

TABLE 1. Tensions required to impose 10° displacements on the distal interphalangeal joint

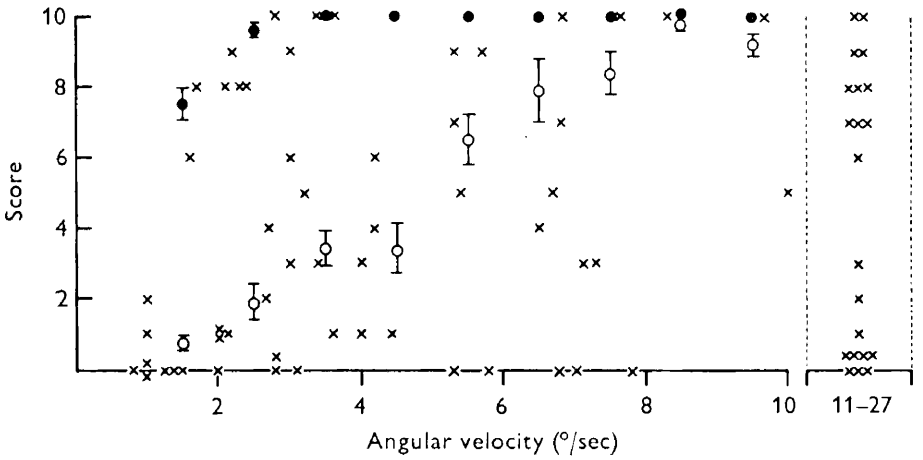
	Tension in flexion (g)		Tension in extension (g)		
Subject	Muscle not engaged	Muscle engaged	Muscle not engaged	Muscle engaged	Maximum flexion tension (g)
G.O.	17	12	40	27	3000
R.D.	20	12	23	13	2000
I.N.	42	70	48	70	2800
S.S.	45	52	47	60	3200
I.M.	23	10	43	32	4500
S.G.	25	12	46	30	3500
Mean	29	28	41	39	3167
Range	17–45	10–70	23–47	13–70	2000–4500

Proprioceptive performance of the joint when muscle mechanisms alone contributed

In seven of the twelve subjects the middle finger was anaesthetized and the hand was positioned so that flexor muscles could move the terminal joint of the middle finger. Thus the ability of the muscles themselves to provide kinaesthetic information was isolated. Subjects were again instructed to refrain from exerting any voluntary tension with their test fingers in order, as the subjects often stated, 'to find out where the fingers were'! In all other respects subjects were prepared as for the earlier tests. They underwent the tests involving 10° displacements at a series of angular velocities. Modification of the ramp generator now allowed displacement of the joint at velocities exceeding 10°/sec. The performance of the seven subjects in this test are plotted with the grouped data for the same subjects without effective muscular attachment, and when their middle fingers were anaesthetized (Text-fig. 6).

With the muscles providing the only source of proprioceptive information, detection was extremely variable. Of the seven subjects, two (R.D. and I.M.) reached a high level of scoring at low velocities, while two others (G.O. and I.N.) did not detect any movements until the angular velocity exceeded 10°/sec. The best score for I.N. was three out of ten at 24°/sec, and for G.O. it was seven out of ten at 27°/sec. The performance of two of the three remaining subjects was between these extremes. One managed perfect scores only at a velocity of 12°/sec, and the other consistently achieved high scores (> 6) at velocities above 11°/sec, but scored only nine at 20°/sec. The seventh subject (F.S.) failed to detect any movements at

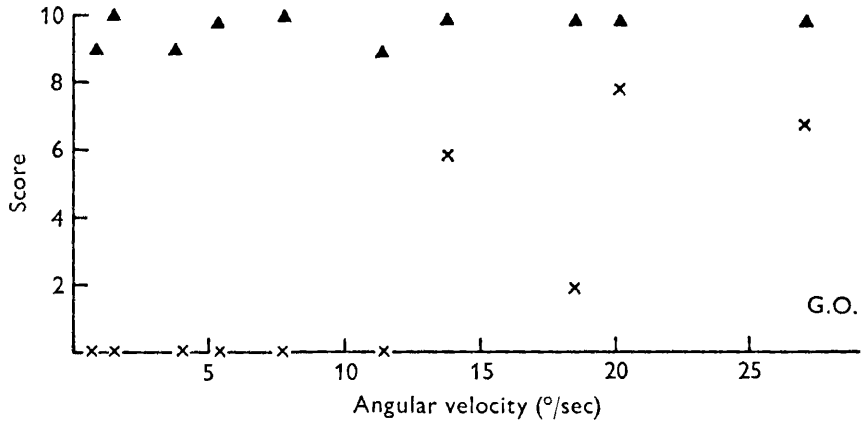
angular velocities less than 2°/sec or more than 10°/sec. In one subject (R.D.), who initially scored eight and nine at angular velocities of 2–3°/sec, the performance decreased to four out of ten (in both flexion and extension) at velocities of 4–5°/sec, but the subject scored faultlessly at velocities of 8–10°/sec. Such variability amongst individual subjects was not seen in the earlier part of the investigation.



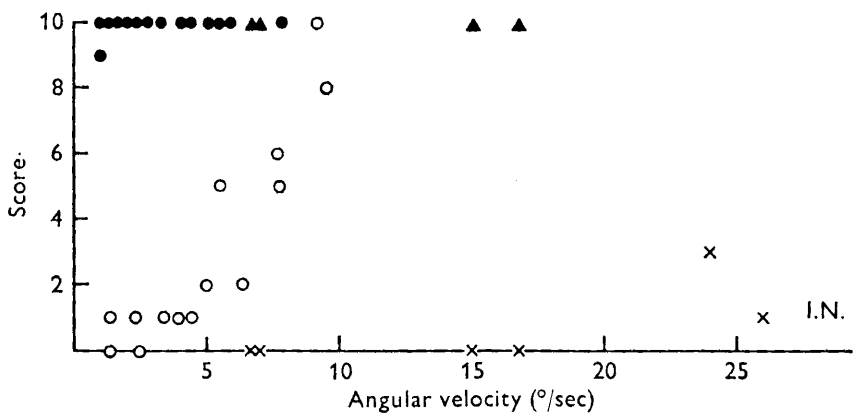
Text-fig. 6. This presents the results from seven subjects for Test *A*, involving 10° displacements at various angular velocities when the test finger was anaesthetized by digital nerve block thus removing the joint and cutaneous contributions to position sense. For the same subjects, when the test fingers were unanaesthetized, the figure shows the mean score (± S.E. of mean) when the muscles were not engaged (filled circles) and when the muscles were engaged at the joint (open circles): see Methods. Individual scores obtained when muscles alone contributed to position sense are represented by crosses. In the angular velocity range 11–27°/sec the scores are grouped together (at right). The performance of muscle sense was very variable. In some subjects it was better than the performance of joint sense, and almost as acute as normal position sense. In other subjects it was much less accurate than joint sense.

If the subjects were allowed to tense their finger flexors the appreciation of the displacements was greatly enhanced. This is shown in Text-fig. 7 for a subject (G.O.) whose muscle alone provided crude perceived proprioceptive signals, but when he exerted tension his performance was indistinguishable from that achieved when joint, muscular and cutaneous mechanisms were intact. When tension was exerted, performance was improved, even in those subjects whose performance in the absence of voluntarily exerted tension had been either poor or variable.

Proprioceptive performance using only the relaxed muscles seemed inconsistent with the marked improvement caused by engagement of muscles when the joint itself was unanaesthetized. This problem is well



Text-fig. 7. This shows the results from one subject for Test *A*, involving 10° displacements at various angular velocities, when his test finger was anaesthetized by digital nerve block, thus removing joint and cutaneous contributions to position sense. In one series he was instructed to exert no tension with his anaesthetized finger (crosses), but in the other he was allowed to exert some tension by contracting his flexor muscles (triangles). When the muscles were relaxed and providing the only source of proprioceptive information, performance was variable; the subject's highest score was eight at 20°/sec. When the flexors voluntarily exerted tension, performance was greatly improved; the subject scored nine or ten at all velocities, even at about 1°/sec.



Text-fig. 8. This shows the results from one subject for all tests involving 10° displacements, with the muscles not engaged (open circles), with the muscles engaged (filled circles), with his finger anaesthetized but not exerting tension (crosses) and then exerting tension (triangles). The muscle sense of this subject was improved by the exertion of tension, but without tension it was the least acute of the seven subjects studied with their test fingers anaesthetized, When muscular mechanisms were brought into play and the finger was unanaesthetized, the full proprioceptive apparatus was very accurate.

illustrated by the data from one subject (I.N.) shown in Text-fig. 8. This subject performed in the usual way when joint sensation was tested, but had a particularly blunt muscular sense (which was, none the less, greatly improved when he developed voluntary tension). When his not unusual joint sense and his crude muscular sense were available together, the resulting position sense was superior to either component, and showed normal acuity.

The effects on position sense of anaesthesia of parts adjacent to those being moved

Enhancement of joint afferent signals by increasing joint capsular tension, or kinaesthetic information arising in the muscles themselves, could have mediated the improvement we found in position sense when muscular attachment was restored to the joint. However, we recognized a third possibility. Anaesthesia of the digit being moved may have removed a facilitatory input which helps signals from muscle afferents reach consciousness (see Discussion).

To investigate this possibility we set out to study position sense at the distal interphalangeal joint when joint and muscular sense were intact but when the skin of the finger was anaesthetized. Using a method for cocaine iontophoresis similar to that described by Rein (1924), we found that it was not possible to achieve anything but slight and patchy cutaneous anaesthesia of the finger-tip. Talbot, Darian-Smith, Kornhuber & Mountcastle (1968) had similar difficulties with the finger-tip. Immersion of the finger-tip in cocaine solution containing dimethylsulfoxide, a solvent capable of carrying substances into human skin (Stoughton & Fritsch, 1964), either with or without an applied current, gave no better result.

To circumvent this problem, cutaneous and joint sensation was removed instead from fingers adjacent to the finger being moved. In three subjects the index and ring fingers were anaesthetized; in another four subjects only the index fingers were anaesthetized. In a specific test, performance with adjacent finger(s) anaesthetized was recorded. Performance was then monitored as the subject slowly recoverd from the anaesthesia (see Methods). The test involved three angular displacements at the same angular velocity (ten movements at each displacement, five in flexion and five in extension). After each repetition of the tests the middle finger was carefully examined for spread of anaesthesia: in no subject did any sign of anaesthesia appear in the test finger.

Of the three subjects in whom both index and ring fingers were anaesthetized, two improved their performance during and after the recovery of sensation. In the third subject the results were equivocal. Of the four subjects in whom only the index finger was anaesthetized, two showed

some impairment of appreciation of movements of the test finger during the period of anaesthesia. All subjects gave the subjective report that movement seemed more difficult to detect during the period of anaesthesia.

DISCUSSION

In the present study we have quantitated 'joint' sense and muscle sense separately and in combination. As 'joint' sense was always enhanced when muscles were pulled upon, the term *joint sense* can no longer be used to describe adequately the full proprioceptive sense. 'Joint' sense, as we have described it here, may be subserved by both articular and cutaneous afferents, although a specific contribution by the latter group is by no means certain (see below). Joint mechanisms alone could not do better than the 'joint' sense quantitated here.

In some subjects, muscle sense was more accurate than when 'joint' sense was intact, while in others it was much less accurate. Tensing of the muscles which moved the joint always improved the muscle sense, to such an extent in some subjects, that performance using muscle sense enhanced by tension was as acute as when all the proprioceptive machinery was intact.

The most likely explanation of the enhancement of performance which occurred when effective attachment of the flexor muscles was restored is that perception was aided by discharges of intramuscular receptors (known to discharge in such circumstances, Vallbo, 1974*a*). An alternative view is that the joint sense component of position sense was increased by engaging the muscles (e.g. muscular engagement may increase joint capsular tension and hence joint afferent discharge: Andrew & Dodt, 1953; Skoglund, 1956; Millar, 1973). This is less attractive as it implies an increase in the resistance to movement. We found little change in the resistance to movement when muscular attachment was effectively restored to the joint. Moreover, movements into extension always met with more resistance than movements into flexion (Table 1), but this was not reflected by easier detection of movements into extension.

As another possibility, it is conceivable that the two postures of the hand create different backgrounds of neural activity which alter the access of proprioceptive signals to consciousness. Thus, the same input from joint receptors might be differently received by the nervous system when presented in a different neural context. This explanation would require neither enhancement of joint afferent firing, nor participation of muscle afferents, to account for the improved performance seen in the posture which also happens to engage muscles.

As the initial angle of the joint employed in all our experiments was

30–40° into flexion, and as the displacements were small (± 10°), the extremes of angular range were not used (see Methods). At extremes of joint displacement the total activity of joint receptors has been shown, in animal experiments, to be maximal (Cohen, 1956; Skoglund, 1956; Burgess & Clark, 1969). Burgess & Clark, however, found that the majority (140 of 209) of slowly adapting units fired maximally at extremes of both flexion and of extension so that their discharges may have been ambiguous to a sensorium requiring information on direction of movement. Rapidly adapting receptors in and around the joint (Skoglund, 1956), and most of the slowly adapting receptors described by Burgess & Clark (1969), could serve as 'event markers' to signal that the finger had started to move. Indeed, our subjects often detected a feeling of movement before they recognized its direction, as reported by Goldschieder (1889) and Laidlaw & Hamilton (1937).

If the discharges set up in muscle receptors were predominantly responsible for the enhanced performance, then our results may have underestimated the usual contribution made by muscle to position sense at most joints. Because movement at the *proximal* interphalangeal joint was prevented in our test procedures, there was engagement only of flexor and not of extensor muscles at the *distal* interphalangeal joint. Thus imposed movements could, at best, have altered only the pull upon the flexor muscles. At other joints, muscle afferent discharges in both agonist and antagonist muscle groups would be altered by passive movements, and at these joints, the muscular contribution might be greater.

Our experiments give no information on the nature of the intramuscular receptors involved in perception. It has been suggested that the muscle spindle afferents may participate in such perceived sensations (Goodwin *et al.* 1972*a*, *b*, *c*; McCloskey, 1973). If the spindle afferents are involved, the variability of muscular sense from subject to subject might be due to a variability of fusimotor tone. While Vallbo (1974*a*) has found little evidence of fluctuations in fusimotor tone in the muscles of normal relaxed subjects, he has (1974*b*) reported that parallel increases in fusimotor and skeletomotor outflow occur when the muscles are contracted. Thus, the variability of performance with muscular sensation alone, both between subjects and for some individual subjects, may reflect subconscious changes in tension exerted by the flexor muscles, despite the instruction to relax the hand. Chambers & Gilliatt (1954) noted in a study of patients with spastic paralysis in whom the hand had been anaesthetized using an anoxic block, that position sense of the fingers was 'strikingly preserved'. When our subjects with anaesthetized fingers were asked to exert tension, there was a marked improvement in the detection of movements. This increased afferent inflow from contracting muscles could well be responsible for the

greater accuracy of position sense which is seen when a joint is actively, rather than passively, positioned (Goldschieder, 1889; Paillard & Brouchon, 1968, 1974; Eklund,1972).

The role of cutaneous sensation in position sense is uncertain. On some occasions we found that cutaneous cues aided our subjects in their detection, but on such occasions we halted the whole test series and started again after making adjustments to remove the cues. Throughout the study we took great care to minimize any specific cues arising in skin. If specific discriminative information from cutaneous receptors did aid our subjects in their detections, it is difficult to see why there were differences in acuity when the musculature was engaged and disengaged. If skin receptors could give the information, they should have done so equally well in both test situations.

While we believe that specific information arising from cutaneous receptors was minimal (cf. Cohen, 1958), we regard the possibility of some non-specific facilitatory input from skin as rather more likely. Loss of such a non-specific input may explain the apparent crudity of muscle sense found here when measured in anaesthetized fingers. It is known that afferents from the skin and joint of the thumb co-operate in the expression of the stretch reflex of the long flexor of the thumb, because, if these afferents are blocked the stretch reflex is almost completely abolished (Marsden, Merton & Morton, 1971). Co-operation between discharges of muscular receptors and the cutaneous input is further suggested by the findings of Goodwin *et al.* (1972*c*) and Cross & McCloskey (1973). They reported that position sense was normal in subjects in whom a joint had been completely removed and replaced with an artificial device, thus effectively removing the joint afferents but leaving intact the cutaneous afferents. We were unable selectively to anaesthetize the skin to test this possibility further (see Results). However, in some subjects, proprioceptive performance was impaired by anaesthetizing the skin and joints of the fingers adjacent to the one being tested. In these subjects the removal of a tonic input from adjacent fingers may have had sufficiently widespread effects within the central nervous system to have made normal proprioceptive discharges referred to the middle finger less readily accessible to consciousness. The hypothesis that muscle afferent signals require tonic facilitation from the skin, and possibly joint afferents, was first suggested by Provins (1958), and it receives some support from these experiments. It deserves further study.

Note added in proof. Recent electrophysiological evidence published after preparation of this paper (Clark & Burgess, 1975, *J. Neurophysiol.* **36**, 1448–1463) casts further doubt on the ability of joint afferents to signal joint angle accurately. The 'joint' sense that we describe may thus

include a significant specific contribution from cutaneous afferents. It may well be that cutaneous afferents have both a specific role in position sense as well as a more general facilitatory function of the type we have suggested in our Discussion.

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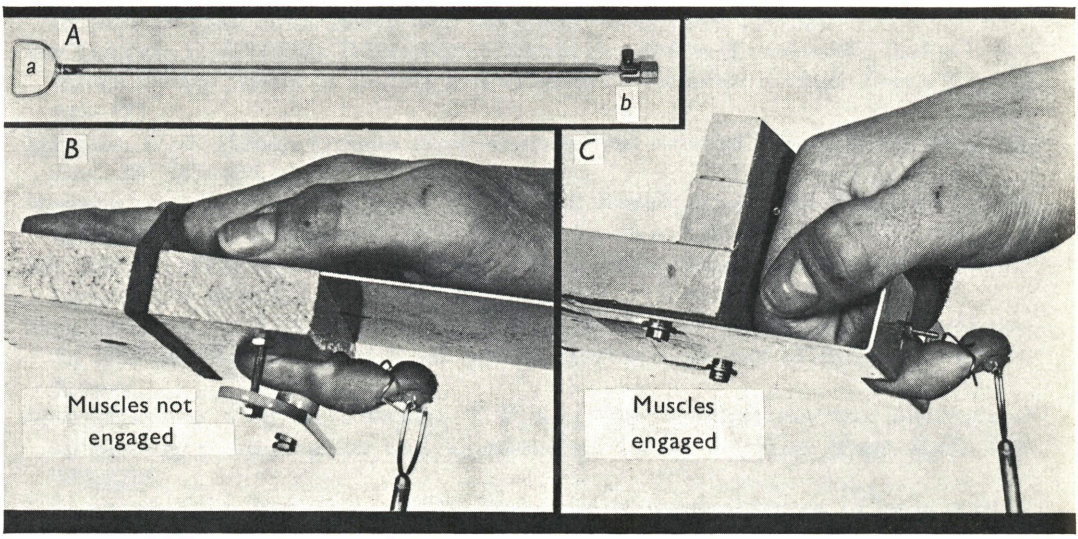
A
a
b
B
Muscles not
engaged
C
Muscles
engaged

EXPLANATION OF PLATE

These photographs show the apparatus used to connect the terminal phalanx of the middle finger to the finger displacer, and to position the hand so that muscle could be engaged or not engaged at the distal interphalangeal joint. *A*, this shows the brass rod which has a forked end (*a*), over which a section of hypodermic needle, glued to the subject's finger-nail, was fitted, completing a stirrup arrangement. Torsional forces on the finger-nail were minimized by having two mechanical joints (*a* and *b*) with axes in the same plane as the axis of movement of the joint. *B*, the position of the hand when the muscles were unable to move the joint and were effectively disengaged from it. The middle finger passed through a hole in a board and was clamped fully flexed, while the remaining fingers were fully extended. In this position only joint and cutaneous mechanisms contribute to position sense. *C*, the position of the hand when the muscles were engaged and able to flex the terminal phalanx of the middle finger. This finger was fully flexed at the proximal interphalangeal joint and slightly flexed at the distal interphalangeal joint, while the remaining fingers were fully flexed at both distal and proximal interphalangeal joints. In this position, joint, cutaneous and muscular mechanisms could contribute to position sense. In both positions of the hand a paper clip was placed across the nail, thus depressing it and reducing pressure sensations. The positions of the hand were posed for photography and do not indicate that the initial angle of the distal interphalangeal joint was always 30–40° into flexion, nor that the angle at the wrist joint was the same in both positions.

36. Joint sense, muscle sense, and their combination as position sense measured at the distal interphalangeal joint of the middle finger.
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SENSATIONS OF HEAVINESS

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INTRODUCTION

ALTHOUGH tests involving the estimation and discrimination of weights have long been used by neurologists and neurophysiologists (Gowers, 1892; Head and Holmes, 1911; Head, 1918; Holmes, 1917, 1922; *see also* Fulton, 1943) and by psychologists (e.g. Harper and Stevens, 1948) the mechanisms subserving the appreciation of weight are poorly understood. Possibly for this reason it is now uncommon to find neurologists using 'leather balls like small cricket balls, containing various weights from two drachms to two pounds' as introduced by Gowers (1892).

In a study of sensory disturbances following cerebral lesions Head and Holmes (1911) studied the appreciation of weight when the arm was allowed to move and when it was supported and concluded that the former demanded 'a power of estimating movement and the force employed in lifting the weight' and the latter depended on 'an appreciation of relative pressure.' Holmes later studied the perception of heaviness in patients with unilateral cerebellar dysfunction, usually the result of gunshot wounds (1917, 1922). He found that 'the majority of my patients over-estimated the weight on the abnormal side' (1922). He ascribed this to a decrease in muscular tone, and not a specific sensory deficit, as the ability to discriminate weights was the same on each side. He reasoned that 'the greater effort which a patient suffering from a unilateral cerebellar lesion must put into all attempts to move the homolateral limbs suggests strongly that he will overestimate, or estimate wrongly, the resistance which these movements encounter' (1917). Holmes thus clearly associated an increased effort with a sensation of heaviness, an association supported by recent physiological experiments. In a study of normal subjects McCloskey, Ebeling and Goodwin (1974) verified the common experience that an object feels heavy when lifted by muscles weakened by fatigue. They proposed that an estimate of the weight of an object depends more on sensing the effort put into the contraction than on the achieved muscular tension: that is, in situations when a greater command is required to lift an object (e.g. when fatigued) it will feel heavy.

Holmes, in both major reports of his studies on the cerebellum, stated in a similar way without elaboration, that 'Every paretic limb exaggerates the load it carries if its sensation be normal' (1922). We have examined the generality of this statement by studying the perception of heaviness in two groups of subjects: patients with paretic limbs but without sensory loss, and normal subjects in whom weakness was produced by partial curarization of the muscles of the forearm and hand. Our results are consistent with Holmes' dictum that objects feel heavy when lifted by paretic muscles. We suggest that there is a perceived command to the muscles, or 'sense of effort,' which is used in estimating the weight of a lifted object. This command arises at levels rostral to motoneurons.

Part of this work has been briefly reported (Gandevia and McCloskey, 1976*a*).

METHODS

The appreciation of heaviness was tested in 8 patients with hemiparesis, and in 10 normal volunteer subjects weakened by partial curarization. Nine of the normal volunteers were medical students, and the tenth was a physiologist. All but the physiologist were uninformed as to the hypotheses being tested. Subjects were always required to match a reference weight presented to the paretic side with a weight similarly presented, at the same time, to the other side. When subjects judged the weights lifted on both sides to be equal, the weight lifted on the unaffected (strong) side was an objective indication of the perceived heaviness of the reference lifted on the weak side.

The criteria used in the selection of patients were as follows. Each patient had an 'upper motor neuron' type of weakness, but without sensory loss over the upper limb. For our purposes it was essential that each patient did not have a sensory deficit in the distal upper limb, as a reduction in the sensory input arising in the hand increases the perceived heaviness of an object lifted by the flexors of the elbow (Gandevia and McCloskey, 1976*b*). Hence each patient was independently examined by a neurologist, using the usual clinical tests for touch, proprioception, pain and temperature. If no anomaly was found we repeated the sensory tests and again if no deficit was detected patients were admitted to the study. The diagnoses of 6 of the patients were as follows: 3 typical motor 'strokes' (A. B., A. H. and R. T.), one of which (A. B.) was confirmed by angiography; a tumour in the cerebellopontine angle which was not associated with cerebellar signs (J. K.); a partial frontal lobectomy for removal of a localized tumour (W. C.); and a cerebral hæmorrhage producing some bilateral motor cranial nerve palsies and hemiparesis of the upper and lower limb (J. D.). In 2 patients (P. L. and J. H.) no definitive diagnosis was available but both had a minimal hemiparesis, without sensory symptoms or signs over the upper limb. In one there was evidence of a deep parietal lesion and in the other minimal involvement of a cerebral peduncle was suspected. To obtain an objective approximation of the degree of paresis the maximum isometric handgrip was always recorded. It is interesting that our patients did not complain of weakness but often of a 'heaviness' or 'leaden feeling' in the affected limbs.

Patients lifted tennis balls, filled with varying amounts of mercury (cf. Gowers, 1892) which were placed in each hand. They chose usually to flex and extend the elbow, or occasionally to flex and extend the wrist. We did not permit the patients to lift the weights merely by elevating the shoulder on the affected side. The reference weight was usually 400 g. To standardize the mode of lifting, and also to use a muscle group especially involved in hemiparesis, some patients lifted weights by extension of the index finger. The hands were placed palms downwards on a table so that extending the finger lifted the curved tip of a horizontal rod upwards. The other end of the rod was the fulcrum of the lever (about 30 cm from the fingernail) and a weight was moved the appropriate distance along the rod, to increase or decrease the weight according to the patient's instructions, on the strong side. The reference weight on

the weak side was usually 100 g. A simple version of this device may be made by hinging two rulers side by side on a piece of wood (20 × 20 cm) and attaching a standard weight to each ruler with a rubber band so that it may be moved to alter the lifted weight. For each patient 10 matches of the reference weight were obtained in any testing session. As some patients were tested more than once (P. L. three times; J. H. twice) averages of all matches made are shown in fig. 1. In one patient (J. D.) only 6 matches were made. Patients rested for several minutes after 3 matches with the tennis balls or 5 matches with index-finger extension, and also whenever the lifting muscles felt fatigued.

In the normal subjects, weakness was produced by retrograde infusion of d-tubocurarine ($\leqslant$ 3 mg) into the forearm while a sphygmomanometer cuff was inflated above systolic pressure on the upper arm (Torda and Klonymus, 1966). The blood supply to the forearm remained occluded for less than ten minutes while the d-tubocurarine, diluted in 20 ml of physiological saline, was slowly infused into a vein on the back of the hand. About five to ten minutes after inflating the cuff and infusing the curare, forearm and hand muscles were weakened, and after removing the cuff strength gradually recovered. During recovery the subject was blindfolded and matched a reference weight (100 or 200 g) lifted on the weak side with a variable weight lifted by the other side. Weights were usually lifted by flexion of the index finger, using apparatus similar to that described for use with patients but modified to allow larger weights to be lifted. We also recorded either the maximum weight that the subject was able to lift (using the same apparatus) or the maximum tension exerted by the subject during an isometric handgrip, to monitor the recovery of strength. Strength was usually fully recovered within an hour of removing the cuff. In this part of the study the usual ethical requirements regarding informed consent were met.

RESULTS

Studies on Patients with Weakness

We initially studied several patients with classical 'sensorimotor strokes' and found that weights were adjudged heavier than they actually were when lifted on the affected side (cf. Head, 1918; Holmes, 1927). However, interpretation of this result is complicated because we have previously shown that a weight lifted by flexing the elbow feels heavier when the hand is anæsthetized (Gandevia and McCloskey, 1976*b*). Peripheral sensation may also affect human stretch reflexes (Marsden, Merton and Morton, 1971, 1973). Consequently we sought those less commonly encountered patients with a hemiparesis but without sensory symptoms and signs. The results of the simple weight-matching task in 8 such patients are shown in fig. 1. The broken line shows the reference weight used and matching weights are shown as the mean $\pm$SEM (usually 10 lifts, *see* Methods). Weights presented to the affected side were perceived as heavier than they actually were in 9 of the 11 tests shown (range 0–80 per cent increase with the tennis balls, mean $\simeq$40 per cent; range 35–171 per cent increase with index-finger extension, mean $\simeq$85 per cent). In all the patients the perceived heaviness of the reference weight exceeded its real weight in one or both of our tests. The 2 patients with the most mild pareses (P. L. and J. H.) were apparently accurate in estimating the weight of the lifted tennis balls (*see* fig. 1). However, in P. L. there was no clinically detected weakness in the flexors or extensors of the elbow and only finger extensors and abductors were found to be weak at the time of testing, so that little deviation was expected. Both these patients were tested on more than one occasion for estimation

of weights lifted by extending the index finger, and consistently chose matching weights in excess of the real weight. In one patient who was unable to grasp the tennis balls (J. D.) there was large overestimation of the heaviness of the reference weight, using index-finger extension to lift the weights, even using reference weights less than that shown in the figure (70 g). The increase in heaviness for the patients is statistically significant ($P < 0{\cdot}02$) in a two-sided sign test from which the result in P. L. when lifting the tennis balls was not included, as there was no detectable weakness in the lifting muscles. For the group of patients lifting with the tennis balls the percentage increase in perceived heaviness above the reference weight showed a significant positive correlation ($P < 0{\cdot}02$) with the percentage reduction in handgrip strength on the weakened side.

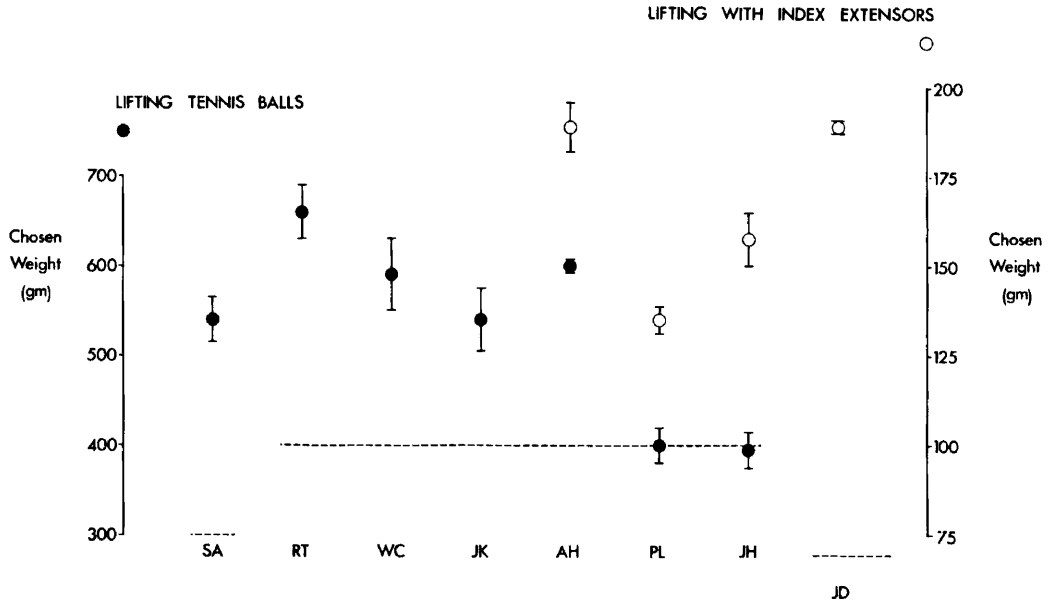

FIG. 1. A summary of data from the patients. This shows the results as a mean ±SEM from the 8 hemiparetic patients without sensory loss in the weight-matching task, using the tennis balls (filled circles: scale on the left) and index finger extension (open circles: scale on the right). The broken line indicates the reference weight being lifted by the weak side and the corresponding circles indicate the apparent heaviness of the reference weight (*see* Methods). With the exception of P. L. and J. H. lifting the tennis balls, all patients chose a matching weight on the strong side which exceeded the actual weight lifted on the weak side. If information from peripheral receptors were the sole basis for the estimations then the chosen weights should have more closely approximated the actual weight. Patients P. L. and J. H., with the most minimal pareses of the group, chose matching weights in excess of the real weight when lifting weights by index extension.

Perceived Heaviness During Partial Curarization

Having shown that objects feel heavier when the descending motor pathways are partially interrupted we next sought to study perceived heaviness in normal subjects during an experimental weakness. Curare was used to impair neuromuscular transmission so that a given motor command to the muscles produced

a markedly reduced tension. Subjects matched weights usually before curarization as a control, then the forearm and hand muscles were weakened by local infusion of d-tubocurarine (as described under Methods) and the subjects matched weights again as strength was slowly regained. For one subject plots of perceived heaviness and of isometric handgrip strength against time after beginning the infusion of curare are shown in fig. 2. It shows that the reference weight was perceived as being heavier than the control matches when the lifting muscles were very weak, but as muscle strength increased so the apparent heaviness of the reference weight diminished. Curves similar to this were obtained for 9 of the 10 subjects, whether

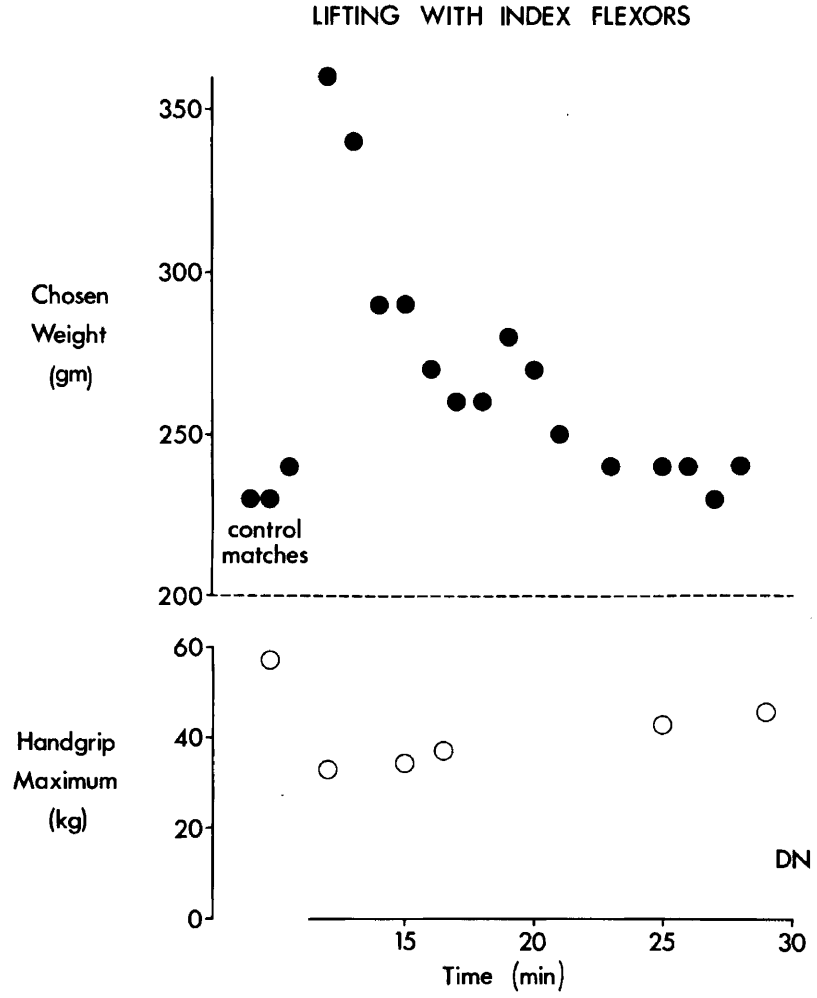

FIG. 2. This shows a typical result from a subject estimating the weight of a 200 g reference weight (broken line) by index flexion during a partial curarization experiment. The upper graph (filled circles) shows the apparent heaviness of the reference weight, and the lower one (open circles) the maximal isometric handgrip strength on the curarized side. The time axis for both graphs refers to the time after infusion of curare into the forearm (*see* Methods). The points at the extreme left show control estimates of the 200 g reference weight (*above*, 3 points) and the control strength (*below*, 1 point) taken before the muscular strength was reduced by partial curarization. When initially weakened by curare the 200 g weight lifted on the weakened side seemed as heavy as a 360 g weight lifted on the strong side, but as strength was regained the apparent heaviness of the weight came down towards control levels.

lifting by index-finger extension, index-finger flexion or thumb flexion. One subject did not show any significant alteration in perceived heaviness as strength returned. This subject, a physiologist, was the only person used in this study who was familiar with earlier experiments carried out in this laboratory on the perception of weights and tensions, and the effects of peripheral sensation on perceived heaviness. His atypical performance indicates that sources of sensory information apart from his 'sense of effort' were available to guide his judgement of heaviness—possibly from intramuscular, articular and cutaneous receptors (*see* McCloskey *et al.*, 1974). If similar sources were available to our other subjects, they clearly paid less attention to them than did our physiologist.

DISCUSSION

These results support the hypothesis that objects feel heavy when an increased command to the muscles is required. In our experiments the increased command was required because the available motor outflow was reduced, or because neuromuscular transmission was impaired. In estimating weights, our patients and subjects placed more reliance upon sensing the effort or command put into lifting an object than upon alternative signals which might have been available related to the forces and tensions actually achieved. The study with the hemiparetic patients suggests that the increased command, or sense of effort, is 'read off' at levels above the spinal motoneurons, because the over-all activity of the pool of motoneurons involved in a lift should not have increased as the perceived heaviness did, during contractions on the affected side.

The conclusions presented above are consistent with Holmes' observations on patients with unilateral cerebellar dysfunction (1917, 1922) and reports that judgements about weights may be impaired in cortical disease (Head and Holmes, 1911; Head, 1918; Holmes, 1927). A controversial issue which has been surprisingly neglected for many years is whether the central effort generated in order to lift an object or the sensations generated by the lift itself are more important in judging the weight of an object (*see* Lewes, 1879; Waller, 1891; Sherrington, 1900). Holmes does not appear to have mentioned it, although he was in a position to resolve this matter. In both reports of his studies on the cerebellum, he quickly dismissed the overestimation of weights lifted on the hypotonic side by saying that this occurs with all paretic muscles (1917, 1922). In his extensive observations on cerebellar disease Holmes did not explicitly state the mechanism which he thought responsible for the estimation of weight—although it may be that he regarded the mechanism that we have proposed here as obvious.

People with weakness often complain of a 'heaviness' in the limbs rather than an awareness of diminished strength. For example, Samuel Johnson took as evidence of his recovery from a 'paralytick stroke' that 'This day I watered the garden, and did not find the watering pots more heavy than they have hitherto been . . .' (letters 850, 855, 1783, published 1952). Several of the case histories

presented by Fisher and Curry (1965) in their study of 'pure motor hemiplegia' also contain reports of sensations of heaviness. Brodal (1973), in an account of his own motor stroke, wrote of his awareness of a 'force of innervation.' By this he meant his awareness of the mental energy required to contract a severely paretic muscle.

We were at first reluctant to use the term 'sense of effort' as a synonym for the perceived command to the muscles, because historically it has been used in a different context—a context which can probably now be neglected. Sensation 'of innervation' was used by Helmholtz (*see* 1925) in his writings on perception on the visual world, and referred to reafferent signals generated within the central nervous system from the efferent motor command to the oculomotor muscles. These compensated for the movement of the retinæ in order to stabilize the visual world. This concept was extended, under the name 'sense of effort,' to include movement of the limbs (Merton, 1964, 1970). Recent experiments indicate, however, that the sense of effort does not provide simple sensation of movement either for the limb muscles (Goodwin, McCloskey and Matthews, 1972; McCloskey and Torda, 1975) or the extra-ocular muscles (Siebeck, 1954; Brindley, Goodwin, Kulikowski and Leighton, 1976; *see also* Stevens, Emerson, Gerstein, Kallos, Neufeld, Nichols and Rosenquist, 1976). We prefer to use the term 'sense of effort' for centrally generated sensations concerned with the estimation of weights and tensions. Whether or not this 'sense of effort' is the same as 'force of innervation' (Brodal, 1973) is not clear, nor can we yet suggest the site of origin within the central nervous system of the signals concerned, except that, as indicated above, they arise rostral to motoneurons.

While we have emphasized the central (efferent) rather than the peripheral (afferent) component in weight estimation, it is likely that the latter component is used in at least two ways. First it seems essential that a subject has some indication that his effort is successful in moving or supporting the weight, before his sense of that effort could be properly interpreted—afferent sensation could provide such indications. Second, the afferent pathways can give a signal of the peripheral tension achieved, a signal which may not always be disregarded in weight estimation (McCloskey *et al.*, 1974), as the result from one of our subjects suggested.

Our findings in normal subjects, weakened with curare, do not agree with results briefly reported by Campbell, Edwards, Hill, Jones and Sykes (1976), using partial curarization, in which it was concluded that the sense of effort was 'largely peripheral in origin.' One reason for the apparent discrepancy may be that Campbell *et al.* required their subjects to estimate the effort subjectively.

The use of partial curarization is not ideal as a model for paresis. As a subject makes repeated contractions sufficient acetylcholine may be released at the neuromuscular junction to 'de-curarize' the contracting muscle fibres competitively: he then would be actually lifting with rather more normal muscle. This may explain our frequent observation that the perceived heaviness returned to control levels before the handgrip strength did (*see* fig. 2). Another problem with curare arises

if the intrafusal fibres are more resistant to curare than the extrafusal ones (Albe-Fessard, Lamarre and Pimpaneau, 1966). Then a relatively high spindle discharge may result during lifting contractions while partially curarized. This discharge from spindles, by facilitating the lifting motoneurons, should reduce the central command required in a lift and thus reduce the apparent weight of the object. Such a 'lightening' effect has been observed in the estimation of tension when the lifting muscles are assisted in their contraction by producing in them a tonic vibration reflex (McCloskey *et al.*, 1974).

A similar argument applies to the patients with hemiparesis: if the increase in tone on the affected side (which all our patients exhibited) were due to a diffuse excitation of the motoneurons, less command would be required. If this were the sole basis of their errors, one would have expected under- rather than over-estimation of heaviness. Such an effect would reduce the magnitude of the increases in perceived heaviness.

Our results suggest that there is a perceivable motor command delivered to the muscles which is used in force and tension estimation. As estimating the weight by a matching task provides objective information with simple apparatus it may provide a useful test in studying weakness.

SUMMARY

We have studied the appreciation of heaviness in two groups of subjects; in 8 patients with varying degrees of unilateral 'upper motor neuron' weakness but without sensory symptoms or signs, and in 10 volunteers during partial curarization of the forearm and hand. In all experiments the subjects matched a reference weight lifted on the weak side with a variable weight on the strong side to provide an objective indication of the heaviness of the reference weight. Patients matched the weights of tennis balls filled with mercury or weights lifted by extending the index finger. Weights were judged as heavier when lifted by the weakened side both in the hemiparetic patients and in normal subjects weakened with curare.

In both the hemiparetic patients and the subjects weakened with curare peripheral sensory information would signal the forces exerted in lifting the weight; however, both groups of subjects clearly placed more reliance on the effort that was being put into the contraction than on peripheral tensions achieved. The concept that we rely in part on a sensing command to the motoneurons when estimating weight agrees with observations by Holmes on patients with unilateral cerebellar dysfunction, and with recent physiological experiments.

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EFFECTS OF RELATED SENSORY INPUTS ON MOTOR PERFORMANCES IN MAN STUDIED THROUGH CHANGES IN PERCEIVED HEAVINESS

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SUMMARY

1. The perception of the heaviness of lifted objects was studied using a weight-matching task when sensory inputs from parts related to the lifting task were altered.

2. A weight lifted by flexing the index finger feels heavier when the thumb is anaesthetized and lighter when the thumb is electrically stimulated. A weight lifted by flexing the distal joint of the thumb feels heavier when the sensory input from the skin and joint of the thumb is abolished by anaesthesia. It also feels heavier when the index (but not the little) finger is anaesthetized, and lighter when the index (but not the little) finger is electrically stimulated.

3. A weight lifted by extending the thumb feels lighter when the sensory input from the thumb is abolished.

4. The perceived heaviness of a weight lifted by flexing the thumb is increased during anaesthesia of the thumb when the flexor of the thumb is the prime mover but not when it is acting simply as a postural fixator to support the weight.

5. The sensation of the heaviness of lifted objects derives from the effort or centrally generated voluntary motor command employed in the lift. Our results indicate that the motor commands to either thumb or index finger flexors are facilitated by sensory inputs arising from a wide sensory field usually involved in co-operative motor performances carried out by both muscle groups together.

INTRODUCTION

Whether the judgement of the weight of a lifted object depends more on the central effort generated in order to lift it or on sensations generated by the lift itself is still debated although the controversy began about a century ago (e.g. Lewes, 1879; Waller, 1891). Holmes studied patients

with unilateral cerebellar dysfunction and found that weights were commonly judged as heavier on the affected, hypotonic side (1917, 1922). He noted that this was associated with the 'greater effort which a patient suffering from a unilateral cerebellar lesion must put into all attempts to move the homolateral limbs' (1917). Recently McCloskey, Ebeling & Goodwin (1974) showed that the effort put into lifting an object was preferred to the muscular tension required to lift it as a signal of its weight. The common experience that an object lifted by fatigued muscles feels heavy, they argued, resulted from the increased effort required to lift it rather than from changes in peripheral sensation. Their experiments indicated that subjects were able to distinguish the sensation of the effort from the sensation of achieved muscular tension. A further study of the sensation of heaviness in hemiparetic patients without sensory symptoms or signs (see below), and normal subjects weakened by the local infusion of d-tubocurarine suggested that a command to the muscle, or 'sense of effort', which arises rostal to motoneurones, is used in estimating the weight of a lifted object (Gandevia & McCloskey, 1977*a*). This concept receives additional support in a following paper (Gandevia & McCloskey, 1977*b*). Brodal (1973) has described the 'mental effort' required to contract a severely paretic muscle, and although he does not mention heaviness, a feeling of heaviness in paretic limbs is often reported (Fisher & Curry, 1965), even when sensation is not impaired. Granit (1972), reporting his subjective sensations during recovery from spinal anaesthesia, comments that when commanding one of his affected legs to be lifted 'it felt dead and heavy, and I was utterly aware of the fact that it actually did move'.

The perceived heaviness of an object thus reflects the centrally generated command required to lift it. We have studied the motor command through the perception of heaviness with a simple weight matching task, while sensory inputs from parts related to the lifting task were altered. We were particularly interested to anaesthetize the thumb, as this is known to abolish the load compensating reflex from its long flexor (Marsden, Merton & Morton, 1971, 1973; Dyhre-Poulsen & Djørup, 1976). Changes in perceived heaviness occurred when the sensory input which we altered arose in a part which commonly participates in co-operative movements requiring the lifting muscle group.

Part of this work has appeared in brief form (Gandevia & McCloskey, 1976*b*).

METHODS

In the major part of this study we used a simple weight-matching task to determine the perceived heaviness of a reference weight lifted by a muscle group on the left side when we changed the sensory information coming from parts on that side which were not necessarily involved in the lift.

Subjects

Experiments were performed on young healthy male and female subjects, usually students or technicians, who were not aware of the hypotheses being tested. The authors did not participate in the experiments.

Weight-matching task

Subjects lifted a reference weight with a muscle group on the left (reference) side and matched it with weights similarly presented to the right (indicator) side. The subject simultaneously lifted the weights on both sides and after one or more lifts asked the experimenter simply to increase or decrease the weight on the right side. No rules were made for subjects about the method of lifting: most lifted the weights on both sides from their supports deliberately and not suddenly, and moved them back and forth through a small excursion (5–30° joint angle) with a period of about 1–3 sec. Most subjects moved both sides together, but some moved them 180° out of phase. Some subjects allowed the weights to rest on their supports between each excursion while others held them still by isometric muscular contraction for a second or two between excursions. The actual lifting method did not appear to influence the results. Weights were added or subtracted according to the subject's instructions until he was satisfied that the weight lifted by the right side was equal to the reference weight lifted by the left side. The experimenter changed the weight in the direction demanded by the subject but chose at random the size of the change so that the loading strategy did not exclude the possibility of 'overshooting' the desired weight. The weight chosen on the right side thus gave an objective indication of the perceived heaviness of the reference weight lifted by the left side. Sensation was then disturbed on the left (reference) side and the perceived heaviness of the reference weight was again determined. For most experimental procedures (see below), except anaesthesia, the subject lifted and made an estimation of the reference weight as a control and then estimated it again during, for example, electrical stimulation of the finger. In this way ten estimates of the reference weight were made as a control, alternating with estimates during finger stimulation. During the ten control estimations the initial weight presented to the subject on the indicator side required him to choose a higher (loading 'up') or lower (loading 'down') weight on an equal number of controls. However, during 'experimental' lifts the subject, unknown to him, was presented on seven or more of the ten estimates, with the same weight as had been chosen as a control. Thus the subject had to load 'away' from the weight chosen initially as a control. When anaesthesia was used and it was not possible to alternate between control and 'experimental' estimates the same loading strategy as described for control lifts was used.

Lifting with the thumb

The subjects sat with both forearms flat on a table before them. The fingers of each hand were folded loosely around a vertical rod (2·5 cm diameter) attached to the table. The thumbs were abducted and rested on a T-piece attached to the top of the rod, so that flexion movement occurred about the distal joint. The pulp of the

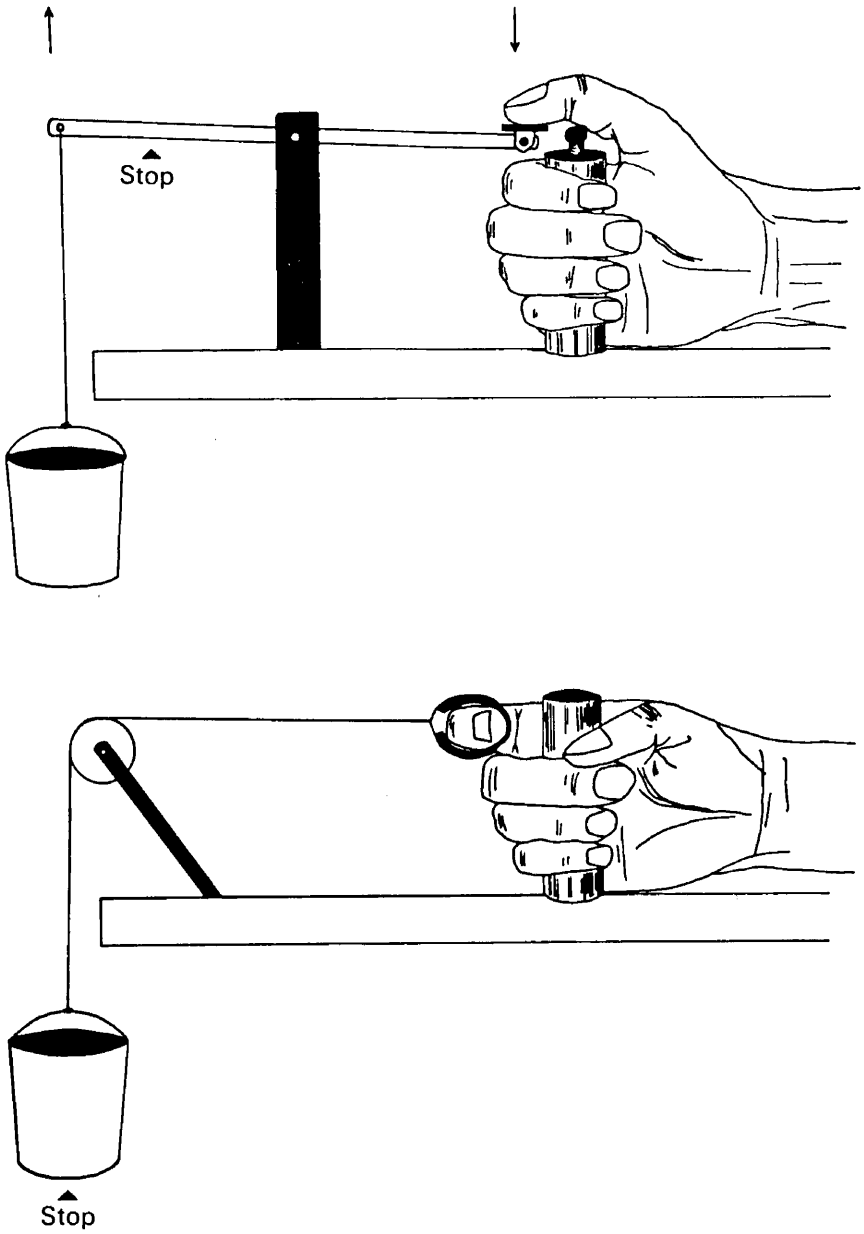

Fig. 1. *Above:* this shows diagrammatically the position of the right hand and apparatus used when weights were lifted by flexing the distal joint of the thumb. The fingers were placed around a cylindrical upright and the pulp of the thumb rested on a flat circular rocker. Flexing the thumb depressed one end of the 'see-saw' and lifted the weight, contained in a bucket, hung on the other end. *Below:* this shows diagrammatically the position of the right hand and the pulley used when weights were lifted by flexing the index finger predominantly at the proximal interphalangeal joint. The adjacent fingers were placed around a cylindrical upright. A wire ran from a thick piece of rubber tubing around the distal interphalangeal joint over a pulley to support the bucket containing the weights. For all modes of lifting the left hand used a similar apparatus to that used by the right hand, and each apparatus had an adjustable stop mechanism so that the weights were 'engaged' when the positions of the lifting digits were similar.

thumbs rested on flat circular (2 cm diameter) plates which formed one end of a low friction 'see-saw' (Fig. 1). On the other end of the 'see-saw' light buckets (about 70 g) were hung, out of sight of the subject. Parts of the device were adjustable, including a stop mechanism, so that movement was predominantly about the distal joint and so that at the beginning of the experiment adjustments could be made so that both thumbs 'felt the same'. The device was able to be quickly adjusted so that the weights were lifted by extending the distal joint of the thumb, while the forearm and hand remained in the same position as described above.

Lifting with index finger flexors

The subjects sat with both forearms flat on a table before them and the fingers of each hand were folded loosely around a vertical rod (1·4 cm diameter). An inextensible string was attached to a piece of rubber tubing which was pulled over the terminal interphalangeal joint of the index finger of each hand (Fig .1). Each string ran over a low friction pulley to support a light bucket (about 100 g) which was out of sight of the subject. Subjects used a 'trigger pulling' action to lift the buckets – the flexion occurred at the proximal interphalangeal joint. The distal joint was fixed in extension by the rubber tubing around it, and the metacarpophalangeal joint was extended and moved minimally during a lift.

Electrical stimulation and digital anaesthesia

For stimulation a surface electrode was placed on each side of the digit, about 1 cm distal to the metacarpophalangeal joint. The two electrodes were connected to a Grass S9 stimulator which produced biphasic square wave pulses. Stimulus parameters were chosen so that the subject reported a pressing sensation referred over the entire finger, and not just beneath the electrodes. The pulse duration was 2 msec, the frequency about 60 Hz (range 40–100 Hz) and the intensity about 90 volts (range 60–110 V). This stimulation produced cutaneous pressure and tingling sensations but was not painful. Stimulation began about 1 sec before the subject lifted the weights and continued until the weights had been lowered to the stops and a change demanded in the weights lifted on the right side. After changing the weight the experimenter restarted the stimulation and the subject again lifted the buckets.

Digits were anaesthetized by digital nerve block using 2 % lignocaine, without adrenaline, injected about 1 cm distal to the base of the digit. The thumb required 4–5 ml. lignocaine for complete anaesthesia and smaller volumes were used for the other digits. Complete anaesthesia was judged by loss of touch, pressure and pain sensations. By placing a wide rubber band around the base of the digit, which partially occluded venous but not arterial flow, the anaesthesia was maintained for the remainder of the experiment (about 0·5 hr). Sensation recovered 1–3 hr after removal of the rubber band.

In all the above experiments the subjects rested for about 5 min after any ten estimates, or whenever the lifting muscles felt fatigued. In experiments involving digital nerve block the ethical requirement of informed consent was fulfilled.

Analysis of data

An unpaired *t*-test (2-sided) of the 10 matches made as a control and the 10 matches made under a particular experimental condition was carried out to indicate the significance of changes in perceived heaviness for individuals. For analysing the group of subjects in a particular experiment a paired *t* test of the means under control and experimental conditions was used. Just for the purposes of illustration, the perceived heaviness in a test condition is shown as a percentage of the

individual's control performance. However Fig. 5 shows the individual performances (mean ± S.E. of mean) in their raw form to indicate the variation between subjects and the individual variability and accuracy of each subject. Descriptions of our findings in the Results section refer to raw data, and not to percentage changes.

RESULTS

1. *Lifting with the thumb*

(*a*) *Thumb flexion*

Subjects estimated the perceived heaviness of 1000 g lifted by flexing the thumb at its distal joint (see Methods and Fig. 1) while the sensory inputs from the thumb itself, the index finger or the little finger were altered. Sensation arising in the thumb was removed by digital nerve block distal to its base; this paralyses joint and skin afferents from the thumb but should not reach its long flexor muscle which lies in the forearm. Results are shown in Fig. 2. Ten estimates of 1000 g were made by six subjects under five test conditions: first as a control, alternating with estimates during electrical stimulation of the index finger through surface electrodes over the digital nerves, and then during anaesthesia of the index finger. When sensation in the index finger returned the subjects made further estimates, initially as a control and then during anaesthesia of the thumb. The electrical stimulation was arranged so as to produce a pressing or tingling sensation referred over the digit. The five sets of estimates made by the six subjects are shown in Fig. 2 (at left). During electrical stimulation of the index finger in five of the six subjects the mean weight chosen to match 1000 g was less than that chosen as a control and was significantly so ($P < 0{\cdot}05$) in two of these. The average change for the group was a 7 % reduction (range 12–+2 %). In all subjects the mean estimate made during anaesthesia of the index finger exceeded that of the control estimate by an average 12 % (range 5–22 %) and in three subjects these estimates were significantly greater than the control set ($P < 0{\cdot}05$). Paired t tests of the mean weights chosen indicate that stimulation of the index finger made the reference weight feel lighter ($P < 0{\cdot}05$) and that anaesthesia of the index finger made it feel heavier ($P < 0{\cdot}02$).

Another set of control estimates obtained after the subjects regained sensation in the index finger was compared with estimates made during anaesthesia of the thumb. In none of the subjects did the second set of controls differ significantly from the first set. In all subjects there was a significant increase in the perceived heaviness of the 1000 g reference weight during anaesthesia of the thumb (average increase 36 %, range 18–75 %). Paired t tests of the mean weights chosen by the group showed that anaesthesia of the lifting thumb made the reference weight feel

heavier ($P < 0{\cdot}025$) and it increased the perceived heaviness of the reference about 3 times more (for the group) than did anaesthesia of the index finger.

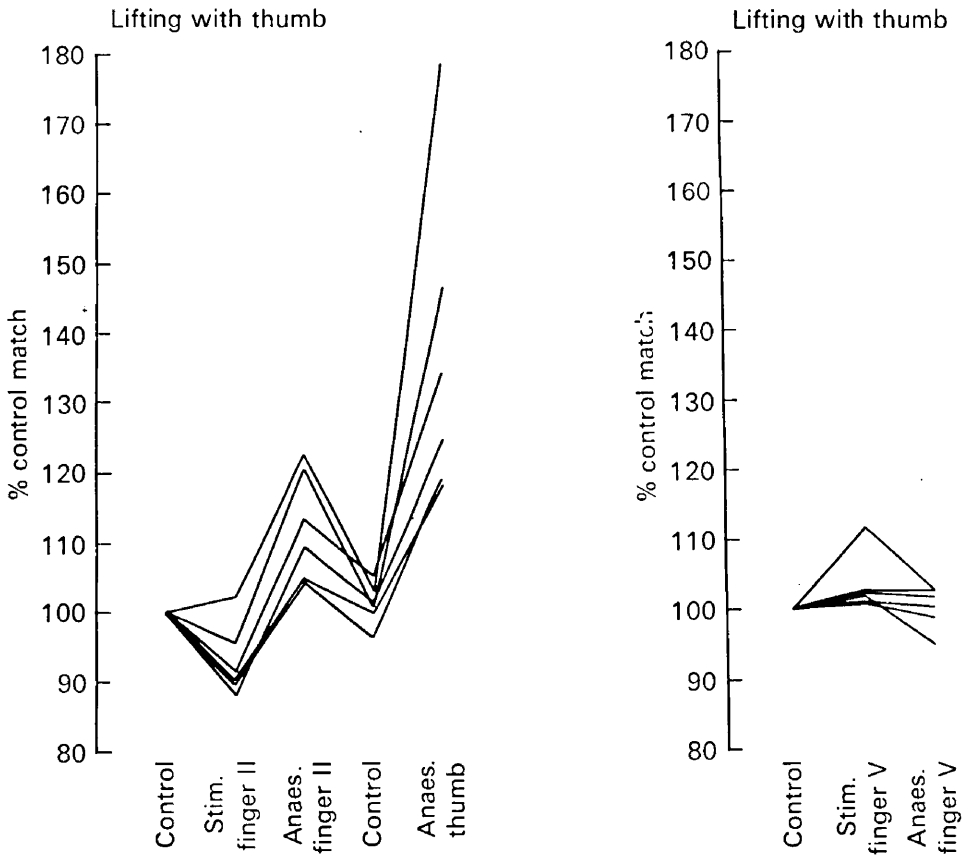

Fig. 2. This shows the results from six subjects when estimating the weight of 1000 g lifted by the flexor of the thumb. Results are expressed as a percentage of control estimates. On the left are results obtained when the sensory input from the index finger (finger II) was increased by electrical stimulation and removed by anaesthesia, and later when the thumb was anaesthetized (paralysing its joint and cutaneous afferents but not its muscle afferents). On the right are results obtained from the same subjects when lifting by flexing the thumb while the sensory inputs from the little finger (finger V) were enhanced by stimulation, and then when they were removed by anaesthesia. For the group, stimulation of the index finger reduced the perceived heaviness of the reference weight and anaesthesia increased it. Anaesthesia of the thumb produced a large increase in the perceived heaviness of the reference weight. For the group, modification of the sensory input from the little finger did not significantly alter the heaviness of the reference weight.

Marsden *et al.* (1971) noticed that a subjectively greater effort was required to move an anaesthetized thumb, a finding confirmed here, at least for flexion of the thumb (see below). Most of our subjects were

surprised at the difficulty they experienced when initially attempting to lift the weights by flexion of the thumb. One subject (M.P., see below) who showed the largest increase in perceived heaviness during anaesthesia of the thumb (in this series), exerted an obviously large effort before even moving the freshly anaesthetized thumb. Although this subject and the others soon regained confidence in their ability to move the thumb, and to lift the weights by flexing it, all subjects chose matching weights in excess of their control estimates. There was no obvious trend towards picking a lighter matching weight as the set of 10 matches was being made by each subject.

The position of the fingers which, in the experiments reported here, were loosely folded around a vertical rod (as described under Methods, Fig. 1), is not critical for obtaining increases in perceived heaviness when lifting by flexing the anaesthetized thumb. Similar changes in perceived heaviness occurred when the fingers were held voluntarily extended (at the metacarpophalangeal and both interphalangeal joints) and were not touching the vertical rod.

To determine whether the afferents from other fingers similarly modify the perceived heaviness of weights lifted by flexing the thumb we performed another series of experiments with the same subjects in which the sensory input from the little finger was altered. Estimates of 1000 g were made as a control, alternating with estimates during electrical stimulation of the little finger, and then during anaesthesia of the little finger. The results are shown in Fig. 2 (at right).

For five of the six subjects there was no significant change in perceived heaviness during stimulation of the little finger. In one subject (M.P.) the estimates during stimulation were significantly greater than the controls. A paired t test of the mean estimates for the group of subjects showed no significant change. No subject showed a significant change in perceived heaviness during anaesthesia of the little finger, nor were the means for the six subjects significantly different during anaesthesia of the little finger.

Clearly the sensory input arising in the little finger is less potent in modifying the perceived heaviness of the weight lifted by the thumb than that arising in the index finger or in the thumb itself.

To compare the changes in perceived heaviness with possible changes in strength the same six subjects made ten maximal isometric contractions of the left long flexor of the thumb before and then during anaesthesia of the thumb. Comparison of the means for the group by paired t test showed that there was no significant change in maximal strength of contraction during anaesthesia of the thumb. In one individual subject (M.P.) there was a significant reduction in maximal contraction during anaesthesia

($\simeq$ 12 %: $P < 0{\cdot}001$) and in two others there were slight reductions (3 and 5 %) but these changes were not statistically significant ($0{\cdot}05 < P < 0{\cdot}10$). The subject whose maximal contraction was significantly reduced by anaesthesia had the largest increase in perceived heaviness in this series (75 %) when flexing with the anaesthetized thumb (Fig. 2) and has shown similarly large increases during thumb anaesthesia in other experiments not reported here. This result should be contrasted with the finding of Lund & Lamarre (1973) who reported that anaesthesia around the teeth reduced the force of maximal jaw closing contractions by 40 %.

(*b*) *Thumb extension*

In another series six subjects estimated the heaviness of a 1000 g reference weight lifted by flexing the thumb at its distal joint (as in the previous series), and then a 500 g reference weight lifted by extending the thumb. The thumb was anaesthetized and extension then flexion estimates were repeated. The results are shown in Fig. 3. As shown previously (Fig. 2) the perceived heaviness was significantly increased when lifting by flexing an anaesthetized thumb (for five of the six subjects: and for the group, $P < 0{\cdot}05$; average increase in this series: 22 %, range -4 to $+40$ %). When extension of the thumb, rather than flexion, lifted the weights the perceived heaviness of the reference weight was significantly reduced in all six subjects and in the group ($P < 0{\cdot}005$) by an average 35 % (range 9–60 %). Thus the background or 'tonic' sensory input arising in the thumb reduces the perceived heaviness when flexing the thumb to lift the weight and increases the perceived heaviness when extending the thumb to lift it.

The subjective responses of the subjects when required to move the freshly anaesthetized thumb into extension to lift the weights was often one of surprise at the ease with which the weight was lifted. One subject (P.Y.), who had participated in the earlier series of index and thumb anaesthesia while flexing with the thumb, said 'this is really easy compared with the other time'.

2. *Lifting with flexors of the index finger*

In this series the index finger lifted weights (reference 2000 g) while the sensory input arising in the thumb was either enhanced by electrical stimulation or abolished by anaesthesia. Subjects first made estimates as a control, alternating with estimates during electrical stimulation of the thumb, and then during anaesthesia of the thumb. The results are shown in Fig. 4.

During stimulation of the thumb while lifting with the index finger the perceived heaviness was reduced by an average 9 % (range 3–16 %) and

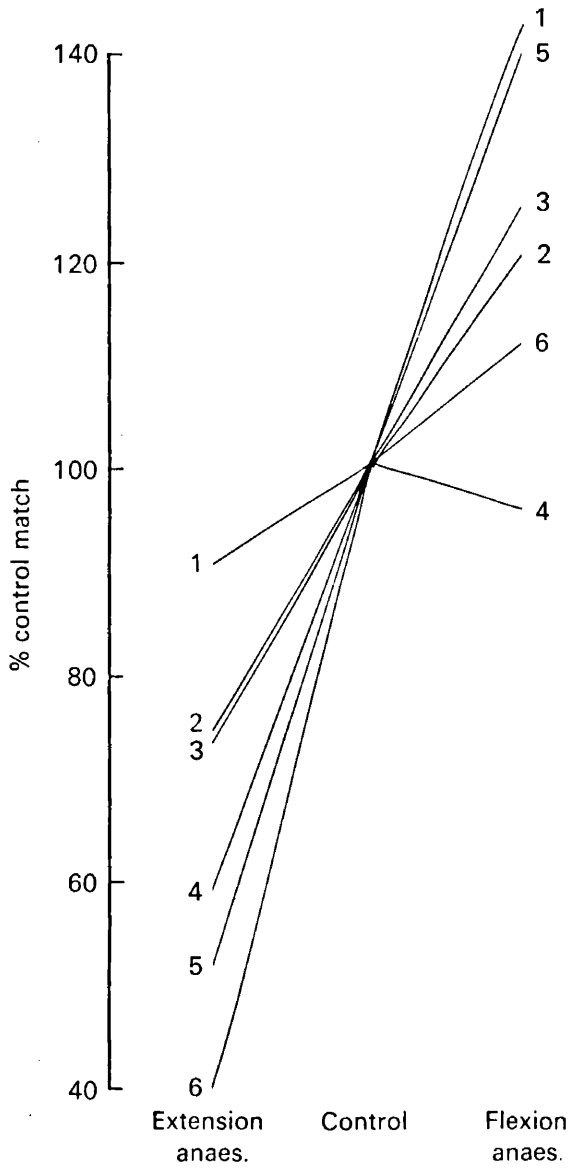

Fig. 3. This shows the results from six subjects when estimating the weight of 1000 g lifted by thumb flexion and 500 g lifted by thumb extension. After controls were taken for both flexion and extension (each expressed as 100 % control match) the thumb was anaesthetized. Results obtained with an anaesthetized thumb are shown on the left for extension and the right for flexion, and are expressed as percentages of control matches. Results from an individual subject are indicated by a numeral at the left and right edges of the figure. For the group, removal of the sensory input from the thumb caused an increase in the perceived heaviness of the reference when it was lifted by flexion, and a reduction in the perceived heaviness when lifted by extension.

in three of the six subjects the estimates during stimulation of the thumb were significantly lighter. For the group the perceived heaviness was significantly reduced ($P < 0{\cdot}001$). During anaesthesia of the thumb in five of the six subjects the perceived heaviness of the reference weight lifted by the index finger was significantly greater than the control estimate. The mean estimates of the six subjects were significantly greater than the control estimates ($P < 0{\cdot}001$), by an average 16 % (range 14–18 %).

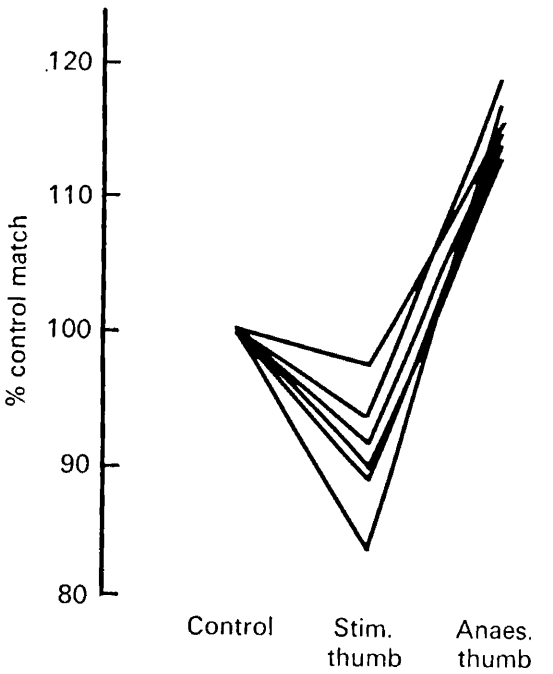

Fig. 4. This shows the results from 6 subjects when estimating the weight of 2000 g lifted by flexing the index finger at the proximal interphalangeal joint. The sensory input from the thumb was increased by electrical stimulation or removed by digital anaesthesia. Results are expressed as percentages of the control estimates. For the group, stimulation of the thumb reduced, and anaesthesia of the thumb increased the perceived heaviness of the reference weight lifted by flexing the thumb.

Thus, just as the sensory input from the index finger affects the heaviness of a weight lifted by the thumb, so the input from the thumb alters the heaviness when lifting with the index finger. When the sensory input from one of these digits is augmented, so the weight lifted by flexion of the adjacent digit feels lighter.

3. *Lifting with thumb and arm adductors*

Subjects estimated the weight of 1000 g lifted by flexing the thumb in the usual way (see Methods) and then by adducting the arm with the long flexor of the thumb supporting the weight. This changes the prime mover

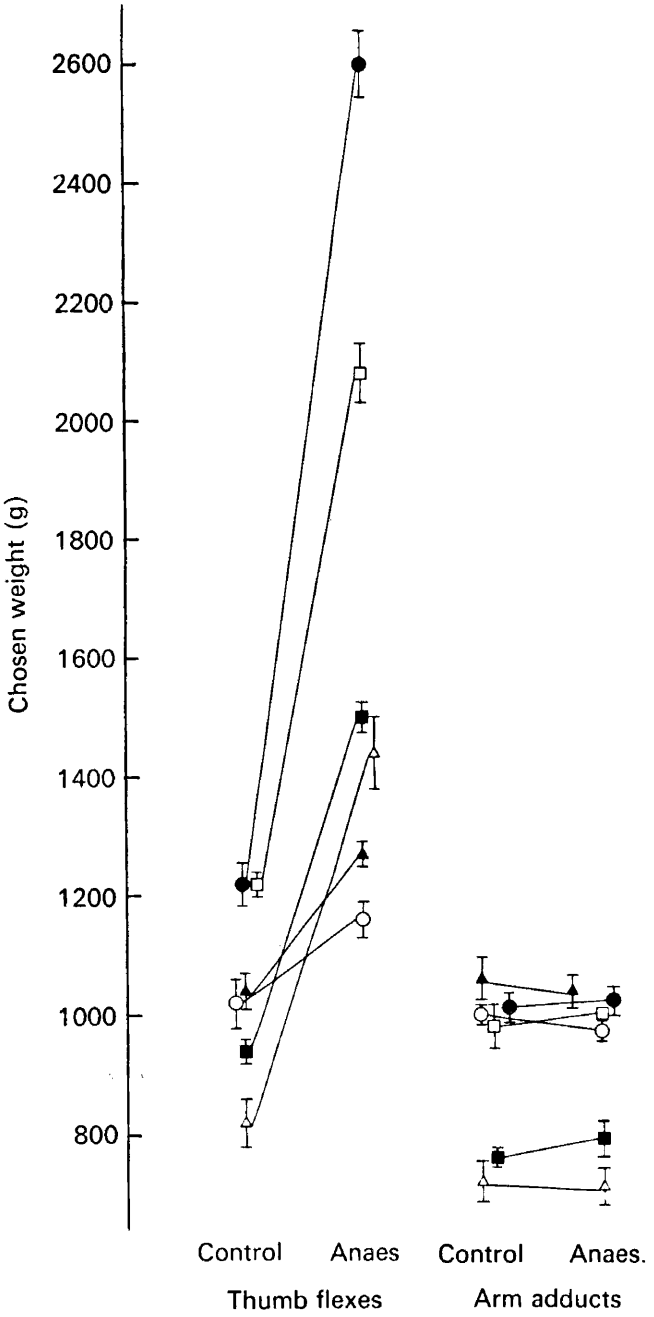

Fig. 5. This shows the results from six subjects when estimating the weight of 1000 g lifted in two different situations during anaesthesia of the thumb. Results are expressed as mean ± S.E. of mean for the ten estimates and not as a percentage of control estimates. In one situation (at left) the thumb flexor lifted the weight in the usual way, and in the other (at right) the weight was lifted by adducting the arm while the weight was also supported through fixed flexion of the thumb (see text). For individual subjects, and for the group, when the thumb alone lifted the weights there was an increase in the perceived heaviness of the reference weight. However, when the arm adductors were the prime muscles used to lift the weight there was no change in the perceived heaviness of the reference weight although the thumb flexor still had to support it.

muscle from the thumb flexor to the arm adductors (pectoralis major) in a similar way to that used by Marsden *et al.* (1976*b*). In both situations the long flexor of the thumb must support the lifted weight. Observations were repeated following anaesthesia of the thumb first with arm adduction and then thumb flexion. The results from the six subjects are shown in Fig. 5, not as in earlier figures as a percentage of control matches, but as a mean ± S.E. of mean to provide an indication of inter-subject variation and the variability and accuracy of individual subjects.

In all six subjects and for the group there was a significant increase in perceived heaviness during anaesthesia of the thumb when it was the prime mover ($P < 0{\cdot}05$; average increase 59 %, range 15–113 %; see also Figs. 5 and 6). However, when arm adductors moved the weights while they were supported by thumb flexors, there was no significant change in the perceived heaviness during anaesthesia of the thumb. This was so for each individual subject, and for the group as a whole.

We noticed that subjects when lifting by adducting the arm and supporting with the thumb did not experience the usual difficulty in using their freshly anaesthetized thumb. When they were required (about 20 min later) to use the thumb flexor as the only muscle to lift the weight, they often expressed surprise at the difficulty they suddenly encountered. For example, one subject (C.E., who had not previously been a subject in these experiments) when making his first lift with the thumb flexor alone, said 'this one feels really heavy – I didn't notice this when I was using my whole arm'.

DISCUSSION

The flexors of the thumb and index finger are used more commonly in co-operation than in isolation. Increasing the sensory input from the inactive ipsilateral index finger when lifting with the thumb flexor, or from the thumb when lifting with the flexor of the index finger, reduces the perceived heaviness of the lifted weight. These sensory inputs have tonic effects because opposite changes in perceived heaviness occur when they are abolished by anaesthesia. The performances of co-ordinated motor tasks, such as using the index finger and thumb together, require activity in many muscles. Our results show that sensory inputs arising from peripheral parts related to the common co-operative performance can modify the perception of the force exerted by a single muscle contributing to the total performance. This occurs even when the peripheral sensory inputs involved do not arise from parts moved by the contraction of the particular muscle itself.

In our Introduction we reviewed evidence that the perception of the heaviness of a lifted object derives from the voluntarily generated motor

command required to move the object and not from the tensions and pressures generated in moved parts. Thus, the perceived heaviness of a lifted object indicates the magnitude of the voluntarily generated motor command employed in lifting it and can be used to study changes in that motor command.

To begin an analysis of mechanisms which might be responsible for the observations reported here we consider the marked increase, caused by anaesthesia of the thumb, on perceived heaviness of objects lifted by thumb flexion. First, anaesthesia may have removed assistance from the long latency stretch reflex (Marsden *et al.* 1973; Dyhre-Poulsen & Djørup, 1976) so that without it, a greater voluntary command to the lifting motoneurones was required. Secondly, anaesthesia of the thumb may have removed a tonic source of facilitation to the motoneurones of the flexor of the thumb so that a greater voluntary command was required to overcome the depression of the lifting motoneurones. Thirdly, when the thumb was anaesthetized the failure of cutaneous and joint receptors to signal that the thumb had lifted the weight, may have required the subject to increase his effort in an attempt to overcome this lack of peripheral information. However, intra-muscular receptors, unaffected here by anaesthesia, are capable of signalling movements (Goodwin, McCloskey, Matthews, 1972; Gandevia & McCloskey, 1976*c*). Moreover, if this third explanation were correct, a weight lifted by a different muscle group, the thumb extensors, would also be expected to have felt heavier when sensation in the thumb was abolished by anaesthesia, but the opposite occurred – it felt lighter. This makes the third mechanism, proposed above, improbable. Little evidence is available on which to consider the second mechanism, although Marsden *et al.* (1973) found that the tendon jerk of the long flexors of the finger were unaffected by anaesthesia of the whole hand while this abolished the long latency stretch reflex from the long flexor of the thumb. Until the tendon jerk of the thumb is also shown to be unaffected by anaesthesia, this finding remains only suggestive that the sensory input from the thumb is exerting its influence at sites other than directly on the motoneurones. If the sensory input from the thumb exerts its effect at a spinal level, then the projection has an interesting property – the input exerts only a small influence if a small effort is produced, when presumably not all the motoneurones for the thumb flexor are activated, and a larger influence as the effort is increased (Gandevia & McCloskey, 1977*b*). The first explanation, that anaesthesia of the thumb depresses the stretch reflex from the thumb, appears on present evidence to be an important component of the increase in heaviness when a weight is lifted by flexing an anaesthetized thumb.

This analysis can be broadened to account for the other findings

reported here. Peripheral afferent signals *from* both the index finger and the thumb must normally facilitate descending motor commands *to* both the index finger and the thumb. Thus, the command to either is reduced (as is perceived heaviness) when such peripheral afferent signals are increased, and must increase (as must perceived heaviness) when peripheral afferent signals are removed. In this respect, a most interesting extension of the findings of Marsden *et al.* was provided by Dyhre-Poulsen & Djørup (1976). They found that the loss of load-compensating reflex in the thumb flexor caused by anaesthesia of the thumb could be offset by electrical stimulation of the unanaesthetized adjacent index-finger. Clearly this finding fits with the analysis we suggest. For the thumb it appears, quite sensibly we believe, that the peripheral afferent inputs so importantly facilitate flexion that they also tonically inhibit extension. Thus, objects lifted by thumb *extension* are made apparently lighter during anaesthesia of the thumb, and apparently heavier during thumb stimulation – the opposite of the effects seen for objects lifted by thumb *flexion*.

In short, then, our results indicate that in the common co-operative performance of thumb and index finger flexion the motor commands to individual muscles involved are facilitated by sensory information arising throughout the whole sensory field of the cooperative movement. It is of interest that a very similar interpretation can be made of our previous, briefly reported, observation that afferent inputs from the hand can facilitate motor commands to the elbow flexors (Gandevia & McCloskey, 1976*a*).

It is not clear at what levels of the nervous system the functional convergence which we have demonstrated occurs. There are many sources of evidence to indicate the close association of thumb and index finger movements in the sensorimotor cortex: from studies of focal epileptic fits (Hughlings Jackson, 1873; Walshe, 1943); from stimulation experiments (e.g. Liddell & Phillips, 1950, 1951); from pyramidal lesions (Laurence & Kuypers, 1968), and from studies of the afferent input to and motor output from cells in the sensorimotor cortex (Doetsch & Gardner, 1972; Rosen & Asanuma, 1972; Lemon & Porter, 1976; see also Goldring & Ratcheson (1972) for comparable data from a study of human motor cortex). The data on sensorimotor cortical cells reported by Doetsch & Gardner (1972; see especially their Fig. 4) is interesting in that they show a 'column' of cells with a sensory input from the index finger and a motor output to the thumb. The authors argued that this was a 'loose' coupling between the afferent input and motor output. However, it may represent the specific co-operation that we have demonstrated between the index finger and thumb. Cutaneous and muscle afferents from the

hand and forearm of the baboon are known to converge on cells in the sensorimotor cortex (Weisendanger, 1973; Heath, Hore & Phillips, 1976).

It is possible that some of the sensorimotor convergence between finger and thumb occurred at a motoneuronal level. Little is known about specific inputs from cutaneous and joint receptors to cervical motoneurones in the primate (although a diffuse afferent projection has been suggested by Asanuma, Stoney & Thompson, 1971). However, in the cat, studies by Lundberg and colleagues on the various inputs to the lumbosacral motoneurones suggest that cutaneous, joint afferents and descending pathways converge along paths to motoneurones (Lundberg, Norrsell & Voorhoeve, 1962; Lundberg, 1972; Lundberg, Malmgren & Schomburg, 1975). For more distal muscles, cutaneous afferents probably reciprocally affect flexor and extensor motoneurones (Hagbarth, 1952; Megirian, 1962).

The evidence which suggests that the changes in perceived heaviness produced by alteration of sensory input are not entirely mediated at a motoneuronal level remains that of Marsden *et al.* (1973) who found that anaesthesia of the hand depresses the stretch reflex from the long flexor of the thumb but fails to reduce the tendon jerk of the long flexors of the fingers. In many respects the studies of Marsden, Merton & Morton (1971, 1973, 1975, 1976*a*, *b*) on the long latency stretch reflex from the human thumb are relevant to our findings, a matter which is taken up again in the following paper (Gandevia & McCloskey, 1977*b*). The subjectively greater effort which their subjects and ours found to be required to move an anaesthetized thumb is likely to correspond with the increase in perceived heaviness that occurs when flexing an anaesthetized thumb. The increased effort is required to replace the assistance previously provided in the sentient thumb by the stretch reflex. If this is so, it follows that the increased perceived heaviness during thumb anaesthesia is a measure of the contribution of this reflex during a normal lift. As our subjects showed an average increase of about 30 % in the perceived heaviness during thumb anaesthesia, this argument allows us to calculate that the stretch reflex contributed an average 23 % ($[30 \div (100 + 30)] \times 100$) of the power when lifting with thumb flexion. For the subject with the largest effect reported here (J.S., 113 %, Fig. 7) the stretch reflex contributed 53 %. Measured in this way the assistance provided reflexly in the performance can be seen to be considerable.

Marsden *et al.* (1975) reported that the long latency stretch reflex from the flexors of the great toe is unaffected by anaesthesia of the toe. We have found changes in perceived heaviness during anaesthesia of the toe when weights were lifted by flexing and by extending the great toe at the metatarsophalangeal joint, using the same apparatus as for the thumb (see

Methods). Although individuals commonly showed significant changes in perceived heaviness when the toe was anaesthetized, no consistent pattern emerged during either flexion or extension (cf. Fig. 3). It would be interesting to know whether the long latency stretch reflex was depressed by anaesthesia only in those subjects in whom anaesthesia of the toe produced large increases in apparent heaviness during flexion, and remained unaltered in the others.

The skin and joint afferents from the thumb are important for the perceived heaviness of weights lifted by its long flexor only when the long flexor is behaving as the prime mover and not merely as a postural fixator. This agrees with the finding of Marsden *et al.* (1976*b*) that the long latency stretch reflex is absent from the long flexor of the thumb during anaesthesia when it is the prime mover, but not when it is a postural fixator.

Our studies of perceived heaviness allow us to make several predictions about the behaviour of the long latency stretch reflex as studied by Marsden *et al.* One of the most important of these is the following: our finding that a weight feels lighter when lifted by extending the anaesthetized thumb should be paralleled by an increase in the stretch reflex of the thumb extensors during thumb anaesthesia (and not depression of the reflex as occurs from the thumb flexor during anaesthesia). Stretch reflexes have been recorded in the thumb extensors, but not during thumb anaesthesia (Adam, Hallett, Marsden, Merton & Morton, 1976).

Another interpretation should be considered. Sears (1974; see also Newsom Davis & Sears, 1970) recognized the possibility that the so-called long latency stretch reflex may be simply a segmental reflex delayed in its action by discharges arising in peripheral receptors. The purpose of the delay was to 'allow time for the significance of the unexpected event' (i.e. the perturbation evoking the response) 'to be analysed centrally and ... allow the subsequent phase of reflex action to be matched in sign and intensity to the voluntary movement occurring consequent on perception of the unexpected load'. This interesting hypothesis conjoined servo action with load perception and took account of the fact that prior instruction could alter the intensity of the apparent stretch reflex (e.g. Hammond, 1956). An implicit assumption in the hypothesis was that the perception of the magnitude of loads depends upon the inputs from peripheral receptors. We have quoted evidence, however, that subjects prefer to disregard such information on loads in favour of signals generated from, or together with, voluntarily generated motor commands.

Whether the correct interpretation of the long-latency stretch reflex is that suggested by Marsden *et al.* or that suggested by Sears is not yet resolved. Whichever is correct, servo action (short, long or delayed latency) assists the voluntarily-generated motor command which

determines the perceived magnitude of a load. When servo-action is enhanced (by peripheral cutaneous stimulation, by prior instruction, by effort), the motor command is assisted and perceived heaviness is thereby reduced; when servo action is reduced (by peripheral anaesthesia, by prior instruction), the motor command must compensate for this and perceived heaviness is thereby increased.

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CHANGES IN PERCEIVED HEAVINESS OF OBJECTS LIFTED BY FLEXION OF THE THUMB DURING ANAESTHESIA OF THE THUMB AND PARALYSIS OF ITS EXTENSOR MUSCLE

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Gandevia & McCloskey (1977) showed that weights lifted by flexing the thumb seem heavier when the thumb is anaesthetized.

They argued that the perceived heaviness of a lifted object depends on the centrally-generated voluntary motor command, or effort, required for a lift, rather than on afferent signals arising peripherally during the lift. Thus, the increase in perceived heaviness associated with thumb anaesthesia was taken as an indication of an increased voluntary motor command; this suggested that thumb anaesthesia removed a source of reflex assistance to flexion of the thumb, and that the increased motor command was a compensation for this. Marsden, Rothwell & Traub, (1978) confirmed that perceived heaviness of objects lifted by thumb flexion increases during thumb anaesthesia, but they reported evidence of an increased level of co-contraction of the thumb extensor during flexion movements made with an anaesthetized thumb. To overcome this co-contraction of the thumb extensor, flexion movements required greater levels of command and of contraction in the thumb flexor in any weight-lifting task. Because of this no changes in reflex facilitation were necessary to explain the phenomenon, they said.

We have now done experiments in 7 subjects in whom the extensor of the thumb was paralysed by injection of local anaesthetic around the radial nerve at the elbow. Perceived heaviness was assessed by a weight-matching procedure as in the original study. In subjects in whom co-contraction of the extensor of the thumb was made impossible by paralysing it, anaesthetization of the thumb by digital nerve block still caused significant increases in the apparent heaviness of objects lifted by thumb flexion. Paralysis of the thumb extensor, without thumb anaesthesia, produced no systematic changes in perceived heaviness, but subsequent anaesthetization of the thumb significantly increased the perceived heaviness. The objections of Marsden *et al.*, (1978) cannot apply in these circumstances, therefore, and the interpretation suggested by Gandevia & McCloskey (1977) can still be supported.

Additional experiments, in which weights were lifted by flexing the distal interphalangeal joint of the middle finger, support the above conclusion. The middle finger can be postured so that its distal joint can be flexed, but not extended, actively. [When the index, middle and ring fingers are flexed maximally at both interphalangeal joints, the terminal joint of the middle finger can be actively flexed, but not extended, presumably because its long extensor is held at a length which is inappropriate for action by its attachment to adjacent digits.] Weights lifted by flexion of the distal interphalangeal joint of the middle finger in this posture appear heavier when the finger is anaesthetized by digital nerve block. The phenomenon cannot be attributed to co-contraction of the extensor of the joint because the extensor cannot operate on the joint in this posture. Again, the interpretation suggested by Gandevia & McCloskey (1977) seems appropriate.

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CHANGES IN MOTOR COMMANDS, AS SHOWN BY CHANGES IN PERCEIVED HEAVINESS, DURING PARTIAL CURARIZATION AND PERIPHERAL ANAESTHESIA IN MAN

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SUMMARY

1. The centrally generated 'effort' or direct voluntary command to motoneurones required to lift a weight was studied using a simple weight-matching task when the muscles lifting a reference weight were weakened. This centrally generated input to motoneurones was increased when the lifting muscles were partially paralysed with curare or decamethonium as judged by the increased perceived heaviness of a reference weight lifted by the weakened muscles.

2. If subjects were asked simply to make matching isometric contractions when the lifting muscles were weakened the isometric tension produced by a weakened muscle was over-estimated.

3. When subjects matched weights by flexing the distal joint of the thumb the perceived heaviness of a reference weight during a control partial curarization was compared with its perceived heaviness during a similar partial curarization when the thumb was also anaesthetized. At any level of maximal strength during curarization the perceived heaviness (which reflects the motor command to lifting motoneurones) was increased when the thumb was anaesthetized.

4. This increased voluntary command to lifting motoneurones may be required because automatic reflex assistance provided by apparent servo action from the long flexor of the thumb is suppressed by anaesthesia of the thumb (Marsden, Merton & Morton, 1971, 1973, 1976*a*; Dyhre-Poulsen & Djørup, 1976).

INTRODUCTION

When making a deliberate muscular contraction in order to develop an isometric force or cause movement about a joint, a neural signal related to the effort required must be delivered to the relevant motoneurones. The final force developed by the muscle depends on the

voluntarily-generated command to the motoneurones and also upon any reflex assistance or hindrance provided to the motoneurones. Assistance may be derived from muscle spindle afferents because of alpha-gamma co-activation, either through spinal arcs (including the monosynaptic reflex) or through supraspinal reflex arcs (via so called 'long latency stretch reflexes'), or even from other afferents excited as a result of the muscle's contraction. The suggestion by Phillips (1969) that muscle spindle afferents may use a transcortical reflex path to assist motoneurones has received support from studies of the discharge of pyramidal tract neurones in behaving monkeys (e.g. Evarts, 1973; Evarts & Tanji, 1974) and studies of long latency stretch reflexes in human muscles (e.g. Hammond, 1955, 1956; Newsom Davis & Sears, 1970; Marsden, Merton & Morton 1971, 1973, 1976*a*, *b*; Melvill Jones & Watt, 1971; Joyce & Rack, 1974; Allum, 1975; Iles, 1976; Schofield, Westerman & Prochazka, 1976; Walsh, 1976). Marsden *et al.* have shown that a perturbation of the thumb during a flexion movement of its distal joint alters the activity of the long flexor muscle to compensate for the perturbation. The latency of this response exceeds that of the tendon jerk but is less than the voluntary reaction time, and they propose that the response is automatic, acting through a supraspinal loop. The response is abolished by anaesthesia of the thumb; this paralyses joint and skin afferents from the thumb but not muscle afferents from its long flexor (see also Dyhre-Poulsen & Djørup, 1976). They also found that the electromyographic response to a disturbance in the actively flexing thumb depends on the effort being put into the contraction, as judged from disturbances made while the initial force required was increased or while the muscle was fatigued and greater effort was required. This apparent increase in the 'gain' of the stretch reflex (or force per unit displacement) with effort has been found by other investigators for the respiratory muscles (Newsom Davis & Sears, 1970), and for abductor digiti minimi at low levels of force (Schofield *et al.* 1976). The increase in gain with increasing load (and effort) allowed Marsden *et al.* (1976*a*) to postulate that the effort put into muscular contraction alters the input to motoneurones and also sets the gain for automatic servo actions; a servo from muscle spindles using a supraspinal path. Sears (1974) has proposed an alternative explanation for the apparent servo action, which he sees as a segmental reflex delayed by the action of afferent discharges and graded in its intensity by higher neural activity. His theory is discussed in more detail in the preceding paper (Gandevia & McCloskey, 1977*b*).

For the argument which we pursue here it is necessary to assume first that gamma motoneurones are driven by the voluntary command, an assumption which is strongly supported by Vallbo's studies of muscle

spindle activity in man which show that parallel increases in skeletomotor and fusimotor outflow occur when muscles are contracted (Vallbo, 1971, 1974), and second that the 'stretch' reflexes, which have been studied in action by halting, resisting or unloading a contracting muscle, operate during a muscular contraction of the type carried out in everyday life. The findings of Vallbo and of Marsden *et al.* certainly support both assumptions. It follows then that when lifting a weight by flexing the distal joint of the thumb a certain amount of the force required to lift it is provided by a direct voluntary input to motoneurones and some is provided by automatic servo action. Evidence has accumulated to indicate that the effort put into a muscular contraction provides an indication of the perceived force that the contraction has achieved or the weight that it has moved, as well as providing a direct input to motoneurones and the setting of gain for stretch reflexes. This evidence is derived from studies of perceived heaviness in patients with unilateral hypotonia (Holmes, 1917, 1922) and hemiparesis (Gandevia & McCloskey, 1977*a*) and from recent physiological studies using fatigue, tonic vibration reflexes and partial paralysis in volunteer subjects (McCloskey, Ebeling & Goodwin, 1974; Gandevia & McCloskey, 1977*a*, *b*). The signal of effort or motor command to the muscles which indicates the force or weight, is 'read off' at levels rostral to motoneurones. That it is not derived simply from recurrent discharges arising in the lifting motoneurones themselves is shown by the observation that the force developed by a muscle during either a tendon jerk or a tonic vibration reflex is unaccompanied by a feeling of effort, and by the observation that the perceived heaviness is increased during hemiparesis unaccompanied by sensory loss (Gandevia & McCloskey, 1977*a*).

As in the preceding paper the perceived heaviness of the lifted object is used to measure the centrally generated direct voluntary input to motoneurones. First, experiments were done to resolve the paradoxical finding (Gandevia & McCloskey, 1977*a*) that during recovery from partial paralysis with D-tubocurarine the weight of an object, which is overestimated initially, may come to be correctly estimated while the strength of the lifting muscle is still reduced. Then the motor output to the long flexor of the thumb was studied when the automatic assistance provided to its contraction by the long latency stretch reflex was abolished by anaesthesia, and when the normal relation between motor command and achieved muscular tension was disturbed by partial curarization of the lifting muscle.

METHODS

Experiments were performed on young healthy male and female subjects, usually medical students, who were unaware of the hypotheses being studied. The authors did not act as subjects.

The methods used for the estimation of weight, the apparatus which allowed subjects to lift weights by flexing or by extending the distal joint of the thumb and the method of digital anaesthesia have been described in the preceding paper (Gandevia & McCloskey, 1977*b*). In brief, subjects were always required to match a reference weight lifted on the left side with a weight similarly presented on the right side. The weight on the right side was altered according to the subjects' instructions. When subjects judged the weights lifted on both sides to be equal the weight lifted on the right (indicator) side was an objective indication of the perceived heaviness of the weight lifted by the left (reference) side. The smallest increment of weight available to the subjects was 10 % or less of the reference weight. Experimental procedures (partial paralysis or anaesthesia) were carried out on the left side. In some experiments subjects lifted weights by flexing the index finger in which movements were confined almost entirely to the metacarpophalangeal joint, using a device similar to the one used and described elsewhere (Gandevia & McCloskey, 1977*a*).

Partial paralysis

Partial paralysis of the forearm and hand on the left side was produced by retrograde I.V. infusion of a paralysing agent into the forearm while a sphygmomanometer cuff, placed around the upper arm, was inflated above systolic arterial pressure (Torda & Klonymus, 1966; McCloskey & Torda, 1975; Gandevia & McCloskey, 1977*a*). D-tubocurarine (< 3 mg) or decamethonium (0·4 mg) diluted in 15–20 ml. of physiological saline was slowly infused into a vein on the back of the hand. When using D-tubocurarine forearm and hand muscles were weakened about 5–10 min after inflating the cuff and making the infusion; the cuff was then removed and strength gradually recovered. During the recovery subjects matched a reference weight on the weak side with a variable weight lifted by the strong side. In some experiments it was necessary to curarize partially the forearm and hand twice during one session of weight matching (see Results) and when this occurred the total dose of D-tubocurarine did not exceed 5 mg. When using decamethonium a slightly different procedure had to be adopted because, unlike curare, decamethonium in the concentrations used remains effective in the muscle only as long as the blood supply is occluded (see Results). Hence, after inflating the cuff and infusing the decamethonium, estimates of the weight were made every 1–2 min for 10–12 min and then the blood supply was re-established.

During experiments involving partial paralysis the degree of weakness was monitored either by measuring the maximal isometric handgrip contraction, or by recording the maximal isometric contraction of the thumb using a Grass FT-03 transducer, modified for large forces.

For all experiments involving partial paralysis or anaesthesia the ethical requirement of informed consent was fulfilled.

RESULTS

Part A:
Partial paralysis of lifting muscles

Weight matching during paralysis with D-*tubocurarine*

If, after making several control estimates of the heaviness of a reference weight lifted on the left side (by matching it with a variable weight lifted on the right), the lifting muscles on the left side are weakened by local infusion of D-tubocurarine, then the first estimates of the weight lifted

with the weakened muscles exceed the control estimates (Fig. 1). This is part of the evidence that the sensation of heaviness depends on sensing the effort or voluntary command put into the lifting contraction rather than on perceiving the actual muscular force or tension achieved (Gandevia & McCloskey, 1977*a*). In the previous study using partial curarization the apparent heaviness of the reference weight usually returned to its control value before the lifting muscles had regained full strength. A typical example is shown in Fig. 1. The subject made three accurate

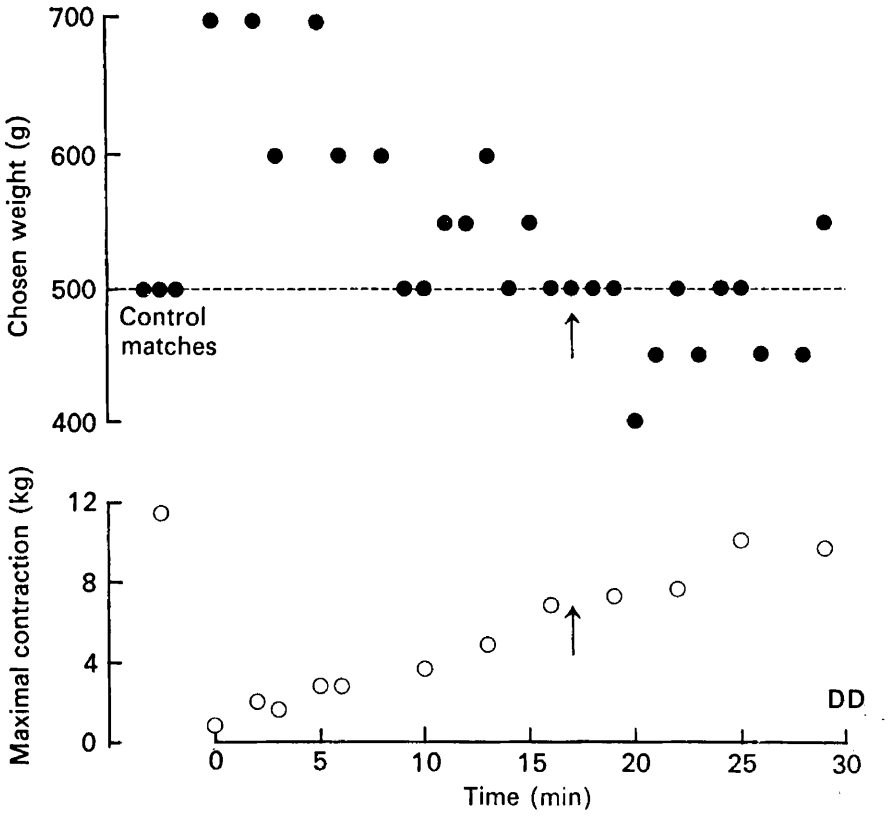

Fig. 1. This shows a result from a subject estimating the weight of a 500 g reference weight (broken line) by flexing the distal joint of the thumb. The upper graph (filled circles) shows the perceived heaviness of the reference weight, and the lower one (open circles) the maximal isometric strength of the flexor of the thumb on the curarized side. The time axis for both graphs begins as the first estimate is being made, after removal of the cuff (see Methods). The points at the extreme left show control estimates of the 500 g reference weight (above, 3 points) and the control maximal strength (below, 1 point) taken before the muscular strength was reduced by partial curarization. When initially weakened with curare the reference weight (500 g) lifted on the left side seemed as heavy as 700 g lifted on the strong side. As strength was regained the perceived heaviness of the weight came down towards control levels. At the point marked with arrows the perceived heaviness had returned to its control value while the lifting muscle had still not fully recovered (see text).

control estimates of 500 g lifted by flexing the thumb at its distal joint, and the maximal strength of his thumb flexor was measured (11·5 kg). When first weakened with curare (maximal contraction < 2 kg) the perceived heaviness of the 500 g reference weight was 700 g. As strength was regained the perceived heaviness came down towards its control level and between the 15th and 20th minutes after removal of the sphygmomanometer cuff the subject again made three estimates at 500 g, i.e. the same as his control estimates. At this time, however, the maximal strength of the lifting muscle was only 62 % of the control strength.

The experimental procedure used in these weight matching experiments usually meant that the subject lifted the reference weight on the left side and the variable weight on the right side before ordering a change in the weight on the right side. The weight was adjusted and the process was repeated, often two or thee times, until the subject was satisfied that the weights lifted on both sides were equal. Maximal contractions were made after each two or three estimates of the reference weight, and only two maximal contractions were made on each occasion. On average, subjects made about twenty lifting contractions for each maximal one. This suggested the possibility that during the repeated lifting contractions sufficient acetylcholine was released at the neuromuscular junction to 'decurarize' competitively the muscle fibres used in lifting the reference weight while other muscle fibres which were activated only during maximal contractions were not decurarized so rapidly. Hence, if this occurred, the subject would be lifting with nearly normal muscle while curarized fibres would be recruited during maximal contractions. To investigate whether the repeated lifting contractions were responsible for the relatively rapid return to the control value of perceived heaviness (compared to the recovery of maximal strength), the experimental procedure was modified. Following removal of the cuff (5–10 min after locally infusing the curare) the subject made three estimates of a reference weight (400 g) lifted by flexing the index finger and then made a series of repeated estimations of the same weight lifted by the thumb flexors. When the estimates made while lifting with the thumb had returned to the control level estimates were recommenced with the index finger. Unknown to the subject, the weight that he had chosen when making his initial matches using the index finger before commencing estimates with the thumb was the first weight presented to him after making the series of lifts with the thumb. When estimates made using the index finger had returned to control levels, the whole partial curarization procedure was repeated and a similar pattern of lifts was made, except that estimates made during the first curarization with the thumb flexors were now made with index flexors and estimates previously made with index flexors were now made with

thumb flexors. A result from one of these double curarization experiments is shown in Fig. 2.

Fig. 2 shows that during the first partial curarization of the forearm and hand the 400 g reference weight was initially matched with a weight of 520–600 g when lifted by the index flexors both immediately before *and* after the perceived heaviness of the 400 g weight when lifted with the

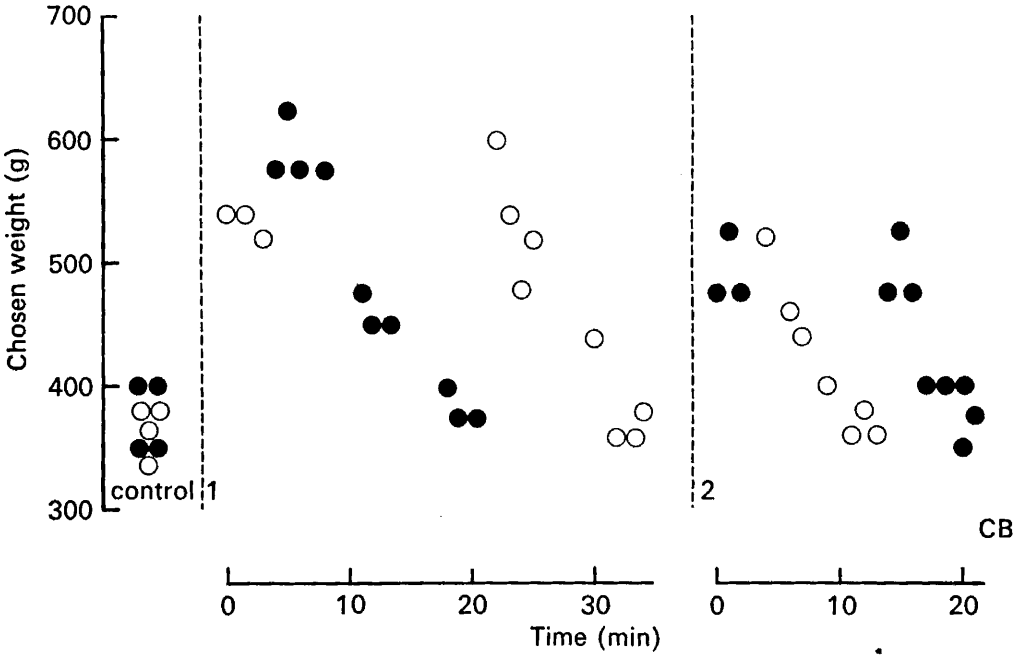

Fig. 2. This shows the result of a double partial curarization experiment (for details see text). The time axis for each curarization begins as the first estimate is commenced. In the first curarization the subject made 3 estimates of the reference weight (400 g) lifted by flexing the index finger (open circles), and then made estimates of the reference weight (400 g) lifted by flexing the thumb (filled circles) until they had returned to control values. Estimates were then made again by flexing the index finger. The pattern of lifting by the two muscle groups (thumb flexor and index flexors) was reversed in the second curarization. The perceived heaviness of the reference weight returns to its control level more quickly when the muscles lifting it make repeated estimates (thumb flexor in the first curarization, at left, and index flexors in the second curarization, at right), and the perceived heaviness remained elevated when estimates were separated by a period of inactivity in the lifting muscle (for the flexors of the index finger in the first curarization, and for the thumb flexor in the second curarization).

thumb had come down from 625 g to the control level (350–400 g). Thus the perceived heaviness came down to the control levels when a muscle group made repeated contractions (thumb flexors) and it remained elevated for a muscle group which was inactive (index flexors). During the second curarization (about 20 min after the first, Fig. 2 at right) when the pattern of lifting was changed over between index and thumb flexors,

a similar result occurred. The perceived heaviness of the reference weight lifted by the thumb flexors remained elevated, when the thumb was not active, but during the time that the thumb remained inactive the perceived heaviness came down to control levels for repeated estimates made with the index flexors. Similar changes in perceived heaviness when two different muscle groups were used to lift the weights (and were interchanged) were found in another two subjects. In a further four subjects we found that the perceived heaviness returned to control levels more rapidly in the more active muscle group, in single periods of regional curarization.

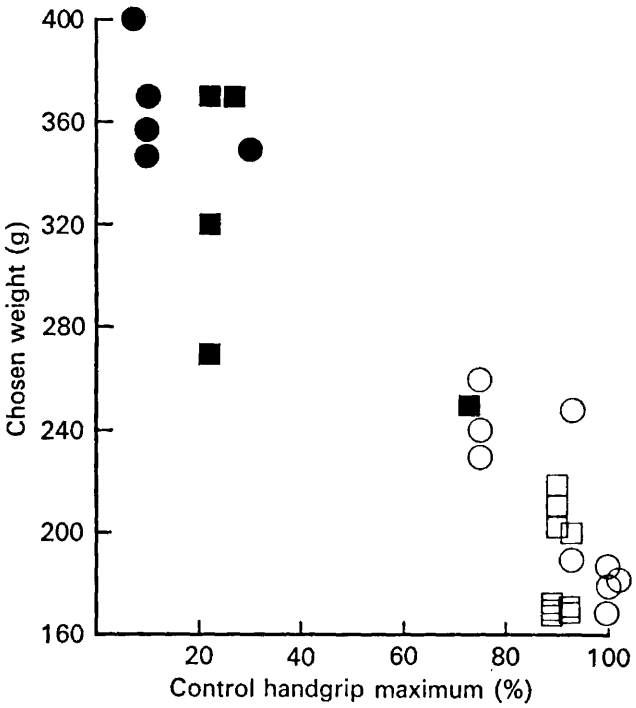

Fig. 3. This shows the results from two subjects when estimating the weight of 200 g lifted by the extensors of the index finger during a control vascular occlusion (open symbols) and then during partial paralysis with decamethonium in a second period of vascular occlusion (filled symbols). Maximal strength is expressed as a percentage of the maximal handgrip contraction taken before the periods of vascular occlusion. The perceived heaviness of the reference weight was increased and the maximal handgrip strength was reduced following infusion of decamethonium distal to the sphygmomanometer cuff.

The finding that the more active muscle group returns to normal more quickly (as judged by perceived heaviness) is consistent with the decurarization hypothesis. If applied to an individual muscle making repeated lifting contractions and only an occasional maximal one the apparent paradox that perceived heaviness may have reached control levels while the lifting muscle is still weak can be explained. Although these results

may be explained by assuming decurarization at the neuromuscular junction, changes in blood flow around more active muscle fibre groups could also contribute.

Weight matching during partial paralysis with decamethonium

Partial paralysis was produced in two subjects using decamethonium, a depolarizing blocking agent. For these experiments the protocol was slightly altered, as the estimates of weight had to be made while the sphygmomanometer cuff around the upper arm remained inflated above systolic pressure. Thus, as a control, subjects made repeated estimates (every 1–2 min) of the reference weight (200 g) lifted by flexing the index finger for 10–12 min after inflating the cuff. The procedure was repeated, after allowing 10 min for recovery, but decamethonium (0·4 mg diluted in 20 ml. saline) was infused into a vein on the back of the hand after inflating the cuff, and then repeated estimates were made. The cuff remained inflated for the same period of time as for the control occlusion. Results from the two subjects are shown in Fig. 3.

During the occlusion with decamethonium there was both an increase in the perceived heaviness of the reference weight and a reduction in maximal handgrip strength as compared to values obtained during the control occlusion.

Matching of isometric forces

Throughout this study, and in a previous study in which the effects of alterations of related sensory inputs on perceived heaviness were investigated (Gandevia & McCloskey, 1976) a matching task requiring *movement* of a lifted object was used. Here we produced partial paralysis with D-tubocurarine in three subjects and required them to match *isometric* forces produced by extending the index finger. The subject was required to produce a reference tension (100 g) with the aid of visual feed-back of achieved force on the left side and to make the 'same contraction' produced without visual information on the other. The way in which the two contractions were to be made 'the same' was not specified, as subjects in other tests are capable of distinguishing between the effort put into a contraction and the tension produced (McCloskey *et al.* 1974). Ten contractions were made before and during partial paralysis.

A typical record of the matching contractions is shown in Fig. 4. In all three subjects there was an increase in the tensions produced above control matches when the lifting muscles were moderately weakened i.e. the reference isometric tension was over-estimated. The subjects chose to make the matching contractions the 'same' as the references ones, not with respect to the tension produced but with respect to the effort put into the

contraction. In these and earlier experiments we obtained a similar result by training subjects to make an isometric handgrip contraction of say, 10 kg with their weakened hands and then asking them to make alternate contractions with the weakened hand and then with the unaffected hand which were the 'same'. Matching handgrip contractions made by the unaffected hand consistently exceeded those made by the weak hand. We also confirmed the finding of McCloskey *et al.* (1974) that subjects are able to differentiate between the effort put into a contraction and the

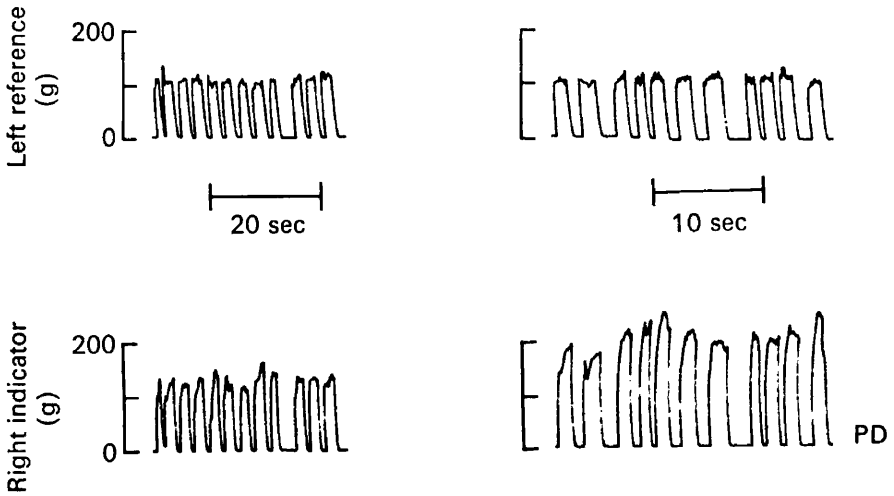

Fig. 4. This shows the records taken from a subject when 'matching' isometric contractions with the extensors of the index finger, as a control (panels at left) and during partial curarization of the left forearm and hand (panels at right). The upper panels indicate the reference tension (which was displayed to the subject) and the lower panels show the matching tension produced on the right (which was not shown to the subject). As a control the subject produced a tension of about 135 g to match the reference tension of 100 g but when partially curarized on the left side he produced a tension of about 200 g on the right side to match the reference tension.

achieved tension by later asking them specifically to make the tension of the matching contraction the same as that of the reference one. They were then able to make contractions which were of similar tension to the controls. However, when asked to make the efforts the same, the subjects produced tensions on the indicator side which were similar to those produced when they had been asked simply 'to make both contractions the same'.

Part B

Perceived heaviness during partial curarization and peripheral anaesthesia

When lifting the weights in the experiments reported above, subjects were using the direct voluntary input to motoneurones as well as any automatic reflex assistance available. Some indication of the possible

importance of reflex assistance to muscular contraction is revealed by considering a simple partial curarization experiment of the type shown in Fig. 1. Early in a period of partial curarization, when a subject may have a maximal strength of, say, one tenth its control value, the perceived heaviness of the reference weight is not increased tenfold. For example, it is increased by only 40 % in the result shown in Fig. 1. The increased motor outflow required to lift a weight at this stage in the partial curarization, as well as manifesting itself as an increased voluntary input to lifting motoneurones (shown by the increase in perceived heaviness) is also said to be responsible for increasing the gain of automatic servo action (Marsden *et al.* 1976*a*) and thus for increasing that proportion of required force which is provided by servo action. If this occurred it would not be necessary to increase tenfold the voluntary input to motoneurones.

The long latency stretch reflex which assists the long flexor of the thumb is abolished by anaesthetizing the thumb (Marsden *et al.* 1971, 1973, 1976*a;* Dyhre-Poulsen & Djørup, 1976), a procedure which should not interfere with its muscle afferents arising in the forearm.

Here we studied the motor command to the thumb, during anaesthesia of the thumb, when a 500 g reference weight required a range of efforts in order to lift it because of partial paralysis of the forearm and hand. These experiments required the subject to estimate the heaviness of the 500 g reference lifted by flexing the thumb at its distal joint, during a control partial curarization (for example, as in Fig. 1). Then the thumb was anaesthetized, the effect on perceived heaviness of the reference weight noted, and the forearm and hand were again partially curarized and estimates of the reference weight made until the maximal strength of the muscle had recovered. This experiment has been performed on four subjects, and the results from the subject in which the data are most complete are shown, plotted in two ways, in Fig. 5. This subject made estimates rapidly (and accurately as judged by the control estimates of 500 g made before the forearm and hand were partially curarized), and a significant and comparable degree of weakness was produced in both partial curarizations.

In Fig. 5 (at left) the control curarization (filled circles) and the curarization combined with anaesthesia of the thumb (open circles) are plotted against the time since the first estimates of each curarization were made. The control curarization is the same as was illustrated in Fig. 1. At right (Fig. 5) the results of both curarizations are plotted against the maximal isometric contraction of the flexor of the thumb (measurements of maximal contraction were made after each two to three estimates). After recovery from the control curarization (approx 3 hr later), the thumb was anaesthetized and there was a predictable increase in the perceived

heaviness of the reference weight from 500 to 625 g (average of four estimates). When the forearm and hand were then curarized the subject, for the first estimate, was only just able to lift the 500 g in order to match it with one lifted by the other thumb. He matched it with a weight of 2500 g and, judging from the comments he volunteered at the time, probably would have matched it with an even greater weight if we had been able to load the bucket more. Fig. 5 shows that a weight lifted by the flexor of the thumb is heavier when the thumb is anaesthetized over a considerable range of efforts required during the partial curarization. The difference between perceived heaviness in the anaesthetized and control states was greatest when the muscle was most weak – that is, when the effort required to achieve the lift was greatest.

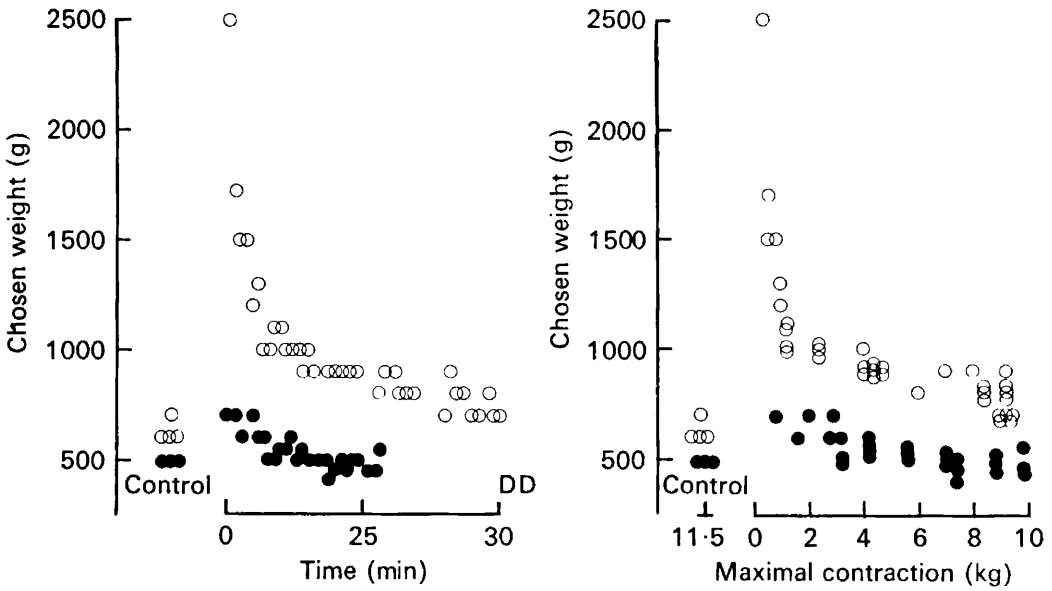

Fig. 5. This shows the results from one subject of a control curarization (filled circles) and curarization combined with anaesthesia of the thumb (open circles). Weights were lifted by flexing the distal joint of the thumb. At left the results are plotted against time since the first estimate was commenced in each curarization, and at right the results are plotted against the maximal isometric strength of the long flexor of the thumb. Control estimates of the 500 g reference weight are shown at the left of each panel, when the maximal contraction of the thumb was 11·5 kg. During the partial curarization with the thumb anaesthetized, the perceived heaviness of the reference weight exceeded the control perceived heaviness at any level of maximal isometric strength. This effect was most marked when the lifting muscle was very weak.

In two of the other three subjects in this experiment the results were similar to those shown in Fig. 5. In the third subject the control curarization curve was similar to that shown in Fig. 5, and the degree of weakness

produced by each curarization was similar. In the absence of weakness anaesthesia of the thumb produced a large increase in perceived heaviness (500–1200 g) and when the flexor of the thumb was weakened estimates made at comparable levels of maximal contraction were much larger when lifting with the anaesthetized thumb. However, the experiment was stopped when, after 50 % of maximal strength had been regained in the second curarization the subject decided he was no longer able to make any decisions about heaviness.

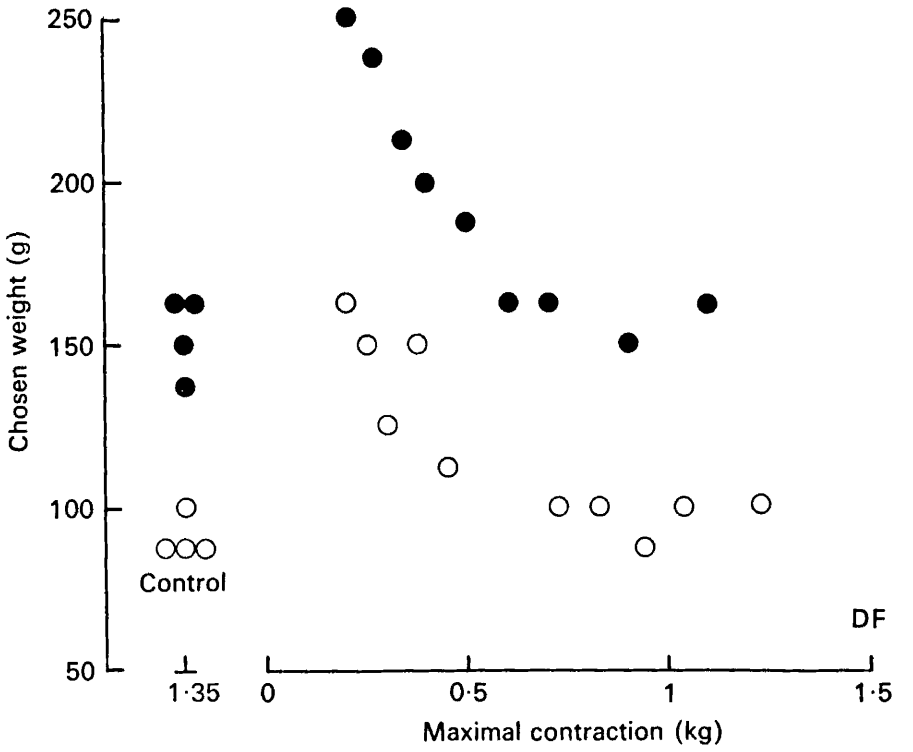

Fig. 6. This shows the results from one subject of a control curarization (filled circles) and a curarization combined with anaesthesia of the thumb (open circles). Weights were lifted by extending the distal joint of the thumb. Changes in perceived heaviness are plotted against the level of maximal isometric strength in the extensors of the thumb. Control estimates of the reference weight (200 g) are shown at the left when the maximal isometric contraction was 1·35 kg. During the partial curarization with the thumb anaesthetized, the perceived heaviness was less than the control perceived heaviness at comparable levels of maximal contraction.

A weight lifted by extending the thumb was perceived as lighter when the thumb was anaesthetized (Gandevia & McCloskey, 1977*b*). In three subjects we duplicated the experiments shown in Fig. 5 when the reference weight (200 g) was lifted by extending the thumb at its distal joint. A typical result, plotted as perceived heaviness against maximal contraction of thumb extensors, is shown in Fig. 6 for a control curarization (filled

circles) and during partial curarization combined with anaesthesia of the lifting thumb (open circles). At any particular level of maximal contraction the perceived heaviness of the reference weight was below the control estimate made when the thumb was anaesthetized.

DISCUSSION

During partial paralysis of the forearm and hand, produced by local infusion of either D-tubocurarine or decamethonium, the perceived heaviness of a reference weight lifted by weakened muscles is over-estimated. Similarly a reference isometric tension produced by muscles weakened with curare is over-estimated. These findings are consistent with the hypothesis that the perception of heaviness of a lifted object or of achieved force in an isometric contraction depends on sensing the effort, or voluntarily generated input to motoneurones, rather than an afferent sensation signalling the muscular force achieved (McCloskey *et al.* 1974; Gandevia & McCloskey, 1977*a*, *b*). Our studies have shown that partial curarization is a valuable method of disturbing the relationship between effort put into contraction and the muscular force achieved, as long as the likelihood of selective decurarization of the most frequently used muscle fibres is considered. This concept of decurarization fits with studies in man on the termination of action of D-tubocurarine at the neuromuscular junction (Feldman & Tyrrell, 1972).

A weight lifted by flexing the distal joint of the thumb feels heavier, over a wide range of efforts, when the thumb is anaesthetized. This increase in perceived heaviness (which may be considerable, e.g. Fig. 5, see also Gandevia & McCloskey, 1977*b*) may reflect the additional voluntary input to motoneurones required to replace the automatic reflex assistance to contraction which is abolished by anaesthesia (Marsden *et al.* 1971, 1973, 1976*a;* Dyhre-Poulsen & Djørup, 1976). The possibility that other sources of assistance to motoneurones apart from the long latency stretch reflex of the thumb are suppressed by removing the joint and cutaneous input from the thumb cannot be excluded.

In other respects the results obtained from these weight-matching experiments relate interestingly with the properties of the automatic servo assistance in the long flexor of the thumb described by Marsden *et al.* (1976*a*). If we assume that the most important source of assistance to the thumb flexor which is abolished by anaesthesia of the thumb is that provided by the long latency stretch reflex, we are able to calculate the assistance this reflex was providing over the range of efforts that the subject exerted to lift the weight during the recovery of maximal strength (Fig. 5, at right). In Fig. 7 we have plotted the increase in perceived heaviness above the control estimate (at changing levels of maxima

contraction during recovery from curarization) against the reference weight (500 g) expressed as a percentage of the existing maximal contraction at the time. Thus when the subject was only just able to lift the reference weight (i.e. the first estimates made with the weakened muscle), it represented 95% of his maximal contraction and the increase in perceived heaviness with the thumb anaesthetized above the control was

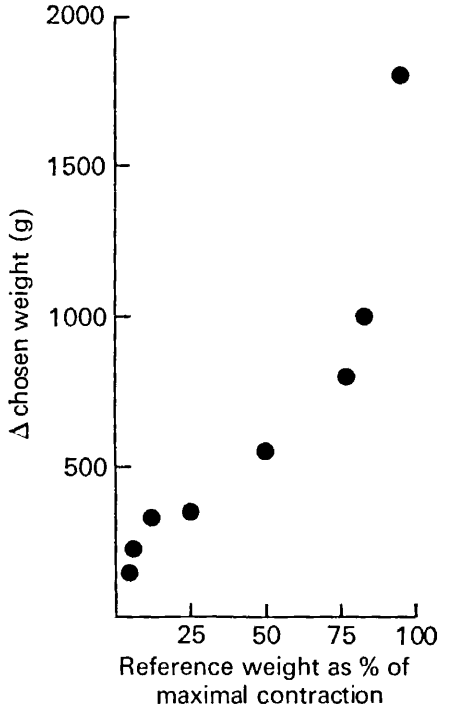

Fig. 7. This shows results taken from Fig. 5 (at right) when lifting by flexing the thumb. The increase in perceived heaviness with the thumb anaesthetized above the control perceived heaviness, at a comparable level of maximal contraction, is plotted against the reference weight (500 g) expressed as a percentage of the strength of the maximal isometric contraction. As the effort increased (along the horizontal axis) so did the change in perceived heaviness. For details see text.

1800 g. A second point for Fig. 7 (the point closest to the origin) was obtained using values collected in the absence of partial paralysis – when the 500 g reference weight was only 4·3% of the subject's maximal contraction, anaesthesia of the thumb produced an average 125 g increase in perceived heaviness. These two points (when first curarized and when uncurarized) indicate that as the reference weight becomes a larger proportion of the maximal force that the subject can lift or, as his effort increases, so the amount of muscular force that automatic reflex assistance can call up is increased. This finding relates interestingly to that of Marsden *et al.* who found that the gain of automatic reflex assistance for

the long flexor of the thumb increases as the force of contraction (and hence effort) increases. Additional points have been added to the graph in Fig. 7 similarly derived from data presented in Fig. 5 (at right), but they cannot take into account the possibility that decurarization may have occurred at a different rate during the two recoveries. Taken together, the studies of perceived heaviness and of servo action in the thumb suggest that increasing the motor output used in a contraction produces a larger direct voluntary input to motoneurones, which usually gives a signal of weight and also controls a mechanism to increase the gain of the reflex assistance.

Our finding that a weight feels lighter when lifted by extending an anaesthetized thumb suggests that the skin and joint afferents from the thumb which strongly facilitate the stretch reflex assistance to the long flexor may inhibit the reflex assistance which is known to exist in thumb extensors (Adam, Hallett, Marsden, Merton & Morton, 1976). By plotting (in the same way as for Fig. 7) the reduction in perceived heaviness against the range of effort used when lifting by thumb extension we again find that the 'gain' (it is really a negative gain) increases as the effort does, although for the subject shown in Fig. 6 the lightening effect does not increase when the reference weight is more than 40% of the maximal contraction. If a similar type of automatic servo assistance operates for the thumb extensors (except that may be partially inhibited from operating by afferents arising in the thumb) it may be saturated at higher efforts. Schofield *et al.* (1976) report that electromyographic responses to similar disturbance of an isometric tension developed by abductor digiti minimi no longer increase with initial force after more than 10% of maximal force is used.

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ROLE OF INPUTS FROM SKIN, JOINTS AND MUSCLES AND OF COROLLARY DISCHARGES, IN HUMAN DISCRIMINATORY TASKS

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INTRODUCTION

When one contracts a muscle to move a part or to develop a tension the position and movement of the part can be perceived, together with the force required or tension developed. Potential sources of such information to the central nervous system are sensory nerves in the joints, muscles and skin, and the centrally-generated motor command itself which may provide "corollary discharges" to centres concerned with sensation.

SENSE OF POSITION AND MOVEMENT

Until quite recently it was widely believed that the conscious awareness of limb position and movement depends almost entirely upon the activity of sensory nerve endings in joint capsules and ligaments. The sensory nerve endings in muscles were thought to play important roles in motor control at a subconscious level, but not to contribute to perception. Recent electrophysiological studies on joint receptors in the cat, however, cast serious doubt on the ability of joint receptors to provide sufficiently detailed information for position sense (1,2,11). Also, intra-muscular receptors have been shown to be capable of providing perceived kinaesthetic signals in the form of illusions of false movement and position during muscle vibration at 100 Hz, and kinaesthetic sensation has been shown to persist after elimination of discharges from joint and cutaneous receptors (10). Conventional views on the basis of the senses of position and movement have, therefore, had to be re-appraised. In particular, the relative contributions of joint, muscle and cutaneous receptors to these sensations have had to be considered.

The distal interphalangeal joint of the middle finger provides a convenient opportunity to consider this problem because at this joint an anatomical peculiarity permits the hand to be positioned so as to disengage the muscles from the joint, or be positioned so that the muscles are again engaged (5). If the index, ring and little fingers are extended and then the middle finger alone is flexed maximally at the proximal interphalangeal joint, the terminal phalanx of the middle finger cannot be moved by voluntary effort because the long flexor and extensor muscles which usually move it are held at inappropriate lengths. In this position the joint is freed from effective muscular attachment. If anaethetized in this position the joint loses all position sense, but regains it when the adjacent fingers are aligned with the test finger, restoring effective muscular attachment. Thus, 'joint' sense (really 'joint plus cutaneous' sense) can be tested by imposing movements on the joint, while the muscles are disengaged, and can be compared with full

position sense similarly tested when the muscles are re-engaged. 'Muscle' sense can be assessed in further tests in which the muscles are engaged but cutaneous and joint receptors are anaesthetized locally within the finger. In all of our tests on this joint movements into flexion and extension were imposed on the joint and subjects were scored according to the number of correct detections of movement and direction made in sets of 10 such displacements.

Three tests of kinaesthetic sensibility were used, first with the muscles disengaged and then with the muscles engaged. In all tests the displacements of the joint commenced from an initial angle of 30° into flexion. In the first test the distal interphalangeal joint was moved 10° into flexion or extension at angular velocities from 1 to 10°/sec. In the second test the joint was moved for a fixed time (1.2 sec) at velocities from 1 to 10°/sec. In the third test the joint was displaced through 2.5°, 5°, 7.5° and 10° at a fixed angular velocity (~8°/sec). In all tests the movements into flexion and extension were given in random order. The first test was then repeated in subjects with muscles engaged at the joint but in whom any contribution from cutaneous and joint receptors was abolished by local anaesthesia of the test finger.

Proprioceptive acuity for the joint ('joint plus skin') was determined in 12 subjects. These subjects were unable to detect any 10° displacements made at 1°/sec, and no subject was able to detect all 10° displacements made at less than 4°/sec. With the muscles engaged, the proprioceptive acuity of all subjects was improved: many subjects could now detect all 10° displacements made at 1°/sec, and all subjects could detect all 10° displacements made at 3°/sec. Similar results were found in all three tests. There was no significant bias towards detection of displacements into flexion or into extension. Figure 1 shows results from one subject.

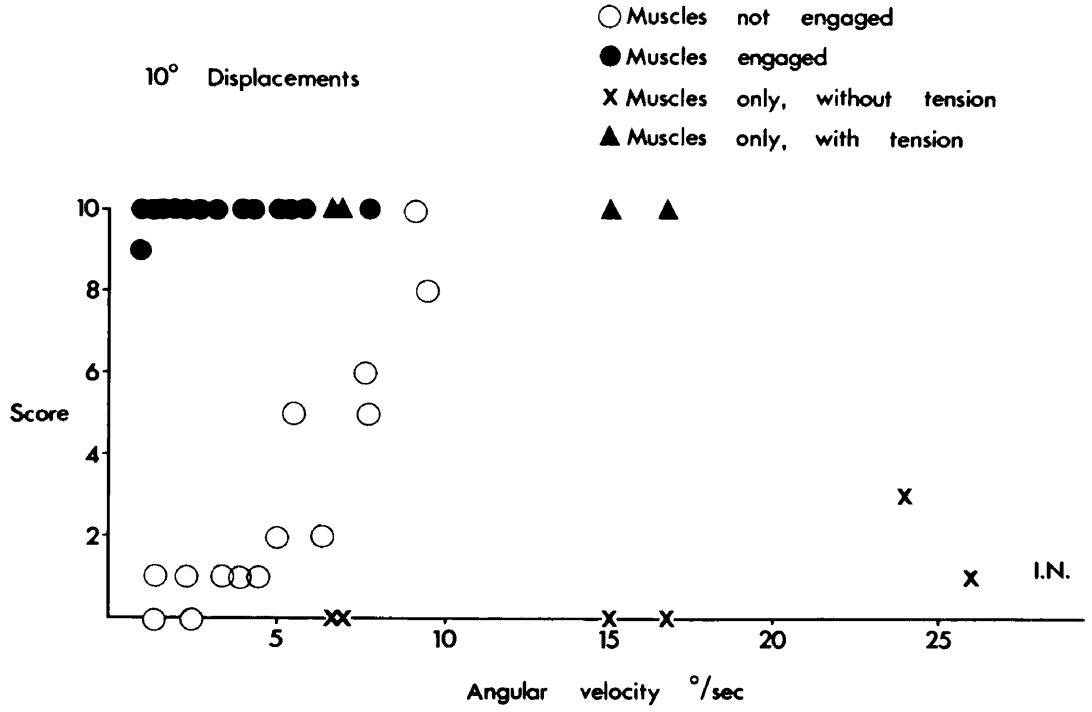

Fig. 1. Detection of joint displacements.

As muscular engagement caused no consistent change in the measured 'stiffness' of the joint it is unlikely that the improved performance resulted from increased discharge from joint receptors. Clearly, intramuscular receptors contribute to normal position sense.

When 'muscle sense' was tested alone following local anaesthesia of the joint and skin some subjects showed very poor proprioceptive acuity (see Fig. 1) while others were almost as accurate as with all the proprioceptive machinery intact. In all subjects muscle sense was greatly improved during the exertion of voluntary muscular force (see Fig. 1).

Intramuscular receptors, therefore, appear essential for full proprioceptive acuity. Receptors in joints or skin can also subserve position sense but it is difficult to anaesthetize one without the other to enable their relative contributions to be assessed. There is very little reduction in proprioceptive acuity in patients in whom the bony joints are totally replaced by prosthetic devices, a procedure which presumably destroys joint receptors (3,12). Because of this, and the electrophysiologically demonstrated inadequacy of joint receptors to signal position sense accurately, it seems likely that cutaneous receptors may be the more important complement to intramuscular receptors in subserving normal position sense. In this respect it is of interest that Knibestöl (15) has recorded in the human finger from cutaneous receptors whose discharges are closely related to the angle of the underlying joint.

No sense of movement or of altered position accompanies voluntary motor commands despatched to paralysed muscles (10,16,20). Corollary discharges do not, therefore, provide perceived sensations of movement or position.

SENSE OF MUSCULAR FORCE OR TENSION

Three mechanisms are usually proposed for the capacity to estimate the weights of lifted objects. First, cutaneous receptors may signal the pressure of the object on the skin; second, receptors in the contracting muscles or in their tendons or joints may signal the forces exerted in the task; and, third, corollary discharges arising from the motor command itself may give an estimate of the effort required to support the object.

It is a common experience that a weight lifted by a muscle until it becomes fatigued feels heavier than it felt before the fatigue. In such a situation peripheral sensory nerves in the skin of the supporting part and in the muscles, tendons and joints employed in the lift presumably continue to provide signals of the true tensions and pressures involved and so seem unlikely to be the basis of the erroneous judgements. The increase in perceived heaviness could be explained, however, if the preferred signal available derives from the centrally-generated voluntary motor command, as this command would have to increase as the muscle fatigues. This common experience has been tested objectively by having subjects match weights lifted by a fatigued muscle with weights similarly lifted on the unaffected side, and it has been demonstrated that subjects prefer to disregard any peripherally-generated sensory signals related to tensions and pressures in favour of alternative signals related to the effort required (19).

An increase in the perceived heaviness of a lifted object occurs whenever the lifting muscle is weakened. It occurs whether the weakness is caused by

muscular fatigue, by partial curarization, by activation of muscle spindle afferents in its antagonist leading to inhibition of its motoneurones, or by neurological disorders (such as simple motor 'strokes' or unilateral cerebellar dysfunction) in which weakness without sensory loss is a feature (7,14,19). In all of these situations subjects prefer to judge the weight of a lifted object according to the effort involved in lifting it and to disregard any available, but conflicting peripheral signals. Figure 2 gives a diagrammatic representation of the motor pathways delivering command signals to a contracting muscle, and shows the points in the pathways at which a lesion or an experimental intervention can cause weakness of the muscle and an increase in the perceived heaviness of objects lifted by it.

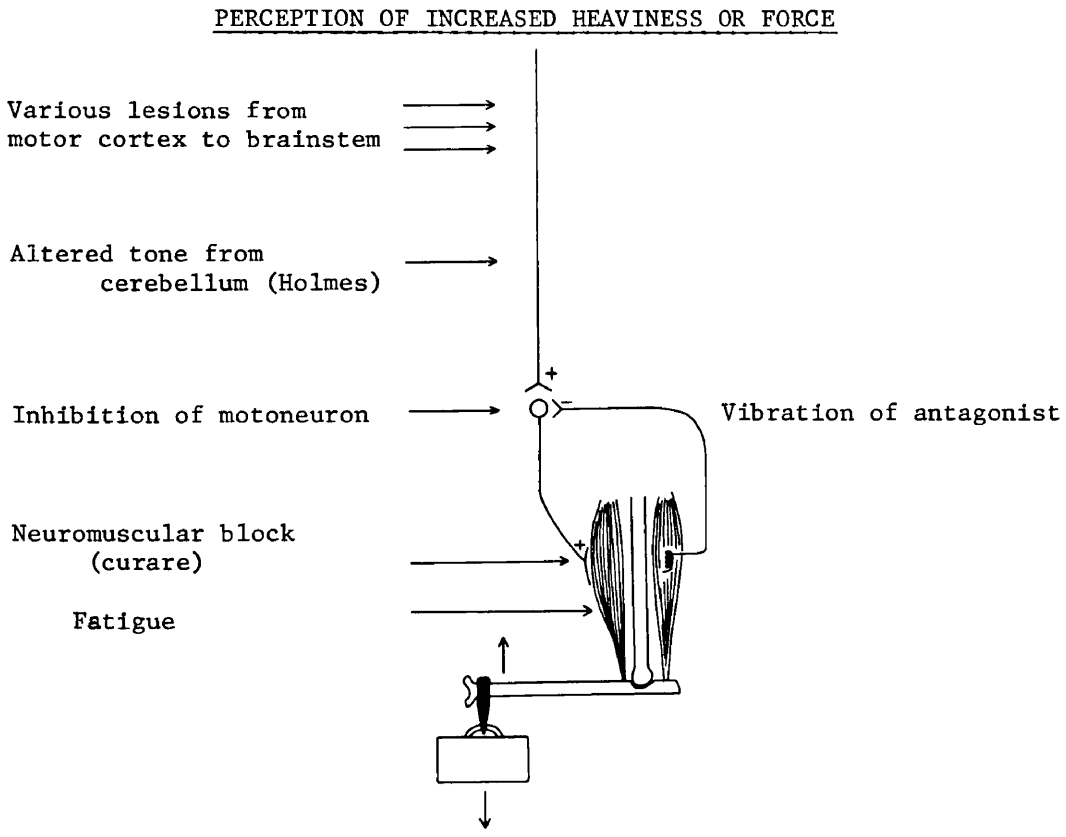

Fig. 2. Factors increasing perceived heaviness or force.

While subjects prefer to rely on centrally-generated command signals as the basis of their judgements on the heaviness of lifted objects, it can be shown that alternative signals do exist. For example, it can be shown that subjects

perceive signals related to cutaneous distortion (18) or to intra-muscular tension (19) when lifting objects - such alternative signals, however, seem usually to be disregarded.

The specific possibility should be considered that, because of parallel activation of skeleto-motor and fusimotor fibres (α-γ co-activation), there is always an increase in the discharge from muscle spindles when effort is increased. Such activity of the muscle spindles might be thought to provide the perceived signals used to estimate heaviness. This is not so. When the muscle spindles in a muscle are activated by vibration of the muscle at 100Hz, no feeling of increased heaviness or weight is induced. Instead, "the subject gets a feeling of relief or lessening of tension" (13), and chooses smaller tensions than before in unaffected muscle to match any tension achieved by the vibrated muscle (19).

The sensation of heaviness, therefore, depends upon sensing the effort or motor command required to lift or support an object, and is preferred to other available signals.

EFFECTS OF SENSORY INPUTS UPON MOTOR COMMANDS

Because the perception of heaviness of a lifted object derives from the centrally-generated voluntary motor command used to lift it, it follows that the central motor command delivered to the motoneurons can be studied through observations on perceived heaviness.

We have investigated the perception of the heaviness of lifted objects when sensory inputs from parts related to the lifting task were altered. In all tests subjects were given a reference weight to lift with a muscle group on the left side and they matched it with weights similarly presented to the right (indicator) side. The weights chosen on the right side thus gave an objective indication of the perceived heaviness of the reference weight lifted on the left side. Matches were made as controls and during disturbances of sensory input on the left side.

Our results indicate that the perception of heaviness is altered by sensory inputs arising peripherally. For example, Fig. 3 shows how sensory inputs from the left index finger and thumb influence the perceived heaviness of objects lifted by flexion of either of these digits. Electrical stimulation of the index finger (90V, 40-100Hz, 2 ms) over the digital nerves, so as to produce a pressing sensation over the whole of the finger, causes weights lifted by flexion of the distal joint of the thumb to feel lighter. Local anaesthesia of the index finger, however, causes weights lifted by thumb flexion to feel heavier. Anaesthesia of the thumb itself, which blocks cutaneous and joint receptors within the thumb but leaves the innervation of its long flexor muscle unaffected, also causes weights lifted by thumb flexion to feel heavier. All these findings, for 6 subjects, are shown on the left of Fig. 3. Similar results are found for weights lifted by flexion of the index finger. A weight lifted by flexion of the index finger feels lighter when the thumb is stimulated electrically, and heavier when the thumb is anaesthetized. (Fig. 3, at right).

These changes in perceived heaviness give some insight into how motor commands must alter when inputs arising peripherally are altered. A weight lifted by thumb or index finger flexion must feel heavier during anaesthesia of either

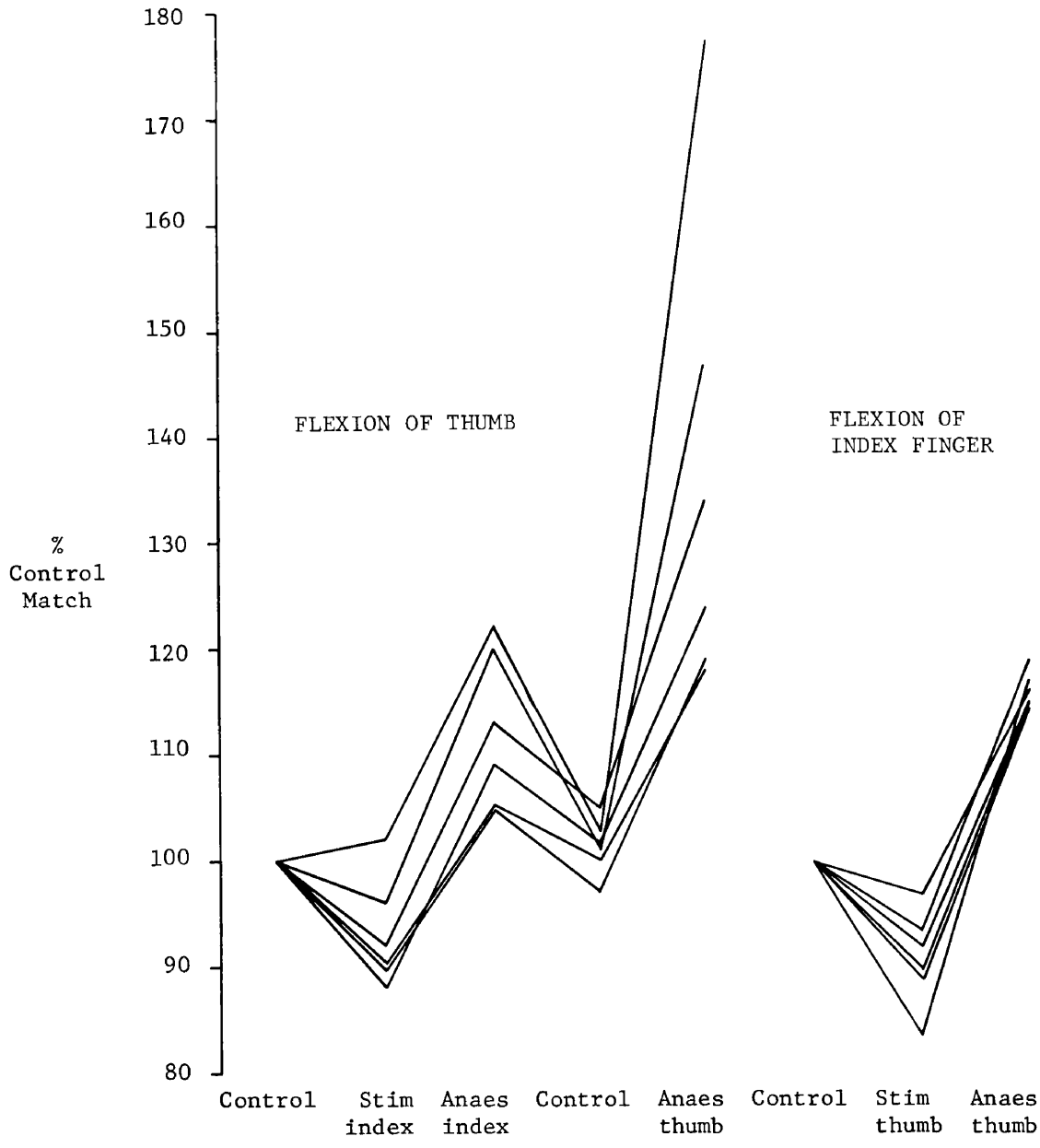

Fig. 3. Effects of alterations of sensory inputs on the perceived heaviness of objects lifted by flexion of the distal joint of the thumb (at left), or by flexion of the index finger (at right). Each line joins the means of 10 estimates of weights chosen by an individual subject in each condition. Paired t-tests show that each experimental intervention (stimulation or anaesthesia) caused a significant departure from the control choice of matching weight. See text.

the thumb or index finger because a greater central command or effort is employed in a lift. It follows that some tonic source of facilitation of the muscular contraction has been removed by the local anaesthesia. Presumably such facilitation arises in cutaneous or joint receptors. When the facilitatory influence is enhanced by electrical stimulation the central command required to perform the lift is decreased and the reduced command is perceived as a reduced heaviness.

A most interesting aspect of our results is that sensory inputs arising from both index finger and thumb (but not from the little finger, which we have also tested) can assist the motor command signals descending to either the index finger flexors or the thumb flexor. The flexors of the index finger and thumb are used more commonly in co-operation than in isolation - indeed, this functional co-operation constitutes the highly evolved 'precision grip' of man. What we have shown is that the motor commands to the flexors of either thumb or index finger flexors are assisted by sensory inputs arising from a wide sensory field usually involved in co-operative motor performances carried out by both muscle groups together. The loop between sensory input and motor output is thus closed in the periphery within the sensory field of the total co-operative performance.

The experiments of Marsden, Merton & Morton (17) and Dyhre-Poulsen & Djørup (4) suggest the mechanisms by which peripheral inputs assist the descending motor commands. Marsden *et al.* applied sudden stretches to the contracting long flexor of the human thumb and found that the principal reflex facilitation to the contraction, presumably caused by excitation of its muscle spindle afferents, is not exerted through a monosynaptic spinal arc onto its motoneurons as occurs with the tendon jerk. Instead, load compensation begins after a longer latency which is consistent with a supraspinal path for the reflex. This reflex assistance has a unique property - it is abolished by anaesthesia of the thumb. Presumably, therefore, afferents from the skin or joint of the thumb co-operate with afferents from the long flexor of the thumb to permit the "long-latency load-compensating" reflex to operate. In our experiments anaesthesia of the thumb or index finger may abolish or greatly reduce the reflex assistance coming from this reflex, thereby requiring a greater centrally-generated effort to lift or support any weight. This increased effort would be perceived as increased heaviness. The findings of Dyhre-Poulsen & Djørup (4) are especially interesting in this respect. These authors found that the load-compensating reflex of the long flexor of the thumb, which could be abolished by anaesthesia of the thumb, could be restored in the thumb by electrical stimulation of the adjacent index finger. Clearly, this fits well with our findings and with the interpretation we have placed upon them (see also 8).

If the reason for the increase in perceived heaviness during thumb anaesthesia is the removal of the long-latency stretch reflex, as we have suggested, then our observations permit us to calculate the contribution made by this reflex in normal lifting contractions of the long flexor of the left thumb. For the subjects shown in fig. 3 the average increase in heaviness during thumb anaesthesia was about 30%. The contribution of the stretch reflex was, therefore, about 23% $\left(\frac{30}{100+30} \times 100\right)$ (see also 9).

The peripheral interaction between sensory inputs and motor outflow which we have described for the finger and thumb can be seen in other areas as well.

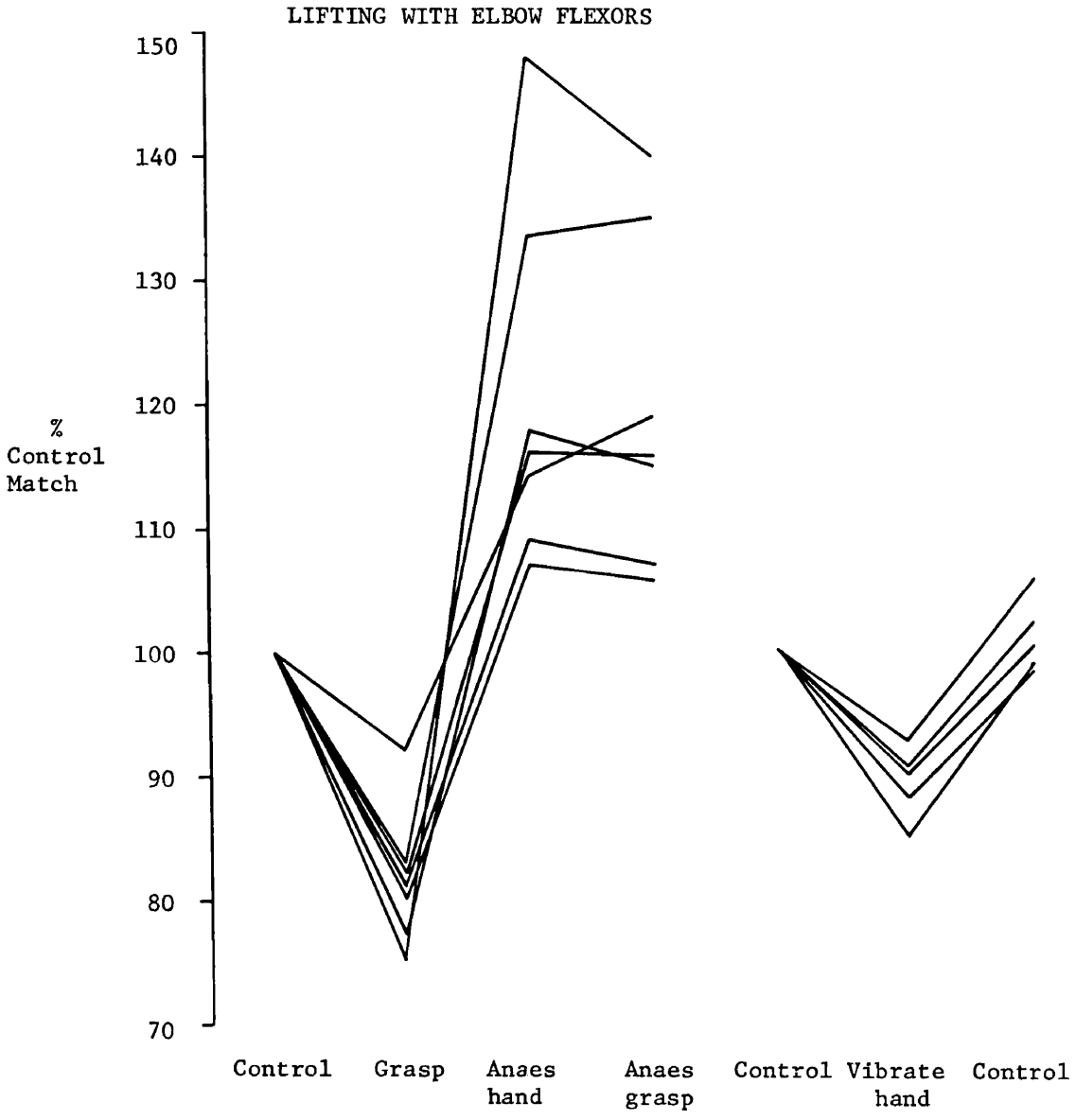

Fig. 4. Effects of alterations of sensory inputs from the hand on the perceived heaviness of objects lifted by flexion of the elbow. Each line joins the means of 10 estimates of weights chosen by an individual subject in each condition. Paired t-tests show that grasping with the hand, anaesthesia of the hand and vibration of the hand caused significant departures from the control choice of matching weight. Grasping did not significantly alter the effect of anaesthetizing the hand. See text.

Closure of the hand and flexion of the elbow are individual movements which often occur together as co-operative motor performances. In another series of weight-matching tasks (6) we looked at the perceived heaviness of objects lifted by flexion of the elbow: in the subjects in these experiments the weights were attached and lifted through a band around the wrist, so that on neither side did the hand participate in the lift. Figure 4 shows the results of these experiments. When the hand on the side (left) that lifts the reference weight at the wrist firmly grasps a piece of rubber tubing, the reference weight is perceived to be lighter than it was when the same tubing simply rested lightly in the hand. When the left hand is anaesthetized by cutting off its blood supply with a sphygmomanometer cuff, the reference weight feels heavier. In this case the sensory inputs from the skin or joints of the hand assist the contraction of the elbow flexors. When the sensory inputs are enhanced, by grasping (Fig. 4 at left), or by vibrating the palm of the hand at 100 Hz (Fig 4., at right), the motor command to the elbow flexors is assisted and so less command is required. Thus, the object lifted by elbow flexion feels light. The sensory inputs involved in this assistance appear to arise in the hand rather than in the forearm, because anaesthesia of the hand causes perceived heaviness to increase whether the anaesthetized hand is involved in grasping or not (Fig. 4). Moreover, vibration of the forearm instead of the hand causes no significant change in perceived heaviness.

The index finger and thumb, and the elbow flexors and the hand, give two examples in which the afferent input from the sensory field of a total co-operative motor performance assists the total performance. This assistance might well arise, as we have suggested, through modulation of the functional stretch reflex assistance available to the muscle groups involved. Whatever the mechanism, the phenomenon provides a means by which the central nervous system can treat common composites of motor performances as wholes, and by which motor activity can be focussed by peripheral feedback from within quite wide, but related, sensory fields.

ACKNOWLEDGEMENTS

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INTERPRETATION OF PERCEIVED MOTOR COMMANDS BY REFERENCE TO AFFERENT SIGNALS

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SUMMARY

1. Weights were lifted by flexing the distal joints of the anaesthetized thumbs. A weight-matching task was used to determine the perceived heaviness of a reference weight during control estimates when it was freely lifted, and during experimental estimates when the weight was not lifted, but simply 'gave way' when a reference isometric tension of the same magnitude was attained.

2. Limitation of the afferent input, by anaesthesia of the digit and by replacing lifting with a sudden unloading, did not grossly impair the judgement of heaviness. The sense of heaviness increased when the muscles became fatigued.

3. These results suggest that the central nervous system can interpret the voluntary motor command as an index of heaviness even when provided with only a crude peripheral signal that the weight has been moved.

INTRODUCTION

In judging the heaviness of a lifted weight normal subjects are guided by the magnitude of the centrally generated voluntary motor command, or effort, which they use. They prefer this to any afferent signals giving information on the pressures or muscular tensions involved. Thus, an increase in perceived muscular force or heaviness occurs whenever the motor commands required to perform any given contraction are increased. This is so when a muscle is weakened by the fatigue induced by a period of prolonged weight-bearing (McCloskey, Ebeling & Goodwin, 1974) or by partial paralysis caused by regional use of neuromuscular blockers (Gandevia & McCloskey, 1977*a*, *c*), when the motoneurones of a contracting muscle are inhibited by activating the muscle spindles in its antagonist with vibration (McCloskey *et al.* 1974), in the hypotonia of unilateral cerebellar disease (Holmes, 1917, 1922; Head, 1920), or in a simple 'stroke' causing motor weakness but no conventional sensory loss (Gandevia & McCloskey, 1977*a*). Centrally generated motor commands are perceived as muscular forces or efforts, not as movements (Laszlo, 1966; Goodwin, McCloskey & Matthews, 1972; McCloskey & Torda, 1975).

A motor command delivered to the motoneurones of a muscle used in lifting could not, alone, signal heaviness. There must also exist a signal that the command has succeeded in lifting or supporting the weight. When one attempts to lift a very heavy object which does not move in response to an effort, one cannot say how

heavy the object is – only that it is heavier than some other object which the same effort *does* lift or support. Nor can one discriminate between the heaviness of two objects when neither one of them can be lifted or supported. Clearly, some afferent signal of the success of a motor command is required before that command can be of use in judging heaviness. Indeed, even if one were to judge heaviness on the basis of signals of intramuscular tension, rather than on the motor commands, this same argument would apply; a signal of tension would only indicate heaviness if that tension were sufficient to move or support a weight.

Here we have studied the nature of afferent information which is sufficient to allow interpretation of motor commands as heaviness.

Part of a preliminary study has appeared in brief form (Gandevia & McCloskey, 1977*d*).

METHODS

A weight-matching task was used to determine the perceived heaviness of reference weights. The subject was required to match a reference weight (see below) lifted by flexing the distal joint of the left thumb with a variable weight lifted by flexing the right thumb. When the weight which was lifted on the right and which had been adjusted according to the subject's instructions, was judged to equal that on the left, then it was an objective index of the apparent heaviness of the reference weight. The 'see-saw' device used for lifting weights by flexing the distal joint of the thumb has been described previously (Gandevia & McCloskey, 1977*b*). Weights were lifted simultaneously on left and right sides. The subjects were blindfolded.

In all experiments presented here the force exerted by the reference weight on the left thumb could be unloaded by a rod driven by an electromagnetic vibrator (Advanced Dynamic Instruments: Vibrator AV-50) which struck the distal end of the see-saw from below. In the major study this left see-saw was heavily counterweighted and did not move until the force exerted by the thumb reached 500 g: at this point movement of the rod was triggered by the signal from a force transducer (Grass FT-03, modified) which replaced the arm of the see-saw (Fig. 1). A small amount of movement occurred at the distal joint of the thumb as the skin of the thumb pad was compressed against the bone of the distal phalanx and to a lesser extent because the transducer was not completely isometric. This movement was less than 2 mm (from the resting position) measured at the tip of the thumb. Using this arrangement subjects could generate a force sufficient to lift 500 g, but once this force was achieved they in fact lifted nothing – instead, the weight to be lifted simply 'gave way', and disappeared from under the thumb. Movement of the matching weight on the right was not restricted in any trials.

After an initial set of experiments in which peripheral sensation in both the left and right thumb was undisturbed, the following experiment was carried out on six healthy young adults, who were not aware of the hypothesis being investigated. First, both the left and right thumbs were anaesthetized about 1 cm distal to their base by digital nerve block. Rubber bands which impaired venous but not arterial flow were placed at the base of the thumb to prevent spread of anaesthesia and also to maintain complete anaesthesia throughout the experiment (about 2 hr). Each subject was required to make ten control estimates of a reference weight (500 g) lifted on the left and ten experimental estimates when the see-saw incorporating the transducer was unloaded at an isometric tension of 500 g. Three of the subjects made the control estimates, then the experimental estimates. For the others the order was reversed. The initial weights presented on the right (matching) side ensured that the subject was required to load 'up' and load 'down' on an equal number of estimates, both for control and experimental lifts.

In the second part of the experiment the long flexor of the left thumb was weakened by asking the subject to support isometrically a large weight (about 50 % of his maximal voluntary contraction) until he was no longer able to continue. Before relaxing the contraction a sphygmomanometer cuff positioned on the upper arm was inflated above systolic pressure to 300 mmHg. This maintained the lifting muscle in a fatigued state (Merton, 1954; Stephens & Taylor, 1972). After about half a minute weight matching was commenced and usually two or three estimates were made of the heaviness of the reference side which unloaded at an achieved force of 500 g.

The whole procedure was repeated until ten estimates had been made during fatigue. The degree of fatigue produced by the weight-bearing was not quantitated: the experimenter relied on the subject to indicate when to inflate the cuff. Further fatigue occurred as the subject made estimates with the circulation to the lifting muscle arrested. Progression of fatigue was usually associated with an increase in the matching weight lifted by the right thumb.

The usual ethical requirements of informed consent were met in these studies.

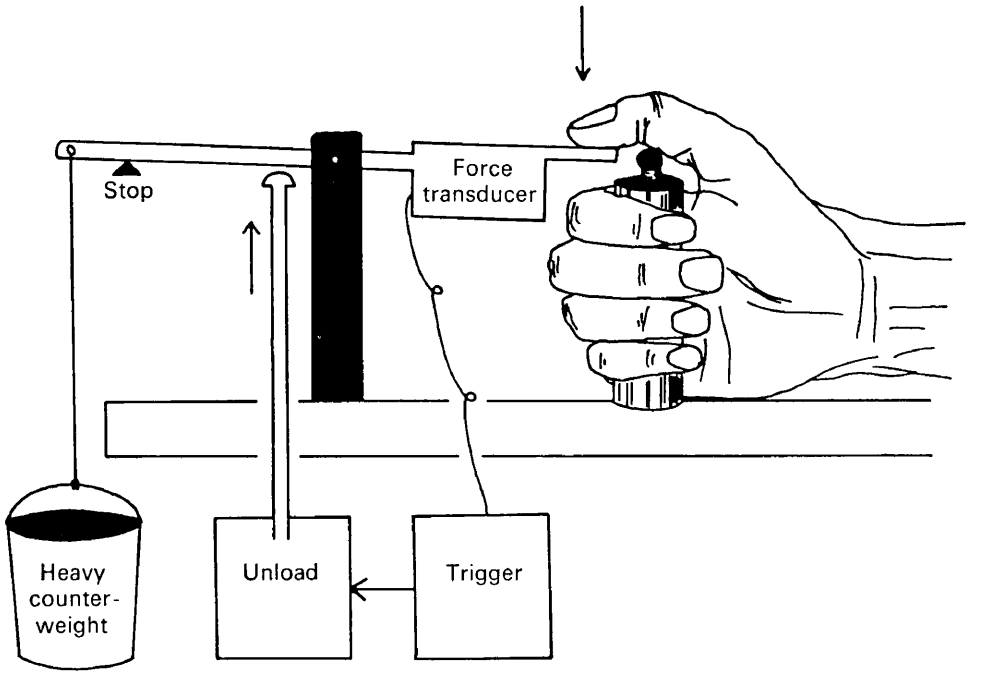

Fig. 1. This shows diagrammatically the position of the hand and the apparatus used when forces produced by flexing the distal joint of the thumb were unloaded. The fingers were placed around a cylindrical upright and the pulp of the thumb rested on a flat circular plate. Flexing the thumb at one end of the 'see-saw' developed a nearly isometric tension until 500 g was reached. Then a trigger was activated which caused rapid upward movement of a rod to strike the see-saw arm near the fulcrum so that the muscular contraction of 500 g was abruptly unloaded. Movement was prevented, apart from that due to compression of tissues in the pad of the thumb and slight distortion of the strain gauge, by placing a large counter-weight (3 kg) at the distal end of the see-saw and using an adjustable stop mechanism. Subjects used the same muscle on the opposite side to lift a variable weight which was adjusted at their request in order to match the apparent heaviness of the reference weight. The see-saw and stop mechanism used on the matching side were similar, but movement of the see-saw was permitted. Allowance was made for the weight of the bucket in measuring the weight chosen to match the unloaded contraction of 500 g on the other side. For control estimates lifting and movement were permitted on both sides.

RESULTS

In all the experiments the subject was required to match with his right thumb a weight or apparent weight presented on the left side; both the left and right thumbs were anaesthetized. When on the left (reference) side the subject developed an isometric tension of 500 g the end of the see-saw which he was attempting to depress 'gave way'. The mechanical arrangement for this is described in the Methods and shown diagrammatically in Fig. 1. Hence, during experimental estimates at no time

did the subject accelerate a weight on the left, he merely produced a ramp of effort until, at a pre-determined force, his muscular contraction was abruptly unloaded. Ramps of force up to the unloading point usually developed over 1–8 sec and rarely were their profiles similar even between successive contractions in the same subject. A typical set of eight successive ramps taken from an individual subject are shown in Fig. 2.

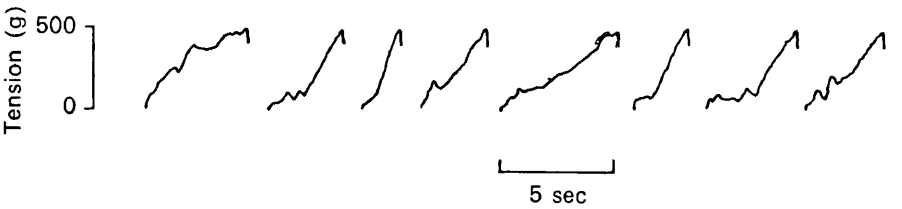

Fig. 2. This shows eight successive ramps of force generated by a subject during an experiment. When 500 g isometric tension was developed by flexing the distal joint of the thumb the contraction was unloaded (see Methods and Fig. 1): the time taken to develop this tension was variable.

Three sets of estimates were made by the subjects: control estimates in which a 500 g reference weight was lifted (unrestricted movement) on the left in the ordinary way; reference isometric tensions on the left unloaded at 500 g; and similar reference isometric tensions unloaded at 500 g made when the contracting muscle on the left was fatigued. Results, expressed as the mean ± S.E. of mean of ten estimates, are shown for the six subjects in Fig. 3.

Unloading the muscle when it had generated the reference tension did not seriously impair judgement of apparent weight.

In four subjects there was no significant change in perceived heaviness when the reference tension was unloaded at 500 g. In two subjects there was a significant increase in perceived heaviness (subjects B and C) although analysis of data from the group of subjects showed overall no significant change (paired t test). The variance of estimates made by individual subjects and by the group of subjects showed no significant change from that of control estimates during unloading at 500 g (F test). In all individual subjects ($P < 0{\cdot}001$) and for the group ($P < 0{\cdot}01$) there was a significant increase in the apparent heaviness of the unloaded 500 g tension when the muscle developing the tension was fatigued.

A similar series of experiments was conducted in which six subjects (with their thumbs anaesthetized) 'carried' reference weights on the left only for a time sufficient to trigger a microswitch (70–80 msec) which then led to unloading as described above. For the group of subjects there was no significant change in perceived heaviness of reference weights, or in the variability of estimates when the weight was thus accelerated for a short time. In one individual subject there was a significant increase in perceived heaviness above control levels during rapid unloading: he was one of two subjects who also participated in the experiments shown in Fig. 3 in which he performed in the same way (subject C, Fig. 3). In these experiments both the size of reference weight (500 or 1000 g) and the presence or absence of unloading were varied at random from estimate to estimate.

There was no consensus in the subjective reports of the subjects when asked

after the experiment about the difficulty of the matching task. Some found it relatively easy during 'unloaded' estimates but others found it difficult and were surprised to learn of their apparent accuracy.

Whether they found it easy or hard, many volunteered that the strategy used was to produce simultaneously a graded muscular contraction on each side and to take the side which moved first as the one carrying the lighter weight. Thus if the contraction on the left was unloaded but the variable weight on the right was not lifted they would often ask for a reduction in the matching weight although they had not moved it. Or if the right matching weight moved without unloading the reference contraction on the left, they would often ask for the weight to be increased on the right.

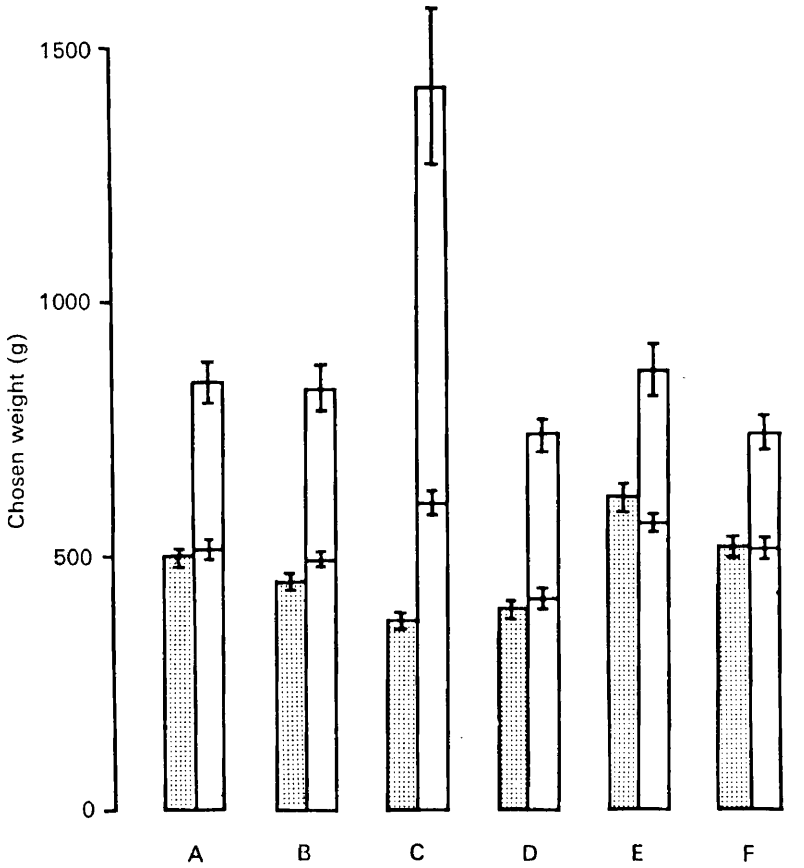

Fig. 3. This shows the results from six subjects (A to F). Perceived heaviness of an isometric reference tension unloaded at 500 g (open bars) and of a lifted reference weight of 500 g (control, filled bars) is plotted (mean ± S.E. of mean of ten estimates under each condition). Estimates were made of the unloaded tension (open bars) when the lifting muscle was not fatigued (lower estimates) and when it was fatigued (upper estimates). Compared to control estimates for the group of subjects there is no consistent change in apparent heaviness during unloading of the reference tension. When estimates were made of the unloaded tension during fatigue the perceived heaviness increased above the unfatigued level.

DISCUSSION

The peripheral signals generated when a weight suddenly 'gives way' in response to a motor command are sufficient to permit an assessment of heaviness to be made. Here, such assessments were made with similar accuracy and variability to those made when the weights were lifted and carried by unrestricted muscular movements. The peripheral signals used in the present experiments probably arose from intramuscular receptors because the joint and skin of the thumb were anaesthetized. In other circumstances, of course, equally suitable afferent signals might be provided from other sources; the important point emerging here is that signals sufficient for an accurate judgement can be quite crude. The afferent signals permit interpretation of the perceived motor command or effort, rather than of any alternative signals available concerning the achieved muscular tensions. This is shown by the increased heaviness occurring during muscular fatigue.

Thus, the judgements of heaviness in these experiments were based upon the motor commands as in other circumstances (see Introduction), and the success of those motor commands, even when quite crudely signalled, was sufficient to permit their accurate use in such judgements. It is as if the peripheral signals are used simply as 'event markers' to indicate to the central nervous system the appropriate point in a changing motor command.

Because only a crude peripheral signal is sufficient for judgement this is likely to explain why cutting the medial lemniscus (Sjöqvist & Weinstein, 1943), dorsal columns (Devito, Ruch & Patton, 1964) or removing the postcentral gyrus (Ruch & Fulton, 1935) does not impair weight discrimination. When peripheral sensation is abolished, however, the absent signal of success of a command may lead to the interpretation that the command has failed, and that the weight lifted is heavy. A personal experience recounted by Granit (1972) illustrates this well. 'During recovery from a spinal anaesthetic I myself ordered one of my legs, stretched out in bed, to be lifted. It felt dead and heavy and I was utterly unaware of the fact that it actually did move, until my toes bumped against the blanket and I had a dull feeling of something like a thud.'

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Kinesthetic Sensibility

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I. INTRODUCTION

The "sixth sense" was what Sir Charles Bell (17) named the sense of the positions and actions of the limbs. This review deals with the whole of Bell's "sixth sense": it concerns perceived sensations about the static position or velocity of movement (whether imposed or voluntarily generated) of those parts of the body moved by skeletal muscles and perceived sensations about the forces generated during muscular contractions even when such contractions are isometric. The general descriptive terms used here for such sensations are *kinesthetic*, which despite its literal translation was coined by Bastian (15) to describe the complex of sensations outlined above (including

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those in which movement is not a feature), and *proprioceptive*, which was used by Sherrington (262, 263) in a rather wider sense than here to include also vestibular sensations and inputs from muscles and joints that are not necessarily perceived.

The classes of afferent fiber that are candidates for subserving kinesthetic sensibility are those from the skin, from the muscles and tendons, and from the joint capsule and ligaments. In the nineteenth century, however, various authors questioned the necessity for any afferent information at all, suggesting instead that normal kinesthetic sensations arise as a consequence of the effort to move and are derived in some way within the central nervous system from centrifugal or motor signals—sensations "of innervation" they were called by Helmholtz (128). Very few authors, from the nineteenth century to the present, have been prepared to concede that the three classes of afferent input *and* sensations "of innervation" can all contribute to kinesthesia: the most frequent exclusions over the years have been the afferents from muscles or the sensations of innervation.

In this review each candidate for a role in kinesthesia is discussed at first alone, starting with the afferent inputs from joints, then from muscles, and then from skin and following with the efferent mechanisms, the sensations of innervation. An analysis of the integrated operation of these various components follows. In considering sensations of position and movement, the viewpoint introduced and defended by Goodwin, McCloskey, and Matthews (104) and subsequently expanded in recent reviews by Goodwin (100) and by Matthews (194) is again taken here—that is, that muscle afferents are important for such sensations and that sensations of innervation per se are not. Sensations of muscular force, or heaviness, also are considered here and the conclusion is reached that both muscle afferents and sensations of innervation are important. The figures chosen to illustrate this review concern these conclusions—conclusions that depart from recent "textbook" views. It is also concluded here, however, that afferents from joints and skin may also contribute to kinesthesia.

II. AFFERENT MECHANISMS: JOINTS AND MUSCLES

A. Innervation and Receptor Properties: Joint Receptors

Three types of specialized receptor endings exist in most joints: a spray type, or Ruffini ending, located in the joint capsule (22, 80, 89, 90, 91, 238, 259, 267, 268); a larger spray type, or Golgi ending, located in ligaments of the joint and similar to the Golgi endings in tendons (9, 80, 238, 253, 267, 268); and encapsulated paciniform endings, rarely associated with the joint capsule, but found commonly in the fibrous periosteum near articular or ligamentous attachments (22, 89, 90, 238, 267, 268). The three kinds of specialized endings are always innervated independently, though a single axon may supply several endings of one kind. In addition, free nerve endings

are found in the adventitia of articular blood vessels and in the joint capsule (68, 89, 90, 238, 253, 267, 268). Great variations occur in the distributions of nerves to joints and in the histological appearance of the joint receptors with age and species (238).

Articular branches arise from the nerve trunks that supply the skin overlying the joints and the muscles that move them [Hilton's law (80, 130)]. The spectra of fiber sizes for some articular nerves have been determined. In the medial and posterior articular nerves of the cat, for example, there are myelinated afferents from 18 μm in diameter downward, with a peak frequency at about 6 μm or smaller, together with large numbers of unmyelinated nerves of sympathetic and dorsal root origin (23, 37, 50, 80, 90, 267). Fiber size does not correlate well with receptor type (7). Afferent fibers in groups I and II that occur in articular nerves may include a significant number of muscle afferents (see below). Thus the anatomical classification of joint and muscle nerves presents problems because "nonmuscular" articular nerves may contain muscle afferents and because the articular nerves contain true joint afferents in groups I and II that may later join muscle nerves (80, 267) and contribute to them afferents that are unlike muscle afferents of groups I and II in being insensitive to muscle stretch (193). Therefore, the central projections of joint and muscle nerves cannot be relied on to define the projections of the individual fiber types.

The characteristics of receptors traveling in articular nerves have been studied with gross recordings from whole articular nerves (10, 56, 267), by recording activity in single active units dissected from such nerves (9, 10, 24, 56, 76, 205, 212–214, 267, 285), or by recording in dissected dorsal roots (38, 50, 112, 113, 115). The experiments with multifiber recordings from whole nerves or recordings made in the dorsal roots indicated that the greatest level of afferent firing occurs at or near the extremes of flexion or extension with comparatively little activity inbetween. However, some of the studies on unitary afferent activity—particularly those where the articular nerves themselves were split down—dealt mainly with receptors responding at intermediate positions. Presumably, such selection of units was necessary because of constraints imposed by the experimental arrangements.

The studies carried out in the 1950's and early 1960's on afferent units in articular nerves gave a seemingly full and consistent picture of joint receptors as receptors that could readily provide the sole basis for kinesthetic sensibility. In 1953, in studies on the knee joint in cats, the discharges of single afferents were recorded in the medial articular nerve by Andrew and Dodt (10) and in the posterior articular nerve by Boyd and Roberts (24). In both studies units were recorded that showed slowly adapting responses to joint movement or to local pressure applied to the joint capsule. Furthermore, in both studies, such units were excited over a rather small range of joint excursions. Thus, Andrew and Dodt (10) stated that the sensory endings involved "seem to be arranged so that each has an arc of maximum sensitivity covering a few degrees of angular movement but these ranges are different for different endings," and they suggested that because of such an arrange-

ment "joint position may be very accurately signalled by the joint receptors since the central mechanism would be connected with a few endings operating in their region of maximum sensitivity . . . over a large arc of joint position." Within their sensitive range these units gave a discharge related to the rate of angular displacement, being increased by movements toward the point of maximal excitation and decreased by movements away from it, and a tonic discharge, which sometimes could be maintained steadily for hours, related to absolute joint position (24). Cohen (56) and Skoglund (267) later studied similar receptor units and confirmed these basic observations. Skoglund (267) also showed that the "excitatory angle" for an individual receptor was not absolutely fixed but depended partly on rotation of the tibia around its long axis and on any muscular tension exerted on the joint capsule. The effects of tibial rotation on the discharges of these slowly adapting receptors had been noted previously (10, 24), but the possible ambiguity of the resulting signals had not been stressed. It was agreed by those who studied wide ranges of joint excursion (10, 56, 267) that "the nearer the joint approaches maximal extension or flexion the greater will be the number of units active and the greater will be their fully adapted discharge frequencies" (10). It also was generally agreed (10, 24, 56, 267) that the slowly adapting units studied were Ruffini-type capsular endings, and supporting evidence from studies with both histological and electrophysiological techniques was presented (22, 267).

In studies on large myelinated fibers from receptor endings in ligaments, a further type of slowly adapting unit was described. This showed little sensitivity to the velocity of movement and was largely independent of the contractions of muscles attached to the joint but responded to tensions applied to the ligament (9, 267). This type of receptor is thus similar to the Golgi tendon organ of muscle and because only the Golgi-type spray endings are found in ligaments they are thought to be the receptors involved. Because of their response characteristics they have been proposed to signal "the exact position of the joint" (267), although no detailed information exists regarding their "excitatory angles" and the distribution of these throughout the range of joint excursion, nor on the effects of rotatory or lateral movement of the joint on their discharge. Moreover, there are many joints in which ligaments, and presumably therefore their accompanying investment with Golgi endings, are rudimentary or absent. A role for the Golgi endings in kinesthetic sensibility is by no means proven.

In many studies rapidly adapting discharges were also recorded. These discharges appear only during movement of the joint and are thought to arise from paciniform endings (22, 24, 38, 49, 50, 112, 267). Receptors of this kind are unlikely to provide detailed information about joint position, velocity of joint rotation, or even direction of joint movement. They may help to signal the simple occurrence of a movement without providing details of its nature.

In 1969 Burgess and Clark (38) attempted to overcome some of the problems arising from sampling bias and limitations on the range of movement encountered when recording directly from articular nerves. They

recorded instead from dorsal root filaments, identifying units by electrical stimulation of the articular nerve, and thus were able both to recognize units quite independently of their mode of physiological activation and to test a complete range of joint movements. Two quite unexpected findings emerged. First, from a total population of 278 single afferent fibers from the posterior articular nerve of the knee joint of the cat, including 209 fibers from slowly adapting receptors (presumably of both Ruffini and Golgi types), only 4 slowly adapting fibers were found that were maximally activated at an intermediate joint angle rather than at the extremes of joint excursion. Second, 140 of the 209 slowly adapting endings were activated at *both* full extension *and* full flexion but were completely silent in the midrange of joint excursion. In 1975 the same authors (50) used a similar technique to study afferent activity in the medial, lateral, and posterior articular nerves of the cat knee joint over most of its working range. In this study they were particularly interested in receptors discharging at intermediate joint angles. However, although their technique permitted sampling of a large percentage of the myelinated fibers in each nerve, again they found that "tonic mid-position activity was rare." Thus only 6 of 672 fibers tested in the medial nerve and 45 of 713 in the posterior nerve gave slowly adapting midrange responses (the smaller lateral nerve showed negligible tonic activity in the midrange in gross recordings and was not studied further). These findings were confirmed when, in other recent detailed studies of the articular nerves of the knee joint of the cat, either no fibers at all (112) or a very small proportion of fibers (49) were found that discharged at intermediate positions of joint excursion. A similar paucity of fibers that discharge maximally in the midrange has been noted in recent studies on the primate knee joint (115), the cat elbow joint (214), and the cat wrist joint (285). Furthermore, it was noted of the discharge of the midrange slowly adapting receptors of the cat's knee (excluding those derived from muscle spindlelike receptors; see below) that "whether the discharge at intermediate positions was over a very small angle, over the entire flexion-extension range, or present at all depended on the degree of outward tibial twist" (38).

Not only were midrange fibers difficult to find in these later studies but the true sites of the receptor endings from which they arose were also called into question. Thus it was observed that discharges of fibers that are tonically active at intermediate positions of the joint often are not altered by changes in the flexion-extension angle of the knee joint, but most respond to small intravenous doses of succinylcholine, suggesting that they might come from muscle spindles (38, 50; but see 76). In additional experiments some such midrange receptors were localized to the popliteus muscle (50). This opened the possibility that some, perhaps all, of the slowly adapting midrange receptors reported by other workers (10, 24, 56, 196, 267) also arose from muscle spindles. Recently McIntyre, Proske, and Tracey (205) recorded in the posterior articular nerve of the cat from units with a resting discharge at intermediate joint angles and found a pause in the discharge during twitch contractions evoked in the popliteus muscle. They also showed an accelera-

tion of discharge in whole articular nerves, and of single units dissected from them, in response to stimulation of fusimotor fibers in the ventral roots, although such fusimotor stimulation was accompanied by no apparent joint or muscle movement. Therefore, at least some of the fibers in the cat's posterior articular nerve, which is the most thoroughly studied articular nerve, have their origin in spindles of the popliteus muscle.

Most slowly adapting fibers in articular nerves of the cat's knee discharge maximally at the extremes of both flexion and extension (38, 49, 50, 112). This appears likely to provide the central nervous system with ambiguous information about the angle of the joint. Nevertheless, in the same nerves there are smaller, but significant, numbers of slowly adapting units that discharge maximally at only either extreme flexion or extreme extension, so that the accompanying activity in these could possibly be used to eliminate such ambiguity. All slowly adapting fibers dissected from the elbow joint nerve in the cat also discharged maximally at full extension and over half of these discharged also at full flexion, although no fibers were found in that nerve that discharged maximally only in full flexion (214). In the dorsal wrist joint nerve of the cat, slowly adapting units fired maximally at full flexion, pronation, or supination of the wrist, but never at extreme extension (285); in the costovertebral joints, receptors were maximally excited at either one or the other extreme of movement, but not at both (97). In the elbow and wrist joint nerves the discharges, although maximal at the extreme end of a range of movement, often remained appreciable near that end of the range but within the working range of joint excursion. In the hip joint nerve of the cat (G. Carli, personal communication) and in the costovertebral joints, activity is maximal at extreme excursion but extends through the whole range of movement. Where units are active within the working range they may provide useful proprioceptive signals.

In other respects the knee (49), elbow (214), and dorsal wrist (285) nerves of the cat are similar in the range of functional characteristics shown by their fibers. In each nerve, apart from the slowly adapting units, there are phasic and paciniform units, together with a significant proportion of units that are activated only weakly, or not activated at all, by even extreme movements of the joint. Clark (49) has suggested that the weakly activated and nonactivated units, which are innervated predominantly by small-diameter fibers, serve a nociceptive function.

The slowly adapting units that run in articular nerves seem to fire in response to joint capsular stretching (10, 49, 112, 115). This would explain their responsiveness at extremes of joint excursion. It would also explain how some of the possible ambiguities of their proprioceptive signals arise: their tendency to alter their firing in response to lateral and rotatory as well as flexion-extension movements of the joint; their responsiveness to the contraction of muscles inserting near the joint capsule (112, 113, 115, 212, 267, 285), even when the muscles involved are not movers of the joint concerned; and the hysteresis manifested by discharges as a joint is moved back and forth through a region of receptor activation (115, 196, 214). These ambiguities

may well be resolved by the central nervous system in the context of other signals simultaneously provided from other sources and on the basis of experience.

Matthews (193) allowed that "one conceivable possibility is that in the more intact animal muscle tone tenses the joint capsule in such a way as to significantly alter the range of response of the endings." However, he later (194) observed that "if this is an essential feature of joint responses then the interpretation of their discharges in terms of joint angle would appear to be nearly as complex as the interpretation of spindle discharges, as the prevailing level and distribution of motor activity would have to be taken into account." The question was examined experimentally in the knee joint (113, 115) by stimulating afferents in articular nerves through activation of adjacent muscles. This led to the conclusion that such high muscular forces were required that one could "rule out the hypothesis that knee joint afferents might discharge at intermediate joint angles by virtue of the presence of innervated but relaxed muscles about the knee" (113).

Short of postulating that the important contribution of joint receptors to kinesthesia is made through nerve endings with unmyelinated afferents—and no electrophysiological studies have been done on such afferents—it is difficult to escape the conclusion that articular receptors, at least in some joints, "are not capable of providing appreciable steady-state position information over most of the working range" (50). Perhaps articular receptors might be capable of giving more reliable information on the velocity and acceleration of joint movement (196), or even on the forces generated by muscles acting at the joint, but these possibilities have not yet been systematically investigated.

B. Innervation and Receptor Properties: Muscle Receptors

The anatomy and electrophysiology of the principal intramuscular receptors, the muscle spindles and the Golgi tendon organs, recently have been extensively reviewed (14, 142, 193, 204) and are dealt with only briefly here.

The total number of afferent fibers to the muscles that act at a joint is large in comparison with the number of afferent fibers to the joint itself: for the cat knee joint, for example, a conservative estimate gives 4000 myelinated muscle afferents but fewer than 400 myelinated joint afferents (104).

The muscle spindles lie in parallel with the extrafusal muscle fibers and usually receive their own motor innervation through small myelinated γ-efferents (fusimotor). Some spindles, however, receive an innervation from fibers (β-fibers) that go to both extrafusal and intrafusal muscles [see Emonet-Denand et al. (71)]. There are two classes of sensory endings in the spindles: the primary endings, which have fast-conducting axons (group Ia) and are particularly sensitive to dynamic stretch, and the secondary endings, which have slow-conducting axons (group II) and are much less sensitive to dynamic stretch. Both classes of spindle fire at steady frequencies monotoni-

cally related to the degree of stretch of the muscles in which they lie and maintain this relation over a wide range of muscle lengths. For spindles in the relaxed flexors of the fingers in man, Vallbo (291) showed the rather low sensitivity to rotation of the metacarpophalangeal joint of 0.18 impulses/deg for primary endings and 0.14 impulses/deg for secondary endings, with the frequency of firing increasing over 100–120° to a maximum at full extension. However, fusimotor tone is low in relaxed muscles (42, 288, 291, 292), and many spindles are silent at intermediate joint positions. With active muscular contraction more spindles discharge (291, 292). Furthermore, in the relaxed state additional spindles can be recruited as joint rotation stretches muscles (41, 291): this means that recruitment of additional spindles could provide information in addition to that given by changes in the frequency of spindle firing.

The discharges of the muscle spindles do not bear a simple relation to muscle length, a fact that has led many investigators to believe that they could not be used to estimate joint position. The spindles fire in response to stretching of the intrafusal muscle fibers near their nonstriated equatorial regions. Thus they respond not only to passive stretch of the whole muscle in which they lie but also to the stretch of these regions caused by contraction of the striated poles of the intrafusal fibers in response to fusimotor drive. In man spindle discharges increase during increasing isometric efforts, at least through the lower ranges of force investigated (42, 118, 119, 288, 289, 292). This is evidence for changing fusimotor activity in this situation. Indeed it is now apparent that in most, perhaps all, forms of voluntary muscular activity there is parallel activation of skeletomotor and fusimotor fibers: so-called α–γ-linkage or α–γ-coactivation (for discussion and review see 40, 108, 110, 120, 193, 204, 234, 272, 290).

Clearly, if spindle discharges are to be useful for kinesthetic sensations, the central nervous system must be able to distinguish which part of the activity is attributable to muscle stretch and which part is caused by fusimotor activity. Also, quantitative analysis of stretch-evoked spindle activity would only be possible if the central nervous system can allow for changes in fusimotor tone, as this determines the sensitivity of the relation between external stimuli and spindle firing (193). Provided that central processing can account for fusimotor activity, however, there is no reason why efferent modulation of receptor discharge should disqualify spindles from a kinesthetic role. Perhaps the simplest mechanism on which such central processing might be based would be for collateral, or reentrant, signals from motor pathways to act centrally on sensory pathways in such a way as to cancel the fusimotor-induced afferent signals and to "set" central receiving points for the prevailing level of spindle sensitivity. Many descending pathways have been demonstrated that might participate in such processing (for review see 106, 255, 284) or the processing might occur entirely at a single level of organization. An alternative mechanism for providing information about fusimotor firing, which does not involve the use of centrifugal signals, could be provided by an appropriate but complex analysis

of the discharges of spindle primaries and secondaries as suggested (but not favored) by Matthews (194). This appears to involve a large amount of central processing of afferent signals in order to avoid the use of readily available centrifugal motor signals for the same purpose. If the discharges from muscle receptors are to be useful in kinesthesia, therefore, the central use of centrifugal signals seems the more likely mechanism for making them so.

The Golgi tendon organs are somewhat simpler sensory endings that lie at musculotendinous junctions in series with small numbers of extrafusal muscle fibers, which pull on and activate them. They have fast-conducting (group Ib) axons and a low threshold for excitation by active muscular contraction (140, 150). For passive, externally applied stretches they have a relatively high threshold, except when these stretches are applied very rapidly (280) or during muscular contraction (273). Recordings from tendon organ afferents have been made in man (41, 288) and a strong relation between muscular force and impulse frequency has been observed. Like the discharges from muscle spindles, those from the tendon organs are altered by both muscular activity and muscle stretch and so do not provide the central nervous system with a signal unambiguously related to muscle length. If these signals are to be used to provide information on joint position or movement, therefore, they would be like those provided by the spindles—that is, useful only if the central nervous system is able to distinguish the activity due to muscle stretch from that due to muscular contraction. It was pointed out in section II*A* that this is true also for those joint receptors that change their firing in response to muscular contraction. Unlike the spindles, however, the tendon organs do provide a signal that is unequivocal for one aspect of kinesthesia: they signal the tension applied to them, the intramuscular tension. Even here, though, central processing of the signals would be required to give useful information because the effective mechanical advantage at which a muscle operates depends on the position of the joint it serves. A given intramuscular tension in, say, the elbow flexors while an object is supported against gravity with the upper arm vertical would support only half the weight with the elbow flexed at 90° that it would support with the elbow at 45°. Thus, the signal of intramuscular tension could give useful information about the weight of a supported object or the force exerted by a moved part only if it were interpreted centrally in the light of other signals about joint position.

C. Central Connections

Many studies have been performed on the thalamic and cortical projections of proprioceptive afferents, and it is generally agreed that such projections are relevant in a consideration of perception. Certainly, the early failure to demonstrate a cortical projection of muscle afferents was taken as evidence against their providing perceived signals. In this review, therefore, attention is given to projections to the thalamus and cortex. Lesions of the thalamus and cortex can seriously disturb kinesthetic sensibility (123–125,

135, 232), whereas lesions in the other major region of projection of proprioceptive afferents, the cerebellum, are not associated with disturbances of position and movement sense (133). Cerebellar and other central projections of proprioceptive afferents are not discussed here (for reviews see 92, 186, 204, 226). The association of certain cerebellar lesions with changes in the perceived heaviness of lifted objects, however, is discussed in section IV*C*.

Evidence considered above indicated that fibers from intramuscular receptors can run in joint nerves and that fibers from joint receptors can run in muscle nerves. This uncertainty about the exact composition of both joint and muscle nerves makes studies aimed at defining the central projections of joint and muscle receptors difficult to interpret because it cannot follow that one or another type of receptor is completely excluded in an experiment by cutting appropriate anatomical nerve types nor that one or another type of receptor is exclusively engaged by stimulating the seemingly appropriate nerve. In studies on the central projections of joint receptors this problem is compounded by the difficulties of achieving, *and adequately testing for*, complete regional denervation of muscles and skin. Thus, in many studies, the responses of central neurons to joint movement are taken to indicate that connections from joint receptors have been established, on the grounds that muscles and skin have been denervated. Of course, if muscles and skin were not completely denervated the central responses might well have been set up by the activation of muscular or cutaneous receptors. In other studies, central cells are claimed to receive inputs from joint receptors if they respond to joint rotation but not to palpation of muscle and skin. One cannot be sure, however, that such tests adequately define joint inputs because muscle receptors, particularly, might escape engagement by palpation and there is no way of excluding this possibility. That such uncertainties exist should be borne in mind in reading the following account, which outlines the current view of connections said to be made by proprioceptive afferents.

The conventional textbook descriptions of the dorsal column–medial lemniscal system recently have been been substantially revised (for reviews see, e.g., 31, 33, 295), and it no longer can be safely assumed that proprioceptive afferents project centrally along only this pathway.

Electrophysiological and anatomical studies indicate that, for the forelimb in both cat and monkey, the projections of joint afferents, and of afferents from muscle spindles, do indeed occur along the dorsal columns (51, 227, 235, 287) to relay in the ipsilateral main cuneate nucleus (33, 250, 251). In addition, Rosén (246, 247) has described a group of cells in the base of the dorsal horn of the ipsilateral rostral cervical cord, activated by group I afferents from distal forelimb muscles: this column of cells appears to be continuous rostrally with the main cuneate nucleus (247). Other pathways for proprioceptive afferents from the forelimb may also exist (92).

Fewer than 10% of axons running in the articular nerves of the knee in the cat, however, project to the upper cervical levels of the dorsal columns, and these are all from receptors of the rapidly adapting type (37, 48, 51, 305). In the monkey, no axons activated from slowly adapting deep receptors in

the hindlimb could be demonstrated in the cervical gracile fascicle, although such projections from the forelimb to the cuneate fascicle were readily demonstrable (303). Muscle, and presumably also joint, afferents from the hindlimb in the cat leave the dorsal columns before reaching the upper lumbar cord to travel with the ipsilateral dorsal spinocerebellar tract (148, 149, 181, 185) and supply branches (which are probably collaterals of the cerebellar projection) to the brainstem relay, which is principally in nucleus Z (151, 165). Nucleus Z was first described in the cat (30), but also exists in man (252) and lies just rostral to the gracile nucleus in the floor of the fourth ventricle. It has components responding only to muscle, joint, or cutaneous inputs (152, 165). Thus, the kinesthetic pathway from the hindlimb of the cat appears to be via the dorsal spinocerebellar tract and nucleus Z for phasic and tonic units, with perhaps some purely phasic units projecting via the dorsal columns. The situation probably is similar in primates because transection of the dorsolateral fascicle removes the deep component of the hindlimb projection to the somatosensory cortex, whereas transection of the dorsal columns leaves this projection intact (66).

All these anatomical and electrophysiological findings fit with neurological observations on hemisection of the cord (as in the Brown-Séquard syndrome) and on lesions confined to one side of the cord (125), where the proprioceptive loss is always ipsilateral.

Some confusion arises, however, from the results obtained in behavioral studies after various experimental spinal lesions. While some early studies found gross disturbances of spatially projected movements in the forelimbs of monkeys with dorsal column lesions (75, 96), others noted little or no such disability after similar lesions (12, 16, 27, 28, 59, 211, 257). Therefore, it seems likely that pathways for proprioceptive afferents from the forelimbs exist in addition to the dorsal columns. This is borne out for proprioceptive connections to the primary somatosensory cortex by the observation that many such connections for the forelimb remain intact after lesions of the dorsal columns (28). Similarly, behavioral studies after experimental lesions have given some cause to doubt that the dorsal spinocerebellar tract is essential for kinesthetic sensibility in the hindlimb (179, 294).

Great care must be taken in the interpretation of behavioral studies. In many cases discriminative abilities of the coarsest kind were tested, and these may well have survived lesions that would seriously disrupt finer abilities. Also, careful histological examination is always necessary for confirmation of the site and extent of lesions, but sometimes was seriously deficient or not even done at all. A cautionary lesson comes from the observation that cats can perform skilled discriminations of visual patterns despite bilateral lesions of the optic tracts that are 98% complete (81).

The ipsilateral hindlimb (nucleus Z) and forelimb (main cuneate nucleus) proprioceptive relays project onward to the thalamus, crossing the midline in the medial lemniscus. The principal thalamic relay for kinesthetic inputs is the ventroposterior nucleus [or ventrobasal complex (245)], which relays information from the medial lemniscus to the cortex. Within this part

of the thalamus there is said to be a strict, well-ordered representation of body topography and preservation of modality specificity (237), although some recent studies suggest that the situation may be less simple (for review see 2, 157, 298). Recording from this area in unanesthetized monkeys, Poggio and Mountcastle (237) found that 26% of the cells they encountered were selectively excited by rotation of joints on the opposite side of the body. In every case these neurons were maximally activated at an extreme of the range of excursion of a joint, with less extreme positions evoking successively lower discharges throughout the excitatory angle. The peak frequency of neuronal discharge in many cases was determined by the rate of joint movement. Excitatory angles averaged 73° and the range of joint positions covered by units firing for flexion overlapped with those firing for extension (221). It was claimed that these thalamic units received their inputs from joint receptors; however, the hazards involved in making such a claim have been pointed out above. Indeed, it is difficult to see how the properties of these central units can be accounted for by the currently known properties of joint receptors, although it should be borne in mind that most [but not all; see Grigg and Greenspan (115)] of the receptor physiology has been done in the cat. Clearly, however, the behavior of these thalamic units gives some insight into the nature of the central processing of kinesthetic signals.

The four cytoarchitectonic subdivisions (3a, 3b, 1, and 2) of the primary somatosensory cortex (SI or postcentral cortex) receive most of their subcortical afferent fibers from the ventroposterior nucleus of the thalamus. Mountcastle and Powell (222) correlated the receptive field properties of cells with the cytoarchitecture of the postcentral cortex in anesthetized monkeys and described a transition from cutaneous to "joint" representation passing back from area 3b to area 2 (area 3a was not studied in their experiments). They described "a certain class of cells of the postcentral gyrus capable of depicting by its patterns of activity the steady angles of the joints of the body, and transient changes in those angles" and sometimes observed "pairs of adjacent cells . . . which are reciprocally related to a particular joint." They also found that some of the cortical neurons activated by joint rotation were inhibited by stimulation of the skin. In a few experiments exposure of the capsule of the rotated joint was carried out during cortical recording and the receptors involved were located in the joint capsule: in other experiments the classification of "joint" units was made on the grounds of responsiveness to joint rotation and insensitivity to direct manipulation of skin or muscle. The recorded units received their inputs from upper and lower limbs, always from the contralateral side of the body, and no units could be found that responded to muscle stretch.

Recent anatomical studies indicate that the densest projections from the ventroposterior nucleus of the thalamus are to areas 3a and 3b of the somatosensory cortex, with areas 1 and 2 receiving fewer fibers, many of which are probably branches of axons going to the other two areas (153, 156). Area 3a receives predominantly muscle input and area 3b mainly cutaneous input, but otherwise the areas seem to have equivalent status because of

their similar connections to association areas and through the callosum (157). Moreover, areas 1 and 2 to a large extent seem to be a rerepresentation via collaterals of areas 3a and 3b (157). As emphasized by Goodwin (100), the problem raised by this observation is that the area said to contain the heaviest "joint" input, area 2, appears to receive its own input as a collateral from the projection to area 3a, and area 3a receives mainly inputs from muscle. The earlier difficulty in finding inputs from muscle to area 2 (222) has not continued (36) and the reports of connections between areas 3a and 2 described above are supported by the observation that electrical stimulation of muscle nerves evokes potentials in both areas (256).

In a study of central connections revealed by electrical stimulation of elbow and knee joint nerves in cats anesthetized with chloralose (51), it was found that projection areas for both nerves occurred within area 3 of the postcentral cortex and that these loci overlapped with the projections of group I muscle afferents. However, further projections to areas 2 and 1 did not overlap with projections of muscle afferents. Low-threshold cutaneous afferents evoked responses in all the loci activated by joint nerve inputs.

It thus appears that joint, muscle, and cutaneous afferents have separate and convergent projections to SI.

Both joint and muscle inputs to the second somatosensory area have also been reported (166).

The principal cortical receiving station for muscle afferents is area 3a, which is a cytoarchitectonic subdivision of cortex sometimes considered to be transitional between "sensory" and "motor" areas. On the basis of its intracortical, commissural, and thalamic connections, however, it is coming to be recognized as part of the primary somatosensory cortex (157). In the cat this region is confined to a small area close to the postcruciate dimple; in the monkey it is located in the depths of the central sulcus. The relatively small area and the inaccessibility of the region may help to explain why cortical projections of muscle afferents escaped detection for so long, although projections to other cortical areas as well have now also been described.

There now exist many reports of projections from muscle afferents, excited by electrical or by functional stimuli, to area 3a in cats and primates (6, 127, 139, 183, 227, 235, 249, 300, 309). Many cortical cells in area 3a receive convergent inputs from group I and group II afferents and "although the discharge of some area 3a neurons also reflected differences in muscle length, most area 3a neurons had low position sensitivities. One unit type in area 3a did not respond to maintained muscle stretch and signalled only velocity of stretch" (139). Moreover, cells not far away in area 4 (precentral cortex) received significant group II projections, and "one type of unit in area 4 had no dynamic component to muscle stretch and signalled only muscle length" (139). Such observations indicate that the signals of both velocity and position contained, but differently mixed, in the discharges of spindle primaries and secondaries can be processed to give, at a cortical level, a firing rate related only to velocity or only to position.

Some of the cells in area 3a respond to electrical stimulation of both

muscle and cutaneous nerves (127, 228, 249), so that there is a neural basis in the cortex for the simultaneous activation of cutaneous and deep receptors during joint movement to be combined to give a composite signal of kinesthetic significance.

Although the projection to area 3a is the densest cortical representation of muscle afferents, projections to the precentral or motor cortex (area 4) have also been described (3–5, 98, 139, 177, 183, 248). Afferents traveling in articular nerves also project to cortical area 4 (51). Neurons in this area, including those whose axons project into the medullary pyramids, commonly discharge in response to passive movement of a joint and less frequently to palpation of muscle or to light touch (78, 177, 183, 248, 301). These sources of input commonly relate closely to the motor outputs of the particular neurons involved (176). A fast pathway to the motor cortex from peripheral afferents is indicated by the observation that some cells in area 4 respond to peripheral inputs with a latency of 10 ms or less, and nearly all responses occur within 25 ms of a stimulus (178). The pathway to area 4 is via the dorsal columns for inputs from the forelimb, because no peripheral inputs remain after the dorsal columns are cut (27, 28), but whether it continues by way of the ventroposterior thalamus is not certain (155, 157, 277–279).

Another cortical receiving station for proprioceptive input is area 5 of the parietal cortex, which lies behind the primary somatosensory area and receives its major input through association fibers from areas 1 and 2 (157, 231). In this area, many of the neurons studied in alert unanesthetized monkeys responded to joint rotation and most of these were related to single joints on the contralateral side (220). A few, however, responded to movements of more than one joint, to the movement of joints on the ipsilateral side, or to the simultaneous combination of skin and joint stimulation.

The proprioceptive afferent projections to motor and primary somatosensory areas of cortex are all from the opposite side of the body. The gross abnormalities of position and movement sense that occur on removal of the postcentral gyrus on one side (72, 233) indicate that the affected contralateral limbs do not send effective proprioceptive projections to the normal ipsilateral hemisphere. Corticocallosal connections between opposite primary somatosensory areas include proprioceptive connections, although the extent of these is debated, there being some doubt about the representation of distal parts of the limbs (144, 154, 260). Interhemispheric transfer of information about simple detections of kinesthetic signals from joints or skin, and from muscle, can be made by subjects in whom the corpus callosum is transected (198), although the same subjects cannot duplicate with one hand complex postures that are imposed on the other (271). This suggests that the corpus callosum is necessary only for the interhemispheric transfer of more complex proprioceptive functions.

D. Are Muscles Sentient?

A large body of evidence and argument has been called on to support the

claim that the discharges from muscles receptors have no access to consciousness. Of course, the sort of conscious experiences relevant in kinesthesia would not be sensations referable to the muscles themselves—for we are no more likely to feel kinesthetic sensations *in* our muscles or joints than we are to hear sounds *in* our heads or see objects *in* our retinas—but would be sensations of movement, or force, or tension, or of altered position in the parts moved *by* the muscles.

The case against this role for muscle receptors must be answered in detail before proceeding to consideration of the kinesthetic role now claimed for these receptors. In brief, the case is: *1*) initial failure to demonstrate cortical projections of muscle afferents; *2*) failure of stimulation of muscle afferents in animals to desynchronize the electroencephalogram (EEG) or to provide a basis for conditioning; *3*) alleged loss of kinesthesia during paralysis of joint but not muscle receptors; *4*) alleged failure of awake patients to perceive when exposed muscles are pulled on at operation; *5*) apparent failure of receptors in oculomotor muscles to give perceived signals during imposed movements of the eyes; *6*) the possible unsuitability for kinesthesia of muscle receptor signals that reflect changes of muscular activity as well as the position, velocity, and tensions of muscles and the claimed incompatibility of the ideas that the same discharges could be used in subconscious levels of motor control as well as for kinesthesia. These arguments are also discussed elsewhere (100, 104, 194, 208, 209).

Projections from muscle receptors to the cortex have been repeatedly demonstrated (sect. II*C*). Nevertheless, attempts to evoke arousal and desynchronization of the EEG by stimulation of muscle nerves at group I threshold have failed (95, 239), as have attempts to use stimulation of group I and group II fibers in muscle nerves as a sensory cue for triggering a behavioral response (281). However, the sensory signals provided in these cases may have simply been inappropriate to elicit a response: that is, it could have been difficult to arouse an animal or condition it to respond simply with the use of a small joint rotation. Human subjects undergoing repetitive electrical stimulation of muscle nerves in the popliteal fossa at low intensity have been reported to express uncertainty about the position of the foot (167), although associated referred cutaneous sensations often obscure the situation (104).

Sarnoff and Arrowood (254) reported that intrathecal injection of procaine blocked muscle reflexes before it blocked position sense. They took this to show that muscle afferents had been blocked while other afferents, which were responsible for position sense, continued to conduct impulses. Bearing in mind that local anesthetics block fibers of smaller diameters before larger ones (93), this interpretation is difficult to accept: afferents from muscle spindles and tendon organs are large fibers and would be expected to survive the effects of local anesthetic better than other afferents. It is more likely that procaine blocked small fusimotor fibers in this experiment, thereby reducing the sensitivity of the muscle spindles and so depressing reflexes dependent on them. The preservation of position sense in such circumstances

may still indicate that muscle afferents are not necessary for position sense or, alternatively, it may indicate only that central thresholds for transmission along kinesthetic pathways are lower than those for muscle reflexes.

It is generally agreed that very large deficits in proprioceptive acuity occur when joints and skin are anesthetized while the innervation of the relevant muscles is preserved intact (35, 46, 84, 102, 104, 208, 209, 215, 241; see also Fig. 1 and sect. II, *E* and *F*). Separation of the effects of anesthesia in this way is easily achieved in the hands or feet where the infiltration of local anesthetic, or the local occlusion of arterial blood supply, can affect the joints and skin of the region without affecting the long flexor and extensor muscles that lie outside the region. Browne, Lee, and Ring (35) reported complete loss of appreciation by their subjects of imposed movements (1–2°/s) made at the anesthetized metatarsophalangeal joint of the big toe, but only when the muscles acting at the joint were relaxed. An observation not systematically investigated was that the subjects "were immediately brought within the normal range when allowed to tense their muscles." Provins (241) later performed similar experiments on the metacarpophalangeal joint of the index finger and reported that the detections of very slow movements (0.6°/s) imposed on the joint were grossly impaired, but not always abolished, in his subjects whether or not the muscles acting at the joint were tensed. Chambers and Gilliatt (46) and Butt, Davies, and Merton (208–210) did similar experiments, anesthetizing the whole hand by cutting off its blood supply with an inflated blood pressure cuff, rather than anesthetizing individual digits. The ability of the subjects to detect imposed movements again was greatly impaired, although in spastic patients, where resting muscular tone was high, it was "strikingly preserved" (46). Merton (208) felt that there was no need to attribute the residual kinesthetic sensations here to discharges from muscle receptors, suggesting instead that "the forearm muscles nudge the top edge of the cuff, where the skin is not anaesthetic, and give a clue to the movement."

Goodwin, McCloskey, and Matthews (102, 104) repeated many of the experiments described above with rather different results. In fact, we stressed the persistence of kinesthetic sensations in conditions where others had disregarded them. In experiments on anesthetization of individual digits with local anesthetics or of the whole hand with ischemia, awareness of imposed flexion-extension movements persisted but was much less acute than normal. Subjects were best able to detect movements that were large and rapid or were imposed when the relevant muscles were tensed. With the whole hand anesthetized subjects could correctly nominate which unseen and anesthetized finger was moved and whether it was held still in a flexed, extended, or intermediate position. Merton's suggestion that the detections were based on cutaneous signals generated by muscle bellies moving under the cuff was shown to be incorrect by the demonstration that such detections could still be made when the cuff around the wrist was temporarily replaced by a cuff around the upper arm or when digits were anesthetized by injection of local anesthetic so that no cuff was used. Importantly, the detections made

during anesthesia of the whole hand could be made only for flexion-extension movements of a finger and not for lateral movements imposed at the same joint. This indicates that the joint and cutaneous receptors were fully anesthetized and points to muscle as the origin of the discharges on which detections were based: in anesthesia of the hand, the intrinsic muscles responsible for lateral movements are themselves anesthetized and only the long flexor and extensor muscles in the forearm remain unaffected. Furthermore, the subjects were unable to distinguish between movement at the metacarpophalangeal joint and the proximal interphalangeal joint of the finger. Both these joints are acted on similarly by the long flexors and extensors – it is the intrinsic muscles of the hand, which were anesthetized in these experiments, that act on them differently. The anatomical observations of Stopford (276) are relevant to this latter point. In a series of careful clinical assessments of various nerve lesions in the forearm, Stopford found that patients with nerve lesions at the wrist often are able to detect the occurrence of an imposed movement and to nominate the finger in which it occurs and its direction, but cannot distinguish which of the joints within the finger moves. Head and Sherren (126) previously had reported similar findings. Although these observations sometimes have been cited as evidence of the importance of joint receptors, they also can be interpreted as showing that when the joints, skin, and intrinsic hand muscles are denervated the receptors in the long flexors and extensors in the forearm can provide the basis for detection of movements.

Gelfan and Carter (94) performed a variation of the experiments discussed above when they pulled on tendons exposed at the wrist during operations performed under local anesthesia. Here local anesthetization of joints and skin was unnecessary – the distal ends of the tendons were simply held still while the proximal ends were pulled on to stretch appropriate muscles. Gelfan and Carter thus were able to confirm the widely held surgical opinion that such maneuvers evoke no kinesthetic sensations. It is not clear, however, to what extent their subjects were asked about movements at relevant joints, as the experimenters seem to have concentrated particularly on asking about "any sensation referable to the muscles." A similar finding was briefly reported by Moberg (215), who stated not at all equivocally: "A hard pull which has its effect proximally on the normal muscles does not give any conscious sensation at all. But a pull in the other direction – flexing a finger, will immediately produce sensation of flexion." Not only does this argue against the access of muscle receptor discharges to consciousness, but it also points to the importance of joint and cutaneous mechanisms in kinesthesia. It is of great interest, therefore, that the experiment has been repeated recently with exactly the opposite result. Matthews and Simmonds (194, 195) pulled on tendons and "without exception the subjects then reported 'you are moving my finger' (or thumb) and allocated the movement to the correct digit. Yet the pulling was performed in such a way that the digit itself did not actually move" (194). Clearly this simple and important experiment must be repeated, for it promises a direct

and decisive answer to the question of the sentience of muscles. Matthews (194) has observed: "it verges on the ridiculous for there to be any doubt over the facts in such a simple experiment."

The tongue is a muscular organ that possesses muscle spindles (60) and has no joints or joint receptors to provide position sense. Surface anesthesia of the tongue has been reported to abolish its kinesthetic sensibility (44), although the experiments said to have established this have been criticized (1) on the grounds that the doses of local anesthetic used were strong enough to have diffused into the main muscular bulk of the tongue. The original report omitted mention of whether or not the motor fibers to the tongue were affected in the experiments. Others (1, 299) have reported that kinesthetic sensibility remains in the tongue after widespread anesthesia of its mucous membrane.

Considerable reliance has been placed on the claimed insentience of extraocular muscles by some who have argued that muscles, in general, are insentient. Their case begins with observations by Helmholtz (128) that pulling on an eye, so as to displace its visual axis, causes apparent movements of objects in the external world—"as if the pulling had no effect on changing the direction of the visual axis." A similar pull causes no apparent movements of afterimages in a closed eye. These observations were later confirmed (26). Strictly speaking, they do not show that muscle receptors provide no perceived discharges, but only that such discharges do not maintain the stability of the visual world during imposed eye movements. More relevant were the claims that subjects in whom vision was occluded were unaware of movements imposed on an eye by gripping its anesthetized surface (26, 145). These claims could not be confirmed in Skavenski's recent carefully controlled study using trained subjects (266) in which rotations of about 10° of the anesthetized, occluded eyes were detected reliably. The same subjects were able, on instruction, to maintain the direction of the visual axis against forces that otherwise would have produced displacement of about 5°; again, visual and nonproprioceptive cues were excluded as providing the basis for the correction. It was suggested that in the previous basically similar experiments weak proprioceptive sensations might have been missed because the subjects were untrained and were "distracted or under some degree of discomfort or duress."

Obviously, no clear-cut, undisputed evidence exists that muscle afferents are denied access to consciousness. Where such evidence has been claimed to exist, closer examination often shows that important elements of the evidence have been ignored or explained away, sometimes quite uncritically. Every important experiment that had been claimed to reveal the insentience of muscles has now been repeated, revealing the opposite. In addition, other observations give positive evidence of the kinesthetic role of muscle afferents. These are considered elsewhere, but include the improved kinesthetic acuity conferred by muscular attachment at a joint (sect. II*A* and Fig. 1), the measurable acuity present when only muscles are available to provide kinesthetic signals (sect. II*F*), and the kinesthetic illusions produced by the excitation of muscle receptors by vibration (sect. II*F*).

The experimental evidence shows that muscle receptors contribute to perception. The problems now to be considered are: what quantitative contributions do the muscle receptors make? What muscle receptors are involved? What must the central nervous system do with the signals from the muscle receptors in order to remove the apparent ambiguities they contain? These questions are discussed below (sect. II*F*) after an analysis of the kinesthetic role of the principal alternative afferent sources of kinesthesia, the joint receptors.

E. Kinesthetic Role: Joint Receptors

Many attempts have been made to define the role of joint receptors in kinesthesia by examination of subjects deprived of signals from them. An early experiment of this kind was done by Goldsheider (99), who passed trains of electrical stimuli through the finger joints of his subjects and found that this raised the threshold for detection of movements imposed at those joints. He argued that the stimuli anesthetized the joints and that the consequent elevation of threshold was evidence for the importance of joint receptors in detection of movement. The validity of this conclusion was called into serious doubt by the demonstration that electrical stimulation of the hand or arm was as successful in raising the threshold for detection of rotation of the elbow joint as was stimulation of the elbow joint itself (236, 306).

In the 1950's and 1960's the case against the participation of muscle afferents in kinesthesia was greatly strengthened by the results of experiments in which joints were locally anesthetized while the muscles that operated the joints were left unaffected (see sect. II*D*). Brown, Lee, and Ring (35) and Provins (241), working with the joints at the base of the big toe and index finger, respectively, described very large deficits in kinesthetic sensibility during local anesthesia. The occurrence of these large deficits was confirmed subsequently in similar experiments (46, 84, 102, 104, 208, 209, 215), although a crucial matter that was not agreed on was whether or not *any* kinesthetic sensibility at all remained in such situations.

A common feature of these experiments was that local anesthesia of the joints was accompanied by anesthesia of the overlying skin. This was so because the methods used to produce anesthesia—either injection of local anesthetic around the digital nerves or occlusion of the arterial supply to the area to produce anoxic, or ischemic, block—affected all the regional innervation, preserving the innervation of the long flexor and extensor muscles only because these are situated remotely in the forearm or leg. Possibly, therefore, it was the anesthesia of the skin rather than the joints that produced the proprioceptive deficits.

In some experiments injections of local anesthetic have been made into joint cavities in an attempt to anesthetize joint receptors while preserving other afferents. In such studies on the temporomandibular joints of the jaw (47, 265) and on the knee joint (50; F. J. Clark, personal communication),

little or no impairment of kinesthetic performance was noted. This may have been because the contribution of joint receptors to kinesthesia in these joints is very slight, but it may also have been because anesthesia of the joint receptors was incomplete. In the cat, intra-articular injections of local anesthetic abolished "nearly all" of the tonic activity in the posterior and medial articular nerves (F. J. Clark, personal communication) but, even if similar results could be assumed in human subjects, "nearly all" may not be enough. Unfortunately, there can be no satisfactory test for joint anesthesia until the magnitude of the contribution of joint receptors to movement and position sense is accurately known. If their contribution is appreciable and not duplicated from other sources, then they can be considered paralyzed only if a significant deficit or even total loss of kinesthesia occurs. If their contribution is only slight, or if it is duplicated by other afferent inputs such as those from muscle, their paralysis will not be detected by kinesthetic tests. In effect, this means that experiments attempting selective paralysis of joint receptors cannot be used conclusively to discover the contribution of these receptors to kinesthesia because their kinesthetic role must be known *before* the criteria for their paralysis can be established.

A similar criticism can be made of experiments on the kinesthetic performances of patients in whom joints have been surgically removed because here, too, the surgical removal of joint receptors may not have been complete and no adequate test exists to assess this. Nevertheless, some surgical procedures involved in total joint replacement are so extensive that the elimination of signals from joint receptors can be assumed more confidently than in the experiments attempting selective anesthetization of the joints. Patients have been examined in whom whole joints have been removed and replaced by prostheses in operations in which the joint capsules are first divided and themselves removed, and in all these patients apparently normal kinesthetic sensation and motor function remains (64, 104, 114). The most detailed study of patients with artificial joints was that carried out by Grigg, Finerman, and Riley (114). In studies on 10 patients before and after surgery they found that "patients with total hip replacement retain an acute awareness of the angular position of the limb with relation to the hip," although in 9 of the 10 some increase in the threshold for detection of passive movements did occur. Despite these increases in threshold, these patients could still detect movements of less than 3° made at 0.6°/s. This suggests either that joint receptors normally make little or no contribution to the sense of position and movement or that any sensory inputs they do provide are duplicated adequately by other sources such as muscle or cutaneous receptors.

In experiments on cats Lindström and Norrsell (180) showed that cutting the posterior, medial, and lateral articular nerves of the knee joint produced no apparent changes in posture or movement.

The striking difference in the experiments involving attempted elimination of joint receptors is between those in which cutaneous sensation was preserved (47, 50, 64, 104, 114, 265) and those in which the cutaneous

receptors were also anesthetized (35, 46, 84, 102, 104, 208, 209, 215, 241). This may mean that cutaneous receptors rather than joint receptors are importantly involved in kinesthesia. Such involvement could be in either the provision of specific signals of joint position and movement or in the facilitation of signals from receptors in muscles or joints: these possibilities are discussed in section III.

Gandevia and McCloskey (84), in another approach to defining the kinesthetic role of joint receptors, made use of an anatomical peculiarity in the distal interphalangeal joint of the middle finger in order to disengage the muscles from effective action at the joint. If the index, ring, and little fingers are extended and held extended, and then the middle finger alone is flexed maximally at the proximal interphalangeal joint, the terminal phalanx of that finger cannot be moved by voluntary effort because the long flexor and extensor muscles that move it are held at inappropriate lengths (111). Effective muscular attachment thus is removed from the joint in this position, but can be restored by flexing the adjacent fingers. Proprioceptive acuity was assessed at the joint in 12 normal subjects when the muscles were disengaged. Unfortunately, it was not possible to anesthetize the skin of the finger without also anesthetizing the joint, so that "joint" sense could not be tested in complete isolation. Nevertheless, "joint" sense could not be better in isolation than the combined cutaneous and joint sense measured this way. When only joint and cutaneous mechanisms were available for kinesthetic sensation, detection of fixed angular displacements was more reliable the faster the velocity was at which they were made, indicating that the sensory mechanisms responsible were sensitive to the velocity of movement. The subjects could detect variable angular displacements made at a fixed angular velocity more reliably the greater the displacements were, indicating that the sensory mechanisms responsible were also sensitive to the absolute angular displacement. When muscular attachment was restored at the joint, making muscular as well as articular and cutaneous mechanisms available for kinesthesia, all subjects showed a marked improvement in proprioceptive acuity. Figure 1 shows the results from one of the tests. Engagement of the muscles caused no consistent change in the measured "stiffness" of the joint, so it is unlikely that the improved performance resulted from a more effective discharge of joint receptors produced by the muscles tensing the joint capsule (213, 267). Instead, it indicates that muscle receptors play an important role in normal kinesthesia, a matter taken up again below.

Although some of the findings reviewed above suggest that joint receptors are relatively unimportant in providing perceived signals of limb position and movement, it might still be argued that their contribution becomes more important at extremes of joint excursion where their discharge rates are maximal (see sect. II*A*). Craske (63), however, has found that normal subjects are prepared to believe that joints have rotated to a position well *beyond* the anatomically possible extreme of excursion when the muscles acting at the joints are vibrated. Vibration excites intramuscular receptors (see sect. II*F*). This suggests that subjects rely on the signals of muscle

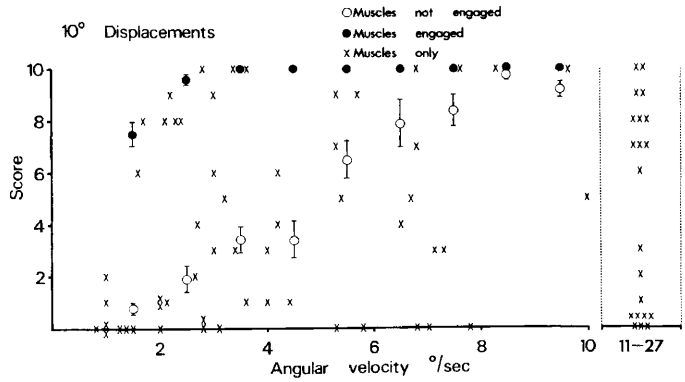

FIG. 1. Results from 7 subjects in a test involving detection of 10° displacement of the distal interphalangeal joint of the middle finger at various angular velocities. Scores give the number of correct detections of displacements (including detection of direction) in sets of 10 similar displacements. Results are given for scores obtained when the muscles operating the joint were engaged and when they were not engaged at the joint; scores from individual subjects have been averaged, in the ranges 1.0–1.9, 2.0–2.9°/s, etc., and mean score ±SE is plotted for each category. In tests when muscles alone contributed to position sense the joints and skin of the finger had been anesthetized by digital nerve block and the muscles were relaxed; individual scores are shown. In the angular velocity range 11–27°/s, scores are grouped together (at right). Joint-plus-cutaneous sense (open circles) is improved by the participation of muscle receptors (closed circles). Muscle receptors acting in isolation give very variable proprioceptive acuity when muscles are relaxed. [From Gandevia and McCloskey (84).]

receptors in their judgments of extreme joint rotation, disregarding any contrary information that joint receptors might provide.

F. Kinesthetic Role: Muscle Receptors

In further studies on the distal interphalangeal joint of the middle finger described above (sect. II*E*), Gandevia and McCloskey (84) measured the proprioceptive acuity when muscles were engaged but joint and cutaneous receptors were anesthetized by digital nerve block. When the muscles were relaxed the measured ability to detect imposed displacements was very variable. In some subjects "muscle sense" was superior to "joint-plus-cutaneous sense" (measured in the same subjects with the muscles disengaged, but before nerve block) and was almost as good as the full kinesthetic sense (measured with all mechanisms able to contribute). In other subjects muscle sense was very poor, and even displacements made at very fast angular velocities were not reliably detected. Figure 1 shows the results from these experiments. This variability may explain how some confusion arose in earlier experiments concerning muscle afferents and perception—if subjects with very poor muscle sense were chosen for testing it is not surprising that the sense was said to be absent. The variability of performance may have reflected slight subconscious changes in muscular tension exerted by the subjects while the muscles were supposed to be relaxed: in all subjects muscle sense was brought into the normal range of full kinesthetic acuity when the engaged muscles were tensed voluntarily. If the muscle spindles provide the

basis for such detections it is worth recalling that fusimotor tone increases with voluntarily exerted force, raising the background level of spindle firing (292), a factor that might contribute to the reductions in detection threshold.

The variable, and frequently poor, proprioceptive acuity contributed by relaxed muscles acting in isolation contrasts with the marked and consistent improvement caused by engagement of relaxed muscles when the joint is unanesthetized (Fig. 1 and sect. II*E*; 84). In many subjects poor muscle sense and quite average joint-plus-cutaneous sense combine to give a complete position sense that is superior to either sense alone. Facilitation between the discharges from the different sources appears likely to account for this improvement. Anesthetization of the fingers adjacent to the one being tested raises the threshold for detection of movements in some subjects (84), so the central interactions may be quite widespread. In particular, facilitatory discharges from cutaneous receptors of the region may be important in kinesthesia since cutaneous rather than joint anesthesia appears to be responsible for the blunting of kinesthetic sensation during regional nerve block.

Muscle receptors not only provide kinesthetic sensations of movement and position, they also provide perceived signals of intramuscular tension. This was first shown (200) in experiments in which subjects exerted isometric tensions using the flexors of the elbow joint. The subjects rested the tip of the elbow on a support and pulled against a strain gauge through an inextensible cable attached to the wrist: the skin of the elbow tip and the whole hand and wrist were locally anesthetized and vision was excluded. The subjects were instructed to keep the tension applied to the strain gauge constant during periods in which vibration at 100 Hz (approx. 1-mm amplitude) was applied transversely to the tendon of the contracting elbow flexor (biceps) or its antagonist (triceps). Such vibration, presumably through its stimulation of muscle spindles (see below), evokes an involuntary contraction, a "tonic vibration reflex" (65, 117), in the muscle to which it is applied or inhibits any existing contraction of the antagonist of the vibrated muscle (105). Despite these disturbances induced by vibration the subjects were able to modify the efforts they made to maintain a constant isometric tension. The basis for making the modifications could not have been visual or cutaneous input, since these were excluded, nor could it have been the effort put into the contraction because this was altered voluntarily to keep tension constant. It follows that the discharges of intramuscular receptors gave the signals by which tension, or at least changes in tension, were sensed. (These experiments are discussed further in sect. IV*C* and are illustrated in Fig. 5.) Because vibration so greatly alters the discharges from muscle spindles it is unlikely that these gave useful signals for tension judgment. Perhaps the Golgi tendon organs provided the signals used. The demonstration that these, too, can be disturbed by vibration (41) need not rule out this possibility, for in the study in which this was shown only a very small fraction of the population of tendon organs was investigated.

Roland (243, 244) tested the ability of subjects to compress springs of different strengths through subjectively equal distances or with subjectively

equal forces. Using the finger and thumb to compress the springs the "subjects could successfully use their normal hand both to match the voluntary force developed in a skin and joint anaesthetized hand and simultaneously to assess the extent of its voluntary movement. They could also match the extent of voluntary movement and simultaneously discriminate spring strength." These results again show that muscle receptors in contracting muscles provide reliable kinesthetic information for judgments of both displacement and muscular force.

An important role in reopening the question of whether the discharges from muscle receptors can influence perception was played by the demonstration that vibration of muscles causes kinesthetic illusions in normal subjects (101, 103, 104). When the tendon of a muscle is vibrated transversely at 100 Hz the illusion is experienced that the joint at which the muscle acts is moving in the direction that normally would stretch the vibrated muscle. Such illusions are easily demonstrated by asking a blindfolded subject to track the apparent position of the joint on the vibrated side by moving the corresponding joint on the other side and are illustrated for the elbow joint in Figure 2. Illusory movements occur in opposite directions when vibration is applied to agonists and to antagonists, but none are experienced when the vibration is applied over the joint. This provides important evidence that muscle receptors rather than joint receptors give the signals that cause the illusions. Even when all the joints and skin of the hand are anesthetized, vibration of the long flexor tendons within the anesthetized hand causes illusory sensations of extension of the fingers and thumb (104). Thus, although there is every likelihood that paciniform corpuscles and other mechanoreceptors within the skin and joints of the region normally would be excited by vibration, the kinesthetic illusions depend not on these but on the excitation of receptors within the muscles. Discharges seen in multifiber recordings from joint nerves during vibration (213) are likely to be due to the excitation of paciniform endings and in any case are not relevant to kinesthetic illusions.

In three subjects undergoing surgery at the wrist under local anesthesia, Matthews and Simmonds (194, 195) tested the effects of applying vibration directly on an exposed tendon. No kinesthetic sensations were reported by the subjects. However, the vibrator was not firmly attached *to* the tendon and "it was uncertain as to how effectively the vibration was being transmitted to the muscle along the length of the tendon" (194).

Vibration-induced illusions are predominantly illusions of continuing movement—of velocity of joint rotation (104, 162, 197)—and continue for as long as vibration is applied. A systematic distortion of static position sense also occurs (63, 69, 104, 197, 216). To some extent the signals of movement and position are signaled or processed separately because vibration of lower frequencies and greater amplitude can cause large illusory effects on the perception of static position without causing illusory movements (69,197).

Significant clues to the identity of the muscle receptors giving kinesthetic sensations are given by the observations on vibration-induced illu-

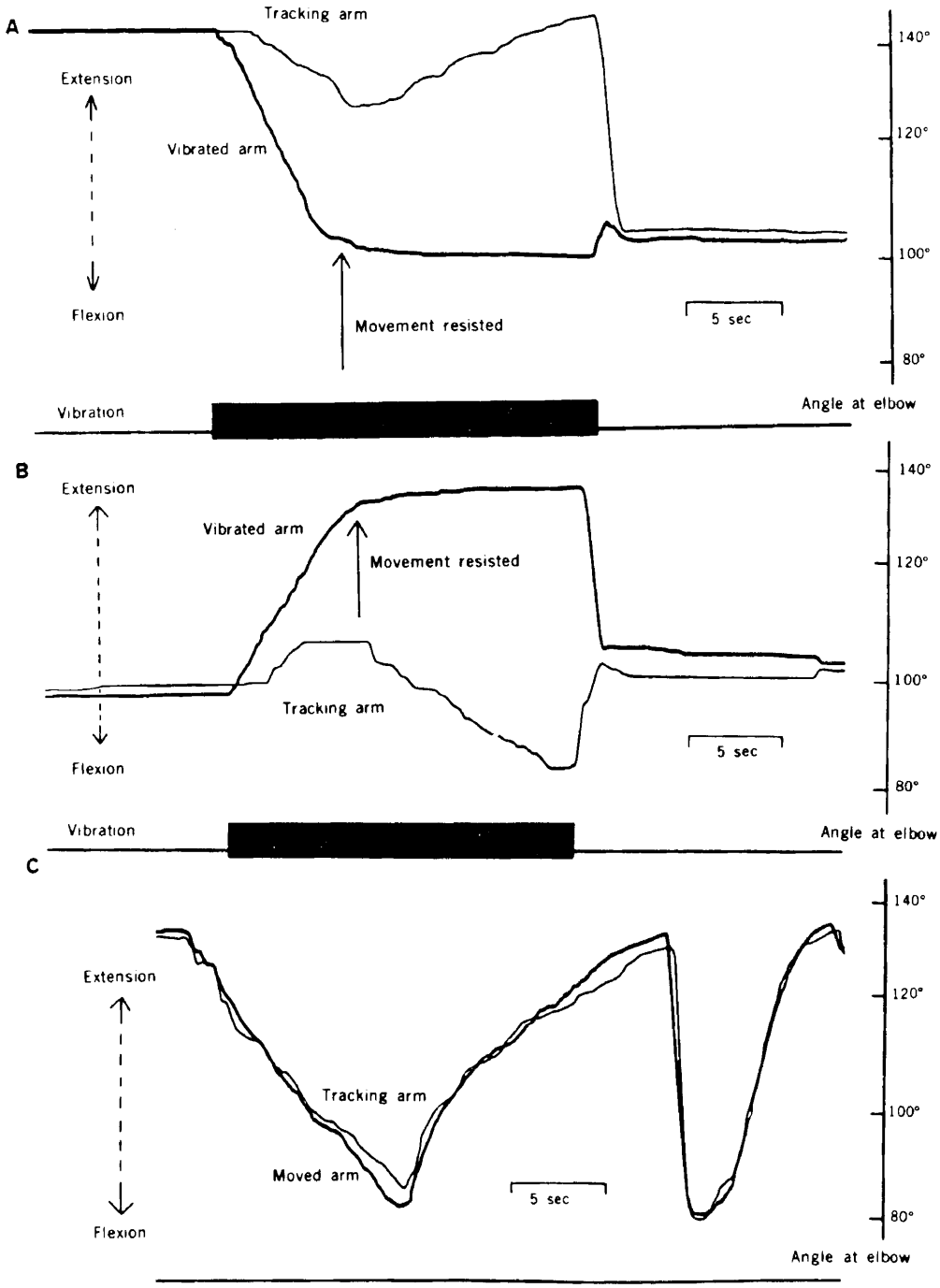

FIG. 2. *A*: effect of vibrating the tendon of the right biceps muscle to produce a tonic vibration reflex, which moved the arm into flexion. Blindfolded subject used the left arm to track what he believed to be the position of the vibrated right arm. From the arrow onward, any appreciable further flexion of the vibrated arm was prevented because the movement gradually pulled taut a long string attached to a splint on the arm and fixed at its far end. *B*: effect of vibrating the tendon of the right triceps muscle to produce a tonic vibration reflex, which moved the arm into extension. Blindfolded subject used the left arm to track what he believed to be the position of the vibrated right arm. From the arrow onward, any appreciable further extension of the vibrated arm was prevented, as in the experiment in *A*. *C*: accuracy of tracking of passively imposed movements. Right arm was moved by the experimenter, and the subject was asked to track it with his left arm. Same subject (still blindfolded) was used as in *A* and *B*. Experimenter held a splint on the subject's arm and not the arm itself. [From Goodwin, McCloskey, and Matthews (103).]

sions. It seems virtually certain that the spindle primaries are involved in the illusions of movement because of their high sensitivity to vibration (19, 34, 41) and because of the appropriateness of illusory *movement* as a sensation arising from activation of a receptor type normally more sensitive to dynamic than to static stimuli. The other principal intramuscular mechanoreceptors, the spindle secondaries and the tendon organs, cannot be denied a role, however, as they are also significantly activated during vibration (41). The signal contained in the discharges of the spindle primaries is of velocity and static stretch, whereas that in the secondaries is just static stretch: simple subtraction could yield a signal of velocity alone, whereas the signal of stretch alone appears in the discharges of the secondaries and in the element of discharge that primaries and secondaries share. It was pointed out above (sect. II*C*) that at a cortical level the discharges from muscle receptors have undergone processing to give, among other things, separate signals of velocity and static stretch (139). Vibration-induced excitation of spindle primaries and secondaries, processed along these lines, could account for the illusions of movement and false position: moreover, at lower frequencies and higher amplitudes of vibration, when the balance of excitation is likely to be shifted in favor of the secondaries rather than the primaries, the persistence of illusory false position in the absence of illusory movement could be explained (197).

Some consideration was given above (sect. II*B*) to the question of how the discharges of muscle spindles could be made useful for a role in kinesthesia; in order to achieve this the central nervous system would need to have some way of discounting that part of the spindle firing attributable to changes in fusimotor tone rather than to stretch of the muscle. Such corrections could be made with central collateral or reentrant motor discharges or by quite elaborate processing of the primary and secondary spindle discharges themselves. That such corrections are indeed made is suggested by one further observation on the sensory effects of muscle vibration. When vibration is applied to a relaxed or gently contracting muscle illusory movements are regularly experienced. However, when the vibration is applied to a very strongly contracting muscle there are no illusions of movement (104, 197), and at intermediate levels of contraction slower than usual illusory movements are perceived (197). This would be expected if the illusions were based on spindle or tendon organ firing and if only part of their discharge—that part in excess of the level "appropriate" for the prevailing contraction—contributed to the illusory sensations. Thus, as the strength of contraction increased, so too would the fusimotor-induced spindle firing (42, 118, 119, 288, 289, 292) and the firing of tendon organ afferents (41, 288): if vibration then were to raise these discharges to a constant level (say by 1:1 entrainment to 100 Hz; see 104, 193, 197), the *excess* discharge caused by vibration would decrease as the force of muscular contraction increased. Assuming, therefore, that the central nervous system does discount for kinesthetic purposes those discharges that are expected or "appropriate" at a given level of contraction, then the observed reduction in velocity and final

abolition of the illusory movement with increasing strength of contraction would be explained. Not only does this consideration provide evidence that discharges from muscle receptors are processed centrally for kinesthetic sensation, but it also provides confirmation that the effects of vibration are mediated by intramuscular receptors because only these should be affected so markedly by the strength of the contraction.

Valuable insights into the roles played by muscle receptors in kinesthesia have come from studies with vibration. Nevertheless, the uncertainties regarding the spread of excitation between receptor types and the nature of the firing patterns adopted in any particular situation (41, 42) are likely to make detailed and quantitative analyses of the sensory effects of vibration much less rewarding than the largely qualitative studies reviewed here.

III. AFFERENT MECHANISMS: SKIN

The properties and connections of cutaneous receptors have been extensively reviewed elsewhere (8, 31–33, 39, 106, 143, 157, 240, 302). Unfortunately, very little work has been done on the possible contributions by these receptors to kinesthesia, so they are not dealt with in the systematic way that joint and muscle receptors are above: instead, a brief review of some possibly relevant studies is given.

Neurological opinion is divided over whether or not the power of recognizing passive movement or position can be lost through a peripheral or spinal nerve injury while cutaneous sensibility is preserved. Ferrier (77) stated emphatically that, "loss of the muscular sense never occurs without general anesthesia of the limb. There does not appear to be a single fact which would indicate that the muscular sense can be abolished and the other forms of sensibility of the limb continue." Others (e.g., 107, 124) did not agree. Head (124), for example, quoted cases where cutaneous sensation was lost while sensations of position and movement were preserved and others where position and movement senses were lost while cutaneous sensibility was preserved. Probably different observers based their judgments on performances requiring very different degrees of sensory discrimination. In 1891, Waller (296) reviewed the neurological opinions then being offered and noted that he found himself "often in considerable doubt whether 'loss of muscular sense' or 'preservation of muscular sense' are verbal formulae or duly authenticated facts."

If cutaneous anesthesia *can* occur without loss of sensations of movement or position, cutaneous receptors cannot be necessary for kinesthetic sensibility. A similar conclusion can be drawn from experiments in which the skin overlying joints was locally anesthetized (50, 124) or grossly distorted by taping or strapping (58) without seriously impairing kinesthetic sensibility. There is not unanimity on this question, however, because it has been claimed that, in certain patients after reconstructive surgery on the hand, intact cutaneous innervation was sufficient to provide good position and movement sense even when muscle and joint receptors could not contribute

(215); unfortunately, it is not clear in this report what objective tests were done to permit the conclusion that joint innervation, in particular, was not intact.

In the fingers and toes (sect. II, *D–F*) it is relatively easy to anesthetize both the joints and skin together, and when this is done in normal subjects there is a pronounced deficit in the appreciation of position and movement (35, 46, 84, 102, 104, 208, 209, 215, 241). In contrast, apparently normal kinesthetic sensibility is preserved when joint receptors alone are interfered with in the fingers or toes (64), in proximal limb joints (50, 104, 114), or in temporomandibular joints (47, 265). These findings suggest a kinesthetic role for cutaneous receptors, at least in the joints of the fingers and toes, but do not indicate whether the contribution is of specific signals of joint position and movement or of less specific signals that act by facilitating the central action of muscle or joint afferents. In any case, the contribution may be important only in distal joints, for in the knee joint neither introduction of local anesthetic into the joint capsule nor anesthetization of a "sleeve" of skin around the joint caused a serious impairment of position sense (F. J. Clark, personal communication). Alternatively, if the cutaneous contribution is a nonspecific facilitatory one, the appropriate cutaneous input even for proximal joints may come from the distal parts moved *by* the joint (i.e., from the foot and hand for the knee and elbow joints) rather than from the skin overlying the joint.

Slowly adapting cutaneous receptors of a type suitable for providing kinesthetic information have been described in animals (45) and man (160, 293). Of particular interest are the recordings made in human subjects by Knibestöl (159) of slowly adapting units that signal joint angle over a wide range. A unit illustrated by Knibestöl gave a discharge rate linearly related to the angle of flexion of the distal interphalangeal joint of a finger with a sensitivity of approximately 0.8 impulses/deg over 80° of rotation. Receptors of this kind are plentiful in the region of the nail bed and respond mainly to rotations of the proximal and distal interphalangeal joints (159): they may represent the human equivalent of receptors thought to signal claw position in animals (39). It remains to be discovered whether or not such potentially useful signals are used in kinesthesia. Sensations associated with maintained indentations of the skin of the forearm fade completely within a couple of minutes, and slowly made indentations are often not felt at all (138), so that signals from cutaneous receptors may be unsuitable for giving a continually perceived signal of static position.

In their study of the distal interphalangeal joint of the middle finger, Gandevia and McCloskey (see Fig. 1; 84) showed that good proprioceptive acuity remained when muscles were disengaged at the joint (although it was always poorer than when the muscles were engaged; see sect. II*E*). If the joint receptors in this joint provide as poor a signal of joint position as do those studied electrophysiologically elsewhere (see sect. II*A*) then the proprioceptive acuity dependent only on joint-plus-cutaneous mechanisms is likely to have been derived largely from cutaneous receptors—and this joint is one of the locations with a rich investment of slowly adapting nail-bed receptors

of the type just discussed. Disengagement of muscles at joints that are not close to nail beds would result in a more marked loss of acuity than was found at the distal joint of the finger.

A quite separate question concerns the possibility that discharges from cutaneous receptors may facilitate the kinesthetic inputs from joints or muscles. Muscle afferents operating in the functional stretch reflex of the long flexor of the human thumb appear to depend on inputs from joints or skin for facilitation (190–192), although similar facilitation does not occur in the flexors of the big toe (192). Facilitation between various kinesthetic inputs is also suggested by the observation that proprioceptive acuity at a joint in one finger may be blunted by anesthetization of the adjacent fingers (84). Unfortunately, experimental separation of the kinesthetic inputs from skin and joints has not been sufficiently successful to permit a choice to be made between them as the likely source of such nonspecific facilitation.

The importance of cutaneous receptors in the estimation of weights placed on a supported part (e.g., 124, 297), or held so as to pull across the surface of the skin (199), is undisputed. Such tasks, however, cannot be considered part of kinesthetic sensibility and are not considered further here.

IV. EFFERENT MECHANISMS

The idea of a sensation "of innervation," a sensation arising within the central nervous system from, or together with, centrifugal command signals for muscular contractions, was debated thoroughly by physiologists, psychologists, neurologists, and philosophers during the nineteenth century. It is not clear when the idea was born, but one can see its attraction to a scientific world not yet fully persuaded of the separate existence of sensory and motor nerves. Bastian (15) claims that "two Italian physicians, Julius Caesar Scaliger in 1557 and Caesalpinus of Arezzo in 1569, quite independently of one another were the first to recognize . . . the existence of a separate faculty or endowment associated with volition, or the mere will to move." By the latter half of last century the idea was well understood and widely known through the writings of Müller (223), Bain (13), Wundt (308), Helmholtz (128), Jackson and Paton (146), Gowers (107), and others. Also, by that time, strong opposition to the idea had developed, notably including Ferrier (77), James (147), and Sherrington (261). The ensuing debate frequently was based mainly on philosophical grounds.

Much of the early neurological evidence on sensations of innervation unfortunately came from patients in whom the neurological lesions were not at all defined, including almost certainly some whose disabilities were primarily psychiatric. Some cases were quite bizarre. William James (147), for instance, gave some prominence to an "account by Professor A. Strumpell of his wonderful anesthetic boy, whose only sources of feeling were his right eye and left ear." In addition, as one reviewer noted at the time, "there is a radical difference of opinion between clinical experts as to the fundamental clinical facts, which are presented as black or white according to the doctrinal point of view from which they are regarded" (296).

A. Eye Movements

The most convincing of the early experiments were those on eye movements. Helmholtz (128) noted that the visual world is perceived to stay still when one makes voluntary eye movements but that "apparent motions" are seen when movements of similar magnitude are imposed on the eyes. On the other hand, positions of afterimages in the closed eye seem to move with voluntary movements, but stay still during imposed movements. "Thus," he wrote, "our judgement as to the direction of the visual axis is not formed either by the actual position of the eyeball or by the actual elongation or contraction of the ocular muscles that is the result of this position. Our judgements as to the direction of the visual axis are simply the result of the effort of will involved in trying to alter the adjustment of the eyes." Helmholtz supported this conclusion with observations made on patients in whom the oculomotor muscles suddenly became weak. On attempting to turn the eye in a direction in which it could not move, these patients saw apparent shifts of the visual world in the direction of the attempted movement. The effort of will to move the eye, it was argued, had given the sensation that the eye *did* move, so that the unchanged position of retinal images made it seem that the visual world had shared the supposed movement of the eye. Others confirmed these findings (26, 53, 107, 146, 184, 208; see also 304).

William James (147) found difficulty in accepting Helmholtz's views, arguing that the interpretations based on judgments made while one eye was displaced or weakened had neglected to take into account the influence of the other eye. Sherrington (261) sided with James. Subsequent clinical studies by Jackson and Paton (146) suggested that there was no substance in this objection, but perhaps the most effective argument against it was Merton's (208). He argued that, if James were correct, "we should have to hold that, when one eye is passively deviated by pulling on the canthus, objects appear to move because the subject judges the direction of the visual axis by reference to the other eye. The reader can easily convince himself that this is not what happens, by pulling on both eyes simultaneously; objects seen by both eyes appear to move, and do so independently of each other."

In attempts to duplicate experimentally the situation occurring in oculomotor paralysis or paresis, severe weakness of the muscles was induced by the injection of local anesthetic or by systemic or retro-orbital administration of low doses of curare (25, 26, 161, 264, 274). In these subjects large apparent displacements of the visual world in the direction of the intended but weakly executed movements occurred. These experiments therefore provided evidence in favor of a sensation of innervation giving the sense of direction of the gaze. A great difficulty arose, however, when enough of the neuromuscular blocking drug was given to paralyze the oculomotor muscles completely: in this situation subjects were said to report *no* apparent movements accompanying attempts to turn the eyes (25, 264, 274). In one study involving total oculomotor paralysis of one of the experimenters on four separate occasions, complete absence of movement or displacement

accompanied attempts to move the eyes on only the first occasion: in subsequent periods of paralysis the subject perceived no apparent *movements* on his attempts, but was said to have had an illusion of *displacement* (274). Others could not confirm this (25). In another study, intended to keep "inflow" signals constant in unparalyzed subjects, sensations of displacement of the visual world attributed to "outflow" mechanisms were reported (266a).

New theories to account for visual perception during eye movements will be necessary if further confirmation is reported of the failure of subjects to perceive apparent visual shifts during attempted voluntary movements of *completely* paralyzed eyes.

The extent to which the sensations of innervation said to be involved in these phenomena are really sensations in their own right may well be queried. In every case the sensations reveal themselves as changes in *visual* perception, as changes in the apparent locations of viewed objects. When there is no vision, little remains in the way of positive sensations. If one closes one's eyes and attempts to move them one can be confident that the movements have occurred; indeed, they can be made accurately (207). But confidence may arise as much from an assumption that what one usually achieves continues to be achieved as it does from a positive kinesthetic sensation. Consider what occurs when some cause is given for doubting one's assumption of a successful movement: if one repeats the attempted eye movements with the eyes closed, but this time presses a finger firmly against the outside of one eyelid as if to prevent the eye from moving, one is much less sure of whether the eye moves or is prevented from moving. When Brindley and Merton (26) occluded both eyes of a subject and then occasionally held their anesthetized surfaces while the subject attempted to move them, they reported that he "could not tell whether the eyes were held or not" but that "he regularly had the impression that he succeeded in moving them through a large angle." It is not clear that this "impression" amounted to a positive sensation. Later, Merton (210) described the same experiments again and concluded that "if voluntary movements are artificially impeded, or if passive movements are imposed, we absolutely do not know what is going on—unless we can see and reason back from the visual illusions we receive." Moreover, if one wears a contact lens to which an image source is attached by a stalk, so that the retinal image is stabilized, "one is repeatedly astonished to discover in what direction the stalk is pointing" (189).

The sensation of innervation said to be involved in perception of the direction of the visual axis therefore may be no sensation at all: instead, it may be an alteration induced by motor activity in the processing of visual sensations. What remains of sensation when the visual input is removed may well be no more than the rather unobtrusive input that derives from receptors in the extraocular muscles (266).

"Corollary discharge" (270) and "efference copy" (136, 137) are two terms often used in current discussions of sensations of innervation (73, 104, 188, 189, 283). Some of the considerations outlined above also apply to these terms. Both terms arose in explanations of the results of experiments on

lower animals that showed that surgically rotating the eye (fish) or the head (insects) would cause the animal to perform repeated circling movements. Thus, Sperry (270) supposed that "any excitation pattern that normally results in a movement that will cause a displacement of the visual image on the retina may have a corollary discharge into the visual centres to compensate for the displacement." Von Holst (136) talked of the subtractive interaction between an "efference copy" and a returning afferent ("reafferent") signal and suggested that "when the reafference is too small or . . . too great . . . the difference can either influence the movement itself, or for instance, ascend to a higher centre and produce a perception." In neither formulation was it necessary for the centrifugal signal itself to produce a perception. Of course, by their operation on afferent signals, efferent signals could *influence* perception; just such an interaction could serve to remove certain ambiguities of muscle spindle discharges before allowing them access to consciousness, as suggested in section II*F*. In the experiments of Sperry and of von Holst, however, no influence on perception was necessary nor was it shown. The behavioral changes occurring in those experiments may well have resulted simply from alteration of the sign of some stabilizing visuomotor reflex.

B. Sensations of Movement

For the voluntary contractions of muscles other than eye muscles, three reasons have been advanced to support the proposition that sensations of innervation manifest themselves as sensations of movement. First is the phenomenon of the "phantom limb," an illusion experienced by amputees that the amputated part still exists and can change its perceived position in space in response to motor commands dispatched to it; second is the ability of animals and man to recover control of complex movements after deafferentation of a part; and third is the claim that human subjects perceive that they successfully execute movements during periods of anesthesia of the moving joints and skin, even when such movements are mechanically obstructed (208). All these claims are reviewed here, with the conclusion that sensations of movement are not generated by centrifugal mechanisms.

A natural phantom limb occurs in more than 95% of cases of amputation (129). Experimental phantoms can also be produced by complete block of the brachial plexus by local anesthetic, after which they appear within 30 min (206). Either form of phantom is associated with a mild tingling sensation and is strongly perceived as having a position in space (129, 206, 242). More distal parts of the limb are more strongly perceived, so that the intensity of sensation referred to them is roughly proportional to the central representation of the part in either the somatosensory or motor cortex (232). Lesions of the postcentral cortex have been reported to be associated with abolition of natural phantoms (125, 275).

Of great importance in a consideration of sensations of innervation is the fact that phantom limbs commonly can be perceived to move in response to motor commands dispatched to them (15, 107, 129, 206, 242). Unfortunately,

however, many reports of this phenomenon fail to make clear whether the movements that were perceived involved alterations of the relative positions of parts *within* the phantom. If the part of the body bearing the stump of the phantom limb is moved, then the phantom limb always moves too, even if in doing so it must pass "through" some solid obstacle. Such a movement of the phantom, however, is irrelevant to any debate about sensations of innervation, for the phantom is merely required to maintain its fixed position on a mobile stump, and this requires no change in the neural representation of the phantom and so no new signals related to it.

More relevant here are reports of movements of phantom joints—movements that alter the relative positions of parts within the phantom (15, 129, 206, 242). Typically, movements of this type are more difficult to make, are limited in range, and cannot be finely graded. They are commonly associated with gross twitching of the muscles in the stump (15, 129, 242). The most extensive study of phantom limbs was that reported in 1948 by Henderson and Smyth (129) in which some 300 cases of phantom limb were investigated in great detail in a prisoner-of-war camp. They found that internal movements of the phantom were always associated with contraction of muscles in the stump and that when this contraction could be abolished, as by cutting the nerves in the stump, then the ability to make internal movements with the phantom was lost. Similarly, in the experimentally produced phantoms, "the total loss of voluntary movement of the phantom limb was reported at about the same time that EMG activity no longer appeared on the records" (206). Henderson and Smyth (129) concluded from their studies that "appreciation of willed movement depends on afferent impulses from muscles which normally move the part." Moreover, a strong argument against the participation of sensations of innervation in movements of a phantom limb is provided by the absence of such perceived movements when all muscular activity is abolished.

The existence of phantom limbs and their static position in space, however, do not depend on sensory input. This is shown by their persistence after denervation of the stump or after nerve block. It therefore follows that a sense of position can be generated by nervous activity that presumably is wholly internal to the central nervous system (100, 116). This static, persisting phantom shrinks and fades over the years, but sometimes can be suddenly restored by appropriate stimulation of peripheral nerves. Thus, the findings of Weir-Mitchell were quoted in 1888 by Bastian (15): "In a case of amputation at the shoulder joint, in which all consciousness of the limb had long since vanished, I suddenly faradised the brachial plexus, when the patient said at once, 'My hand is there again. It is all bent up and hurts me'."

Despite some early experimental failures to retrain purposive movements after deafferentation of a limb by cutting the dorsal spinal roots (169, 217, 286), it is now generally agreed that good recovery of voluntary movements can follow such procedures in experimental animals (20, 67, 282) and in man (79, 224; see also 168). Retraining of the movements under vision is very important for recovery and, in animal experiments, normally innervated structures must be prevented from being used during retraining as

substitutes for the denervated part, which otherwise will simply be neglected. That such recovery is possible suggests that the integration and grading of complex movements can occur in the absence of afferent kinesthetic sensations. Nevertheless, the possibility cannot be excluded that some information may be gained by afferent fibers traveling in the ventral roots (54, 55).

If complex, graded movements are possible without afferent feedback from the moving part, a strong case can be made that the grading is performed by reference to perceived sensations of innervation. There is no need to suppose, however, that such sensations are perceived as movements. It is argued below (sect. IV*C*) that sensations of achieved muscular *force* can be sensations of innervation. It may well be that retraining after deafferentation depends on an association of perceived commands for muscular force with the visually observed movements that result from those commands.

Part of the evidence claimed to demonstrate the failure of muscle receptors to influence consciousness came from an experiment by Merton (208) on thumb flexion performed during local anesthesia of the skin and joints of the thumb. It was reported that movements made by the anesthetized thumb could be made "with much the same accuracy" as before anesthesia and, importantly, "if the movement is restrained by holding the thumb, the subject believes he has made it just the same." A later account of the same experiment, however, was less positive: "if the subject attempts to flex his thumb, he cannot tell whether he has been successful, or whether the experimenter has prevented it from moving" (210). When the experiment was repeated by Goodwin, McCloskey, Matthews (104), a different result was obtained: "subjects could readily detect for both the fingers and the thumb when the course of a large movement was manually obstructed by an experimenter." The magnitude of the movements tested may well have been of crucial importance. During cutaneous and joint anesthesia, muscle sense is blunted considerably (see sect. II, *D* and *F*) and subjects making small voluntary movements are barely aware that they are succeeding in doing so even when the movements are unobstructed. This situation therefore is like the one that usually exists for finer movements. It is a common experience of anyone who works with a microscope that fine movements can be executed and graded, which can be sensed only by visual and not by kinesthetic means (see also 208, 261). Possibly, therefore, the earlier report of the inability of subjects to detect obstruction to movements of the thumb depended on the movements then tested being rather smaller [apparently about 20° (209)]. If those movements had been so small as to have been undetectable by the prevailing, blunted muscle sense, they may have been trained under vision but not kinesthetically perceived as movements either when they were properly executed or when they were obstructed: they were simply *assumed* to have occurred in response to the usual motor commands.

The most direct approach to the question of sensations of innervation as sensations of movement is simply to paralyze a part, have the subject attempt to move it, and ask whether it is perceived to move. The answer to this simple question is that there is no perception of movement (104, 170, 201,

206). This is so whether anesthesia of the paralyzed part is a consequence of the experimental procedure (104, 170, 206) or not (201). It also is true for situations in which cutaneous stimuli consistent with a successfully achieved movement are presented at the time the movement of the paralyzed part is attempted (201).

It is not necessary to rely on subjective reports in such experiments in reaching these conclusions: if a subject is asked to make repeated attempts to move while paralysis is developing, he can be asked to mimic the perceived movement by using the corresponding, but unaffected, muscles on the other side of the body. When paralysis is produced in the absence of local anesthesia, as when neuromuscular blockade is achieved regionally in one arm, movements made by the affected hand are accurately perceived and mimicked by the unaffected side: when movement is abolished on the affected side, so too is the perception that it causes, and the unaffected opposite hand indicates that this is so by not moving (201). When, however, both paralysis and anesthesia are produced in a forearm and hand, as occurs during the ischemia produced by arterial occlusion, a subject regularly underestimates the extent of movements achieved on the affected side. Such a case is illustrated in Figure 3. In this latter form of experiment, when paralysis is nearly complete, movements can be achieved that are not perceived at all. This brief period in which movements can be made but not perceived has been used extensively in a series of interesting psychophysical studies on motor control (171–175). The perceptions of movement occurring early in such an experiment must come from afferent discharges in the weakening limb, and presumably the subject underestimates their extent later because the afferent fibers are paralyzed slightly in advance of the motor fibers (104, 170). These experiments on paralysis, whether local anesthesia is also caused or not, indicate that motor commands do not give sensations of movement.

One further point of interest illustrated in Figure 3 is the performance of a subject deprived of joint and cutaneous sensation, but with intact muscle innervation. This state is achieved when only the hand is made ischemic instead of the whole arm (Fig. 3, *right*). Typically, movements made are perceived but their extent is underestimated, a fact attributable to the blunted state of the muscle sense in this state. As discussed above, still smaller movements may be made but not perceived at all, even when the sensory nerves of muscle are intact.

C. Sensations of Force or Heaviness

A sensation of heaviness accompanies muscular weakness. For example, it is a common experience that a weight feels heavier than normal when lifted or supported by a muscle that has been fatigued by prolonged weight bearing: this has been confirmed objectively by having subjects match weights lifted by a fatigued muscle on one side with weights similarly lifted on the unaffected side (200).

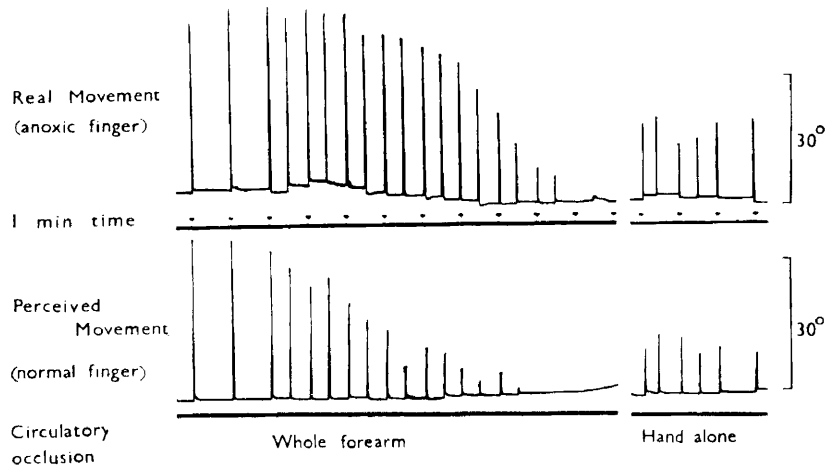

FIG. 3. Records demonstrating that on progressive paralysis of a limb the perception of movement may be more severely impaired than the actual ability to move, making it unlikely that perception of movement can depend primarily on sensations of innervation. Top trace shows movements at the metacarpophalangeal joint of the index finger of 1 hand at a time when circulation to the arm was occluded; interphalangeal joints were fixed in full extension by strapping. Periodically, the subject was asked to raise his finger to full extension and then to lower it again; inbetween the finger lay partly flexed under the action of gravity. Immediately afterward he was asked to make an equivalent movement with the index finger of his other hand, thus providing an objective measure of his perception of the extent of the movement that was being paralyzed. *Left*: circulation to the whole of the forearm and hand was occluded by a pressure cuff above the elbow, which eventually led to complete paralysis of all the muscles involved and to complete loss of sensation. Even when paralyzed the subject still continued to attempt the movement at half-minute intervals. *Right*: pressure cuff had been shifted to the wrist so that the hand remained anesthetized, but the muscles of the forearm had been able to recover. Upper cuff was inflated for 13 min before the beginning of the records shown. There was an interval of 14 min between the left and right sets of records. Recordings were made by connecting the fingers to freely moving potentiometers. Subject could not see either his hands or the recordings. [From Goodwin, McCloskey, and Matthews (104).]

In considering why such increases in perceived heaviness occur it is difficult to propose a mechanism that depends on altered afferent discharges because it is likely that the sensory receptors in the skin, tendons, joints, and muscles of the contracting part would continue to provide signals of the true pressures and tensions involved. An exception might be the muscle spindles because, when a centrally generated effort increases (as it must, to maintain tension in a fatigued or otherwise weakened muscle), the fusimotor drive could also be expected to increase, with a resultant increase in the activity of muscle spindles (see sect. II*C*). As Granit (109) has observed, "the periphery itself is 'corollarized' by alpha-gamma linkage." That such increases in spindle activity might form the basis of the perceived increases in heaviness can be discounted, however, on the basis of experiments with muscle vibration. As discussed above (sect. II*F*), vibration is a powerful stimulus for muscle spindles. Hagbarth and Eklund (117) were the first to report that "a subject gets a feeling of relief or lessening of tension," not a feeling of heaviness or increased force, as a muscle involuntarily contracts in response

to vibration. In an objective test, subjects were asked to exert a set isometric force with the aid of visual feedback using the elbow flexors of one side and to match the perceived force exerted with an isometric contraction of the elbow flexors of the other side. No visual feedback of achieved force was given on the "indicator" side. During vibration of the tendon of the contracting elbow flexor biceps, on the reference side, subjects chose *smaller* rather than *larger* matching tensions on the indicator side than they had during control trials (200). These findings indicate that judgments of heaviness or achieved force are not made on the basis of muscle spindle activity.

Discharges from Golgi tendon organs should continue to indicate true intramuscular tensions in circumstances where increased centrally generated efforts are required. Therefore, there is no reason to suppose that the discharges from Golgi tendon organs form the basis of the overestimates of achieved muscular force in these circumstances. Any vibration-induced discharges in Golgi tendon organs (41) in the experiments just described should have led to *overestimation* of achieved force had they been attended to—but *underestimates* of force were made.

Although it is difficult to account in terms of altered afferent input for the apparent increase in heaviness occurring in fatigue and other states of muscular weakness (see below), the magnitude of the centrally generated motor command would be related to the perceived force in these cases. Thus, Wundt (308) noted that: "A patient whose arm or leg is half paralyzed, so that he can only move the limb with great effort, has a distinct feeling of this effort: the limb seems to him heavier than before, appearing as if weighted with lead; he has, therefore, a sense of more work effected than formerly, and yet the effected work is the same or even less. Only he must, to get even this effect, exert a stronger innervation, a stronger motor impulse, than formerly." A sensation of innervation in the form of a sense of muscular force or effort must be considered. Of course, once such a sensation is suggested there is a danger of reopening the rather barren philosophical debate pursued so vigorously last century. Therefore, whether a sense of muscular force or effort is a "sensation of innervation," a "sense of effort," a "felt will," or whatever is not the concern of this review. What is discussed here is the objective evidence concerning our consciousness of the motor force we command. That it may be no more than simply "knowing what we are doing" (131)—or at least trying to do—may make it no more palatable philosophically than if it is left as a "sensation of innervation."

Several conditions have been studied in which the normal relations between centrally generated motor commands and the muscular contractions they evoke have been disturbed. The experiments usually have involved asking a subject to lift a reference weight or exert a reference tension with a muscle group on one side and to match the apparent weight or force involved by choosing a similar weight, or by exerting an apparently similar force, with the corresponding muscle group on the other side. The matching weights or tensions chosen give an objective indication of the perceived heaviness or force on the reference side. Thus, when some disturbance exists

or is introduced that alters the relation between motor command and muscular force on the reference side, the perceived muscular force involved is indicated by the match made with the other side. When a muscle on one side is weakened by fatigue (85, 199) or by partial paralysis caused by regional use of a neuromuscular blocking agent such as curare or decamethonium (86–88), weights lifted by that muscle feel heavier than normal and isometric forces exerted by it feel greater than normal. If, instead of weakening a muscle locally, the muscle spindles in its antagonist are stimulated by vibration, inhibition of the neural pathways mediating the agonist's contraction is caused (105, 199). Such inhibition probably involves inhibition of the motoneurons of the agonist by the spindle afferents of the vibrated antagonist. When a subject exerts an isometric force with a muscle during vibration of its antagonist, he perceives (and indicates by matching) that a greater force is involved than when he achieves exactly the same tension in the absence of vibration (105, 199). In all these experiments subjects behave as if their judgments of heaviness or achieved muscular force are based on the magnitudes of the motor commands involved in the tasks rather than on the real muscular tensions achieved (Fig. 4).

Neurological lesions provide further evidence. It has been known since

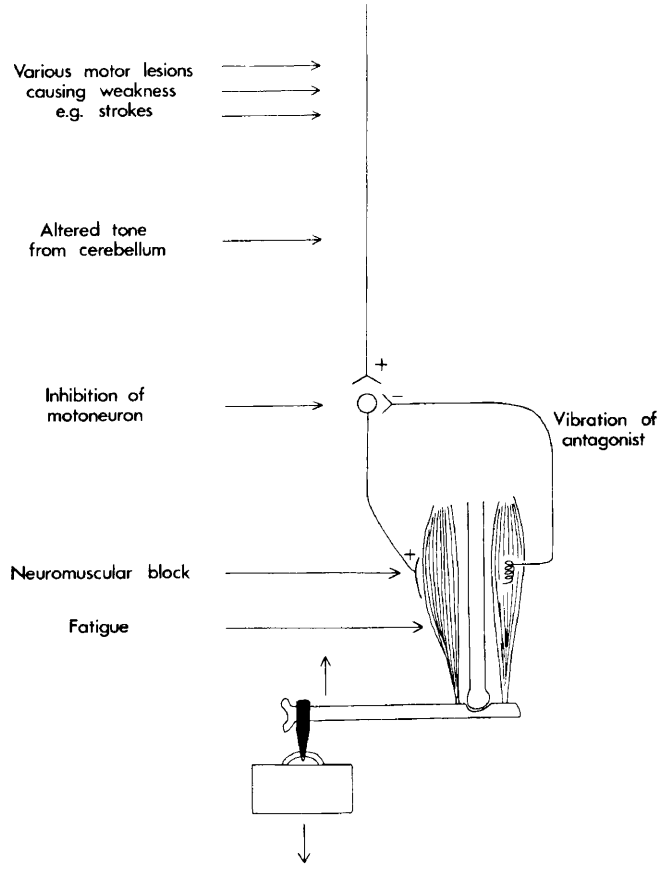

FIG. 4. Factors increasing perceived heaviness or force.

the classical descriptions by Holmes (133, 134) that unilateral cerebellar lesions cause no conventional sensory loss, but are associated with sensations of increased heaviness or weight on the affected side (Fig. 4). As the affected side is "hypotonic" it would require greater than normal motor commands to achieve any given level of muscular force. Holmes clearly saw the association of an increased effort with a sensation of heaviness as a general neurological principle, and wrote: "Every paretic limb exaggerates the load it carries if its sensation be normal" (134).

Similarly, in simple "strokes," where severe weakness or even paralysis occurs on the affected side of the body, a perception of increased heaviness occurs. This is so even when the stroke causes only a motor deficit with no conventional sensory loss (86). Brodal (29), writing of his own motor stroke that produced weakness but not paralysis, mentioned his awareness of the "force of innervation" required to produce muscular contractions. Again a relation between the magnitude of motor commands and the perception of heaviness is revealed (Fig. 4).

The motor commands providing the signals that are perceived as heaviness or force are "upstream" of the spinal motoneurons. The results obtained with vibration, and the neurological cases, indicate this. Vibration of the contracting agonist "assists" a contraction and reduces the perceived force involved. Vibration of the antagonist of a contracting muscle "inhibits" the contraction and increases the perceived force. Yet, in each case, the total motoneuronal discharge at any given level of muscular tension would be the same—it would be the command signals arising "upstream" that change. Similarly, in the neurological conditions discussed, the total discharge of spinal motoneurons required for any given level of contraction would not be altered—only "upstream" command signals.

Because simple strokes involve interruption of corticofugal motor pathways, it might be thought that the changing command signals responsible for the perceptions of increased heaviness arise "upstream" even of the affected cortical cells. This need not be so, however, in cases of *partial* interruption of corticofugal projections, since the uninterrupted pathways could then be expected to carry extra neural traffic to compensate for the loss, and this heavier traffic might provide the perceived signals of heaviness or force. Therefore, strokes in which *total* paralysis occurs are of great interest. In at least some such cases there may be complete, or nearly complete, interruption of the relevant corticofugal pathways so that an absence of sensations of heaviness here could be most significant. For this reason the following account by Ernst Mach of his own motor stroke, published in 1886 in *The Analysis of Sensations* (187) is most interesting:

> I was in a railway train, when I suddenly observed, with no consciousness of anything else being wrong, that my right arm and leg were paralysed; the paralysis was intermittent, so that from time to time I was able to move again in an apparently normal way. After some hours it became continuous and permanent, and there also set in an affection of the right facial muscle, which prevented me from speaking except in a low tone and with some difficulty. I can only describe my

> condition during the period of complete paralysis by saying that when I formed the intention of moving my limbs I felt no effort, but that it was absolutely impossible for me to bring my will to the point of executing the movement. On the other hand, during the phases of imperfect paralysis, and during the period of convalescence, my arm and leg seemed to me enormous burdens which I could only lift with the greatest effort. . . . The paralysed limbs retained their sensibility completely . . . and thus I was enabled to be aware of their position and of their passive movements.

This finding of absent heaviness during complete paralysis, but increased heaviness during subsequent recovery, has been confirmed in two further patients in a brief preliminary study (S. C. Gandevia, unpublished observations). In view of the arguments outlined above, this question deserves further study, for the findings presented suggest a corticofugal origin of the sense of heaviness. Certainly, when complete paralysis is caused peripherally, by nerve block (104, 206) or by use of a neuromuscular blocking drug (201), the perception of a large effort accompanying attempts to move persists.

One further piece of evidence that suggests that the motor signals for heaviness are provided at a relatively low level comes from studies on patients in whom the cerebral hemispheres are disconnected surgically. In such patients Gandevia (82) has found that weights can be matched by lifting with corresponding muscles on opposite sides of the body and that, if a muscle on one side is fatigued by a period of prolonged weight bearing, the matching weight chosen by the unaffected side is larger than before. Thus, the signals of heaviness cross the midline even when the corpus callosum is divided, although heaviness still seems to depend on the size of the motor command.

An objection to the idea that sensations of muscular force or heaviness come from centrifugal motor signals was suggested in 1876 by Ferrier (77). He proposed that the perceived sensations arise instead from afferent signals set up by activity of other muscles, such as the respiratory muscles, which are called into graded contraction at the time of the effort. Indeed, for James (147) this consideration seemed to "prove conclusively" that sensations of innervation do not exist. Similar proposals have been considered (e.g., 20, 282) to explain how graded movements can be retrained after deafferentation. It is difficult to see how such a mechanism could form the basis of judgments made in the many tasks described above where comparisons are made between muscular forces exerted simultaneously by muscle groups on each side of the body. A decisive answer to the objection cannot yet be given, however. Perhaps it would come from an experiment in which a subject is totally paralyzed *except* for, say, both arms (perhaps protected from systemic curarization with cuffs), which then could be used to perform weight-matching tasks before and after weakening of one arm. The appeal of such an experiment must be related to the cogency seen in Ferrier's objection.

If motor command signals give rise to the perception of muscular force there is a problem, not yet considered, concerning the use of this capacity in judgments of heaviness. In a judgment of heaviness there must be not only a signal of the force exerted (or the tension achieved), but some indication that

the force is successful in lifting or supporting the object whose heaviness is being assessed. If an object is not lifted or supported by a muscular exertion one cannot say *how* heavy the object is—just that it is heavier than another object that the same exertion *will* lift or support. Similarly, one cannot discriminate between the heaviness of two objects when neither one can be lifted or supported by muscular effort. The nature of peripheral signals necessary to judge heaviness by indicating which motor command is successful in lifting or supporting an object has been studied recently (85). Blindfolded subjects matched weights lifted by flexion of the terminal joint of the thumb on each side during local anesthesia of the thumbs, but on some trials the weight on one side was rapidly unloaded as soon as the subject started to move it, so that he had little or no opportunity to "carry" it. Nevertheless, it was matched as accurately by the other side, which continued to lift and "carry" weights as normal, as it had been in control trials. Also, when fatigue was produced by a period of weight bearing in the muscles on the side that could be rapidly unloaded, weights larger than control were chosen as matches. It therefore appears that a very crude peripheral signal is sufficient to indicate which level of motor command is successful in a lift. In the experiments described the signal probably arose from receptors in the lifting muscle. It is as if the peripheral signal is simply an "event marker" to indicate to the central nervous system the point in a ramp of centrally generated command at which the command has succeeded.

That a peripheral signal is necessary for the interpretation of motor command signals in the assessment of heaviness is shown by the experience of subjects deprived of afferent signals—that is, of signals of success of a particular motor command. Even if a weight is actually moved by such subjects in response to a command, failure to perceive the movement means that the command seems to have failed, and so the weight appears heavy. Thus, the personal experience recounted by Granit (109) is typical: "During recovery from a spinal anaesthetic I myself ordered one of my legs, stretched out in bed, to be lifted. It felt dead and heavy and I was utterly unaware of the fact that it actually did move, until my toes bumped against the blanket and I had a dull feeling of something like a thud." Granit quoted this experience as evidence against the existence of sensations of innervation, although he was quite clearly considering only sensations of movement in his argument.

In no way does the demonstration that a sensation of muscular force or heaviness is dependent on motor command signals conflict with the demonstration that there are alternative afferent signals of intramuscular tension. The evidence for such afferent signals was reviewed above (sect. II*F*). Despite this, almost all normal subjects appear to neglect any alternative signals in favor of the centrifugal commands in their judgments of force and heaviness, even when this choice leads to error. Nevertheless, occasional subjects consistently prefer signals of true muscular tension—which presumably are afferent—to the centrifugal command (86, 200). All subjects, however, can pay attention to either the centrifugal motor command or to the achieved

muscular tension and can adjust either one when the relation between them is disturbed (88, 200, 244). This is illustrated in Figure 5, which shows a subject's ability to maintain either perceived motor command or intramuscular tension when the relation between them was disturbed by vibration of the contracting agonist or of its antagonist (200).

As subjects can perceive and act on signals of true intramuscular tension, one must be careful to ensure that they are not specifically instructed to do this when one is hoping to observe sensations dependent on motor commands. Subjects prefer the latter signal and so it is usually sufficient only to ask them to "make forces (or heaviness) the same" in matching tasks of the type described above, without being specific about the exact way they are to be made the same: they then choose to be guided by the motor command signal (83, 86–88, 200). Where experiments have failed to demonstrate dependence on command signals in such judgments, the subjects have been instructed (244), or for some other reason have chosen (43), to base their judgments on signals of actual intramuscular tension.

Because the perception of the heaviness of a lifted object derives from the centrally generated voluntary motor command used in lifting the object, it follows that the central motor command delivered to the motoneurons can itself be studied through observations on perceived heaviness (83, 87, 88). Pursuing this idea in further series of weight-matching tasks with the use of similar muscle groups on opposite sides of the body, it was found that afferent inputs from peripheral regions can interact with various motor commands. Thus, a weight lifted by flexion of the terminal joint of the thumb feels heavier than normal when the skin and joint of the thumb are locally anesthetized (87, 190, 192). It follows that a motor command greater than normal is required to achieve the lift in this state, presumably because some facilitatory effect from the skin or joints of the thumb has been removed. It is

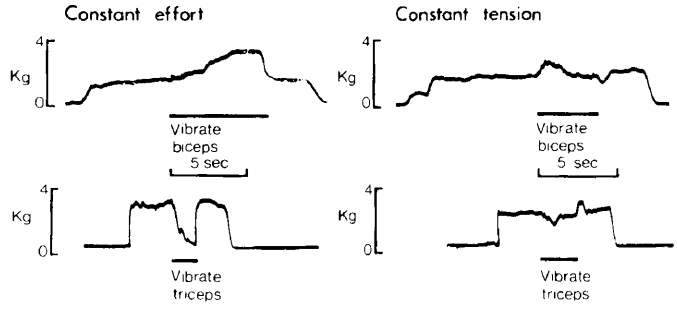

FIG. 5. Demonstration of ability to adjust perceived motor command and muscular tension independently. Subject exerted a force against a strain gauge by contracting his biceps brachialis muscles: the wrist through which he exerted the force, and the tip of his supporting elbow, were anesthetized, and vision was excluded. He was asked to keep either his effort (traces at left) or the tension he exerted (traces at right) constant. Vibration at 100 Hz of the contracting muscle or of its antagonist (triceps) was applied where shown. Records of tension achieved show that vibration led to considerable changes when the subject was asked to keep his effort constant. When asked to keep tension constant, he was able to adjust his effort to do so. [From McCloskey, Ebeling, and Goodwin (200).]

not necessary to anesthetize the thumb to produce this effect, for anesthetization of the adjacent index finger has a similar, although smaller, effect on commands delivered to the thumb flexor. Electrical stimulation of the index finger, giving a pressing or tingling sensation but no pain, has the opposite effect on motor commands to the thumb flexor—it facilitates them. Similar effects from sensory receptors in the thumb can be demonstrated on the commands to the flexors of the index finger (87). The flexors of the index finger and thumb are frequently used together in a total cooperative motor performance, the highly evolved "precision grip" of man. The experiments described above indicate that this total motor performance receives facilitation from the whole of the sensory field involved in the total performance. A similar phenomenon has been demonstrated for the flexors of the elbow and their peripheral sensory field in the hand (83). For the cooperative movements of the thumb and index finger, only flexion movements appear to receive facilitation from the sensory field involved. Anesthetization of the thumb causes weights lifted by thumb *extension* to feel lighter, implying a smaller motor command to the extensor in this state. Presumably, for extension, the peripheral sensory inputs provide an inhibitory tonic influence on the motor commands (87).

V. PERFORMANCES REQUIRING KINESTHETIC SENSIBILITY

The ability to detect displacement of a joint, the ability to direct a limb to a given point, and the ability consciously to control and grade muscular movements and forces in the absence of vision depend on kinesthetic sensibility. Some of these abilities have been considered in the preceding discussions of the various components of kinesthetic sensibility. However, they are not always tested in terms of their component parts, and they certainly are not used in such a way that their components can contribute only one at a time, so it is appropriate to consider some combined kinesthetic performances further. Where such combinations have already been discussed, as in the combination of joint-plus-cutaneous sense with muscle sense to provide position and movement sense (sect. II, *E* and *F*), or in the combination of the centrally generated sense of force with afferent inputs to provide a sensation of heaviness (sect. IV*C*), they are not mentioned further. Nor is it possible or appropriate in this review to consider many of the more complex psychophysical aspects of kinesthesia (141, 283).

A. Detection of Joint Displacement

Clearly, the appreciation of movement or of altered position must depend on afferent inputs.

The traditional experimental approach has been to impose movements of constant angular velocity on a joint and to ask the subject to indicate in some way when he is confident that a movement has occurred. The subject usually

is required to relax muscular tension, and implicit in this requirement is the assumption that muscular tension will aid detections. Often the subject also is required to nominate the direction of the detected movement. This method was introduced by Goldsheider (99) and has been adopted as the sole test of kinesthetic sensibility in most neurological examinations. In the clinical situation the magnitude of displacement prior to detection is judged against the performance on the opposite side of the body (when that is normal) or against the examiner's clinical experience of normality. In the experimental situation the results are given as the detection threshold, which is the angular displacement occurring prior to detection.

Goldsheider (99) showed that the detection thresholds for proximal joints are much lower than for distal joints, but the lowest thresholds were obtained on occasions when the subject could not state the direction of the detected movements. In such circumstances it is likely that the detections were based on the discharges of relatively nonspecific phasic receptors. The data presented by Laidlaw and Hamilton (163, 164), who used similar testing procedures but required their subjects to indicate the direction of detected movements, showed no consistent differences between proximal and distal joints. Also, corresponding joints on opposite sides of the body were found to have similar thresholds, and no difference was found between movements into flexion or extension. It was noted that "the ability to determine whether the movement that is felt is in one of two directions appears to be a separate factor, for the movement is apperceived before one can decide in which direction it is" (164). This is borne out by the finding that in certain cases of cerebral cortical damage patients can be aware of imposed movements long before they know their direction or can detect the altered position to which they lead (18, 125).

Only when an awareness of both movement and its direction is required of a subject can tests of detection of movement be regarded as specific for kinesthetic mechanisms. In such tests the thresholds for the same joint reported by various workers vary considerably (52, 99, 163, 164). This variability probably depends on whether or not subjects were given a warning signal immediately before each displacement and on the different methods of supporting and counterbalancing the tested joints.

Even if Goldsheider's (99) claim of greater sensitivity of proximal joints could be borne out this need not imply a greater concern of the central nervous system for proximal rather than distal joints. Distal joints are more strongly perceived in phantom limbs (129) and are more severely affected by cortical lesions (124, 135), and so appear to have an importance related to the area of cortical representation of the body parts (232).

As every position is arrived at through a movement and every movement causes a change in position, it is difficult to devise a test of static position sense in which movement could not be implicated. In the tests described above the detections were of movements rather than of discrete positions, and increasing the velocity of displacement lowered the threshold for detection (35, 52, 84, 99). In a recent study, however, Horch, Clark, and Burgess

(138) made a definite attempt to have subjects judge and match different static positions. The subjects relaxed their muscles and the knee joint was displaced through 3–4° at an angular velocity of less than 1°/min, which is below the threshold for movement detection found in any of the studies reported above. The subjects reported no perceived movements. Nevertheless, they could detect the altered position and could direct an experimenter moving the other leg to a correct matching position. It also was found that sensations associated with maintained indentation of the skin fade in a shorter time than it took to make the slow displacements, so that it seems unlikely that cutaneous receptors were responsible for the awareness of knee position. This was borne out in a later study in which performance was unaffected by cutaneous anesthesia or intra-articular injection of local anesthetic, permitting the conclusion that inputs from muscle receptors were sufficient to account for it (F. J. Clark, personal communication).

To some extent position and movement are signaled or processed separately and evidence has been reported indicating that, at least for sensations based on the discharges of muscle receptors, movement and altered position can be perceived separately 63, 104, 197; see sect. II*F*).

B. Ability to Direct a Limb to a Given Point

In analyzing the ability to direct a limb to a given point in the absence of vision several factors must be considered. The method by which the subject originally locates his target is clearly important, for any errors in the locating mechanism will be compounded with those of the kinesthetic systems (and perhaps motor systems; see below) used in attempting to direct a limb to it. If different sensory systems are used in locating the target and guiding the limb to it, the internal neural calibrations of these systems are also important, particularly the internal alignments of such calibrations. ("Internal neural calibrations" are taken here to mean simply the internal neural schemas or gauges against which signals are translated into perceptions of joint position, velocity of movement, or direction of visual axis.) The subject's ability to remember the location of a target also will require consideration, especially when some time elapses between locating the target and directing a limb to it.

It is unlikely that the fineness of motor control is a limiting factor in directing a limb to a given point. Normal subjects can execute finer movements under visual guidance than they can detect kinesthetically (see sect. IV*B*). Furthermore, observations on patients with various neurological deficits support the idea that limitations of performance in directing a limb are imposed by sensory rather than motor disturbances. Thus, Head (124) wrote: "Whenever the faculty of recognising posture is disturbed by a lesion of the brain, the patient experiences greater difficulty in finding the affected limb with the normal hand than vice versa" (see also 125).

If a blindfolded subject points to an object, lowers his arm, and then attempts to point again to the same place with the same arm, the mean

errors made are about 2.5° at the shoulder joint (57). Bearing in mind that the errors consist of the errors of initial positioning as well as those of the succeeding trials, it follows that the true mean accuracy in this test is about 1.3°. This exceeds the threshold for detection and registration of direction of imposed movements at this joint, which Laidlaw and Hamilton (164) reported as about 0.4° (at 0.2°/s), and is closer to the discrete static positions recognized as different in the studies of the knee joint mentioned above (138).

If a subject locates a target visually, pointing is more accurate than when the location is made by a hand that is lowered before pointing again with it (21). Location by a hand that is held extended near the target before pointing again with it permits accuracy that is about equal to that achieved with visual location (207). Least accurate of all is location by one hand and pointing with the other (21). Whether the subject is seated or standing may also be important, as body sway may influence performance (141). In all these tasks not only the kinesthetic sensitivities of the locating and pointing parts are important, but also the delays involved (207).

Another consideration is the strength and retention of the memory of the target position. It has been shown that the ability of subjects to match the angle of a passively positioned knee joint by active positioning of the opposite leg from 15 s to 3 min later is nearly constant and that their ability to match the angle from memory is equally good (138). Thus proprioceptive memory is good.

An important point arising from this last finding is that continuing input from peripheral receptors may seem unnecessary for knowledge of static joint position if signals generated during movement can be accurately perceived and remembered. However, the finding that there is perception of altered position after imperceptible movements indicates that awareness of static joint position *is* provided, at least in part, by continuing inputs (138). Such signals of altered position are not obtained through integration (in a mathematical sense) of signals of velocity (197).

Any errors in directing a limb to a given point are likely to be increased when that target is another part of the body. This is because the task involves the simultaneous use of kinesthetic sensation in the moved limb and the tactile or kinesthetic abilities required to localize the target. Again, errors will be compounded. Nevertheless, the ability is readily assessed and has formed the basis of many tests of proprioceptive sensibility. Most such tests are modeled on that introduced by Slinger and Horsley (269) and involve asking a blindfolded subject to point, say, the two hands to the same location on two scales on opposite sides of a glass plate. Errors are read directly off the surface of the target plate.

Paillard and Brouchon (229) tested the ability of blindfolded subjects to align the index fingers of the outstretched arms by movements at the shoulder joint. They found less error and variability when the subjects actively moved the target arm into position than when it was passively placed there by an experimenter (see also 182). Interestingly, they found that *movement* of the target arm was important for accuracy because, if it was

positioned passively, it then could be actively held in position without improving performance. Once the target arm was positioned the estimates of its position altered gradually with time, so that the indicator arm pointed progressively lower for longer delays between positioning and matching. This decay was more marked after active positioning and, after delays of about 12 s, the systematic errors were the same for both active and passive positioning. Such decays are unlikely to be due to a fading of the memory of the proprioceptive signals or to an adaptation of receptors signaling static position (138). Instead, they are likely to reflect the changing discharges of receptors that are sensitive to active movement. Other studies by the same workers have explored this matter further (230).

Of importance in aligning body parts is the internal neural calibration of position sense that appears to exist for every joint. This calibration is not fixed, but can be modified on the basis of various sensory experiences. An example was given by Harris (122), who described an experiment in which a subject learned to guide one hand to a target viewed through prisms so that its location was apparently shifted laterally. When this ability had been acquired for one hand, however, the subject could not point directly to the target with the other hand, but pointed instead toward its apparent, displaced location (see also 62, 121). Also, when only the first hand had been trained under distorted vision, the subject would err when attempting to place his two unseen hands a known distance apart. The adaptation did not involve simply the learning of a new pattern of movement for the trained hand because it was just as great when the subject pointed at different targets. Instead, it was as if the internal calibration of the position of the trained hand had altered independently of the internal calibration of the opposite hand. Harris concluded that "when proprioception and vision provide conflicting information . . . proprioception gives way," but the generality of this has been strongly contested (141).

A recent finding also bears on the question of internal calibration of position sense. Craske (63) observed that vibration of the muscles operating about the wrist or elbow can cause subjects to perceive that the joint is bent to a position well beyond its maximal normal excursion. As the anatomy of the joints would have precluded the subjects from having any previous experience of such positions, it follows that the central nervous system can extrapolate from its existing internal calibrations to provide such perceptions of impossible limb positions.

C. Kinesthesia during Motor Performances

Training of complex, graded movement is possible after deafferentation (sect. IV*B*), showing that centrifugal mechanisms can provide an adequate sensory basis for learning and execution of such movement. However, no proprioceptive afferent feedback about the progress or outcome of the movement is available and vision is relied on heavily. Mechanical interference with the movement is not detected and cannot be consciously corrected for

(168). Because normal movements are not handicapped in this way, it follows that afferent propioceptive inputs are used in their execution.

Goodwin, McCloskey, and Matthews (104) asked subjects to make slow ramplike movements of flexion and extension of the elbow joint while the kinesthetic input from muscle receptors was disturbed by vibrating the elbow flexor biceps. The subjects were required to move the elbow on the vibrated side voluntarily to track a movement imposed by an experimenter on the other side. During the periods of vibration, the voluntarily moved arm was flexed unduly compared with the target arm, as illustrated in Figure 6. This indicated that the illusory kinesthetic sensations of extension occurring in such circumstances (see sect. II*F*) were perceived and acted on by the subjects during their formulation of the appropriate motor commands required for their task. In this experiment inappropriate kinesthetic signals were acted on, leading to error. However, the experiment demonstrates that continuing reference to kinesthetic afferents is made during relatively slow movements.

Similarly, during sustained muscular contractions there is ample opportunity for kinesthetic afferent inputs to contribute perceived signals on the basis of which the contractions can be modified. This is especially likely to occur when a blindfolded subject is required to support a weight, or even his own outstretched limb, in some fixed posture against gravity. Any deviation from the required posture is then like an imposed movement and would set up kinesthetic afferent signals according to which the force of the muscular contraction could be modified voluntarily. The outstretched limb of a blindfolded subject deprived of kinesthetic afferent feedback slowly sags under the influence of gravity as he attempts to hold it still (168).

Other indications of the dependence of voluntary motor control on perceived kinesthetic afferent inputs are the various constant errors occur-

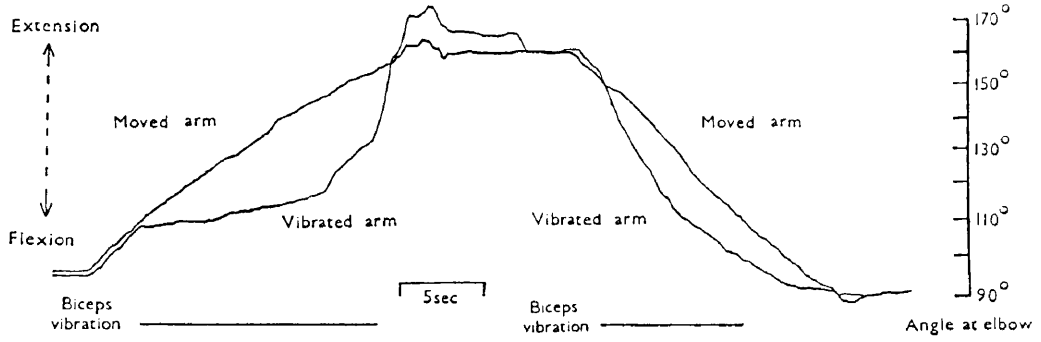

FIG. 6. Effect of vibration applied to an arm that the subject was using to make a voluntary movement. Left arm was moved by the experimenter to provide a reference and the subject was asked to track it with his right arm. During periods indicated, vibration was applied to the biceps of the right arm, which was the one being moved voluntarily. This caused the subject to position the vibrated arm so that it was unduly flexed with regard to the reference arm—that is, so that its vibrated muscle was unduly short. This occurred irrespective of whether the vibrated arm was being moved into flexion or extension, although the effect was more dramatic when the arm was being moved into extension. The arm was moving in the vertical plane with the upper arm lying horizontal, so that the biceps muscle was contracting throughout. [From Goodwin, McCloskey, and Matthews (104).]

ring in the execution of movements that are variously loaded or obstructed while in progress (e.g., 132, 307). These have been recently reviewed by Granit (109).

The postural contractions necessary to permit one to stand upright without swaying may not depend entirely on inputs from the vestibular system: subjects with bilateral vestibular loss can regain their ability to stand upright with their eyes closed (141). Such stability presumably depends on tactile and kinesthetic inputs. Interestingly, these subjects "are just as likely to swim downwards as upwards when submerged in water" (141).

When proprioceptive afferent inputs are disturbed postural stability is impaired. The classical example is the swaying, sometimes to the point of falling, that occurs when patients with tabes dorsalis close their eyes (Romberg's sign). Similarly, when the kinesthetic inputs from postural muscles are altered by vibration in normal subjects whose eyes are closed, the subjects sway and may fall. Thus, vibration of both Achilles tendons causes a subject to sway and even fall backward as if compensating for an apparent stretch of the vibrated muscle (69, 104): the subject, however, is unaware of the movement until the fall is imminent, suggesting that vestibular input is strongly overridden. Indeed, if the subject is simply prevented from swaying backward by an experimenter placing a hand against his back, he perceives that he is being pushed forward (104). These observations indicate that kinesthetic afferent inputs from muscle are important for postural stability. No similar evidence exists for the importance of inputs from joint receptors and it is known that subjects with bilateral total replacement of the hip joint can stand upright with their eyes closed without swaying (104, 114).

All the considerations above apply to slow or sustained muscular contractions in which there is time for conscious adjustments of motor command to be made on the basis of kinesthetic signals. Faster movements—so-called "ballistic" movements—usually are considered to be completed in so short a time that voluntary intervention, whether based on kinesthetic or other afferent inputs, is thought to be impossible. Such movements are those completed in less than a voluntary reaction time, which usually is considered to be 200–250 ms (158), although some suggestions of a considerably shorter time have recently been offered (61, 74, 225, 258). Some modification of rapid movements that are in progress may be possible, however, on the basis of internal centrifugal mechanisms (11). For rapid movements, in particular, the kinesthetic afferent signals available *prior to* a movement are likely to have considerable importance in the framing of appropriate commands.

VI. SUMMARY AND CONCLUSIONS

Movement and *position* of joints are signaled entirely by afferent mechanisms. Each can be perceived independently and, to some extent at least, can be signaled or processed independently. Nevertheless, in most circumstances they are likely to be treated together by the nervous system.

Thresholds for detection and registration of the direction of imposed movements are similar for all joints, although distal joints are more strongly "represented" cortically than proximal ones. There is no reason to believe that actively executed movements are signaled by mechanisms different from those that signal passive movements, although the sensitivities of the sensory mechanisms involved probably are enhanced during voluntary activity. This is especially so for sensations based on intramuscular receptors.

The role of joint receptors in the senses of movement and position is doubtful. Electrophysiological studies of joint receptors indicate that in many joints, especially in the midrange of joint excursion, these receptors cannot give sufficiently detailed information to account for observed proprioceptive acuity. Anesthetization of joints impairs kinesthetic sensation only when accompanied by anesthetization of the overlying skin. Total replacement of joints with prostheses causes only minimal kinesthetic impairment. Possibly joint receptors have greater importance in some joints than in others and at extremes of joint excursion more than in the midrange. Possibly they provide some degree of central facilitation for discharges from intramuscular receptors. However, their positive contribution to kinesthetic sensibility has yet to be demonstrated. Therefore the use of the term "joint sense" for the senses of movement and position is not desirable.

Cutaneous receptors appear to support or facilitate the specific kinesthetic signals from intramuscular and possibly joint receptors. In addition, they may provide specific perceived signals of joint position and movement, particularly in distal joints.

The principal receptors subserving the senses of movement and position are intramuscular receptors, probably the primary and secondary endings of the muscle spindles. Of the evidence advanced over the past 25 years purporting to show that intramuscular receptors have no role in kinesthesia, none now stands unchallenged. Instead, positive evidence exists for a kinesthetic contribution from intramuscular receptors in both limb muscles and extraocular muscles. For joints in the fingers and toes the discharges of intramuscular receptors probably are facilitated centrally by discharges from regional cutaneous and possibly joint receptors. For more proximal joints central facilitation of this kind may be less important.

The demonstration of important contributions by muscle afferents to consciousness in no way diminishes their importance in unconscious reflex motor controls.

"Corollary" or collateral motor signals probably are used centrally for the interpretation of discharges from muscle spindles. These motor signals are not themselves perceived as movements or altered positions, nor are the fusimotor-induced discharges from the spindles perceived. Instead, the motor signals are used centrally to discount fusimotor-induced activity from spindles, leaving only that part of the spindle discharge that is evoked by muscle stretch to reach consciousness.

No sensation of movement or of altered position arises from collateral, corollary, or reentrant motor signals within the central nervous system. This

is so for motor commands involving all limb muscles that have been investigated and is also probably true for commands to extraocular muscles.

There is a sensation of muscular force or effort accompanying centrally generated voluntary motor commands. This sensation is not evoked by the discharges of afferent nerves, but arises within the central nervous system from, or together with, motor commands. It arises rostral to the spinal motoneurons, possibly from corticofugal motor pathways. Most people rely on this sensation of muscular force or effort in judging muscular tensions or the weights of lifted objects, preferring it to any alternative signals that might be available. Some signal must be available, however, to enable one to choose which of a range of motor commands and accompanying sensations of force or effort is appropriate in any particular judgment. In judging heaviness of a lifted object, for example, some signal must be provided to indicate which command is sufficient to lift or support the object.

Despite a normal reliance on sensations of force or effort in judging muscular tensions, normal subjects can perceive afferent signals related to the tensions and pressures generated during muscular contractions. These include afferent signals of tension from intramuscular receptors.

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CARBON DIOXIDE AND THE CAROTID BODY

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I shall consider three questions about carbon dioxide and the carotid body.
1. Does hypercapnia excite chemoreceptors by increasing the rate of release of the hypoxic transmitter?
2. What evidence is there that autoregulation of blood flow can occur in the carotid body, what is the importance of this phenomenon there, and is carbon dioxide involved?
3. In what ways are the responses of the chemoreceptors to suddenly applied hypoxic and hypercapnic stimuli different, and how might any differences be explained?

The arterial chemoreceptors are directly excited by pH and CO_2: the experiments of Eyzaguirre & Koyano (1965) on the superfused preparation show this simply and clearly. These stimuli may well, in addition to their direct effects, have local vasomotor ones within the chemoreceptors and these may be important in producing the complex interaction between hypoxia and hypercapnia (Neil & Joels, 1963), but clearly such effects are not all important.

CHEMORECEPTOR DISCHARGE AND BLOOD PRESSURE

The experiments which Krylov has described at this symposium help to answer the first of my questions in that they show that poisons or cooling will abolish the hypoxic response while leaving that to lactic acid unaffected.

Our approach is derived from that of Neil on the transmitter (Lee, McCloskey & Torrance, 1964). Hypoxic excitation is usually thought of as occurring through an increased rate of release, within the glomus, of an excitatory transmitter which can be washed away in the blood. If hypercapnia acts by increasing the rate of release of this same transmitter, or by making the nerve endings more sensitive to transmitter already present, then hypercapnic discharge should, like hypoxic discharge, be reduced by increasing the rate of blood flow through the carotid body.

Hypoxic discharge is reduced by raising the blood pressure, but hypercapnic discharge is independent of blood pressure (Lee, McCloskey & Torrance, 1964; Fig. 1).

On the argument stated above, this observation shows that hypercapnic discharge is not caused by increasing the rate of release of hypoxic transmitter or by increasing the sensitivity of nerve endings to transmitter already present. This conclusion is however, based on the assumption that altering the blood pressure will always alter the blood flow through the glomus.

The possibility that hypercapnia *does* act through the hypoxic transmitter, and elicits a discharge independent of pressure because, in its presence, flow is independent

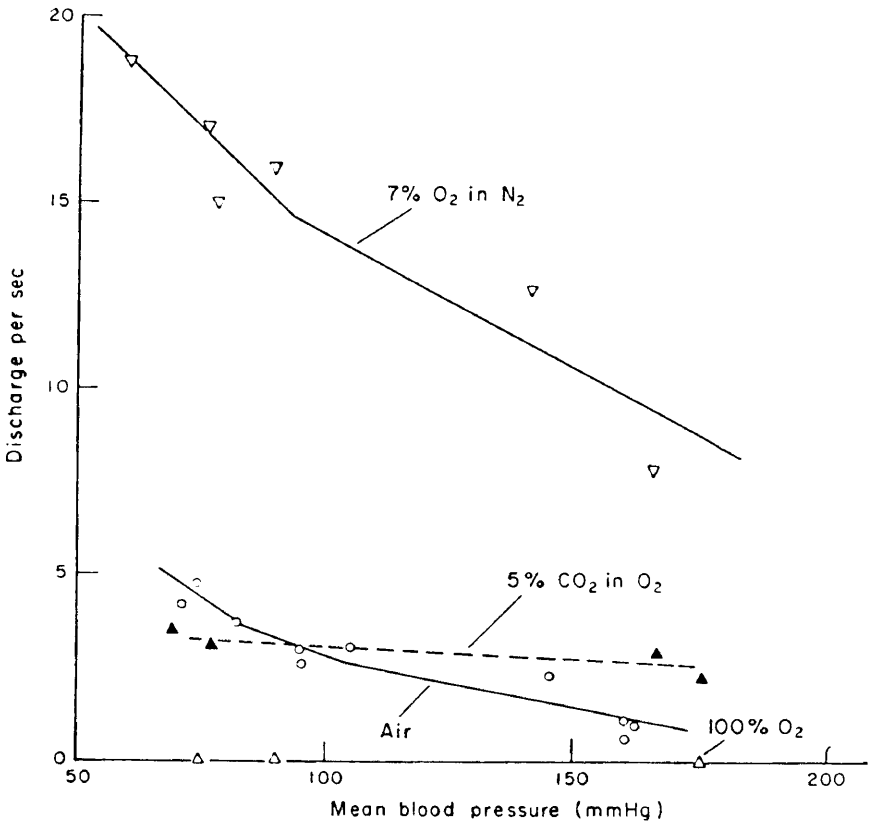

FIG. 1. Cat. Few fibre carotid chemoreceptor preparation. Steady-state discharge is plotted against blood pressure. Animal artificially ventilated with gas mixtures indicated.

of pressure (autoregulation of flow), must be considered, as we have obtained evidence which I will discuss later that CO_2 does sometimes have this effect on the pressure-flow relations of the carotid body. However, this possibility can be rejected for three reasons: (i) hypercapnic discharge is independent of pressure over a very wide range of pressures, about 30–300 mmHg, which far exceeds the range over which autoregulation of flow occurs in the glomus or elsewhere (Johnson, 1964); (ii) there is not even a transient change of hypercapnic discharge when blood pressure is changed abruptly—but as autoregulation of flow is a *response* to changed pressure and takes some time to bring

flow back to its control level, a transient change of discharge would be expected if the hypercapnic discharge were made independent of blood pressure by autoregulation; (iii) the chemoreceptor responses to suddenly applied hypoxic and hypercapnic stimuli are not qualitatively similar as I shall later show, though they would be expected to be if they both acted through the same transmitter.

Thus the original conclusion stands, and it can be said that hypoxia and hypercapnia, as chemoreceptor excitants, converge beyond the release of the hypoxic transmitter.

CAROTID BODY BLOOD FLOW

I now turn to my second question: 'What is the evidence that autoregulation of blood flow occurs, and what is its significance?'

In 1951 de Castro reported that no changes in carotid body blood flow could be observed microscopically in the cat when blood pressure was altered by mechanical means. Daly, Lambertsen & Schweitzer (1954), on the other hand, found an approximately linear relation between blood pressure and venous outflow from the carotid body cats. The fundamental disagreement between these observations is important, not for hypercapnic discharge, which has been shown above to be independent of blood flow, but for hypoxic discharge. If flow is normally independent of blood pressure, so too should be hypoxic discharge; if flow is dependent on blood pressure, so too should be hypoxic discharge.

Carotid body blood flow has been measured in rabbits by observing the rates of inflow of blood under known pressures into a carotid arterial segment from which only vessels to the carotid body drain (McCloskey & Torrance, 1965). All nerves to the carotid body were cut. Flows of the order of magnitude of those reported by Daly *et al* (1954), 2000 ml/100 g/min, were found, and the most common relation between pressure and flow was a linear one. In eight of the thirty-six experiments in which it was possible to measure flow, however, autoregulation of blood flow was observed—that is, over a range of pressures of about 80–150 mmHg, blood flow was independent of blood pressure. In several other experiments flow did not change as much with pressure as might have been expected if a linear pressure-flow relation held—that is, with an increase in pressure, the resistance did increase, but not enough to hold the flow constant.

It is known that autoregulation of flow is usually a most labile phenomenon wherever it is observed (Johnson, 1960, 1964; Hinshaw, 1962; Green & Rapela, 1964), and Johnson (1964) has stated that as such 'it is to be expected that experimental conditions will significantly influence the result'. Just what experimental conditions are required for the demonstration of autoregulation in the carotid body is not known, as is only too obvious from the number of experiments in the rabbit in which no autoregulation was seen. There is, however, reason to believe that a level of carbon

dioxide or acid in the arterial blood, close to the level present during normal breathing, is one condition without which no autoregulation of flow is seen.

In four of the rabbit experiments, autoregulation of flow was observed in animals breathing air spontaneously, but in no experiment was autoregulation observed in an animal artificially hyperventilated with a gas mixture which did not contain CO_2. In one of the spontaneously breathing animals autoregulation of flow was abolished when the animal was hyperventilated with the objective of blowing off CO_2 (Fig. 2).

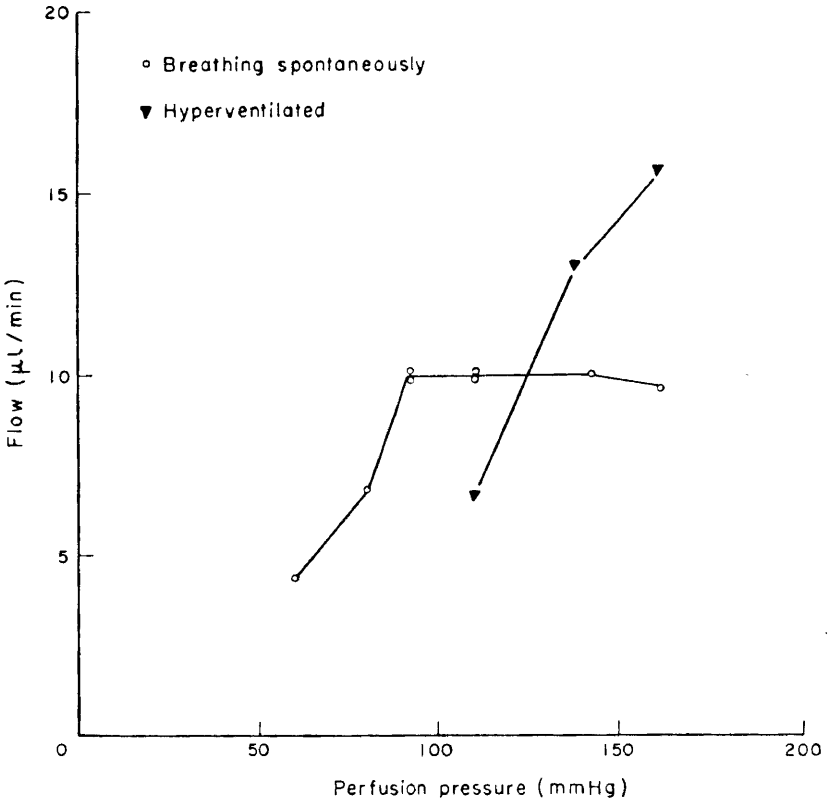

FIG. 2. Rabbit. Carotid body blood flow. Autoregulation of flow (open circles), disappeared when the animal was artificially hyperventilated with air (filled triangles).

In four other experiments autoregulation of flow was not initially present, but appeared when the animals were ventilated with CO_2 rich gas mixtures (Fig. 4). All these observations suggest that carbon dioxide plays a permissive role in the appearance of autoregulation in the carotid body.

Factors other than the level of carbon dioxide in the arterial blood must also be important for the appearance of autoregulation of flow as in many of the rabbit experiments autoregulation was not precipitated by the administration of CO_2. The absence of undue mechanical stress within the glomus is probably one of these, as it has been

possible to destroy autoregulation and replace it with a linear pressure-flow relation by raising the perfusion pressure very high for a short time. Possibly other factors also are involved.

Because autoregulation of flow is characteristically a labile phenomenon, demonstration of it at all experimentally must make one consider the possibility of its being present always in the normal intact animal. When blood flow is independent of blood

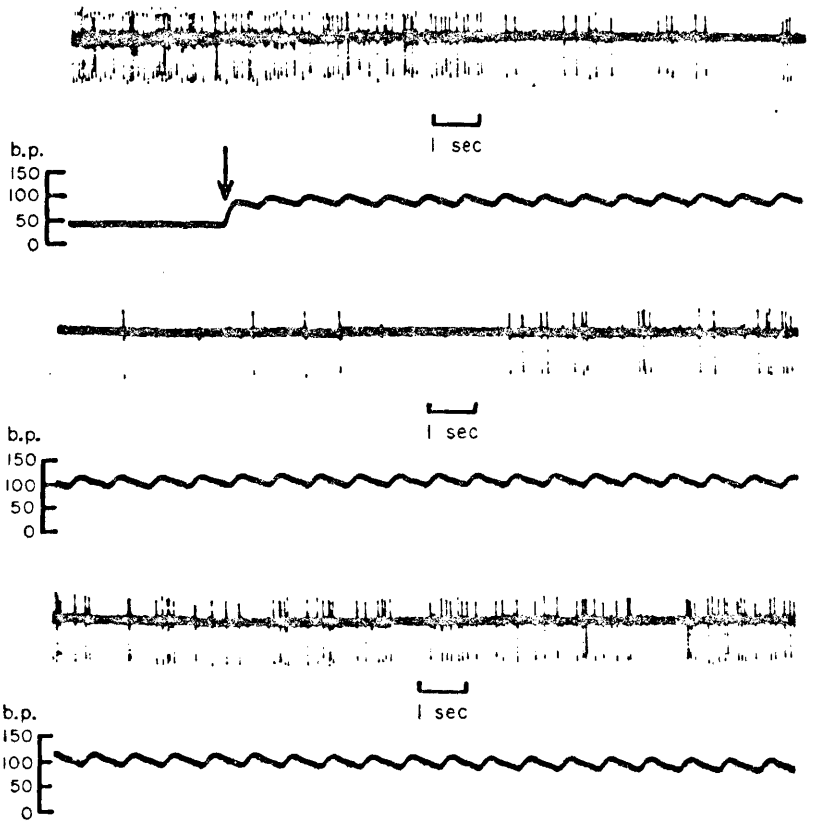

FIG. 3. Cat. Single chemoreceptor fibre. The three panels show one continuous experimental record. Blood pressure records are concurrent with the impulse records above them. At the arrow, a clip on the common carotid artery was removed. Note rapid reduction of discharge followed by recovery. Animal breathing 10 per cent O_2 in N_2.

pressure, so too is chemoreceptor discharge. A carotid body which is sensitive both to the level of hypoxia and to the blood pressure is functionally a receptor which reports inadequacy of oxygen *transport*: a carotid body which is sensitive only to the level of hypoxia, however, is more truly a 'chemoreceptor', being functionally a receptor for oxygen *tension*.

Any results which show a dependence of hypoxic discharge on blood pressure above a pressure of 80–90 mmHg must argue against the presence of autoregulation. Landgren

& Neil (1951), and Lee, Mayou & Torrance (1964) have produced results showing this (see also Fig. 1 of this paper). In all these experiments, however, the experimental animals were artificially ventilated, and in some experiments the carotid bodies had been exposed to very high pressures, so it is possible that autoregulatory activity had been abolished. Samaan & Stella (1935), and Hornbein & Roos (1963) reported that chemoreceptor discharge is independent of pressure 'within the physiological range'. An observation which can be easily explained by postulating autoregulatory activity in the glomus vascular bed is that there is very often a striking adaptation of hypoxic

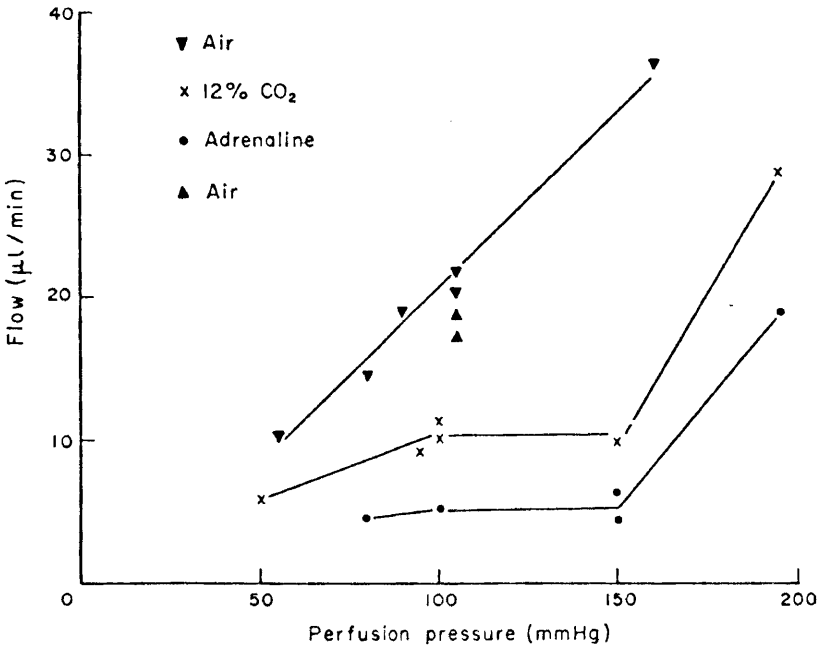

FIG. 4. Rabbit. Carotid body blood flow. Artificial ventilation. The pressure-flow relations were determined in the sequence shown on the figure. Autoregulation of flow occurred when the animal was ventilated with CO_2 in O_2. When adrenaline (20 μg i.v.) was administered with the animal still inspiring CO_2 in O_2, the level of autoregulated flow was lowered.

discharge following a 'step' change of blood pressure. As autoregulation of flow is a response of a vascular bed to a pressure change and takes some time to adjust flow, flow will first increase and then return towards its initial level in response to a pressure increase. In the glomus, such a sequence of changes as this could be expected to cause an initial drop in discharge, followed by a recovery of discharge towards its initial level and such changes have been seen (Fig. 3).

De Castro (1951) suggested that the independence of flow on pressure which he observed was achieved through a reflex mechanism. Although my experiments on the rabbit show that the mechanism is local as the nerves to the rabbit glomus were cut,

it is still possible that neural and hormonal vasomotor effects can play upon a background of autoregulation, protecting it or setting the level at which autoregulation holds flow constant. It is known from the experiments in the rabbit and from the results of Daly *et al* (1954) that sympathetic stimulation and the administration of vasoconstrictor drugs can reduce glomus blood flow. In only one of the rabbit experiments was it possible to give adrenaline into the blood flowing through a glomus exhibiting autoregulation, and in this case the effect of adrenaline was to reset the level at which autoregulation held the flow independent of pressure (Fig. 4).

Floyd & Neil (1952), Lee, Mayou & Torrance (1964) and Biscoe & Purves (1965) have all produced results which show that activation of the sympathetic-adrenal system increases the chemoreceptor discharge at any blood pressure. Thus reflex sympathetic effects can change the sensitivity of the chemoreceptors. Lee *et al* pointed out that such a change in sensitivity may serve only 'to maintain a constant response of the receptors to chemical stimuli in the face of reflex rises in blood pressure'. However, if autoregulation were normally present, the chemoreceptor responses to chemical stimuli would not be changed by changes in blood pressure, and reflex sympathetic effects on the carotid body would invariably increase its sensitivity.

The answers I would give to my second question are: that autoregulation of flow can occur in the carotid body; that carbon dioxide is involved in its appearance; that it is potentially important with regard to the chemoreceptor responses to hypoxia, as it changes the nature of the chemoreceptors as receptors; and that it may provide a background on which the sympathetic-adrenal system works to increase hypoxic sensitivity.

RESPONSES OF THE CHEMORECEPTORS TO SUDDENLY APPLIED STIMULI

My third question is: 'What are the differences between the responses of the chemoreceptors to suddenly applied hypoxic and hypercapnic stimuli, and how can one account for the differences observed?'

The experimental method used for suddenly changing the stimulus to the carotid body from one steady level to another was as follows: arterial blood was taken through a short perfusion cannula in the external carotid artery of cats breathing a known gas mixture, and was stored in a warmed storage sac; the gas mixture being breathed was then replaced by another; the chemoreceptor discharge was observed until it was judged to be fairly steady (this usually took 1–3 minutes); then the stored blood was forced back into the common carotid artery by applying a known pressure to the surface of the storage sac. By these means the direction of flow in the carotid artery was reversed without an appreciable change in the pressure in it, and one steady respiratory gas stimulus in the blood to the carotid body was abruptly replaced by another. An added

advantage of the method was that it allowed an abrupt change of stimulus in the reverse direction to be made at the conclusion of the perfusion of stored blood (Black, McCloskey & Torrance, 1966).

Hypoxia

The chemoreceptor responses to suddenly applied hypoxic stimuli are very variable. The discharge rises smoothly to a maximum, and there is little evidence of adaptation. The time for maximum discharge to be attained varied from 3–4 seconds to over a minute, but in any preparation the response was slower than the response to hypercapnia. The experiments done with hypoxia suggested that it is necessary to control carefully the condition of the glomus before the stimulus is applied if consistent responses are to be obtained, as the degree and duration of preceding *hyper*oxia can slow the response, and an increase in the perfusion pressure at which the stimulus is delivered can hasten the response.

Hypercapnia

The chemoreceptor response to a suddenly applied hypercapnia is abrupt. The discharge rises to a maximum at about 1 second, then adapts more slowly, with a half-time of 5–10 seconds, to reach a new steady level (Fig. 5, 6b, 8). The hypercapnic stimuli used here were large (15–30 per cent CO_2 in O_2). Stimuli of this magnitude are required if clear results are to be obtained with single or few-fibre preparations, as the responses to smaller stimuli are 'lost' in the natural randomness of firing in these cases.

Von Euler, Liljestrand & Zotterman (1939), Witzleb (1963), and Hornbein & Roos (1963) have all reported a linear relation between chemoreceptor discharge and P_{CO_2} extending well beyond the physiological range. Cropp & Comroe (1961), Fitzgerald, Zajtchuk, Penman & Perkins (1964), Chernick, Hodson & Dutton (1965) and Dutton & Fenner (1966) have all reported rapid ventilatory responses, elicited from the chemoreceptors in response to hypercapnic stimuli. Fitzgerald *et al* (1964) and Dutton & Fenner (1966) used increments of P_{CO_2} as small as 2–3 mmHg. Chernick *et al* (1965) and Dutton & Fenner (1966) reported adaptation of the ventilatory response.

On abrupt removal of a hypercapnic stimulus, the chemoreceptor discharge falls quickly to a minimum, then slowly rises back to the control level. This is also seen in Fig. 6a where the chemoreceptor responses to changing from one level of hypercapnia to another are shown. Dutton & Fenner (1966) reported that they did not see this corresponding negative phase of adaptation on removal of a hypercapnic stimulus.

If a hypercapnic stimulus is re-applied within about 30 seconds of its removal, the peak to which the chemoreceptor discharge rises is less than that in response to the same stimulus when it is first given (Fig. 6b).

Thus we can see that there is a striking difference between the time courses of the responses to hypercapnia and hypoxia. The differences between these two stimuli are emphasized in the following experiments. When hypoxic and hypercapnic stimuli

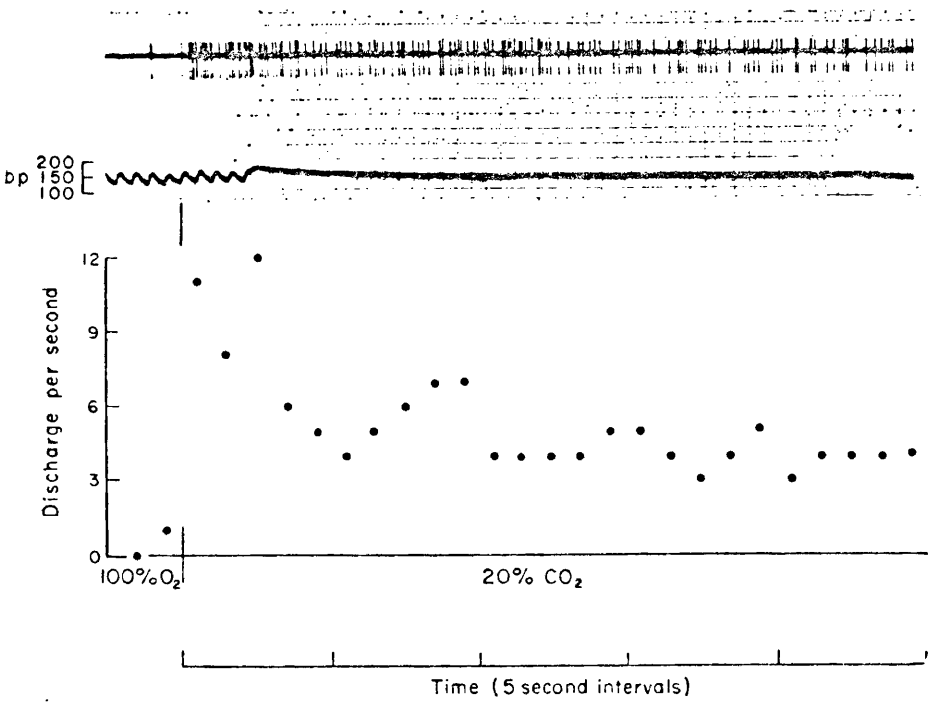

FIG. 5. Cat. Single chemoreceptor fibre. The upper panel shows the discharge in response to sudden application of hypercapnia at the mark. The lower panel shows the same response graphically. At the point where the blood pressure record becomes non-pulsatile, a clip was placed on the common carotid artery but perfusion continued into the carotid artery. CO_2 was given in O_2. The gases indicate the mixtures breathed when the perfusing blood was taken.

were selected which produced the same chemoreceptor discharge in the steady state, it was found that sudden replacement of one by the other did not hold the discharge steady. There was a transient peak of discharge at the replacement of hypoxia by hypercapnia, and a transient fall of discharge at the replacement of hypercapnia by hypoxia (Fig. 7a). When a hypercapnic stimulus was added to a maintained background of hypoxia, discharge rose immediately and began to adapt; when the hypercapnic stimulus was removed during maintained hypoxia, discharge fell below its level in hypoxia alone, although the hypoxia persisted, and then recovered back to its hypoxic level (Fig. 7b). This last observation shows that the negative phase of adaptation to hypercapnia can abolish, transiently, the steady state response to hypoxia.

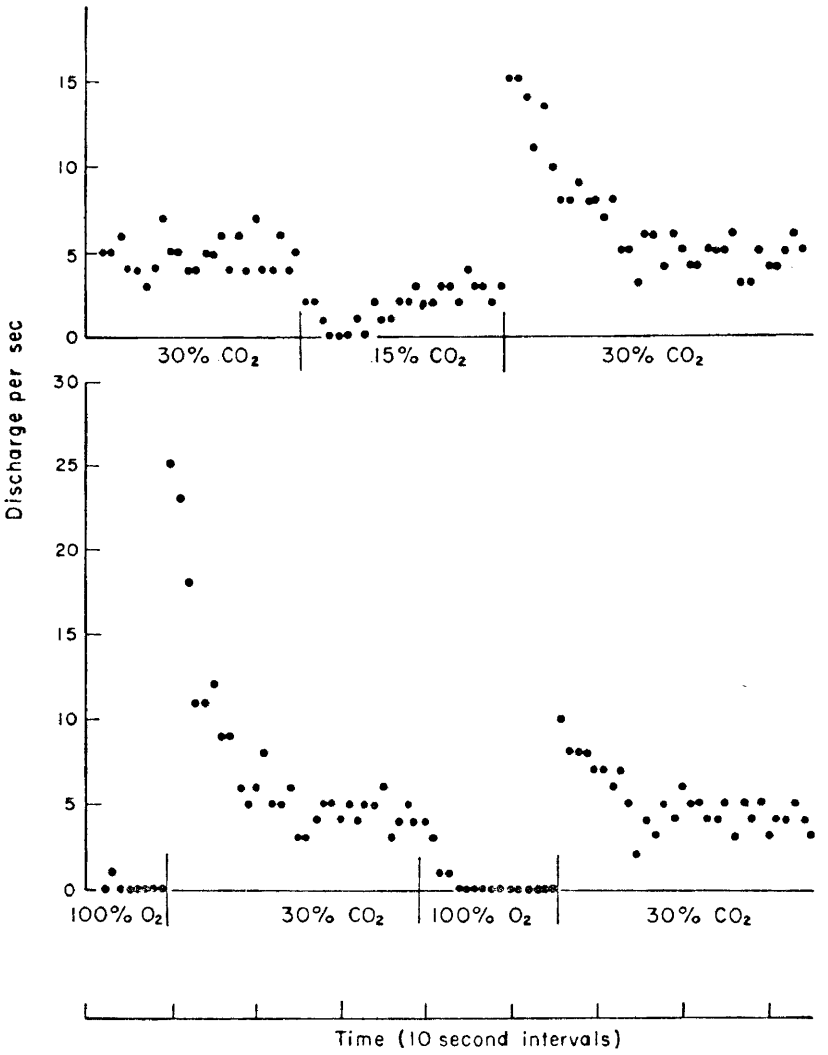

FIG. 6a (Upper): Cat. Single chemoreceptor fibre. Discharge in response to a sudden decrease, followed by a sudden increase, in the level of hypercapnic stimulus.
FIG. 6b (Lower): Cat. Single chemoreceptor fibre. Discharge in response to a hypercapnic stimulus, given, then removed, then re-applied 16 seconds later.

Carbonic Anhydrase

The enzyme carbonic anhydrase occurs in the carotid body (Lee & Mattenheimer, 1964, 1965). This enzyme is inhibited by the drug acetazolamide (Diamox). Use of this drug has enabled us to show that carbonic anhydrase is involved in the rapid chemoreceptor response to hypercapnia. Hypercapnic blood was taken into the perfusion system and stored there. Then Diamox was given intravenously, and the animal

was given a gas mixture to breathe which did not contain CO_2. This gave the drug access to the glomus, but not to the stored blood carrying the hypercapnic stimulus. The chemoreceptor response of the Diamox-treated glomus to a hypercapnic stimulus in normal blood was then observed: the discharge rose slowly to a steady level close to the final steady level attained before Diamox. The sharp peak of discharge followed by

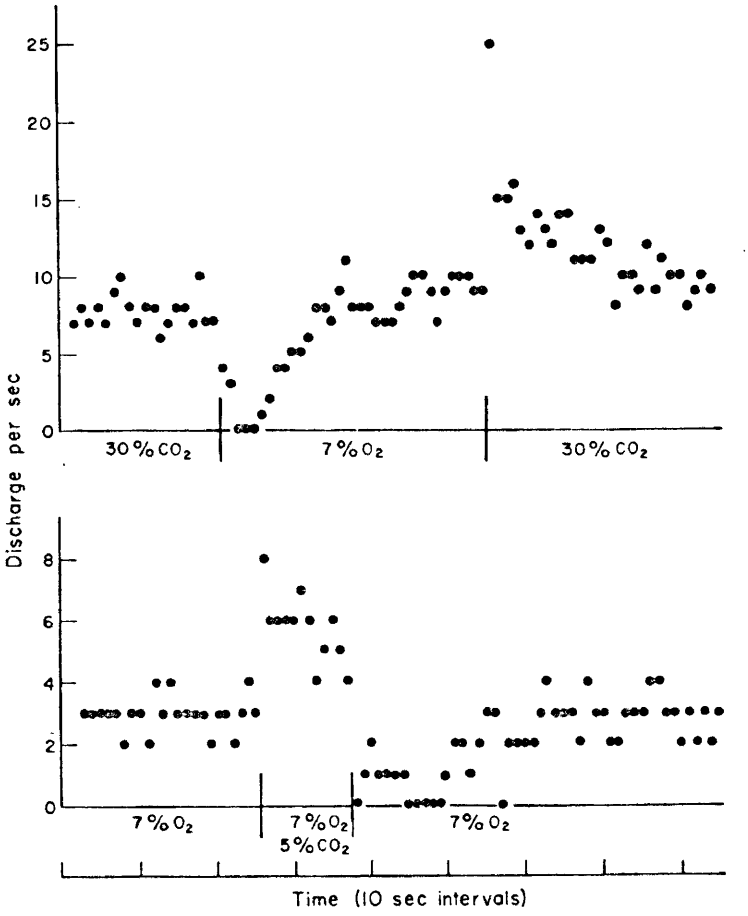

FIG. 7a (Upper): Cat. Single chemoreceptor fibre. Changes in discharge on alternating a hypercapnic and a hypoxic stimulus which in the steady state gave similar responses.
FIG. 7b (Lower): Cat. Single chemoreceptor fibre. Changes in discharge when a hypercapnic stimulus is applied and then removed during maintained hypoxia.

striking adaptation had been abolished (Fig. 8). This observation suggests that CO_2 acts in an ionic form, although it is possible that carbonic anhydrase acts to accelerate its diffusion to a point where it acts in an unionized form (Longmuir, Forster & Woo, 1966).

It should be observed that the presence of unpoisoned carbonic anhydrase in the

blood carrying the hypercapnic stimuli in all our experiments might account for the faster chemoreceptor responses observed here than in the experiments of Gray, Munro & Tenney (1966) where the hypercapnic stimuli were carried in buffered Ringer's solution.

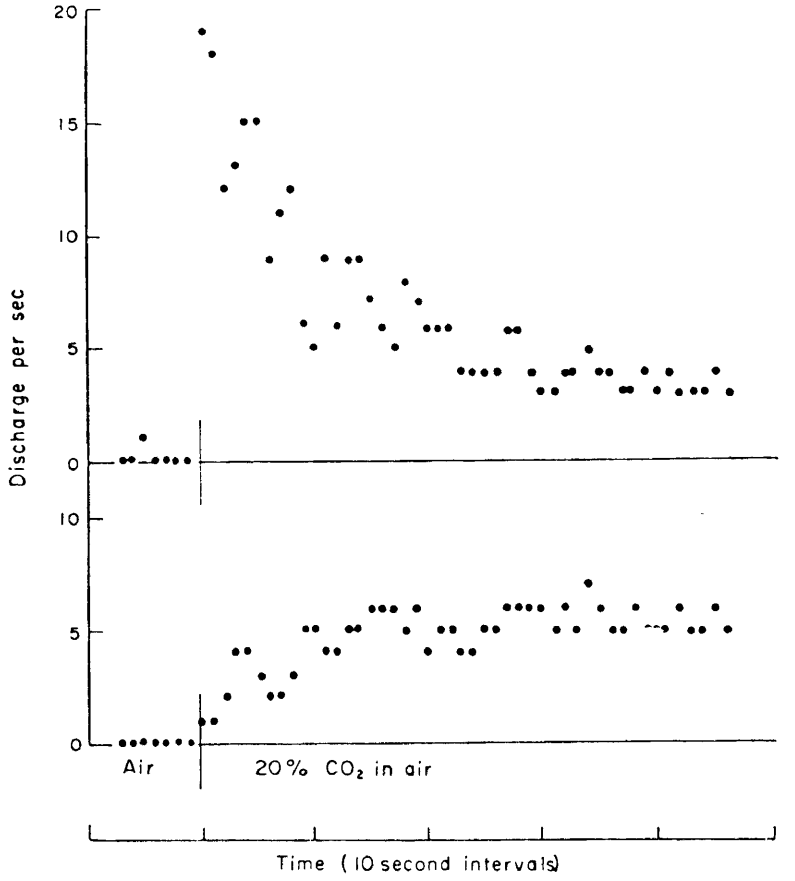

FIG. 8. Cat. Single chemoreceptor fibre. Changes in discharge on sudden application of a hypercapnic stimulus before (upper), and after (lower), inhibiting the carbonic anhydrase of the carotid body with acetazolamide (Diamox).

Interpretation

None of the results on responses to suddenly applied stimuli make it necessary to change the conclusion previously reached—there is no reason to deny that hypoxia acts by releasing a transmitter, and there is no reason to deny that hypercapnia does not release this transmitter.

The experiments with Diamox suggest that hypercapnia acts in an ionic form, possibly intracellularly, but this need not necessarily be so. In this respect the results of Gray, Munro & Tenney (1966), are especially interesting. They found that changing

the P_{CO_2} of the fluid with which they perfused their carotid bodies caused only a transient change in chemoreceptor discharge if the (HCO_3^-) was also changed by an amount which held pH constant. This result could be taken to mean that CO_2 acts only through the pH change it causes. As however, they found also that the response to a pH change was considerably faster when accompanied by a P_{CO_2} change than when not, their results would confirm the conclusion to which the Diamox experiments lead—that an ionic change somewhere remote from the perfusing blood is concerned in the excitation, and that the great diffusibility of CO_2 allows it to carry this stimulus most rapidly from the blood.

The exact mechanism by which hypercapnia excites the chemoreceptors can only be guessed at, but it may perhaps be helpful to have a model which will account for the results presented. Essentially it explains adaptation in terms of a gradient of pH with respect to space rather than with respect to time. Consider a two compartment system within the glomus tissue:

Compartment I	*Compartment II*
Contains carbonic anhydrase	No carbonic anhydrase
Low buffering capacity	High buffering capacity

and suppose that a gradient of (H^+) in the direction I→II causes increased discharge, and in the direction II→I causes decreased discharge.

Examination of this model will reveal that it will account for the response to application and removal of hypercapnia, for Gray, Munro & Tenney's (1966) observations, for the diminished responses to repeated hypercapnic stimuli, for the responses after Diamox, and for the steady-state discharge of the receptors to hypercapnia. It is interesting to note that if one postulates that hypoxia acts by causing H^+ ions to be produced in compartment I, then the interactions of hypoxia and hypercapnia can be explained, as well as the dependence of hypoxic discharge on blood flow. Also the space gradient idea allows one to retain the idea of a pH receptor for P_{O_2} in the face of the low steady-state sensitivity of chemoreceptors to pH. I confess that these final postulates are not particularly appealing to me.

In considering the exact mechanisms of hypercapnic excitation, it should be borne in mind that carbonic anhydrase is often associated with the pumping of H^+ ions, as Lee has reminded us, and that some manifestation of such a pump might profitably be sought in the glomus.

Significance

It is extremely difficult to assess the functional significance of responses seen in one small isolated part of the respiratory system, but two comments are worth making.

First, the controversial theory of Yamamoto (1960) which supposes that ventilation

responds less to a steady P_{CO_2} than to an oscillating P_{CO_2} with the same mean value, might seem suited by receptors which respond rapidly to an increase in P_{CO_2}, but adapt slowly. The carotid chemoreceptors behave in this way, as has been shown here and by Chernick *et al* (1965) and by Dutton & Fenner (1966), but the corresponding negative phase of adaptation on removal of hypercapnia, which Dutton & Fenner (1966) did not see, argues against the suitability of the chemoreceptors for Yamamoto's theory. In addition, the finding that repeated stimuli give diminished peak responses would not suit the theory.

Second, the peripheral receptors, which respond rapidly to a hypercapnic stimulus and adapt, might be considered to compensate for what deficiencies there are in the central receptors, which respond more slowly and do not adapt. On this consideration the peripheral chemoreceptors might be seen, so far as the rapid, adapting part of their response is concerned, as receptors dealing with breath-to-breath variations in P_{CO_2}. The response to P_{CO_2} in the steady-state, as our Diamox experiments, the results of Hornbein & Roos (1963) and those of Gray *et al* (1966) all suggest, can be more properly regarded as a response to pH. It is this aspect of peripheral chemoreceptor activity to which Mitchell's (1966) recent work has attributed so much significance.

As a final reflection it is interesting that the response of the peripheral receptors to hypercapnia is more rapid than their response to hypoxia, whilst the capacity of the body for storing oxygen is slight in comparison with its capacity for buffering CO_2. But perhaps it is only in the laboratory and in mines that the respiratory control system is *suddenly* presented with a lack of oxygen which is not accompanied by an increase in P_{CO_2}.

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DISCUSSION

PERMUTT: I had the impression that in your responses to CO_2 the area of overshoot was considerably greater than the area of the undershoot. Is this so? And if so, would this not perhaps give a little more credence to Yamamoto's hypothesis?

MCCLOSKEY: If it did happen, it would give more credence to the hypothesis of

Yamamoto, but I can't say whether the area of the undershoot is less because in most of the undershoots we have seen, discharge falls to zero.

GRAY: I have some results which suggest that the receptor responsible for the acid-base response of the carotid body is freely accessible to extracellular bicarbonate. Accessible, but less readily accessible than it is to CO_2. When I acidify the perfusate with CO_2 at constant bicarbonate there is very little, if any, overshoot but if the chemoreceptors are subjected to the same increase in P_{CO_2} and the acidification is prevented by a proportional increase in bicarbonate, the response has an overshoot and then returns to the base line or control discharge. This would suggest that the overshoot in the blood-perfused preparation might be explained by a rapid diffusion of CO_2 to the chemoreceptor site and a slower secondary movement of bicarbonate across the capillary endothelium, or the receptor cell membrane, to the H^+ receptor.

LLOYD: My suggestion would be that the Diamox reduces the effectiveness of the CO_2 because it could take as long to combine and form a hydrogen ion as the bicarbonate takes to get in, so they are going in together and you don't see the effect.

MATTENHEIMER: If you have a high concentration of bicarbonate in the blood, you have to have carbonic anhydrase acting to get this across as CO_2, assuming that only CO_2 can cross cell membranes. We don't know yet where the carbonic anhydrase is. It may be intracellular or on the cell membrane. We know in the kidney it occurs both in the cell and in the cell membrane. This is one place where bicarbonate is readily reabsorbed as CO_2.

MCCLOSKEY: Forster has pointed out that it takes some time for Diamox to get into cells so maybe we should consider the possibility that the carbonic anhydrase it acts upon is in the membrane.

DEJOURS: What is the P_{CO_2} below which you don't find autoregulation?

MCCLOSKEY: I am afraid I can't answer that. Once I found that I could precipitate it with an inspired CO_2 of about 8 per cent, I was reluctant to gives less than that for fear that I wouldn't find it. On many occasions I did give CO_2 and did not get autoregulation. In one experiment, I abolished spontaneous autoregulation by overventilating the animal. This may be my most significant observation for answering your question. Reducing the P_{CO_2} below the resting level abolished autoregulation.

DEJOURS: In all the experiments we have done we have found similar time lags and time courses of the transient ventilatory responses to short-term N_2, O_2 or CO_2 breathing.

MCCLOSKEY: Most of our very slow hypoxic responses are with blood pressures of 50 or 60 mmHg. Usually we see a maximal hypoxic response within 10 seconds, although even then there is quite a considerable variation in the speed of hypoxic responses. The delay of the hypoxic response may depend on the degree or duration of the preceding hyperoxia.

LAHIRI: We have some evidence that CO_2 can stimulate the carotid body in a lower

range of P_{CO_2}—30–50 mmHg. We have investigated the effects of H^+, CO_2 and O_2 in anaesthetized cross-circulated dogs. The recipient dog's carotid body receives blood exclusively from a donor dog, so we can study the carotid body response only, as opposed to the total response to ventilatory stimuli. We found that a change of carotid body P_{CO_2} at a constant P_{CO_2} in the recipient's body produced a small but definite ventilatory response even in the absence of hypoxia.

DOMIZI: With regard to the overshoots, did you see overshoots and undershoots if your change in P_{CO_2} was less? In my experience, a small stimulus is less likely to give an overshoot than a strong one. Have you tried anything stronger in hypoxia to see if you get overshoots there?

MCCLOSKEY: The smallest P_{CO_2} change we have used has been 5 per cent CO_2 inspired and I realize this is big. We find that if we work with single chemoreceptor fibres we have to use large stimuli if we want a response the time course of which is not lost in the natural randomness. Hornbein, Witzleb and others have shown that P_{CO_2} and discharge remain linearly related well outside the physiological range and the Baltimore group and also your own have shown rapid CO_2 effects with increments of P_{CO_2} of only 2–3 mm of mercury.

CUNNINGHAM: Your animals were ventilated with a pump so I must point out that a 5 per cent CO_2 'only' means a change of up to 35 mmHg in arterial blood.

PAINTAL: In the aortic nerve, the chemoreceptors are not influenced by CO_2 in the physiological range. I am interested by your observations. The high dose effect and the short latency of response are very interesting and are like the response to a drug like ACh. We are back to the same first node I think.

MCCLOSKEY: On this point, I might say that when we give hypoxia and hypercapnia they do not block each other—they add or even multiply.

PAINTAL: It is the same with ACh and hypoxia. ACh gives a bigger response in hypoxia because it is acting at the regenerative region.

MCCLOSKEY: However, the Baltimore group have found the same thing in ventilatory responses with very small P_{CO_2} increments.

PAINTAL: Yes, but the medulla oblongata is there between their stimulus and their response.

KRYLOV: Is the effect on the ventilation of excitation of the carotid body by lack of oxygen identical with that of excitation of the carotid body by CO_2? There are two kinds of shortness of breath clinically—shortness of breath in inspiration and in expiration. How can the carotid body give these two effects if there are identical mechanisms of excitation by these two stimuli?

MCCLOSKEY: I have no information on this, but it might be of interest that Black has shown in our laboratory that a sudden short-lasting stimulation of the carotid chemoreceptors will increase whichever part of the respiratory cycle, inspiration or expiration, is in progress at the time when the stimulus is given.

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STAGNANT ASPHYXIA IN THE CAROTID BODY OF THE CAT

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Abstract. Stagnant asphyxia was allowed to develop in the carotid body when blood pressure was dropped abruptly to zero by simultaneously clamping the common carotid artery and opening a tap in the external carotid artery to the atmosphere. Discharge in single chemoreceptor fibres was observed as it increased in response to the stagnant asphyxia. When discharge was maximal, blood equilibrated with various gas mixtures was allowed to flow through the bifurcation for different periods of time before again dropping the local blood pressure to zero. After such transient interruptions of stagnant asphyxia with normoxic or hyperoxic blood, the return of stagnant asphyxic discharge was delayed in proportion to the degree and duration of preceding hyperoxia – *i.e.* the organ established an "oxygen credit". It is suggested that the carotid body may have a capacity to store oxygen.

Arterial chemoreceptors Control of breathing

The peripheral arterial chemoreceptors are stimulated by stagnant hypoxia (LANDGREN and NEIL, 1951) as well as by hypoxic hypoxia. We have observed the onset of chemoreceptor discharge in response to stagnant asphyxia developing when the blood flow through the carotid body in the cat is abruptly halted. It has been demonstrated that the onset of this chemoreceptor response is delayed in proportion to the amount of oxygen supplied prior to the stoppage of flow. The existence of a capacity of the carotid body chemoreceptors to store oxygen is suggested.

A preliminary account of these findings was presented to the Australian Physiological and Pharmacological Society in May 1968.

Methods

Experiments were done on ten cats, anaesthetized with pentobarbitone 40 mg/kg, (Nembutal: Abbott) intraperitoneally. The trachea was cannulated low in the neck and the pretracheal muscles, pharynx and larynx were removed up to the level of the hyoid bone. A cannula was inserted into the lingual artery to measure blood pressures in the region of the carotid bifurcation. Another cannula was inserted into the external carotid artery with its tip directed towards the carotid bifurcation, and was connected to a tap which could be opened to the atmosphere. Small arterial branches in the region

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of the carotid bifurcation were tied, particular care being taken to avoid interfering with the carotid body or its arteries or veins.

The vago-sympathetic trunks were cut low in the neck. The carotid sinus nerve was identified where it joined the glossopharyngeal and was dissected under paraffin on a rigid, earthed stainless steel plate with a blackened upper surface. Chemoreceptor fibres were identified by their sporadic discharge, but were accepted only if they responded to changes in the oxygen content of the inspired gas. Only single-fibre preparations were used in this study.

The recording electrodes were made of fine stainless steel wire. Impulses were led into a Tektronix type 122 preamplifier and then to an oscilloscope for preliminary observation or to one channel of the recording apparatus, a Mingograf Cardirex 24B, a direct-writing ink-jet recorder with galvanometers of natural frequency of 610 cps. Blood pressure in the lingual artery was measured with an Elema-Schönander Electromanometer type 460 with a variable inductance pressure transducer (type EMT 490A, 0-300 mm Hg). The output was recorded on a second channel of the Mingograf.

Observations were made with the cats artificially ventilated with a Starling Ideal pump. Gas mixtures were made up with flowmeters and stored in Douglas bags. Rectal temperatures were kept constant within the range 37–39°C, and the paraffin pool was kept at a similar temperature.

Using these preparations it was possible to stop the blood flow in the carotid bifurcation abruptly by simultaneously clamping the common carotid artery and opening the tap in the external carotid artery to the atmosphere. That the pressure in the carotid bifurcation fell to zero was confirmed by the reading of blood pressure recorded from the lingual artery. Neither clamping the venous outflow of the carotid body, nor applying a small, constant negative pressure (−10 cm water) within the bifurcation, during the period of stoppage of flow, altered the results observed.

Observations

When the blood pressure in the carotid bifurcation was dropped suddenly to zero the discharge in single-fibre chemoreceptor preparations rose. When the blood pressure and blood flow through the bifurcation were restored the discharge fell. In all the fibres investigated it was found that the discharge rose to a high, fairly steady level in response to the stoppage of flow, but that the time taken to reach this level varied, depending on the conditions of perfusion prior to the stoppage of flow.

To investigate this further, the following procedure was followed: flow was abruptly stopped, and the discharge was allowed to build up to a high, fairly steady level. At this point arterial blood at systemic arterial blood pressure was allowed back into the bifurcation for various lengths of time, and then the pressure was again dropped abruptly to zero. The discharge was observed as it rose. By altering the oxygen content of the gas mixtures used to ventilate the cats the chemical composition of the blood allowed into the bifurcation could be chosen.

In all, 14 single-fibre preparations were investigated in 10 cats, and while the maximal levels of asphyxic discharge varied, the time-courses of the onsets of the

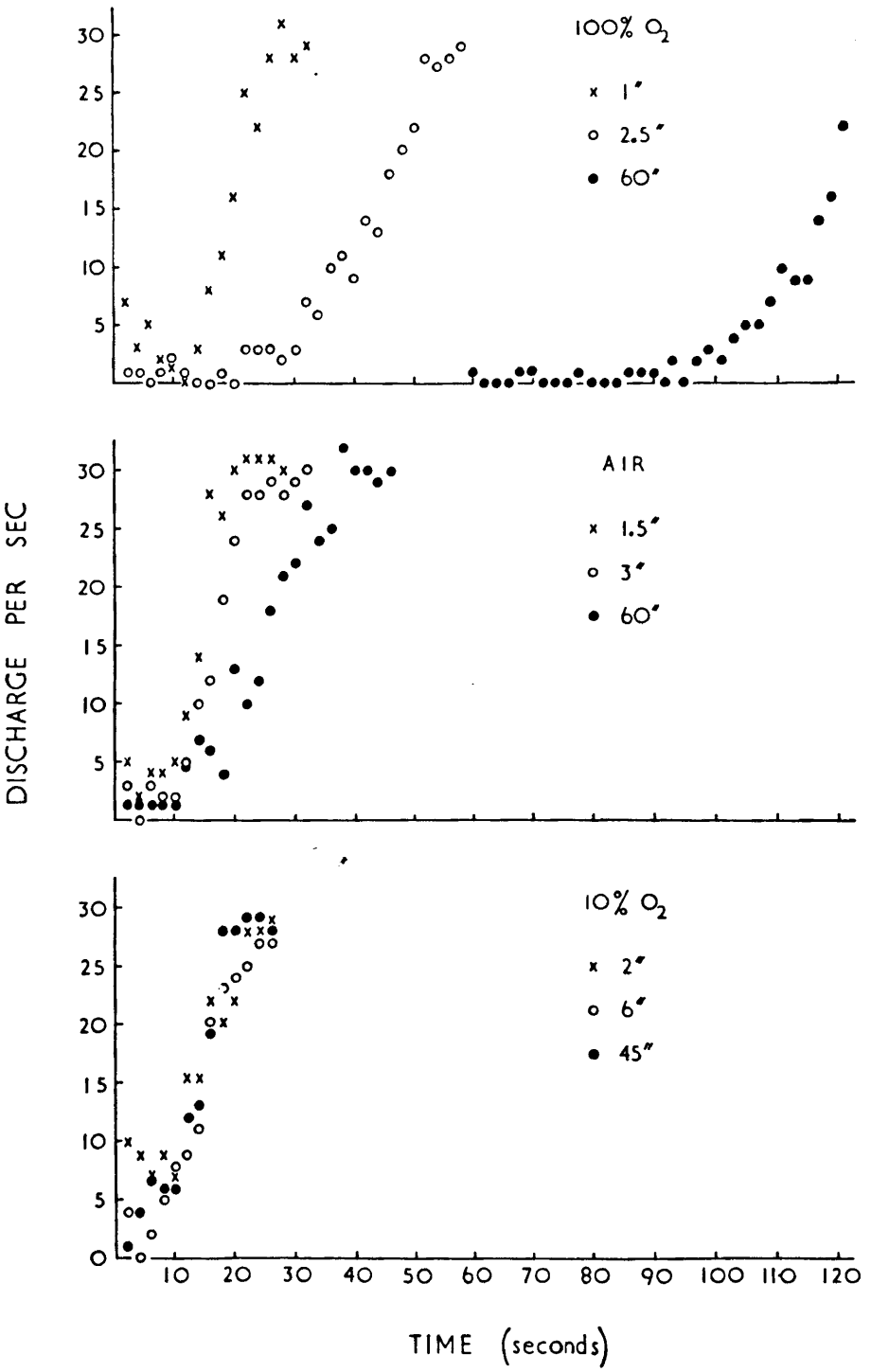

Fig. 1. Single chemoreceptor fibre. Cat. The experiment involved interrupting complete stagnant hypoxia with perfusions of various durations, at a pressure of 120 mm Hg. At zero time on the figure, the perfusion pressure was returned to zero. The panels show the returns of discharge after perfusions with (a) hyperoxic, (b) normoxic, and (c) hypoxic blood, for the durations, in seconds, shown.

discharge were similar, particularly for the faster returns of discharge. Only for the slower returns after prolonged hyperoxia was there appreciable variation: the discharge recommencing between 60 and 120 sec after stopping flow. In any one preparation, however, this delay time was constant.

Figure 1 shows the results of one complete experiment. At zero time the blood pressure was dropped to zero following various durations of perfusion which interrupted previously stagnant asphyxial conditions. In (a) hyperoxic, in (b) normoxic, and in (c) hypoxic blood, was used. When the perfusion had been with hypoxic blood, the discharge returned rapidly at a rate independent of the duration of the perfusion. When the perfusion had been with normoxic or hyperoxic blood, and of short duration (up to 1.5 sec), the discharge returned equally rapidly. However, when the perfusion had been with normoxic or hyperoxic blood, and was of longer duration (up to 60 sec), the discharge returned more slowly and its speed of return depended upon the duration of the preceding perfusion. Moreover, after perfusions of comparable duration the rate of return was slower after the hyperoxic perfusion than after the normoxic perfusion. Perfusions of longer than 60 sec duration did not further delay the return of discharge.

Discussion

In these experiments the carotid body chemoreceptors were made to discharge in response to stagnant asphyxia caused by abruptly halting the blood flow to them. It is not suggested that this manoeuvre abruptly halted the oxygen supply to the receptors, since some oxygen must have been present in the blood trapped in the vessels of the carotid body when flow was stopped, and also in physical solution in the extravascular tissue of the carotid body. An estimate of the amount of oxygen trapped in this way can be made and is given below. When this is done it is found that there is not enough oxygen available from these sources to maintain a normally metabolizing carotid body for the periods for which the onset of discharge is delayed following prolonged hyperoxic perfusions. Moreover, when the amounts of oxygen available from these sources are similar, as after comparable durations of perfusion with normoxic and hyperoxic blood, the delay before discharge recommences is greater after hyperoxia than after normoxia. Thus the delay in response to stagnant asphyxia in proportion to the degree and duration of preceding hyperoxia (a process which might be called "incurring an oxygen credit"), cannot be explained by variations in the amount of accountable oxygen present at the onset of stagnant conditions. Calculations leading to these conclusions are given below, and we consider the possibilities that the carotid body may have a capacity to store oxygen or energy-rich compounds in proportion to its exposure to hyperoxia, or that it may be inhibited from discharging by some chemical factor produced in proportion to the degree of hyperoxia.

DALY, LAMBERTSEN and SCHWEITZER (1954) gave a figure of 2 mg for the weight of the carotid body: if its density is that of water its volume is 2 μl. LEITNER and LIAUBET (1971) stripped carotid bodies very strenuously to beyond their capsules and reported a considerably smaller weight for the organ. (We use the figures of DALY *et al.* as these

are in agreement with our own unpublished measurements of the weights of carotid bodies from 10 cats.) If the solubility of oxygen in blood and carotid body tissue is similar, this 2 μl would contain 0.04 μl of oxygen in simple solution at one atmosphere. Assume that 25% of the volume of the unperfused carotid body is trapped blood: when saturated with oxygen this blood would contain a further 0.1 μl of oxygen in chemical combination. This is possibly overestimating the combined oxygen, as DE CASTRO and RUBIO (1968) suggest that carotid body capillaries may collapse when not perfused. Thus when stagnant conditions begin after a prolonged hyperoxic perfusion, there would be approximately 0.14 μl of oxygen available for the carotid body's metabolism. If no other source of oxygen or energy exists, it is this 0.14 μl of oxygen on which the carotid body has been maintained following prolonged hyperoxic perfusions of the type shown in fig. 1a.

Using similar assumptions one can calculate that after prolonged normoxic perfusion there is 0.106 μl of oxygen in the blood and in physical solution in the glomus tissue. This is not much less than the amount present after hyperoxia since the oxygen combined with haemoglobin is approximately the same in both cases because of the shape of the haemoglobin dissociation curve. Figure 1a shows that the delay before discharge starts after hyperoxia is 100 sec, whereas after normoxia (fig. 1b) the delay is only 20 sec. The difference in accountable available oxygen between these two is 0.04 μl. Is 0.04 μl enough to maintain the metabolism of the glomus for the 80 sec difference between the two? Is the 0.14 μl present after hyperoxia enough to maintain the metabolism for 100 sec?

DALY *et al.* (1954) found an oxygen consumption of 9 ml/100 g/min in the blood perfused carotid body of the cat. PURVES (1970) gave a similar figure for the denervated carotid body (the carotid bodies in our experiments were denervated). He reported a dependence of oxygen consumption upon arterial oxygen and carbon dioxide tensions and upon blood pressure in the innervated, but not in the denervated carotid body, so this is not relevant here. In contrast to these results are the figures given by FAY (1970): in a saline perfused preparation he found an oxygen consumption of 1.5 ml/100 g/min, less than 20% of the value originally found by DALY *et al.* Because JOELS and NEIL (1968) have reported that saline perfusion considerably reduces the responsiveness and vascular tone of the carotid body, our further calculations rely more on the figures of the other workers. LEITNER and LIAUBET (1971) measured oxygen consumption of the carotid body *in vitro*, and reported absolute values of the same order as those reported by FAY (1970), when their preparations were exposed to an outside oxygen tension of 680 torr. However, an unoxygenated core of tissue can exist in the *in vitro* preparation, and the figures given by FORSTER (1968) indicate that an external oxygen tension of 2000 torr is required to supply the whole of a sphere of the dimensions of the carotid body. It is difficult to estimate what fraction of the carotid body's metabolism Leitner and Liaubet were observing. This is particularly so because the organs they used were exposed for some time during dissection to an oxygen tension equal only to that of room air before being investigated, so that an inner core of cells may have died before they commenced their experiments.

If the figures of Daly *et al.* and Purves are correct, the glomus would consume 0.3 μl of oxygen in 100 sec, or 0.24 μl in 80 sec. But it has already been shown that one can account for only 0.14 μl of oxygen after prolonged hyperoxia, when discharge is delayed for 100 sec, and it is extremely unlikely that all of this available oxygen would be consumed before discharge began. It has also been shown that discharge begins some 80 sec later after hyperoxia than after normoxia, when the difference in accountable available oxygen is only 0.04 μl. Clearly, in neither case can we account for enough oxygen to maintain carotid body metabolism for the observed periods. On FAY's (1970) figures for oxygen consumption, however, the glomus would consume only 0.05 μl in 100 sec, and 0.04 μl in 80 sec: in both cases considered the accountable available oxygen would suffice to maintain glomus metabolism. Accepting the oxygen consumption given by Daly *et al.* and Purves, instead of Fay's, means, in he light of the above calculations, that a separate oxygen storage system in the carotid body itself can be postulated.

It is clear from fig. 1a that a large part of such a store is filled only in hyperoxic conditions, and that in these conditions it takes a considerable time to fill. The only oxygen available to fill such a store in hyperoxic conditions must come from physical solution in the perfusing blood, which could explain the long filling time. The same oxygen could be removed from a store by hypoxic blood flowing through much faster than by stagnant conditions because hypoxic blood has reduced haemoglobin with which to take it away. In perfused preparations the sudden replacement of hyperoxic by hypoxic perfusing blood gives a chemoreceptor response in a few seconds (MC CLOSKEY, 1968; MCCLOSKEY and BLACK, unpublished observations), suggesting that the oxygen credit we have described here is a store of oxygen *per se.*

If the store is not oxygen, but energy-rich compounds, then its rapid dissipation in hypoxic (perfusion) hypoxia but not in stagnant hypoxia is difficult to explain. Moreover, it would mean there is a metabolism in the carotid body tissue in which the balance of an ATP:ADP or similar system is shifted towards the energy-rich moiety over a high P_{O_2} range. MILLS and JOBSIS (1970) have described a carotid body endoxidase with an unusually high critical P_{O_2}, but this peculiarity alone would not provide an energy store.

On the argument we have used oxygen may be regarded as an inhibitor of discharge. Our results are satisfactorily explained if its level builds up slowly in the carotid body during hyperoxic perfusion, can be slowly dissipated in stagnant hypoxic conditions, and more rapidly discharged in hypoxic conditions (*i.e.* hypoxic perfusion). EYZAGUIRRE and ZAPATA (1968) have suggested that an inhibitory transmitter may be released in the carotid body in some circumstances. Such a transmitter would explain our results if it satisfied the above criteria given for oxygen as an inhibitor: slow accumulation during hyperoxic perfusion, slow dissipation in stagnant hypoxia, and faster dissipation in perfusion hypoxia. An inhibitory chemical produced at a rate dependent on arterial oxygen tension, and able to be either washed away in perfusing blood or gradually overcome in a stagnant asphyxic situation, would fill this role. Nevertheless, as PURVES (1970) has shown no dependence of oxygen consumption upon oxygen

tension in the denervated carotid body, the previous calculations on oxygen gesau remain applicable. An inhibitory chemical substance would, to explain our results, have to be powerful enough to suppress discharge long after all available oxygen has been used. We cannot exclude this alternative explanation of our results, although we do not find it attractive.

If no inhibitor of discharge apart from oxygen itself is involved in our experiments, then our results can be taken to suggest the presence of a specialized carotid body tissue oxygen store. It is of interest that CHALAZONITIS (1969) has reported sensitivity to hypoxia in certain giant neurones of Aplysia and Helix in which oxygen can bind to a haemoglobin-like pigment. Alternatively our results might be taken to show that if there is no capacity of the glomus to store oxygen, then the oxygen consumption figures of FAY (1970) are more likely to be correct than those given by DALY *et al.* (1954) and PURVES (1970).

Whatever the explanation of our observations, the stagnant preparation is of interest in that it is particularly suited to experiments in which it is desired to distinguish a direct chemoreceptor effect from an effect occurring secondarily to vasomotor changes within the carotid body.

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AUTOREGULATION OF BLOOD FLOW IN THE CAROTID BODY

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Abstract. Autoregulation of blood flow has been observed in the denervated carotid bodies of rabbits and cats, using a method which measures the arterial inflow at various perfusion pressures. In almost half of experiments in rabbits, autoregulation was observed. It was abolished by hyperventilation, and by raising the perfusion pressure very high. It has been produced by administering carbon dioxide into the inspired gas. Sympathetic stimulation and adrenaline or noradrenaline reduced carotid body flow, and in one experiment adrenaline lowered the level of flow without abolishing autoregulation. Autoregulation of flow was also observed in the carotid bodies of cats under chloralose, but not when barbiturate anaesthesia was used. The significance of autoregulation of flow for carotid body function, and possible mechanisms causing the phenomenon are discussed. An elaboration of the myogenic hypothesis of autoregulation is proposed.

Arterial chemoreceptors
Autoregulation of blood flow
Carbon dioxide
Carotid body
Catecholamines

In this paper, we report some observations on the circulation of the carotid body which show that, under certain circumstances, the resistance to the flow of blood through it rises if the perfusion pressure is raised; that is, autoregulation of blood flow takes place.

Daly, Lambertsen and Schweitzer (1954) found that the blood flow through the cat's carotid body, which weighs only 2 mg, is 40 μl/min so that the flow, expressed per unit weight, is 2000 ml/100 g/min and is the largest blood flow yet reported for any organ. Daly *et al.* (1954) found also that flow was approximately linearly related to pressure, but de Castro (1951), using a quite different technique of microscopical observations of the carotid body *in vivo*, claimed that the blood flow did not alter when the blood pressure was raised by occluding the aorta in the abdomen, though in other circumstances, there might be marked changes in blood flow.

Some of this work has been presented in brief form elsewhere (McCloskey and Torrance, 1965; McCloskey, 1968, 1970).

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Methods

Rabbits, weighing 1.6–3.8 kg, were anaesthetized with a solution, given intravenously, containing 7.5 mg of pentobarbitone (Nembutal: Abbott) and 220 mg of urethane (ethyl carbamate) per ml. Anaesthesia was maintained with pentobarbitone alone.

The trachea was cannulated low in the neck, and the pretracheal muscles, pharynx and larynx removed up to the level of the hyoid bone. Then a paraffin pool was made in the neck and dissection was completed under paraffin in the belief that this would reduce the temperature changes to which the carotid body would be exposed and so would keep it in better condition. A mercury manometer recorded femoral artery pressure. Rectal temperature was maintained at 36°–38 °C, and the paraffin pool was kept at a similar temperature. Warm dextran was used occasionally to maintain the blood pressure.

Our method of measuring the blood flow to the carotid body, measures arterial inflow at constant known perfusion pressures.

Under a dissecting microscope, we tied all arterial branches leaving the carotid bifurcation region, except the internal and external carotid arteries and the vessels to the carotid body. The anatomy of the region was variable (CHUNGCHAROEN, DALY and SCHWEITZER, 1952a). When vessels continued after sending branches into the carotid body they were tied as far beyond the branch to the glomus as practicable. Often such vessels supplied the superior cervical ganglion in the rabbit (CHUNGCHAROEN *et al.*, 1952b) which could then be easily deprived of its arterial supply. The venous drainage of the carotid body was carefully avoided while tying off the small arteries.

The carotid sinus nerve was cut; the sympathetic nerve from the superior cervical ganglion to the carotid body was cut close to the ganglion. The vagus and sympathetic nerves, on the experimental side, were cut low in the neck.

A nylon cannula (internal diameter, 0.8 mm; length 15 cm) was then tied into the external carotid artery. This cannula coiled within the paraffin pool before connecting through a metal 3-way tap with a glass tube of internal diameter 1.0 mm and of length 80 cm. The tube was held horizontal at a level not more than 3 cm above the carotid bifurcation, and was connected to a mercury manometer and a large air pressure bottle through a glass 3-way tap at its remote end.

At no point in the dissection was the blood supply to the glomus interrupted.

The animals were heparinized (Pularin: Evans Medical Limited: 2500 I.U. per kg), and a small quantity of blood was drawn back into the nylon cannula, coming into contact with heparinized Ringer-Locke solution which had previously filled the cannula, and which extended into the glass tubing where there was a clearly visible air-saline interface. The internal and common carotid arteries were then occluded with "bulldog" clips, thus trapping blood in a sac from which only the glomus vessels drained. The blood in the nylon cannula could then be returned to the sac under a known pressure applied from the pressure bottle, and its rate of inflow determined

by measuring to the nearest 0.5 mm the distances travelled by the saline meniscus in 30-second intervals.

Between 45 and 60 sec were allowed for arterial elasticity to be taken up. The rate of inflow was then equal to the carotid body blood flow, and readings taken after this time indicated a constant flow. Usually two readings were made at any one perfusion pressure. Readings were rarely made at more than two different pressures from any one sample of blood stored in the nylon cannula. Between measurements the clips were removed from the carotid arteries and the normal blood supply to the glomus was restored – the glomus was never deprived of its normal blood supply for more than 6 min. Pressure flow points were determined in a random sequence. To check the stability of the preparation with time flow was measured at one reference pressure at intervals throughout the experiment. Figure 2 shows a phenomenon which was observed in many experiments: with time there is a gradual reduction in the flow in otherwise comparable conditions, and this occurs without an appreciable change in the shape of the relation between pressure and flow.

That only the carotid body was draining from the arterial sac was confirmed, during the experiment, by perfusing dilute Evan's Blue solution into the sac to make all drainage channels visible, and after the experiment, by placing a clip on the carotid body itself to show that no further drainage then occurred. Readings made before and after the perfusion of Evan's Blue were comparable. Readings taken 1 min and 5 min after starting a perfusion were comparable which suggests that progressive changes in the blood in the cannula, or in the arterial segment, were not sources of error. Flow often decreased with time. This could mean either that the whole vascular bed of the carotid body gradually constricted or that parts of it successively clamped down or clotted completely. In only a few experiments did perfusion with dye suggest that part only of the carotid body was perfused. If, after some procedure, flow did not return to close to a control level, the experiment was abandoned. Figure 2 shows the order of drift tolerated. Vasoconstriction of this kind may account for the experiments in which no flow could be found. Vessels which respond briskly to a mechanical stimulus and so achieve autoregulation could well clamp down and stop flow if irritated during the making of the preparation.

With the whole perfusion system connected to a dead animal without clips on the carotid arteries, the meniscus could be made to travel down the tube at a rate much faster than any measured in experiments by applying a pressure of 2 mm Hg in the pressure bottle. The pressure drop due to the resistance of the tubes was thereafter regarded as négligible.

Whenever possible, the animals were permitted to breathe spontaneously, but often breathing failed or was badly depressed, and they were then artificially ventilated with a Starling Ideal pump. Gas mixtures were made up with flowmeters, and were administered through the respiratory pump from Douglas bags.

In some experiments, an Electro-Physiological Instruments Limited Class Stimulator, CS-32, giving trains of stimuli of 10 volt, 1.5 msec duration, at 32/sec was used to stimulate nerves.

Carotid body flow was measured in the cat using a similar method. Because the internal carotid artery is usually absent in the cat, the common carotid and external carotid arteries were those clamped to close the arterial sac, perfusion being through a cannula in the lingual artery. The anaesthetic used in the cat was either pentobarbitone, 35 mg/kg (Nembutal: Abbott), or, chloralose 80 mg/kg after induction with ether.

Injections: (i) Dextran: "Dextravan" 6% w/v dextran in 0.9% NaCl. Benger Laboratories Limited.

(ii) Adrenaline: Adrenaline hydrochloride. Parke, Davies and Co. Limited.

(iii) Noradrenaline: "Levophed", noradrenaline bitartrate. Bayer Products Limited.

Observations

CRITERIA USED FOR AUTOREGULATION

If the arterial pressure suddenly rises, the flow of blood through a vascular bed immediately rises. Autoregulation is a response to these immediate changes: the resistance to flow through the vessels rises to a higher level than that to which it had been immediately reduced by the rise in arterial pressure.

Autoregulation is complete if the flow is brought back to its control level. If the resistance increases to be higher than it was in the control period, but not to be high enough to bring the flow back to its control level, autoregulation is still said to have taken place. A less strict criterion requires only that resistance increase from the low level to which it fell immediately after the rise in pressure: it need not return to its control level.

If a curve relating pressure and flow has the form $F=KP^n$ over the relevant range of pressures, the first criterion states that $n=0$, the second that n is less than 1.0,

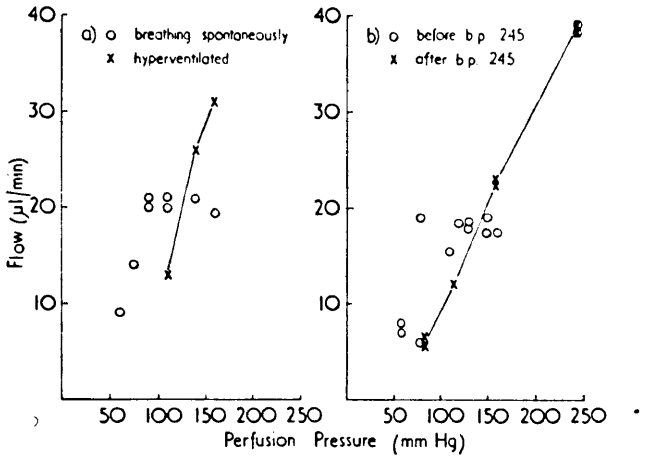

Fig. 1. Flow-pressure relations in rabbit carotid bodies. (a) Autoregulation of flow (open circles) disappeared when the animal was artificially hyperventilated with air (crosses). (b) Autoregulation of flow (open circles) disappeared after the perfusion pressure had been raised to 245 mm Hg (crosses).

and the third that, though n is always greater than 1.0, it is less in the steady state than it was in the unsteady state immediately after the blood pressure changed. If n is less than 1.0, the tangent to the curve cuts the flow axis: if it is greater than 1.0, the tangent cuts the pressure axis.

We have applied the first two criteria to our observations. We could not apply the third and least strict one because it requires that changes in blood flow be followed over the few seconds after a change in blood pressure and the elasticity of the arterial sack in our preparation made this impossible.

FLOW INDEPENDENT OF PRESSURE

In four experiments, the relation between pressure and flow satisfied the strictest criterion of autoregulation. Over the range of pressures from 80–150 mm Hg, the flow was independent of pressure (fig. 1a and b). In all four experiments the animal was breathing spontaneously.

If one of these experiments (fig. 1a) the animal was artificially ventilated with air for 10 min in order to blow off CO_2, and the flow was then no longer independent of pressure. In another of them (fig. 1b) the pressure was raised to 245 mm Hg for a short time. The flow then became independent of pressure and remained so. (*cf* JONES and BERNE, 1964).

In some other experiments, the flow was sometimes independent of pressure but it was not consistently so. In 32 experiments, we did not find a range of pressures over which the flow was consistently independent of pressure. If the results of these 32 experiments are all taken together, they give mean values for pressure and flow as follows: 70 mm Hg, 6.5 μl/min (2.3–10.4); 100 mm Hg, 16.2 μl/min (4.8–22.6); 130 mm Hg, 21.2 μl/min (8.5–30.8). A straight line joining the points at the two higher pressures extrapolates to pass very near to the origin, so over this range of pressures, $F \simeq KP^{1.0}$. Over the lower range of pressures, the slope of the curve relating flow to pressure is steeper.

If the curves from the 32 experiments are studied individually, they vary in their slopes. 11 are concave to the pressure axis and there is a range of pressures over which the tangent to the curve cuts the flow axis. By the less strict criterion we used, autoregulation was present in these experiments for the resistance to flow was higher at the higher pressures. Thus in a total of 15 out of 36 experiments autoregulation was regularly present. In 4 more it was sometimes present but in the remaining 17 experiments, it was not seen.

THE EFFECT OF CO_2

In some experiments the flow was not spontaneously independent of pressure but was made so by ventilating the animal with 8–12% CO_2, in O_2 for 5 min. We do not suppose that equilibrium for CO_2 was reached within so short a period. CO_2 was given to 12 animals in this way and in four of them the flow became independent of pressure. When the animal was again ventilated with air, the flow eventually reverted to varying with pressure. In one of these experiments, the CO_2/O_2 mixture was changed

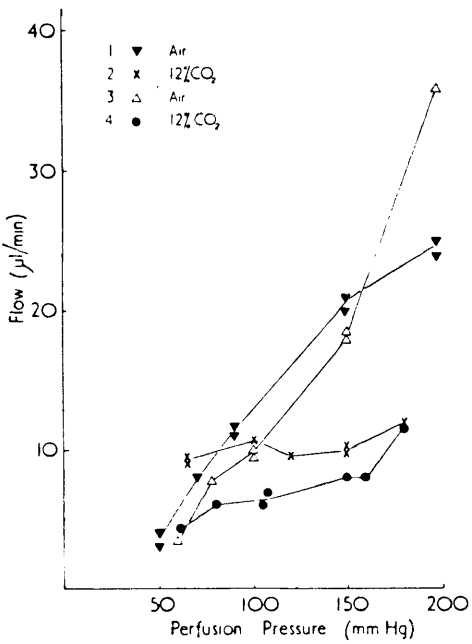

Fig. 2. Flow-pressure relation in rabbit carotid body. Artificial ventilation. The sequence of determinations was: (1) ventilated with air – closed triangles; (2) 12% CO_2 in O_2 – crosses; (3) air – open triangles; (4) 12% CO_2 in O_2 – closed circles. Autoregulation of flow occurred on both occasions when the animal inspired a CO_2-rich gas mixture.

to pure oxygen. The flow ceased being independent of pressure, thus showing that it was the CO_2 rather than the high O_2 content of the gas mixture which had made the flow independent of pressure.

In two other experiments, ventilation with a gas mixture containing CO_2 altered the shape of the pressure flow curve, making the tangent to the curve cut the flow instead of the pressure axis. The less strict criterion of autoregulation was then satisfied. In 6 out of 12 experiments CO_2 produced autoregulation when previously it had not been present. Thus if we consider all the observations we made without administration of CO_2 to the animal, by our less strict criterion autoregulation was present in nearly half of our experiments (*i.e.* 15+?4 of 36). If however, we consider only the experiments in which flow was spontaneously independent of pressure or an attempt was made to make it so by administering CO_2, autoregulation was present in nearly 2/3 of those experiments (10 of 16), and was present by the stricter criterion in half of them (8 of 16).

DALY *et al.* (1954) gave the blood flow through the carotid body of the cat as 2000 ml/100 g/min at 130 mm Hg. In the eight experiments in which autoregulation was present by the strictest criterion, the flow at 130 mm Hg averaged 11.8 µl/min. The average flow in the other experiments at the same pressure was 21.2 µl/min. The mean wet weight of carotid bodies taken from 5 rabbits was 1.65 mg (1.05–2.45 mg). Thus when perfect autoregulation was present, the blood flow was about 700

ml/100 g/min at Daly's standard pressure of 130 mm Hg, but when the flow was not independent of pressure, it averaged about 1350 ml/100 g/min. These figures are about 1/3 and 2/3 of the figure given by DALY *et al.* for the cat. According to ADAMS (1958) the carotid body of the rabbit contains more fibrous tissue than the carotid body of the cat, so the blood flows through true chemoreceptor tissue are more nearly the same than the figures for overall flow would at first suggest.

ADMINISTRATION OF ADRENALINE AND NORADRENALINE

In five experiments, arterial blood was taken into the perfusion system at the peak of the rise in blood pressure which followed the intravenous injection of 10–20 μg of adrenaline or noradrenaline, and the relation between pressure and the flow of this blood was determined. In all five experiments, the flow was reduced by 10–50% of its control value. In three experiments, two with adrenaline and one with noradrenaline the flow eventually returned to control levels but in the other two experiments, both of them with adrenaline, the flow remained permanently reduced. In these five experiments, the flow varied with pressure. In an experiment in which the flow had been made independent of pressure by administering CO_2, adrenaline reduced the flow at all pressures (fig. 3a), but there was still a range of pressure over which the flow was independent of pressure. Thus adrenaline had reduced the level at which autoregulation held the flow independent of pressure.

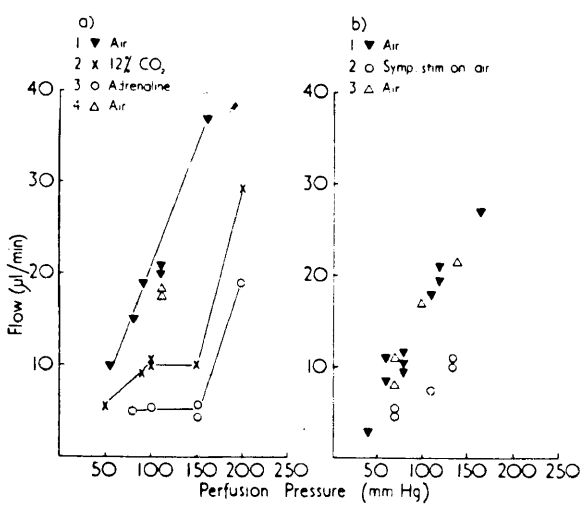

Fig. 3. Flow-pressure relations in rabbit carotid bodies. (a) Artificial ventilation. The sequence of determinations was (1) ventilated with air – closed triangles; (2) 12% CO_2 in O_2 – crosses; (3) CO_2 continued during adrenaline administration (20 μg intravenous) – open circles; (4) air – open triangles. During adrenaline administration the level of autoregulated flow was lowered. (b) Spontaneous respiration. The sequence of determinations was (1) breathing air – closed triangles; (2) stimulation of the postganglionic sympathetic nerve – open circles; (3) air – open triangles. Sympathetic stimulation caused a marked reduction in flow.

EFFECT OF SYMPATHETIC NERVES

In three experiments in which the blood flow was not independent of pressure, during stimulation of the postganglionic sympathetic nerve to the carotid body blood flow was 20–50% less at all pressure than it was in control periods before and after stimulation (fig. 3b). (*cf.* DALY *et al.*, 1954).

EFFECT OF THE CAROTID SINUS NERVE

In four experiments, the distal end of the cut carotid sinus nerve was stimulated close to the carotid body without any effect upon blood flow. In each of these experiments, the flow was not independent of pressure.

OBSERVATIONS ON THE CAT

Our finding of autoregulation in the rabbit stands in contrast to the findings of DALY *et al.* (1954) and of PURVES (1970a) in the cat that the resistance to blood flow falls when the arterial pressure rises. We did six experiments on cats under pentobarbitone, the anaesthetic used by DALY *et al.* and by PURVES, using a technique similar to the one we used in the rabbit. Like DALY *et al.* and PURVES, we found that the blood flow rose steeply with pressure and autoregulation was not present (fig. 4a). Thus it was not differences in the technique of dissection alone that gave the different results. It has been reported that barbiturate anaesthetics may destroy autoregulation (WAUGH, 1964; GRUPP, 1959), so we tried chloralose as an anaesthetic in six cats

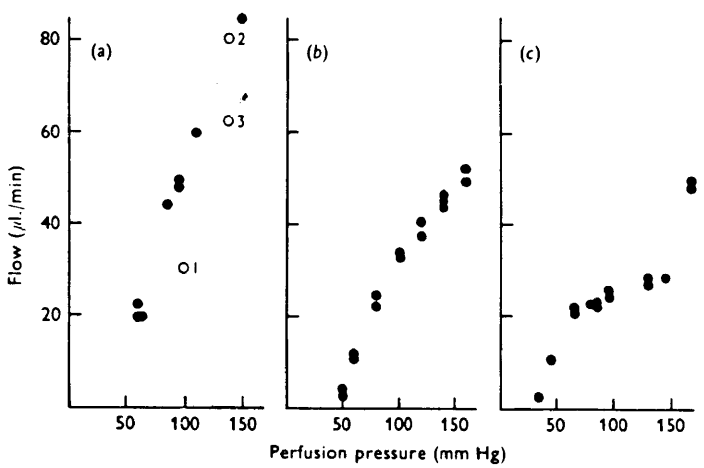

Fig. 4. Flow-pressure relations in carotid bodies of cats. (a) Pentobarbitone anaesthesia. No autoregulation. Also shown are points (numbered circles) taken from PURVES (1970a, fig. 4A): These show the flow at a pressure of 100 mm Hg (1), in the first 5 sec after an abrupt pressure increase to 140 mm Hg (2), and 30 sec after that change in pressure (3). Purves' figures show autoregulation (see text). (b) Chloralose anaesthesia. Resistance increased with rise in pressure, so that tangent to curve between pressures of 100 to 140 mm Hg cuts flow axis. This is autoregulation. (c) Chloralose anaesthesia. Greater increase of resistance with increase of pressure. Tangent to curve between 60 and 150 mm Hg cuts flow axis. Autoregulation.

and found autoregulation to be present in three of them by the strictest criterion that flow should be independent of pressure (fig. 4c), and in another by the less strict criterion that the resistance to flow should increase with pressure (fig. 4b). Thus autoregulation of the blood flow through the carotid body is not a phenomenon peculiar to the rabbit. In the cat we found that stimulation of the carotid sinus nerve slightly increased blood flow, as also had NEIL and O'REGAN (1969) and PURVES (1970a).

Discussion

Our results confirm the basic finding of DALY *et al.* (1954) that the carotid body has a blood flow that is very large in proportion to its weight. We have used criteria of autoregulation which require that there be a range of blood pressures over which the resistance is higher at a higher blood pressure. By these criteria autoregulation was present spontaneously in nearly one half of all experiments. By the strictest criterion that flow be independent of pressure, we have found or were able to produce autoregulation in $\frac{2}{9}$ of our experiments on the rabbit. We also found it in the cat under chloralose. These figures lead one to consider whether autoregulation is regularly present in the intact animal and, if so, whether it is regularly complete. We have found that it is destroyed by a very high blood pressure and also by hyperventilation. That administering CO_2 at times precipitated autoregulation suggests that hyperventilation destroyed it by blowing off CO_2. But in many experiments the blood pressure had not been raised very high and CO_2 did not precipitate autoregulation. Either autoregulation is not regularly present in the intact animals or we have not found out all the ways in which we unwittingly destroyed it. The experiments with cats suggest that anaesthesia may have been one of these. DALY *et al.* (1954) and PURVES (1970a) used barbiturate anaesthesia and did not find autoregulation by the two criteria we have used. However, they measured carotid body flow by collecting venous outflow, a method which does not preclude using the third, and least strict, criterion for autoregulation. Purves regularly observed greater changes in resistance immediately after a pressure change than some 10–15 sec later when a new steady state was reached (see fig. 4a which includes points from PURVES (1970a, fig. 4A). Although Purves does not remark on the significance of this finding, it is, by definition, autoregulation, and the resistance changes he sees follow a similar time course to those seen in similar experiments on the kidney (*e.g.* WAUGH, 1964).

Complete autoregulation seems now to be accepted as normal in the kidney of the healthy intact animal (PITTS, 1968), although, historically, first its presence, and later its completeness, were questioned. It is recognized that "autoregulation in most experimental circumstances is a somewhat labile phenomenon" (JOHNSON, 1964).

If autoregulation is normally present and complete, it must be of great significance in the carotid body. Several workers (NEIL and JOELS, 1963; LEE, MCCLOSKEY and TORRANCE, 1964) have reported that the discharge of the carotid body changes if the blood pressure changes and this effect has usually, though not always (BISCOE, BRADLEY and PURVES, 1970; PURVES, 1970a), been attributed to a change in the

blood flow through the carotid body. If however, in the intact unanaesthetized animal, the blood flow is held independent of blood pressure by autoregulation, the discharge should also be independent of blood pressure.

We have studied a vasoconstrictor agent in only one experiment in which autoregulation was complete and in that experiment it reduced the level at which autoregulation held flow constant, (*cf.* GILMORE, 1964). One can speculate from this experiment that in the normal animal the blood flow is independent of pressure and so also is the afferent nervous discharge. But if the hormonal or nervous influence on the vessels of the carotid body changes, autoregulation holds flow steady at a different level and so it also holds the discharge steady at a different level. If the systemic blood pressure changes when the hormonal and nervous influences on the carotid body change, the change in blood pressure does not affect discharge, provided of course that the blood pressure remains within the range of values over which autoregulation is effective. In this way the responses of the carotid body can be controlled by the nervous system (BISCOE and PURVES, 1967): vasoconstrictor tone does not serve merely to hold the response of the carotid body constant in the face of a changing blood pressure (LEE *et al.*, 1964).

MECHANISM OF AUTOREGULATION

DE CASTRO's (1951) suggestion that a central reflex pathway from the baroreceptors of the carotid body itself is involved, cannot be the explanation of the response we observed because the nerves to the carotid body had been cut in all our experiments. We cannot exclude the possibility that the baroreceptors of chemoreceptor tissue (DE CASTRO, 1951) take part in some form of local reflex, but it should be pointed out that DE CASTRO's (1951) proposal is one of a positive feedback upon the systemic arterial pressure rather than the negative feedback usually associated with the baroreceptors.

NEIL and JOELS (1963) considered the possibility that plasma skimming may account for some of their observations on the carotid body. As an explanation of complete autoregulation it cannot stand for any vascular bed because the theory states (PAPPENHEIMER and KINTER, 1956) that the resistance to blood flow increases at a rise of arterial pressure because more intense plasma skimming results from the more nearly complete cell separation which takes place when the velocity of blood is greater. But if autoregulation is complete, the velocity of blood flow is independent of pressure and so also is cell separation. Thus the cell separation theory cannot, without accessory hypotheses, account for a finding that flow is quite independent of pressure. Some other mechanism must be involved.

Vasodilator metabolites have been proposed to account for autoregulation in tissues such as muscle, but it is unlikely that they are involved in the carotid body where the blood flow is so great that arteriovenous concentration differences are trivial. A tissue pressure mechanism (WINTON, 1933) is conceivable, for massive fibrous septa surround the glomeruli of the rabbit's carotid body, but this theory would not account for the effects of CO_2, just as in the kidney it will not account

for the effect of cyanide and other drugs in abolishing autoregulation (MILES, VENTOM and DE WARDENER, 1954).

By exclusion, we are left with the myogenic theory which supposes that vascular smooth muscle responds to changes in the tension to which it is exposed. If one regards the vascular resistance as being made up of a single ideal autoregulating arteriole, its wall has the odd relation between tension and length, that tension is inversely related to the cube of the length: $T \propto L^{-3}$. This is because F (flow) $\propto R^4P$ (Poiseuille). But $P=T/R$ (Laplace). Therefore $F \propto R^4T/R$. But in complete autoregulation F is constant. Therefore $T \propto R^{-3}$. The problem with the myogenic theory is to suggest how the wall of the arteriole might achieve this unusual average behaviour. FOLKOW (1964) suggested that the wall of the arteriolar resistance can be divided up into several rhythmically contracting units which respond to an increase in tension within them by changing both the length to which they contract and also the frequency with which they contract. This theory requires that the units periodically relax, but JOHNSON's (1967) direct observations of autoregulating arterioles did not show this, at least at the level of the whole arteriole. Also rhythmical activity of arterioles in chemoreceptors, by altering flow through chemoreceptors should cause their discharge to wax and wane, but we have very seldom seen this in the cat, though we have seen it a few times in chemoreceptor fibres dissected from the depressor nerve of the dog.

The myogenic theory could be elaborated in another way: one could think of the arteriolar media being made up of a series of functionally distinct annular elements distributed along the length of the arteriole. Each of them can be triggered into a sustained all or nothing contraction if the pressure within it exceeds some threshold value. So contraction extends distally along the arteriole to a point at which the pressure has been brought down to the threshold value for eliciting contraction. Thus the pressure presented to the vascular bed distal to this point is held constant just below the threshold level for triggering contraction, and so the flow through the constant distal vascular resistance is also held constant.

But any theory of autoregulation has also to account for the fact that the resistance falls when the blood pressure falls, so one has to postulate that vascular smooth muscle has a property similar to one found in insect fibrillar muscle (PRINGLE, 1967) which ceases developing active tension if it is allowed to shorten.

An alternative elaboration of the myogenic theory can be developed from FOLKOW's idea (1964) that there are pacemaker regions in the arterioles. If these were at the capillary end of the arteriole and they responded to an increase in the pressure within them by setting up activity which propagated proximally and caused the resistance of the arteriole to increase, they would act as part of a negative feedback mechanism which would hold the pressure at the distal end of the arteriole constant. One could get round the problem of the response to a falling pressure by supposing that the pacemaker regions do not themselves develop significant tension and so are always exposed to the pressure in the part of the vessel in which they are situated.

The latter two elaborations of the myogenic theory predict that a change in venous

pressure should have a more striking effect on vascular resistance than an equal change in arterial pressure because the receptors are at the venous end of the arterioles. JOHNSON (1965) has found this to be true in the intestine, but THURAU (1964) did not find it in the kidney. But the kidney, having two arterioles in series, with the upstream one responsible for autoregulation, is a peculiar case.

GUYTON (1964) and WAUGH (1964) have remarked that it is surprising that autoregulation has often been found to be complete but that no one has ever found it to be excessive in such a way that an increase in pressure actually decreases the flow. The receptor mechanisms we propose sense the pressure at the distal end of the arteriolar resistance and so they would not be expected ever to give an excessive autoregulation. Vasomotor agents might alter the threshold pressure for exciting the receptor mechanism and so alter the level at which autoregulation holds flow constant, in the way that GILMORE (1964) has already reported in the kidney, and we have seen once in the carotid body.

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THE RESPONSES OF CAROTID BODY CHEMORECEPTORS IN THE CAT TO SUDDEN CHANGES OF HYPERCAPNIC AND HYPOXIC STIMULI

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Abstract. Chemical stimuli in the arterial blood supplying the carotid bodies of cats were suddenly changed from one steady level to another, while chemoreceptor activity was recorded from single or few-fibre strands of the carotid sinus nerve. When a hypercapnic stimulus was given, the discharge rose to a maximum at about one second after the start of the stimulus and then adapted to a lower steady level over the succeeding 10–20 sec. On removal of hypercapnia there was a sudden undershoot in discharge before it settled at a steady level. In response to a hypoxic stimulus discharge always increased more slowly than in response to hypercapnia. There was little, if any, overshoot, and on removal of the stimulus, discharge declined without undershoot. When the carbonic anhydrase of the carotid body, but not of the perfusing blood was inhibited, the response to hypercapnia was slower, did not overshoot, and slowly came to the same steady level which it had reached in the steady state of its response before carbonic anhydrase was inhibited. Mechanisms of chemoreceptor activation are discussed.

Arterial chemoreceptors
Carbonic anhydrase
Carotid body
Excitation mechanism
Hypercapnia
Hypoxia

We have observed the time course of the change in discharge of chemoreceptor fibres of the carotid sinus nerve in cats when the pO_2 or pCO_2 of the blood in the carotid artery was suddenly changed from one steady level to another.

In this paper we pay particular attention to the responses to hypercapnia. SAMAAN and STELLA (1935) reported a prompt response to the inhalation of CO_2. CROPP and COMROE (1961), FITZGERALD *et al.* (1964), BLACK and TORRANCE (1967), and DUTTON *et al.* (1967), all reported very rapid reflex respiratory responses to a sudden rise of pCO_2 in the carotid arterial blood. FITZGERALD *et al.* (1964) were able to show this response when the arterial pCO_2 was raised as little as 2 torr. DUTTON *et al.* (1967) found considerable adaptation within seconds of the peak ventilatory response.

Our results confirm, with direct recording from single chemoreceptor fibres, that the response to hypercapnia is immediate and that adaptation of the response occurs.

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On removal of the stimulus, discharge falls to a minimum and then rises to a new steady level. When the carbonic anhydrase of the carotid body is inhibited the response to hypercapnia is strikingly slowed.

Preliminary accounts of this work have previously been published (BLACK, MCCLOSKEY and TORRANCE, 1966; MCCLOSKEY, 1968).

Methods

RECORDING APPARATUS

The recording electrodes were made of fine stainless steel wire. Impulses were led into a Tektronix type 122 preamplifier and then to an oscilloscope for preliminary observation or to one channel of the recording apparatus, a Mingograf Cardirex 24 B (Elema-Schönander, Stockholm). This direct writing ink-jet recorder has galvanometers with a natural frequency of 610 cps. Blood pressure was measured with an Elema-Schönander Electromanometer type 460 and was recorded on a second channel of the Mingograf.

EXPERIMENTAL

Cats were anaesthetized with 40 mg/kg pentobarbitone (Nembutal: Abbott) intraperitoneally. The trachea was cannulated low in the neck, and the pretracheal muscles,

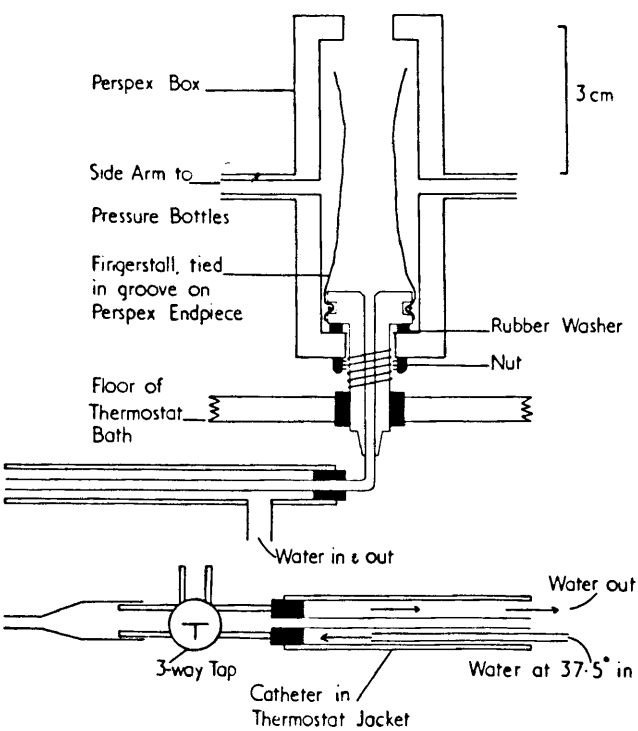

Fig. 1. Perfusion apparatus. Upper: storage sac. Lower: Catheter connecting storage sac to the external carotid artery of the experimental animal.

larynx and pharynx were removed up to the level of the hyoid bone. A femoral vein was cannulated. Cotton loops were passed through the flank around the abdominal aorta cephalic to the coeliac artery and caudal to the superior mesenteric artery: various fractions of the arterial bed below the diaphragm could be occluded temporarily by pulling one of these loops into a narrow tube. A perfusion system was connected through a 3-way tap to a nylon cannula tied into the external carotid artery beyond the origin of the lingual artery.

The perfusion system was of simple design: a rubber fingerstall was used as a storage reservoir from which blood could be expelled by applying a known air pressure to the outside of it (fig. 1). Each end of the section of fingerstall was tied to a siliconed end-piece which fitted through a hole in the end of a perspex box, and screwed tight. The perspex box had an airtight lid and was clamped vertically in a water bath held at a temperature of 37.5 °C. The upper end-piece was used only in washing the sac through with heparin saline between observations and was sealed by another tap. The lower end-piece was connected through the floor of the bath to the 3-way tap attached to the nylon cannula in the external carotid artery. Between the heated bath and the animal the cannula was enclosed in a jacket through which heated water from the bath was circulated, so that the distance from the end of the jacket to the artery was less than 3 cm. A side tube in the perspex box could be connected to either of two pressure bottles, fitted with Hg manometers, so that any desired air pressure could be applied to the surface of the sac. The capacity of the sac was about 10 ml.

Abrupt changes of stimuli were obtained as follows: the storage sac was allowed to fill with blood while the animal was inspiring one gas mixture. The inspired gas mixture was then changed, and when it was judged from the continuously monitored chemoreceptor discharge that a new steady state had been reached, the stored blood was perfused back. Usually this meant holding blood in the storage sac for approximately 3 min. In many experiments the common carotid artery below the bifurcation was left open during the return perfusion, and in these experiments the perfusion caused a reversal of the direction of flow in the common carotid artery with little change (approximately 5–20 mm Hg) in the blood pressure measured from the lingual artery. An advantage of this procedure was that there was another abrupt change of stimulus at the conclusion of the perfusion, when the tap in the inflow line was momentarily opened to the atmosphere to allow rapid return of systemic arterial blood through the bifurcation. Perfusions given in this way were of relatively short duration, 10–60 sec. Small arterial branches running from the bifurcation were usually tied, and the occipital, ascending pharyngeal, and, when present, internal carotid arteries were tied when it was certain that this could be done without interfering with the venous drainage of the glomus. In a number of experiments a "bulldog" clip was applied to the common carotid artery a few seconds after the start of the perfusion, which could then be continued for up to 3 min. Blood pressure within the arterial sac so formed was recorded through the lingual artery.

In all experiments where blood was taken into the perfusion apparatus, the animals were first given heparin (Pularin: Evans Medical Limited; 2500 i.u. per kg). Some

observations were made with animals breathing spontaneously, but in most cases spontaneous respiration was suppressed by artificial ventilation with a Starling Ideal pump.

The vago-sympathetic trunks were cut low in the neck. The carotid sinus nerve was identified and cut where it joined the glossopharyngeal, and was dissected on a rigid, earthed, stainless steel plate with a blackened upper surface. Preparations were identified by their sporadic discharge, but were accepted only if they responded to hypoxia. Preparations were tested to confirm that they contained no baroreceptor fibres by occluding the upper abdominal aorta and examining the discharge for evidence of impulses with a cardiac rhythm.

Gas mixtures were made up with flowmeters and stored in Douglas bags. They were administered through a respiratory valve or through the respiratory pump. Rectal temperature was kept constant within the range 37–39 °C, and the paraffin pool was kept at a similar temperature. Warm dextran was used to maintain the blood pressure if necessary.

The gas mixtures used in the experiments to be described were: hypoxic, 5–14% O_2 in N_2; hypercapnic, 5–50% CO_2 in O_2; "mixed", hypoxic and hypercapnic stimuli together.

For very low pO_2s blood was tonometered and the pO_2 measured.

Injection: Acetazolamide sodium: Diamox, Lederle Laboratories.

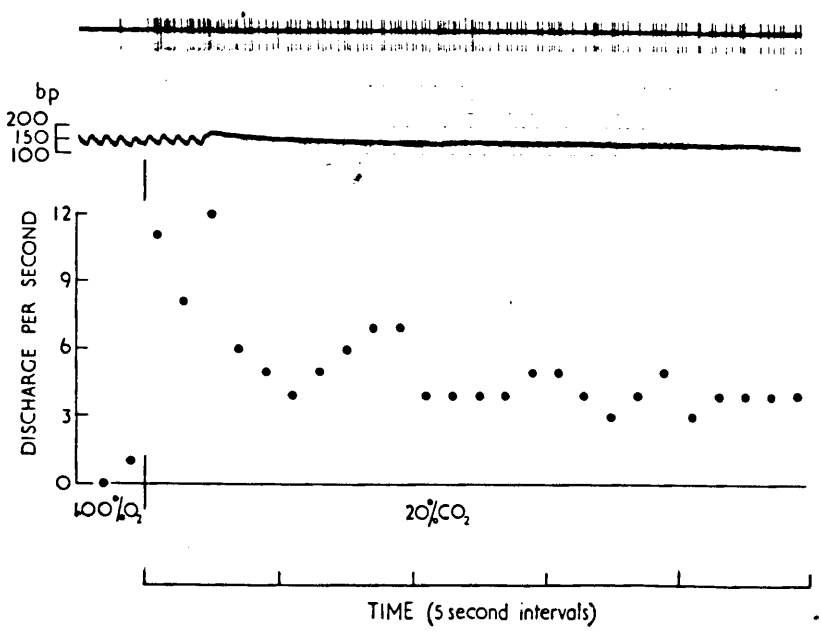

Fig. 2. Single chemoreceptor fibre. The upper panel shows the discharge response to sudden application of hypercapnia at the mark. The lower panel shows the same response graphically. At the point where the blood pressure, measured in the lingual artery, becomes non-pulsatile, a clip was placed on the common carotid artery. CO_2 was given in O_2. The gases indicated are the mixtures breathed when the perfusing blood was taken.

Results

HYPERCAPNIA

The fibres from which we recorded were defined as chemoreceptor if they responded to hypoxia: all these fibres responded also to hypercapnia. In investigating responses to hypercapnia we gave the carbon dioxide in oxygen so that no hypoxic stimulus would be present simultaneously. The concentration of CO_2 given was chosen so that a level of discharge was attained comparable to that seen in moderately severe hypoxia: in practice this meant that high concentrations of inspired CO_2 were used (see fig. 5a).

The response of chemoreceptors to the sudden application of a hypercapnic stimulus is immediate. The discharge usually reaches a maximum within about 1 sec and always within 2–3 sec. It adapts to a lower steady level with a half time of about 5–10 sec (fig. 2). When the stimulus is removed suddenly, the reverse of this process is observed – the discharge falls rapidly to a minimum, though perhaps a little less rapidly than it rises when hypercapnia is applied, and then returns slowly to its

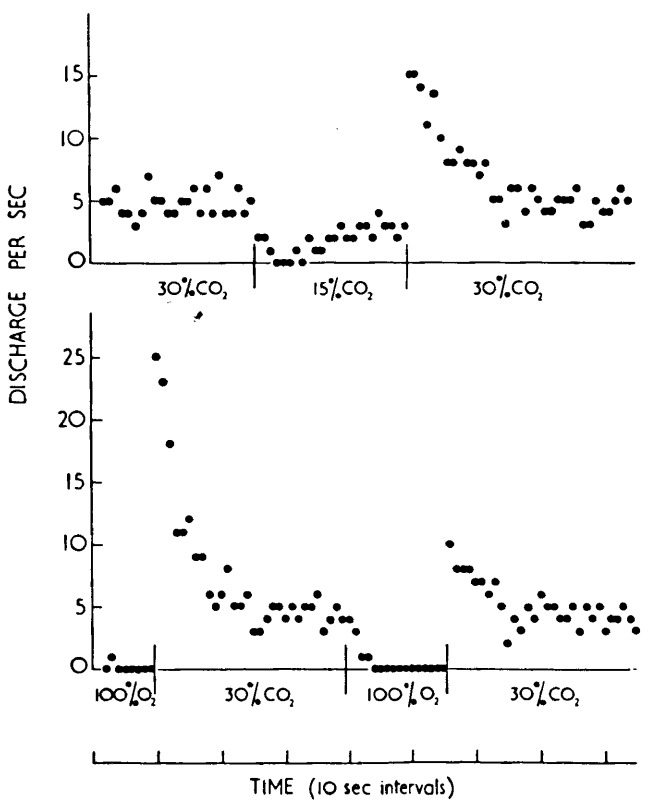

Fig. 3a (upper). Single chemoreceptor fibre. Discharge in response to a sudden decrease, followed by a sudden increase, in the level of hypercapnic stimulus.

Fig. 3b (lower). Same fibre. Discharge in response to a hypercapnic stimulus given, then removed, then re-applied 16 sec later.

control level. A similar effect is seen if the intensity of the stimulus is reduced and then restored to its initial level (fig. 3a). As with any adapting receptor, reducing the stimulus may temporarily abolish discharge, and then the discharge builds up to a steady level below the initial level.

When a hypercapnic stimulus is applied, then removed, and within a short time reapplied, the second response to the stimulus does not reach as high a level as the first before adapting. A second stimulus applied at 30 sec or less after removal of the first gives a diminished response (fig. 3b). A second stimulus given 45 sec after removal of the first gives a maximum peak response.

All the effects described above were best seen when both the systemic arterial pressure and the perfusion pressure were greater than 100 mm Hg: below this pressure the response was slower. The levels of hypercapnia used in this part of the work were 15–50% CO_2 in O_2, inspired.

HYPOXIA

Although the response to hypoxia was sometimes very fast, reaching a maximum within 1–5 sec, it was always slower than the response to hypercapnia of the same preparation at a comparable perfusion pressure. Figure 4 shows one of the fastest responses to hypoxia that we saw, and also the still faster response to hypercapnia of the same preparation. The fall of discharge on removal of hypoxia was less variable, starting within 1–3 sec, and being complete within 5–7 sec. Adaptation of the response to hypoxia was only occasionally seen, and when present was less striking than that observed regularly in the response to hypercapnia. In general, the response to a change in the level of hypoxia was fastest when the perfusion pressure was greater

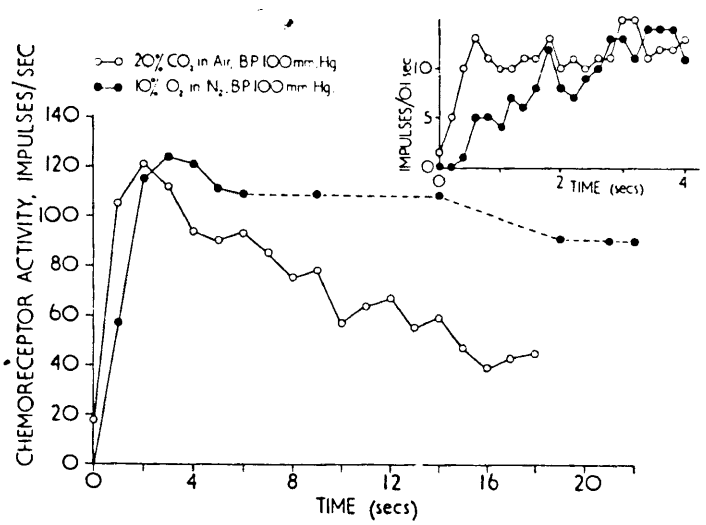

Fig. 4. Multifibre chemoreceptor preparation. Comparison of a response to hypercapnia with the fastest response to hypoxia seen in the same preparation at the same blood pressure. Both responses are plotted through 20 sec in the main part of the figure, and through 4 sec on an expanded time-scale in the inset upper-right figure.

than 100 mm Hg: if the pressure was below 60 mm Hg the response could take more than 20 sec to reach its peak. It would appear that the fastest responses are the most "normal".

If the blood perfused was made intensely hypoxic, by tonometry to a pO_2 of 10 torr or less the response quickly reached a maximum and then declined to a lower level than that at which it was sustained by less severe hypoxia. As this later decline was seen only with the most intense hypoxia it was attributed to failure of the nerve ending rather than to adaptation (*cf.* PAINTAL, 1967). Substitution of normoxic, or less severely hypoxic blood, in such a "failed" preparation could restore its responses. We have seen similar failures of response after prolonged stagnant asphyxia, as have WIEMER and OTT (1963).

HYPOXIA AND HYPERCAPNIA

When steady hypercapnia was replaced suddenly by hypoxia which would eventually give approximately the same steady rate of discharge, the discharge did not remain steady. When hypoxia replaced hypercapnia the discharge dropped immediately to a

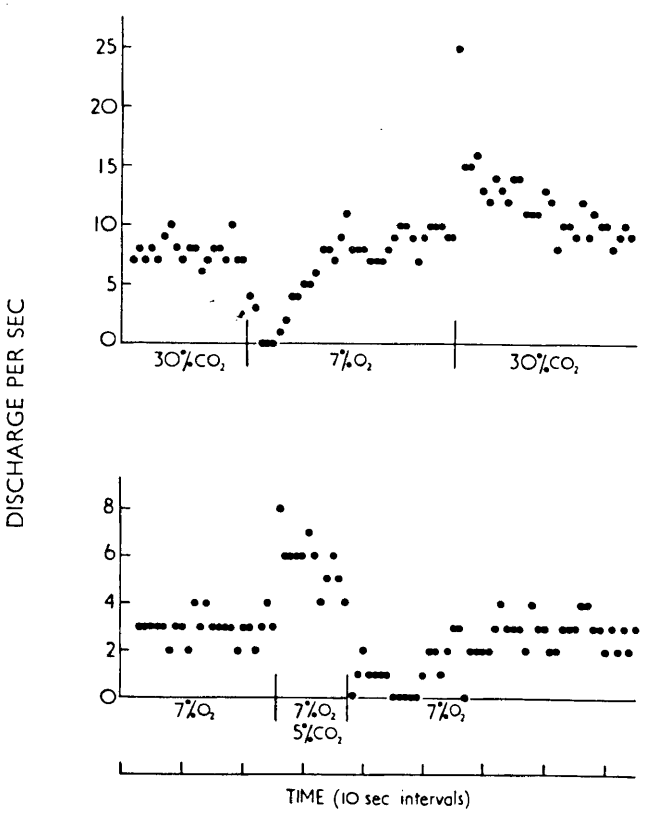

Fig. 5a (upper). Single chemoreceptor fibre. Changes in discharge on alternating a hypercapnic and a hypoxic stimulus which in the steady state gave similar responses.

Fig. 5b (lower). Single chemoreceptor fibre. Changes in discharge when a hypercapnic stimulus is applied and then removed during maintained hypoxia.

minimum, then slowly built up to its steady hypoxic level. When hypercapnia replaced hypoxia, the discharge rose immediately to a maximum, then adapted to its steady hypercapnic level (fig. 5a).

In another type of experiment, hypercapnia was added suddenly to a maintained level of hypoxia, and then removed suddenly from it. At the addition of hypercapnia to hypoxia the discharge rose to a peak and adapted "down"; at the removal of hypercapnia, the discharge fell immediately to a minimum which was lower than the level for hypoxia in the control period, even though hypoxia was still present, and then adapted "up" (fig. 5b). The smallest hypercapnic stimulus used here was 5% CO_2 in 7% O_2.

THE EFFECT OF A CARBONIC ANHYDRASE INHIBITOR ON THE RESPONSE TO HYPERCAPNIA

The enzyme carbonic anhydrase has been reported to occur in the carotid body (LEE and MATTENHEIMER, 1964, 1965; WOODS, 1967). It was thought that this enzyme might be necessary for the rapidity of the response of chemoreceptors to hypercapnia. To test this hypothesis acetazolamide (Diamox) was given to inhibit the carbonic anhydrase of the carotid body.

The control response to hypercapnia was obtained. A sample of hypercapnic blood was then taken into the perfusion apparatus, and the animal was given a CO_2-free gas mixture to breathe. Acetazolamide was administered intravenously (50–100 mg/kg), and was given 3–4 min to act in the animal: if the drug has access to the enzyme it achieves 95% inhibition in this time (MAREN, PARCELL and MALIK,

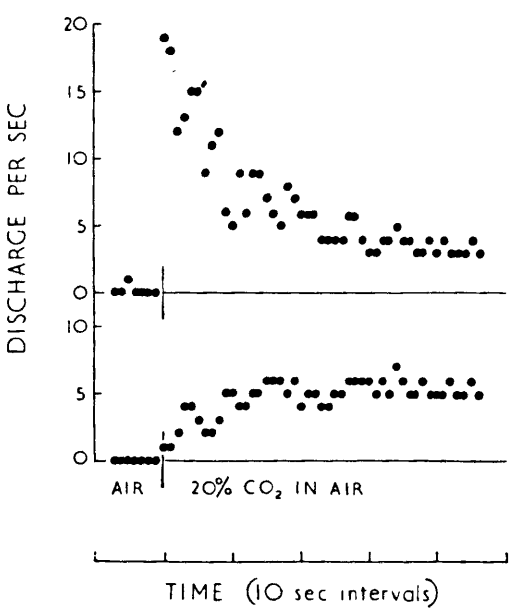

Fig. 6. Single chemoreceptor fibre. Discharge response to sudden application of a hypercapnic stimulus before (upper), and after (lower), inhibiting the carbonic anhydrase of the carotid body with acetazolamide (Diamox).

1960). The stored hypercapnic blood was then perfused back. This method of testing the effect of acetazolamide allows it to act on the glomus but prevents it from affecting the rate at which the hypercapnic blood to be perfused can give off CO_2 to the carotid body. It allows only one observation in any experiment: six experiments were done. In each of them the control response to hypercapnia was, as described previously, a very fast increase in discharge, followed by a slower adaptation (fig. 6a). After acetazolamide, the response to hypercapnia was a slow rise in discharge (fig. 6b). In one experiment the discharge after acetazolamide rose almost to the level of the peak response of the control; in the other five experiments the discharge reached a level lower than the maximum in the control response. Adaptation was not seen.

The response to hypoxia was not strikingly altered after acetazolamide.

Discussion

The present experiments were aimed at investigating the effect of a sudden change in the stimulus to chemoreceptors. At the start of a perfusion with hypoxic blood, the carotid artery appeared to change colour instantaneously. The change in the stimulus at the arterial end of the sinusoids of the carotid body must have been at least as sudden in onset as the response to which it gave rise: with hypercapnia the response began within a second of the start of the perfusion.

Many of the errors that might have been introduced by the use of the perfusion apparatus can be discounted on the grounds of two findings. First, it was usual, as a control, to take blood into the perfusion system and to perfuse it back without changing the inspired gas meanwhile: the discharge of chemoreceptors was not influenced by this procedure. Second, a change in the stimulus could be given either at the start of a perfusion or at the end: all our observations, except those on the response after acetazolamide were made both when the stimulus was carried in the perfused blood and when it was carried in the systemic blood. These controls show that no significant errors were introduced by dead space in the perfusion system, changes in the viscosity or temperature of the blood whilst it was in the perfusion system, or changes in pressure at the start or finish of a perfusion.

For reasons recently re-emphasised by PAINTAL (1968), we have used single or few-fibre preparations of the carotid sinus nerve. By doing this we have had to use large stimuli when studying hypercapnia in the presence of hyperoxia: the time course of the development of the slight response to a small hypercapnic stimulus is lost in the natural randomness of the discharge of chemoreceptors (BISCOE and TAYLOR, 1963; STEIN, 1968). However, most workers (VON EULER *et al.*, 1939; WITZLEB, 1963; HORNBEIN and ROOS, 1963), though not all (BISCOE *et al.*, 1970; HORNBEIN, 1968) have reported an approximately linear relation between pCO_2 and discharge which extends far beyond the physiological range. And further, FITZGERALD *et al.* (1964) and DUTTON *et al.* (1967) found that the response of ventilation to sudden hypercapnia was about as rapid as the responses we recorded from chemoreceptors, although they used increments of pCO_2 sometimes as small as 2–3 torr.

SAMAAN and STELLA (1935), CROPP and COMROE (1961), FITZGERALD *et al.* (1964), DUTTON *et al.* (1967), GRAY (1968) and BLACK and TORRANCE (1967), all reported that chemoreceptors respond very rapidly to hypercapnia. DUTTON *et al.* found considerable adaptation of the ventilatory response within seconds of its initial peak. Our work confirms with direct recording from single and few-fibre preparations, that chemoreceptors respond rapidly to hypercapnia and that they adapt to this stimulus. Further we have found that on removal of hypercapnia, the discharge falls rapidly to a minimum and then rises to a steady level. Similar observations have been made by FITZGERALD *et al.* (1969). DUTTON *et al.* (1967) however, did not see the corresponding negative phase of adaptation, or "off-effect", when hypercapnia was removed. FIDONE and SATO (1969) showed that acid, ACh and NaCN, injected into the carotid artery, gave a discharge in carotid chemoreceptor A fibres which reached a maximum well within a second of its start, but that the carotid chemoreceptor C fibres responded more slowly. While it is likely that, by our methods, we selected principally A fibres because of their size, it is possible that some of the slower responses we observed were in C fibres.

Two aspects of the responses we observed raise interesting problems. First, the response to hypercapnia was more rapid than the response to hypoxia, and it adapted. Second, when the carbonic anhydrase of the carotid body was poisoned, the response to hypercapnia developed slowly and did not adapt.

The onset of the response to CO_2 is very rapid and that to hypoxia is distinctly slower. However, when FORSTER (1968) considered the rate at which the gas tensions would change within the carotid body at a sudden change of the gas tensions presented to it by the blood in the sinusoids, he calculated that even at the remotest points from the vessels the pO_2 would come to within 5% of its equilibrium level within 0.38 sec. In contrast, the time for pCO_2 came to 8 sec if he assumed that the carbonic anhydrase of the carotid body was uniformly distributed throughout it so that the CO_2 is rapidly hydrated and buffered in the carotid body. If, however, he assumed that the carbonic anhydrase of the carotid body was inactive and that the hydration of CO_2 was therefore slow, less CO_2 had to move and so the time for pCO_2 came out to be very similar to that for pO_2. If one considers also a point made by BARGETON (1967) the contrast between calculations and the observed speeds of response to these two gases becomes even more striking. FORSTER (1968) supposed that the capacity of the carotid body for O_2 was similar to that of water and so very much less than that of the blood, but that the difference for CO_2 was very much less. Thus if the pCO_2 of the arterial blood were suddenly changed, the pCO_2 of the blood at the ends of the sinusoids would reach a new steady level more slowly than would the pO_2 at the same point after a sudden change in arterial pO_2.

In view of these considerations the response to CO_2 of the carotid body with normal carbonic anhydrase is so prompt that it appears at first sight as if it is a response of nerve endings which are directly exposed to the blood as it enters the sinusoids, rather than as a response of nerve endings situated at the venous end of the sinusoids or remote from the sinusoids. But histology provides no support for

such a suggestion: BISCOE and SILVER (1966) showed that such endings as there are near to the sinusoids are of sympathetic origin rather than glossopharyngeal.

GRAY (1968) examined the responses to changes of pCO_2 and pH of the saline perfused carotid body and concluded that the behaviour of that preparation fits well with the response being one to extracellular pH and being determined by the movement from the perfusate of CO_2 rapidly and of bicarbonate more slowly. He did not see responses to CO_2 as rapid as ours. This could in part be due to the dead space in his perfusion system, which took 3 sec to wash through and which would delay his stimuli and reduce their rate of change. Gray's preparation was perfused with a bicarbonate buffered saline so the extracellular fluid also would have contained only a bicarbonate:CO_2 buffer. In such a situation, the carbonic anhydrase at the receptor site would be less important than in the blood perfused preparation since there would be no extracellular buffer for CO_2 present in the carotid body and so inhibition of carbonic anhydrase would not be expected to change much the speed of response. Gray's preparation differed from ours also in the fact that his saline perfusate, lacking carbonic anhydrase, would not give up CO_2 to the carotid body as quickly as would blood. This may account for his usually seeing less rapid responses to CO_2 than we did, in spite of the point about extracellular buffering which would argue the reverse.

The very rapid onset of the response to CO_2 might be explained if the carbonic anhydrase of the carotid body were not uniformly distributed within it. Suppose that it is concentrated in scattered small regions. Then CO_2 would diffuse through the carotid body as quickly as oxygen. If the receptors for pH were near to the carbonic anhydrase they would be excited quickly. One possible particular case would be that carbonic anhydrase is located on the surface of Type II cells where these ensheath fine nerve endings (DE KOCK and DUNN, 1968). Carbon dioxide diffusing into this space would be hydrated and so would quickly change the pH to which the nerve endings are exposed. The space being small, little CO_2 would have to be hydrated to give a rapid and maximal swing of pH within it. The relation between the initial and the final swing of pH would be determined by the relation between the buffering capacities for CO_2 of the restricted space and that of the blood.

If the buffering capacity of the restricted space we have discussed is sufficiently low but the bicarbonate of the blood has slow access to it, GRAY's (1968) postulate of a simple pH receptor will account for adaptation of the response to hypercapnia. And if, further, there is carbonic anhydrase within or on the membranes surrounding the space, the sudden onset of the response to CO_2 and its slowing by acetazolamide are also explained.

In our experiments acetazolamide slowed the response to hypercapnia within 3–4 min of being injected intravenously. This timing fits well with the idea that the enzyme it affected to slow the response to hypercapnia was easily accessible from the blood and was not within cells. In another respect also our findings are not easily fitted by a model consisting of a receptor which responds, not to the extracellular pH, but to the intracellular pH of cells which contain carbonic anhydrase. In the

cells of such a model, the pH would initially fall rapidly as CO_2 was hydrated within them by carbonic anhydrase, and then it would continue falling, but more slowly, as bicarbonate diffused out of them as in the chloride shift of red blood cells. Thus only if an intracellular receptor for pH adapted strikingly would it respond, as we have found that carotid chemoreceptors do respond to hypercapnia, with an initial peak of discharge followed by a decline.

FIDONE and SATO (1969) found that chemoreceptors respond to cyanide as quickly as they respond to acid and to acetylcholine, and all these three responses were as quick as those we found to hypercapnia. It is surprising that the response to cyanide was more rapid than the responses we found to hypoxia. The mechanism of excitation of chemoreceptors by cyanide was discussed by FORSTER (1968): our observations, taken with those of Fidone and Sato support his suggestion that cyanide does not excite chemoreceptors only by stopping oxygen uptake by cytochrome oxidase.

Our finding that the response to sudden severe hypoxia starts to fail well within a minute shows that oxygen lack is concerned in the failure of the response to complete ischaemia (WIEMER and OTT, 1963), and also shows how soon may severe hypoxia (PAINTAL, 1967) start to impair the function of chemoreceptors. This behaviour was sometimes seen if the pO_2 was above 20 torr, which would question the explanation HORNBEIN (1968) has given of the reduction in discharge he sometimes sees at low pO_2. Although the carotid body does contain lactic dehydrogenase (LEE and MATTENHEIMER, 1964) it seems to be unable to sustain a response to severe hypoxia on glycolysis alone: oxidative metabolism is necessary. This behaviour would hardly be expected on the older view that the carotid body is a rugged receptor, the *ultimum moriens*, but it is more consistent with the more recent view of it that it is a delicate mechanism, sensitive to changes of pO_2 at, or even well above, levels typical of life at sea level.

All the fibres we investigated responded to hypercapnia as well as to hypoxia and consistently the response to hypercapnia was more rapid than that to hypoxia. This would suggest that hypercapnia does not act by affecting an early stage in whatever set of reactions leads to the response to hypoxia. It leaves it conceivable though, that hypoxia achieves its effect through a change in pH.

Although it has been calculated (TORRANCE, 1968) that the shift of pH which would occur in the blood leaving chemoreceptors upon switching the metabolism of the carotid body from aerobic to anaerobic would be too small to account for the responses of chemoreceptors to hypoxia, the possibility that pH changes restricted to a small compartment of the carotid body are important may require reconsideration of whether hypoxia excites nerve endings by causing a localised acidification.

The differences we have found between the responses of chemoreceptors to step changes to hypoxia and hypercapnia suggest that their response would follow oscillations in a stimulus up to a higher frequency if the stimulus was hypercapnia than if it was hypoxia, and this is what FITZGERALD *et al.* (1969) found. It is surprising in view of that one of their findings that they do not seem to have found a significant difference between the speeds of response of chemoreceptors to *step* changes in

hypoxia and in hypercapnia: the speed of each response was similar to that we found to hypoxia. In earlier work, however, LEITNER and DEJOURS (1968) had found responses to acid as rapid as those we have found to hypercapnia, and FIDONE and SATO (1969) have recently confirmed LEITNER and DEJOURS (1968). Overshoots were not seen in these studies, but on GRAY's (1968) theory they were not to be expected, for the stimulus was blood to which acid had been added in a closed system from which CO_2 was not allowed to escape.

GRAY (1971) recently reported some small effects of inhibitors of carbonic anhydrase upon the carotid body. It seems to us that in studying a response as rapid as that of chemoreceptors to hypercapnia, it is essential to apply the stimulus suddenly, or else to know how it develops. Our method of reversing flow in the carotid artery against a buffer of the aortic blood pressure allowed us to do this and we have found very marked effects of acetazolamide on the speed of response. GRAY (1971) assumes that the pCO_2 throughout the carotid body instantaneously reaches a new steady level. We have already remarked that it is unlikely that this is so.

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Intracellular potentials in the carotid body

Here we report experiments in which we looked for, but failed to find, changes in the membrane potentials of carotid body cells in response to centrifugal impulses in the carotid sinus nerve.

De Castro[3] described carotid body cells as having sensory synapses of glossopharyngeal origin upon them. He suggested therefore that the carotid body is a receptor organ, and Heymans confirmed this suggestion[12]. De Castro[4] also stated that there are efferent fibres in the carotid sinus nerve and asserted that these supplied the blood vessels of the carotid body, as also do sympathetic fibres. It is now established that the sympathetic innervation provides vasoconstrictor tone to the carotid body vessels[5,14,17], and that the efferent carotid sinus nerve innervation can cause vasodilatation[14,15]. However, it has recently been suggested that the synapse which de Castro regarded as sensory is in fact an efferent one, and that stimulation of the carotid sinus nerve affects the cells of the carotid body[1,18]. Efferent activity has been recorded in the carotid sinus nerve[2,16], and it has been claimed that the efferent fibres are inhibitory to the chemoreceptors[10,15,18]. Also, there has been described recently a different set of nerve endings in the carotid body, which do not synapse with cells[13], and this second group of endings could be responsible for the undoubted chemoreceptor function of the carotid body.

If this new view of the carotid body is correct, stimulation of the carotid sinus nerve could well give junctional potentials in carotid body cells.

In the present study intracellular potentials were recorded in 26 carotid bodies. The major part of the study was carried out in the *in vitro* preparation described by Eyzaguirre and Lewin[8]. For this, carotid bodies were removed from pentobarbitone anaesthetized cats and immediately transferred to a perfusion chamber through which Ringer–Locke solution, equilibrated with 95% O_2 and 5% CO_2, flowed at 1–5 ml/min. Throughout any one experiment pH of the fluid was constant at about 7.45, and its temperature was 36–37°C. A stationary layer of paraffin oil floated above the moving fluid bathing the carotid body, and the carotid sinus nerve could be drawn up into this and laid over a pair of Ag–AgCl electrodes for stimulation or recording. Further observations were made *in vivo* in 5 cats anaesthetized with pentobarbitone sodium (Nembutal: Abbott, 35 mg/kg), in which the carotid bodies were exposed by a medial excision in the neck.

Glass microelectrodes filled with 3 *M* KCl (resistances 15–100 MΩ) were used, joined through a Ag–AgCl connector to a cathode follower. Intracellular potentials were displayed on an oscilloscope, and could be photographed. The microelectrodes were moved by a Huxley mechanical micromanipulator which allowed movements of 0.2 μm. An isolated stimulator was used. In preliminary experiments the strength–duration relation for maximal activation of carotid nerve C-fibres was determined by observations of compound action potentials in nerves removed and maintained as in the principal study. Thereafter, stimuli supramaximal for A- and C-fibre activation were always given: usually 600 μA for 1.5 msec.

The criterion for penetration of a cell was a sudden change of potential upon

advancing the microelectrode. Confirmation that the potentials recorded were from cells was the regular observation that addition to the perfusate of the *in vitro* preparation of 0.1–1.0 ml of KCl solution (150 mEquiv./l) led to a depolarization, usually to less than half the resting potential, followed by a repolarization upon washing away the KCl. Depolarization and repolarization followed a variable time course, but both were usually complete in 30–45 sec. A similar test was more difficult to use *in vivo* because the potassium caused fasciculations in the nearby skeletal muscles which dislodged the microelectrodes. Also, the blood supply of the carotid body was apparently halted (as judged by simple inspection of its veins), presumably because the potassium caused depolarization and spasm of the vascular smooth muscle. Nevertheless, on two occasions injection of KCl into the common carotid artery close to the carotid body did lead to depolarization, then repolarization of cells, complete within 30 sec.

As it was not always possible to judge the responsiveness of the carotid body *in vitro* from the activity in the whole carotid nerve, on several occasions the nerve was split to obtain single and few-fibre preparations. Whenever this was done it was found that these chemoreceptor preparations discharged in response to stoppage of saline flow, or to the injection of NaCN (100 μg) into the perfusate, and that they retained this responsiveness for several hours. All observations on intracellular potentials were made within 2–3 h of commencing perfusion. In 3 experiments *in vitro* the carotid nerve was stimulated while recording from a slip of it containing a single chemoreceptor fibre (*cf.* refs. 10, 15, 18), and in these depression of chemoreceptor activity was observed. This may have been a real depression, or possibly an artefact due to stimulus spread[10].

Only a small proportion of microelectrodes impaled cells, the remainder being broken by the connective tissue of the carotid body. Although partial digestion with chymotrypsin will soften this connective tissue[6,7,9], we preferred to break electrodes rather than risk damage to the synapse by using chymotrypsin. Because of the tough connective tissue probably only the most superficial cells were penetrated. This may have been an advantage as the carotid body requires for its metabolism more oxygen than it can get by diffusion in from its surface[11], so that, *in vitro*, cells near the centre of the organ may be dead.

Eyzaguirre and his co-workers recorded intracellular potentials of 15–45 mV in their studies, and failed to produce any changes in these by classical physiological or pharmacological stimuli to the chemoreceptors[6,7,9], or by electrical stimulation of the sympathetic nerve[9], or even of the carotid body itself[6]. They did not look for effects of carotid sinus nerve stimulation.

Here, membrane potentials of 15–60 mV (mean 27 mV) were recorded from 176 cells *in vitro*. Potentials of 15–60 mV (mean 31 mV) were recorded from 24 cells in the supplementary *in vivo* study. It is not known which cell types were penetrated, although the larger rounder Type I cells, which tend to cluster together, were probably more often impaled than Type II cells. Usually a cell could be held for 10 min or more in the superfused preparation, although in some cases the potential decayed rapidly after penetration. If the microelectrode was advanced after penetrating a

cell the potential was usually lost in an aprubt change after an advance of 10–20 μm. Occasionally, however, advances of up to 100 μm were made before the potentials were lost. This may have been due to the physical displacement of the loosely fixed organ with the electrode. Alternatively, it may have occurred with the passage of the electrode from one to another Type I cell within a cluster, or 'glomerulus', of these cells. *In vivo*, cells were usually held for shorter periods (up to 3 min): pulsations of the underlying carotid artery frequently dislodged microelectrodes.

The addition of drugs (NaCN 100 μg, or ACh 20 μg) to the perfusate had no effect on membrane potentials, nor did transient stoppage of flow, although all these increased afferent chemoreceptor activity. Moreover, the addition of saline equilibrated with carbon dioxide had no effect on membrane potentials, although this excited chemoreceptor fibres in similar preparations.

Stimulation of the carotid sinus nerve at strengths well supramaximal for C-fibre activation, at frequencies of 1–50 c/sec, had no effect on membrane potentials. Both small, transient changes of potential upon stimulation, and slower, long-term shifts of potential upon repeated stimulation were looked for, but were not seen. Even prolonged stimulation of the carotid nerve at 10 or 20/sec for a minute, had no effect on membrane potentials.

These findings confirm the results of Eyzaguirre and co-workers[6,7,9] on the size of membrane potentials of carotid body cells and on the absence of effects of classical chemoreceptor stimuli on these potentials. They extend them to show that these potentials are not changed by carotid sinus nerve stimulation, or by hypercapnia. As there is disagreement over the presence or absence of degeneration of synaptic elements in the carotid body after cutting the glossopharyngeal nerve above its ganglion[1,3], the evidence for an efferent innervation of carotid body cells through the carotid nerve depends principally upon the observation that carotid nerve stimulation depresses chemoreceptor activity[10,15,18]. This observation has been shown to be partly artefactual, the only physiological depression being mediated by C-fibres[10].

The present study has failed to demonstrate an effect of stimulation of all carotid nerve fibres on the membrane potentials of carotid body cells. Although such negative results cannot be conclusive, it would seem that these fibres may exert their effect elsewhere, unless inhibitory efferent effects can be exerted synaptically without producing membrane potential changes. A vasomotor effect within the carotid body seems likely, especially as stimulation of the carotid nerve can increase carotid body blood flow[14,15].

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REFLEX CARDIOVASCULAR AND RESPIRATORY RESPONSES ORIGINATING IN EXERCISING MUSCLE

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SUMMARY

1. In anaesthetized and decerebrate cats isometric exercise of the hind limb muscles was elicited by stimulating the spinal ventral roots L7–S1. This caused a rise in arterial blood pressure, with small increases in heart rate and pulmonary ventilation. These changes were abolished by cutting the dorsal roots receiving afferents from the exercising muscle.

2. When the triceps surae muscle was made to exercise by ventral root stimulation, occlusion of the femoral artery and vein through and beyond the period of exercise caused the blood pressure to remain raised until the occlusion was removed. The ventilatory and heart rate responses were not markedly altered or prolonged by such circulatory occlusion.

3. Injection of small volumes of 5 % NaCl or isotonic KCl into the arterial blood supplying hind limb muscles gave cardiovascular and respiratory responses similar to those evoked by exercise. Like the responses to exercise, these responses were abolished by dorsal root section.

4. Direct current anodal block of the dorsal roots receiving afferents from the exercising muscle was used to block preferentially large myelinated fibres: this form of block did not abolish the evoked cardiovascular and respiratory responses. Local anaesthetic block of the dorsal roots was used to block preferentially unmyelinated and small myelinated fibres: this form of block abolished the cardiovascular and respiratory responses. It is concluded that the reflex responses are mediated by fibres within groups III and IV (small myelinated fibres and unmyelinated fibres).

INTRODUCTION

That reflexes originating in exercising muscle can give cardiovascular and respiratory responses has been suggested from work done on man (Alam & Smirk, 1937, 1938; Asmussen, Nielsen & Wieth-Pedersen, 1943;

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Lind, McNicol & Donald, 1966; Dejours, 1967) and has been proved by experiments on animals (Kao & Ray, 1954; Coote, Hilton & Perez-Gonzalez, 1971).

Voluntary isometric exercise in man is accompanied by marked increases in blood pressure, cardiac output, heart rate (Lind *et al.* 1966), and pulmonary ventilation (Wiley & Lind, 1971; Myhre & Andersen, 1971). Isometric exercise in the hind limb of the anaesthetized or decerebrate cat induced by stimulation of the appropriate spinal ventral roots causes an increase in the arterial blood pressure accompanied by small increases in heart rate and ventilation (Coote *et al.* 1971).

It has been suggested that the responses described during exercise in animals were reflexly induced by small myelinated and unmyelinated afferents from muscle, since electrical stimulation of such nerve fibres produces similar responses (Gordon, 1943; Johansson, 1962; Senapati, 1966; Mitchell, Mierzwiak, Wildenthal, Willis & Smith, 1968; Coote & Perez-Gonzalez, 1970). The present study demonstrates by the use of nerve-blocking techniques that these afferent fibres are responsible for the cardiovascular and respiratory responses that come from muscle during exercise. A preliminary report of these observations has been published (McCloskey & Mitchell, 1972).

METHODS

Experiments were done on twenty-eight cats which weighed between 1·6 and 3·2 kg. They were anaesthetized by one of two methods: (1) I.P. injection of pentobarbitone sodium, 35 mg/kg (Nembutal: Abbott), (2) I.V. injection of chloralose, 80 mg/kg (α-chloralose: B.D.H. Chemicals Ltd) after induction with ether; or were decerebrated at the intercollicular level after preliminary anaesthesia with ether. In the anaesthetized animals small additional doses of the original anaesthetic were given I.V. as required.

Experimental procedures

The trachea was cannulated low in the neck. Blood pressure was recorded from either the left common carotid artery or the left axillary artery, via a saline-filled nylon cannula connected to a pressure transducer (SE Laboratories: SE 4-82). Respiratory flow was recorded by a pneumotachometer attached to the tracheal cannula, integrated electronically, and calibrated to record ventilatory volumes. The outputs of the blood pressure and ventilatory records, plus the electrocardiogram, were amplified and displayed on a 4-channel U.V. recorder (SE Laboratories: SE 3006).

A laminectomy was performed to expose the spinal cord segments L4–S1. The skin high at the back of the limb to be exercised was opened to expose the sciatic nerve. In several experiments all muscles on the experimental side were denervated except the triceps surae: in these animals the completeness of this denervation was confirmed when only the triceps contracted upon stimulation of the ventral roots, L6, L7, S1. Also in these animals a cannula was inserted retrogradely into the artery supplying the gracilis muscle with its tip just in the femoral artery. Drugs injected through this cannula rapidly reached the triceps muscle (this was confirmed by

injection of dilute Evans blue dye) and could be held in the muscle by occluding the femoral artery and vein with a thread drawn into a thin polyethylene tube. In some experiments the skin of the hind limb to be exercised was removed from thigh to ankle in order to denervate the skin, and then stitched back.

Animals were fixed in a prone position on a table by pins driven into the iliac crests and through the bones of the knee and ankle joints on the experimental side. Pools were made with paraffin warmed to 37 °C and bubbled with 95% O_2+5% CO_2 over the laminectomy and in the upper thigh where the sciatic nerve was exposed. The spinal cord was exposed by a lengthwise incision through the dura.

A diagram of the experimental preparation used for stimulation and recording of spinal and peripheral nerves is shown in Fig. 1. Spinal roots L5, L6 and S2 downwards were always cut, and L4 was also cut in most experiments. The dorsal roots

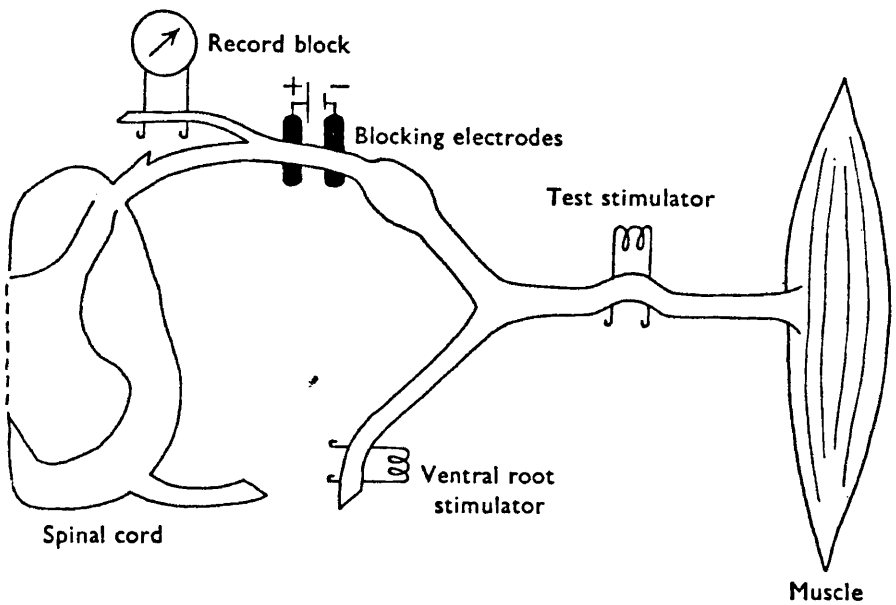

Fig. 1. Diagram of experimental set-up. Muscles in a hind limb were caused to contract isometrically by applying trains of stimuli to the peripheral cut ends of the ventral roots of spinal segments L7 and S1. Afferent nerves from the contracting muscle entered the spinal cord in the dorsal roots of these segments: other dorsal roots supplying the hind limb were cut. Direct current could be passed between two electrodes placed under the intact dorsal roots in order to produce an anodal block. Alternatively, lignocaine (0·125%) could be applied to the dorsal roots where they passed over these electrodes in order to produce a local anaesthetic block. The degree of block achieved by either method could be gauged by stimulating the sciatic nerve high in the back of the thigh with a test stimulator, and monitoring the changes produced by the block in a compound action potential recorded monophasically in a slip of the dorsal root after it had passed the blocking region.

of L7 and S1 were carefully placed across a pair of Ag–AgCl electrodes individually bound in saline-soaked cotton wool, and these electrodes were used to apply direct-current for anodal block. A small slip of the dorsal root of L7 was cut close to the cord after passing over the blocking electrodes, and was placed over a pair of Ag–AgCl electrodes, with its cut end crushed, to monitor the dorsal root action potentials

during blocks. The ventral roots of L 7 and S 1 were cut close to their exit from the spinal cord and placed over a pair of Ag–AgCl electrodes. Stimulation of the ventral roots at 20–50 Hz, with square-wave pulses of 0·1–0·2 msec duration, delivered by an isolated stimulator, was used to elicit contraction of the hind-limb muscles. An additional pair of stimulating Ag–AgCl electrodes was placed under the sciatic nerve in the upper thigh. Test stimuli delivered here by a further isolated stimulator at 1/sec (0·1 msec duration) elicited the compound action potentials which were picked up from the sampling slip of dorsal root beyond the blocking electrodes in the spinal cord. Action potentials picked up in this way were amplified in a Tektronix type 122 pre-amplifier and then displayed on an oscilloscope and could be photographed with a Cossor camera.

Periods of exercise of 10–45 sec were usually given. The exposed spinal cord and nerve roots were washed, every 20–30 min, with warmed Ringer solution made up as described by Brown, Lawrence & Matthews (1969), and bubbled with 95 % O_2-and 5 % CO_2. Rectal temperatures were maintained at 36–38° C throughout.

Nerve blocking techniques

In the experiments performed, two types of nerve block were used. In these experiments it was not always possible to distinguish reliably the Aδ- and C-waves of the sampled compound action potential, and so the nerve block achieved was inferred from the presence or absence of the A-wave only – this represents the large myelinated nerve fibres. The A-waves of the compound action potentials recorded in these experiments covered the range of conduction velocities 20–120 m/sec: that is, they were A$\alpha\beta\gamma$-waves. Direct current anodal block was achieved by passing a direct current between the two electrodes under the dorsal roots, the anode cephalad: for this a 9 V battery was used with a variable resistance placed in series with the nerve. Block of the A wave of the sampled potential was achieved with a current of 50–250 μA. A period of at least 1 min was always allowed to elapse from application of the block to testing of cardiorespiratory responses, as it is known that the blocking procedure can stimulate the nerve to be blocked during the first minute of its application (Casey & Blick, 1969; Trenchard & Widdicombe, 1972). The completeness of the block was checked immediately before and after such tests.

The local anaesthetic, lignocaine (0·125 %), was used for the second type of reversible differential block. Here, cardiorespiratory responses were tested every 60–90 sec after application of a few drops of the local anaesthetic to the dorsal roots as they passed over the DC electrodes. With this form of block it is the unmyelinated and small myelinated fibres which should be blocked first, and so the A-wave beyond the block was watched for a reduction in its amplitude.

RESULTS

Response to induced isometric exercise

Tetanic contractions of the hind-limb muscles elicited by stimulation of the ventral roots L 7 and S 1 for 10–45 sec usually caused a rise in arterial blood pressure of 20–50 mm Hg (Fig. 2). This response was most consistently seen in those preparations in which all the muscles innervated by these ventral roots were exercised (nineteen cats): in preparations in which only the triceps surae was exercised (nine cats) the pressor response was often small (10–20 mm Hg), and occasionally there was no pressor response.

The magnitude of the pressor response appeared from these observations to be dependent upon the mass of muscle exercising, although it is possible that the denervation procedure may have damaged the responsiveness of the triceps-only preparations. At the conclusion of an exercise period the blood pressure frequently dropped below the resting level for some 10–20 sec before returning to normal.

The pressor response was seen in all preparations in which the skin of the

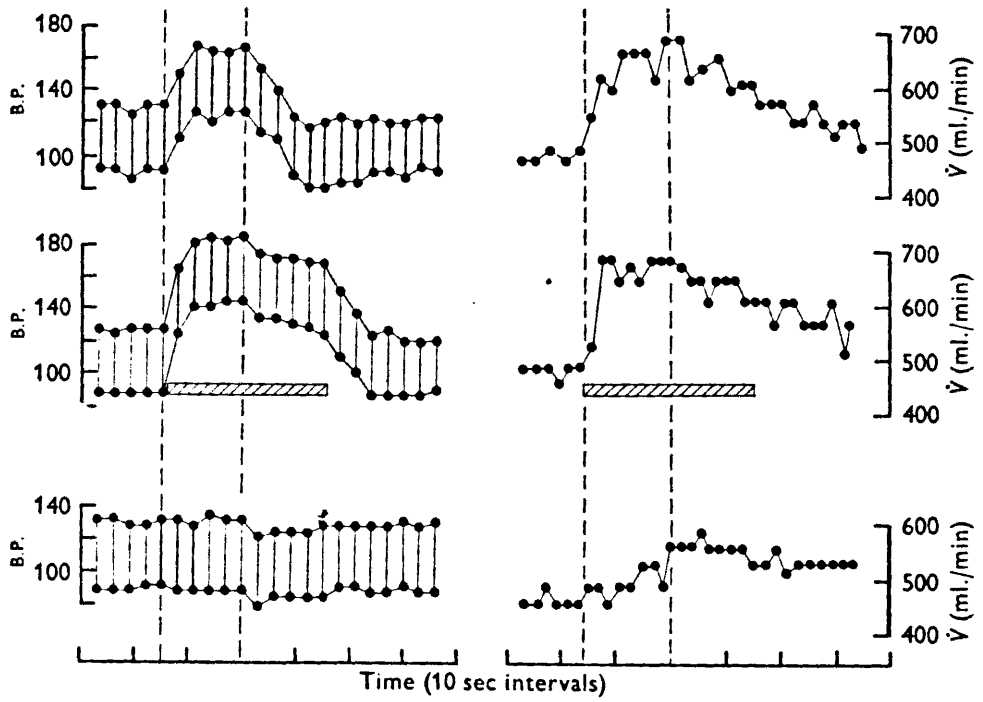

Fig. 2. Cat, chloralose. Records of arterial blood pressure and ventilation (calculated breath by breath from tidal volume and frequency). The records are in pairs, pressure on the left and ventilation on the right, taken in the same periods of exercise. From above downwards three periods of isometric exercise in the triceps surae are shown. The upper pair of records show the pressor and ventilatory responses to a control period of exercise. The middle pair show the responses when the femoral artery and vein were occluded from the commencement of exercise until 15 sec after the conclusion of exercise: the duration of the occulsion is indicated by the bar underlying each record. The lower pair of records shows a further period of exercise after the dorsal roots receiving afferents from the exercising muscle were cut.

exercising limb was denervated (six cats). It was prolonged, usually at a level slightly less than the exercise level, if arterial and venous occlusion was applied during the exercise, lasting for as long as the occlusion was maintained (Fig. 2). Occlusions lasting up to 30 sec after the conclusion of exercise were used.

In the exercise confined to the triceps surae, the cardiovascular and

respiratory responses were similar whether the ventral roots were stimulated at 1·5 times the threshold voltage for motor contraction, or, as was more usual, at 10 times that voltage.

All the pressor responses described were abolished by cutting the dorsal roots which remained in connexion with the exercising muscle (Fig. 2).

In preparations giving a pressor response there was usually a tachycardia in response to exercise. The increase in heart rate was small ($< 5\%$). In cats in which the heart rate was over 250 beats/min before exercise began, no heart rate changes were seen. In no experiments did a slowing of the heart accompany exercise, although the carotid sinus baroreceptors responded to clipping of the common carotid arteries by causing a reflex hypertension and tachycardia both at rest and during exercise. The increases in heart rate were also abolished by cutting the remaining dorsal roots.

An increase in both the rate and depth of breathing was seen in preparations giving pressor responses (Fig. 2). Breathing was always increased within two breaths of the commencement of exercise, and usually continued to increase to a maximum at 15–20 sec after the exercise began. Ventilation usually increased by approximately 50% of its resting level during exercise. At the conclusion of exercise, ventilation did not decrease abruptly, but slowly declined over the succeeding 30–45 sec to reach its resting level. After cutting the dorsal roots from the exercising muscle, no fast ventilatory response was seen, although ventilation did show increases of up to 25% over the resting level late in the period of exercise, or commonly in the 15 sec after exercise. These remaining ventilatory changes were interpreted as being due to metabolic effects on chemoreceptors remote from the muscle.

Response to arterial injections

Cardiovascular and respiratory responses similar to and often larger than those seen during exercise were seen when 1 ml. 5% NaCl (850 m-equiv/l.) was injected beyond an occlusion in the femoral artery into the blood supplying the triceps-surae in eight animals in which only this muscle group remained innervated. These responses were maintained for as long as the occlusions trapping the NaCl in the muscle were maintained.

Similar but less striking responses followed injections of 1 ml. isotonic KCl (150 m-equiv/l.). No response was seen to injection of isotonic NaCl.

Response to exercise during dorsal root blocking experiments

Two types of differential nerve block were used on the dorsal roots. Anodal block with direct current blocks nerve fibres of large diameter before smaller ones and local anaesthetic agents block small fibres before larger ones.

Anodal block was applied to the dorsal roots receiving afferents from the exercising muscle in eighteen cats. The current passed was gradually increased until the A wave of the compound action potential sampled beyond the block was just abolished. Exercise of the limb during this block produced the same reflex pressor, heart rate, and ventilation changes

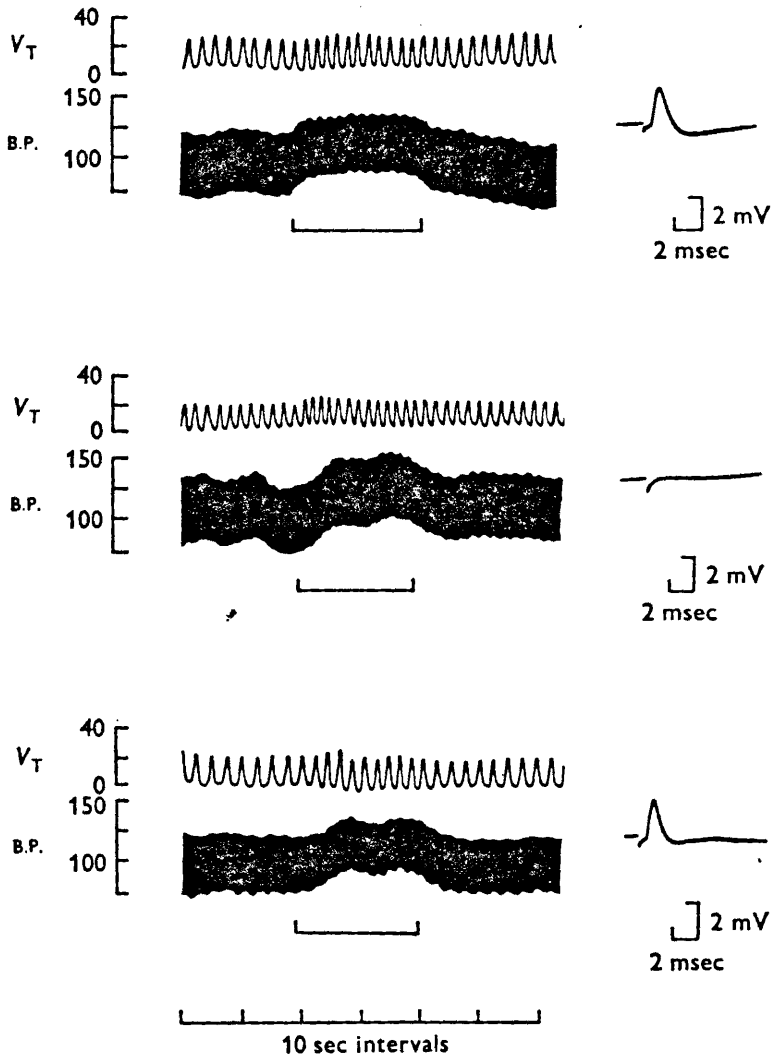

Fig. 3. Cat, pentobarbitone. Records of tidal volume and arterial blood pressure are shown from three periods of isometric hind-limb exercise. Together with each pair of records is shown the compound action potential sampled from a slip of dorsal root beyond the experimental blocking region: the action potential was evoked by a supramaximal test stimulus applied to the sciatic nerve about 5 cm from the sampling electrode. From above downwards are shown: a control period of exercise before anodal block was applied; a period of exercise 1 min after application of anodal block just sufficient to block the A-wave of the compound action potential; and a further control period after removal of the anodal block. Ventilation and pressure are retouched U.V. records.

as had been produced before the block was applied (Fig. 3). In three experiments in which 5% NaCl or isotonic KCl solutions were injected into the blood supplying triceps-only preparations, anodal block of the A wave did not block the responses to these agents.

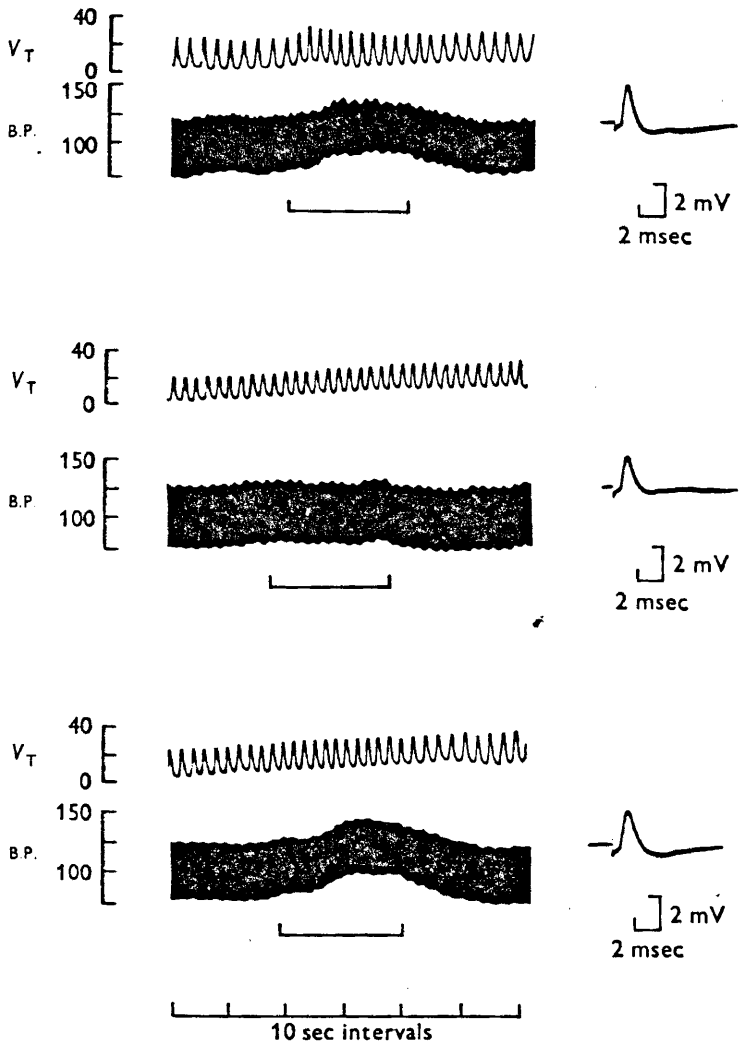

Fig. 4. Cat, chloralose: same cat as Fig. 3. Records of tidal volume, arterial blood pressure, and dorsal root compound action potential from three periods of isometric hind-limb exercise. From above downwards are shown a control period of exercise; a period of exercise which commenced 3½ min after application of a few drops of 0·125% lignocaine solution to the dorsal roots. Note that this period of exercise produced no pressor or ventilatory response, although the A-wave of the compound action potential was little, if at all, reduced; and in the bottom set of records, a further control period of exercise begun some minutes after the lignocaine had been washed away with warm saline. Ventilation and pressure are retouched U.V. records.

Local anaesthetic block was achieved with lignocaine (0·125 %) applied to the dorsal roots. In a sequence of periods of exercise given about one minute apart after applying this drug, it was possible to find one or two periods of exercise when the A wave of the compound action potential was unaltered but the cardiovascular and respiratory responses were abolished. This usually occurred between 2 and 5 min after applying the lignocaine. In many experiments the compound A wave was partly reduced before the exercise responses were completely gone, but in three experiments the A wave was unaffected when the exercise responses were entirely abolished (Fig. 4).

Both forms of block are reversible, and in some experiments several observations with each could be made. The margin between the desired degree of anodal block and a level which caused irreversible damage to the nerve roots was narrow, and frequently its misjudgment prematurely ended experiments. The block with lignocaine always proceeded to complete block of the sampled compound A-wave. Full recovery from the lignocaine block, both of the sampled action potential and of the cardiovascular and respiratory responses, was usual after the treated nerve roots had been washed 2 or 3 times with warm Ringer solution.

DISCUSSION

The reflex cardiovascular and respiratory responses seen during isometric exercise in this study and in that of Coote *et al.* (1971) are initiated within the muscle: neither denervation of the skin of the exercising limb, as described here, nor section of the articular nerves as done by Coote *et al.*, alters the responses.

Although Coote *et al.* (1971) showed some effect of arterial occlusion on the pressor response, they did not look at the effects of arterial and venous occlusion. In the present study at the conclusion of exercise performed during circulatory occlusion there was a slight fall of blood pressure, but this did not fall completely to normal until the occlusion was removed (Fig. 2). This suggests that a chemical factor activating the endings of afferent nerves causes the pressor response, although the initial fall despite occlusion may implicate mechanoreceptors as well. In human subjects in which circulatory occlusion is maintained in the exercising limb beyond the exercise, it has been reported that the blood pressure rises over the succeeding minute (Alam & Smirk, 1937), that it remains at the level reached in exercise (Lind *et al.* 1966), that it falls half-way back towards the resting level (D. J. C. Cunningham, T. G. Pickering & P. Sleight, personal communication), and that it falls and then rises again to the exercise level (Wiley & Lind, 1971). These conflicting descriptions have in common the

possibility that at least part of the pressor response seen is attributable to a chemical factor exciting nerve endings in the muscle.

Although circulatory occlusion extending beyond the end of exercise gave valuable information regarding the initiation of the pressor reflex described, it was of less value in investigating the heart rate and ventilatory responses. The heart-rate changes were small, and it cannot be said with certainty whether or not they remained during the post-exercise occlusion; in human subjects doing isometric work, where the tachycardia is greater, they are not (Lind *et al.* 1966). The ventilatory responses were complicated late in exercise, and after, by effects attributable to chemoreceptors elsewhere in the body: for circulatory occlusion to have yielded important information on this point considerable efforts would have had to be made to correct for changes in these remote effects and this was not done here. In human subjects circulatory occlusion of the working limb does not prolong hyperventilation (Wiley & Lind, 1971).

The increments in heart rate seen during isometric exercise in the cat were small. Much larger increments of heart rate are seen in human subjects doing isometric exercise (Alam & Smirk, 1938; Lind *et al.* 1966). It might be that the rise in blood pressure caused by the stimulated exercise acts through the arterial baroreceptors to obscure a larger reflex tachycardia in the cat. In man, where the exercise is done voluntarily, the sensitivity of the baroreceptor reflex is reduced during exercise (Bristow, Brown, Cunningham, Howson, Petersen, Pickering & Sleight, 1971), and would permit larger changes in heart rate initiated by muscle reflexes. Alternatively it might be that the greater part of the tachycardia in man has its stimulus elsewhere than in the exercising muscle.

The ventilatory responses to exercise were small in comparison with the four- to fivefold increases seen in isometric exercise in humans (Wiley & Lind, 1971; Myhre & Andersen, 1971), and followed a different time course. The responses commenced promptly enough to correspond to the fast increases in ventilation described by Dejours (1967) for rhythmic exercise in man (that is, within the first two breaths), but such prompt responses are not seen during isometric exercise in man (Wiley & Lind, 1971; Myhre & Andersen, 1971). Dejours has suggested from several lines of work that the muscle spindle primary afferents may be responsible for the fast responses he describes (Dejours, 1967; Leitner & Dejours, 1971). The present study suggests that these afferents do not cause the prompt responses seen here because the anodal block of large myelinated fibres does not abolish them. Nor, for the same reason, are the large myelinated afferents from Golgi tendon organs likely to be involved in the responses. Moreover, low threshold motor stimulation, which, by activating principally the alpha motor efferents, unloads the muscle spindles and should

maximally activate Golgi tendon organs (Harvey & Matthews, 1961), leads to the same exercise responses as higher threshold motor stimulation which activates alpha and gamma efferents. This, and the observation that the cardiovascular and respiratory responses to both high- and low-threshold motor stimulation were unaffected by anodal block, point against either the muscle-spindle afferents or the Golgi tendon organs being involved in the responses described.

It is possible that some of the ventilatory response mediated by the muscle afferents was due to an increase in peripheral chemoreceptor drive. It is known that sympathetic nervous activity can increase the discharge rate of peripheral arterial chemoreceptors (Lee, Mayou & Torrance, 1964; Biscoe & Purves, 1967). However, Parida, Senapati & Kalia (1969) showed that the ventilatory response to exercise was unaffected by denervation of the carotid body chemoreceptors. No attempt was made in the present study to investigate this possibility.

Anodal block as used in this study was established by Mendell & Wall (1964) as a technique in which conduction could be blocked in larger before smaller diameter fibres according to the magnitude of current passed. Casey & Blick (1969) in experiments testing the reliability of this technique showed that the Aδ-wave in a compound action potential was the first to disappear as current was increased, then the A-wave, leaving an almost normal C-wave. Simultaneous single fibre studies showed that the Aδ-wave had disappeared because some of its component fibres had been blocked while others had only been slowed, and consequently spread out. Although single A-fibres were also slowed, none were found to conduct after the 'A' compound action potential had disappeared. Similar results have recently been found by Trenchard & Widdicombe (1972) on the vagus nerve. Nevertheless, it is conceded that a possible weakness of this method is that some apparently blocked fibres may only have had their conduction slowed. It would be necessary, however, for these fibres to retain the full cardiovascular and respiratory reflex potency of the whole population of such afferents if the responses described here were to be considered as carried in them.

Since Gasser & Erlanger (1929) used cocaine to block smaller before larger myelinated fibres, various local anaesthetic agents have been used to achieve differential nerve blocks. In the present study this technique proved difficult to manage and gave less clear-cut separation of A-fibre conduction from reflex responsiveness than did anodal block. The technique requires repeated testing of reflexes after application of the anaesthetic agent, and at its best provided only one or two periods of separation of reflex response from A-fibre conduction. Usually the reflexes were not fully abolished until the A-wave had begun to be diminished. It was always

found, however, that some of the A-wave remained when the responses had been stopped, so that one is again forced to argue about the reflex potency of the unblocked myelinated fibres if their involvement is supported, only this time the view must be taken that the reflex potency is reduced greatly by a slight reduction in the number of conducting fibres. Moreover, three experiments did produce full separation of block of the response from block of the A-fibres.

Because the Aδ- and C-waves were not reliably distinguished in the sampled compound action potentials in this study, it is not possible to say more than that the A-fibres (groups I and II) were not involved in the reflexes observed. Fibres in either or both of group III (small myelinated fibres) or group IV (unmyelinated C-fibres) were responsible. These fibre groups are heterogeneous, containing mechanoreceptor fibres and pressure–pain fibres amongst others. It has been argued that fibres contributing to the responses are activated by metabolites from the exercising muscles (Lind *et al.* 1966; Wildenthal, Mierzwiak, Skinner & Mitchell, 1968; Hník, Hudlická, Kučera & Payne, 1969; Coote *et al.* 1971), and the present study supports this while not ruling out as well a contribution from mechanoreceptors. Coote *et al.* have outlined the reasons for believing that the reflex responses are not responses to pain. Responses to stimuli other than exercise, such as muscle squeezing (Kalia, Senapati, Parida & Panda, 1972) or the injection of KCl or 5% NaCl as reported here, although similar to the exercise responses, are probably at least in part responses to pain.

The experiments reported here give no information about the relative contributions of this peripheral reflex mechanism during exercise. Krogh & Lindhard (1913) proposed that an important stimulus for the cardiovascular and respiratory responses in exercise might be the 'irradiation' of the command to exercise upon the mass transport control centres. This idea has had recent support in the work of Freyschuss (1970) and Goodwin, McCloskey & Mitchell (1971). The muscle reflex effects described here must be considered together with this direct 'irradiation' as peripheral and central components of the neural drives present in exercise, though these neural drives are but part of the whole stimulus pattern of exercise.

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CARDIOVASCULAR AND RESPIRATORY RESPONSES TO CHANGES IN CENTRAL COMMAND DURING ISOMETRIC EXERCISE AT CONSTANT MUSCLE TENSION

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SUMMARY

1. Experiments were designed to show whether elements of the command descending from higher centres to exercising muscles provide an input for cardiovascular and respiratory control. Vibration, known to be a powerful stimulus to the primary afferents from muscle spindles, was applied to the biceps tendon of human subjects performing sustained isometric contractions with the biceps or the triceps muscle. When the biceps was contracting this activation of muscle spindle primary afferents in it provided an element of reflex excitation, so that less central command was required to achieve a given tension. When triceps was contracting, the activation of muscle spindle primary afferents in its antagonist, biceps, contributed an element of reflex inhibition, so that more central command than normally was required to achieve a given tension. The cardiovascular and respiratory responses to an isometric effort could thus be investigated at any tension when the central command was normal, decreased, or increased.

2. Blood pressure, heart rate, and pulmonary ventilation all increase in an isometric effort. The increase in each is less when the central command is reduced. The increase in each is greater when the central command is increased.

3. It is concluded that there is irradiation of cardiovascular and respiratory control centres by the descending central command during voluntary muscular contractions in man.

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INTRODUCTION

Reflexes from contracting muscle are known to affect the cardiovascular and respiratory systems during exercise (Kao & Ray, 1954; Coote, Hilton & Perez-Gonzalez, 1971; McCloskey & Mitchell, 1972). It has not been established whether, in addition, there are effects dependent upon central 'irradiation' (Krogh & Lindhard, 1913), that is, whether the central command descending from higher centres to the exercising muscles provides an input for the cardiovascular and respiratory control.

In the present study a method was used to vary the central command required for a particular muscular action, in this case prolonged isometric contraction of the biceps or triceps muscles of the arm. The tension actually achieved was constant, so that reflex effects from the working muscle should then remain similar whereas responses dependent upon central 'irradiation' would vary. These experiments show that blood pressure, heart rate, and pulmonary ventilation all change with the level of central command.

A brief report of this work has been published previously (Goodwin, McCloskey & Mitchell, 1971).

METHODS

Principle. A subject was asked to hold a constant tension, which was never more than half the tension of his maximal voluntary contraction, with either the biceps or triceps muscle of the arm. The subject was shown a display of the tension he was achieving, which he was asked to align with a marker of required tension. His isometric effort always led to increases in arterial blood pressure and heart rate (Lind, McNicol & Donald, 1966), and ventilation (Wiley & Lind, 1971; Myhre & Andersen, 1971). These changes were compared with those which occurred when the same tension was held by the same muscle for the same time while the central command required to produce the tension was different.

If a small physiotherapy vibrator (Vibratory Massager, Pifco Ltd) oscillating at 100 Hz is applied to the tendon of either the exercising muscle or its antagonist, the central command required to produce a constant tension may be altered. Vibration is known to be a powerful stimulus to muscle spindle primary endings, and can be used, for example, to elicit reflexly a tension in the muscle without central command (De Gail, Lance & Neilson, 1966; Hagbarth & Eklund, 1966). This tension in most subjects was small, being about 10 % of the maximum of which the subject was capable. Because the cardiovascular and respiratory responses to isometric exercise are best seen at tensions of more than 10 % of the maximum (Lind *et al.* 1966) it was more satisfactory to add an element of voluntary contraction to a reflex contraction. That is, a subject would be asked to produce a tension of, say 30 % of his maximal voluntary contraction, but the applied vibration would allow some of this to be achieved reflexly, so that he would require a central command equivalent only to about 20 % of his maximum. A diagram of this principle is shown in Fig. 1.

Alternatively, vibration of an antagonistic muscle will produce disynaptic inhibition of the motoneurones of the active muscle and a greater central command will be required for any muscle tension. In our experiments a subject was asked to produce a given tension with triceps while vibration of biceps, by activating the primary

afferents of muscle spindles there, would contribute a reflex inhibition to the motoneurones of triceps. This meant that it was necessary for the subject to call forth a greater central command to achieve the required tension. A diagram of this principle is shown in Fig. 2. The reflex inhibition is not accompanied by detectable contraction of the vibrated antagonist. It is not surprising that the vibrated biceps did not contract, for its motoneurones were presumably being inhibited by elements of the descending command and by spinal reflexes from the contracting triceps. The most satisfactory indicator of contraction here was found to be simple manual palpation of the vibrated antagonist: in random blind trials on our subjects it was found that contractions of 2% of the maximum could be reliably detected by this

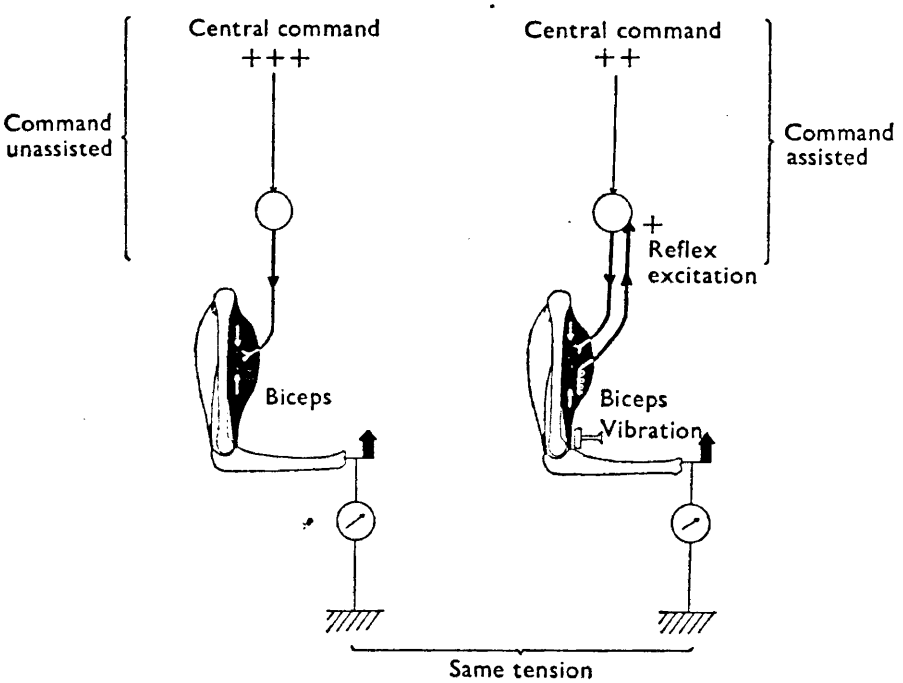

Fig. 1. Principle of an experiment designed to reduce the central command required to achieve a muscle tension. On the left is shown the situation that exists when an upward force is exerted by the forearm through the voluntary contraction of the biceps muscle: the magnitude of the central command required is given as + + +. On the right is shown how vibration is used to excite the primary afferents from muscle spindles of the contracting muscle, thereby contributing an element of reflex excitation to the motoneurones innervating the muscle: the same upward force can thus be exerted by a contraction of biceps which achieves the same tension while requiring less central command (now given as + +).

method. No contraction of the vibrated antagonist was found in these experiments. Also no evidence of contraction of the vibrated antagonist could be demonstrated by electromyography, although this proved a less sensitive method because of interference caused by vibration.

Evidence that the assisting and inhibiting manoeuvres were working as described was found in the responses seen when vibration was suddenly removed. It was usual in all our vibration experiments, at the conclusion of the period of contraction, to remove the vibrator after first covering up the tension record on the oscilloscope

and instructing the subject to 'continue pushing (or pulling) just as hard'. When this was done, the tension achieved fell when the vibration had been assisting the contraction, and rose when the vibration had been inhibiting the contraction. These changes in tension were usually short-lived because the subjects quickly detected the undershoot or overshoot from changes in the pressure exerted by the wrist on the strain gauge, and corrected for them. Fig. 3 shows the typical behaviour in records obtained during the experiments illustrated in Figs. 5 and 7.

Subjects. Experiments were done on fifteen healthy male volunteers aged from 20 to 30 yr. Five of these subjects were judged unsatisfactory because of large variations in their measured parameters at rest or in response to minor extraneous

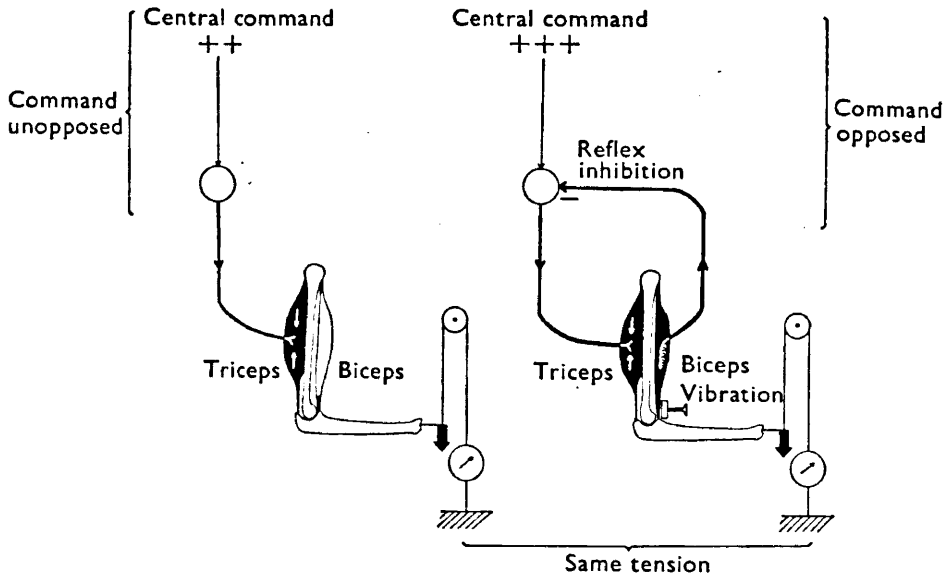

Fig. 2. Principle of an experiment designed to increase the central command required to achieve a muscle tension. On the left is shown the situation that exists when a downward force is exerted by the forearm through the voluntary contraction of the triceps muscle: the magnitude of the central command required is given as + +. On the right is shown how vibration of the biceps, an antagonist of the contracting muscle, is used to excite the primary afferents from muscle spindles in biceps. This contributes an element of reflex inhibition to the motoneurones innervating the contracting triceps. The same downward force can thus be exerted by a contraction of triceps, only if a greater central command (here + + +) is given. The vibrated biceps does not contract during an effort with triceps.

events (e.g. movement of an experimenter in their sight, noises outside the room etc), or because they expressed a particular dislike of the tasks required of them. Results obtained on these subjects will not be presented here. Of the remainder, three were familiar with the aims of the study at the time of the experiments, and seven were not (non-medical volunteers, technicians, or medical students). Several satisfactory subjects were used on more than one occasion.

In parallel experiments done with intra-arterial blood pressure recording, two subjects and one of the authors (D.I.M.) were studied.

Experimental procedures. Subjects were seated in a comfortable arm-chair, with their elbows resting on the padded arms of the chair, and their forearms projecting

beyond the ends of the arm supports. Isometric contractions of the biceps or triceps of the right arm were usually investigated. For these the right wrist passed through a strong webbing sling attached to a wire cable which connected to a strain gauge fixed to the floor. During biceps contractions the wrist pulled upwards directly from the strain gauge; during triceps contractions, the wire cable from the strain gauge was passed over a pulley fixed to a firm frame above the subject's wrist, so that

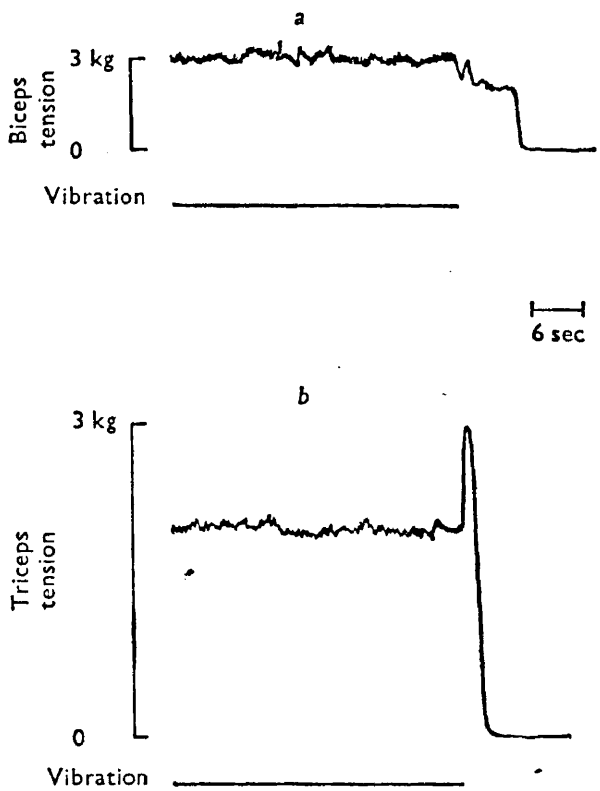

Fig. 3. The effects of removal of vibration during contractions in which vibration was being used to contribute reflex assistance or inhibition. In *a*, a subject was performing the experiment illustrated in Fig. 5, an effort with biceps in which vibration was supplying reflex assistance: removal of vibration led to a fall in achieved tension, presumably to the level appropriate to the reduced central command he was using. In *b*, a subject was performing one of the experiments illustrated in Fig. 7, an effort with triceps in which vibration of biceps was supplying reflex inhibition: removal of vibration led to a rise in achieved tension, presumably to the level appropriate to the increased central command he was using. In each case the subject was told to relax as soon as the extent of the undershoot or overshoot was determined.

downwards pressure of the wrist again registered a tension through the strain gauge. For either type of contraction the wrist was rotated so that the plane of the hand was vertical, and the sling always met the wrist at the same distance from the elbow. Similarly the point of the elbow of the exercising arm was always in the same position on the arm support. The angle at the elbow for any subject in any one study was thus always constant (usually this angle was between 90 and 120°).

Subjects were instructed to confine their efforts in any experiment to the biceps or triceps muscle being tested, and were specifically instructed to avoid using shoulder or trunk movements to alter their leverage. In many experiments the subjects were firmly strapped into the arm-chair with a belt diagonally crossing the right shoulder. Care was taken also to ensure that the tip of the elbow was always firmly in contact with the support during efforts with triceps, as occasional subjects were noted to lift the elbow otherwise in an attempt to alter their leverage on the system. Despite all precautions, some activity would be expected in muscles fixating the shoulder joint, but this activity was not apparent from surface electromyography, nor did it become so when vibration was used.

Experiments were conducted in a quiet room, or with soft music playing in the background, according to the subjects' preferences. As far as possible the experimenters and the recording apparatus were kept out of the subjects' view. All subjects practised the tasks required, experienced muscle vibration, and were given an outline of the protocol to be followed, before the experiment was begun. In addition, a complete exercise trial involving muscle vibration, with all recording procedures working, was given when a subject was ready. This trial was disregarded for experimental purposes, although the subject did not know this: this trial served to allay any initial anxiety in the subject, and to allow all experimental procedures to be preceded by a previous period of exercise. The experiment commenced with a period of exercise 20 min after the trial, and successive periods followed with 20-min rest periods between. In the rest periods, subjects removed the mask or mouthpiece used for ventilatory measurements, and were encouraged to read.

Isometric exercise was performed for 2–8 min, usually 3 or 4 min. The exercise level chosen was between 20 and 50% of the maximal voluntary contraction. To determine this maximum the subject was asked to make several maximal efforts of 2 or 3 sec duration: because of the instruction to avoid using the shoulders, most subjects probably registered tensions which were less than the true maximal tensions. Nevertheless, the level chosen was repeated in comparable manoeuvres of the experiment, and its absolute level in kilograms was known. Vibration of either the contracting muscle or its antagonist did not alter the maximum registered by a subject even if he was, for the purposes of this test only, allowed to move his shoulder and trunk as he chose. The subjects sat during the experiments facing the screen of an oscilloscope on which the tension achieved was displayed on one beam and the other beam was set at the desired level of tension: in exercise, they were asked to align the beams.

The sequence in which the steps of the experiment were conducted was chosen to minimize any complications arising from the effects of muscle fatigue (see Results section).

Recording. Arterial blood pressure, the electrocardiogram, ventilation, and end-tidal carbon dioxide were measured, and the tension achieved in the working arm was monitored.

Blood pressure was usually measured by sphygmomanometry in the nonexercising arm. For this, the bell of a stethoscope was strapped over the brachial artery, and a tube led from it over the subject's shoulder to an experimenter seated immediately behind. The blood pressure cuff was rapidly inflated by turning a tap from a drum charged to a pressure of about 200 mm Hg, and deflated in the usual way through a variable valve. Measurements were made one after another, the pressure in the cuff always dropping to zero between observations. Systolic and diastolic pressures were taken thus every 20–30 sec, the exact timing of the measurement being marked on the experimental record by the experimenter through a remote control marker. In a supplementary study, blood pressures were measured intra-arterially in three sub-

jects with a transducer (SE Laboratories: SE 4–82) connected to a nylon cannula in the brachial artery. Ventilation was not measured in these three experiments. These studies were done with the informed consent of the subjects. The heart rate was counted from standard electrocardiograms.

The subjects breathed through a low resistance, small dead-space valve (Cunningham, Johnson & Lloyd, 1956) connected to a mouthpiece or to a tight-fitting, small dead-space face mask. They inspired room air. The expired gas was led through a curved metal tube immersed in ice, to remove moisture, and then through a gas-meter. Electrical contacts were arranged on the dial of this meter to produce a pulse on the record for every 5 l. of gas passing through it.

Expired gas was withdrawn at 30–60 ml./min and led through a CO_2 analyser. The output of this analyser gave end-tidal carbon dioxide tension.

The electrocardiogram, the ventilatory volume, the carbon dioxide tension, the tension recorded in the strain gauge, and the marker for the blood pressure observations, were all recorded with an ultra-violet-light recorder (SE Laboratories: SE 3006).

RESULTS

Repeated exercise and fatigue. Comparisons between responses to the same muscular effort repeated a number of times must allow for the possible influence of fatigue. Fatigue might alter the afferent neural activity from the working muscle which is responsible for cardiovascular and respiratory responses. Moreover, a fatigued muscle might require a greater central command to achieve a given tension than it would normally. Either effect would complicate the present study in which it is assumed that reflex activity is similar from trial to trial at a constant tension, and that the central command is altered only by the experimental manoeuvres with vibration.

To investigate the effects of fatigue, we asked subjects to make repeated efforts with only short recovery periods between them. When fatigued in this way, subjects showed greater than normal responses in blood pressure, heart rate, and ventilation to a given level of work. The pressor responses of a subject to the same work load repeated so frequently as to cause fatigue are shown in Fig. 4: both the heart rate and ventilation changed in a similar way, but these parameters did not return to control levels as quickly or precisely as blood pressure.

A full study of the effects of fatigue was not made here because of the difficulty in distinguishing between reflex and central influences. Nevertheless, the principal part of the present study was arranged so as to minimize any complications caused by fatigue. First, all studied contractions were less than half the maximum a subject could achieve, and were spaced 20 min apart to allow good recovery. Secondly, by using the first contraction period as a 'trial', it was possible to have each experimental contraction preceded by a contraction 20 min earlier. With such precautions, the reproducibility of responses to an effort simply repeated was good: the

pressor response was most reliable (note its reproducibility before there was appreciable fatigue in the first three contractions shown in Fig. 4); the increments in heart rate and ventilation were also well reproduced, although slight shifts in the resting values did occur throughout the period of an experiment (e.g. see Fig. 5). As well as requiring only moderate efforts, and giving long periods for recovery, a further precaution was taken against interference from fatigue. Experiments were conducted

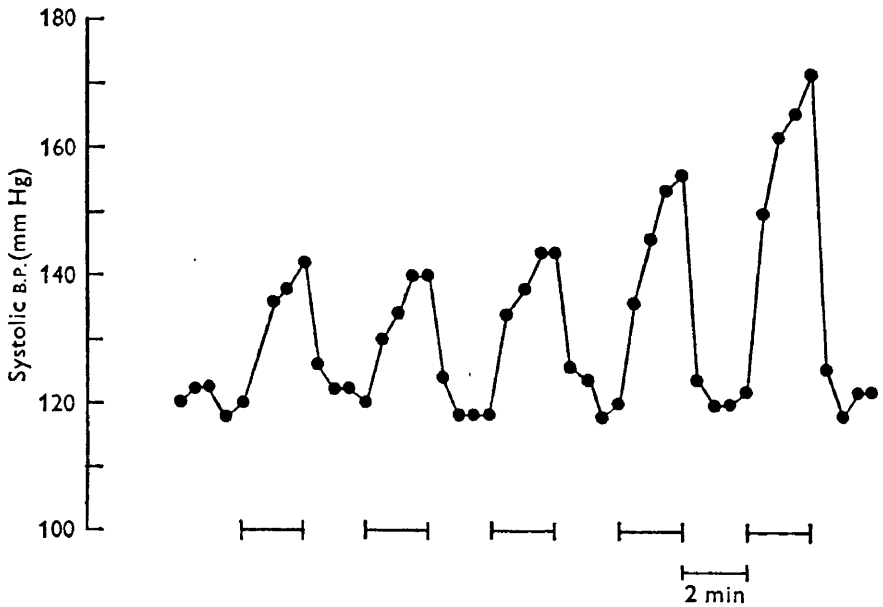

Fig. 4. Fatigue. The systolic blood pressure (B.P.) is shown during a period in which a subject made repeated isometric contractions of biceps to achieve a tension of 8 kg at the wrist, which was 40% of his maximal voluntary contraction. Each contraction lasted 2 min, and there were recovery periods of 2 min between efforts. Each effort is shown by a bar underlying the plotted pressures. The pressor response to an effort was well reproduced for the first three efforts, then increased in the next two efforts. The subject was unable to maintain the same tension throughout a further 2-min effort.

in paired efforts of contractions with and without vibration: in these pairs the effort in which the central command was greater, according to the principle of our method, was done first. That is, a contraction with vibration was done first when vibration was intended to inhibit, and was done second when vibration was intended to assist. This way the effects of fatigue were working against the interpretation we came to put on our results, for central command was always greater in the first of a pair whereas fatigue could be greater only in the second of the pair.

Reduction of central command. Ideally, the experiment desired here was one in which a purely reflex contraction was compared with one of the

same magnitude performed voluntarily. Such an experiment gave results in only one out of the ten satisfactory subjects, because most subjects produced reflex contractions of only 10–15 % of their maxima, levels which produce little or no cardiorespiratory responses when done voluntarily (Lind *et al.* 1966). In none of the subjects with these small reflexes was the vibration associated with increases in blood pressure, heart rate, or ventilation. One of our subjects, however, had a vibration reflex contraction of about 40 % of his maximum: his heart rate and ventilation increased in response to this contraction (blood pressure was not measured), and the same parameters increased more when he did a voluntary contraction of the same magnitude. These results strongly indicate a cardiorespiratory drive from central irradiation: nevertheless, it was a single experiment, and the subject was a physiologist who was familiar with the aims of our study.

In the later half of this study, the usual way of reducing the central command was to allow vibration to provide part of a given tension reflexly, while the subject contributed some voluntary command: this allowed study of tensions in the range which produce good cardiorespiratory responses. Reduction of the central command reduced the pressor, heart rate, and ventilatory responses seen at the same achieved muscle tension, as shown in Fig. 5. In this part of the study particularly, it was often found that one of the measured parameters was not clearly altered when others were: in this respect heart rate or ventilation was generally more difficult to separate clearly from the levels they attained in a simple voluntary contraction than was blood pressure, perhaps because of the slight variations observed even at rest in these parameters (e.g. heart rate in Fig. 5). Nevertheless, the manoeuvre used here to decrease the central command was never associated with increases in any of the measured parameters above the levels they attained during control efforts and clear cut decreases in one or more of the parameters were seen in eight out of ten experiments on five subjects.

A variation of the above method was used on three occasions to minimize the variability of heart rate responses. In this method a subject was asked to make a simple voluntary contraction during which vibration was applied for a time to give reflex assistance and then removed: this provided a period within a single contraction when the central command was reduced below the level at which it was held for the remainder of the contraction. During the period of vibration, the heart rate in each case fell below the level which it had attained during the simple voluntary contraction (see Fig. 6).

Increase of central command. As described in the Methods section, it was possible to require a greater than normal central command for given

tensions by using vibration of an antagonist. When this was done blood pressure, heart rate, and ventilation increased more during a given effort when the central command was greater. This is shown in Fig. 7 for two levels of muscular tension achieved by a subject each at a normal and at an increased level of central command.

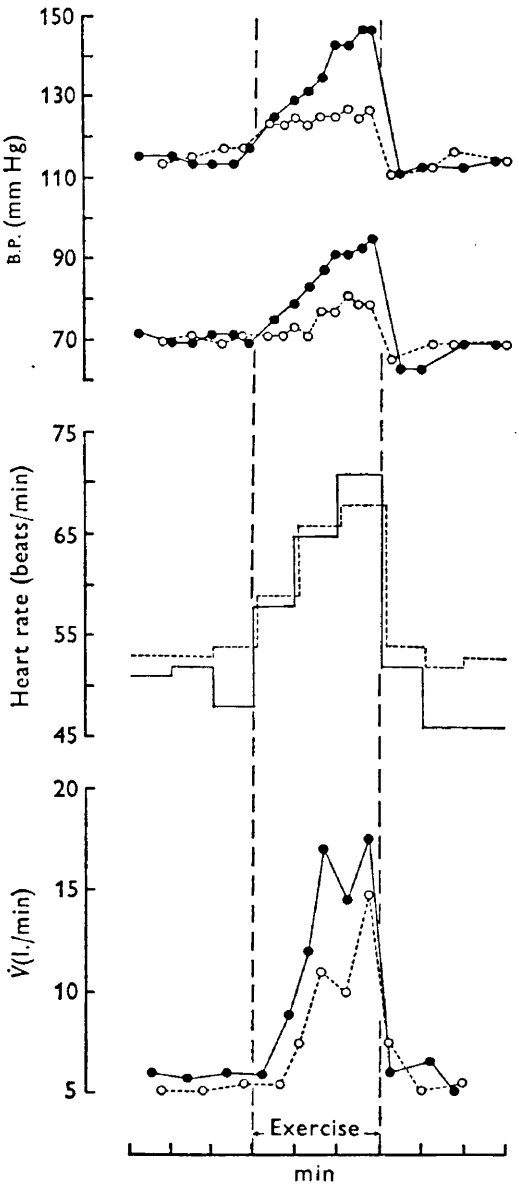

Fig. 5. Reduction of central command. Systolic and diastolic blood pressures (B.P.), heart rate, and ventilation ($\dot{V}$) are plotted before, during, and after two isometric contractions of biceps in which a tension of 3·2 kg was developed at the wrist (20 % of maximum). The responses to a normal contraction are shown by the filled circles and continuous lines; the responses when vibration was applied to allow a reduced central command are shown by the open circles and interrupted lines.

A similar experiment done in another subject is shown in Fig. 8. In this study the ventilatory response is shown together with end-tidal P_{CO_2} measurements. Again, the same tension achieved when the central command was greater was associated with increased ventilatory and heart rate responses. Results like those illustrated were obtained in all ten satisfactory subjects (in fifteen out of eighteen experiments.)

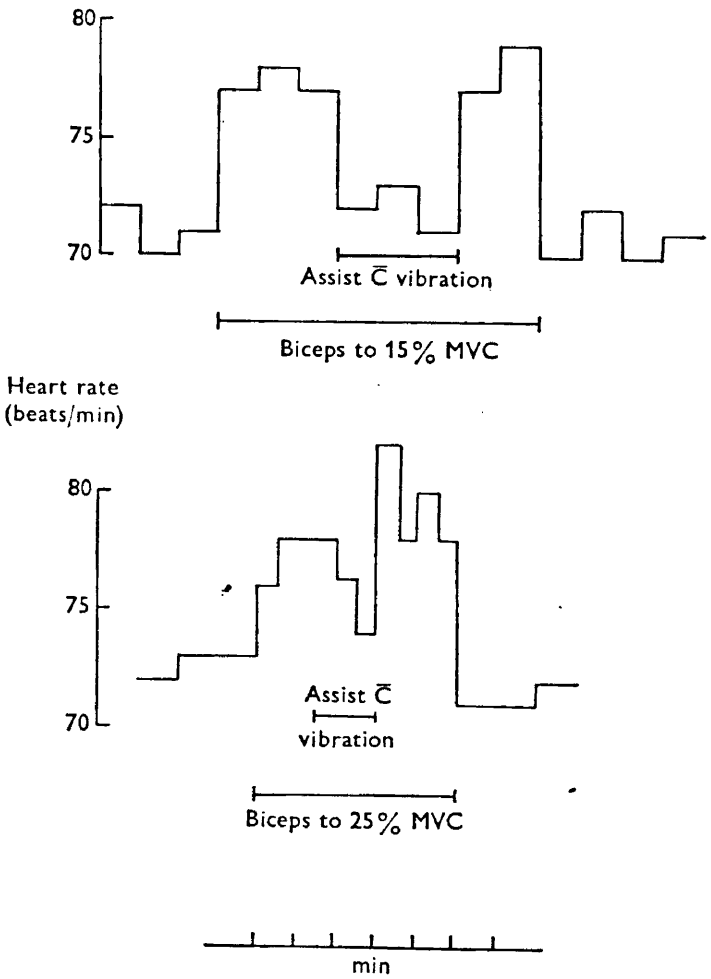

Fig. 6. Reduction of central command. Heart rate responses in two subjects during prolonged isometric contractions of biceps at 15 and 25% of the maximal voluntary contraction (MVC) tensions. In each subject vibration of the contracting biceps was used as described to reduce the central command during a period which commenced after contraction had begun and ended before the contraction had ceased.

Introspective analysis. Subjects were always asked, at the conclusion of an experimental series, to comment upon their experiences in the studies. All subjects found that each effort required of them was not difficult to begin with, but that it became more difficult as it continued. This is con-

sistent with fatigue. All subjects found that vibration applied to either the contracting muscle or its antagonist required greater concentration in holding a desired tension. This was probably because of subtle proprioceptive illusions induced by the vibration (Goodwin, McCloskey & Matthews, 1972), which all subjects experienced. When vibration was applied to antagonistic muscles to require an increase of central command, all subjects felt that the effort required to achieve a given tension was greater. When vibration was applied to the contracting muscle itself to assist it

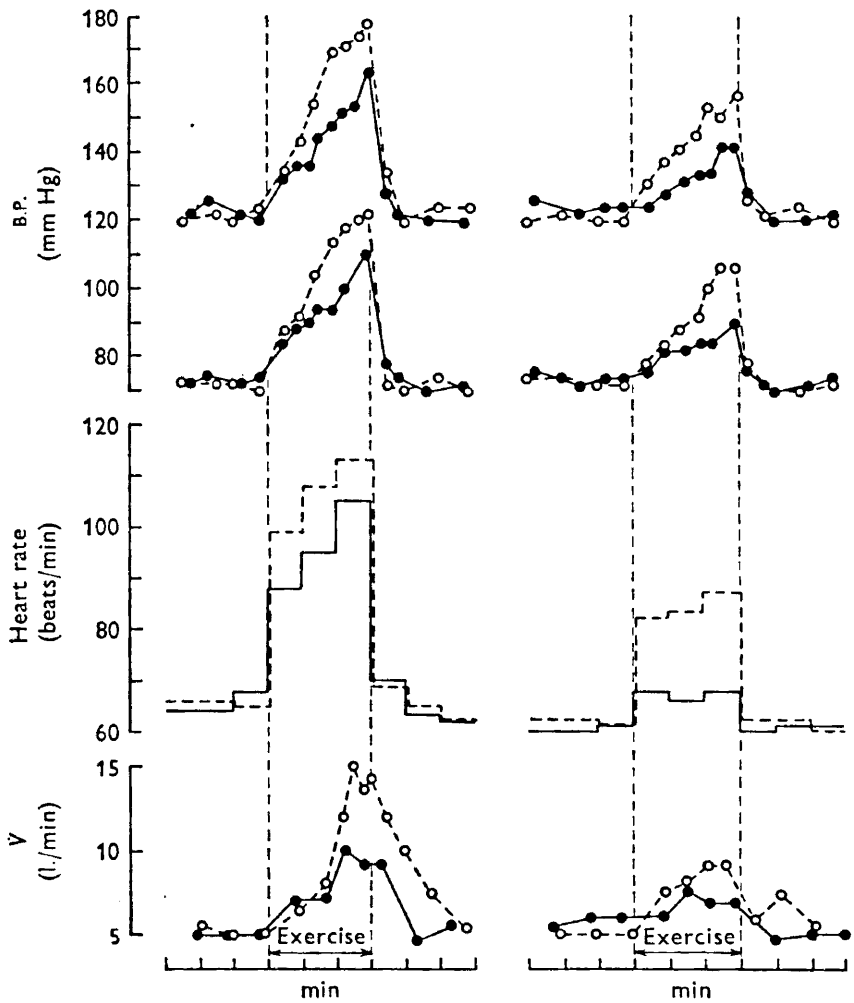

Fig. 7. Increase of central command. Systolic and diastolic blood pressures, heart rate, and ventilation are plotted before, during, and after two pairs of isometric contractions of triceps in which tensions of 4·9 kg (35 % of maximum) in the left panel, and 2·1 kg (15 % of maximum) in the right panel, were developed at the wrist. The responses when the central command to triceps was increased by vibration of biceps are shown by open circles and interrupted lines; and are to be compared with the responses to contractions of the same tension achieved normally, shown by filled circles and continuous lines.

reflexly so as to require less central command, a few subjects experienced that less effort was required; more often, subjects found the effort neither easier or harder (e.g. the subject in Fig. 4); and some subjects found the reflexly assisted effort more difficult (e.g. subjects of Fig. 5), perhaps because of the increased mental concentration required.

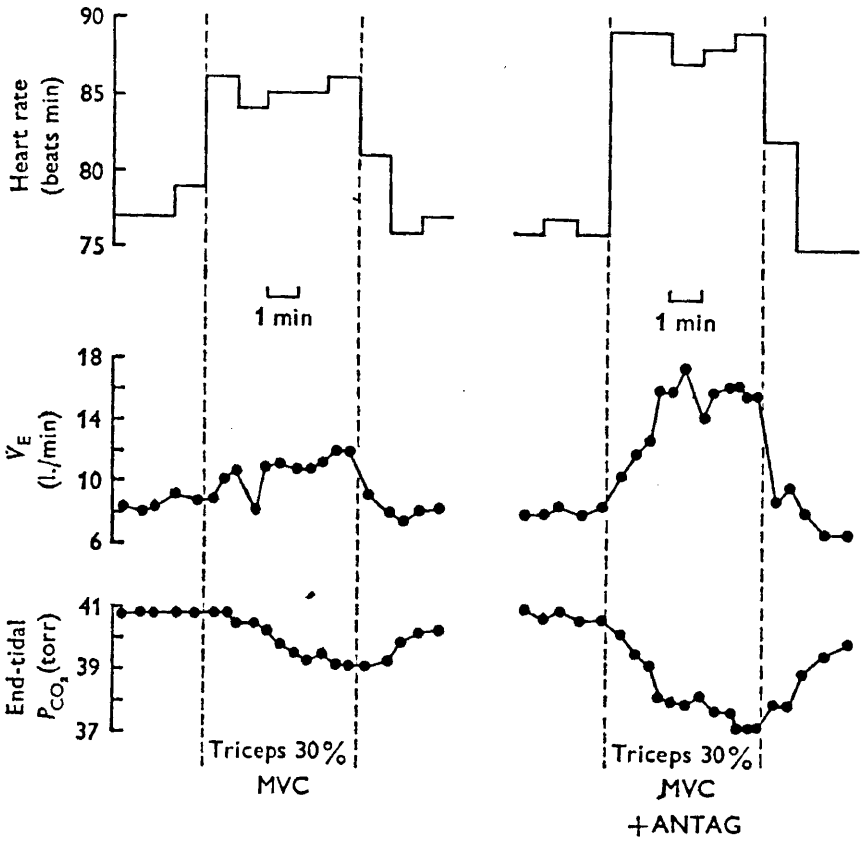

Fig. 8. Increase of central command. The heart rate, ventilation, and end-tidal CO_2 tension are plotted during two isometric contractions of triceps to achieve a tension of 5·5 kg (30 % of maximum) at the wrist. On the left are shown the responses to the contraction performed normally. On the right are the responses to a contraction of the same force in which the central command required was greater because of vibration applied to the antagonist, biceps.

DISCUSSION

The present experiments indicate that elements of the descending motor command stimulate increases in blood pressure, heart rate, and ventilation during voluntary muscular contraction. That such an effect might exist was suggested by Krogh & Lindhard (1913), who called it 'cortical irradiation'. Our experiments give no indication of the source of the irradiation, which might or might not be cortical.

The influence of command signals given to muscles unable to respond

was investigated by Freyschuss (1970) who found that blood pressure and heart rate increased in subjects attempting to make handgrips with an arm paralysed with succinylcholine. Our own experiments of this type, done in subjects attempting handgrips in an arm paralysed by anoxia through vascular occlusion also showed increases in heart rate and blood pressure. Nevertheless, experiments of this type are unsatisfactory because subjects are aware of their inability to achieve the attempted task when acutely paralysed (Goodwin *et al.* 1972), and a considerable physiological stress may be involved.

Another method of looking for an effect of central 'irradiation' has been to reduce muscular strength without paralysis by partial curarization of human subjects. In this type of experiment a greater central command is required to achieve a given level of muscular work when the subject is weakened than normally, and the increases in ventilation, blood pressure, and heart rate accompanying the work are also greater (Ochwadt, Bücherl, Kreuzer & Loeschcke, 1959; Asmussen, Johansen, Jørgensen & Nielsen, 1965). These observations can also be taken to establish the importance of central irradiation, although Asmussen *et al.* preferred an alternative explanation. They argued that the work was achieved in the weakened state by an 'increased activation of the gamma loop', that this entailed a greater activity in the afferent nerves from muscle spindles, and that the enhanced cardiovascular and respiratory responses were consequent upon this increased peripheral afferent activity. This explanation of their results seems unlikely to be correct. Experiments on animals indicate that activation of muscle spindle primary afferents by vibration produces no appreciable ventilatory or cardiovascular responses (Hodgson & Matthews, 1968; D. I. McCloskey, P. B. C. Matthews & J. H. Mitchell, unpublished work), and nerve block of only the large myelinated afferents, which include afferents from muscle spindles and Golgi tendon organs, does not alter the cardiorespiratory responses mediated by muscle afferents during contraction (McCloskey & Mitchell, 1972). Moreover, the experiments reported here give no indication of a stimulus to the measured parameters by the excitation of muscle spindle primary afferents by vibration. For these reasons, the experiments with partial curarization also argue for the importance of central irradiation.

The present experiments have used a different approach to answer the same question. Vibration is known to be a powerful stimulus to the primary endings of muscle spindles in animals (Brown, Engberg & Matthews, 1967; Matthews, 1972) and is assumed to act through these same afferents to cause the tonic vibration reflex in man (De Gail *et al.* 1966; Hagbarth & Eklund, 1966). It was used here to assist or to inhibit reflexly a voluntary isometric contraction. That such assistance or inhibition did

occur is shown by the effects of suddenly removing the vibration while a subject maintained a constant effort, as was shown in all experiments, and illustrated in Fig. 3. Indeed, this demonstration indicates that the central command was altered according to the design of the experiment whether or not the assumption is correct that the mechanism involved activation of muscle spindle primary afferents.

The method also depends on the assumption that the activity of muscle afferents involved in cardiorespiratory reflexes remains similar in compared trials. Clearly the activity of primary afferents from the muscle spindles differed, as also probably did activity of afferents from spindle secondary endings, but, as discussed above, there is little reason to implicate these afferents in cardiorespiratory reflexes. It is known that several important muscle metabolites (lactate, ATP, creatine phosphate, glycogen) come to attain very similar levels during each of a series of contractions except the first (J. Karlsson, personal communication). The first contraction was commonly rejected for experimental purposes in our studies, so that it is likely that the muscle was in comparable biochemical state in compared trials. It has been explained above (Results, section 1) how precautions were taken against complications that might have been caused by fatigue.

The present experiments might be influenced by the contraction of muscle groups other than those primarily involved in the study. For example, muscles stabilizing the shoulder joint might vary their activity from trial to trial, although we were not able to detect such changes electromyographically. However, Lind *et al.* (1966) found that the cardiovascular responses to an isometric effort varied according to the proportion of its maximum which a muscle group was achieving, and that if two muscle groups were contracting the responses were determined by the group achieving the greater proportion of its own maximum. Thus, variations in the activity of accessory or other muscles in our study would be expected to influence the responses only if they were achieving a greater proportion of their own maxima than the experimental muscle was of its maximum. That activity of such magnitude could have occurred without being detected is most unlikely. Activity in the vibrated antagonist of a contracting muscle could have presented a more specific problem, because this would have meant that the voluntarily contracted muscle would have had to increase its own tension by an amount equal to that elicited by vibration in the antagonist in order to register the required tension externally. This possibility was excluded in all cases where it might have occurred by palpation, which could readily detect contractions of 2% of maximum, and on occasion by less sensitive electromyographic testing.

All our subjects thought any effort was more difficult when an antagonist was vibrated, and it might be argued that their responses were to the subjective assessment of difficulty rather than to the magnitude of the descending command signal. This objection also applies to the partial curarization experiments of Ochwadt *et al.* (1959) and Asmussen *et al.* (1965). Nevertheless, it carries less weight when it is noted that subjects in whom vibration supplied reflex assistance did not usually report that the effort, although it produced smaller cardiorespiratory responses, was subjectively easier: some even noted that such assisted efforts were subjectively more difficult. These observations suggest that emotional factors did not play a significant part in the present study.

Once it is accepted that the neural drive to the mass transport systems in exercise has both central command and peripheral reflex components, the relative contributions made by both become of interest. This introduces several problems, First, it cannot be concluded that the contribution of each component drive to each cardiovascular and respiratory parameter is identical. Nor can it be assumed that the component drives simply add to produce their combined effect. For example, Asmussen, Nielsen & Wieth-Pedersen (1943) concluded that central irradiation gave no responses because the responses caused by electrical stimulation of muscle through the skin gave similar responses to similar contractions voluntarily achieved: such a conclusion is based on the assumption that peripheral and central mechanisms are additive. Even if these experiments, done on only two subjects, could be repeated, they would not mean that central radiation was without effect, for simple neural occlusion is possible, Moreover, it should be noted that the parameters measured here, and others which may be found to be similarly influenced by both central irradiation and reflex mechanisms, may interact one with another through other mechanisms (e.g. a pressor response tends to slow the heart rate through baroreceptor reflexes), so that the change seen in any single parameter will be induced by the two parts of the neural drive acting together with influences brought into play indirectly by other responses.

The present experiments seemed to allow the interesting possibility that the reflex component and the central component of the cardiorespiratory drive in isometric exercise could be varied more or less independently. Thus, it might have been possible to work out how the two components interacted quantitatively. This would have been feasible if a satisfactory means could have been devised for estimating the magnitude of the command during assisting or opposing vibration. The steady tension reached after the sudden removal of the vibrator might have served as such a measure of the prevailing central command. However, in practice the tension changes seen in these circumstances, examples of which are

illustrated in Fig. 3, were too variable in size and too short in duration to give much confidence in this method. Consequently, the present results constitute qualitative evidence for the existence of a central component, without showing how this should be expected to summate with the better known reflex contribution from the periphery.

We thank Dr P. Sleight for his assitance with intra-arterial recording, and Pifco Ltd. for the gift of vibrators used in this study.

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Absence of appreciable cardiovascular and respiratory responses to muscle vibration

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McCLOSKEY, D. I., P. B. C. MATTHEWS, AND JERE H. MITCHELL. *Absence of appreciable cardiovascular and respiratory responses to muscle vibration.* J. Appl. Physiol. 33(5): 623–626. 1972.—The triceps surae muscles of both hindlimbs of decerebrate or anesthetized cats were vibrated longitudinally at frequencies of 100–300 Hz with amplitudes of 100–200 μ (peak-to-peak). This had no appreciable influence on systemic arterial blood pressure, heart rate, or respiratory rate or depth. Since vibration is known to be a powerful stimulus to the primary afferents of muscle spindles, it is argued that these receptors are not significantly involved in reflex cardiovascular and respiratory responses, including those seen in muscular exercise.

blood pressure; heart rate; ventilation; exercise; muscle spindle

HEART RATE, BLOOD PRESSURE, and pulmonary ventilation can all change rapidly at the start or finish of a period of voluntary exercise. This observation has prompted some investigators to suggest that mechanoreceptors in the exercising muscle, in particular the primary afferents from muscle spindles, might be involved in these responses but the matter remains controversial (6, 25).

In the present experiments an examination was made in the cat of whether activation of the muscle spindle primary endings by vibration produced any changes in blood pressure or heart rate, but none were noted. Nor did muscle vibrations produce any appreciable increase in breathing, which confirms the earlier observations of Hodgson and Matthews (13), but disagrees with Leitner and Dejours (20) who found a slight stimulation of breathing in response to muscle vibration.

METHODS

Experiments were done on eight adult cats weighing 1.7–3.2 kg. Two experiments were done under chloralose anesthesia (α-chloralose, British Drug Houses; 80 mg/kg) after induction with ether. The remainder were done on animals decerebrated at the intercollicular level while under deep halothane (Fluothane, ICI) anesthesia. In the decerebrate cats no observations were made until at least 1 hr after the anesthetic had been discontinued. Either both common carotid arteries (3 cats) or both external carotid arteries (3 cats) were ligated before the decerebration and remained so throughout the experiment. It was occasionally necessary to ventilate a cat artifically for a few minutes during or immediately after the decerebration but otherwise all animals breathed spontaneously. All the decerebrate cats displayed typical decerebrate rigidity, and both decerebrate and anesthetized cats had stretch reflexes in the vibrated muscle.

The muscles of both hindlimbs were vibrated in all but one of the anesthetized cats, where only the right hindlimb was vibrated. The Achilles tendon together with a small piece of bone was separated from the calcaneum for connection to a single vibrator so that all the muscles attaching to this tendon were vibrated (both heads of gastrocnemius, soleus, and plantaris; these muscles are here collectively called the triceps surae). The nerves to the triceps remained intact, but all other nerves to the hindlimbs were severed under the initial anesthesia (cf. 23), and particular care was taken to cut the medial popliteal nerve beyond its branches to the triceps surae. All wounds to exposed nerves were closed by suture, and the triceps remained covered by skin.

The muscles were vibrated by an electromagnetic vibrator (26) which pulled along the length of the muscle and thus rapidly stretched and released it at the frequency of the vibration. Frequencies of 100–300 Hz were used with amplitudes of vibration of 100–200 μ (peak to peak). The muscles were always moderately taut before applying vibration; the tension was estimated to be over 100 g wt but was not recorded in these experiments. The vibration was usually applied for periods of about 20 sec, at intervals of a minute or more, although several series of vibrations of only 2 sec duration were done at shorter intervals. Respiration was recorded as airflow by a low-resistance pneumotachometer connected to the tracheal cannula and integrated electronically to give tidal volumes. Blood pressure was recorded from either the external or common carotid artery through a saline-filled nylon cannula connected to a pressure transducer (SE Laboratories, SE 4–82). The outputs of the blood pressure and respiratory records, plus the electrocardiogram, were amplified and displayed on a UV recorder (SE Labortories, SE 3006).

RESULTS

In six of the eight experiments, vibration produced no detectable changes in blood pressure, heart rate, or respiratory rate or depth. Records of blood pressure and ventilation from one of these experiments, which are typical of results of all six, are shown in Fig. 1.

The criteria used to conclude that no changes had occurred were as follows. For blood pressure measurements,

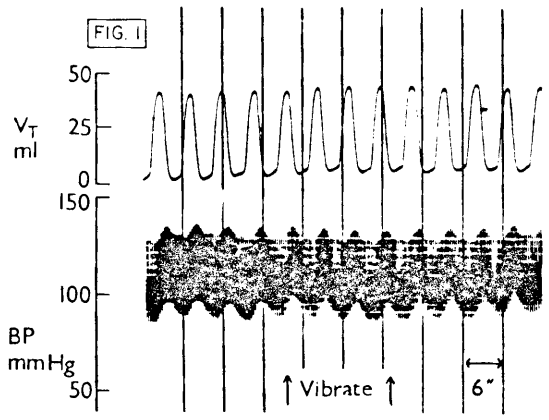

FIG. 1. Decerebrate cat. Tidal volume and arterial blood pressure records are shown. Between arrows, longitudinal vibration of triceps surae muscles of both hindlimbs was applied (200 μ peak-to-peak, 200 Hz). Time markers are 6 sec apart.

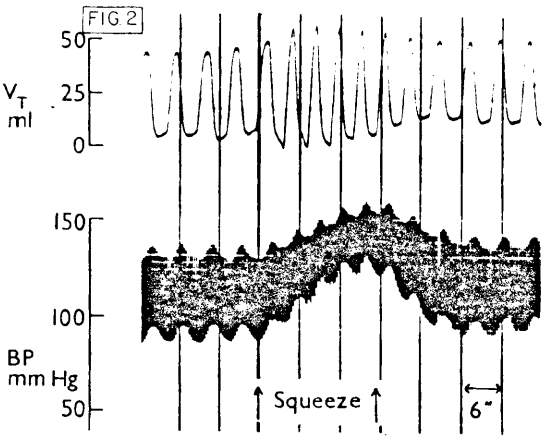

FIG. 2. Decerebrate cat: same animal as in Fig. 1. Tidal volume and arterial blood pressure records are shown. Between arrows, triceps surae muscles of both hindlimbs were squeezed rhythmically by an experimenter as described in the text. Time markers are 6 sec apart.

there was no consistent change of 5 mm Hg or more: in some experiments the variation of blood pressure with respiration was greater than 5 mm Hg, in which case the criterion used was that neither systolic nor diastolic pressures were raised at their maxima by 5 mm Hg or more. In all the blood pressure records in decerebrate cats there were slow drifts in pressure throughout an experiment, and in these, comparisons were made of pressures in adjacent time intervals. For heart rate measurements, the criterion used was that the duration of 20 heartbeats during vibration was less than 5% different from the duration of 20 beats immediately before or after vibration. For respiratory measurements, it was judged that no change in ventilation had occurred if the ventilation per minute, as calculated breath by breath from the measurements of respiratory rate and depth, was less than 10% different during the period of vibration from the values found in a comparable period before vibration. Particular attention was always paid to the period of the first 20 heartbeats and the first 2 complete breaths after commencing vibration: the conclusion that no changes occurred applies to these periods as well as to the total period of vibration.

In the remaining two experiments vibration was associated with some increase in blood pressure and respiratory depth and rate. In one of these, in a decerebrate cat, vibration of the two hindlimbs produced an obvious "arousal" of the whole animal, so that it contracted the muscles of its trunk and forelimbs strongly for the duration of the vibration. Clearly, reflexes from these other muscles, and from afferents other than muscle spindle primaries, may have been involved in the responses seen in this cat. In another decerebrate cat there was again some increase in blood pressure and respiratory rate and depth associated with vibration, although in this animal there was not any gross "arousal." But when vibration was applied again after paralyzing the animal with gallamine (Flaxedil, 5 mg/kg), the blood pressure then did not increase in response to vibration. This suggests that the rise had been due to the muscle contraction rather than to spindle afferent discharges which should still have been evoked by vibration even after curarization. It was not necessary to do this type of control in those experiments in which there were no blood pressure or ventilatory changes caused by vibration, even though some reflex contraction of the vibrated muscle did occur in all experiments. In none of the eight experiments was there any change in heart rate accompanying the vibration.

In rhythmic exercise it is probably that the primary endings of the muscle spindles fire in bursts in phase with the movements, and it might be suggested that such rhythmic or intermittent discharge is essential for producing cardiovascular or respiratory responses. However, when periods of vibration of 1–2 sec apart were given with similar intervals between, no changes in blood pressure, heart rate, or ventilation were seen.

In all experiments rhythmic manual squeezing of one or both triceps surae muscles was used to provide a powerful reflex stimulus to the cardiovascular and respiratory systems. Results typical of all experiments are shown in Fig. 2: the illustrated records are taken from the same experiment as Fig. 1. In all experiments blood pressure rose in response to this stimulus by 20–70 mm Hg, and ventilation increased variably, but always by more than 25% of its unstimulated level. Heart rate did not always increase in response to squeezing: increases of 5–15% were found in five of the eight experiments. The stimulus of squeezing was given principally to establish that receptors in the triceps surae were functioning, and that certain of them had access to cardiovascular and respiratory control centers: it is not suggested that the maneuver necessarily mimics any particular physiological situation. Squeezing was applied between the finger and thumb of an experimenter at a rate of 2–3/sec. The pressure exerted was not measured: a similar pressure applied to a finger was uncomfortable but not painful. In all experiments, cutting the nerves to the triceps abolished the responses to squeezing— the criteria for concluding that no responses remained being the same as those outlined above for reaching similar conclusions concerning the ineffectiveness of vibration.

DISCUSSION

The present experiments show that activation of the primary endings of the muscle spindles does not produce any appreciable increase in blood pressure, heart rate, or ventilation in the decerebrate or anesthetized cat. It can be safely assumed that the vibration used powerfully stimulated the primary endings of the muscle spindles of the triceps surae, because of its frequency and amplitude (4), and also because it consistently elicited a reflex contraction in the vibrated muscles, an effect attributable to excitation of the primary endings. It is probable that the majority of the primary endings of the vibrated muscle were driven to discharge at the frequency of the vibration (100–300 Hz). Since the frequency of discharge of the primary endings would be expected to have been well below 100/sec before applying the vibration (cf. 7, 14, 15), the vibration would have caused a considerable increase in their frequency of discharge.

Hodgson and Matthews (13) used similar vibration applied to the triceps of just one hindlimb of decerebrate cats and found that there was no appreciable ventilatory response. The present study, done with vibration applied to the triceps surae of both hindlimbs, confirms their results and extends them to show that vibration also causes no appreciable blood pressure or heart rate responses. The use of both legs was necessary because Leitner and Dejours (20) recently applied vibration bilaterally and found a slight stimulation of breathing, although they also found no effect on vibrating a single leg. They attributed the occurrence of an effect on bilateral, but not unilateral, stimulation to the central mechanisms involved having a high threshold. They reported very little detail of their denervation procedure, and it seems possible that they may have excited a variety of receptors outside the muscles which were primarily being vibrated. Moreover, Leitner and Dejours did not attempt to show whether their responses were primarily due to the activation of muscle spindle primary afferents or to the reflex contractions, whether specific or nonspecific, which occur as a consequence of this. This could have been done by cutting the spinal ventral roots, or by curarization.

It is perhaps surprising that the reflexly induced contractions of the triceps surae did not of themselves produce significant effects on both the cardiovascular and respiratory systems for they had the opportunity of doing so both by reflex and by humoral mechanisms. This failure of action is probably a simple consequence of the relative weakness of the vibration-induced contractions which would have developed less than 10% of the maximum tension of which the muscles were capable (cf. 24); in man such contractions have a negligible effect (21).

Both the electrical stimulation of nerve trunks and the administration of pharmacological agents have been used to activate the afferents from muscle spindle primary endings in the investigation of cardiovascular and respiratory reflex responses. Neither method is completely specific. Electrical stimulation of group I fibers in a muscle nerve has been reported to cause slight cardiovascular and respiratory responses (3, 16, 19, 30). However, such experiments cannot provide unequivocal evidence on the nature of the receptors responsible for the observed effects. Nerves of any particular fiber diameter innervate receptors of more than one kind, and a reflex action produced by stimulation of all fibers of a given size cannot be safely ascribed to the most numerous kinds of fiber of that size.

The chief pharmacological evidence was produced with succinylcholine, a drug which is often regarded as a specific excitant of muscle spindle primary endings. On administration of this agent an increase in ventilation and a very slight increase in heart rate (176 to 180 beats/min) have been observed (9, 10). However, Kidd and Kucera (17) have shown that this drug can also excite the endings of smaller myelinated fibers so that the responses to it need not necessarily be attributed to muscle spindle primary activation.

Further evidence against the participation of large myelinated afferents in cardiovascular and respiratory reflex responses has recently come from experiments of a different kind. Coote, Hilton, and Perez-Gonzalez (5) and McCloskey and Mitchell (22) showed that the cardiovascular and respiratory responses to isometric exercise induced by ventral root stimulation at 50/sec were no different whether the ventral root stimulation was at twice the motor threshold, which stimulates principally α motor fibers (12) and and should unload the muscle spindles, or at 10 or more times the motor threshold, which stimulates α and γ motor fibers and might be expected to give some muscle spindle activation. In addition, McCloskey and Mitchell (22) showed that the cardiovascular and respiratory reflex responses to isometric contractions were unchanged when the large myelinated afferent nerves were blocked in the spinal dorsal roots by a direct current anodal block which would have allowed only small myelinated fibers and unmyelinated fibers to continue conducting. Both these lines of evidence weigh against the participation of muscle spindle afferents in the reflexes studied.

The participation of muscle spindle afferents in cardiovascular and respiratory reflexes is sometimes supported on the grounds of rapidity of onset of the responses alone. However, this argument is unconvincing even after disregarding the experimental evidence discussed above. In isometric exercise the muscle spindle primary afferent activity increases (31), but there is no obvious abrupt increase in ventilation (27, 32), although blood pressure and heart rate do increase (21, 29). On the other hand, in rhythmic exercise, where presumably there is also increased spindle activity, ventilation increases abruptly (6) as does heart rate, although blood pressure alters variably. Different additional factors must operate in the two cases, but the involvement of muscle spindle primary afferents is certainly not immediately suggested by the response patterns. Any mechanoreceptor, either within muscle or outside it, if excited by movement or muscular contraction, could be the basis of the afferent limb of the reflexes on the criterion of speed alone. Equally, the outflow of the command from higher centers to the motoneurons of the exercising muscles might be tapped off to provide an input to the cardiovascular and respiratory control centers, and this could give rapid, and slower, responses. Such a tapping of the central command was first postulated by Krogh and Lindhard (18) and called "cortical irradiation." Lately

its importance has been demonstrated by Freyschuss (8) and Goodwin, McCloskey, and Mitchell (11).

When human subjects are weakened by partial curarization, the ventilatory and to a lesser extent the blood pressure and heart rate responses to a given work load are greater in the weakened than in the normal state (1, 28). Asmussen et al. (1) could have attributed the increased responses to an increased "irradiation" of the central command on to cardiovascular and respiratory control centers but preferred to explain them in terms of a peripheral reflex mediated by muscle spindle afferents. They suggested that in the weakened state a given level of work was achieved through a "greater activation of the gamma loop" than normal, and that this activation would provide an increased spindle primary afferent activity. They preferred this explanation of their findings to that of central irradiation because they had earlier found that the ventilatory responses to work done by voluntarily contracting the muscles were the same as those when the work was done by inducing involuntary muscular contractions with electrical stimulation through the skin (2). This latter finding was taken to show that there was no central contribution to cardiovascular and respiratory control. However, a stricter interpretation would be that, in the absence of a central input, the muscle reflex is adequate to provide a normal response, as, by similar argument, the central input, in the absence of a muscular reflex, might be adequate for a normal response (8, 11). In any case, the experiments reported in the present study make it unlikely that muscle spindle primary afferents are significantly involved in cardiovascular and respiratory reflexes originating in muscle, whatever the relative contribution that such reflexes make to the overall response.

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CHEMORECEPTOR RESPONSES TO SYMPATHETIC STIMULATION AND CHANGES IN BLOOD PRESSURE

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Abstract. Discharges from 24 single carotid chemoreceptor fibres were examined in 11 anaesthetized cats for the effects of mechanically induced alterations of arterial blood pressure and of stimulation of the preganglionic sympathetic nerve in the neck. In 10 fibres, discharge was increased when blood pressure was lowered: in the reamining 14 fibres, there was no apparent dependence of discharge upon blood pressure. Sixteen fibres increased their discharge in response to sympathetic stimulation, the remainder did not. Fibres were found which were: (a) sensitive to both blood pressure and sympathetic stimulation (6 fibres); (b) sensitive to neither (4 fibres), and (c) sensitive to one but not the other stimulus. The implications of these findings upon the hypothesis that local blood flow in the carotid body affects discharge in the steady state are discussed.

Arterial blood pressure
Arterial chemoreceptors
Cats
Carotid body
Sympathetic stimulation

Landgren and Neil (1951) demonstrated a rise in carotid body chemoreceptor activity when arterial blood pressure was lowered to about 50 mm Hg by haemorrhage. Similarly, Lee *et al.*, (1964) showed that the discharge from aortic chemoreceptors in the cat increased as arterial pressure was lowered throughout the range 200 down to 60 mm Hg. However Samaan and Stella (1935) and Biscoe *et al.* (1970) reported that carotid chemoreceptor discharge was independent of arterial pressures within the physiological range.

Stimulation of the sympathetic nerve supplying the carotid body causes a decrease in the blood flow through it (Daly *et al.*, 1954; Purves, 1970; McCloskey and Torrance, 1971). This has also been reported to increase chemoreceptor activity (Floyd and Neil, 1952; Eyzaguirre and Lewin, 1961; Biscoe and Purves, 1967), although this, too, is not universally agreed (Hornbein, 1968).

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The present study began with the hypothesis that some carotid chemoreceptor fibres may be much more sensitive than others to a decrease in local blood flow whether it be caused by hypotension or by sympathetic vasoconstriction. It was thought that if this were so, then fibres would show similar sensitivities to both stimuli. Contrary to the working hypothesis it was found that fibres could be found sensitive to one but not the other of these stimuli, or sensitive to both, or to neither.

Methods

Experiments were performed on cats, anaesthetized with pentobarbitone (Nembutal: Abbott; 35–40 mg/kg) given intra-peritoneally. The trachea was cannulated low in the neck, and the pretracheal muscles, larynx and pharynx were removed up to the level of the hyoid bone. A cannula was inserted into the lingual artery to measure blood pressure in the region of the carotid bifurcation. A femoral vein was cannulated. Cotton loops were passed through the flank around the abdominal aorta cephalic to the coeliac artery and caudal to the superior mesenteric artery: various fractions of the arterial bed below the diaphragm could be occluded temporarily by pulling one of these loops into a narrow tube.

The vago-sympathetic trunks were cut low in the neck. The carotid sinus nerve was identified where it joined the glossopharyngeal and was dissected under paraffin on a rigid, earthed stainless steel plate with a blackened upper surface. Chemoreceptor fibres were identified by their sporadic discharge, but were accepted only if they responded to changes in the oxygen content of the inspired gas. Only single-fibre preparations were used in this study.

The recording electrodes were made of fine stainless steel wire. Impulses were led into a Tektronix type 122 preamplifier and then to an oscilloscope for preliminary observation or to one channel of the recording apparatus, a Mingograf Cardirex 24B, a direct-writing ink-jet recorder with galvanometers of natural frequency 610 cps. Blood pressure in the lingual artery was measured with an Elema–Schönander Electromanometer type 460 with a variable inductance pressure transducer (type EMT 490A, 0–300 mm Hg). The output was recorded on a second channel of the Mingograf.

Observations were made with cats breathing spontaneously through low-resistance respiratory valves. Gas mixtures were made up with flow meters and stored in Douglas bags. Rectal temperatures were kept constant within the range 37–39 °C, and the paraffin pool was kept at a similar temperature.

The preganglionic sympathetic nerve in the neck was cut and its cephalic end placed on Ag–AgCl electrodes for stimulation with an isolated stimulator. The stimulus strength and duration were determined by observing the ipsilateral pupil for maximal dilation: a voltage 50% in excess of that required to achieve this was chosen. Usually the stimulus strength was 10–12 V, and duration 500 μsec. Trains of stimuli were given at 5, 10 or 20 per sec, for 30 or 60 sec.

Twenty-four single chemoreceptor fibres were examined in 11 cats. Usually

discharges were examined while the animals breathed room air and while they breathed hypoxic gas mixtures (10–12% O_2 in N_2). The responses to changes in blood pressure and to sympathetic nerve stimulation were not qualitatively different with different inspired gas mixtures. Gas mixtures were breathed for at least 5 min before any observations were made. Blood pressure was raised by occluding the abdominal aorta and lowered by clipping the common carotid artery on the experimental side. Action potentials were counted from the records: counts were made of discharges occurring between 30 and 60 sec after a change of pressure.

Results

Twenty-four single chemoreceptor fibres were examined. In 10 of these there was a dependence of steady-state discharge upon arterial pressure: discharge was increased when blood pressure was lowered, and decreased when blood pressure was raised. In the remaining 14 fibres there was no apparent dependence of steady-state discharge upon pressure. These steady-state changes in discharge were established within 30 sec of a change in blood pressure, and were not further altered over the succeeding 60 sec. The majority of fibres (9 of the 10 pressure sensitive fibres, and 11 of the 14 pressure insensitive fibres), however, did show transient changes of discharge when blood pressure was abruptly changed. Usually these transient changes were of the type described by McCloskey (1968): a decrease of discharge when blood pressure was raised, and an increase of discharge when blood pressure was lowered. These transient changes of discharge were complete within 30 sec of the change in blood pressure. In two fibres in different animals, however, there were striking transient changes of discharge in the opposite direction: discharge rose when blood pressure was raised, and fell when it was lowered, and again these transient changes of discharge were complete within 30 sec of the change in blood pressure. In no one animal were two or more fibres found which did not respond alike to blood pressure in the steady-state.

Sixteen of the fibres examined increased their discharge in response to sympathetic stimulation. In the remaining eight fibres sympathetic stimulation had no apparent effect upon discharge. In two cats, fibres were found which behaved differently in response to sympathetic stimulation. In one cat, two fibres increased their discharge in response to sympathetic stimulation and one fibre did not; in another cat, one responsive fibre and one non-responsive fibre were found.

Of the 10 fibres responding classically to changes in blood pressure, six were also responsive to sympathetic stimulation. An example of this type of fibre is shown in fig. 1, upper left. See table 1.

Four of the fibres which responded to changes in blood pressure were not responsive to sympathetic stimulation: see fig. 1, upper right, and table 1.

Of the 14 fibres which did not alter their steady-state discharge at different blood pressures, 10 were responsive to sympathetic stimulation: see fig. 1, lower left, and Table 1.

Four chemoreceptor fibres did not alter their steady-state discharge in response

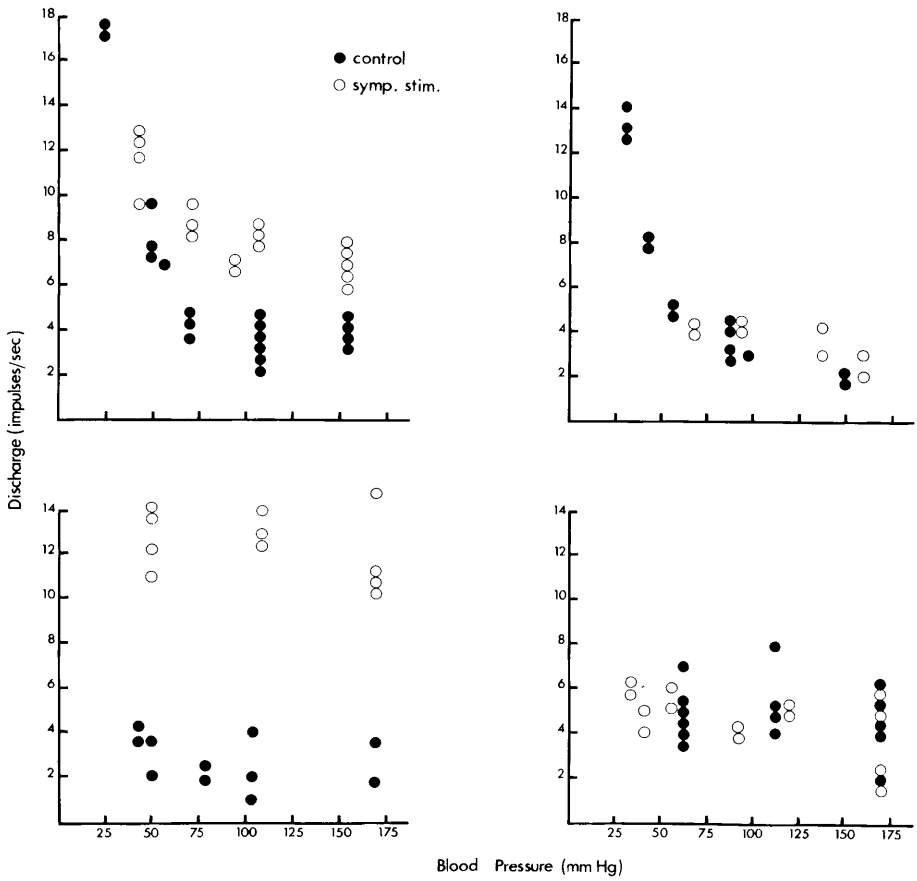

Fig. 1. Relations between discharge and blood pressure in four different single carotid chemoreceptor fibres. The control relation is shown together with points obtained during stimulation of the preganglionic sympathetic nerve. Upper left: a fibre sensitive to hypotension and to sympathetic stimulation. Upper right: a fibre sensitive to hypotension but insensitive to sympathetic stimulation. Lower left: a fibre insensitive to hypotension but sensitive to sympathetic stimulation. Lower right: a fibre insensitive to both hypotension and sympathetic stimulation.

TABLE 1

This shows numbers of single chemoreceptor fibres examined which were sensitive to changes in arterial blood pressure and/or stimulation of the sympathetic nerves to the carotid body.

		Blood Pressure	
		Sensitive	Insensitive
Sympathetic Stimulation	Sensitive	6	10
	Insensitive	4	4

to either blood pressure or sympathetic stimulation. An example of this type of fibre is shown in fig. 1, lower right. See table 1.

Discussion

Neil (1951) supposed that a change in blood pressure or vasomotor tone alters the discharge of chemoreceptor fibres by altering the blood flow through the carotid body. The blood flow was found by Daly *et al.* (1954) to be approximately linearly related to blood pressure, although McCloskey and Torrance (1971) later reported autoregulation of flow in some of their experiments. Sympathetic stimulation reduces overall flow. Some of the sympathetic fibres run in the ganglioglomerular nerves but others follow a more devious route, ultimately reaching the carotid body along the carotid sinus nerve, which was cut in the present experiments. Vasoconstrictor influences can lower the level at which autoregulation holds blood flow constant (McCloskey and Torrance, 1971). Most of the observations reported here can therefore be accounted for by Neil's hypothesis: at a change of blood pressure discharge changes because blood flow changes. If the discharge in the steady-state has returned to the control level, autoregulation is complete; if it does not, autoregulation is not complete. Sympathetic stimulation reduces blood flow and so increases discharge. The fibres which were not affected by sympathetic stimulation came from regions supplied by sympathetic fibres which run in the carotid sinus nerve. The fibres which were not affected by blood pressure in the steady-state, but were affected by sympathetic stimulation, came from regions in which autoregulation is complete and the level at which it holds blood flow constant is affected by sympathetic stimulation.

The two occasions on which discharge rose transiently in response to a rise in blood pressure are difficult to account for. The vascular bed of the carotid body is a complex anastomosing set of tortuous capillaries, and it is conceivable that flow could increase in two or more through-channels at a rise of blood pressure, but that flow might be reduced in a channel connecting points some way along them, rather as in a Wheatstone bridge circuit in which the resistances are not linear. The situation would be rather like that seen in capillary networks in the skin of the frog in which flow in a vessel may reverse, though of course it is supposed that vasomotion precipitates the changes in the skin.

These simple explanations are not entirely satisfactory. The discharge of some fibres was independent of blood pressure over a much wider range of blood pressures (*e.g.* fig. 1, lower left: 50–170 mm Hg) than that over which autoregulation has been found to hold flow constant. Also, the present studies were done using pentobarbitone anaesthesia, which McCloskey and Torrance (1971) observed might destroy autoregulation: in their experiments, but not here, however, dissection close to the glomus was necessary, which was another factor likely to destroy autoregulatory ability. One further problem is that while Biscoe, Bradley and Purves (1970) confirmed McCloskey's (1968) observation that transient changes in discharge accompanied alterations in blood pressure, they did not find evidence of autoregulation of blood

flow which was measured simultaneously. In their experiments discharge returned towards control after a change of blood pressure, but blood flow remained unaltered. Only by postulating a redistribution of flow between glomus capillaries and alternative through paths can one circumvent this objection.

If the idea that local blood flow affects discharge in the steady-state is rejected, then it is necessary to reject also the view that the sympathetic, or parasympathetic (cf. Goodman, 1973), exert effects upon discharge by vasomotion.

Acknowledgement

We thank Dr. R. W. Torrance for his interest in this study.

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BARORECEPTOR AND CHEMORECEPTOR INFLUENCES ON HEART RATE DURING THE RESPIRATORY CYCLE IN THE DOG

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SUMMARY

1. Brief stimuli were delivered to the carotid chemoreceptors or baroreceptors in dogs anaesthetized with pentobarbitone or chloralose. Chemoreceptor stimulation was achieved by rapid retrograde injections of 0·2–0·5 ml. warmed, CO_2-equilibrated saline through a cannula in the external carotid artery. Baroreceptor stimulation was achieved by forceful retrograde injection of 2–5 ml. air-equilibrated saline, or of freshly drawn arterial blood, into the external carotid artery after first clamping the common carotid artery.

2. Brief baroreceptor stimuli had no noticeable effect on breathing. Brief chemoreceptor stimuli had no effect on breathing in some dogs, but in many produced a reflex increase in the depth of inspiration when delivered during inspiration. In these same dogs, brief chemoreceptor stimuli delivered in expiration either prolonged the expiratory pause or evoked an active expiratory effort.

3. Prompt decreases in heart rate were elicited by brief sudden chemoreceptor or baroreceptor stimuli when these were delivered during the expiratory phase of respiration. The stimuli did not modify the control heart rate pattern when delivered during inspiration. If the carotid sinus nerve or the vagus nerves were cut the responses were abolished.

4. Brief chemoreceptor or baroreceptor stimuli remained effective in evoking prompt decreases in heart rate during periods of apnoea in the end-inspiratory position (Hering–Breuer inflation reflex). In periods of apnoea after prolonged artificial hyperventilation the stimuli were sometimes ineffective at first, but were always effective late in the period of apnoea, again producing prompt cardiac slowing.

5. After denervation of the lungs, brief baroreceptor and chemoreceptor stimuli continued to evoke prompt falls in heart rate when given during

expiration. When delivered during inspiration the same stimuli were either ineffective, or less effective.

INTRODUCTION

Stimulation of the carotid sinus baroreceptors is well known to cause a reflex bradycardia (e.g. Hering, 1927). Stimulation of the carotid arterial chemoreceptors also causes a primary reflex bradycardia, although this may be obscured or reversed by secondary effects due to the stimulation of breathing (Daly & Scott, 1958).

Experiments on cats have established that when a brief stimulus is delivered to the carotid chemoreceptors during an inspiration, the depth of that inspiration is reflexly increased. When a similar stimulus is delivered during the expiratory phase of a respiratory cycle, it has little effect, or simply prolongs the expiratory pause (Black & Torrance, 1971; Eldridge, 1972). The effects upon the heart rate of similar stimuli to the chemoreceptors, and of brief stimuli to the carotid baroreceptors, were investigated here in anaesthetized dogs. We found that such stimuli cause prompt reflex slowing of the heart when they are delivered during expiration, but are without effect upon the heart rate when delivered during inspiration.

Part of this work has been reported in brief form (Haymet & McCloskey, 1974).

METHODS

Experiments were performed on twenty-five adult dogs of both sexes weighing from 5 to 12 kg. The animals were anaesthetized with (i) I.V. or I.P. pentobarbitone (Nembutal: Abbott: 35 mg/kg: eight dogs), or (ii) I.V. thiopentone (Pentothal: Abbott: 25 mg/kg), followed by I.V. chloralose (α- chloralose: British Drug Houses: 80 mg/kg: seventeen dogs). Eight dogs (four of each above category) were given a supplemental dose of morphine (1–2 mg/kg I.V.) early in the period of anaesthesia before the experimental procedures. In each dog the trachea was cannulated low in the neck, and nylon cannulae were inserted, with their tips pointing towards the heart, into the lingual and external carotid arteries on one or both sides. On each side the tips of these cannulae were positioned close to each other and in close communication with the carotid sinus. A nylon cannula was inserted into the right external jugular vein and advanced so that its tip lay within the thorax in or near the right atrium. Rectal temperature was kept between 37 and 39° C.

Arterial pressure was recorded from a lingual artery using a Statham P23AC transducer. Right atrial pressure was recorded through the jugular venous cannula using a similar transducer. Both pressures were recorded on a Grass Polygraph pen recorder. On another channel of the recorder either the electrocardiogram or the heart rate was recorded using a Grass 5P4D pre-amplifier. Respiration was recorded on the fourth channel of the polygraph. Usually this was achieved by the bag-in-box method similar to that described by Donald & Christie (1949) in which the animal inspired through a valve from a bag enclosed in an airtight box into which expired

air was led: pressure in the box was measured using a Grass PT5A volumetric pressure transducer. Alternatively, respiratory movements of the chest were recorded from tension changes produced through an elastic band sewn to the chest wall and connected to a Grass FTO3 force transducer (cf. Levy, DeGeest & Zieske, 1966).

Brief chemoreceptor stimuli were delivered by the sudden retrograde injections into an external carotid artery of small volumes (0·2–0·5 ml.) of warmed, physiological saline through which 100% CO_2 had been bubbled (CO_2 saline: cf. Black & Torrance, 1971; Eldridge, 1972). These injections produced only slight transient alterations, if any, in carotid sinus pressure as measured from the lingual artery.

Brief baroreceptor stimuli were delivered by the sudden retrograde injection into an external carotid artery of a larger volume (2–5 ml.) of warmed, air-equilibrated, physiological saline, after first clamping the common carotid artery. Prior to these injections the carotid sinus pressure was reduced below systemic arterial pressure by 25–75 mmHg because of the common carotid arterial occlusion. Usually the sinus pressure remained pulsatile, presumably because of open anastomotic channels. At the injection of saline the carotid sinus pressure rose by 50–150 mmHg, and then fell back to its initial control level, the whole change taking about 1 sec to complete. On some occasions freshly drawn arterial blood was re-injected instead of saline.

In three dogs anaesthetized with pentobarbitone, recordings were made from single afferent fibres in the cut carotid sinus nerve (four chemoreceptors and seven baroreceptors) during the manoeuvres described above. These recordings were made using stainless steel electrodes, and the impulses were amplified on a Tektronix 122 pre-amplifier and recorded on a Y.E.W. ultra-violet recorder with galvanometers giving a flat frequency response to 1000 Hz. Injections of 0·2–0·5 ml. CO_2 saline set up intense short-lasting (1–4 sec) volleys of impulses in chemoreceptor fibres, but had almost no effect upon the discharges of baroreceptor fibres. Injections of larger volumes of air-equilibrated saline, or of arterial blood, after clipping the common carotid artery, set up intense volleys of impulses in baroreceptor fibres, lasting as long as the carotid sinus pressure disturbances, but had no effect upon chemoreceptor afferent discharge (see Fig. 1).

RESULTS

(i) *Effects upon breathing.* Brief baroreceptor stimuli had no noticeable effect on breathing. Brief chemoreceptor stimuli delivered during an inspiration reflexly increased the depth of that inspiration in fourteen of the twenty-five dogs. In the same animals, brief chemoreceptor stimuli delivered early in an expiration either prolonged the expiratory pause (five dogs) or caused an active expiratory effort (nine dogs). Stimuli delivered late in the expiratory phase evoked an inspiratory effort in these animals. These findings are similar to those reported by Black & Torrance (1971) and by Eldridge (1972) for the cat, except that those authors did not see active expiratory efforts in response to stimuli given in expiration. Active responses to inspiratory and expiratory stimuli are shown in Fig. 2. In the remaining eleven of the twenty-five dogs investigated, including seven of the eight dogs given morphine, brief chemoreceptor

stimuli evoked no respiratory responses. In three dogs the carotid sinus nerve was cut on the experimental side: in all three this abolished active responses to inspiratory and expiratory chemoreceptor stimuli.

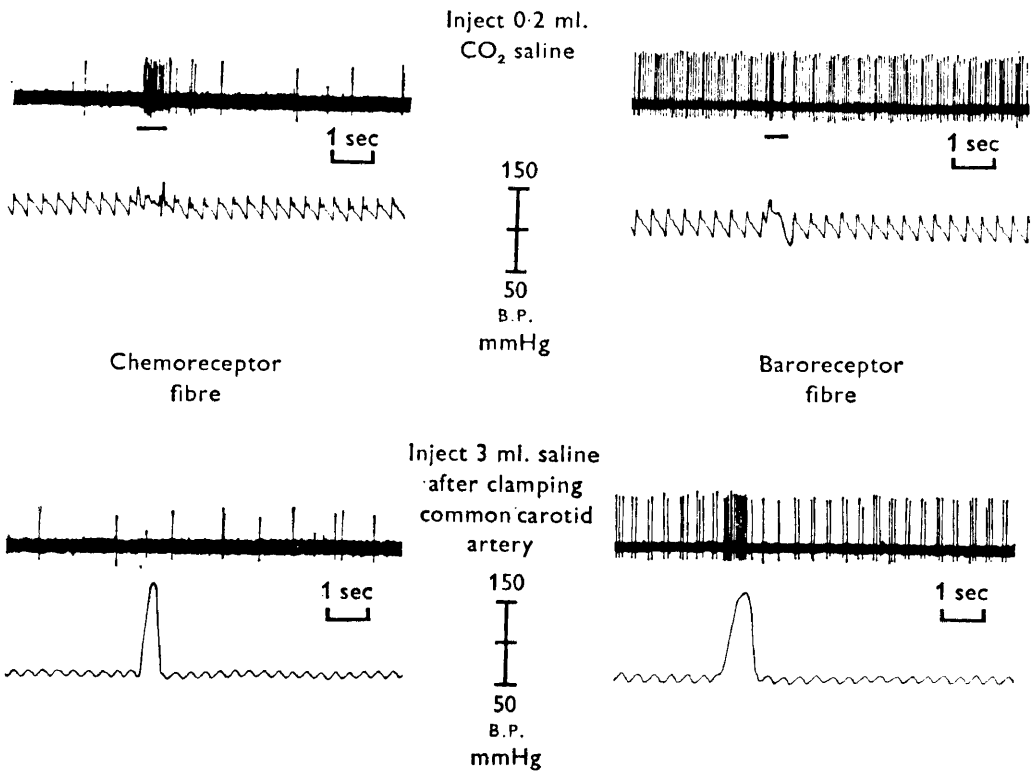

Fig. 1. Dog. Pentobarbitone. Chemoreceptor afferent activity (left panels) and baroreceptor afferent activity (right panels), recorded from filaments dissected from the carotid sinus nerve, are shown together with records of blood pressure simultaneously recorded from near the carotid bifurcation. The effects on both forms of activity of injection into the carotid bifurcation of 0·2 ml. CO_2-equilibrated saline are shown in the top two panels. The effects of forceful injection of 3 ml. air-equilibrated saline into the carotid sinus, after first occluding the common carotid artery, are shown in the lower two panels (neural activity records retouched).

(ii) *Effects upon heart rate.* Brief chemoreceptor or baroreceptor stimuli delivered during expiration caused a prompt and brief decrease in heart rate. When delivered during inspiration similar stimuli either failed to alter heart rate, or failed to modify a control pattern of sinus arrhythmia when this was present. The decreases in heart rate which could be evoked during the expiratory phases of breathing could no longer be evoked after the carotid sinus nerve was cut on the experimental side (three dogs), or after bilateral vagotomy (five dogs), or after intravenous administration of atropine (1·2 mg, three dogs).

Responses to brief chemoreceptor stimuli are shown in Fig. 2. When 0·1–0·2 ml. of air-equilibrated saline was injected instead of a similar volume of CO_2-saline, no effects upon heart rate were observed.

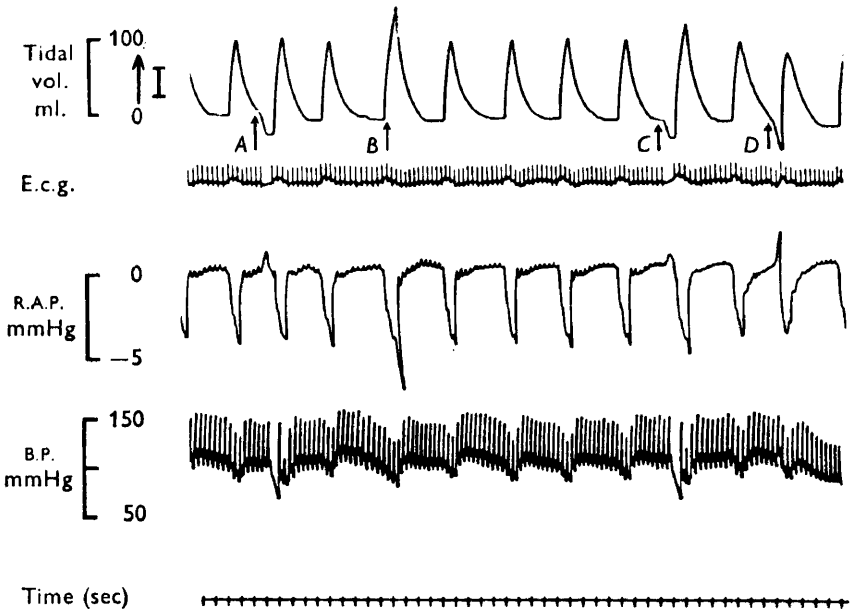

Fig. 2. Dog. Chloralose. Records of tidal volume (inspiration upwards), electrocardiogram, right atrial pressure, and arterial pressure are shown. At *A*, *B* and *C* injections of CO_2-saline were made into the carotid bifurcation to provide brief chemoreceptor stimulation. When these stimuli were delivered in expiration (*A* and *C*), they evoked a prompt slowing of the heart, and an expiratory effort. When the stimuli were delivered in inspiration (*B*), they evoked an increased inspiratory effort but no change in heart rate. As a control, the chest was squeezed at *D* to mimic the thoracic and atrial pressure changes seen with the chemoreceptor stimuli given in expiration, but this did not affect heart rate.

Responses to brief baroreceptor stimuli are shown in Fig. 3. Frequently the baroreceptor stimuli evoked less dramatic alterations in heart rate than did the chemoreceptor stimuli chosen. The phase of the respiratory cycle during which baroreceptor stimuli were effective in evoking a reflex bradycardia commenced after the peak of inspiration and during expiratory air flow, and lasted through the expiratory pause until the commencement of the next inspiration. This is shown in Fig. 3. The phase of the respiratory cycle during which chemoreceptor stimuli were effective was similar, although the chemoreceptor stimuli also altered the respiratory cycle so that no two cycles were alike during alterations in timing of such stimuli. We were unable to demonstrate any relation between the magnitude of the heart rate response and timing of the stimuli within the expiratory phase.

(iii) *Effects of lung and thoracic volumes upon heart rate responses.* From the observations reported above it appeared to us that some event associated with inspiration is capable of making the vagal centres completely or partly refractory to afferent inputs from arterial baroreceptors or chemoreceptors. One obvious possible event is the physical expansion of

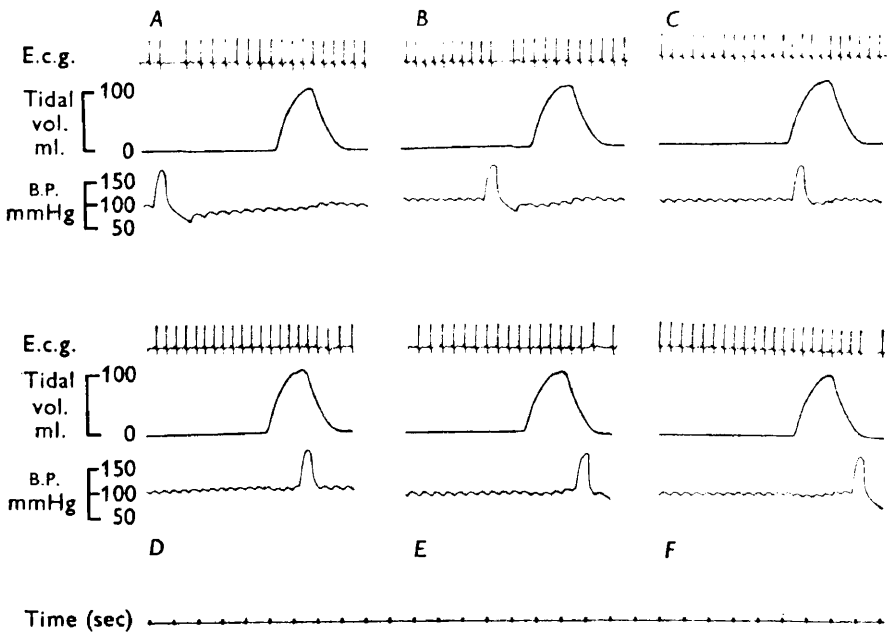

Fig. 3. Dog. Chloralose and morphine. Records of electrocardiogram, tidal volume and carotid sinus blood pressure are shown. Baroreceptor stimuli were timed to occur at various points in the respiratory cycle. Stimuli occurring during the expiratory pause (*A*, *B* and *F*), or during expiratory air flow (*E*), produced prompt cardiac slowing. Stimuli given during inspiration (*C* and *D*) did not slow the heart.

the lungs and thorax which would, of course, be associated with the activation of numerous pulmonary and thoracic mechanoreceptors. In order to investigate this possibility, we gave brief stimuli to the baroreceptors or chemoreceptors during periods of apnoea evoked by the Hering–Breuer inflation reflex. This reflex was called into play by occluding the expiratory line so that the animals' lungs remained inflated at normal end-inspiratory volume. During the ensuing period of respiratory arrest the usual brief baroreceptor or chemoreceptor stimuli remained effective in producing reflex bradycardia (see Figs. 4 and 5). Often the stimuli appeared less effective during the inflation reflex, as illustrated in Figs. 4 and 5, but the responses were still quite marked. In other animals the bradycardia evoked by brief stimuli given during the inflation reflex was extreme, and much

more pronounced than the slowing evoked during the expiratory phases of breathing. In the example shown in Fig. 6, which is not the most dramatic response we have seen, the heart stopped for over 7 sec in response to a brief chemoreceptor stimulus given during the inflation reflex.

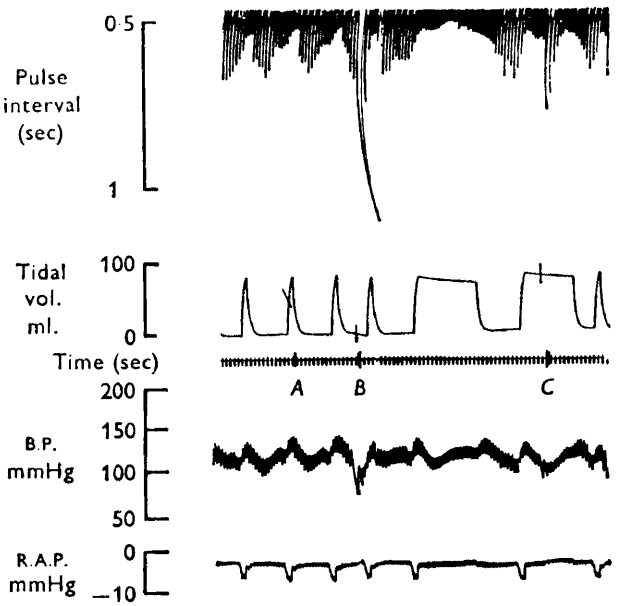

Fig. 4. Dog. Pentobarbitone. Records of pulse interval, tidal volume, carotid sinus blood pressure and right atrial pressure are shown. On two occasions the expiratory line was occluded so that the animal was held at his end-inspiratory position. At the marks *A*, *B* and *C* brief chemoreceptor stimuli were delivered into the carotid bifurcation. Stimuli given in inspiration (*A*) evoked no heart rate responses. Stimuli given in expiration (*B*), and stimuli given during inspiratory apnoea (*C*), evoked prompt cardiac slowing.

We also made a different approach to the question of whether changes in the volumes of thorax or lungs are the important phasic events which determine the effectiveness of baroreceptor and chemoreceptor stimuli in slowing the heart. In this we artificially hyperventilated dogs so that they would remain apnoeic for over 1 min upon cessation of pumping. In these animals the lungs could be left passively deflated, or else inflated to any chosen degree during the period of apnoea. Chemoreceptor or baroreceptor stimuli were typically ineffective upon heart rate early in such periods of apnoea, regardless of the degree of lung inflation, but became effective later in the period of apnoea. This was seen repeatedly in experiments on five dogs, the results from one of which are shown in Fig. 7.

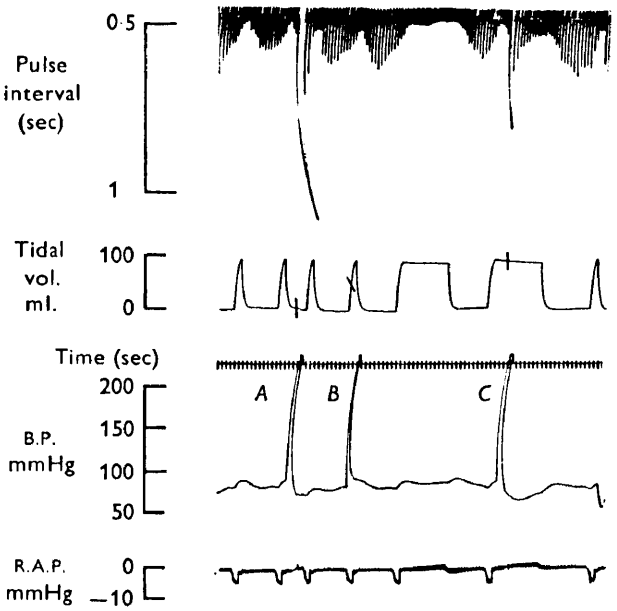

Fig. 5. Dog. Pentobarbitone. Records of pulse interval, tidal volume, carotid sinus blood pressure and right atrial pressure are shown. On two occasions the expiratory line was occluded so that the animal was held at his end-inspiratory position. At the marks *A*, *B* and *C* brief baroreceptor stimuli were delivered. Stimuli given in inspiration (*B*) evoked no heart rate responses. Stimuli given in expiration (*A*), and stimuli given during inspiratory apnoea (*C*), evoked prompt cardiac slowing.

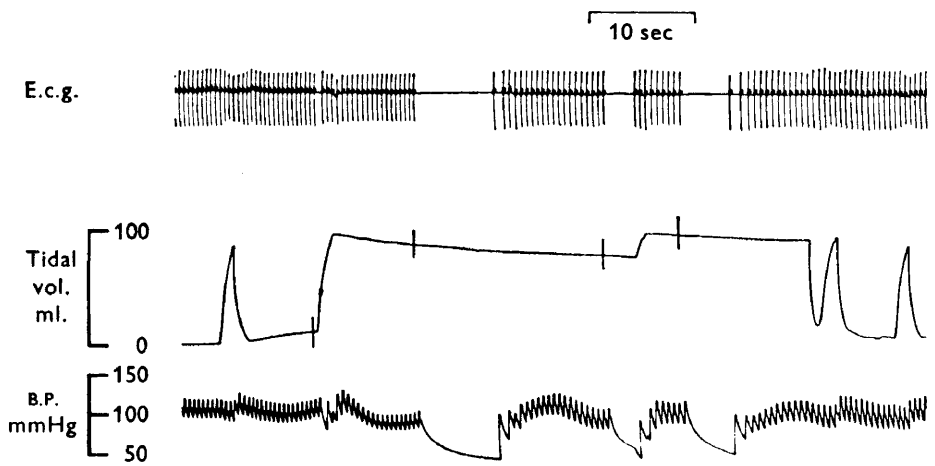

Fig. 6. Dog. Pentobarbitone. Records of electrocardiogram, tidal volume and carotid sinus blood pressure are shown. At the marks on the respiratory record brief chemoreceptor stimuli were delivered within the carotid sinus. After the first such stimulus the expiratory line was occluded and produced inspiratory apnoea. After the third stimulus the animal made a further inspiratory effort, and then became apnoeic again. All stimuli evoked prompt falls in heart rate.

When stimuli were delivered during a period of continuing artificial hyperventilation they were usually ineffective regardless of the phase of the imposed cycle in which they were given. We found that only when the respiratory pump was adjusted so that the animal was making occasional spontaneous respiratory efforts did the stimuli slow the heart. On these occasions the effectiveness of the stimuli was related to the phase of these spontaneous respiratory efforts in the same way as during control periods of spontaneous breathing.

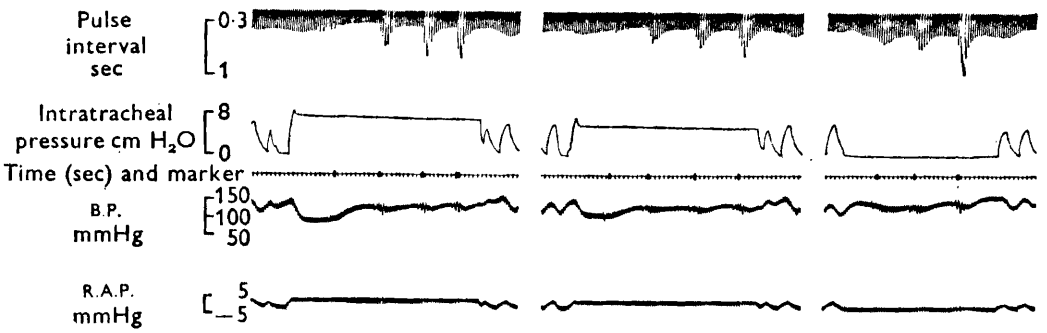

Fig. 7. Dog. Chloralose. Records of pulse interval, intratracheal pressure, carotid sinus pressure and right atrial pressure are shown. Each segment of record is taken in a period of apnoea after at least 2 min of artificial hyperventilation. Brief chemoreceptor stimuli were delivered into the carotid bifurcation where indicated by the stimulus marker. Stimuli delivered late in the period of apnoea were more effective in evoking falls in heart rate.

(iv) *Effects of denervation of the lungs.* In six dogs the lungs were denervated. This was done, on the right-hand side, by opening the chest through the fourth intercostal space and cutting the vagus close to the hilum of the lung. The vagosympathetic trunk was cut also below the hilum of the lung. This is the method used by Daly & Scott (1958) to denervate the lungs without interrupting cardiac vagal branches. The chest was closed, the pneumothorax reduced, and spontaneous breathing re-established. On the left-hand side the vagus was cut in the neck. Evidence for successful pulmonary denervation was that no sign of a Hering-Breuer inflation reflex remained after the denervation procedure, even when the lungs were grossly over-inflated. The resting heart rates after denervation, however, were little altered from their control values prior to the thoracotomy.

Brief stimuli delivered to the arterial baroreceptors or chemoreceptors after pulmonary denervation evoked a prompt bradycardia when delivered during expiration in all six dogs. In three dogs, similar stimuli were

ineffective when delivered during inspiration (see Fig. 8). In the other three dogs, slight falls in heart rate were evoked by such stimuli given during inspiration: in these the increases in pulse interval produced by inspiratory stimuli of either type were always smaller than those produced by similar stimuli given during expiration. The results from these three dogs are summarized in Fig. 9. No changes in heart rate could be evoked by our stimuli in any of the six dogs after cutting the right vagosympathetic trunk in the neck.

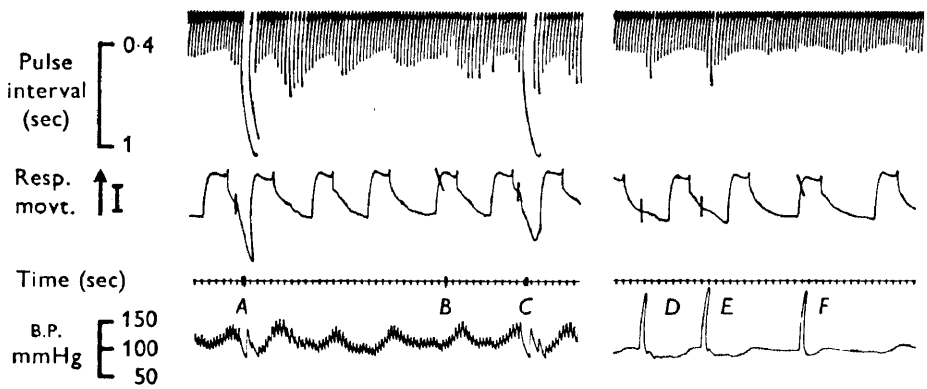

Fig. 8. Dog. Chloralose. Pulmonary vagi cut. Records of pulse interval, respiratory movements (inspiration upwards) and carotid sinus pressure are shown. Brief chemoreceptor stimuli were given at *A*, *B* and *C*, and brief baroreceptor stimuli at *D*, *E* and *F*. Stimuli given in inspiration (*B*, *F*) did not affect heart rate. Stimuli given in expiration (*A*, *C*, *D*, *E*) evoked prompt falls in heart rate.

(v) *Heart rate and the respiratory cycle.* Brief intense stimuli of the type described above do not occur in nature. The phenomenon of respiratory modulation of vagal efferent effects on the heart may still, however, manifest itself when the intense baroreceptor or chemoreceptor stimulation is sustained. Schweitzer (1937) noted that conspicuous sinus arrhythmia developed in response to a sustained increase in carotid sinus pressure, and Levy *et al.* (1966) found a similar response to a sustained hypoxic stimulus presented to the isolated carotid body. While these authors did not draw attention to it, it appears from their records that the sinus arrhythmia they saw was produced by a cardiac slowing confined almost entirely to the expiratory phase of the respiratory cycle. This would fit well with the findings we have reported. A similar phenomenon can be simply demonstrated by occluding the trachea of a dog at the end of a normal expiration (see Fig. 10). As asphyxia develops and blood pressure rises, bradycardia develops, and is clearly most pronounced in expiration.

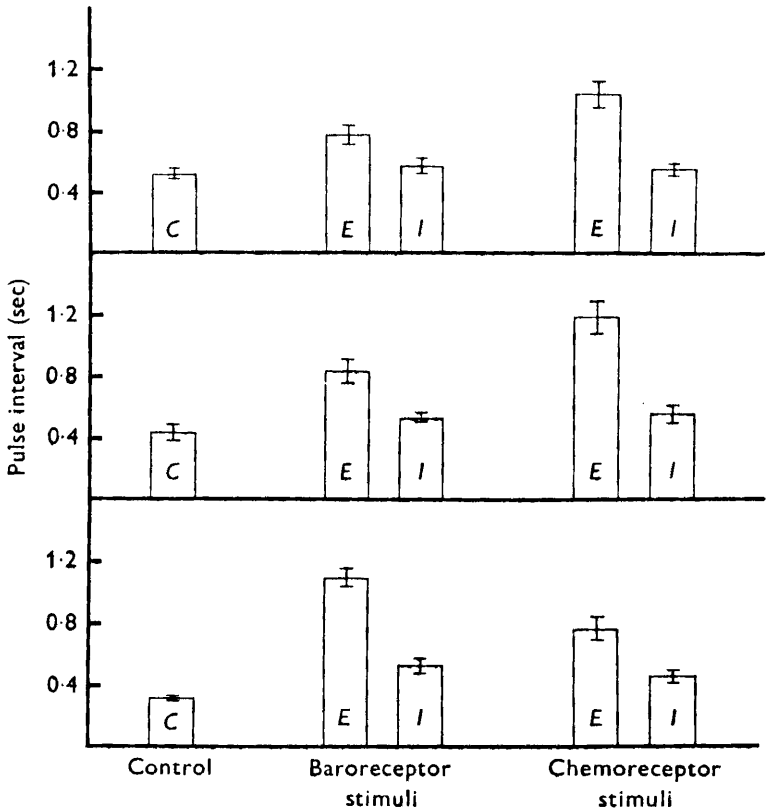

Fig. 9. Data from three dogs anaesthetized with chloralose, and with their pulmonary vagi cut, are shown. For each dog the pulse interval in the control condition (*c*) is shown. The greatest responses to baroreceptor stimuli or chemoreceptor stimuli delivered during expiration (*E*) or inspiration (*I*) are shown for each animal. The height of each panel shows the mean pulse interval, and the bars give ± 2 S.E. of mean, for ten intervals.

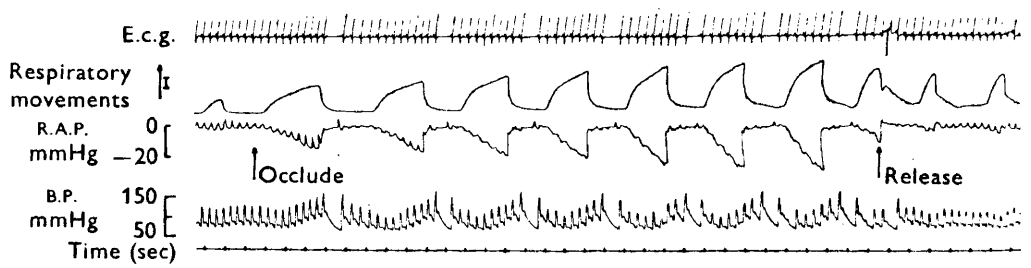

Fig. 10. Dog. Chloralose. Records of electrocardiogram, respiratory movements, right atrial pressure and carotid sinus pressure are shown. At the first arrow the airway of the animal was occluded with the lungs and thorax in the normal end-expiratory position. At the second arrow this occlusion was released. Note that bradycardia developed, and was confined almost entirely to the expiratory phase of the respiratory cycle.

DISCUSSION

This study indicates that cardio-inhibitory vagal efferent mechanisms are rendered wholly or partly refractory to excitatory afferent inputs from arterial baroreceptors or chemoreceptors during the inspiratory phase of the respiratory cycle.

The refractoriness of the vagal mechanisms is not entirely caused by the activation, during inspiration, of slowly adapting mechanoreceptors in the thorax or lungs because it does not persist during maintained inflation either in the Hering–Breuer inflation reflex or during periods of apnoea following hyperventilation. Nor is the phasic refractoriness abolished by pulmonary denervation. However, some participation of intrapulmonary or thoracic receptors, particularly of a rapidly adapting kind, cannot be ruled out by our experiments.

A consistent association in our observations exists between the activity of the inspiratory centres and the refractoriness of the efferent vagal mechanisms. When inspiratory centres are active, even after pulmonary denervation, the refractoriness is present. When the inspiratory centres can be presumed to be inactive, as in the Hering–Breuer inflation reflex, then the refractoriness is absent. Some activity in the respiratory centres is probably necessary, however, for our stimuli to be effective in evoking reflex bradycardia. In periods of apnoea following hyperventilation in our study, such stimuli were at first ineffective, at which times probably little activity was present in the respiratory centres. Later in the periods of apnoea, however, when some activity of the respiratory centres may have begun at a low level, the stimuli became effective (see Fig. 7). It might be preferable, therefore, to regard our results as indicating that expiratory centre activity renders the vagal efferent mechanisms accessible to baroreceptor and chemoreceptor stimuli, rather than that inspiratory centre activity renders them refractory to these stimuli.

Iriuchijima & Kumada (1964) showed that impulses could be evoked in vagal efferent nerve fibres in the dog by electrical stimulation of the central cut end of the carotid sinus nerve, and that such responses were more reliably evoked by stimuli delivered during expiration than during inspiration. Those stimuli probably excited both baroreceptor and chemoreceptor afferents. Our experiments confirm their findings and show that discharges from either receptor type have similar effects. On some occasions Iriuchijima & Kumada were able to evoke vagal responses by stimuli delivered during inspiration, indicating that the inspiratory refractoriness of the vagal mechanisms is not absolute.

Biscoe & Sampson (1970) found that the discharge of phrenic motoneurones could be inhibited by the stimulation of carotid baroreceptors

with brief pulses of pressure similar to those used here. It is therefore surprising that we observed no ventilatory responses to baroreceptor stimulation. It is possible that small respiratory influences would be more reliably detected by phrenic nerve recording than by the less sensitive measurements of ventilation employed here, so that very slight respiratory effects were not detected in this study.

Boushey, Richardson, Widdicombe & Wise (1974) have shown that CO_2 can excite laryngeal afferent nerves. It is conceivable that the CO_2-saline injections given in our experiments may have spread to arteries supplying the larynx and produced reflex effects through their action on laryngeal receptors. This is suggested particularly by our demonstration of active expiratory responses in some dogs, because expiratory efforts are not a usual feature of the carotid body reflex but might be accounted for by a laryngeal reflex (i.e. cough). This possibility was excluded here for those experiments in which the carotid sinus nerve on the experimental side was cut, abolishing both respiratory and heart rate responses to the CO_2-saline stimuli. Moreover, in our first four experiments in this series a more extensive dissection was done than was later found necessary: in these experiments the pharynx and larynx were removed in a block dissected from just above the sternum up to the level of the hyoid bone. In all four experiments typical heart rate responses were evoked as we have described, and in two there were active inspiratory and expiratory responses to the chemoreceptor stimuli.

Black & Torrance (1971) found that brief chemoreceptor stimuli effectively increase ventilation if delivered in inspiration. We have made similar findings in the dog, and find in addition that such stimuli effectively evoke bradycardia only if delivered in expiration. Black & Torrance observed that the prompt responses of the chemoreceptors which would enable them to 'follow' normal oscillations of arterial gas tensions could have importance in respiratory control. They noted that the circulatory time lag from pulmonary capillaries to carotid bodies delays the presentation of the oscillating blood gas stimuli to the receptors. If this time lag could be altered, then the rising phase of chemoreceptor discharge could be made to alter its timing in relation to the respiratory activity which is proceeding. In exercise, for example, the rising phase of discharge might be shifted by a more rapid circulation from coincidence with expiration to coincidence with inspiration, and so provide a more effective ventilatory stimulus. Our results allow this interesting hypothesis to be extended. It would be expected that a shift in phase between chemoreceptor responses and breathing which favoured respiratory stimulation would minimize the reflex bradycardia, and a shift which minimized respiratory stimulation would favour reflex bradycardia. Such alterations would seem

appropriate in exercise, for example, if Black & Torrance's suggestions were correct.

The phenomenon we have described is essentially a modulation imposed by the respiratory system upon the cardiovascular system, and is likely to require consideration in a number of situations. Clearly it may contribute importantly in sinus arrhythmia. In general, whenever there is an alteration in respiratory activity, the effectiveness of baroreceptor and chemoreceptor reflexes mediated through the vagus can be expected to be changed.

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MUSCULAR REFLEX STIMULI TO THE CARDIOVASCULAR SYSTEM DURING ISOMETRIC CONTRACTIONS OF MUSCLE GROUPS OF DIFFERENT MASS

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SUMMARY

1. The cardiovascular responses to voluntary isometric contractions performed by human subjects are determined by the proportion of maximal tension achieved by the muscles contracting, and not by the mass of the contracting muscles, nor by the absolute tension achieved (Lind & McNicol, 1967; confirmed here). When two or more muscle groups contract simultaneously at different relative tensions, the increments in heart rate and blood pressure are the same as when the muscle group at the higher relative tension contracts alone at that tension (Lind & McNicol, 1967). It is known that there are both central and reflex stimuli to the cardiovascular system in exercise, and the present study examines whether the muscular reflex stimuli are related to the proportion of maximal tension achieved or to the mass of contracting muscle.

2. Isometric hind-limb contractions were induced in anaesthetized dogs and cats by stimulation of spinal ventral roots. Pressor responses to contraction of both hind limbs were greater than responses to contractions of either hind limb alone. No differences were observed between heart rate responses to single or combined hind-limb contractions.

3. When human subjects perform isometric contractions, a pressor response can be maintained beyond the conclusion of the exercise by occluding muscle blood flow. This response is generally attributed to a reflex set up in the muscle by the action of chemical factors on afferent nerves. When comparable pressor responses were evoked by comparable proportional efforts with either the whole hand or the little finger, it was found here that the pressor responses remaining during the period of post-exercise occlusion were greater when the greater mass of muscle had been exercised.

4. It is concluded that the muscular reflex drive in isometric exercise is related to the bulk of contracting muscle.

INTRODUCTION

When human subjects perform sustained hand-grip contractions at tensions above 15% of the maximum attainable, the heart rate, cardiac output, and systolic and diastolic arterial pressures all increase, and the magnitude of these increases is determined by the intensity of the contraction and its duration (Lind, Taylor, Humphreys, Kennelly & Donald, 1964). It has been suggested that the physiological advantage of these responses is the increased flow which is possible in the contracting muscle group when the blood pressure rises (Humphreys & Lind, 1963).

There are certain peculiar features of the cardiovascular responses to such isometric contractions. For example, when two or more muscle groups contract at the same proportion of their maximal tension, the increments in blood pressure and heart rate are the same whether they contract separately or together (Lind & McNicol, 1967). Or, when two or more muscle groups contract simultaneously at different relative tensions, the increments in heart rate and blood pressure are the same as when the muscle group at the higher relative tension contracts alone at that tension (Lind & McNicol, 1967). These findings hold true even when the muscle groups involved are of quite different total mass.

Isometric exercise has been used in experiments on the nature of the stimuli to the cardiovascular system in exercise. These stimuli include 'irradiation' of the cardiovascular control centres by elements of the command signals descending from higher centres to the contracting muscles (Goodwin, McCloskey & Mitchell, 1972), and reflex stimuli originating in nerve endings in the contracting muscles (Coote, Hilton & Perez-Gonzalez, 1971; McCloskey & Mitchell, 1972). It is not known whether both central and reflex stimuli are related to the proportion of maximal tension achieved rather than to the mass of muscle involved in the contraction. Nor is it known whether these two components of the cardiovascular drive contribute similarly in similar relative contractions of different muscle groups.

In the present study the reflex contributions to the cardiovascular drives during isometric contractions of muscle groups of different masses have been investigated in animals and in man. In the animal experiments isometric contractions of hind-limb muscles were induced by spinal ventral root stimulation, as this allows the reflex part of the cardiovascular drive to be seen alone. In the experiments on human subjects, reflex circulatory effects were investigated by using occlusion of the blood supply to the contracting muscle. This causes the maintenance of a pressor response beyond the conclusion of the exercise for as long as the occlusion persists (Alam & Smirk, 1937). This is generally attributed to a reflex set up in the

ischaemic muscle by the action of chemical factors on sensory nerve endings. Such a reflex is probably part, and perhaps the whole, of the muscular reflex element of the cardiovascular drive in exercise, and can be observed when it is the sole drive to the cardiovascular system. Our results indicate that the muscular reflex component of the cardiovascular stimulus in isometric exercise is related to the mass of the muscle group performing the contraction.

METHOD

Animal experiments

Experiments were performed on nine cats (1·8–3·8 kg) anaesthetized with pentobarbitone sodium (Nembutal: Abbott, 40 mg/kg, I.P.), and on six dogs (6–14 kg) anaesthetized with chloralose (α-chloralose: British Drug Houses, 80 mg/kg I.V.), after thiopentone induction. A tracheal cannula was inserted low in the neck. Blood pressure was recorded from the axillary artery through a saline-filled nylon catheter connected to a Statham P 23 AC transducer, and was recorded on a Grass polygraph pen recorder. On another channel of this recorder either the electrocardiogram or heart rate was recorded using a Grass 5P4D pre-amplifier.

A laminectomy was performed to expose the sacral and lower lumbar segments of the spinal cord. Animals were fixed in a prone position on a table by pins driven into the iliac crests and through the knee joints, and the ankle joints were firmly clamped to prevent movement. A pool was made over the laminectomy with paraffin warmed to 37° C and bubbled with 95 % O_2 + 5 % CO_2. The spinal cord was exposed by a lengthwise incision through the dura. The ventral roots of L 6, L 7 and occasionally S 1 were cut close to their exit from the spinal cord on each side and were placed over pairs of Ag–AgCl electrodes. Stimulation of the ventral roots at 20–50 Hz with square wave pulses of 0·2–0·5 msec duration, delivered by an isolated stimulator, were used to elicit sustained isometric contractions of the hind-limb muscles. The voltage used for maximal contractions was twice motor threshold. Periods of contraction of 10–40 sec were used. The exposed spinal cord and nerve roots were washed every 30–40 min with warmed Ringer solution bubbled with 95 % O_2 + 5 % CO_2 (cf. Brown, Lawrence & Matthews, 1969). Rectal temperatures were maintained at 36–38° C throughout.

Human experiments

Ten normal volunteer subjects (eight male and two female), aged between 19 and 26 yr, acted as experimental subjects. The experiments were performed with the understanding and consent of the subjects.

Subjects were required to perform isometric contractions using muscle groups of the preferred hand or forearm. Usually, handgrip contractions and 'trigger-pulling' contractions of the little finger of the same hand were compared. Three subjects performed combined contractions of the index and middle finger of the same hand, attempting to close the extended digits in a scissors-like action on the strain gauge: this form of contraction, when undertaken, was used instead of the contraction of the little finger for comparison with the hand-grip. Contractions were performed at about 40 % of the maximal voluntary tension for 1–1½ min. Handgrip contractions alternated with contractions of the smaller muscle group, and there were rest periods of at least 10 min between contractions. During contractions the subject could see only the tension gauge against which he was pulling, and the face of an oscilloscope on which were displayed the achieved tension and a target beam for alignment.

All other equipment, and the experimenters, were out of sight, and the room was kept silent. Five seconds before the conclusion of each contraction a sphygmomanometer cuff was inflated above the elbow on the experimental side to a pressure of 250 mmHg, and was kept inflated after the conclusion of the effort for a further 1–1½ min. The first contraction in a series was always neglected for purposes of analysis, and served only to familiarize the subject with the experimental procedure.

Blood pressure was measured continuously through a short Teflon catheter inserted through the skin into the radial artery of the resting arm. This catheter was connected to a Statham P23Dc transducer, and blood pressure was recorded on a Grass polygraph pen recorder. Heart rate was obtained through a Grass 5P4D preamplifier from the radial pulse, and was also recorded. The tension achieved during the isometric effort was recorded on a third channel of the polygraph.

RESULTS

Animal experiments

In all the animal experiments the pressor and heart-rate responses to maximal induced contractions of one hind limb alone were compared with the responses to maximal contractions of both hind limbs together. In all but two experiments the pressor response to combined contractions exceeded the response to contraction of either limb contracting alone. In these thirteen experiments the maximal increase in blood pressure on contraction of a single hind limb ranged from 10 to 35 mmHg for individual animals, and the maximal pressor response for combined hind-limb contractions ranged from 20 to 50 mmHg. When the maximal increase in pressure for combined contractions was expressed as a percentage of the maximal increase in response to contraction of a single hind limb in the same animal, the range for individual experiments was 150–230 %. In the remaining two experiments, both done on cats, the maximal pressor responses to single and combined hind-limb contractions were of similar magnitude: in both experiments these were small (10 and 15 mmHg). In all experiments, the reflex nature of the responses observed was confirmed when the responses were abolished by cutting the spinal dorsal roots from L 5 downwards. After cutting the dorsal roots there were often small transient changes in blood pressure at the start of a contraction, possibly due to mechanical alterations in peripheral resistance, and slight reductions in pressure at the conclusion of contractions, possibly due to reactive hyperaemia in the exercised muscle. Bilateral ventral root stimulation was performed in two dogs and one cat which had been paralysed with gallamine, and this induced no changes in blood pressure or heart rate. Typical pressor responses to single and combined hind-limb contractions are shown in Fig. 1.

Heart rate increased in response to hind-limb contractions in all experiments. The increases were variable in magnitude, and never exceeded 20 %

of the resting heart rate. We were unable to demonstrate any differences between heart rate responses to single or combined hind-limb contractions in any animals.

In five experiments submaximal limb contractions were investigated. In all five experiments (three cats and two dogs) there was a smaller pressor response to a maximal contraction of one hind limb than to a similar contraction of that hind limb combined with a submaximal

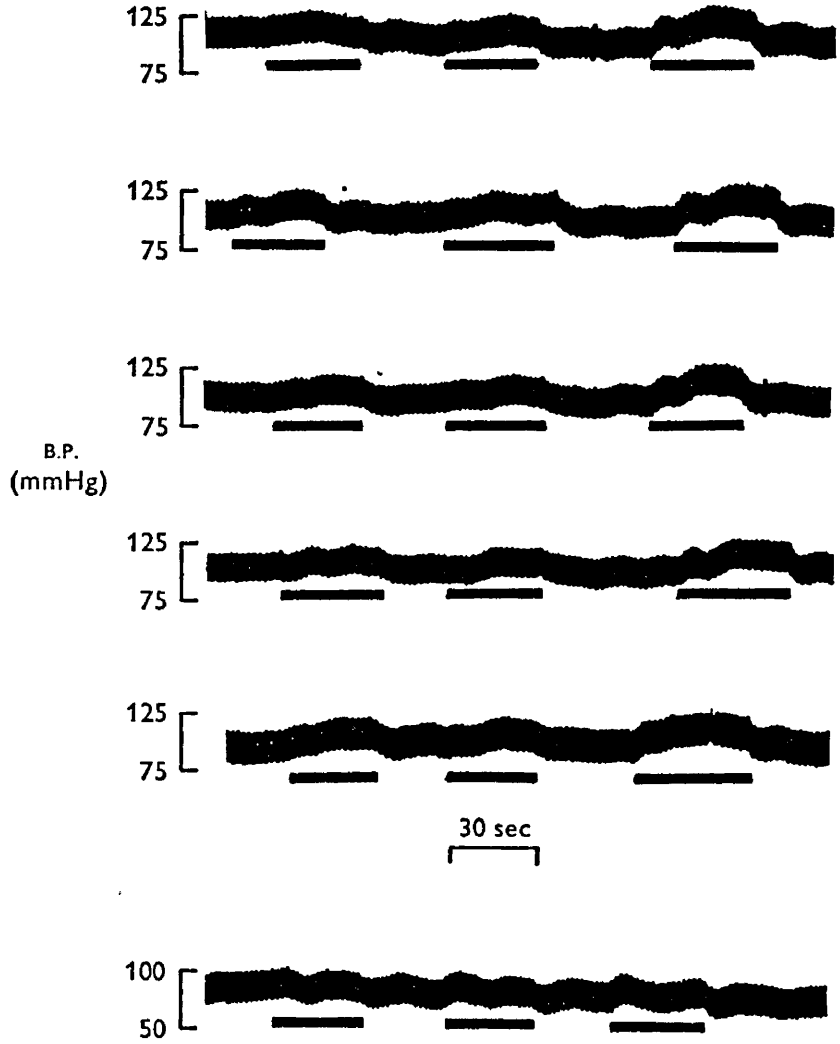

Fig. 1. Records of systemic arterial pressure in a cat anaesthetized with pentobarbitone. Maximal isometric hind-limb contractions were induced by ventral root stimulation at each marker. In each panel the sequence of contractions shown is: left hind limb alone, right hind limb alone, both hind limbs together. In the upper five panels all dorsal roots were intact, and reflex pressor responses occurred. The pressor responses to combined maximal hind-limb contraction were greater than the responses to either hind-limb contracting maximally alone. The lowest panel shows the effects of cutting the spinal dorsal roots from L5 downwards: hind-limb contraction was associated with only transient alterations of blood pressure.

contraction of the other hind limb. Fig. 2 shows typical responses. Again we were unable to demonstrate any relation between mass of contracting muscle and increase in heart rate in any experiment.

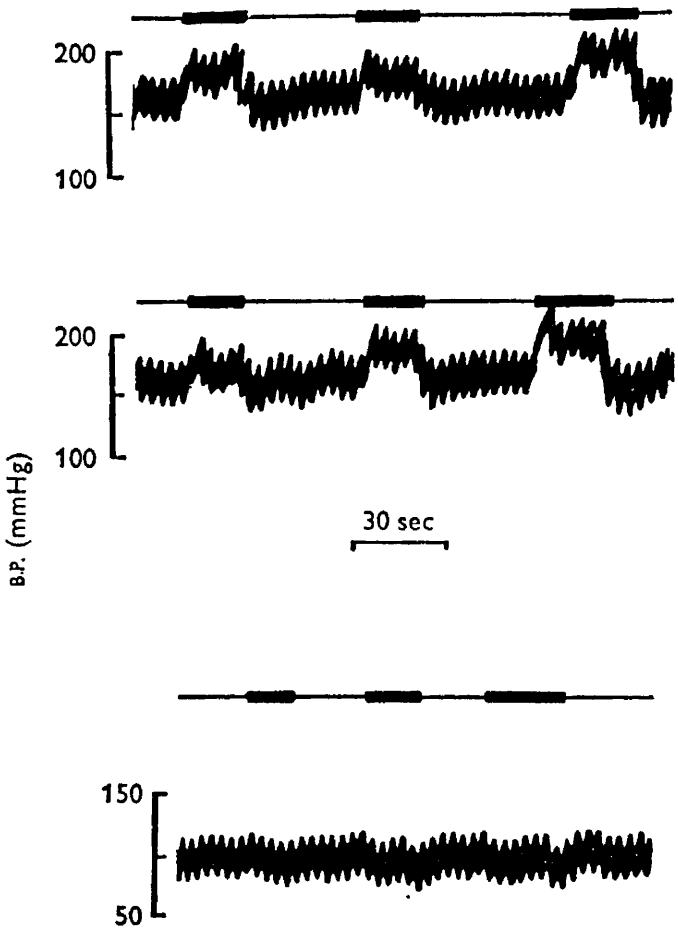

Fig. 2. Records of systemic arterial pressure in a dog anaesthetized with chloralose. Hind-limb contractions were induced by ventral root stimulation at each marker. The upper two panels show reflex prossor responses when the dorsal roots were intact. In the top panel the sequence of contractions was: left hind limb alone, right hind limb alone, both hind limbs together; in the second panel the sequence was right hind limb, left, then both together. In each sequence the left hind limb contracted maximally and the right submaximally. The pressor responses to combined maximal and submaximal hind-limb contraction were greater than the responses to either hind-limb contracting alone. The lowest panel shows the sequence of contractions of the top panel repeated after cutting the spinal dorsal roots from L5 downwards.

Human experiments

Handgrips and contractions of a smaller muscle group of the same arm were performed alternately by all subjects, with rest periods between. Usually there were three or four contractions of each type. We aimed to produce increases in systolic pressure of the same magnitude during each

form of contraction: this was achieved by altering the magnitude of the effort required of the smaller muscle group. Handgrip contractions of 40 % of the maximal voluntary contraction (MVC) were always used, and efforts producing similar pressor responses were within the range 35–45 % MVC for the smaller muscle group.

TABLE 1. Comparison of mean systolic arterial pressure and heart rate response to sustained handgrip contractions and to contractions of smaller muscle groups

Control systolic pressure (mmHg)	Control heart rate (beats/min)	Muscle group	During isometric effort: Systolic pressure (mmHg)	During isometric effort: Heart rate (beats/min)	During post-exercise occlusion: Systolic pressure (mmHg)	During post-exercise occlusion: Heart rate (beats/min)
105	65	Hand	155	82	140	72
		Finger	150	80	112	78
115	76	Hand	140	95	132	70
		Finger	148	104	120	72
115*	55	Hand	160	80	134	50
		Finger	160	74	118	56
120	60	Hand	172	92	146	64
		Finger	176	88	130	56
122	80	Hand	156	124	146	86
		Finger	152	120	134	82
122	62	Hand	190	76	178	54
		Finger	182	82	148	56
128*	66	Hand	165	90	144	70
		Finger	172	88	138	72
134*	85	Hand	184	104	160	90
		Finger	192	100	148	84
138	72	Hand	166	102	152	60
		Finger	170	110	144	62
140	68	Hand	170	96	158	58
		Finger	174	98	148	64

* All subjects used flexion of the little finger as the effort with a small muscle group, except those marked * where a scissors-like contraction of the index and middle fingers was employed.

Occlusion of the circulation through the exercising forearm was commenced 5 sec before the end of the exercise. When the contraction stopped, there was typically an abrupt fall in blood pressure and heart rate, which had risen during the exercise. Often the blood pressure began to rise again slowly after this initial fall, sometimes stabilizing some 15–45 sec after the

end of the contraction. Consistent changes were not observed in heart rate during the post-exercise occlusion period.

We compared the increases from control levels of blood pressure and heart rate in the last 15 sec of the voluntary effort, and between 45 and 60 sec of the post-exercise occlusion period. Table 1 summarizes the results. Systolic arterial pressure in each experimental condition was taken as the mean of systolic pressure throughout one or two complete respiratory

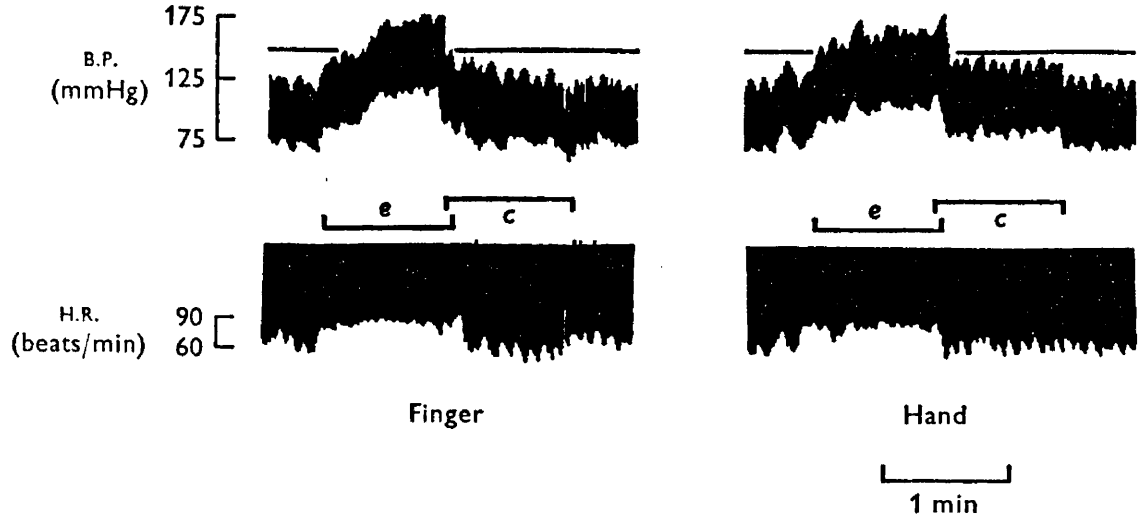

Fig. 3. Records of blood pressure and heart rate from a normal human subject performing isometric contractions. On the left are shown the responses to efforts made by flexing the little finger at 40 % of its maximal tension, and on the right, the responses to a handgrip contraction at 40 % of maximum. In each case the duration of the voluntary effort is marked *e*. The pressor responses to both efforts were comparable in size. Just before the conclusion of each voluntary effort, an occlusion of the blood supply through the exercising muscle was applied: the duration of the period of vascular occlusion is marked *c*. During the period of post-exercise occlusion part of the pressor response was maintained. This maintained part of the pressor response was greater for the larger muscle group, as can be seen by reference to the line drawn across the blood pressure record.

cycles, so as to minimize the influence of respiratory fluctuations in blood pressure. In each subject the mean of these systolic arterial pressures, and the mean heart rate, for the three or four efforts in each category were determined, and are set out in Table 1. Typical responses from one subject are shown in Fig. 3. In all subjects, the blood pressure was higher during circulatory occlusion after handgrip contractions than after contractions of the smaller muscle group. Heart rate was not elevated during the post-exercise occlusion in any subject for either form of contraction: in some subjects, the heart rate was slower in comparison to the control level during this period.

DISCUSSION

In this study, using muscle groups of quite different total mass and strength, we have confirmed the finding of Lind & McNicol (1967) that the pressor and heart rate responses to isometric contractions are related to the proportion of maximal tension achieved rather than to the bulk of the contracting muscle group. The muscular reflex component of the stimulus to the pressor response, however, does not conform to this relation: our experiments in animals and in humans indicate that the muscular reflex drive is proportional to the bulk of contracting muscle.

The animal experiments reported here simply illustrated the interactions of pressor reflexes elicited during muscular contractions. While there was considerable variability in the extent of interaction, all but two of our fifteen experiments showed some additive drive when the bulk of contracting muscle was increased, and this was so whether the added muscle was contracting maximally or submaximally. The human experiments were a less direct approach to the question, examining the reflex drives only after the isometric efforts were completed. When circulatory occlusion is applied at the end of a period of contraction induced by ventral root stimulation in animals, the pressor response which is maintained is not the full response which was achieved during the contraction (McCloskey & Mitchell, 1972). This may mean that intramuscular mechanoreceptors contribute part of the reflex drive during induced contractions. Such mechanoreceptors would not be the muscle spindles or tendon organs, however, as these have been shown not to contribute to the cardiorespiratory drives in exercise (McCloskey & Mitchell, 1972; McCloskey, Matthews & Mitchell, 1972). It must be conceded that the reflex stimuli we investigated in man were probably only part of the total reflex drive present during contractions and that the value of the human experiments is the confirmation they provide of the observations made in the animal experiments of this study.

The arguments above refer only to the pressor responses to isometric contractions. In none of our experiments, whether in animals or in humans, were we able to relate the reflex increases in heart rate to the bulk of the muscle group exercising. This might lead to the simple conclusion that primary muscular reflex effects upon heart rate are not related to the mass of contracting muscle. While this conclusion may be quite correct, it should be recognized that other factors also operate upon heart rate. In particular, the baroreceptor–cardiodepressor reflex may be of importance here. In studies in man, Cunningham, Petersen, Peto, Pickering & Sleight (1972) showed that the baroreflex is reset and its sensitivity reduced during isometric handgrips, but that the sensitivity is substantially

restored during periods of post-exercise occlusion. We have found also that in isometric hind-limb contractions induced by ventral root stimulation in the dog the baroreceptor–cardiodepressor reflex is reset, but we found no evidence that its sensitivity is reduced (K. A. Streatfeild & D. I. McCloskey, unpublished observations). These observations open the following possibilities. During a voluntary isometric effort the heart rate rises partly because the baroreflex sensitivity is reduced (presumably the sensitivity is reduced by some factor operating during voluntary contractions, but not during the post-exercise occlusion period, nor during induced contractions in animals). When the isometric effort is concluded, the baroreflex regains a great deal, or all, of its sensitivity so that if a pressor response is maintained, then the heart rate is slowed by the baroreceptor reflex. This would explain why the heart rates during the periods of post-exercise occlusion were often slower than the control heart rates in this study and in the experiments of Cunningham *et al.* (1972). While there is a powerful primary cardio-acceleratory reflex set up in the exercising muscle, its effects are often wholly or partly masked by the baroreceptor reflex. Our conclusions regarding the influence of muscle mass on heart rate must therefore be much less definite than those regarding the pressor responses.

In view of our results there is now an apparent paradox. The pressor response to a voluntary isometric effort is related to the proportion of maximal tension achieved, and not to the mass of muscle contracting, but the muscular reflex component of the stimulus for the pressor response *is* related to the mass of muscle contracting. If one were to believe that the total stimulus in exercise is the simple sum of contributing stimuli, one would be forced to the conclusion that pressor stimuli other than those of a muscular reflex kind are inversely related to the bulk of muscle involved in a contraction. This is a conclusion which we find unattractive. There is no reason to assume that the cardiovascular stimuli in exercise simply summate to produce their effects. It is possible that a considerable element of occlusion exists. Irradiation of the central command is an important cardiovascular stimulus in exercise (Goodwin *et al.* 1972), and its interaction with the muscular reflex stimulus may be of a largely occlusive kind. Present knowledge would be accounted for if the effective cardiovascular stimulus were whichever one of irradiation or muscular reflex was the greater, and if the potency of irradiation as a stimulus were related to the proportion of maximal effort attained.

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MECHANISMS OF AUTONOMIC CONTROL OF CAROTID CHEMORECEPTOR ACTIVITY

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Abstract. Single chemoreceptor fibres dissected from the cut carotid sinus nerves of cats were studied when carotid body blood flow was normal, and when it had been abruptly halted by reducing the local perfusion pressure to zero. Ten chemoreceptor fibres which, when normally supplied with blood, increased their discharge by at least 25% in response to sympathetic stimulation, and 7 fibres which, when normally supplied with blood, decreased their discharge by at least 10% in response to carotid sinus nerve stimulation, were chosen for study. The development of discharge during the period of stagnant asphyxia following stoppage of flow was reproducible in repeated control trials for each fibre investigated. Neither sympathetic nor carotid sinus nerve stimulation, commencing at the stoppage of flow and continued throughout the period of asphyxia, produced any significant alteration from the control pattern of developing chemoreceptor discharge. These experiments provide evidence that the effects of sympathetic and carotid sinus nerve stimulation on carotid chemoreceptor discharge are mediated through alterations in carotid body blood flow. When there is no flow there are no effects on discharge.

Arterial chemoreceptors	Carotid sinus
Asphyxia	Carotid body blood flow
Autonomic control	Control of breathing

De Castro (1928) described carotid body cells as having sensory synapses of glossopharyngeal origin upon them, and suggested, therefore, that the carotid body is a receptor organ. He also stated (de Castro, 1951) that there are efferent fibres in the carotid sinus nerve and that these supply the blood vessels of the carotid body, as also do sympathetic fibres. It is now known that the sympathetic innervation provides vasoconstrictor tone to the carotid body vessels (Daly *et al.*, 1954; Purves, 1970; McCloskey and Torrance, 1971), and that the efferent carotid sinus nerve innervation can cause vasodilatation (Neil and O'Regan, 1971a; McCloskey and Torrance, 1971).

Efferent activity has been recorded in the carotid sinus nerve (Biscoe and Sampson, 1968; Neil and O'Regan, 1971b), and evidence has been presented that

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the efferent fibres are inhibitory to the chemoreceptors (Fidone and Sato, 1970; Sampson and Biscoe, 1970; Neil and O'Regan, 1971b; Goodman, 1973). The sympathetic innervation is usually agreed to be excitatory to the chemoreceptors (Floyd and Neil, 1952; Eyzaguirre and Lewin, 1961; Biscoe and Purves, 1967), although it has also been claimed it has little effect on carotid body activity (Hornbein, 1968). While the effects of stimulation of carotid sinus or sympathetic nerves supplying the carotid body could be explained conveniently in terms of alterations induced in local blood flow, it has been suggested that both sympathetic (Purves, 1970), and carotid sinus efferent effects (Sampson and Biscoe, 1970; Neil and O'Regan, 1971b) might be exerted directly upon the chemoreceptive cells themselves.

In the present work single chemoreceptor fibres from the carotid body of the cat were studied when carotid body blood flow was normal, and after it had been abruptly halted by reducing the local perfusion pressure to zero. Such preparations provided the opportunity to investigate whether the effects of sympathetic or carotid sinus innervation could still be exerted when there is no local blood flow for them to alter.

Method

Experiments were performed on cats (1.6–4.5 kg) of both sexes, anaesthetized with pentobarbitone (40 mg/kg: Nembutal, Abbott).

The trachea was cannulated low in the neck, and the pretracheal muscles, pharynx and larynx were removed up to the level of the hyoid bone. A cannula was inserted into the lingual artery to measure blood pressure in the region of the carotid bifurcation. Another cannula was inserted into the external carotid artery with its tip directed towards the carotid bifurcation, and was connected to a tap which could be opened to the atmosphere. Small arterial branches in the region of the carotid bifurcation were tied, particular care being taken to avoid interfering with the carotid body or its arteries or veins.

The vagosympathetic trunks were cut low in the neck. The carotid sinus nerve was identified and cut where it joined the glossopharyngeal and was dissected under paraffin on a rigid, earthed, stainless steel plate with a blackened upper surface. Chemoreceptor fibres were identified by their sporadic discharge, but were accepted as chemoreceptors only if they responded to changes in the oxygen content of the inspired gas. Single-fibre preparations were used throughout the study.

The recording electrodes were made of fine, stainless steel wire. Impulses were led into a Tektronix 122 preamplifier and then to an oscilloscope for examination or to one channel of the recording apparatus, a Y.E.W. Ultraviolet Photorecorder with galvanometers giving a flat frequency response to 1000 Hz. Blood pressure from the lingual artery was measured with a Statham P23 Ac transducer and was recorded on another channel of the UV recorder. Observations were made with the animals spontaneously breathing pure oxygen. The paraffin pool was maintained at 37–39 °C throughout. Rectal temperatures were kept at a similar temperature.

The preganglionic sympathetic trunk was identified and separated low in the neck. Stimuli were delivered to it through Ag–AgCl electrodes. Stimuli chosen were 0.5 msec duration pulses given in trains at 5–20 Hz. The voltage chosen was in every case 50% in excess of that required to achieve maximal pupillary dilation on the ipsilateral side: usually this was 10–12 V.

When the carotid sinus nerve was stimulated, all filaments except the filament being recorded from were gathered together and passed over fine platinum electrodes. The junction between the stimulated nerve bundle and the recorded filament was in contact with the surface of the earthed dissecting plate. The stimuli here were pulses 0.1 msec in duration given at 20 Hz, and at strengths of 1–20 V. Throughout this part of the study the precautions described by Goodman (1973) against adventitious excitation of the recorded afferents by the electrical stimuli were employed: successive sweeps of an oscilloscope beam were triggered by the electrical stimulus, and the presence of the silent period after the stimulus was taken as an indication that the stimulus was causing excitation of the afferent fibre. Only results obtained in the absence of such indications of adventitious excitation are reported here. All stimuli referred to above were square-wave stimuli isolated from earth.

Results

1. SYMPATHETIC STIMULATION

Twenty-two single carotid chemoreceptor fibres were examined while the animals were spontaneously breathing room air. Ten of these, recorded in 7 cats, increased their rate of discharge by at least 25% during sympathetic stimulation, and were selected for further study. These fibres remained responsive to sympathetic stimulation when the animal spontaneously breathed oxygen. The average increase in discharge on sympathetic stimulation was 35% (range 25–200%). The proportion of responsive fibres found here is similar to that described by Mitchell and McCloskey (1974). Responsiveness to sympathetic stimulation was confirmed in all fibres after the stop-flow experiments described below.

Each of the ten fibres which were responsive to sympathetic stimulation was then examined for its responses to stagnant asphyxia by a method similar to that described by McCloskey and Black (1971). While the cat spontaneously breathed oxygen, the blood flow to the carotid body was abruptly halted by simultaneously clamping the common carotid artery and opening a tap in the external carotid artery to the atmosphere. As stagnant asphyxia developed within the carotid body the chemoreceptor discharge rose, at first slowly and then more rapidly, reaching a maximum in 70–150 sec. Between periods of stagnant asphyxia normal flow was restored for at least 5 min. The rate of development of discharge was similar in repeated episodes of asphyxia. When blood flow was restored, the discharge was reduced to its control level within 5–7 sec.

To test whether sympathetic stimulation could influence chemoreceptor firing during ischaemia, stimuli were delivered to the cervical preganglionic nerve as

asphyxia developed. Stimulation commenced within 5 seconds of cessation of flow, and the stimuli used were in all respects similar to those effective in increasing chemoreceptor discharge during normal flow. Sympathetic stimulation was applied during alternate asphyxial episodes. Twelve episodes of asphyxia were observed, six combined with sympathetic stimulation and six without.

Chemoreceptor discharges were counted over successive 10-sec intervals in every

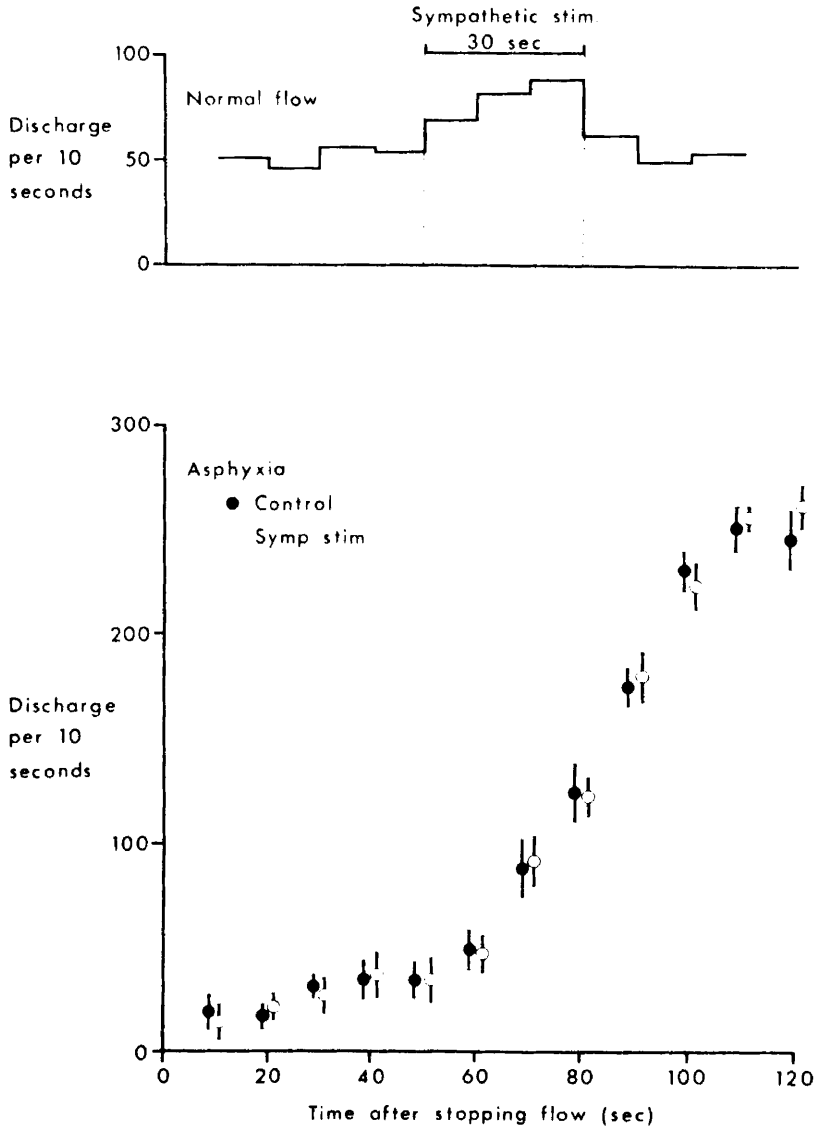

Fig. 1. The figure shows plots of discharge from a single chemoreceptor fibre dissected from the cut carotid sinus nerve of a cat. The upper panel shows the effect on chemoreceptor discharge from the normally perfused carotid body (animal breathing air) when the preganglionic cervical sympathetic nerve was stimulated for the period shown (10 V, 0.5 msec, 15 Hz). In the lower panel the development of discharge in the same fibre is shown for successive 10-sec intervals after abruptly dropping the local perfusion pressure to zero (animal breathing oxygen). The filled circles show the development of discharge during control periods of asphyxia. The open circles show discharge during asphyxial episodes throughout which the cervical sympathetic nerve was stimulated as in the top panel. Each point is mean of 6 determinations; bars represent ± 1 S.E.M. In ischaemia sympathetic stimulation does not affect discharge.

asphyxial episode, commencing at the time of stoppage of flow. The means of discharges in every 10-second interval from asphyxial episodes with and without sympathetic stimulation were compared by the Student *t*-test. No significant difference was observed between the stimulated and unstimulated condition in any interval from any of the tested fibres ($P > 0.2$). Figure 1 shows results from one of these fibres.

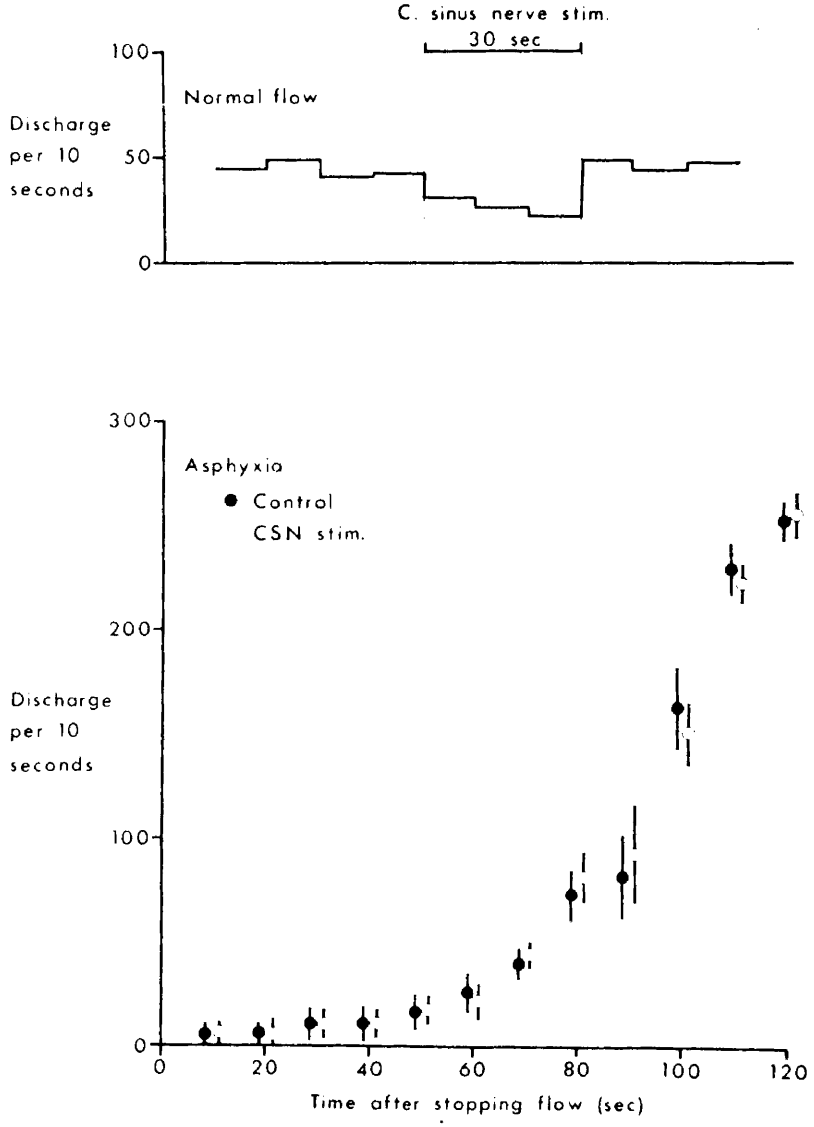

Fig. 2. The figure shows plots of discharge from a single chemoreceptor fibre dissected from the cut carotid sinus nerve of a cat. The upper panel shows the effect on chemoreceptor discharge from the normally perfused carotid body (animal breathing air) when the carotid sinus nerve was stimulated for the period shown (7 V, 0.1 msec, 20 Hz). In the lower panel the development of discharge in the same fibre is shown for successive 10-sec intervals after abruptly dropping the local perfusion pressure to zero (animal breathing oxygen). The filled circles show the development of discharge during control periods of asphyxia. The open circles show discharge during asphyxial episodes throughout which the carotid sinus nerve was stimulated in the top panel. Each point is mean of 6 determinations; bars represent ± 1 S.E.M. In ischaemia carotid sinus nerve stimulation does not affect discharge.

II. CAROTID SINUS NERVE STIMULATION

Forty-five single carotid chemoreceptor fibres were examined for the effects of carotid sinus nerve stimulation while the animals were spontaneously breathing room air. Seven of these, recorded from 6 cats, showed a reduction of discharge of at least 10% during sinus nerve stimulation. This effect of sinus nerve stimulation was a true inhibition, and was not due to adventitious excitation of the recorded afferents by stimulus spread (see Methods). The average decrease in discharge during sinus nerve stimulation was 25% (range 10–40%). Fidone and Sato (1970) and Goodman (1973) found true inhibition by sinus nerve stimulation in similarly small proportions of the chemoreceptor population. Responsiveness to carotid sinus nerve stimulation was confirmed in all fibres after the stop-flow experiments described below.

Each of the 7 fibres which was responsive to sinus nerve stimulation was then examined for its responses to stagnant asphyxia. The method used was similar to that described above for seeking effects of sympathetic stimulation during cessation of flow. The means of discharges in every 10-second interval during asphyxial episodes with and without sinus nerve stimulation were compared by the Student t test. No significant difference was observed between the stimulated and unstimulated condition in any interval from any of the tested fibres ($P > 0.1$). Carotid sinus nerve stimulation did not alter discharge in responsive fibres in the absence of blood flow. Figure 2 shows results from one of these fibres.

Discussion

These experiments provide strong evidence that the effects of sympathetic and carotid sinus nerve stimulation on carotid chemoreceptor discharge are mediated through alterations in carotid body blood flow. When there is no flow there are no effects on discharge.

The conclusion that sympathetic effects on the chemoreceptors are mediated through changes in local blood flow is not surprising. It is known that the sympathetic input to the carotid body is vasoconstrictor (Daly *et al.*, 1954; Purves, 1970; McCloskey and Torrance, 1971). Eyzaguirre and Lewin (1961) and Belmonte and Eyzaguirre (1974) found that sympathetic stimulation was without effect on chemoreceptor discharge in the superfused carotid body. Sympathetic stimulation was found to be without effect on membrane potentials recorded from cells in the carotid body (Eyzaguirre and Lewin, 1961).

The mechanism of carotid sinus efferent inhibition of chemoreceptor discharge has been vigorously debated. Biscoe *et al.* (1970) claimed on histological evidence that the large nerve endings on the type I cells of the carotid body were efferent. More recently Hess and Zapata (1972) confirmed De Castro's (1928) original claim that these nerve endings are afferent, and so contradicted Biscoe *et al.* (1970). Efferent activity has been recorded in the carotid sinus nerve (Biscoe and Sampson, 1968; Neil and O'Regan, 1971b) and there is evidence that the efferent fibres are

inhibitory to chemoreceptor discharge (Sampson and Biscoe, 1970; Fidone and Sato, 1970; Neil and O'Regan, 1971a; Goodman, 1973; Belmonte and Eyzaguirre, 1974). It has been shown, however, that some of the carotid sinus nerve efferent inhibitory effects described were experimental artefacts caused by stimulus spread (Fidone and Sato, 1970; Goodman, 1973; Belmonte and Eyzaguirre, 1974) and that the only true inhibition of discharge is mediated by unmyelinated efferents (Fidone and Sato, 1970). Experiments which were claimed to show that the efferent inhibition was mediated through non-vascular pathways (Neil and O'Regan, 1971b) can be criticized (*e.g.* Goodman, 1973) because precautions were not taken to avoid artefactual depression from stimulus spread. In the present study precautions of the type described by Fidone and Sato (1970) and Goodman (1973) were used to avoid such artefacts, and inhibition was seen only when there was a normal local blood flow.

Belmonte and Eyzaguirre (1974) recorded from carotid sinus nerve filaments during perfusion of the carotid body with oxygenated Locke solution, and during superfusion with a similar solution. They described four chemoreceptor fibres where discharge was inhibited by carotid sinus nerve stimulation during perfusion, but in which similar stimulation was ineffective during superfusion. They found no fibres in which there was a reduction of discharge in response to carotid sinus nerve stimulation in superfused preparations. These findings support the results and conclusions of the present study.

On the other hand, experiments very similar to those described here were outlined in a recent brief report by O'Regan (1974). He recorded from chemoreceptor filaments peeled from an otherwise intact sinus nerve, and halted local flow by reducing perfusion pressure to zero. He gave adrenaline intravenously to the animal and found that the asphyxial discharge of the recorded chemoreceptor was reduced for some 5–20 seconds. He concluded that the reduction of discharge was effected through non-vascular efferents travelling in the sinus nerve. His experiment provides evidence for a non-vascular efferent mechanism in the carotid sinus nerve, and conflicts with the results found in the present study. It is possible, however, that his adrenaline injections were associated with a pressor response which opened collateral channels and so partly relieved the carotid body asphyxia. His further claim that inhibition did not occur when the sinus nerve was cut argues against this interpretation. Nevertheless, there is a possibility of some variable relief of carotid body asphyxia in such stop-flow experiments, and careful controls against this would be required before a reduction in asphyxial discharge could be accepted as evidence for non-vascular efferent neural effects.

In the absence of uncontested histological evidence for non-vascular efferents in the carotid sinus nerves, the functional evidence for such nerves remains slight. Goodman and McCloskey (1972) failed to find evidence that postulated synapses from carotid sinus nerve efferents altered the membrane potentials of carotid body cells. However, efferent sinus nerve mechanisms can cause vasodilatation in the carotid body (Neil and O'Regan, 1971a; McCloskey and Torrance, 1971), and the

simplest view of the matter remains that any reduction in discharge is effected through vascular mechanisms. In this, and other studies on carotid sinus nerve efferent effects (Fidone and Sato, 1970; Goodman, 1973; Belmonte and Eyzaguirre, 1974; O'Regan, 1974), it has been observed that the effects are small, difficult to elicit, and occur in only a small proportion of chemoreceptor fibres. Although the functional importance of the effects has not yet been assessed, it would appear unlikely that their physiological role is a powerful one.

Acknowledgement

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CHANGES IN THE PATTERN OF BREATHING CAUSED BY CHEST VIBRATION[1]

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Abstract. Vibration of 100 Hz was delivered longitudinally onto the sternum of anaesthetized cats and rabbits. Vibration consistently reduced the tidal volume by 10–15 % without altering the end-expiratory point, and occasionally reduced the respiratory rate. Vibration applied during inspiration reduced the tidal volume as much as if delivered over several breaths. Expiratory vibration did not alter the course of the expiration, nor the volume of the following inspiration.

The inhibition of inspiration was unaffected by deafferentation of chest wall skin, bilateral vagotomy, bilateral division of the phrenic nerves and low thoracic spinal transection. Spinal transection above the thoracic cord (C8/T1) abolished usual responses to vibration. The receptors for this reflex probably lie in the chest wall. Vibration inhibited the development of alae nasi tension during inspiration indicating that supraspinal reflex loops were involved. A role for intercostal muscle spindles is suggested.

Breathing pattern	Respiratory rate
Intercostal afferents	Tidal volume
Muscle spindles	Vibration

Several investigators have studied respiratory responses to vibration. Duffner *et al.* (1962) and Hoover and Ashe (1962), in experiments on human subjects, reported an increase in minute ventilation when the whole body was vibrated at frequencies of 2–15 Hz. This response has since been observed in dogs (Hood and Higgins, 1965). In contrast, in a study of the intercostal muscle spindles in the cat, von Euler and Peretti (1966) observed incidentally that vibration at frequencies of about 400 Hz applied directly to a rib caused an increase in respiratory frequency unaccompanied by a change in tidal volume. They pursued this observation no further, beyond

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suggesting that it may explain the hyperventilation of some aircrew. Remmers (1970) found that a similarly applied vibration, of about 300 Hz, produced a third and different result, namely a reduction in the respiratory frequency and a reduction of the integrated phrenic discharge. Remmers showed that these responses were mediated by intercostal afferents, possibly via a supraspinal pathway. Evidence for this hypothesis accrued when Krieger *et al.* (1972) demonstrated the importance of a spinoreticular pathway in the lateral cord, for the control of respiratory pattern. The afferents are Group I fibres in intercostal nerves and they inhibit inspiration at a supraspinal site (Remmers, 1973; Remmers and Tsiaras, 1973).

In the present study, reductions in the depth and sometimes in the frequency of breathing were observed during vibration of the rib cage and associated structures in spontaneously breathing anaesthetized animals and awake human subjects. Part of this work has appeared in brief form (Gandevia and McCloskey, 1975).

Methods

ANIMAL STUDIES

Experiments were performed on nine adult male and female cats weighing 1.9–4.1 kg and on ten male and female rabbits weighing 2.1–2.8 kg. The cats were anaesthetized with intraperitoneal pentobarbitone (Nembutal: Abbott: 40 mg/kg). Seven rabbits were anaesthetized with a pentobarbitone urethane mixture (each ml contained 7.5 mg pentobarbitone and 220 mg urethane) and three with urethane in a dose sufficient to achieve surgical anaesthesia. Supplementary anaesthetic was given as required through a nylon cannula inserted into the femoral vein. The trachea was cannulated low in the neck and a nylon cannula was inserted into a carotid or femoral artery. Rectal temperature was kept between 37 and 39 °C.

The tidal volume was measured using a variation of the bag-in-box method introduced by Donald and Christie (1949). The animal inspired from a bag filled with oxygen and expired into an air-tight container surrounding the bag: the volume (and pressure) changes in the container therefore reflected the tidal volume, and were recorded using a Grass PT5A volumetric pressure transducer. The apparatus added 10–12 ml to the respiratory dead space. Pressure from the arterial cannula was recorded using a Statham P23AC transducer.

In several experiments intrapleural pressure was monitored, using a Statham P23AC transducer, either directly from a cannula inserted into the pleural space, or indirectly from a cannula inserted in the right external jugular vein and advanced until the tip lay within the thorax in or near the right atrium. In two experiments on rabbits the head was fixed and a silk tie stitched through the nostril and attached to a Grass FTO3 force transducer. This provided another indication of the output of the respiratory centres (*cf.* Heymans and Heymans, 1928: see Discussion). A four channel Grass polygraph pen recorder displayed all transducer outputs.

The following surgical procedures were performed on different occasions to determine the afferent and efferent components of the responses to vibration: (1) bilateral division of the vago-sympathetic trunks in the neck (5 rabbits, 7 cats); (2) bilateral division of the phrenic nerves in the neck (2 rabbits, 2 cats); (3) de-afferentation of the skin overlying the chest wall by entirely removing it and then repositioning it over the chest with sutures (2 rabbits, 2 cats); (4) spinal transection immediately above the thoracic spinal cord, at C8/T1 (3 cats). Laminectomies were done after the initial surgery, but before the first periods of vibration. After spinal transection the blood pressure was maintained by intravenous infusion of phenylephrine (Neo-synephrine: Winthrop).

A small physiotherapy vibrator (Vibratory massager: Pifco Ltd: 100 Hz) transmitted vibration longitudinally onto the sternum through a cylindrical brass rod of 20 mm^2 cross-sectional area. In later experiments the cylindrical rod was fitted into a 'crocodile' clip directly attached to the top of the sternum. This modification ensured a less variable connection between the rod and the sternum. Once a suitable positioning of the rod was achieved, it was maintained as long as possible, vibration being initiated from a remote switch. The amplitude of vibration produced, as measured under a dissecting microscope, was nearly 1 mm in the midline, about 0.5 mm in the mid-axillary line and palpably less along the animal's thoracic vertebrae.

HUMAN STUDIES

Six adult males, two of whom were aware of the results obtained in the animal experiments, were subjected to vibration produced by a vibrating cushion (Niagara thermocyclopad: 70 Hz). The subject lay face upwards on a bed with the pad (40 × 60 cm) strapped to his anterior chest wall. A 3.5 kg weight attached to the top of the vibrating pad stabilized it and aided spread of vibration. The frequency and amplitude of vibration were dependent on input voltage and could not be independently varied. The maximum amplitude produced in the mid-axillary line was about 2 mm. There was a delay of about half a second after turning on the vibratory pad before maximum amplitude and frequency were achieved. Vibration was delivered for 2–5 respiratory cycles after a period of stable respiration and was timed to reach maximum amplitude and frequency early in inspiration. Tidal volume was recorded using a Palmer spirometer filled with oxygen and fitted with low resistance valves.

Results

EFFECTS OF VIBRATION IN ANIMALS

In 17 of the 19 animals longitudinal sternal vibration at 100 Hz over several respiratory cycles consistently reduced the tidal volume by 10–15 %, and in some preparations

by as much as 40 %. A slight reduction of respiratory rate occasionally occurred during periods of vibration, especially early in an experiment, but this effect was elusive, and could not be studied thoroughly. Figure 1 (at left) shows the usual tidal volume reduction and a slight reduction of breathing frequency during a control period of vibration. Vibration reduced the tidal volume in all ten rabbits and seven of the nine cats.

During prolonged periods of vibration (20–40 sec) the tidal volume recovered steadily, and not surprisingly there was an overshoot for one or two breaths after stopping the vibration. Presumably the accumulation of chemical stimuli mediated the recovery and the overshoot. Blood pressure was unaffected by vibration.

A period of vibration during inspiration reduced inspiratory flow (fig. 2). The reduction of tidal volume caused by vibration during inspiration was not accentuated by vibration over several respiratory cycles (throughout inspiration and expiration). Vibration during expiration did not alter the course of that expiration nor the volume of the following inspiration (fig. 2).

The rabbits' responses to sternal vibration were similar to those of the cats with one exception. This exception was a common expiratory prolongation, or delay in commencing the following inspiration, associated with expiratory bursts of vibration. The volume of the following inspiration, as in the cat, remained unaffected. This response was not present in vagotomized rabbits.

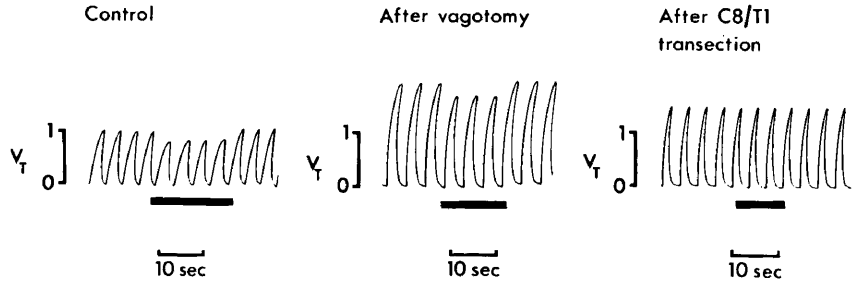

Fig. 1. Results from one cat in which the skin overlying the chest wall had been denervated. It shows a record of tidal volume (inspiration upwards), with the heavy bars indiating the periods of vibration. Tidal volume is measured in an arbitrary unit (1 unit is approximately 30 ml). Vibration reduced the tidal volume in the control period, and after bilateral vagotomy, but not after spinal transection at C8/T1. In the control period of vibration there was a slight decrease in respiratory rate.

DENERVATION PROCEDURES

Vibration reduced the tidal volume after deafferentation of the skin overlying the chest wall and after bilateral vagotomy (fig. 1). After bilateral division of the phrenic nerves the usual responses to vibration were still present.

Spinal transection immediately above the thoracic cord abolished the usual responses to vibration in the three cats in which it was performed. The abolition of the effect provided cogent evidence that an artefactual reduction of the tidal volume

(perhaps due to inspiration of an oscillating column of air), was not the explanation for the observed effects. Prior to transection above the thoracic cord, lower spinal transection at T13/L1, T8/9, and even T2/3 (each in one preparation) did not qualitatively alter the responses to vibration. Successful experiments were not performed on rabbits with spinal transections.

NATURE OF THE EFFECT

Vibration at 100 Hz is known to cause reflex muscular contraction – the tonic vibration reflex (De Gail *et al.*, 1966; Hagbarth and Eklund, 1966). It seemed possible that such a reflex, by 'freezing' the chest wall, might be responsible for the reduction of tidal volume during a period of vibration. But intrapleural pressure records indicated that no progressive change in end-expiratory point occurred during vibration (fig. 2), as would be expected if chest wall compliance altered as a result of intercostal muscle contraction; only at the end of inspiration was intrapleural pressure altered.

We next pursued the question of whether the effects arose from a simple spinal segmental reflex, or whether reflex loops to higher levels were involved. We attempted to observe the behaviour of phrenic motoneurones during vibration, using conventional techniques for multifibre and single fibre recording. However, mechanical and electrical interference caused by the vibration, made this task unrewarding. Instead, alae nasi tension was recorded as an indicator of central respiratory activity in the rabbit (*cf.* Heymans and Heymans, 1928). Sternal vibration inhibited the development of alae nasi tension, as is shown in fig. 3. Alae nasi tension was similarly inhibited after vagotomy. Figure 3 also shows a comparable change in tidal volume and in alae nasi tension during an augmented breath induced by vibration. Vibration occasionally evoked such augmented breaths (as defined by Glogowska *et al.*, 1972), but not after vagotomy.

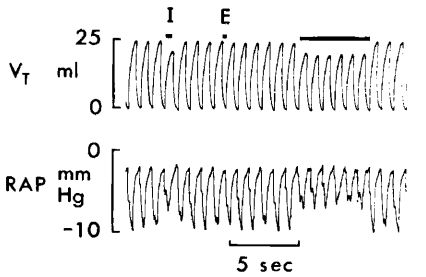

Fig. 2. Rabbit: Records show simultaneous changes in tidal volume (inspiration upwards), and right atrial pressure (inspiration downwards). The heavy bars indicate the periods of vibration. Vibration during inspiration (marked I) reduced the tidal volume; this reduction was not accentuated by vibrating over several breaths (long bar at right). Vibration during inspiration reduced the usual inspiratory excursion of the right atrial pressure. Vibration during expiration (marked E) did not alter the course of the expiration nor the volume of the following inspiration. During prolonged vibration (long bar at right) the inspiratory, but not the expiratory, end-point was altered. See text.

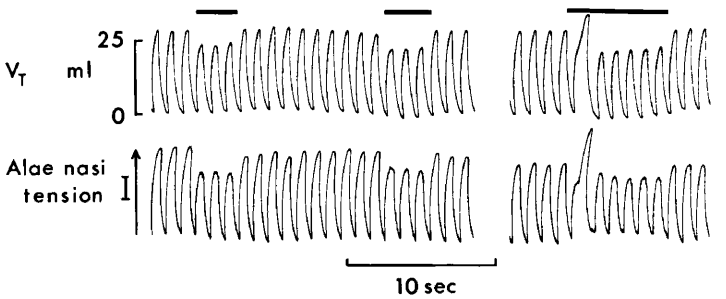

Fig. 3. Results from a rabbit showing simultaneous records of tidal volume and alae nasi tension (inspiration upwards in both). The heavy bars indicate the periods of vibration. Vibration reduced the tidal volume and similarly inhibited the development of alae nasi tension. At right, vibration was associated with an augmented breath. The ventilatory response was comparably reflected by alae nasi tension.

HUMAN STUDIES

Vibration at 70 Hz delivered from a large pad strapped to the chest produced variable responses. Six males received periods of vibration lasting 2–5 respiratory cycles beginning early in inspiration. Two subjects found the vibration mildly discomforting.

Ventilation did not increase in any subject during any vibration period (*cf.* Duffner *et al.*, 1962; Hoover and Ashe, 1962). In more than half the vibration periods given the tidal volume was reduced by 10% or more in 3 of the 6 subjects, and the respiratory rate was reduced by 10% or more in 2 further subjects with no consistent change in tidal volume. The sixth subject gave a variable response: there was either a reduction in the respiratory frequency, a reduction in the tidal volume, or no change in ventilatory pattern, on repeated trials of vibration. One naive subject consistently reduced his tidal volume by 40% without any change in respiratory frequency. This subject, and another who commonly reduced his tidal volume in response to vibration, volunteered that they believed their rate and depth of breathing had increased during vibration. These subjective responses are consistent with the subjects' having experienced proprioceptive illusions of the type described by Goodwin *et al.* (1972).

Discussion

Evidence from the animal experiments indicates that longitudinal sternal vibration at 100 Hz reflexly inhibits inspiration. On the basis of denervation procedures (deafferentation of skin overlying the chest wall, bilateral vagotomy, division of the phrenic nerves, and spinal transection above and below the thoracic cord) it seems probable that the receptors for the reflex lie in the chest wall. A contribution from receptors in abdominal muscles or from accessory muscles is unlikely because the reflex was preserved after spinal cord transection at T2/3 and abolished by transection

above the thoracic cord. The failure of vibration to alter the end-expiratory point suggests that a tonic vibration reflex in the respiratory musculature was not prominent in causing the inspiratory inhibition.

Afferent impulses responsible for this inhibition of inspiration probably enter the spinal cord along the intercostal nerves and inhibit inspiratory activity in a manner similar to that reported by Remmers (1970). A contribution from afferents travelling with the sympathetic nerves is possible. That the inhibitory pathway activated by sternal vibration travels supraspinally is indicated by the reflex reduction of inspiratory activity of alae nasi tension. It is not clear why the chest compression, intercostal muscle stretch, and rib vibration used by Remmers (1970) reduced the respiratory rate, and our sternal vibration rarely affected it.

Our consistent impression was that the inhibition of inspiration appeared more pronounced if the burst of vibration was delivered late in inspiration. Calma (1952) suggested that non-vagal reflexes affecting phrenic motoneurones were modulated by the respiratory cycle. The latter part of inspiration has since been reported to be more receptive for expression of non-vagal reflexes involving phrenic, intercostal and laryngeal motoneurones (Decima and von Euler, 1969; Remmers, 1970; Irani *et al.*, 1972). Baroreceptor and chemoreceptor reflexes are also modulated by the phase of respiration (Koepchen *et al.*, 1961; Black and Torrance, 1971; Haymet and McCloskey, 1975).

An occasional augmented breath was sometimes initiated by vibration, although not in vagotomized animals. The genesis of an augmented breath requires intact vagi (Larrabee and Knowlton, 1946) but is facilitated by other inputs, such as hypoxia and laryngeal irritation (Glogowska *et al.*, 1972). Chest wall afferents may also be capable of summating with other inputs to cause an augmented breath.

The mechanoreceptor involved in the reflex inhibition of inspiration could well be the primary ending of the muscle spindle with its well known sensitivity to vibration and small changes in length (*e.g.* Brown *et al.*, 1967). Muscle spindles, more plentiful in the upper than the lower thoracic segments, outnumber joint receptors by more than 12 : 1 (Huber, 1901–2; Godwin-Austin, 1969). Moreover, Godwin-Austin (1969) found an average of only two active costovertebral joint receptors in each unilateral segment and the majority (48 of 53) were slowly adapting and not the phasic type recently reported capable of following vibration of 100 Hz (Millar, 1973).

The responses on vibrating the chest wall and associated structures in humans were variable but do not contradict those from the animal experiments. They are to be contrasted with well documented increases in ventilation on whole body vibration at low frequencies (Duffner *et al.*, 1962; Hoover and Ashe, 1962). However, the gross mechanical disturbance used in those studies caused joint movements and muscular contraction, both of which would stimulate ventilation (*e.g.* Coote *et al.*, 1971; Barron and Coote, 1973); any inhibitory reflexes from the chest wall could have been obscured.

The present status of reflexes from the chest wall in the control of rate and depth of breathing, especially during loading, is uncertain (Shannon, 1975). In a study of

resistance loading in anaesthetized cats Bruce *et al.* (1974) produced a similar pattern of tidal volume response to that induced by sternal vibration. They observed that only the initial decrease in tidal volume remained if P_{O_2}, P_{CO_2} and pH were kept at pre-loading levels (see also Callanan and Read, 1974).

In summary, we see our results and their significance as follows. Sternal vibration reflexly inhibits inspiration. It almost certainly stimulates intercostal muscle spindle afferents which, according to Remmers (1970, 1973), inhibit breathing. Stimulation of these afferents may occur during respiratory loading, a situation which vibration may mimic. Alternatively, activation of these receptors by vibration might signal prematurely and erroneously the attainment of a tidal volume preset by the respiratory centres. The reduction of tidal volume as a response to activation of the receptors would be expected in either case.

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RESPIRATORY MODULATION OF BARORECEPTOR AND CHEMORECEPTOR REFLEXES AFFECTING HEART RATE AND CARDIAC VAGAL EFFERENT NERVE ACTIVITY

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SUMMARY

1. Brief stimuli were delivered to the carotid chemoreceptors or baroreceptors in dogs anaesthetized with chloralose. Chemoreceptor stimulation was achieved by rapid retrograde injections of 0·2–0·5 ml. CO_2 equilibrated saline through a cannula in the external carotid artery. Baroreceptor stimulation was achieved by forceful retrograde injection of 2–5 ml. air-equilibrated saline into the external carotid artery after first clamping the common carotid artery.

2. Prompt decreases in heart rate were elicited by brief sudden chemoreceptor or baroreceptor stimuli when these were delivered during the expiratory phase of respiration. The stimuli did not modify the control heart rate pattern when delivered in the inspiratory phase of respiration. This respiratory modulation of reflex effectiveness persisted when the animals were completely paralysed and the phase of the respiratory cycle was monitored through a phrenic electroneurogram.

3. Single cardiac vagal efferent nerve fibres were dissected from the cut central end of the right cervical vagus nerve. They were classified as cardiac efferents by their cardiac and respiratory rhythmicity, and by their increased activity in response to stimulation of a carotid sinus nerve or to mechanical elevation of the systemic arterial pressure. These efferent fibres increased their activity in response to brief chemoreceptor or baroreceptor stimuli delivered in expiration, but did not respond to stimuli delivered in inspiration. This respiratory modulation of both reflexes persisted after bilateral cervical vagotomy.

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INTRODUCTION

In 1961, Koepchen, Lux & Wagner demonstrated that the reflex slowing of the heart evoked by stimulation of the carotid sinus baroreceptors is more pronounced when the baroreceptor stimuli are timed so as to coincide with the expiratory, rather than with the inspiratory, phase of the respiratory cycle.

Haymet & McCloskey (1975) confirmed these findings, and observed that the reflex bradycardia evoked by stimulation of the carotid chemoreceptors was similarly more pronounced when the stimuli were given during expiration rather than inspiration. They showed also that the respiratory modulation of the baroreceptor and chemoreceptor reflexes is not entirely caused through the activation, during inspiration, of slowly adapting mechanoreceptors in the thorax or lungs: both reflexes remain strong during the inspiratory apnoea of the Hering–Breuer inflation reflex, and during maintained inflation in periods of post-hyperventilation apnoea. Moreover, the respiratory effects upon both reflexes persist after pulmonary denervation.

In the present study we show first, that respiratory modulation of both reflexes persists in dogs which are paralysed, and second, that the observations of Haymet & McCloskey (1975), referred to above, are borne out by the responses of single cardiac vagal efferent nerve fibres to brief baroreceptor or chemoreceptor stimuli. Part of this work has been reported in brief form (Goldner & McCloskey, 1975).

METHODS

Experiments were performed on twenty-seven adult dogs of both sexes weighing from 5 to 17 kg. The animals were anaesthetized with I.V. chloralose (α-chloralose: British Drug Houses: 80 mg/kg) after induction with thiopentone. Usually a supplemental dose of morphine (1–2 mg/kg) was given early in the period of anaesthesia before the experimental procedures. In each dog the trachea was cannulated low in the neck, and nylon cannulae were inserted, with their tips facing towards the heart, into the lingual and external carotid arteries, usually on the left side. The tips of these cannulae were positioned close to each other and in close communication with the carotid sinus. A nylon cannula was inserted into a femoral or external jugular vein for administration of anaesthetics and drugs and, in some dogs, a balloon-tip cannula was inserted through a femoral artery and advanced so that the inflatable balloon lay in the upper abdominal aorta. Rectal temperature was kept between 37 and 39 °C.

Arterial pressure was recorded from a lingual artery using a Statham P23 AC transducer. In paralysed animals, respiratory activity was recorded from a whole de-sheathed phrenic nerve through Ag-AgCl electrodes, and this phrenic neural discharge was integrated using a Grass 7P3B preamplifier. To produce paralysis I.V. D-tubocurarine (1–2 mg/kg) was given slowly until all respiratory movements ceased; the animals were then ventilated on pure oxygen using a Starling Ideal pump,

adjusted so that some phrenic neural activity remained. Observations on reflex effectiveness during paralysis were made in periods of 20–40 sec during which the respiratory pump was temporarily stopped. In these same animals records of electrocardiogram and heart rate were obtained using a Grass 5P4D preamplifier. Blood pressure, e.c.g., heart rate, and phrenic neural activity were recorded on a Grass polygraph.

Spontaneously breathing animals were used in the study of activity in cardiac vagal efferent nerves. In these animals a record of tracheal air-flow was obtained by passing a wide (2 mm i.d.) nylon tube about 5 cm into the trachea and connecting it to a Grass 5PT5A volumetric pressure transducer. Arterial pressure was obtained from a lingual artery as before. The entire pharynx and larynx were removed from just above the sternum up to the level of the hyoid bone, and the skin flaps were raised to make a pool which was then filled with liquid paraffin. The vagus nerve on the right-hand side was then cut, desheathed, and the central end was laid across a rigid, earthed, stainless-steel plate with a blackened upper surface. The nerve was then divided into filaments under the microscope with fine forceps. Neural activity in the filaments was recorded by lifting them, one by one, on to fine stainless-steel electrodes, which were connected through a Tektronix 122 preamplifier to an oscilloscope and speaker. Filaments were dissected until single cardiac efferents were recorded. Nerves were considered to be cardiac efferents if they demonstrated a cardiac rhythm, and a waning of their activity during inspiration (Jewett, 1974). Confirmation of this characterization was always obtained in one of two ways, (i) the nerve responded with a latency of 40–60 msec to single shocks applied to the central end of a carotid sinus nerve (cf. Iriuchijima & Kumada, 1964) or (ii) the nerve increased its discharge while maintaining its cardiac and respiratory rhythms, in response to a 'mechanical' elevation of blood pressure produced by inflating an aortic balloon, Records of carotid sinus blood pressure, tracheal air-flow, and cardiac vagal activity were obtained on an ultraviolet recorder (Y.E.W. Type 2901), with galvanometers giving a flat frequency response to 1000 Hz. Records obtained with this instrument have required retouching.

Brief baroreceptor and chemoreceptor stimuli were given in the way described by Haymet & McCloskey (1975). The chemoreceptor stimuli were provided by sudden retrograde injections into an external carotid artery of small volumes (0·2–0·5 ml.) of warmed CO_2-equilibrated saline. Injections of similar small volumes of air-equilibrated saline were always without reflex effect. Baroreceptor stimuli were delivered by sudden retrograde injections of 2–5 ml. air-equilibrated saline of freshly drawn arterial blood into an external carotid artery, after first clamping the common carotid artery downstream of the carotid sinus.

RESULTS

(i) *Respiratory modulation of reflexes during paralysis.* In this part of the study eight dogs were used. All showed the phenomenon described by Koepchen *et al.* (1961) and Haymet & McCloskey (1975): brief baroreceptor or chemoreceptor stimuli evoked no reflex bradycardia when delivered during inspiration, but did evoke prompt bradycardia when given in expiration. The dogs were then paralysed, as described, and artificially ventilated on O_2. During periods in which the ventilation was temporarily stopped, baroreceptor and chemoreceptor stimuli were again delivered. The activity recorded from the phrenic nerve was used to indicate the

phase of the paralysed animals' continuing respiratory cycle. Baroreceptor and chemoreceptor stimuli which evoked no reflex bradycardia when delivered in the inspiratory phase of the neural respiratory cycle, evoked prompt bradycardia when delivered in the expiratory phase of the cycle. This occurred in all dogs. Characteristic responses from one dog are shown in Fig. 1.

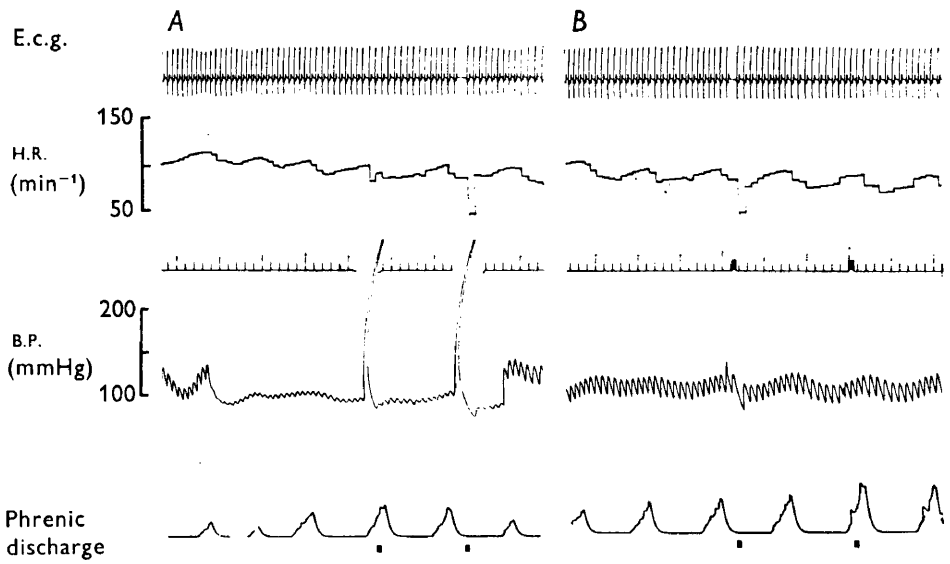

Fig. 1. This shows recordings made in a dog anaesthetized with chloralose and paralysed with D-tubocurarine. The animal had been artificially ventilated on pure O_2 until immediately before each panel of this Figure was recorded: during each recorded period the ventilator was temporarily stopped. In the period between recording the left and right panels of the Figure, artificial ventilation had been resumed for about 3 min. Records of e.c.g., heart rate, carotid sinus blood pressure, and integrated phrenic electroneurogram are shown. In the left panel, two brief baroreceptor stimuli were delivered, one during the inspiratory, and one during the expiratory phase of the respiratory cycle. Only the expiratory stimulus slowed the heart. In the right panel, two brief chemoreceptor stimuli were delivered, one during the inspiratory, and one during the expiratory phase of the respiratory cycle. Again, only the expiratory stimulus slowed the heart.

(ii) *Responses of cardiac vagal efferents to baroreceptor and chemoreceptor stimuli.* Fourteen single cardiac vagal efferent nerves from twelve dogs were studied in detail. Of these fibres (dissected from the right vagus), twelve gave their responses to stimuli given in the left carotid reflexogenic area, and two to stimuli given on the right (this grouping simply reflects the more common use of the left side for delivery of stimuli). Nine fibres responded to both baroreceptor and chemoreceptor stimuli, although commonly one form of stimulus evoked larger responses than the other.

Three fibres gave responses to baroreceptor stimuli given on the test side but not to chemoreceptor stimuli on the same side, and two fibres responded to chemoreceptor but not baroreceptor stimuli on the same side. About an equal total number of fibres, identified as cardiac efferents by our criteria, did not respond to either form of stimulus. Presumably these fibres received their afferent inputs from another source. All did, however, receive baroreceptor or chemoreceptor inputs from some source, as our identifying procedures depended upon the responses to such inputs.

All responding fibres behaved similarly. All gave bursts of activity in response to baroreceptor or chemoreceptor stimuli delivered during expiration, but were silent, or occasionally responded with just a single action potential, to similar stimuli delivered during inspiration. Typical responses are shown in Figs. 2 and 3.

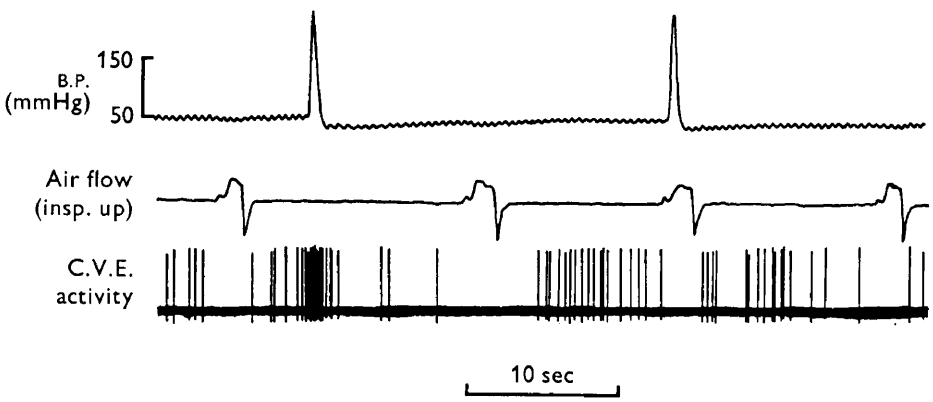

Fig. 2. Dog, chloralose and morphine. Records of carotid sinus blood pressure, respiratory air flow, and the activity of single cardiac vagal efferent nerve (C.V.E.) are shown. A burst of firing in the cardiac efferent nerve was evoked by a baroreceptor stimulus timed so as to occur in the expiratory pause. No firing was evoked when a similar stimulus was given during inspiration (the amplitude of recorded action potentials in this and other experiments was in the range 100–300 μV).

Bursts of firing were always elicited in response to baroreceptor or chemoreceptor stimuli delivered during the inspiratory apnoea of the Hering–Breuer inflation reflex (trachea occluded at normal inspiratory end-point).

The respiratory modulation of baroreceptor and chemoreceptor reflex effectiveness continued after the left vagus nerve was cut (the right vagus was cut in all experiments prior to recording from nerve fibres). In some animals, complete vagotomy led to a pattern of breathing characterized by inspiratory spasms lasting some seconds. Although no air-flow was occurring during large parts of these periods of inspiratory spasm, the

inspiratory block of vagal responses to baroreceptor and chemoreceptor stimuli remained throughout. Fig. 4 shows the responses of one of the fibres to chemoreceptor stimulation during the respiratory cycle after complete vagotomy.

It is possible that the inspiratory block of the reflex pathways, although remaining operative during periods of inspiratory spasm after vagotomy,

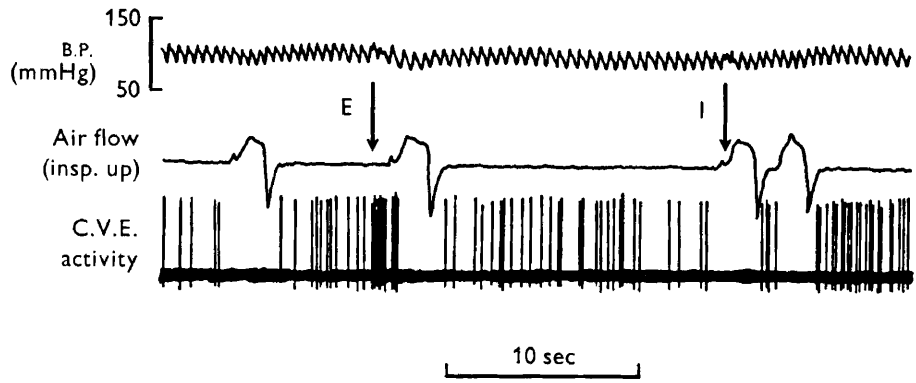

Fig. 3. Dog, chloralose and morphine. Records of carotid sinus blood pressure, respiratory air flow, and the activity of a single cardiac vagal efferent nerve (C.V.E.) are shown. A burst of firing in the cardiac efferent nerve was evoked by a chemoreceptor stimulus timed so as to occur in the expiratory pause (marked E). No firing was evoked when a similar stimulus was given during inspiration (marked I), although this stimulus was associated with the animal taking a second breath sooner than would have been expected from his previous respiratory pattern. Induced irregularities of breathing of this kind did not affect the nature of the responses observed.

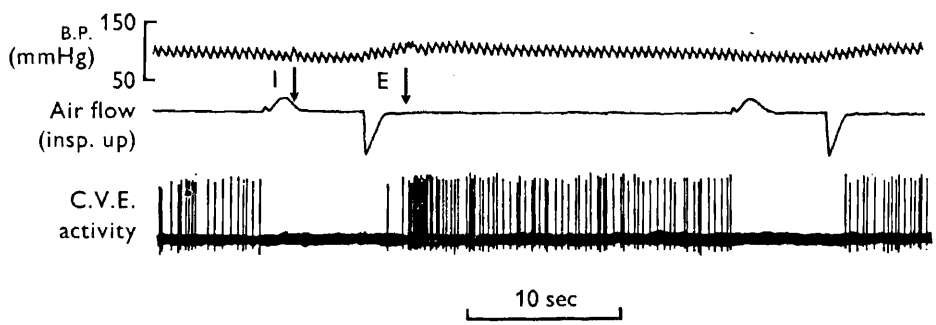

Fig. 4. Dog, chloralose and morphine, bilateral vagotomy. Records of carotid sinus blood pressure, respiratory air flow, and the activity of a single cardiac vagal efferent nerve are shown. After vagotomy this animal adopted a respiratory pattern characterized by prolonged inspiratory spasms. A burst of firing in the cardiac efferent nerve was evoked by a chemoreceptor stimulus timed so as to occur in the expiratory pause (marked E). No firing was evoked when a similar stimulus was given near the peak of inspiration (marked I).

does vary in its effectiveness. This is difficult to test using the functional, but variable, stimuli we have used here. We note, however, that when the arterial pressure is raised mechanically by aortic occlusion, the intense vagal efferent activity evoked is frequently blocked entirely at the start and finish of an inspiratory spasm, but is only reduced during the spasm (see Fig. 5). We have seen responses of this kind in six of nine fibres tested.

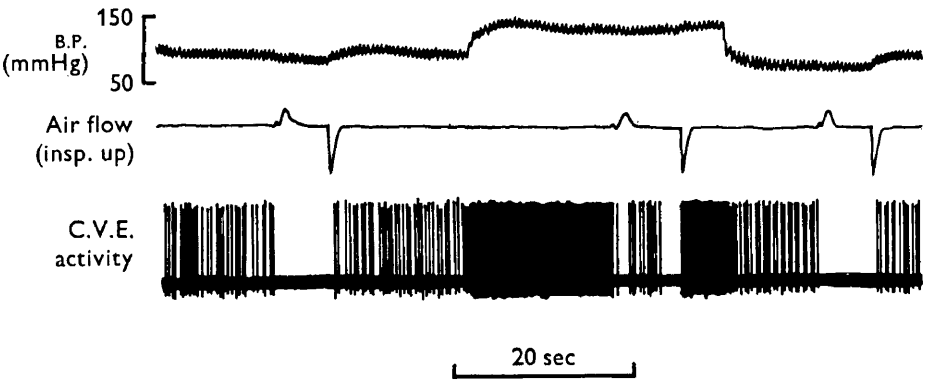

Fig. 5. Dog, chloralose and morphine, bilateral vagotomy. Records of carotid sinus blood pressure, respiratory air flow, and the activity of a single cardiac vagal efferent nerve are shown. After vagotomy, this animal adopted a respiratory pattern characterized by prolonged inspiratory spasms. At a normal blood pressure these spasms were associated with complete abolition of discharge in the cardiac efferent nerve. When the arterial pressure was raised mechanically by the inflation of a balloon in the aorta, the discharge of the cardiac efferent nerve was intensified. At an elevated blood pressure the pattern of discharge during the respiratory cycle was altered. During an inspiratory spasm there was complete abolition of discharge in the cardiac efferent nerve only at the start and finish of the spasm: some firing of the nerve occurred in the middle of the inspiratory period.

DISCUSSION

This study confirms and extends the work of Koepchen *et al.* (1961) and Haymet & McCloskey (1975). The experiments on paralysed animals indicate that the cycling of central neural respiratory mechanisms is sufficient to impose a modulation upon the effectiveness of both baroreceptor and chemoreceptor reflexes on heart rate. It remains possible that this centrally imposed modulation can be altered, perhaps augmented, by phasic afferent inputs in the spontaneously breathing animal.

The studies in which activity in cardiac vagal efferent nerves was recorded provide direct confirmation of the principal findings of Koepchen *et al.* (1961) and Haymet & McCloskey (1975) in experiments in which heart rate was recorded. Similar results for baroreceptor reflex effects were recently reported in brief form by Neil & Palmer (1975). The criteria

we used for identifying vagal efferents as cardiac are not new (cf. Jewett, 1964; Iriuchijima & Kumada, 1964), and indeed, their use is further vindicated here by the reproducibility of Haymet & McCloskey's findings in the fibres so identified. Our sample of fibres is not large enough for us to gauge accurately the extent of convergence of chemoreceptor and baroreceptor inputs on to vagal efferents. Some of our efferents were very responsive to one or other input while showing only small responses, or no responses at all, to the other. Certainly our findings suggest that inputs from one reflexogenic zone may fail to influence vagal efferents which receive inputs from some other zone. Moreover, it should be noted that there may be efferents to the heart which we did not identify or test because they did not receive the baroreceptor or chemoreceptor inputs by which we identified cardiac efferents.

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ISOMETRIC EXERCISE AS CARDIOVASCULAR STRESS

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In dynamic exercise there are large increases in cardiac output, heart rate and stroke volume: systolic arterial pressure rises, but diastolic does not, and there is relatively little change in mean arterial pressure. In isometric (i.e. static) exercise, on the other hand, there are quite small changes in cardiac output and heart rate, but systolic and diastolic pressures rise markedly, so that mean arterial pressure is also increased. Whereas dynamic exercise imposes primarily a volume load on the heart, isometric exercise produces predominantly a pressure load (7, 13). Because of this, isometric exercise has potential value as a cardiac stress test.

Isometric exercise offers many advantages to the laboratory investigator. It can be undertaken with a minimum of exercise equipment - a simple stiff-spring handgrip dynamometer is sufficient for most studies and the subject can perform the exercise while seated. Depending on the level of isometric effort required, a satisfactory test can be completed in 1 - 4 minutes.

Several features of the cardiovascular response to isometric exercise are peculiar. The increases in arterial pressure, cardiac output and heart rate are, as in dynamic exercise, closely related to the degree of exertion. Unlike the situation in dynamic exercise, however, it is neither the absolute tension developed nor the mass of muscle contracting which determines the magnitude of the cardiovascular changes; rather, the important factor is the percentage of maximal tension achieved by the particular muscle group involved. Thus, blood pressure is similarly elevated by isometric efforts of 20% of maximum with the hand, with the quadriceps muscles of the thigh, or with the adductors of an individual finger, despite very great differences in the absolute tensions developed and in the energy requirements of the respective efforts (8, 11). It follows from this observation that less cardiovascular stress is caused by carrying a given load with a large, strong group of muscles, such as the shoulders or thighs, than with a smaller weaker group, such as the hand (9).

Another feature of the cardiovascular response to isometric contractions is that the effects of simultaneous isometric efforts are not additive, but are determined solely by the greatest existing proportional contraction. Thus, the responses during a handgrip contraction at 30% of maximum are the same whether or not there is a simultaneous contraction of quadriceps at 20% of its maximum (8). When two muscle groups contract to the same degree, the cardiovascular response is identical to that observed when only one of the groups contracts. Thus, it follows that if a 20 kg weight is carried as a single load by one muscle group, it constitutes a greater cardiovascular stress than if it were distributed as two 10 kg-loads between similar muscle groups (7, 8, 9).

Although the responses to simultaneous isometric efforts do not add to each other, the response to an isometric effort does add to the response to dynamic exercise (5, 8). This persistence of the whole response to isometric exercise, during dynamic exercise, is evidence of the great strength and dominance of the cardiovascular drive during isometric contractions.

It is known that at least two mechanisms cause the increases in blood pressure, heart rate and cardiac output which accompany isometric contractions. First, there are reflexes, originating in the contracting muscles, which contribute to the responses. It can be shown that typical cardiovascular responses are evoked in anaesthetized animals when isometric contractions are caused by electrical stimulation of the spinal ventral (motor) roots. That these responses are

* Supported by the National Heart Foundation of Australia.

abolished when the dorsal roots carrying sensory nerves from the contracting muscles are cut, is evidence of the reflex nature of the response (2, 10). By selective nerve blocking techniques it can be shown that the sensory nerves mediating the cardiovascular reflexes are unmyelinated and small myelinated nerves, and that afferents from muscle spindles and Golgi tendon organs are not involved (10).

An interesting feature of the reflex stimulus to the cardiovascular stress, is that it can be preserved, at least in part, after an isometric effort has concluded. Alam & Smirk in 1937 (1) noted that blood pressure remained elevated after an isometric effort in subjects in whom an occluding cuff was applied above the contracting muscles before the contraction finished. This pressor response persists for as long as the cuff remains inflated and is presumably due to a pressor reflex arising through the stimulation of sensory nerves in the muscle by chemical factors trapped by the occlusion.

There is a second important cardiovascular stimulus in isometric exercise. This arises directly from the motor command "irradiating" the cardiovascular control centres, as the command signals descend from higher neural centres towards the motorneurones of the muscles. Experimental situations can be contrived in which subjects generate the same isometric tension in circumstances in which the magnitude of the command required is varied: in these situations the cardiovascular response varies with the command, or effort, put into the contraction (4). It follows, and it has been shown, that as a muscle group fatigues, and a larger command or effort is required to cause it to achieve a given tension, then the magnitude of the cardiovascular response increases (4).

The two stimuli (reflex, central irradiation) to the cardiovascular system in isometric exercise behave rather differently. The muscular reflexes alone evoke responses which depend upon both the mass of exercising muscle and the tension achieved, although the total response is not dependent upon muscle mass (11). Moreover, the muscular reflexes alone do not decrease the sensitivity of the baroreceptor-cardiodepressor reflex (12), although the total response to isometric exercise in intact man includes dramatic reductions in the sensitivity of this reflex (3). The relationship of response to proportion of maximal tension achieved rather than to absolute tension, and the effects upon baroreceptor reflexes, appear to be caused principally by central irradiation rather than by muscular reflexes.

Already some diagnostic use of isometric exercise in patients with cardiovascular disease has been made (see 13, for review). Perhaps the greatest clinical value will be as a cardiac stress test. For the physiologist, it suggests interesting questions, and provides a convenient and important method for analysis of the control of cardiovascular responses to exercise.

Isometric exercise has, in recent years, had considerable appeal for busy people seeking a convenient form of exercise. Unfortunately, even intense and prolonged programs of isometric training lead to little or no significant increase in maximal oxygen uptake or cardiac reserve (6). As Mitchell & Wildenthal have observed in the 1974 Annual Review of Medicine (13), "from a cardiological viewpoint isometric exercise is a relatively useless form of physical training and should not be recommended as a substitution for dynamic exercise. Indeed it remains possible that intense isometric exercise should be avoided in certain conditions."

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MUSCULAR REFLEX AND BAROREFLEX INFLUENCES ON HEART RATE DURING ISOMETRIC CONTRACTIONS

BY

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Muscular reflex and baroreflex influences on heart rate during isometric contractions[1]

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SUMMARY Isometric hindlimb contractions were induced in anaesthetised dogs by stimulation of appropriate spinal ventral roots. During such contractions there were appreciable reflex systemic pressor responses accompanied by small increases in heart rate. The heart rate responses during contractions were small because the primary cardioacceleratory reflexes from muscle were partly masked during contractions by opposing baroreceptor-cardiodepressor reflexes.

In isometric, or static, exercise in man there are large increases in systolic and diastolic blood pressures and moderate increases in heart rate (Lind *et al.*, 1964). This form of exercise has been used in studies on the nature of the stimuli to the cardiovascular system in exercise. These stimuli include 'irradiation' of the cardiovascular control centres by descending command signals (Goodwin *et al.*, 1972), and reflex stimuli originating in nerve endings in the contracting muscles (Coote *et al.*, 1971; McCloskey and Mitchell, 1972).

By stimulating the spinal ventral roots in anaesthetised animals it is possible to cause muscular contractions and to subject the cardiovascular system to only the stimuli from muscle afferents. When this is done in the cat or dog only very small increases in heart rate are elicited, although appreciable pressor responses do occur (Coote *et al.*, 1971; McCloskey and Mitchell, 1972; Fisher and Nutter, 1974). It might be that the muscular afferent reflex drive has little direct effect on heart rate or, alternatively, that the accompanying reflex pressor response acts through baroreceptors to oppose and partly obscure larger primary reflex effects upon heart rate. These possibilities were investigated in the present study.

Methods

Experiments were performed on 24 adult mongrel dogs of both sexes weighing from 6.5 to 14 kg. For anaesthesia, either pentobarbitone (Nembutal, Abbott; 40 mg·kg^{-1}, intravenously, supplemented as required), or chloralose (α-Chloralose, British Drug Houses; 80 mg·kg^{-1}, intravenously, after thiopentone induction) were used. In 9 dogs a supplemental dose of morphine (1–2 mg·kg^{-1}) was given early in the period of anaesthesia.

Blood pressure was recorded from an axillary artery through a saline-filled nylon cannula connected to a Statham P23AC transducer. A tracheal cannula was inserted low in the neck. In some dogs ventilation was measured by a method similar to that described by Donald and Christie (1949). These dogs inspired through valves from a bag enclosed in an airtight box into which the expired air was returned: pressure in the box was measured using a Grass PT5A volumetric pressure transducer. Blood pressure and respiration were recorded on a Grass polygraph pen recorder. On another channel of this recorder either the electrocardiogram or heart rate (tachometer triggered from the ECG) was recorded using a Grass 5P4D preamplifier.

A laminectomy was performed to expose the sacral and lower lumbar segments of the spinal cord. Animals were fixed in a prone position on a table by pins driven into the iliac crests and through the knee joints, and the ankle joints were firmly clamped to prevent movement. A pool was made over the lumbo-sacral vertebrae with paraffin warmed to 37°C and bubbled with 95%O_2+5%CO_2. The spinal cord was exposed by a longitudinal incision through the dura. The ventral roots of L6, L7, and occasionally S1 were cut close to their exit from the spinal cord on one side and were placed over a pair of Ag-AgCl electrodes. Stimulation of the ventral roots at 20–50 Hz with square wave pulses of 0.2–0.5 ms duration, delivered by an isolated

[1]This work was supported by a grant from the National Heart Foundation of Australia.

stimulator, were used to elicit sustained isometric contractions of the hindlimb muscles. The voltage used was twice motor threshold. Periods of contraction of 10–40 s were used. The exposed spinal cord and nerve roots were washed every 30–40 mins with warmed Ringer solution bubbled with 95% $O_2 + 5\%CO_2$ (Brown *et al.*, 1969). Rectal temperatures were maintained at 36–38°C throughout.

Baroreflex effects upon heart rate were investigated at rest and during contractions by altering blood pressure mechanically. This was achieved by inflating a balloon at the tip of a catheter lying in the descending thoracic aorta. The catheter was introduced through the femoral artery of the non-exercising limb.

Results

In the organisation of results of this study, the principal findings are placed in Section (iii). They are preceded by two brief sections: Section (i) summarises the basic observations made here which confirm other studies, and Section (ii) gives results that are intended simply to illustrate the principal points (see also Discussion) which are analysed in greater detail in Section (iii).

(i) Responses to induced isometric contractions

Tetanic contractions of the hind-limb muscles elicited by stimulation of the ventral roots L6, L7, and sometimes S1, for 10–40 s usually caused a rise in arterial blood pressure of 2.7–8.0 kPa (20–60 mmHg). Systolic and diastolic pressures increased together. Accompanying the pressor response was a tachycardia. This increase in heart rate was small, usually about 5–15% of the resting heart rate, and never more than 20% of the resting rate. Breathing was also increased within the first 3 or 4 breaths after commencement of the contraction. All these responses were abolished by cutting the dorsal roots from L5 to S4 on the experimental side, or by transecting the spinal cord at the level of L3, although the stimulated muscle contractions were unaffected by these procedures. These responses are similar to those described in cats (Coote *et al.*, 1971; McCloskey and Mitchell, 1972) and dogs (Fisher and Nutter, 1974; McCloskey and Streatfeild, 1975).

(ii) Baroreflex interaction

In 7 dogs the pressor and heart rate responses to isometric contractions of the hindlimb were determined. The aortic catheter-tip balloon was then positioned so that inflating it produced a mechanical increase in blood pressure of the same magnitude as the pressor response accompanying the contractions. Isometric hindlimb contractions were then again induced by stimulation of the spinal ventral roots, but on conclusion of each period of contraction the aortic balloon was inflated so as to maintain arterial pressure at the exercise level. This manoeuvre, through which we attempted to maintain similar levels of baroreceptor activation during the contractions and just after (see Discussion), invariably caused a pronounced bradycardia which began at the conclusion of the muscular contraction and persisted for the duration of balloon inflation (see Fig. 1).

The tachycardia during contractions seems slight in comparison with the control heart rate. When compared with the heart rate at resting blood pressure similar to that achieved during contractions, however, the difference in heart rate is considerable. In our experiments the increase in heart rate between rest and contractions, measured at the blood pressure level achieved during contractions, was 45% of the resting rate on average (range 30–110% for individual dogs).

It might be concluded from these observations that the reflex stimuli arising in contracting muscles have a potent effect upon heart rate. This would be so, however, only if the baroreceptor reflex retains the same sensitivity during contractions as it has at rest. Our further experiments, therefore, were aimed at determining the baroreceptor-cardiodepressor reflex sensitivity during induced isometric contractions.

(iii) Baroreflex sensitivity

Baroreceptor-cardiodepressor reflex sensitivity at any blood pressure can be measured as the slope of a line relating the time interval between cardiac contractions (the pulse interval or heart period) to the arterial blood pressure. This form of analysis has been widely used in studies in man (Cunningham *et al.*, 1972) and in the rabbit (Korner *et al.*, 1973). In man this relation is a straight line over the physiological range of pressures, but in the rabbit has been shown to depart from a straight line at high and at low pressures, although it approximates a straight line over an intermediate range of pressures.

In our study we have assumed the relation between pulse interval and blood pressure to be a straight line (see below).

Systolic blood pressure and pulse interval were measured at rest before and during the inflation of the aortic balloon, and were plotted on a pulse interval-blood pressure graph. A line was drawn joining these points and its slope taken as a measure of baroreceptor-cardiodepressor reflex sensitivity at

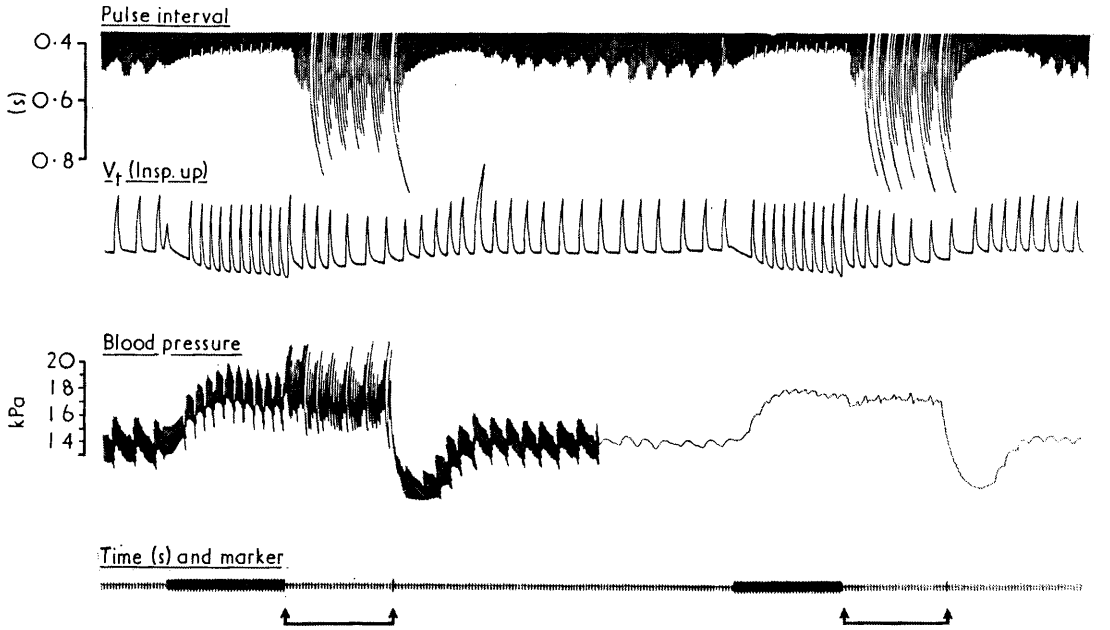

Fig. 1 *Cardiovascular and respiratory adjustments to isometric contractions in a dog. Pulse interval, tidal volume, and blood pressure are shown from above downwards. The heavy continuous markers indicate where two periods of isometric hindlimb contraction were induced. The arrowed markers following these periods indicate where a balloon was inflated within the aorta to maintain blood pressure at its contraction level after the conclusion of the contraction. In the first part of the record pulsatile blood pressure was recorded, in the second part mean pressure was recorded. During a contraction, breathing and blood pressure increased, and there was a small increase in heart rate. The change in heart rate was large, however, when compared with its resting level at the mechanically elevated blood pressure (see text). (Upon deflation of the aortic balloon there was a fall in blood pressure below its control level, attributable to a fall in resistance during reactive hyperaemia in areas in which the aortic occlusion had reduced the arterial inflow.)*

rest. The same variables were measured during isometric hindlimb contractions before and during inflation of the aortic balloon, and again plotted. A line joining these points was taken as a measure of baroreceptor-cardiodepressor reflex sensitivity during induced hindlimb contractions. In every case the blood pressure plotted was systolic pressure (*cf* Cunningham *et al.*, 1972): systolic blood pressure and pulse interval were taken as the means of values measured through one or two complete respiratory cycles (this minimised variability caused by sinus arrhythmia). During balloon inflations measurements were made between 5 and 15 s of the start of the inflation (*ie* at the peak of the pressor response): during isometric contractions, measurements were made between 5 and 30 s of the start of the contraction. For statistical analysis either 5 or 8 baroreflex sensitivity lines were collected at rest and during limb contractions in each experiment. Fig. 2 shows data from one of the experiments.

The slope of the baroreflex sensitivity lines at rest and during contractions were compared in individual dogs using Student's t test. In 10 of 13 dogs no significant difference between slopes could be demonstrated ($P > 0.05$ in all, $P > 0.2$ in 8 of these). Moreover, the slight numerical differences in mean slopes, which were not significantly different, were not systematically related to contractions. On four of the 10 occasions the mean slope during contractions was numerically greater than at rest and on six occasions it was less. In all animals there was highly significant positive correlation between pulse interval and blood pressure.

The range of mean slopes measured was from 16.9 ms·kPa^{-1} (2.25 ms·mmHg^{-1}) to 60.5 ms·kPa^{-1} (8.05 ms·mmHg^{-1}). In 3 dogs there was a significant reduction in the slope of the baroreceptor sensitivity line during contractions ($0.01 < P < 0.05$). We regard these 3 animals as exceptional as they were the only ones in our study in which systolic pressures of over 26.7 kPa (200 mmHg) were recorded. During each period of combined contraction and balloon inflation in these dogs the systolic pressure exceeded 26.7 kPa (200 mmHg).

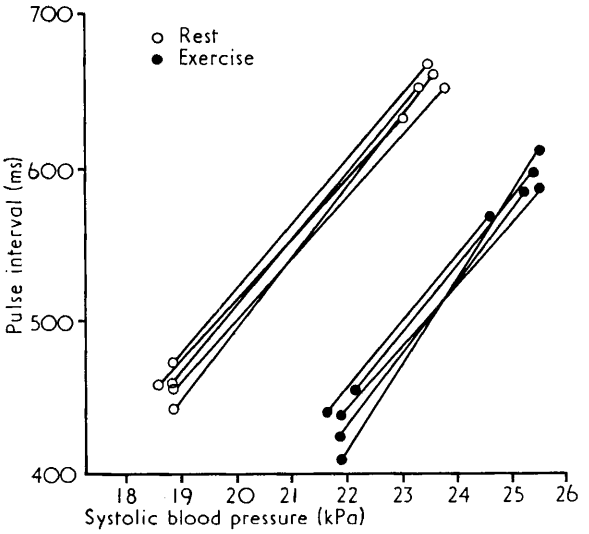

Fig. 2 *Baroreflex activity in a dog. Points for pulse interval and systolic blood pressure are plotted at rest (open circles), and during induced isometric contractions of hindlimb muscles ('exercise': closed circles). In each case points are plotted at a control level of blood pressure and at the peak of the rise in blood pressure caused by inflating a balloon in the thoracic aorta. The lines joining these pairs of points give, by their slopes, indications of baroreceptor-cardiodepressor reflex sensitivity (see text). During isometric contractions the baroreceptor-cardiodepressor reflex sensitivity is not altered.*

While we found little evidence of an alteration of baroreceptor-cardiodepressor reflex sensitivity during contractions, we did find that contractions consistently displaced the pulse interval-blood pressure lines to the right (see Figs. 2 and 3). In order to apply some statistical test to this observation we constructed, for each dog, a horizontal line parallel to the blood pressure axis at the midrange of pulse interval values measured before and during balloon inflation. The pressure axis values of the intersections of individual systolic pressure pulse interval relations with this horizontal line were measured and compared by Student's *t* test. In 12 of the 13 dogs the intercepts for contractions occurred at a significantly higher systolic pressure than at rest ($P < 0.05$; $P < 0.01$ for 8 of the 12).

Finally, as a partial test of our assumption that there is a straight line relation between pulse interval and blood pressure, we collected data at rest and during contractions at three instead of two levels of arterial pressure in 3 dogs. These pressures were control blood pressure, the pressure achieved during inflation of the thoracic aortic balloon as before, and an intermediate pressure achieved when that balloon was partly withdrawn and then inflated in the abdominal aorta. Fig. 3 shows data from one of these experiments. In each case we collected eight baroreflex slopes for rest and during contractions for pressure changes from control to higher pressure, and from control to intermediate pressure. We compared the means of these slopes as before. No mean slope was significantly different from another ($P > 0.2$), whether we compared both resting slopes, both slopes for contractions, or either resting slope with either slope during contractions.

(iv) 'RESETTING'

Baroreceptor-cardiodepressor reflex behaviour has been widely studied by analysis of the pulse interval-blood pressure relation in man (*eg* Cunningham *et al.*, 1972) and in the rabbit (*eg* Korner, 1971). The slope of the relation is taken as an indication of the 'sensitivity' or 'gain' of the reflex, as we have taken it in our experiments. Displacement of the relation,

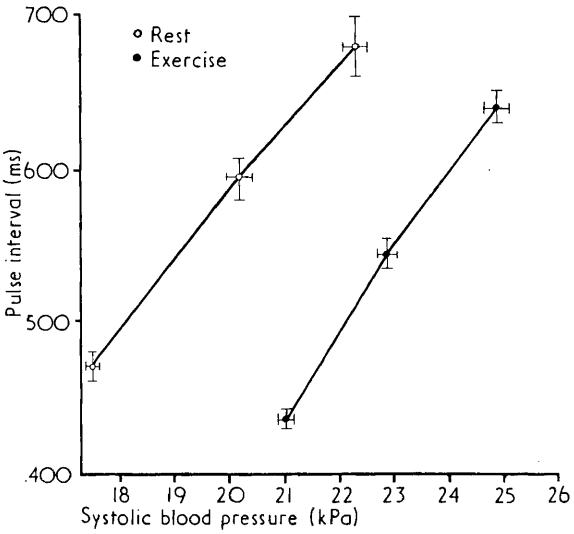

Fig. 3 *Baroreflex activity in a dog. Points for pulse interval and systolic blood pressure are plotted at rest (open circles), and during induced isometric contractions of hindlimb muscles ('exercise': closed circles). In each case points are plotted at a control level of blood pressure and at the peaks of the rises in blood pressure caused by inflating a balloon in the thoracic aorta or in the abdominal aorta. The mean of eight pulse interval-blood pressure determinations in each condition is plotted, and the bars represent ±SEM. The lines joining the control and contraction points give, by their slopes, indications of baroreceptor-cardiodepressor reflex sensitivity (see text). During isometric contractions the baroreceptor-cardiodepressor reflex sensitivity is not altered.*

without alteration in its slope, is taken to indicate a 'resetting' or 'change in set point' of the reflex. Korner (1971) has explained this idea thus: 'the controlling system . . . establishes a set-point which serves as a standard of comparison with the measured output of the system, the difference between the two providing an actuating or "error" signal for the effector . . . the set-point can be modified through independent external command systems'. On this form of analysis, the results we have described above would be explained as follows. Afferent signals from the contracting muscles modify ('reset') the cardiovascular control system thus setting a higher blood pressure as the standard of comparison. This provides an error signal which drives the autonomic effectors to align the measured systemic blood pressure with the higher central set-point.

We have tested this interpretation using variants of the experiment described in Section (ii) above and shown in Fig. 1. In these experiments an aortic catheter-tip balloon was positioned so that inflating it produced a mechanical increase in blood pressure of the same magnitude as the pressor response accompanying hindlimb contractions. The hindlimb contractions were then repeated, except that as they were about to commence the aortic balloon was inflated. This produced a situation in which the arterial blood pressure was raised mechanically to the level at which muscular afferent signals would be claimed to 'reset' the cardiovascular control centres. If such 'resetting' did occur, this manoeuvre should have prevented any error signal from arising, and no autonomic effectors should have been actuated. This was not so, however, as the muscular contractions raised the blood pressure well above the level already achieved by the balloon inflation, and raised the heart rate above the level to which it had fallen abruptly on inflation of the balloon: both variables simply came to the levels they would have attained had the balloon been inflated after the response to contractions had been established.

Discussion

The reflex cardiovascular and respiratory responses originating in isometrically contracting muscles include powerful primary cardioacceleratory effects. These effects can be partly obscured because the reflex pressor response to the exercise evokes a secondary reflex, a baroreceptor-mediated slowing of the heart, which opposes the primary reflex.

In this study, established methods of analysis of the behaviour of the baroreceptor-cardiodepressor reflex have been used. These methods present some problems. The total discharge from the baroreceptors depends not only on the level of arterial pressure, but also on the heart rate, the pulse pressure, and the rate of rise of arterial pressure. Yet in the method we have employed, which is essentially similar to that used by Korner (1971) and by Cunningham *et al.* (1972), the assumption is made that the level of arterial pressure indicates the level of baroreceptor stimulation. We concede that this assumed relation is just an approximation. The problem is well illustrated by the experiment depicted in our Fig. 1, where we maintained the level of arterial pressure attained during a contraction, by inflating a balloon after the contraction. After the contraction, however, the heart rate fell (a factor which would reduce baroreceptor firing) and the pulse pressure rose (a factor which would increase baroreceptor firing). There are similar problems in the other experiments we have reported. Despite this difficulty, the method does provide results which permit comparisons with the studies of Korner (*eg* Korner, 1971) and Cunningham *et al.* (1972), which were performed under the same handicaps. An important advantage of the method is that inputs from *all* the high pressure baroreceptors are made to alter simultaneously. A more precise control of the baroreceptor input from a single source could be achieved, by perfusing, say, an isolated carotid sinus. However, if some control system alters the sensitivity or 'set-point' of the baroreceptor reflexes, the process cannot be analysed correctly if only one of the baroreceptor inputs is controlled. The input from the *un*controlled baroreceptor regions, differently processed centrally, would still evoke their own altered responses in such conditions.

There is evidence from the present study that in the range of arterial pressure from resting level up to 26.7 kPa (200 mmHg) systolic the operating relation between blood pressure and pulse interval is altered during muscular contractions, but no evidence that the sensitivity of the baroreceptor-cardiodepressor reflex is altered. We use here the concept of reflex sensitivity used by Bristow *et al.* (1971) and by Korner (1971). Bristow *et al.* (1971) have advanced cogent arguments for the use of the relation between pulse interval and blood pressure, rather than heart rate and blood pressure, as the preferred index of baroreceptor-cardiodepressor reflex sensitivity. We agree with their arguments on this question. Korner *et al.* (1973) have used a similar approach over a wider range of arterial pressures in the unanaesthetised rabbit, and give data also on the 'heart period range' (the range of pulse intervals through which the baroreflex operates), and on the 'average gain' of the reflex (the sensitivity of the reflex at the centre of the heart period range). Over a considerable range of pressures in their studies,

however, the pulse interval-blood pressure relation approximated a straight line.

We have done experiments on the specific question of whether or not the shift to the right of the pulse interval-blood pressure relation which we have described represents a 'resetting' of the baroreceptor-cardiodepressor reflex. Our results indicate that such a 'resetting', or 'change in set-point', of the baroreflex is not the mechanism operating to change pressure and heart rate during muscular contractions. It is difficult to envisage any mechanism operating through baroreceptor-dependent autonomic neurons which would not alter the baroreflex set point (as defined in our quote from Korner (1971)—see Results, Section (iv), above). But Korner (1971) has written further that, 'a change in apparent set-point' (as defined by the position of the pulse interval-blood pressure relation) '. . . may mean either (1) that distinctive neurons in a particular pool not connected with the arterial baroreceptor projections are being excited or inhibited or (2) that the new input and the arterial baroreceptor projections both make synaptic contact with most of the neurons in the pool and alter their excitability'. Our results would favour the first of these alternatives as an important mechanism operating during muscular contractions, without excluding the possibility of some participation of mechanisms of the second kind as well. We feel that the term 'set-point' to indicate the position of the pulse interval-blood pressure relation is inappropriate and should be avoided. In support of this we note that Korner more recently refers to the behaviour of the baroreceptor reflex along the lines of his analysis quoted above, recognising 'baroreceptor-dependent' and 'baroreceptor-independent' mechanisms (Korner *et al.*, 1973).

In our experiments we have used a quite narrow range of pressures, and have assumed a straight line relation between pulse interval and blood pressure. We looked only at these pressures because our interest was confined to the range of pressures from rest to those achieved during isometric contractions. Our assumption of a straight line relation is vindicated by the studies at three separate pressure levels in which we were unable to demonstrate changes in slope over different ranges within this pressure spectrum. At higher levels of systolic pressure it is probable that the relation would depart from linearity, and that further increases in pressure would not further slow the heart. We note that in only 3 animals was there evidence of a reduction of baroreflex sensitivity during contractions, and that in only these 3 animals were there systolic pressures above 26.7 kPa (200 mmHg). Quite possibly, in these animals, the combination of muscular contraction and inflation of an aortic balloon moved the pulse interval-blood pressure relation out of its approximately linear range.

Changes in the operating relations of the baroreflex controlling systemic blood pressure, without changes in reflex sensitivity, have been reported to occur during sciatic nerve stimulation in the anaesthetised dog (Ulmer, 1969). Sciatic nerve stimulation is a non-specific input, albeit easy to deliver, and its relevance to muscular exercise is unclear. The method used in the present study produces muscular contractions using the normal route of excitation, and the sensory fibres activated are more likely to include only those involved in isometric exercise. Anaesthesia is known to depress sensitivity and cause a shift in the pulse interval-blood pressure relation of the baroreceptor-cardiodepressor reflex in man (Bristow *et al.*, 1969), and is likely to have modified the reflexes studied here. This may explain the variability of the reflex sensitivities reported here. There is no reason, however, to doubt that the present results give a qualitatively correct picture of the interaction of muscle reflexes with baroreflex mechanisms. It would be extremely difficult to devise an animal experiment upon the reflex part of the cardiovascular drive in isometric exercise in which anaesthesia is not required.

When normal human subjects perform sustained isometric handgrip contractions at 30% of their maximal voluntary effort, there is a shift of the pulse interval-blood pressure relation and reduction in sensitivity of the baroreceptor-cardiodepressor reflex (Cunningham *et al.*, 1972). There are more stimuli in operation there, however, than the muscular reflex studied here: in particular the cardiorespiratory drive from irradiation by the descending voluntary command signals (Goodwin *et al.*, 1972) would contribute to the response. Possibly the reduction in baroreflex sensitivity seen in isometrically exercising man is evoked by stimuli other than muscular reflex.

It has long been known that occlusion of the blood supply to an isometrically contracting muscle will cause the maintenance of a pressor response beyond the conclusion of the exercise for as long as the occlusion persists (Alam and Smirk, 1937). This is generally attributed to a reflex set up in the ischaemic muscle by the action of chemical factors on sensory nerve endings. Such a reflex is probably part, and perhaps the whole, of the muscular reflex element of the cardiovascular drive in exercise. Cunningham *et al.* (1972) have investigated baroreflex sensitivity in such periods of maintained elevated blood pressure during occlusion after exercise. They claim that baroreflex sensitivity returns only about half way from its depressed

exercise level towards its resting level at these times. This claim seems not to be borne out by their published data (their Table 1) where comparisons of occlusions before and after handgrip exercise were made. In 8 subjects, 4 showed a reduced baroreflex sensitivity, in 2 there was no change, and in 2 baroreflex sensitivity was increased. We are not persuaded that the evidence from conscious man or from the anaesthetised dog indicates that reflexes arising in exercising muscle reduce baroreceptor-cardiodepressor reflex sensitivity.

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REDUCTION IN INSPIRATORY ACTIVITY IN RESPONSE TO STERNAL VIBRATION

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Abstract. It has been shown previously that there is a reduction in tidal volume in response to longitudinal sternal vibration at 100 Hz. In the present study it was shown that the effect of such vibration is to reduce tidal volume (VT) and prolong inspiratory time (ti) in such a way that points from vibrated and non-vibrated breaths fall on the same VT:ti curve. This indicates that the normal mechanisms which terminate inspiration are unaffected by vibration. The effect of vibration is simply to reduce the rate at which inspiration proceeds. This was illustrated here when vibration reduced the rate of fall of intrapleural pressure during inspiration, and also reduced the instantaneous ventilation at any level of chemical drive. Electrophysiological recordings made here from phrenic motoneurones support these findings. It is concluded that sensory nerves in the chest wall, which can be excited by vibration, can inhibit inspiration.

Inspiratory time	Tidal volume
Intercostal afferents	Tracheal pressure
Muscle spindles	Vagus nerve
Respiratory loading	Vibration

Recently Gandevia and McCloskey (1976) reported that longitudinal sternal vibration at 100 Hz reflexly decreases the tidal volume, and that the receptors responsible lie within the chest wall. As this reflex response suggests a possible role for chest wall receptors in respiratory control, we have studied it further. We have asked whether the observed fall in tidal volume in response to vibration is due to the premature termination of an inspiration proceeding at a normal rate, or whether it is due to a decrease in the rate at which inspiration proceeds before being terminated by usual vagal or pneumotaxic mechanisms.

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In pursuing this question we compared pairs of non-vibrated and vibrated breaths for possible changes in a number of variables; these included tidal volume, inspiratory time, instantaneous ventilation, and intrapleural and intratracheal pressures. Tidal volume was plotted against inspiratory time during rebreathing (*cf.* von Euler *et al.*, 1970; Clark and von Euler, 1972) for individual breaths during which vibration was or was not applied. The instantaneous level of ventilation was compared for such breaths at different times during rebreathing, and the rate of fall and overall decrease in intrapleural and intratracheal pressures were recorded during inspiratory efforts, in the presence and absence of vibration. Electrophysiological recordings of phrenic motor activity were also made.

Part of this work has appeared in brief form (Colebatch *et al.*, 1976).

Methods

Experiments were performed on twenty-five adult male and female cats (2–5 kg), anaesthetised with either intraperitoneal pentobarbitone (Nembutal: Abbott: 40 mg/kg, 15 cats) or with intravenous chloralose (α-chloralose: British Drug Houses: 80 mg/kg, after induction with ether, 10 cats). Supplementary anaesthetic was given as required through a nylon cannula in the femoral vein. In all experiments the trachea was cannulated low in the neck. Rectal temperature was maintained between 37 and 39 °C. Flow was recorded as a pressure drop (Grass PT-5A transducer) across a low resistance pneumotachometer which added less than 5 ml to the total dead space. Tidal volume was obtained by electronic integration of the flow signal (Grass 7P10 integrator). In all but the electrophysiological studies (see below) these variables were recorded on a four-channel Grass polygraph pen recorder.

The vibrator used was of the same type as described by Gandevia and McCloskey (1976) (Vibratory massager: Pifco Ltd: 100 Hz). Vibration was transmitted through a brass rod fitted into a 'crocodile' clip clamped to the top of the sternum. Once the vibrator was suitably connected it was left undisturbed and vibration was initiated by means of a remote switch. The amplitude of the resultant vibration was nearly 1 mm in the midline, about 0.5 mm in the midaxillary line and palpably less along the animal's thoracic vertebrae.

REBREATHING EXPERIMENTS

Nine cats were used. Flow, tidal volume and intrapleural pressure were recorded, the latter sometimes indirectly by means of a cannula advanced down the external jugular vein so that its tip lay in or near the right atrium. Ventilation, when calculated, was obtained from the record of tidal volume and breath duration.

Each animal was artificially hyperventilated to apnoea and was then allowed to rebreathe from an anaesthetic bag which initially contained 1.5 l of oxygen. The

total period of rebreathing varied from 11 to 30 minutes. Every 5–10 breaths vibration was applied for the duration of one breath, commencing just prior to inspiration. Data for breaths in the presence and absence of vibration were obtained during the same rebreathing period: the breaths taken as controls (no vibration) were 2 breaths before those throughout which vibration was applied. In some animals the procedure was repeated after division of the vago-sympathetic trunks in the neck.

INTRAPLEURAL AND INTRATRACHEAL PRESSURES

Eight cats were used. Intrapleural pressure was measured directly through a cannula whose tip lay within the intrapleural space. The maximum fall in intrapleural pressure during inspiration was also obtained directly from the pen recording.

Intratracheal pressure was studied during tracheal occlusions applied at the end of expiration. We observed both the rate of development of intratracheal pressure and the maximal negative pressure developed. Vibration was applied throughout one or several attempts to breathe against the tracheal occlusion. Comparisons were made with control values obtained before and after the vibration series.

LOADING EXPERIMENTS

In three cats we compared the effect of sternal vibration during external resistive loading with the effect of vibration during unloaded breathing. Air flow and tidal volume were recorded.

ELECTROPHYSIOLOGICAL STUDIES

Eight cats anaesthetised with α-chloralose, were used. After a paramedian incision, the right phrenic nerve was cut low in the neck and a paraffin pool was made. The central end of the nerve was dissected from underlying tissue for about 2 cm and placed on a rigid, earthed, stainless-steel plate with a blackened upper surface. To record spike activity, filaments were laid across stainless-steel electrodes and amplified with a Tektronix 122 preamplifier. This signal was then displayed on an oscilloscope. Dissection continued until only one or two active fibres were in the filament being recorded. Records of spike activity were made on an ultraviolet recorder (Y.E.W. Type 2901) with galvanometers giving a flat frequency response to 1000 Hz, together with a flow signal obtained from sampling intratracheal pressure.

Results

REBREATHING EXPERIMENTS

Values for tidal volume and inspiratory time, expiratory time, and total breath time were obtained throughout periods in which cats rebreathed from apnoea from a

1.5 l bag of oxygen. Vibration was applied throughout one respiratory cycle every 5–10 breaths during the rebreathing period.

In eight of nine cats tested, points obtained during vibrated and non-vibrated breaths fell on the same curve relating tidal volume to inspiratory time during oxygen rebreathing. Vibration produced a shift down the control curve to a position with a lower tidal volume and greater inspiratory time (*i.e.* a decrease in ventilation – see below) than the preceding non-vibrated breath (fig. 1). A shift away from this control

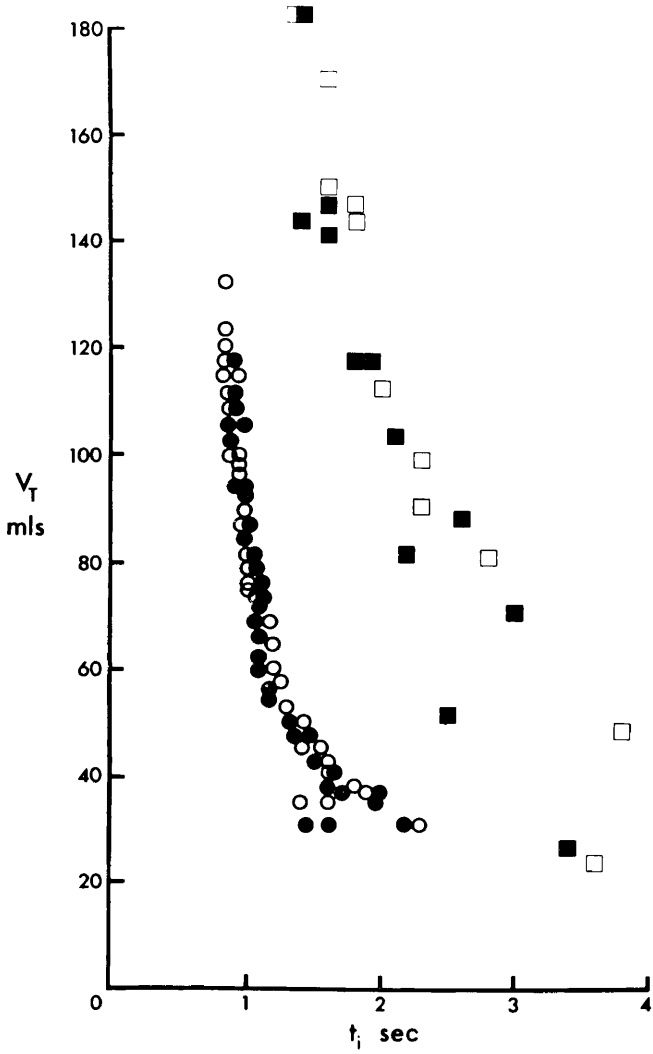

Fig. 1. Cat, anaesthetised with pentobarbitone. Points plotted from the tidal volume and inspiratory times for a series of breaths during two rebreathing trials. Circles indicate data obtained with intact vagi and squares show breaths from the trials after vagotomy. Points for vibrated breaths (filled symbols) fell on the same curve relating tidal volume to inspiratory time as those for non-vibrated breaths of the same rebreathing run (open symbols). Vibration caused a shift down the curve, *i.e.* a diminished rate of increase of inspiratory activity. Vagotomy increased the scatter of both groups of breaths but the same response to vibration occurred.

relation would have been expected if vibration acted to alter the normal mechanisms which terminate tidal volume at a given rate of increase of inspiratory activity (see Discussion). A shift (to the left of the control relation) was observed in one cat. In the 5 cats in which rebreathing tests were performed after vagotomy, vibration again caused no consistent shift from the control relation, although there was considerably more scatter in both the post-vagotomy control and vibrated points. A consistent finding was that both inspiratory time and tidal volume altered during the increasing chemical drive after vagotomy (*cf.* Widdicombe and Winning, 1974).

In all cats inspiratory time was plotted against expiratory duration for both control and vibrated breaths. In all but one animal the points from vibrated breaths again were not consistently separated from the control group. In one cat the vibrated breaths had longer expiratory times than the control breaths, but there was no shift from the control curve when tidal volume was plotted against inspiratory time.

The drop in ventilation which occurs with vibration was represented by plotting breath-by-breath ventilation (tidal volume divided by breath time) against duration of rebreathing. When points from comparable non-vibrated and vibrated breaths were plotted in this way the points from the vibrated breaths lay below those from the non-vibrated ones (fig. 2). The level of chemical drive to breathing would have been very nearly the same for each of the pair of breaths compared.

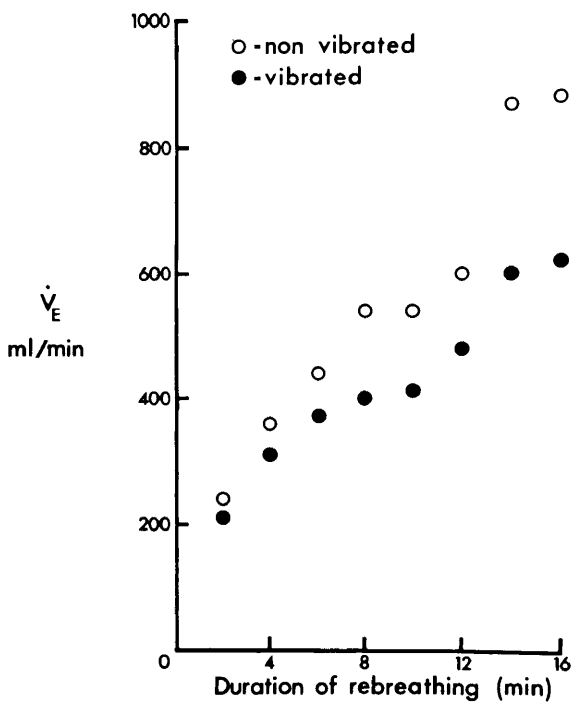

Fig. 2. Cat, anaesthetised with pentobarbitone. Data obtained from non vibrated (open circles) and subsequent vibrated breaths (closed circles) at different times during a single period of rebreathing. Each application of vibration results in a lower level of ventilation; this occurs throughout the period of changing respiratory stimulation (see text).

INTRACHEAL AND INTRAPLEURAL PRESSURES

Observations were made of the effects of sternal vibration on the rate and magnitude of the fall in intratracheal pressure during inspiratory efforts against an occluded trachea, and of the rate and magnitude of the fall of intrapleural pressure during normal inspirations.

The trachea was occluded at the end of expiration, and observations were made of a series of inspiratory efforts. Vibration was applied during single efforts or was sustained throughout five efforts. Vibration consistently decreased the maximum fall and also the rate of fall of intratracheal pressure. This also occurred when corresponding inspiratory efforts were compared during prolonged vibration: in successive efforts during vibration, the falls in intratracheal pressure were always less than those obtained in the control manoeuvre (fig. 3). We commonly observed that the durations of inspiratory efforts made against a closed airway during vibration were prolonged when compared with efforts made in the absence of vibration. An example of this can be seen in the lower 2 panels of fig. 3.

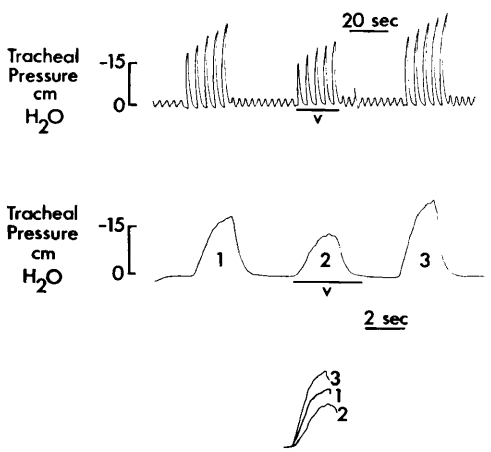

Fig. 3. Cat, anaesthetised with chloralose. Records of intratracheal pressure (inspiration upwards). The upper trace shows three series of five inspiratory efforts against an occlusion of the trachea imposed at the normal end-expiratory point. The intervening, smaller, deflexions were obtained during unoccluded breathing. The first and third series with tracheal occlusion are controls and show increasing negativity with each successive attempt to breathe. The central group, during which sternal vibration was applied for the period of the marker bar, also shows increasing deflexions on successive attempts but each is less in magnitude than that developed during the corresponding control effort. The middle tracing shows three inspiratory efforts against an occluded trachea recorded at a faster paper speed; on this occasion vibration was applied for only the second of the three attempts. Again the maximum intratracheal pressure developed is less with concurrent vibration. The lowest part of the figure is a superimposition of the initial increase in intracheal pressure for the series immediately above, the numbers identifying the corresponding effort. The rate of change of tracheal pressure is less during vibration than the rate for the preceding or succeeding, non-vibrated, breaths. The duration of the inspiratory effort is greater during vibration than in its absence (see text).

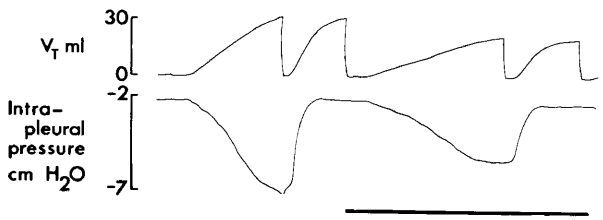

Fig. 4. Cat, anaesthetised with pentobarbitone. The upper record shows integrated airflow, reset at periods of zero flow. Thus the first two deflexions represent inspiratory and expiratory volume, respectively. The lower part of the figure shows intrapleural pressure measured from a cannula within the intrapleural space and recorded simultaneously with the upper trace. Vibration was applied for the period of the horizontal bar; it caused the usual reduction in tidal volume: there was a reduced maximum fall and reduced rate of fall of intrapleural pressure during vibration.

The rate of fall and maximum fall of intrapleural pressure measured during normal breathing were similarly reduced by vibration (fig. 4). The end-expiratory intrapleural pressure was not changed by vibration.

LOADING EXPERIMENTS

The object of these studies was to investigate whether the effectiveness of vibration was altered during imposition of external resistive loads. During eupnoea a resistive load of a size sufficient to drop the tidal volume about 20 % was obtained by progressively occluding with a screw clamp the rubber tube through which the cat was inspiring and expiring.

Vibration was applied during eupnoea and the resultant fall in tidal volume noted (usually about 20 %). The resistive load, previously chosen, was then added and the cat was made to rebreathe from a 0.5-l bag of oxygen. The increasing ventilatory drive caused a progressive recovery of the tidal volume. When the tidal volume equalled that of the initial (unvibrated) breath, vibration was applied in the subsequent breath and effect noted (fig. 5). The reduction in tidal volume caused by vibra-

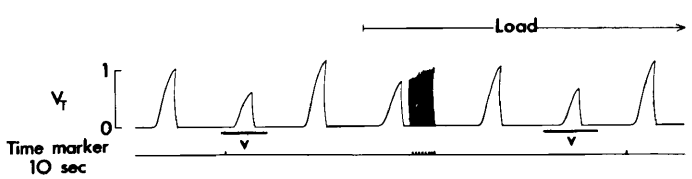

Fig. 5. Cat, anaesthetised with chloralose. Record shows tidal volume (inspiratory phase only) obtained during a period of rebreathing oxygen from an anaesthetic bag. Note slower paper speed for the middle part of the record. The initial application of vibration (marked with horizontal bar) results in a diminished tidal volume. A resistive load chosen to produce a reduction in tidal volume of a similar magnitude is then added and maintained. As the animal rebreathes from the bag, a progressive increase in tidal volume occurs until a tidal volume equal to that of the control unloaded breath is attained. Vibration is again applied and produces a reduction in tidal volume of the same magnitude as obtained during the first application. During loading the full effectiveness of vibration is preserved (see text).

tion was never demonstrably different from that which was obtained initially without load.

ELECTROPHYSIOLOGY

Electrical recordings from the phrenic nerve were difficult to obtain due to persistent electrical and mechanical interference produced by sternal vibration. Initially, we compared the total numbers of phrenic motoneuronal spikes discharged during control and vibrated breaths. We found this method of analysis unrewarding. A particular problem was the prolongation of inspiratory time which occurs with vibration, and which may have offset any decrease in discharge frequency or delay in the recruitment of the discharging fibre.

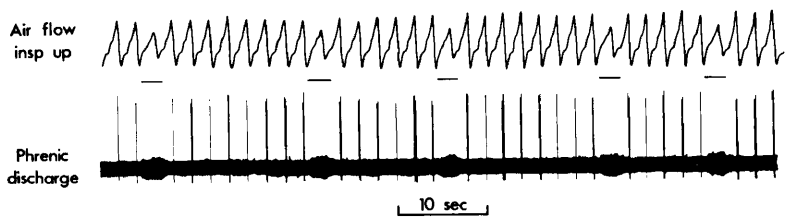

Fig. 6. Cat, anaesthetised with chloralose. Air flow is shown in the upper trace and the simultaneous activity in one phrenic nerve filament is recorded in the lower tracing. Sternal vibration was applied during the periods marked with the horizontal bars. This phrenic motoneurone was not recruited during vibrated breaths.

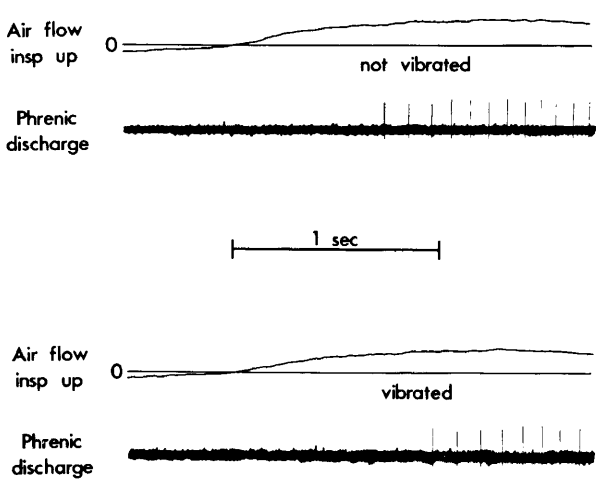

Fig. 7. Cat, anaesthetised with chloralose. The records consist of pairs of traces, the upper in each case represents air flow and the lower the activity of one phrenic motoneurone. Sternal vibration was applied throughout the period of the lower two traces. The records are aligned so that the commencements of inspiratory air flow (indicated by the flow record crossing the zero level) are placed one vertically above the other. The application of vibration caused the recruitment of this motoneurone to be delayed relative to the non-vibrated breath.

Subsequently a fibre was found which was recruited late in the course of normal inspiration, but consistently failed to be recruited during vibration (fig. 6). Such clear-cut inhibition was not found again. However, this finding led us to concentrate on the possibility that vibration could delay the recruitment of phrenic motoneurones. The record of air flow was used to indicate the beginning of inspiration. Thus the time between commencement of flow and the first phrenic spike indicated the delay for recruitment of the particular phrenic motoneurone. In two fibres examined in this way, vibration consistently prolonged the time to recruitment (fig. 7). Both of these motoneurones were normally recruited late in inspiration. We were unable to detect any change in the other fibres, which generally had only short delays to recruitment.

OTHER

Vibration is only effective when presented during inspiration (Gandevia and McCloskey, 1976). This may be because expiration is normally passive. We examined active expiration by occluding the trachea at the end of inspiration: active expiratory efforts were recognised by the increase in intratracheal pressure over that recorded for passive recoil when first occluded. Although vibration consistently decreased the magnitude and rate of fall of intratracheal pressure during inspiration, we were unable to demonstrate any change, either inhibitory or facilitatory, during periods of (active) expiration.

Discussion

Our results indicate that the vibration causes a single consistent alteration in the nature of respiratory activity: it decreases the level of respiratory activity and does not 'prematurely halt' the breath. Evidence for this conclusion exists in the preservation of the control V_T–ti curve, and also the diminished rate of fall of intrapleural and intratracheal pressures during vibration. Moreover, we have shown that vibration decreases the level of ventilation at a given level of chemical respiratory stimulation, as shown by the fall in ventilation in paired non-vibrated and vibrated breaths during rebreathing.

Since the experiments of Larrabee and Knowlton (1946) it has been generally accepted that vagal afferent mechanisms act simply to terminate inspiratory activity and do not otherwise alter the proceeding activity. Thus it has been believed that respiratory control is provided by two systems, summarized by Davies *et al.* (1976): "One, central, governs the rate of increase of inspiratory activity. The other, from the lung reflexes studied, modifies only the duration of the activity." Our results indicate that other mechanoreceptors, probably lying in the chest wall, may act to adjust the level of respiratory outflow during an inspiration. Such mechanoreceptors, therefore, act in a way which is quite unlike the vagal afferent mechanisms.

We have considered the possibility that the responses observed were due simply to a change in the mechanics of the lungs and chest wall. The shift of points from vibrated breaths down the control VT–ti relation indicates only a decreased final rate of lung expansion and is not itself evidence of a diminished central outflow. It has been shown, however, that there is no shift in end-expiratory intrapleural pressure with sustained vibration (Gandevia and McCloskey, 1976), a result confirmed in the present studies. This suggests that any reflex change in the mechanics of the lungs or chest wall would have to be phasic in nature to explain the effects of vibration. In experiments of the type illustrated in fig. 4, we measured intrapleural pressure and tidal volume simultaneously and so were able to calculate the dynamic compliance of the lungs: there was no consistent change in this with vibration. We sought direct electrophysiological evidence to determine the actual neural contribution, and the results reported here from single phrenic units show that part at least of the decrease in the rate of inflation of the lungs is the result of a fall in inspiratory efferent discharge. A similar conclusion can be drawn from the observations of Gandevia and McCloskey (1976) that the reduction of tidal volume which occurs in response to vibration is paralleled by a reduction in the development of alae nasi tension.

The shape of the VT–ti relation may explain why Gandevia and McCloskey (1976) reported that reductions in respiratory rate in response to vibration were slight and elusive. In their studies vibration was applied only during eupnoea. If the values of tidal volume and inspiratory time for normal breathing in their animals fell on the steep part of the VT–ti relation only small increases in inspiratory time would be expected in response to vibration. A large fall in the rate of increase of inspiratory activity (a shift down the curve) for such a breath would cause a marked drop in tidal volume but little prolongation of inspiratory time.

Gandevia and McCloskey (1976) presented evidence for a thoracic, probably chest wall, location for the receptors responsible for the reflex changes seen in response to vibration. They further suggested that these receptors could be the intercostal muscle spindles. It has been shown that small amplitude vibration differentially excites primary spindle afferents, particularly if the muscle is relaxed (Brown *et al.*, 1967). It might be argued that the amplitude employed here (1 mm) was too great to ensure any selectivity in the muscle receptors excited. However, the effective amplitude of vibration acting on any receptors lying within intercostal muscles would have been only a small fraction of the sternal displacement, since adjacent ribs would have moved nearly in phase. If secondary spindle afferents had been excited to a significant degree, then one could predict from the observations of Remmers and Marttila (1975) that there would be a shift off the control VT–ti curve. These workers showed that electrical stimulation of external intercostal nerve afferents at Group II threshold (presumably arising from muscle spindles) cut short normal phrenic discharge. Such premature termination was not observed in our experiments except in one cat, in which vibrated breaths fell on a displaced VT–ti relation. Group II muscle spindle afferents may have been significantly excited in this animal.

Whatever receptors are responsible for the effect of vibration in our studies, the

magnitude of the reflex reflects the increase in discharge of these receptors during periods of vibration. For primary spindle afferents this increase is from their normal discharge rate to 100 Hz, the rate to which they are probably 'driven' by vibration (*e.g.* Matthews, 1972). A one-to-one discharge has been demonstrated for primary spindle afferents of the de-efferented soleus muscle of the cat with amplitudes of 40 μ (Brown *et al.*, 1967). If increased primary spindle afferent activity caused the changes seen here, then the higher their discharge before vibration the smaller the reflex magnitude should be. Resistive loading would be predicted to result in higher discharge in spindle afferents from inspiratory muscles, due to the greater discrepancy between the degree of intrafusal and extrafusal muscle fibre contraction. An increase in discharge of primary afferents from external intercostal muscles occurs during tracheal occlusion (Corda *et al.*, 1964). Thus in the loading experiment the discharge rate of most inspiratory primary spindle afferents could be assumed to have been significantly higher for the loaded control breath, although its tidal volume was equal to that of the initial (unloaded) control breath. The application of vibration, however, resulted in the same magnitude of fall in tidal volume. The diminution in size of the reflex, which was predicted if inspiratory primary spindle afferents were responsible for it, was not seen. This result suggests that if the primary spindle afferents were responsible for the reflex they are unlikely to have come from the loaded inspiratory muscles.

Gandevia and McCloskey (1976) speculated that vibration might mimic the discharge which results from respiratory loading or, alternatively, might prematurely signal the attainment of a tidal volume preset by the respiratory centres. Our studies do not support either of these possibilities. The lack of occlusion of the reflex under conditions of resistive loading shows that afferents excited by this manoeuvre are not responsible for the effect of vibration. Similarly vibration does not alter the normal determination of appropriate tidal volume. The nature of the reflex adjustment is more appropriate to afferent activity interpreted as an increased velocity of chest expansion. It is pertinent perhaps to recall that Gandevia and McCloskey (1976), who also vibrated the chests of 6 human volunteers, reported that two of their subjects felt that they had increased their rate and depth of breathing during vibration, whereas no such alteration actually happened. An augmented discharge in the primary spindle afferents of expiratory intercostal muscles, by indicating a faster rate of stretch of these muscles, might imply such a circumstance.

Acknowledgement

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Reflex effects on circulation and respiration from contracting skeletal muscle

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MITCHELL, JERE H., WILLIAM C. REARDON, AND D. IAN MCCLOSKEY. *Reflex effects on circulation and respiration from contracting skeletal muscle.* Am. J. Physiol. 233(3): H374-H378, 1977 or Am. J. Physiol.: Heart Circ. Physiol. 2(3): H374-H378, 1977. – Isometric exercise induced by ventral root stimulation in the anesthetized cat caused heart rate (HR) to increase from 199 ± 6 beats/min to 206 ± 6 ($P < 0.001$); mean arterial pressure (MAP) from 99 ± 5.3 mmHg to 112 ± 5.8 ($P < 0.001$); and left ventricular dp/d*t* at developed pressure of 25 mmHg from 3,960 ± 204 mmHg/s to 4,380 ± 220 ($P < 0.001$), while end-diastolic pressure remained unchanged. Respiratory volume (RV) increased from 755 ± 71 ml/min to 1,160 ± 123 ($P < 0.001$). These changes were abolished by cutting the dorsal roots receiving afferents from the exercising muscle. Beta-adrenergic blockade with propranolol (1 mg/kg) abolished the changes in heart rate and contractile state; however, changes in MAP and RV still occurred. Induced isometric exercise causes a small rise in HR with a more marked increase in MAP, the contractile state of the left ventricle and RV. In this preparation the cardiovascular and respiratory changes reflexly originate from contracting skeletal muscle as proven by section of the corresponding dorsal roots, and the cardiovascular changes are mediated in part by activation of beta-adrenergic receptors in the heart.

isometric exercise; heart-muscle reflex; cardiovascular response

IN MAN voluntary isometric exercise is accompanied by an increase in arterial blood pressure, heart rate, cardiac output, and pulmonary ventilation (1, 2, 9, 22). Further, it has been shown in man that part of this response is due to activation of a skeletal muscle heart reflex (7, 10, 15, 17).

Isometric exercise in the hindlimb of the anesthetized animal induced by stimulation of ventral roots also causes an increase in blood pressure accompanied by small increases in heart rate and ventilation (3, 4, 12). Also it has been shown that electrical stimulation of small myelinated and unmyelinated afferents from exercising muscle causes similar changes (13) and that the exercise response is not present when these same fibers are blocked (12).

The purpose of the present study was to further characterize the cardiovascular and respiratory responses that occur during electrically induced isometric exercise in the cat hind limb and to investigate the controlling mechanisms. A preliminary report of this work has been published (16).

METHODS

Experiments were performed on 20 cats (2.6–4.0 kg) which were anesthetized with intraperitoneal injections of sodium pentobarbital (35 mg/kg). The trachea was cannulated. Arterial pressure was measured via a cannula in the right femoral artery connected to a pressure transducer (Statham P23Db), and left ventricular pressure by a high-fidelity pressure transducer (Millar PC-350) passed into the left ventricle via the left carotid artery. An electrocardiogram was used with a cardiotachometer amplifier to determine heart rate. Respiratory flow was measured by a pneumotachometer attached to the tracheal cannula and ventilatory volume calculated by an integrating preamplifier. The triceps surae muscle was prepared for tension recording by detaching its tendon from the calcaneum and securing it to a Statham tension transducer (model UC2). All signals were recorded simultaneously on an 8-channel Ampex tape recorder and on an eight-channel Elema-Schonander Minograf.

The animals were fixed on the experimental table in a prone position by pins through the hindlimb joints. A laminectomy was performed to expose spinal roots L_4 through S_1. A paraffin pool warmed to 37°C and bubbled with 95% O_2 and 5% CO_2 was made over the spinal cord, and the spinal cord exposed by an incision through the dura.

Spinal roots L_5, L_6, and S_2 downward were cut. The ventral roots L_7 and S_1 were cut close to their exit from the spinal cord and the peripheral end was placed over a pair of Ag-AgCl electrodes. Stimulation of the ventral roots at 40 Hz with square-wave impulses of 0.1-ms duration delivered by an isolated Grass S4 stimulator with voltages of from 0.1 to 1.0 V was used to elicit contractions of the hindlimb muscles. Periods of induced isometric exercise of 15–30 s duration were given. The exposed spinal cord was frequently washed with warmed Ringer solution. Rectal temperature was maintained at 36–38°C throughout the experiment.

A high-fidelity tracing of left ventricular pressure was recorded on analog magnetic tape. This was later played into a digital computer (PDP-12), sampled at 1-

ms intervals, and several cycles averaged. The rate of pressure development and the developed pressure (total left ventricular pressure minus left ventricular end-diastolic pressure) was calculated at 1-ms intervals. Left ventricular end-diastolic pressure was measured at the peak of the R wave of the electrocardiogram. These values were plotted with rate of pressure development of the left ventricle on the x-axis and developed pressure on the y-axis during rest and during induced isometric exercise. Also the rate of development of left ventricular pressure at a developed pressure of 25 mmHg was determined during rest and exercise.

In 20 cats studies were made during rest and during isometric exercise. Similar studies were performed in two of these cats before and after section of the corresponding dorsal roots. In six of these cats, studies were performed before and after beta-adrenergic receptor blockade with propranolol (1 mg/kg). The block was checked by an injection of isoproterenol.

RESULTS

Induced isometric exercise in one hindlimb caused a small increase in heart rate and marked increases in arterial blood pressure, respiratory volume, and the contractile state of the left ventricle. A typical experiment is shown in Fig. 1 with the mean results from 20 animals given in Table 1. In Fig. 1 isometric exercise was induced by stimulation of the ventral roots during the 15 s identified by the time marks. Heart rate, aortic pressure, left ventricular systolic pressure, maximal rate of left ventricular pressure development, respiratory flow, and respiratory volume all increased. After the cessation of exercise all the parameters returned to control values.

The effect of induced isometric exercise on the relationship between left ventricular rate of pressure development and the developed pressure (total left ventricular pressure minus left ventricular end-diastolic pressure) in one experiment is shown in Fig. 2. During induced exercise the rate of pressure development was higher at any given developed pressure than it was during the resting study. In order to look at data from all 20 animals, the rate of pressure development at a developed pressure of 25 mmHg was used.

The mean results from the 20 animals are shown in Table 1. There was no change in left ventricular end-diastolic pressure during induced static exercise. Mean aortic pressure increased 13 mmHg, heart rate increased 7 beats/min, rate of left ventricular pressure

TABLE 1. *Results from experiments on 20 cats*

	LVEDP, mmHg	MAP, mmHg	HR, beats/min	dp/dt at P_D = 25 mmHg, mmHg/s	RV, ml/min
Control	1 ± 0.4	99 ± 5.3	199 ± 6	3960 ± 204	755 ± 71
Exercise	1 ± 0.3	112 ± 5.8	206 ± 6	4380 ± 220	1160 ± 123
P	NS	<0.001	<0.001	<0.001	<0.001

Values are means ± SE. LVEDP = left ventricular end-diastolic pressure; MAP = mean aortic pressure; HR = heart rate; dp/dt at P_D = 25 mmHg = rate of left ventricular pressure development at developed pressure of 25 mmHg; and RV = respiratory volume.

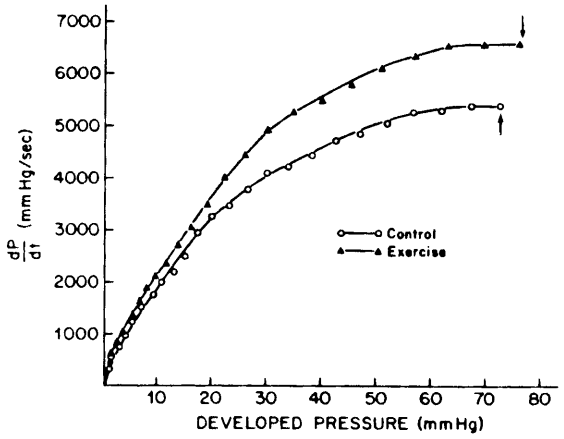

FIG. 2. Relation of rate of pressure development to developed pressure of left ventricle at rest and during induced isometric exercise.

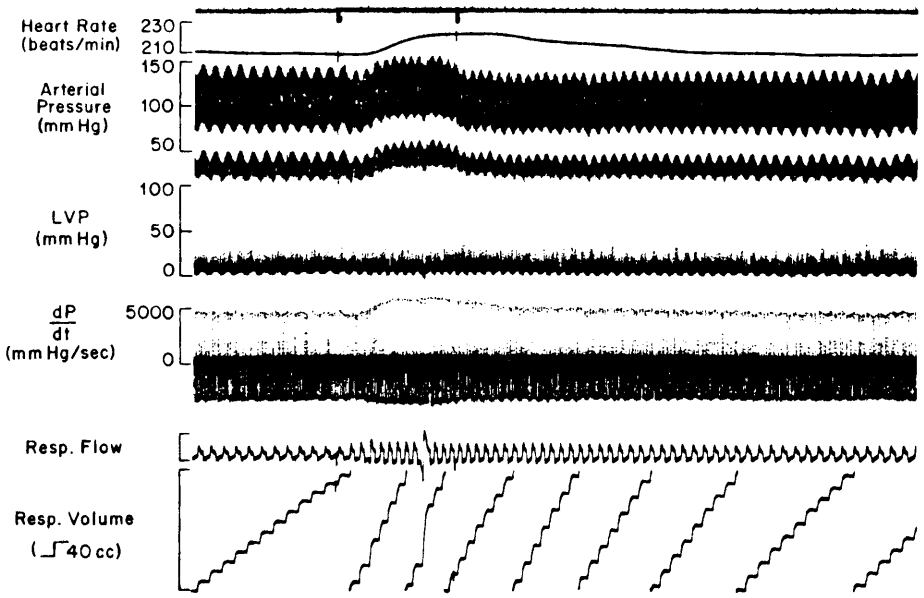

FIG. 1. Response to induced isometric exercise. LVP, left ventricular pressure; dp/dt, rate of left ventricular pressure development. Time marks = 1 s. Induced exercise between bars.

development at 25 mmHg developed pressure increased 420 mmHg/s, and respiratory volume increased 405 ml/min. All of the changes were significant at a P value <0.001.

All these changes were abolished in two animals by section of the dorsal roots receiving afferents from the exercising muscle. The results in these two animals are shown in Table 2.

Beta-adrenergic receptor blockade with propranolol abolished the reflex changes in heart rate and the contractile state of the left ventricle during induced isometric exercise. However, the changes in arterial blood pressure and respiratory volume still occurred. A typical experiment after beta-adrenergic blockade is shown in Fig. 3. During induced static exercise the heart rate and the maximal rate of left ventricular pressure development remained constant while aortic pressure, left ventricular systolic pressure, respiratory flow, and respiratory volume all increased. After the cessation of exercise all the parameters returned to control values.

The effect of induced isometric exercise on the relationship between left ventricular rate of pressure development and the developed pressure before and after beta-adrenergic receptor blockade in one experiment is shown in Fig. 4. As shown previously, during the control study the rate of pressure development was higher at any given developed pressure during exercise than during the resting study. After beta-adrenergic receptor blockade there was no change in this relationship from rest to exercise.

The mean results for the six animals studied before and after beta-adrenergic receptor blockade are shown in Table 3. Before beta-adrenergic receptor blockade,

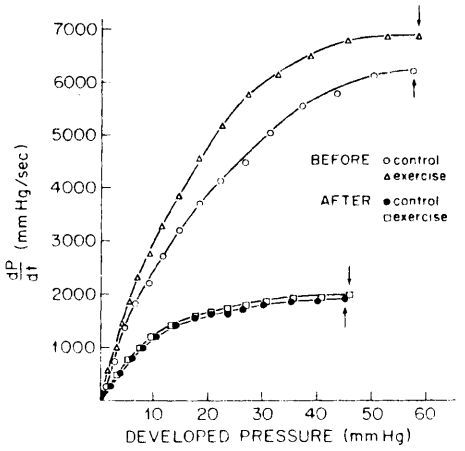

FIG. 4. Relation of rate of pressure development to developed pressure of left ventricle at rest and during induced isometric exercise before and after propranolol.

TABLE 2. *Values from experiments on two cats before and after section of dorsal roots*

	Dorsal Roots Intact					Dorsal Roots Sectioned				
	LVEDP, mmHg	MAP, mmHg	HR, beats/min	dp/dt at P_D = 25 mmHg, mmHg/s	RV, ml/min	LVEDP, mmHg	MAP, mmHg	HR, beats/min	dp/dt at P_D = 25 mmHg, mmHg/s	RV, ml/min
1										
Control	6	107	186	4,198	420	8	102	178	3,340	400
Exercise	6	116	190	4,616	820	7	102	178	3,290	400
2										
Control	1	131	207	3,904	1,280	0	124	206	5,100	960
Exercise	1	138	210	4,593	1,880	0	124	205	5,075	960

Symbols as in table 1.

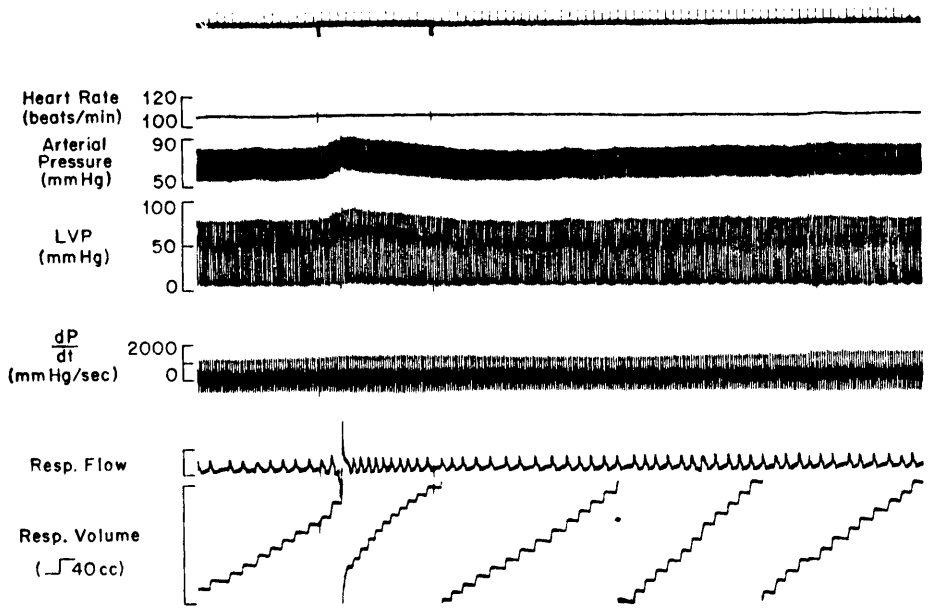

FIG. 3. Response to induced isometric exercise after propranolol. Symbols as in Fig. 1.

TABLE 3. *Results from experiments on six cats before and after propranolol*

	Before Propranolol					After Propranolol				
	LVEDP, mmHg	MAP, mmHg	HR, beats/min	dp/d*t* at P_{LV} 25 mmHg, mmHg/s	RV, ml/min	LVEDP mmHg	MAP, mmHg	HR, beats/min	dp/d*t* at P_{LV} 25, mmHg, mmHg/s	RV, ml/min
Control	1 ± 0.3	99 ± 7.6	181 ± 13	4,167 ± 522	787 ± 132	5 ± 3.0	74 ± 6.1	117 ± 6	1,737 ± 328	720 ± 117
Exercise	1 ± 0.3	113 ± 8.8	187 ± 13	4,545 ± 561	1,350 ± 300	5 ± 3.0	81 ± 5.0	118 ± 6	1,815 ± 360	1,000 ± 161
P	NS	< 0.0125	< 0.01	< 0.01	< 0.01	NS	< 0.01	NS	NS	< 0.01

Values are means ± SE. Symbols as in Table 1.

the results were similar to those shown in Table 1. There was no change in left ventricular end-diastolic pressure while mean aortic pressure, heart rate, rate of left ventricular pressure development at 25 mmHg developed pressure, and respiratory volume all increased ($P < 0.01$). After beta-adrenergic receptor blockade, there was no change in left ventricular end-diastolic pressure, heart rate, or rate of left ventricular pressure development at 25 mmHg developed pressure. However, mean arterial pressure and respiratory volume still increased ($P < 0.01$).

DISCUSSION

The reflex cardiovascular and respiratory responses including the increase in heart rate, blood pressure, and respiratory volume seen during induced isometric exercise in the anesthetized animal are similar to those of previous investigations (3, 4, 12). In addition, however, the contractile state of the left ventricle has been shown to increase in response to isometric exercise induced by ventral root stimulation.

Fisher and Nutter (4) have found similar cardiovascular changes in anesthetized dogs during ventral root stimulation. Also they demonstrated an increase in a left ventricular contractility index (dp/d*t*/common peak developed isometric pressure) during simulated exercise. Studies in normal man have also indicated an increase in contractility of the left ventricle during voluntary isometric exercise (6, 18). This has been shown by analysis of ventricular function curves and by other indices of myocardial contractility. Studies of plasma catecholamines during sustained isometric exertion suggest that the responses are due to a powerful activation of the adrenergic nervous system (8).

In the present study there was a marked increase in the maximal rate of pressure development of the left ventricle during induced isometric exercise. However, it has been shown that several parameters can alter this measurement (14, 19, 20). These include fiber length or end-diastolic volume, heart rate, and arterial blood pressure as well as a change in the contractile state of the left ventricle. This becomes important since all of these parameters may change during isometric exercise.

The magnitude of change of heart rate seen in this study was small, on the order of 10 beats/min or less. It has been shown that dp/d*t* changed significantly only after changes in heart rate of 30–40 beats/min (14). Heart rate, therefore, probably does not contribute significantly to changes in maximal rate of pressure development of the left ventricle in this study.

It must also be noted that left ventricular end-diastolic pressure did not change significantly from control conditions to the periods of isometric exercise. Therefore, a change in the initial fiber length may be excluded in this experiment as contributing significantly to a change in the maximal rate of pressure development of the left ventricle.

Techniques have been described to correct left ventricular rate of pressure development for changes occurring in aortic pressure by correlating the rate of pressure development and the developed pressure (total left ventricular pressure minus left ventricular end-diastolic pressure) (5, 11). This method of evaluating changes in the contractile state is relatively independent of changes in arterial blood pressure and in left ventricular end-diastolic volume. A greater rate of development of pressure at any developed pressure represents an increase in the contractile state and a smaller rate of development at any pressure represents a decrease in the contractile state of the left ventricle. Using this method the present study has shown that induced isometric exercise in cats causes an increase in the contractile state of the left ventricle.

It has been shown that the changes in arterial blood pressure, heart rate and respiratory volume that occur during induced isometric exercise are abolished after sectioning the corresponding dorsal roots (3, 12). This finding was confirmed in the present study; and in addition, it was shown that the increase in contractility of the left ventricle was also absent after appropriate dorsal root sectioning. This demonstrates that the response is reflex in nature with the afferent limb located in the dorsal roots which receive fibers from the contracting skeletal muscle.

It has previously been demonstrated that small myelinated and unmyelinated afferent fibers from muscle mediate the changes in heart rate, blood pressure, and ventilation (12). Also activation of the high threshold afferents from skeletal muscle causes an increase in heart rate and an increase in the contractile state of the left ventricle (13). Therefore it seems a reasonable assumption that these same fibers are the afferent limb from muscle mediating the changes in contractility of the left ventricle in response to isometric exercise. The activation of these afferent fibers during exercise probably depends on multiple factors both chemical and mechanical (21).

Further, it has been demonstrated in this study that beta-adrenergic blockade with propranolol abolishes the reflex increases of heart rate and contractile state of the left ventricle but does not alter the responses in arterial blood pressure and respiratory volume. This indicates

that the reflex induced cardiovascular effects seen in the anesthetized cat are mediated in part by the beta-adrenergic receptors in the heart.

In summary, induced isometric exercise in the anesthetized cat causes a small rise in heart rate with a more marked increase in arterial blood pressure, the contractile state of the left ventricle and respiratory volume. In this preparation the cardiovascular and respiratory changes reflexly originate from contracting skeletal muscle as proven by section of the corresponding dorsal roots, and the cardiovascular changes are mediated in part by activation of beta-adrenergic receptors in the heart.

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POSSIBLE ROLE OF MUSCLE RECEPTORS IN THE CARDIOVASCULAR RESPONSE TO EXERCISE

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The mechanisms that are responsible for bringing about the cardiovascular changes that occur during muscular exercise remain incompletely understood. It would seem that a neurogenic mechanism is responsible since the onset of the changes in heart rate, arterial pressure, and contractile state of the left ventricle is so rapid.

Over the years, two general theories of neurogenic control of the cardiovascular responses to exercise have evolved (FIGURE 1). An early suggestion that one or both of two distinct mechanisms might exist was published by Johansson in 1894.[1] One postulate holds that the cardiovascular responses are due to a direct action of central command in the motor cortex on the medullary cardiovascular center (central control); the other holds that the responses are reflexly elicited by afferent neural activity from receptors in the skeletal muscles or joints on the medullary cardiovascular center (peripheral control). Obviously, these two theories are not mutually exclusive.

The hypothesis that the cardiovascular responses during exercise are due to a direct action of higher motor centers on the cardiovascular center (central irradiation) was elaborated most clearly by Krogh and Lindhard.[2, 3] Asmussen, Christensen, and Nielsen [4] thought they had found support for this hypothesis when they showed that the cardiac output response during dynamic leg exercise was related to the intensity of the work, even when circulation to the legs was blocked and the oxygen consumption was halved. Ochwadt *et al.*[5] and Asmussen *et al.*[6] found that heart rate and blood pressure responses were greater at a given work load when muscular strength was reduced by partial curarization. Thus, the cardiovascular response was related to the greater motor command needed to achieve a given level of muscular work when the subject was weaker. This finding suggested that central irradiation was involved. Freyschuss demonstrated an increase in blood pressure and heart rate in subjects whose muscles were unable to respond to command signals to perform handgrips.[7] The muscular groups involved in handgripping were paralyzed by injection of succinylcholine into the brachial artery. Significant cardiovascular responses developed

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in response to intended isometric handgrips, although the changes were less than with handgrips in the absence of succinylcholine.

Goodwin, McCloskey, and Mitchell investigated the cardiovascular response of human subjects to isometric exercise in experiments where the central motor command required to achieve a given tension was varied.[8] High-frequency vibration of a muscle excites the primary afferent nerves of muscle spindles. If the primary afferents are activated in a contracting muscle, they reflexly cause an involuntary increase in motor activation of the muscle, so that less central command is required to maintain the same tension. On the other hand, if the spindle afferents are activated in the antagonists of a contracting muscle, they cause reflex inhibition of the contracting muscle, so that a greater central command is required and the subject perceives that the conscious effort has increased. When the same muscle tension was achieved with less central command during isometric exercise, the resultant hypertension and tachycardia decreased; and when the same tension was achieved with more central com-

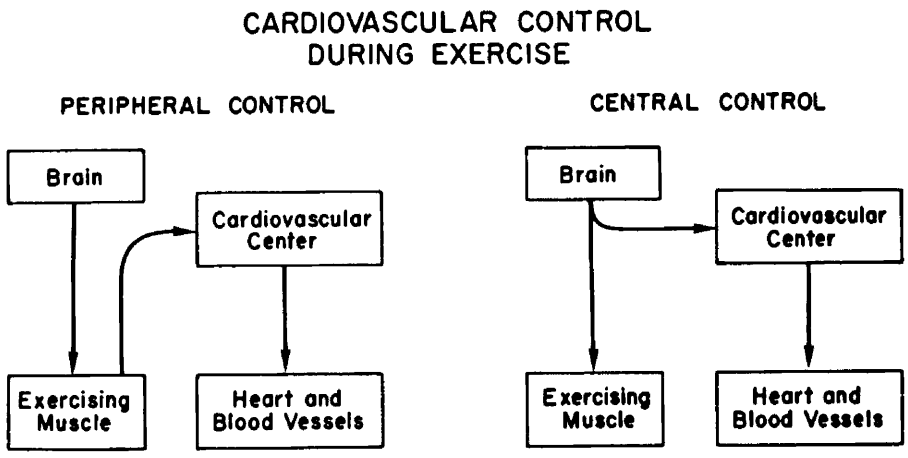

FIGURE 1. Diagrammatic representation of two postulated mechanisms for cardiovascular control during exercise.

mand, the resultant hypertension and tachycardia increased. It was concluded, therefore, that there is radiation of cardiovascular control centers by the descending central command during voluntary isometric contraction in man.

The hypothesis that the cardiovascular responses during exercise are due to a reflex originating in contracting skeletal muscle received its first major experimental support in the work of Alam and Smirk.[9, 10] They demonstrated an increase in blood pressure and in heart rate while the leg was performing predominantly isometric exercise during local circulatory occlusion. After exercise stopped the responses remained until the vascular occlusion was removed. They concluded that receptors located in the skeletal muscles were activated by some byproduct of the contraction and stimulated a reflex increase in blood pressure and heart rate. Similar conclusions were reached by Staunton, Taylor, and Donald.[11]

More recent work by Hollander and his co-workers has also suggested the existence of a muscle-heart reflex.[12, 13] In their studies in conscious man, exercise induced by direct electrical stimulation of the skeletal muscle caused an

increase in heart rate that was identical in its time course and magnitude to one obtained during voluntary contraction of the same muscle.

In this paper we will be concerned only with the peripheral control or skeletal-muscle–cardiovascular-reflex theory. For this concept to be viable, the neural pathway for the reflex must be present. Studies have shown that a pressor response can be elicited when the central cut end of a muscle nerve is stimulated.[14–16] To define this reflex further a study was performed in anesthetized dogs to elicit cardiovascular changes by stimulating the central cut end of a nerve from skeletal muscle.[16] The experimental preparation for this study is shown in FIGURE 2. Measurements were made of aortic pressure, left ventricular pressure, aortic flow, and heart rate. In some of the studies heart rate, aortic

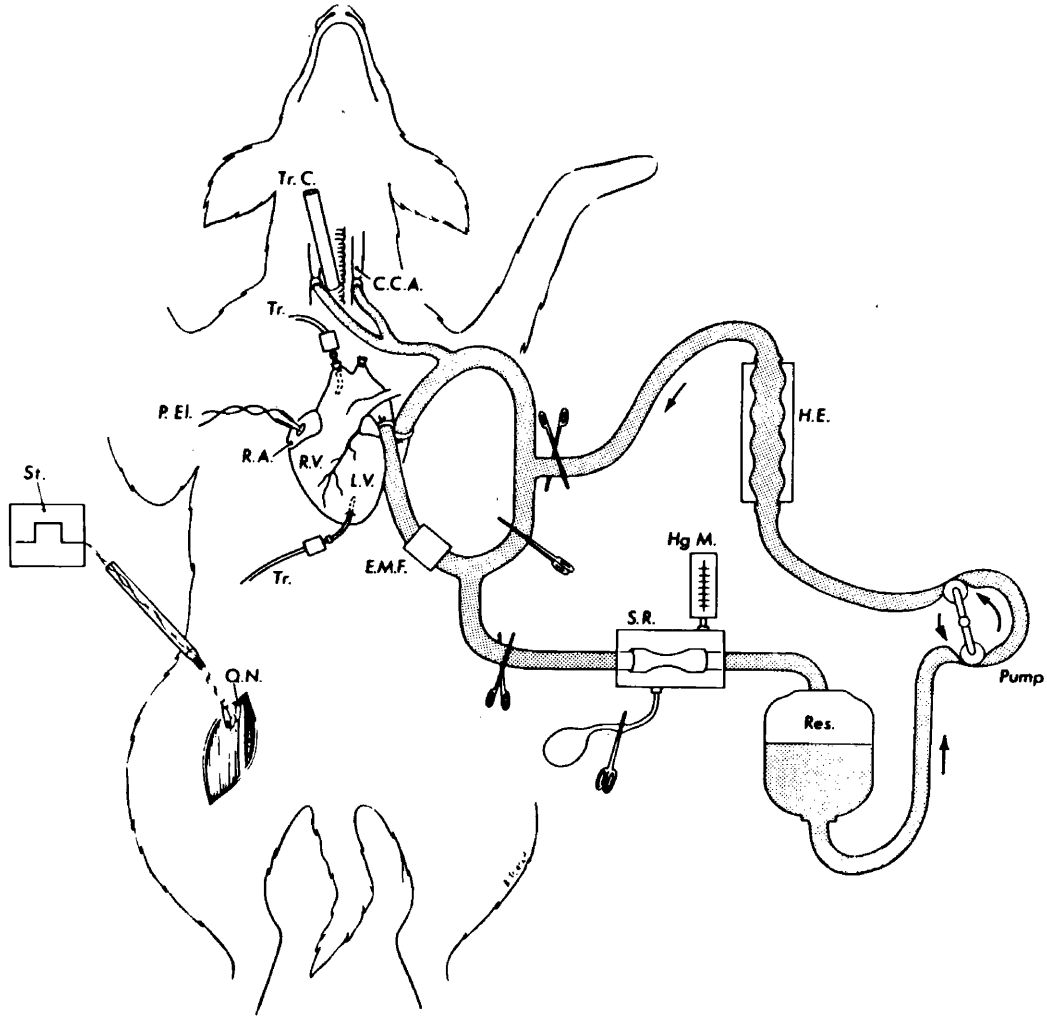

FIGURE 2. Preparation for stimulation of afferent fibers from skeletal muscle during measurement of cardiovascular variables: (Tr.C) tracheal cannula; (C.C.A.) common carotid artery; (R.A.) right atrium; (R.V.) right ventricle; (L.V.) left ventricle; (E.M.F.) electromagnetic flowmeter transducer; (S.R.) Starling resistance; (Hg M.) mercury manometer; (Res.) blood reservoir; (Pump) rotor pump; (H.E.) heat exchanger; (P.El.) pacing electrode; (Tr.) pressure transducer; (St.) Grass stimulator; (Q.N.) quadriceps nerve. (From Mitchell *et al.*[16] By permission of *Circulation Research.*)

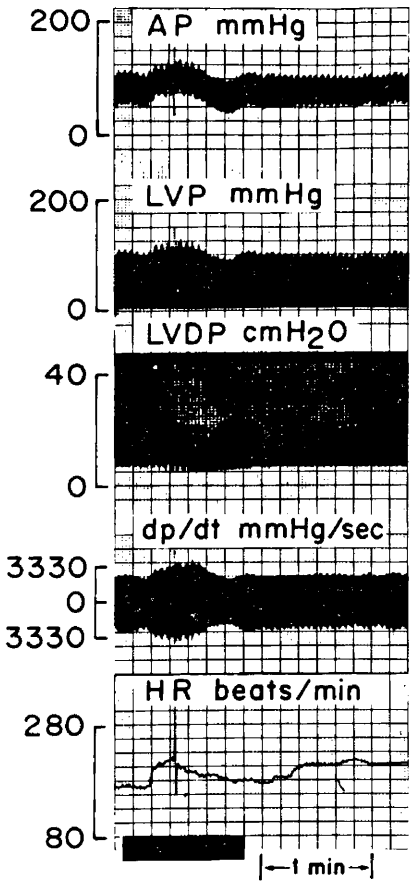

FIGURE 3. Pressor response to stimulation of afferent fibers of the quadriceps nerve: (AP) aortic pressure; (LVP) left ventricular pressure; (LVDP) left ventricular diastolic pressure; (dp/dt) rate of left ventricular pressure development; and (HR) heart rate. Stimulation of the quadriceps nerve at 25 times threshold for the flexion response is indicated by the black bar. (From Mitchell *et al.*[16] By permission of *Circulation Research.*)

pressure, and aortic flow were controlled; in others these factors were allowed to vary by disconnecting the Grass stimulator and excluding the Starling resistance, blood reservoir, and rotor pump from the extracorporeal circuit. In the controlled studies the heart was paced at a rate well above the spontaneous rate, while the aortic pressure and aortic flow were maintained constant by setting the Starling resistance and rotor pump, respectively. The quadriceps nerve was dissected free for several centimeters from its cut peripheral end and mounted on a pair of electrodes. Small-sized, high-threshold afferent fibers were activated by stimulations at 5 to 25 times the threshold for the flexion reflex.

An example of the response observed when the small-sized, high-threshold afferent fibers from muscle were stimulated is shown in FIGURE 3. There was an increase in aortic pressure, left ventricular pressure, maximal rate of left ventricular pressure development, and heart rate, and a decrease in left ventricular end-diastolic pressure.

When aortic pressure, aortic flow, and heart rate were held constant during stimulation of the central and of the quadriceps nerve, there was still an increase in the maximal rate of left ventricular pressure development and no change in end-diastolic pressure. Thus, stimulation of these afferent fibers caused an increase in the contractile state of the left ventricle. The administration of propranolol abolished the changes in heart rate and contractile state of the left ventricle. This demonstrates the importance of the cardiac beta-adrenergic receptors in the response observed in this anesthetized dog preparation.

It was next necessary to show that contraction of skeletal muscle by stimu-

lating neural input below the central motor command could cause appropriate cardiovascular changes. This has been accomplished in several studies.[17-20] In our experiments a laminectomy was performed on anesthetized cats and the spinal cord was exposed by an incision through the dura.[18, 20] Both dorsal and ventral spinal roots L_5, L_6 and S_2 downward were always cut, leaving L_7 and S_1 for use in the experiment. The experimental preparation used for stimulation of the ventral roots to produce exercise in one hind limb of the cat is shown in FIGURE 4. The ventral roots of L_7 and S_1 were cut close to their exit from the spinal cord and placed over a pair of electrodes. Electrical stimulation of the spinal ventral roots, which contain predominantly motor fibers to skeletal muscle, was used to elicit contractions in the muscles of one hind limb. The corresponding dorsal roots, which carry the sensory input from the muscle to the brain, were left intact. Periods of simulated exercise of 30 to 45 seconds were given. Measurements were made of heart rate, arterial pressure, left ventricular pressure, and the rate of left ventricular pressure development.

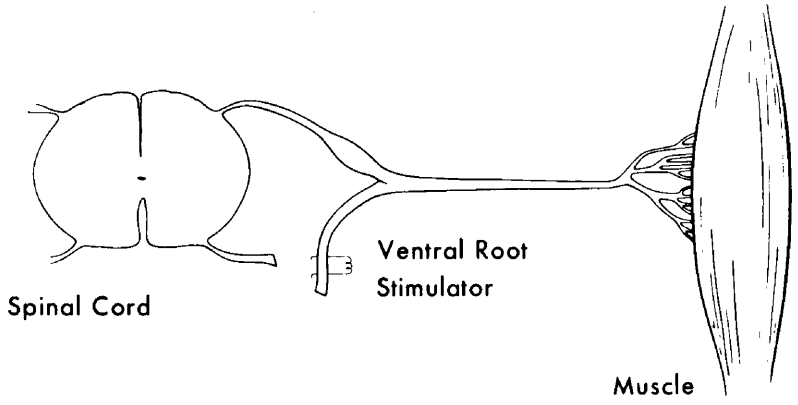

FIGURE 4. Preparation for simulated exercise. Muscles in a hindlimb were caused to contract by stimulating the peripheral cut ends of the ventral roots of spinal segments L_7 and S_1. Afferent nerves from the contracting muscles entered the spinal cord in the dorsal roots of these segments; other dorsal roots supplying the hindlimb were cut.

The response to simulated exercise is shown in FIGURE 5. At the arrow muscular contraction was induced by stimulation of the ventral root. During induced exercise there was an increase in heart rate, arterial pressure, left ventricle systolic pressure, and the maximal rate of left ventricle pressure development. After the cessation of exercise all these factors returned to control values. Vascular occlusion applied before the conclusion of muscular contraction could maintain the pressor response.[18] In this respect the findings in cats are similar to those of Alam and Smirk [9, 10] and others [11] in man.

As shown in FIGURE 4 it would also be possible to section the dorsal roots receiving afferents from the exercising muscle. After such sectioning the increase in heart rate, arterial pressure, left ventricular systolic pressure, and left ventricular rate of pressure development were all abolished. This means that the changes induced by simulated exercise were not mediated by release into the circulation of active compounds, but rather was caused by a local phenome-

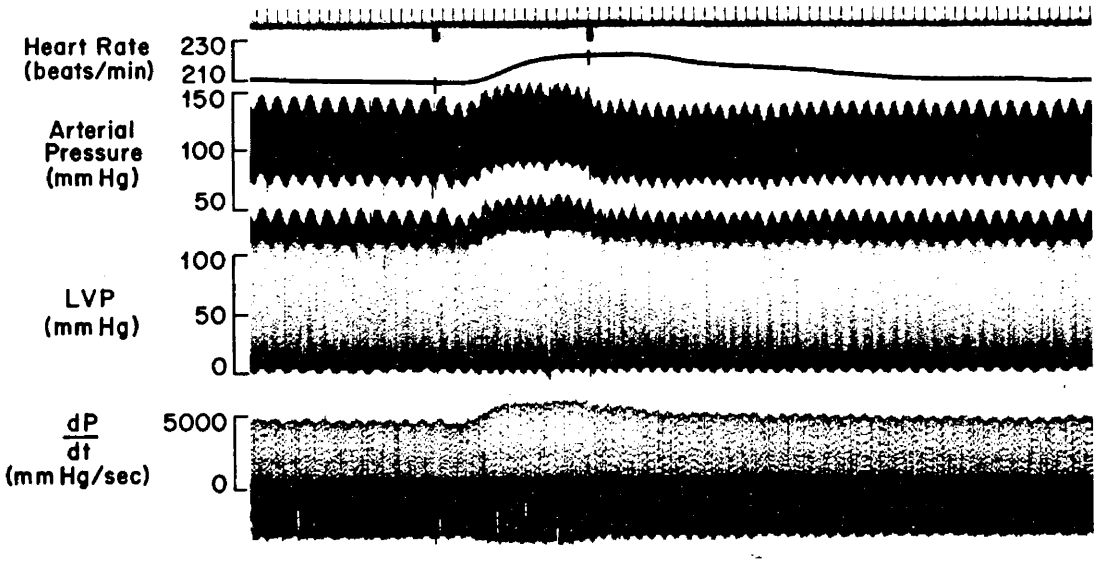

FIGURE 5. Response to induced exercise: (LVP) left ventricular pressure; (dp/dt) rate of left ventricular pressure development. Time marks are at intervals of 1 second. Exercise was induced between bars. (From Mitchell *et al.*[20] By permission of the *American Journal of Physiology*.)

non in the contracting muscle, which produced changes in afferent or sensory input into the cardiovascular center. The responses maintained by vascular occlusion after a contraction are also abolished when the dorsal roots are sectioned.[18]

The type of sensory or afferent fibers coming from skeletal muscle are shown in TABLE 1. All these fibers run into the dorsal roots. Types Ia and Ib are myelinated with a diameter of 12 to 20 μm and a conduction velocity of 70 to 120 meters/sec. The Ia fiber originates in the primary ending of the muscle spindle and the Ib fiber in the Golgi tendon organ. The type II fiber is myelinated with a diameter of 4 to 12 μm and a conduction velocity of 15 to 70 meters/sec. This fiber innervates the secondary ending of the muscle spindle. The type III fiber is myelinated with a diameter less than 4 μm and a conduction

TABLE 1

CLASSIFICATION OF SENSORY (AFFERENT) FIBERS FROM SKELETAL MUSCLES

Type	Diameter	Velocity (meters/sec)	Receptor
Ia	12–20 μm, myelinated	70–120	Muscle spindle, primary ending
Ib	12–20 μm, myelinated	70–120	Golgi tendon organ
II	4–12 μm, myelinated	15–70	Muscle spindle, secondary ending
III	$<$4 μm, myelinated	12–24	Pressure-pain receptors
IV	Unmyelinated	0.5–2	Pain: unknown

velocity of 12 to 24 meters/sec. This fiber originates in so-called pressure-pain receptors, among others. The type IV fiber is unmyelinated with a conduction velocity of 0.5 to 2 meters/sec and principally originates in free nerve endings. Some of these free nerve endings mediate sensations of pain; however, whether or not they play any other physiological role is unknown.

Studies were performed to identify the type of afferent fiber that was responsible for the cardiovascular changes that were observed during induced exercise. Direct current anodal block of the dorsal roots receiving afferents from the exercising muscle was used to block preferentially large myelinated fibers.[18] This should include types Ia and b, II, and even the large type III fibers. The technique is demonstrated in FIGURE 6. A test stimulator was placed on the sciatic nerve. Test stimuli were delivered here by a second isolated stimulator. This elicited a compound action potential that was picked up from a sampling slip of dorsal root beyond the anodal blocking electrode. The compound action potential was displayed on an oscilloscope and photographed. Test stimuli were applied and anodal block was used until the sampled compound action potential showed that the large myelinated afferents had been blocked. After this procedure was carried out, the test stimuli were turned off and the ventral roots were again stimulated to produce contraction of the muscles of the hind limb.

The results of experiments performed before and after anodal block are shown in FIGURE 7. In the upper panel is shown blood pressure during the control study when no anodal block was being applied. The sample compound action potential is shown on the right. When the ventral root was stimulated causing contraction of the muscles of the hind limb there was an increase in both systolic and diastolic blood pressure. In the middle panel the anodal block was applied. The sampled action potential on the right shows that the large myelinated fibers have been blocked. During stimulation of the ventral roots there is still an increase in arterial blood pressure. In the lower panel the anodal block was turned off and exercise again produced by ventral root stimulation with the usual response. In this and all similar experiments, when the large

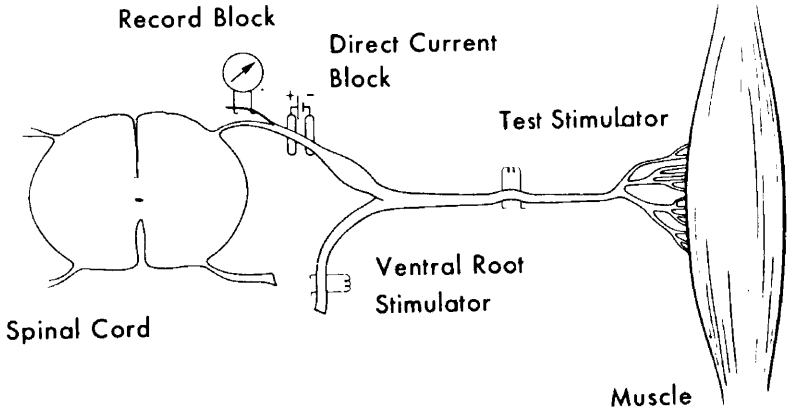

FIGURE 6. Preparation for exercise during anodal block with direct current. Direct current could be passed between two electrodes placed under the intact dorsal roots. The degree of block achieved was gauged by stimulating the sciatic nerve high in the back of the thigh with the test stimulator, and monitoring the changes produced by the block in the compound action potential recorded from a slip of the dorsal root after it had passed the blocking region.

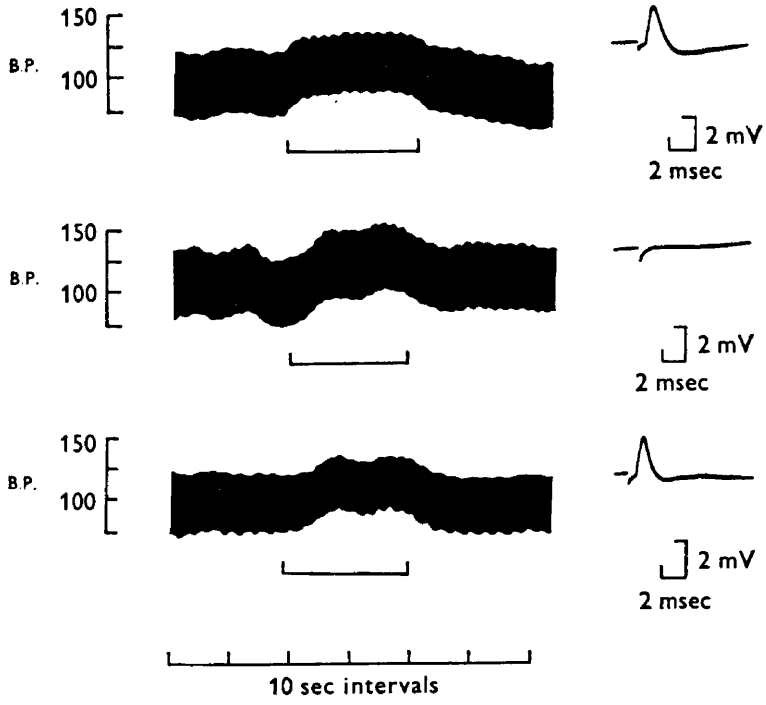

FIGURE 7. Blood pressure response to induced exercise during anodal block. Records of arterial blood pressure (B.P.) and the compound action potential are shown from three periods of exercise: (upper panel) control period of exercise before anodal block; (middle panel) period of exercise after anodal block just sufficient to block the A-wave of the compound atrium potential; (lower panel) control period of exercise after removal of the block. (From McCloskey & Mitchell.[18] By permission of the *Journal of Physiology*, London.)

myelinated fiber types I, II, and large type III were blocked there was no effect on the response of blood pressure during induced exercise.

Local anesthetic block of the dorsal roots receiving afferents from the exercising muscle was used to block preferentially small myelinated type III fibers and unmyelinated type IV fibers.[18] The technique is demonstrated in FIGURE 8. Test stimuli again were used to elicit the compound action potential, which was picked up from a sampling slip of dorsal root beyond the local anesthetic block in the spinal cord. Test stimuli were applied and then 0.125% lidocaine was applied to the dorsal root.

Bouts of exercise were performed both before and during the local anesthetic block and results are shown in FIGURE 9. In the upper panel exercise was performed before applying lidocaine and an increase in blood pressure occurred. In the middle panel during stimulation of the ventral root after lidocaine there is no change in arterial blood pressure even though the sampled action potential on the right shows no change. In the bottom panel after the anesthetic block has disappeared there is again an increase in arterial blood pressure during exercise of the hind limb muscles. Thus the exercise response disappeared but the compound action potential caused by type I, type II, and large type III fibers was still present. Therefore, one must assume that when the small type III and type IV fibers are blocked, the response disappears.

In summary these studies show that a peripheral control or skeletal-muscle–

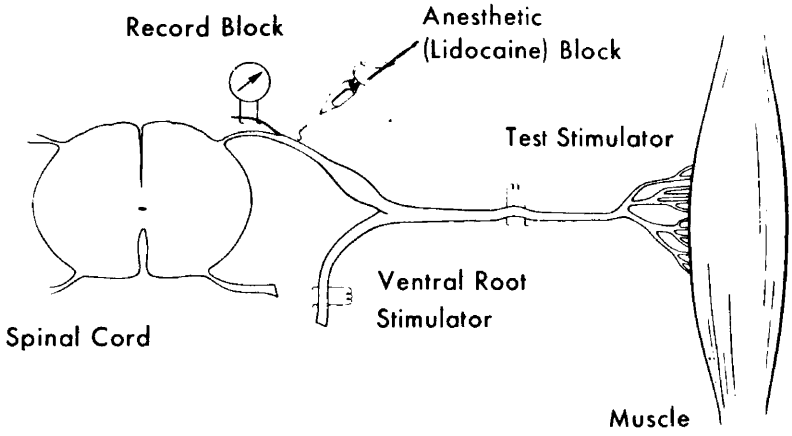

FIGURE 8. Preparation for exercise during anesthetic block. Lidocaine (0.125%) could be applied to the dorsal roots to produce a local anesthetic block. The degree of block achieved was monitored as described in FIGURE 7.

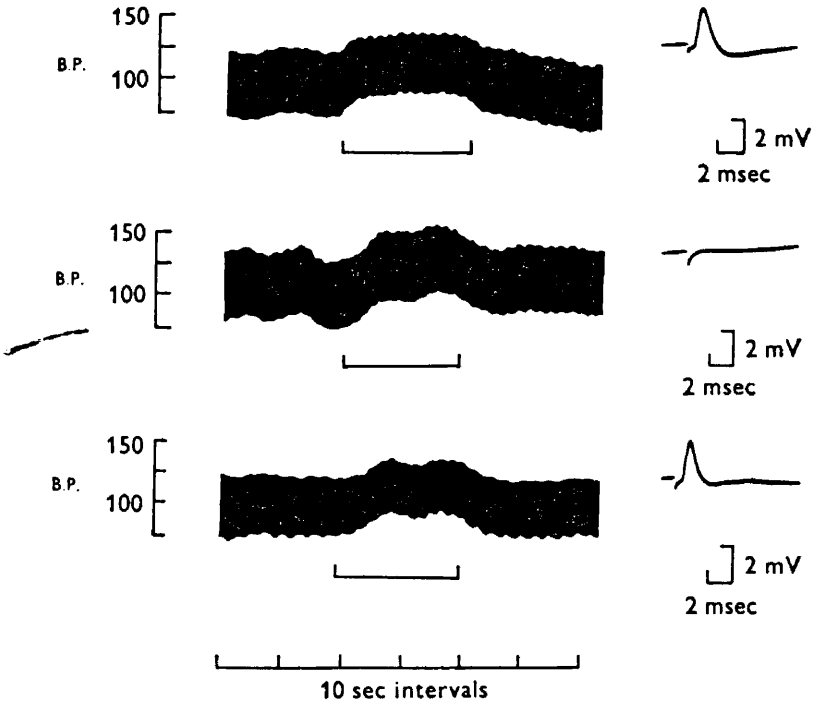

FIGURE 9. Blood pressure response to induced exercise during anesthetic block. Records of arterial blood pressure (B.P.) and the compound action potential are shown from three periods of exercise: (upper panel) control period of exercise before anesthetic block; (middle panel) period of exercise several minutes after application of lidocaine to the dorsal roots; (lower panel) control period of exercise after the lidocaine had been washed away. (From McCloskey & Mitchell.[18] By permission of the *Journal of Physiology*, London.)

circulation reflex does exist and that the afferent fibers of this reflex are small type III or type IV fibers. These fibers principally originate in free nerve endings.

There are two major questions that remain concerning this skeletal-muscle–circulation reflex. First, what are the factors that activate the receptors involved in this reflex physiologically during contraction? Work from our laboratory has suggested possible roles for increases in interstitial potassium and in hyperosmolarity in activating the receptors,[21, 22] but their physiological importance remains uncertain. Second, how important is the peripheral control mechanism in the conscious exercising animals in comparison to central command? Final answers to these questions require more experimental work.

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RESPIRATORY MODULATION OF BARORECEPTOR AND CHEMORECEPTOR REFLEXES AFFECTING HEART RATE THROUGH THE SYMPATHETIC NERVOUS SYSTEM

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SUMMARY

1. Brief stimuli were delivered to the carotid body chemoreceptors or the carotid sinus baroreceptors at different phases of the respiratory cycle in anaesthetized dogs. Chemoreceptor stimulation was achieved by injecting small volumes (0·2–0·5 ml.) of warmed saline equilibrated with CO_2 near to the carotid bodies on both sides. Baroreceptor stimulation was achieved by injecting larger volumes (2–5 ml.) of saline equilibrated with air into the region of the carotid bifurcation on both sides, after first clamping the common carotid arteries.

2. When the vagus nerves were intact, but sympathetic nervous effects on heart rate were blocked by administration of propranolol, there was a prompt and pronounced bradycardia evoked when either baroreceptor or chemoreceptor stimuli were given in expiration, but little or no change in heart rate when they were given in inspiration.

3. When the vagus nerves were cut, but sympathetic nervous function was intact, respiratory modulation of both baroreceptor and chemoreceptor reflex effects on heart rate could still be demonstrated. The bradycardia evoked by either stimulus was more marked for stimuli given in expiration than for stimuli given in inspiration. A complementary response pattern for brief decreases in baroreceptor stimulation (carotid occlusions) was demonstrated: the tachycardia evoked by occlusions timed during inspiration was greater than that evoked by occlusions timed during expiration. All the reflex effects were mediated by the sympathetic system because they were abolished by administration of propranolol.

4. Typically, the sympathetic reflex effects were slight in comparison with the vagal reflexes evoked by either chemoreceptor or baroreceptor stimuli.

INTRODUCTION

Stimuli delivered to the carotid arterial baroreceptors or chemoreceptors evoke reflex bradycardia more effectively when they are timed to occur during the expiratory, rather than the inspiratory, phase of the respiratory cycle (Koepchen, Wagner & Lux, 1961; Haymet & McCloskey, 1974, 1975; Neil & Palmer, 1975; Kordy, Neil & Palmer, 1975). That the bradycardia is mediated principally by the vagus nerve has been shown by blocking it by vagotomy or with atropine, and by recording directly from cardiac vagal efferent nerves (Haymet & McCloskey, 1975; Neil & Palmer, 1975; Kordy *et al.* 1975; Davidson, Goldner & McCloskey, 1976).

It is known, however, that the carotid baroreceptors and chemoreceptors can also slow the heart reflexly by withdrawing cardiac sympathetic tone (e.g. Bronk, 1933; Daly & Scott, 1958; Downing, Remensynder & Mitchell, 1963). We were therefore interested to see whether or not the sympathetic effects of these reflexes can be similarly modulated during the respiratory cycle. The results we present here indicate that they can.

METHODS

Experiments were performed on twenty-one adult dogs of either sex weighing from 6 to 18 kg. All but four of the animals were anaesthetized with I.V. pentobarbitone (Nembutal, Abbott; 35 mg/kg). The remaining four received I.V. chloralose (α-chloralose, British Drug Houses; 80 mg/kg), after induction with thiopentone. In each dog the trachea was cannulated low in the neck, and nylon cannulae were inserted, with their tips pointing towards the heart, into the lingual and external carotid arteries on both sides. On each side the tips of these cannulae were positioned close to each other and in close communication with the carotid sinus. Arterial pressure was recorded through one of the lingual arteries using a Statham P23 AC transducer, and was recorded on a Grass Polygraph pen recorder. Intra-tracheal pressure, as an indicator of air-flow, was recorded through a wide (2 mm i.d.) catheter inserted into the trachea, using another Statham transducer, and was also recorded on the polygraph. In five experiments, respiratory movements were recorded by the alternative method of registering tension changes produced through an elastic band sewn to the chest wall and connected to a Grass FT03 force transducer (cf. Levy, DeGeest & Zieske, 1966). On the two remaining channels of the polygraph were recorded the electrocardiogram and the beat-by-beat heart rate (Grass 7P4 Cardiotachometer, triggered from the e.c.g.). The calibration of the cardiotachometer was checked by running simultaneous records of e.c.g. and heart rate at a fast paper speed.

Brief chemoreceptor and baroreceptor stimuli were given as decribed by Haymet & McCloskey (1975). The chemoreceptor stimuli were provided by sudden retrograde injections into the external carotid arteries of small volumes (0·2–0·5 ml.) of warmed CO_2-equilibrated saline. Injections of similar small volumes of air-equilibrated saline were always without reflex effect. Baroreceptor stimuli were delivered by sudden retrograde injections of 2–5 ml. air-equilibrated saline, or of freshly drawn arterial blood, into the external carotid arteries after the common carotid arteries had first been clamped below the carotid sinus. Stimuli were usually given simultaneously on both sides.

In order to study the effects of the sympathetic nervous system on heart rate, the vagi were cut after the reflex responses with vagi intact had been observed (see Results). To ensure removal of vagal efferent effects, atropine was also given (usually 1 mg, repeated hourly). Electrical stimulation of the cardiac ends of the cut vagi was then without effect on heart rate. There then remained a slight sinus arrhythmia. This could be attributed to the waxing and waning of sympathetic tone with the respiratory cycle because in all animals it could be abolished, at the end of the experiments, by administration of propranolol (1 mg/kg). It was found that this sympathetically mediated sinus arrhythmia was most pronounced when the respiratory rate was slow, and most experiments were performed in such conditions. This was achieved by keeping the level of anaesthesia deep, and by maintaining the animal at a slightly cool temperature (35–37 °C).

RESULTS

(i) *Responses in which sympathetic effects were excluded.* Responses to brief baroreceptor and chemoreceptor stimuli were always examined first with the vagi intact. The findings of Haymet & McCloskey (1975) were confirmed: there was a prompt and pronounced bradycardia evoked when the stimuli were given in expiration, but little or no change in heart rate when they were given in inspiration. These responses were preserved in three animals in which any possible effects from sympathetic withdrawal were excluded by pretreatment with propranolol in a dose sufficient to abolish any heart rate response to administration of 10–20 μg isoprenaline (see Fig. 1). The usual dose of propranolol was 1 mg/kg. The responses were subsequently abolished by vagotomy in these animals.

(ii) *Baroreceptor responses.* After vagotomy and administration of atropine, the responses to brief bilateral baroreceptor stimuli were again tested in eighteen dogs. In ten of these, there was a slowing of at least 15 beats/min (range 15–25) whenever the baroreceptor stimuli were timed to occur in expiration, but less than 10 beats/min (range 5–10) when the stimuli were given in inspiration (for these comparisons the heart rates at corresponding points in the two respiratory cycles before stimulation were taken as controls). Typical responses of this kind are shown in Fig. 2. In the remaining animals, there was either no response to the brief baroreceptor stimuli whenever delivered (four dogs), or a small (5 beats/min) and variable response, which bore no demonstrable relation to the respiratory cycle (four dogs).

The responses to baroreceptor stimulation were typically much slower after vagotomy than when the vagi were intact. Slowing usually commenced about 1–2 sec and was most marked about 5–7 sec after the stimulus was given. Fig. 3 shows the time course of a typical response, which can be compared with the very rapid responses seen when the vagi were intact (Fig. 1).

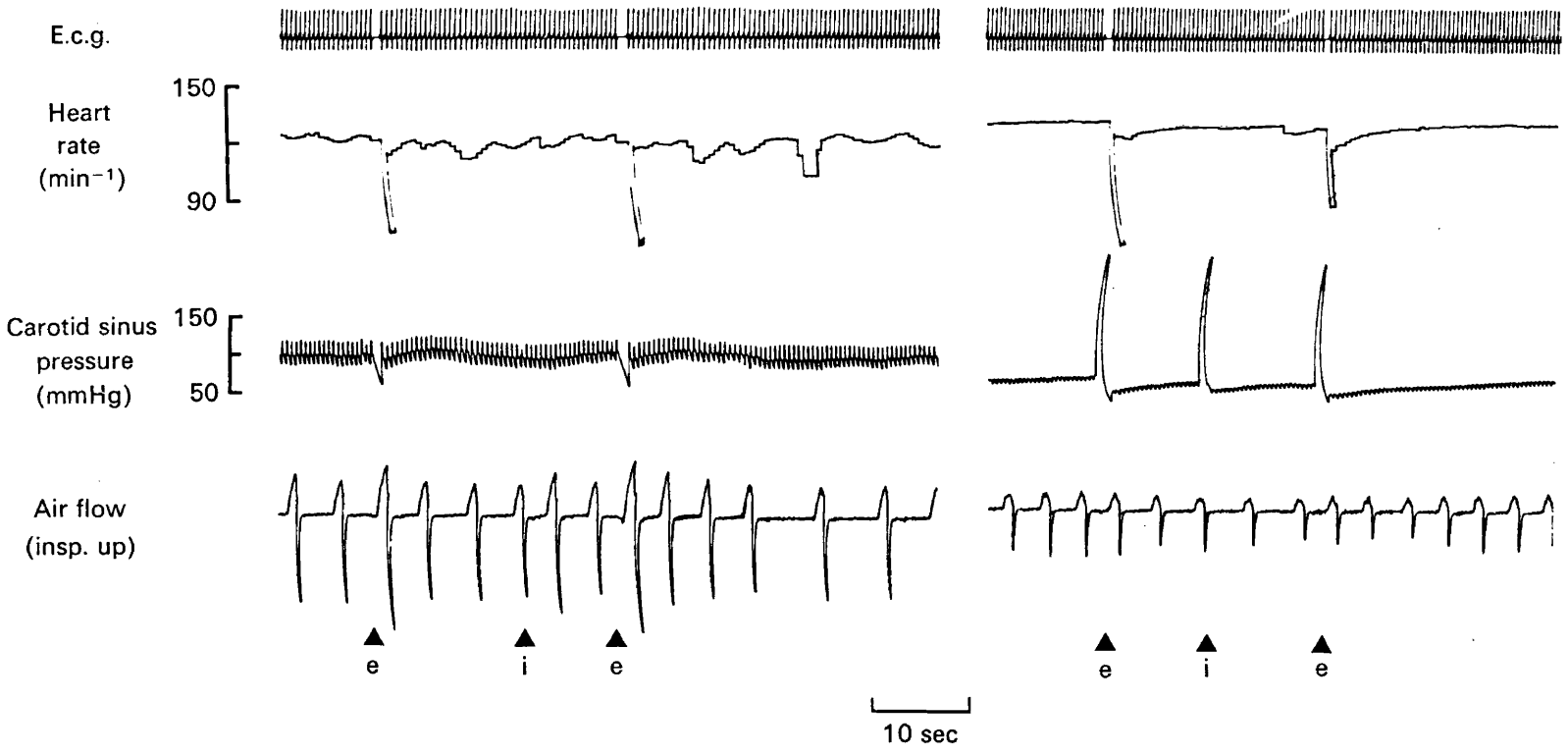

Fig. 1. Dog: chloralose and propranolol. These records show reflex effects of brief chemoreceptor and baroreceptor stimuli delivered at different points in the respiratory cycle – during expiration marked 'e', or during inspiration marked 'i'. Electrocardiogram, heart rate, carotid sinus blood pressure and tracheal air flow are shown. In the panel on the left are shown the effects of three successive chemoreceptor stimuli (injections of 0·5 ml. CO_2-equilibrated saline into the carotid bifurcation): the first and third stimuli, which were given during the expiratory phase of breathing, evoked a prompt reflex bradycardia; the second stimulus, given during inspiration, did not affect the heart rate. In the panel on the right are shown the effects of three successive baroreceptor stimuli (injections of approx. 3 ml. air-equilibrated saline into the carotid bifurcation after clamping the common carotid artery): the first and third stimuli, which were given during the expiratory phase of breathing, evoked a prompt reflex bradycardia; the second stimulus, given during inspiration, did not affect heart rate (the sensitivity of the tracheal air flow trace was altered between records).

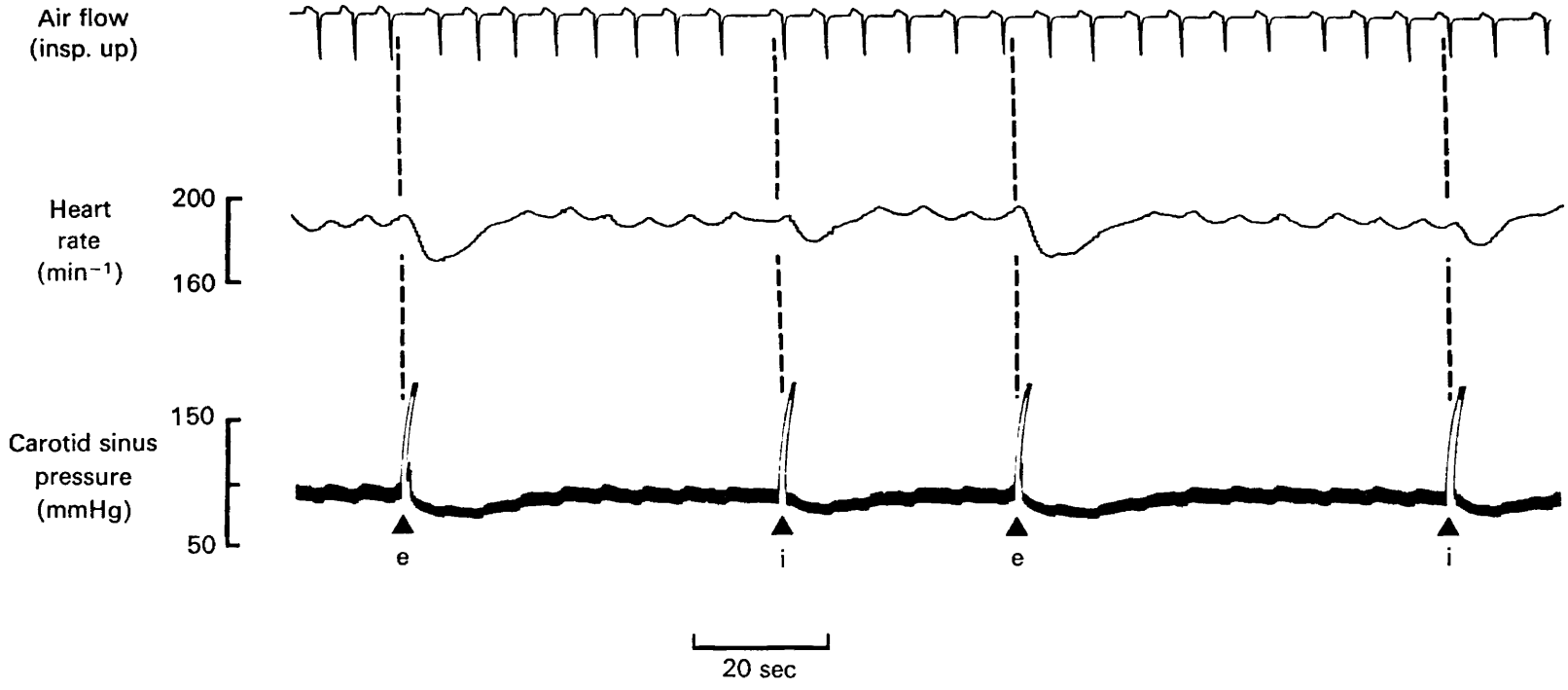

Fig. 2. Vagotomized dog, anaesthetized with pentobarbitone and given atropine. Record shows tracheal air flow, heart rate and carotid sinus blood pressure (both common carotid arteries clamped). Four brief baroreceptor stimuli were delivered, by simultaneous injections of approx. 3 ml. air-equilibrated saline into both carotid sinuses, at the markers. The first and third stimuli (marked 'e') were delivered during the expiratory phase of breathing, and slowed the heart rate more than the second and fourth stimuli (marked 'i'), which were delivered during inspiration.

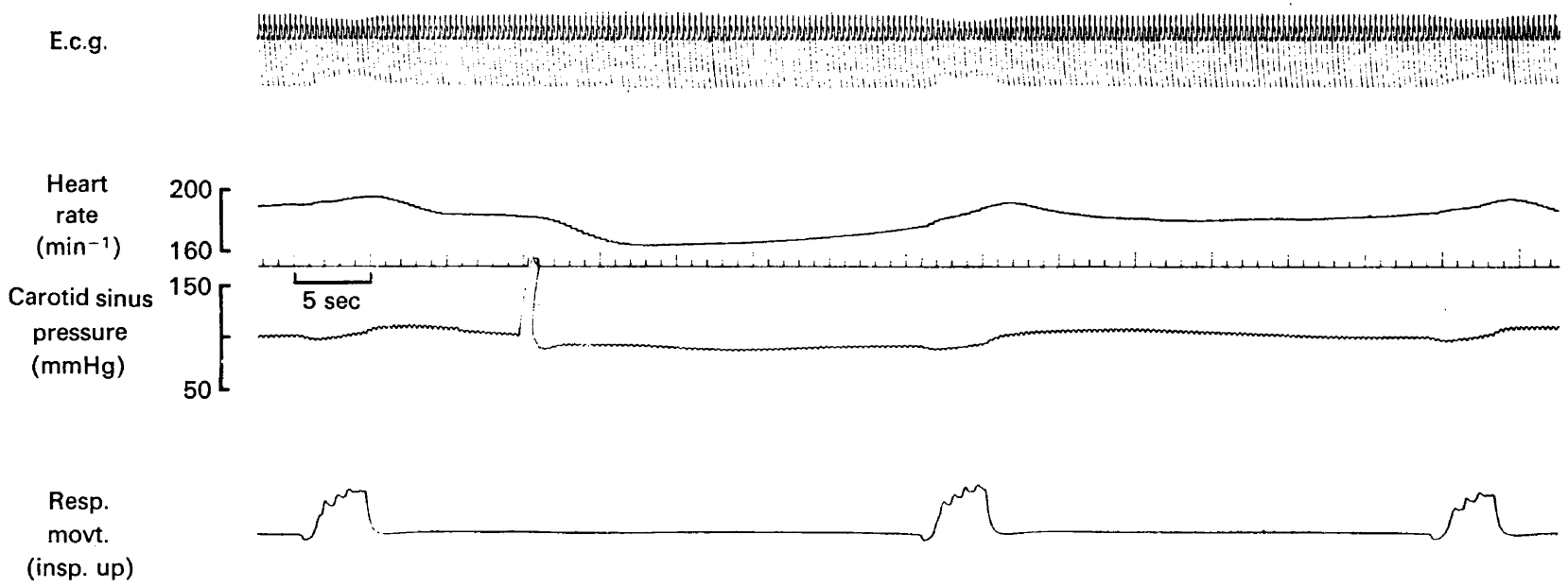

Fig. 3. Vagotomized dog, anaesthetized with pentobarbitone and given atropine. Record shows tracheal air flow, heart rate, carotid sinus blood pressure, and respiratory movements. A brief pulse of pressure in the carotid sinus, caused by the sudden injection of approx. 3 ml. air-equilibrated saline, was a baroreceptor stimulus delivered during the expiratory phase of breathing. The time course of the reflex slowing of the heart evoked by the stimulus is shown.

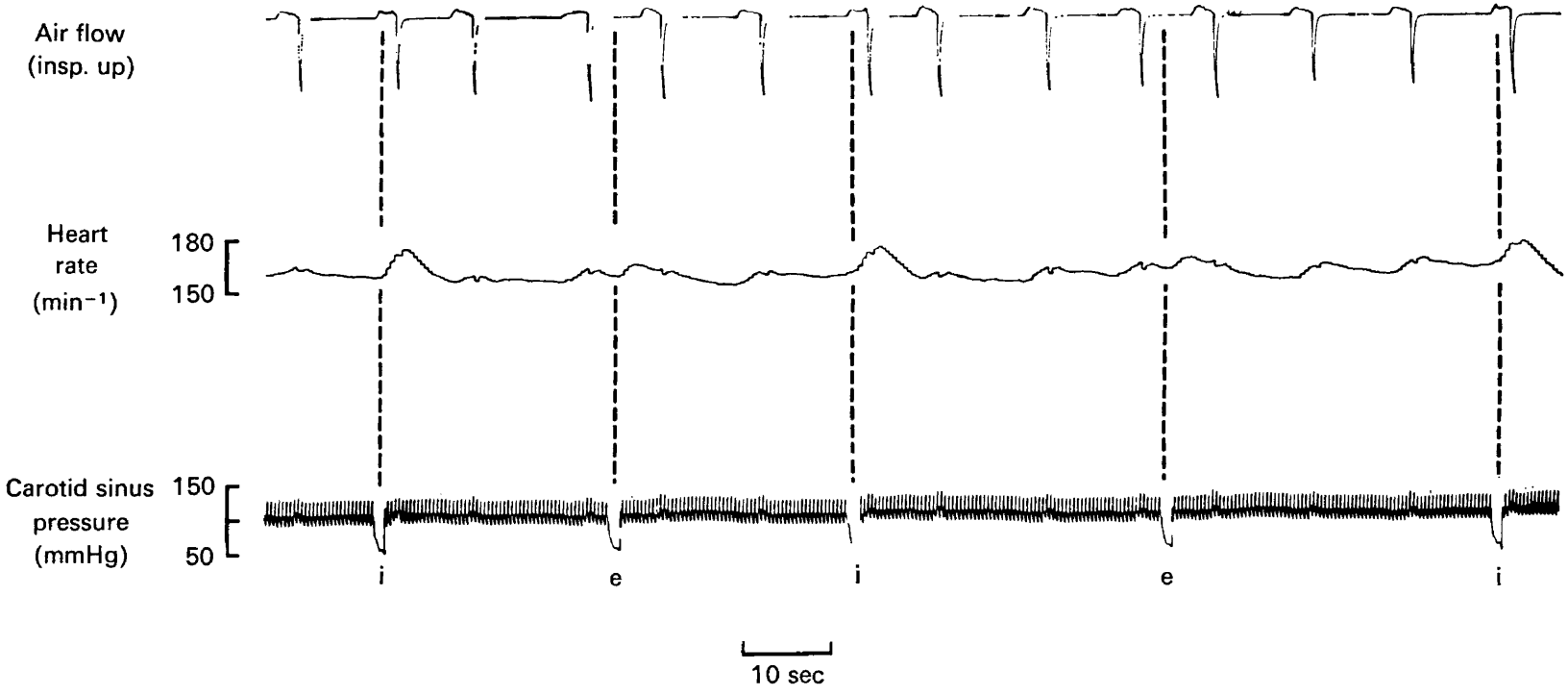

Fig. 4. Vagotomized dog, anaesthetized with pentobarbitone and given atropine. Record shows tracheal air flow, heart rate and carotid sinus blood pressure. The five falls in carotid sinus blood pressure were caused by briefly occluding both common carotid arteries. When the occlusions were timed to occur during the inspiratory phase of breathing (marked 'i') they evoked reflex increases in heart rate which were greater than those evoked by occlusions timed to occur during the expiratory phase of breathing (marked 'e').

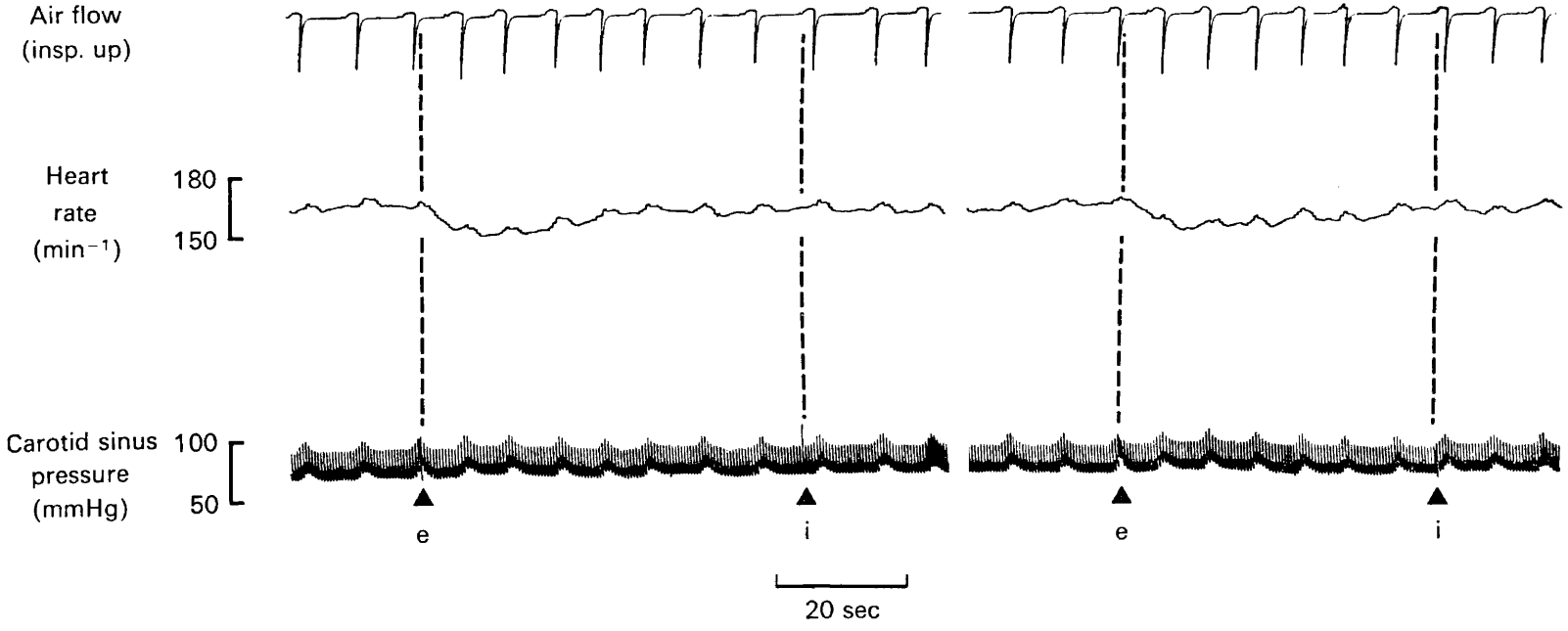

Fig. 5. Vagotomized dog, anaesthetized with pentobarbitone and given atropine. Record shows tracheal air flow, heart rate and carotid sinus blood pressure. Four brief chemoreceptor stimuli were delivered by simultaneous injections of 0·5 ml. CO_2-equilibrated saline into both carotid sinuses, at the markers. The first and third stimuli (marked 'e') were delivered during the expiratory phase of breathing, and slowed the heart more than the second and fourth stimuli (marked 'i'), which were delivered during inspiration.

In ten of the vagotomized animals the effects of decreased baroreceptor activity were investigated. Cotton loops passed around both common carotid arteries low in the neck were pulled upon to produce brief reductions in the pressure within the carotid sinus. During this manoeuvre care was taken not to pull *along* the common carotid arteries, so as to avoid stimulating stretch-sensitive baroreceptors further downstream. In six of the animals, occlusions timed to occur during inspiration caused reflex increases in heart rate of at least 15 beats/min (range 15–30), whereas occlusions occurring during the expiratory phase of the respiratory cycle caused increases of less than 6 beats/min (range 2–6). An example of this type of response is shown in Fig. 4. This pattern of response complements the pattern described above for responses to brief rises of carotid sinus pressure: it is easier to evoke a reflex bradycardia with pressure increases timed in expiration, and easier to evoke a reflex tachycardia with pressure decreases timed in inspiration (we also looked for responses to brief withdrawals of baroreceptor, and chemoreceptor, stimulation in animals with intact vagi – responses which would have involved withdrawal of vagal tone – but found no consistent effects). In the remaining animals in which brief carotid occlusions were performed, variable responses (sometimes of as much as 20 beats/min) were observed, but no relation to the respiratory cycle could be demonstrated.

All of the baroreceptor responses, whether to pulses of increased pressure or to brief carotid occlusions, were abolished following administration of propranolol (1 mg/kg).

(iii) *Chemoreceptor responses.* Brief bilaterial stimuli were delivered to the carotid arterial chemoreceptors by retrograde injections of 0·2–0·5 ml. CO_2-equilibrated saline into the external carotid arteries in the same eighteen vagotomized dogs in which the brief baroreceptor stimuli were given. In six of these animals, chemoreceptor stimuli given during expiration evoked a reflex slowing of the heart of at least 15 beats/min (range 15–20), while stimuli given during the inspiratory phase of breathing evoked reflex responses of less than 5 beats/min (range 0–5). These same animals gave similarly modulated responses when baroreceptor stimuli were applied during different phases of the respiratory cycle. Records obtained from one of these animals are shown in Fig. 5.

In the experiments using chemoreceptor stimuli, marked changes in breathing were frequently evoked. It thus became difficult to compare the exaggerated sinus arrhythmia immediately following stimulation with that which preceded it. The six animals described above in which respiratory modulation of changes in heart rate was clearly shown were notably poor in their ventilatory responses to chemoreceptor stimulation. The most common problem encountered in the other animals was that

stimuli delivered during the expiratory pause evoked an immediate inspiratory effort. The tachycardia associated with such premature inspirations probably masked any immediate direct reflex effects on heart

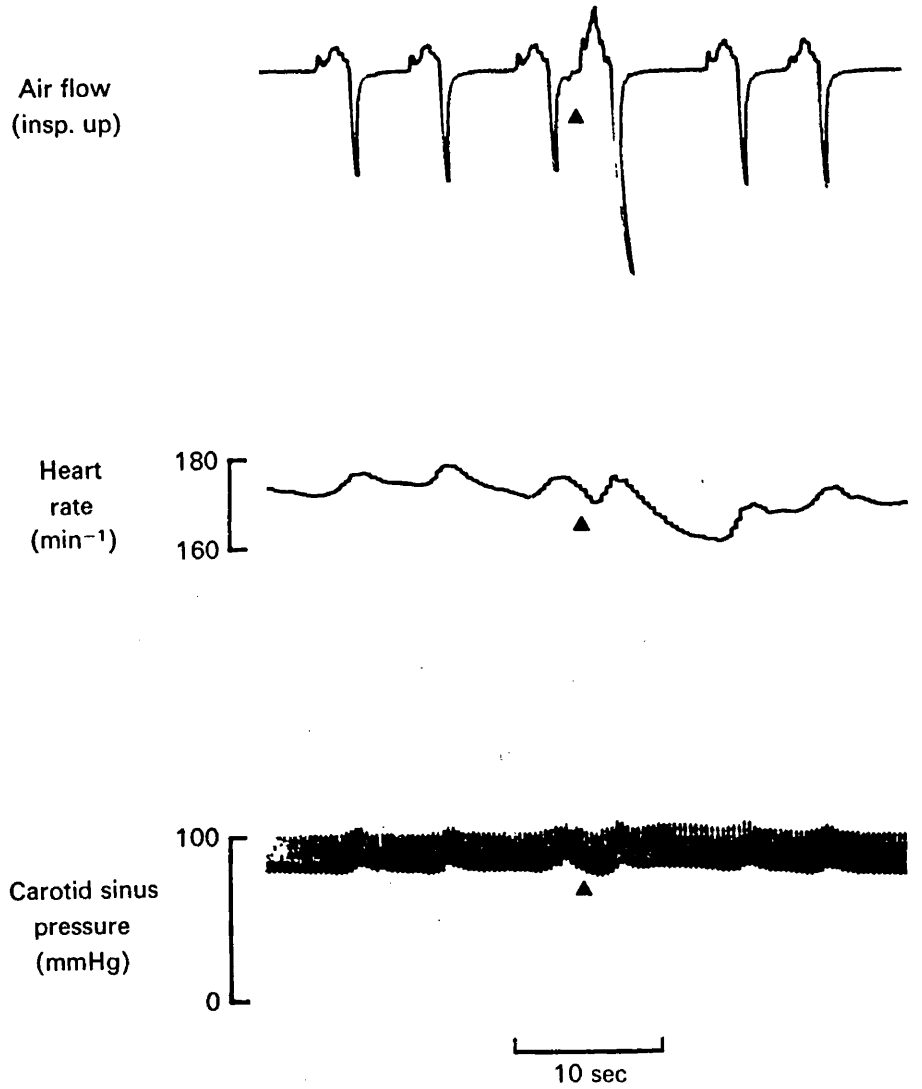

Fig. 6. Vagotomized dog, anaesthetized with pentobarbitone and given atropine. Record shows tracheal air flow, heart rate and carotid sinus blood pressure. At the marker, a brief bilateral chemoreceptor stimulus was given. The stimulus was given during the expiratory phase of breathing, but immediately evoked a large premature breath. There was a bradycardia following the evoked breath.

rate. In many animals, however, a marked bradycardia occurred in the expiratory pause following the premature inspiratory effort (see Fig. 6).

In further experiments we attempted to examine the effects of brief reductions in chemoreceptor stimulation. Retrograde injections of small volumes of O_2-equilibrated bicarbonate solution were made in animals

breathing air or hypoxic gas mixtures. Only slight and variable reflex effects on heart rate were observed in these experiments. All of the changes in heart rate evoked by arterial chemoreceptor stimulation were abolished following administration of propranolol (1 mg/kg).

DISCUSSION

The experiments we have described here show that the effectiveness of carotid baroreceptor and chemoreceptor stimuli in evoking reflex changes in heart rate through the sympathetic nervous system depends on the phase of the respiratory cycle in which the stimuli are given. The sympathetic efferent components of these reflexes are thus modulated by the respiratory cycle in a manner similar to the vagal components (Koepchen *et al.* 1961; Haymet & McCloskey, 1975). We have demonstrated the sympathetic modulation in the absence of vagal effects, and the vagal modulation in the absence of sympathetic effects. The responses mediated by withdrawal of sympathetic tone are slower and smaller than vagally mediated reflex changes in the same direction, and we found them considerably more difficult to demonstrate than the vagal effects.

There have been reports that it is difficult to demonstrate a sympathetically based sinus arrhythmia following vagotomy or the administration of atropine (e.g. Anrep, Pascual & Rossler, 1936). Most of our animals showed the phenomenon, probably because our efforts to slow the respiratory rate meant that there was time for the rather sluggish sympathetic effects to develop fully with each breath. The same slow respiratory rate probably also gave time for the sympathetic reflex effects to become apparent. If this is so, the responses we have described here are likely to be much less marked in animals with a more normal respiratory rate. Certainly, we had difficulty in demonstrating responses in faster breathing animals, and often saw them only after the respiratory rate had been slowed by moderate cooling or by deepening the level of anaesthesia.

Respiratory effects on reflexes involving the sympathetic nervous system have been described previously. Seller, Langhorst, Richter & Koepchen (1968) showed that a more pronounced vasodilatation in the vascular bed of the gracilis muscle was evoked by electrical stimulation of the carotid sinus nerve applied in the expiratory phase of breathing, than by similar stimuli given in inspiration. It has also been found that electrical stimuli given to the carotid sinus nerve during the expiratory phase of breathing gives a stronger inhibition of abdominal, cervical and lumbar sympathetic neural activity than stimuli given during inspiration (Seller *et al.* 1968; Richter, Keck & Seller, 1970). Difficulty in interpreting these results arises, however, because both baroreceptor and chemoreceptor

afferents would have been excited by electrical stimulation of the sinus nerve, and these are known to have opposite effects on sympathetic vascular tone: chemoreceptor stimulation causes sympathetic vasoconstriction (Daly & Scott, 1963), and baroreceptor stimulation withdraws sympathetic tone (Koizumi, Seller, Kaufman & Brooks, 1971). Seller *et al.* (1968) argued that the chosen intensities of electrical stimulation applied to the sinus nerves in their experiments were such as to stimulate baroreceptor afferents alone, without exciting chemoreceptor afferents. This is supported by their finding little evidence of respiratory responses to their stimuli. Nevertheless, it is known that baroreceptor and chemoreceptor afferents are represented in both the myelinated and the unmyelinated fibre groups of the sinus nerve (Fidone & Sato, 1969), and complete selectivity in any form of electrical stimulation would appear impossible. Indeed, in other studies (e.g. Black & Torrance, 1971; Eldridge, 1972), electrical stimulation of the sinus nerve has been employed specifically to study the effects of excitation of the chemoreceptor fibres within it. If Seller *et al.* (1968) are correct in assuming that their electrical stimuli involved mainly baroreceptor afferents, then their results are consistent with those we have presented here: if they stimulated mainly chemoreceptors, then their results and ours are at variance. By studying the sympathetic control of heart rate, however, we have chosen to examine a system in which stimulation of either chemoreceptors or of baroreceptors will evoke a similar response, namely sympathetic withdrawal (e.g. Bronk, 1933; Daly & Scott, 1958). It is worth noting that we also performed another long series of experiments (more than twenty dogs) in which we looked for changes in the resistance of the vascular bed of the isolated gracilis muscle in response to specific functional baroreceptor and chemoreceptor stimuli of the type used here: we found only small and variable responses which bore no obvious relationship to the phase of the respiratory cycle in which they were given.

The respiratory modulation of cardiac sympathetic activity which we have described here was clearly not imposed by phasic afferent traffic travelling along the vagi, because the vagi were cut in our experiments. Nevertheless, it remains possible that the modulation could be altered, perhaps augmented, by such afferent inputs in intact animals. An augmentation of the effect might indeed by expected from the work of Daly & Scott (1958), who showed that the activation of intrapulmonary receptors by inflating the lungs could accelerate the heart by both vagal and sympathetic reflex mechanisms.

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COROLLARY DISCHARGES: MOTOR COMMANDS AND PERCEPTION

[Short title: Corollary discharge]

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CHAPTER CONTENTS

INTRODUCTION

Sherrington adopted a philosophical rather than a scientific viewpoint when he wrote:

> "Since Hume it has been admitted that the perceived results of our volition are the outward ends obtained, and not the inward action of the neuromuscular machinery" (175).

Sherrington recorded this view in an analysis of the proprioceptive, or kinesthetic, sense - which he called "the muscular sense". In particular he was stating his opposition to the idea, variously attributed to Johannes Müller, Helmholtz, Wundt, and others (see below), that internally generated motor signals might have perceptual consequences. Briefly, this idea is that signals are generated within the central nervous system from, or together with, the commands for movements, and that these signals influence sensory perception either by modifying the processing of incoming sensory information or by irradiating higher sensory areas so as to evoke, in their own right, sensations of various kinds. This idea, to which Sherrington and others before and since were so opposed, is examined in this Chapter.

The view that one must attribute various aspects of kinesthetic or other sensibility either to central, command-related signals or to sensory signals arising peripherally, is an extreme one. Too frequently the claimed demonstration of a contribution to some aspect of sensation by one of these classes of signal is taken as evidence against the participation of the other class. Such arguments are based on an assumed exclusiveness of contribution which need not, and does not, exist. A comprehensive view of kinesthetic sensibility, for example, must allow for contributions by both afferent and internal, command-related signals (61, 134, 136). This Chapter is about only one of these classes of signals and, therefore, will focus on such signals. The reader is assured, however, that no exclusive role is claimed or implied by this treatment.

This Chapter concerns the perceptual consequences of motor commands. Other demonstrable or conceivable consequences of motor commands (see

'Terminology' section, below) - such as involvement in triggering other commands in various sequences, in modifying reflex excitability, or in affecting vegetative, visceral, neurohumoral or even higher intellectual functions - are not the prime concerns of this Chapter: some are briefly dealt with here, and some are the subjects of more detailed reviews in other chapters of this Handbook (e.g. see Arbib, Baldissera & Illert, Grillner, Sears, Willis & Coulter).

In the terms of Sherrington's view, quoted above, the present Chapter concerns the perceptual effects (if any) which are attributable to the internal workings of the neural machinery that formulates and despatches commands for muscular contractions, rather than effects resulting from the excitation of peripheral sensory receptors by those contractions. In this context an effect is taken to be "perceived" simply if one can become consciously aware of it.

Arrangement and Scope

This Chapter is entitled "Corollary Discharges", a term coined by Sperry (187) to describe supposed internal signals which arise from centrifugal motor commands and which influence perception. Various other terms, such as "efference copy" (86), "sensation of innervation" (77, 207) or "sense of effort" (144) are often loosely applied as synonyms for "corollary discharges", although these terms were originally defined for quite different applications. This review begins, therefore, with a consideration of the historical development of ideas in this area, so that the subsequent section on 'Terminology' can be given historical perspective. More detailed analyses of various aspects of corollary discharges follow the section on 'Terminology'.

The review of the history of ideas in this area serves to define the major problems to be considered in this Chapter. There are historical as well as practical reasons for considering separately the corollaries of motor commands to limb and trunk muscles and those of motor commands to oculomotor muscles. Here, corollaries of commands to limb and trunk muscle

will first be analysed: do they cause sensations of movement or altered position?, do they modify incoming kinesthetic or somesthetic signals?, do they contribute sensations of muscular force or heaviness? Then, corollaries of motor commands to oculomotor muscles will be considered: do they contribute to the sense of the direction of the gaze?, do they 'stabilize', or otherwise influence, visual perception? In brief, the answers provided here to these questions will be that corollary discharges are involved in sensations of static muscular force, or effort, but not in sensations of movement or of altered position; that this conclusion seems as likely to hold for the eyes as for limbs and trunk, so that a traditional role claimed for corollary discharges to the eyes seems doubtful; and that corollary discharges are involved in extracting 'useful' kinesthetic information from the discharges of intramuscular receptors.

Because of the concern of this Chapter with perceptual processes, it deals almost exclusively with neurophysiological studies on human subjects. Some aspects of this subject have been reviewed elsewhere (38, 62, 126, 136, 147, 198). In order to provide bridges, on the one hand, to possibly relevant reports of electrophysiological studies and, on the other, to reports of non-perceptual consequences of motor commands, brief sections on these topics are given at the end of this Chapter.

HISTORICAL DEVELOPMENT

In the nineteenth century there was considerable debate amongst physiologists, neurologists, psychologists and even philosophers about the mechanisms underlying 'kinesthetic sensibility' (10). This sense or consciousness of the positions and actions of the limbs (the "sixth sense" of Sir Charles Bell, 12) was variously proposed to be based on afferent sources which included sensory nerves in muscles, tendons, ligaments, joints and skin. From the outset, however, some argued that sensations which accompany muscular acts are directly caused by commands for motor action. This concept is old and its origins obscure. Bastian (10) claims that "two Italian physicians, Julius Caesar Scaliger in 1557 and Caesalpinus of Arezzo in 1569, quite independently

of one another, were the first to recognize ... the existence of a separate faculty or endowment associated with volition, or the mere will to move." Debate about the concept in the nineteenth century has been traced to the writings of Berkeley, Reid, Stewart and Steinbuch (94), and is generally believed to have been given physiological prominence by Johannes Mullër (154) and his circle: Helmholtz (77), Ludwig (118), Mach (120) and Wundt (207). In Britain the initial advocate of the idea was Bain (7).

In its simplest form, the proposal was for a "sensation of innervation" - a sensation arising as a direct central neural consequence of a motor command, without first involving some interaction with incoming sensory signals. A simple enunciation of the idea was made by Johannes Müller in 1840: "The appreciation of weight and pressure, in cases where we raise or resist, should be in part at least not a sensation in the muscle, but a notion of the quantity of nerve-force which the brain is excited to call into action" (154). Similarly, Wundt (207) noted: "A patient whose arm or leg is half paralysed, so that he can only move the limb with great effort, has a distinct feeling of this effort: the limb seems to him heavier than before, appearing as if weighted with lead; he has, therefore, a sense of more work effected than formerly, and yet the effected work is the same or even less. Only he must, to get even this effect, exert a stronger innervation, a stronger motor impulse, than formerly".

Helmholtz (77) argued a more complex case (see also 80, 120, 207). He noted that the visual world is perceived to stay still when one makes voluntary eye movements but that "apparent motions" are seen when movements of a similar magnitude are imposed on the eyes as, for example, by tapping or pressing against them through the margin of the eyelid. On the basis of these observations he suggested that, "our judgement as to the direction of the visual axis is not formed either by the actual position of the eyeball or by the actual elongation or contraction of the ocular muscles that is the result of this position. Our judgements

as to the direction of the visual axis are simply the result of the effort of will involved in trying to alter the adjustment of the eyes". Figure 1 illustrates the observations which led Helmholtz to this conclusion. Helmholtz supported his conclusions with observations on patients whose oculomotor muscles had suddenly become severely weakened. He noted that when such a patient attempts to turn his eyes in a direction in which they cannot move, the visual world appears to jump in the direction of the attempted movement. He argued that the judgement of the direction of the gaze was formed "as if the will had produced its normal effects .... and since no change has taken place in the images on the retina of the paralysed eye, we get the impression as if the objects shared the supposed movements of the eye". This case is also depicted in Figure 1. Helmholtz noted that his explanation also accounted for observations that after-images (i.e. images with a fixed retinal location) seem to move with real or frustrated voluntary movements, but stay still during imposed movements.

Figure 1 near here

What Helmholtz explained in terms of an "effort of will" may not necessarily be as simple an example of a sensation of innervation as is sometimes proposed. It is not clear whether Helmholtz proposed that one <u>feels one's eyes move</u> in response to commanding them to do so. Perhaps he was, and perhaps such is the case, but he framed his arguments in terms of changes in <u>visual</u> perception. It is possible, therefore, that a mechanism of the kind Helmholtz proposed could have produced no perceived sensations in its own right, but could have interacted in some way (unspecified by Helmholtz) with afferent visual signals to produce the observed effects. This matter is taken up again below.

The debate which surrounded proposals such as these towards the end of last century often centered on neurological cases in which paralysis, paresis or sensory loss was conspicuous. Unfortunately,

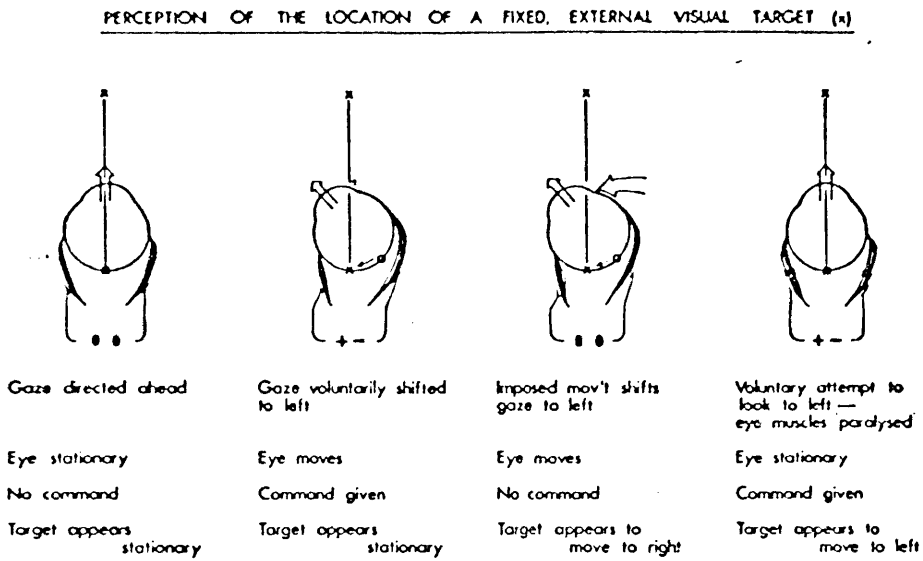


Figure 1. This figure depicts the circumstances which have been important in the historical development of ideas regarding corollary discharges and visual stability. The diagrams show the actual positions of eye, viewed target and retinal image: the bottom line under each diagram summarizes what <u>appears</u> to the subject to be happening.

the neurological deficits of the patients studied were often very poorly defined, and in many cases the disabilities noted seem, in retrospect, to have been primarily psychiatric. Fact and opinion were often difficult to distinguish in the arguments advanced. Often the debate was based mainly on philosophical grounds - as Sherrington's view of the matter, which was quoted in the Introduction to this Chapter, showed. Sherrington seems to have followed William James in this. In 1890, James (89) had written,"Since the time of Hume it has been a commonplace in psychology that we are only conversant with the outward results of our volition, and not with the hidden inner machinery of nerves and muscles which are what it primarily sets at work".

In his chapter on "The Muscular Sense" in Schäfer's 'Textbook of Physiology' which was published in 1900, Sherrington (175) gave a summary of the variants of theories on sensations of innervation advanced by Müller, Wundt, Lewes, Bain, Helmholtz, Munk, Wernicke and others. In their opposition to the idea that such sensations can exist, Sherrington and James were in the company of Ferrier (40) and Bastian (10, 11), and against the views of those just mentioned as well as Gowers (68) and Hughlings Jackson (88).

The demonstration by Goldsheider (60) that there is a well-developed capacity for blindfolded subjects to detect movements passively imposed on the limbs had indicated that this aspect, at least, of kinesthetic sensibility could not be claimed to derive solely from centrally generated command signals. However, the other proposals, so vigorously debated at the turn of the century, could not be conclusively tested, and the debate waned. Only Helmholtz's arguments regarding eye movements continued to be widely accepted and discussed, and these gained support from other experiments (104,117 ; see below).

In 1950, however, two important conceptual advances occurred, and the terms "corollary discharges" (187) and "efference copy" (84, 86) were introduced. "Corollary discharges" is the broader term. It arose as a suggestion by R.W. Sperry to explain behavioral findings obtained in experiments on fish. Sperry had found that surgical rotation of the eyeball through 180^{o} around the visual axis resulted in a "forced circling" or "spontaneous optokinetic reaction" (183, 184, 186, 187) in which the animals with inverted vision turned continuously in circles. The effect could be observed following rotation of both eyes, or just one eye (with blinding of the other), or by cross-connection of the optic nerves to the wrong side of the brain (185): it persisted even after bilateral extirpation of the labyrinths and severance of the oculomotor muscles (187). Sperry noted that, "in all these situations movement on the part of the animal causes the visual image to pass over the retinal field or its central projection in a direction opposite to normal."

The first explanation he offered for the circling phenomenon was as follows: "With the eye rotated, any movement that is visually initiated or guided, like that involved in centering the gaze on a peripheral object, would only exaggerate, instead of resolving, the stimulating situation which induced it. This in turn would reinforce in cyclic fashion more of the same (erroneous) response. This interpretation has an advantage in that it can be expressed in purely reflex terms without requiring the assumption of an illusory spinning sensation in the animal" (187). It is important to note that the findings can be explained in this way. Apart from the suggestion that the false movements may have represented an attempt to "center the gaze on a peripheral object", this explanation remains extremely attractive. Many fish have no fovea and little or no vision during rapid eye

movements (205), so it is unlikely that the false movements observed by Sperry were obligatory reorientations to external, visible objects (as, indeed, Sperry himself noted). In contrast, the slow, smooth, optokinetic system operates on the rate at which images slip across the retina (c.f. 161), and a change of sign in this reflex (as, by rotating the eyes) would ensure forced circling through an automatic reflex mechanism. Perception need not be considered. Sperry's explanation in terms of a reflex, therefore, when applied to this smooth pursuit system rather than to re-orientation responses, seems the most likely one for the phenomenon he observed.

Sperry, however, while noting that the continuous forced circling he observed "simulates exactly the circling produced by actual rotation of the visual field", looked beyond a reflex for an explanation - although the reflex he specifically rejected was a re-orientation response. He considered that the circling was due to an "illusory spinning of the visual field" for which not only the retinal stimulation but also the animal's own movements were important. Because similar retinal signals could arise in normal circumstances through movements of either the visual field or of the animal itself, Sperry concluded that the direction of movement of the "perceiving animal" was a critical factor required for the central interpretation of signals from the retina. Sperry considered the possibility that kinesthetic receptors or the labyrinths may normally provide such information on the animal's own movements to stabilize its visual perception. As the labyrinths were removed and the extraocular muscles cut in his experiments, however, this seemed unlikely. He therefore proposed: "that any excitation pattern that normally results in a movement that will cause a displacement of the visual image on the retina may have a corollary discharge into the visual centers to compensate for t e retinal displacement" (187). With respect to his own studies he noted

that, "with the retinal field rotated 180° any such ... adjustment would be in diametric disharmony with the retinal input, and would therefore cause accentuation rather than cancellation of the illusory outside movement". He also noted that his proposed "corollary discharges" would provide a neural basis for Helmholtz's sensation of the "effort of will", referred to above. Thus, Sperry rejected the likely reflex explanation in favor of one in which he considered perception and for which he proposed "corollary discharges".

It should be noted that Sperry, like Helmholtz, did not suggest that the proposed mechanism involved a direct perception in its own right. He saw it as a "central adjustor factor" which affected visual perception. Moreover, he suggested that similar adjustor factors based on corollary discharges, "may be involved in the perception of movement and spatial relations in other sense modalities such as audition and cutaneous sensibility." (187)

Whereas Sperry framed his proposal regarding "corollary discharges" entirely in terms of their perceptual consequences, the more exacting terminology of "efference copy", introduced in 1950 by von Holst and Mittelstaedt (86) did not necessarily involve perception. Amongst a series of experiments on postural and visual adjustments in invertebrates, lower vertebrates and man, von Holst and Mittelstaedt performed an experiment similar to Sperry's experiment on fish. They rotated the whole heads of flies through 180° around the longitudinal axis so that the two eyes were spatially interchanged. Like Sperry's fish the operated flies turned continuously in small circles, and, like Sperry, von Holst and Mittelstaedt asked, "How does the central nervous system 'know' which particular image displacement it should expect when the animal is moving?" The answers offered were that "either the CNS preserves for a period of time certain data regarding the efference

transmitted ... which are computed against the retinal image migration; or ... it relies upon ... receptors in the moving legs to 'calculate' the direction and speed of running, in order to compute the result against the retinal reafference" (86). It is again important to note that the results obtained were explicable by the alternative which Sperry suggested, but did not favor - that is, the behavioral changes may have resulted from alteration of the sign of some stabilizing visuo-motor reflex without involving perception either directly or indirectly.

Von Holst and Mittelstaedt (86) went on to formalize their proposals on the preservation and use of efferent signals within the central nervous system. These proposals were framed in general terms, and they applied them to data obtained in experiments of many different kinds (see also, 85). Their first postulate was that a command descending from a motor center to an effector (which could be a "lower" center within the nervous system, a muscle, a limb, or the entire body) produces within the central nervous system a closely correlated alteration in activity - the "efference copy". Afferent impulses evoked in the periphery as a result of this command were called "reafference", and were distinguished from afferent impulses which were not a direct consequence of the efference, but arose instead as a result of external influences. These latter afferences were termed "exafference". (The terms "reafference" and "exafference" make an important distinction in sensory and motor physiology regardless of the generality of the theories for which they were invented.) The proposal was then developed as follows: "The reafference interacts with the efference copy. The efference and its copy can be arbitrarily marked with a plus (+), whilst the reafference is maked with a minus (-). (See figure 2.) The efference copy and the reafference exactly cancel one another out. As soon as the entire afference is too large

Figure 2 near here

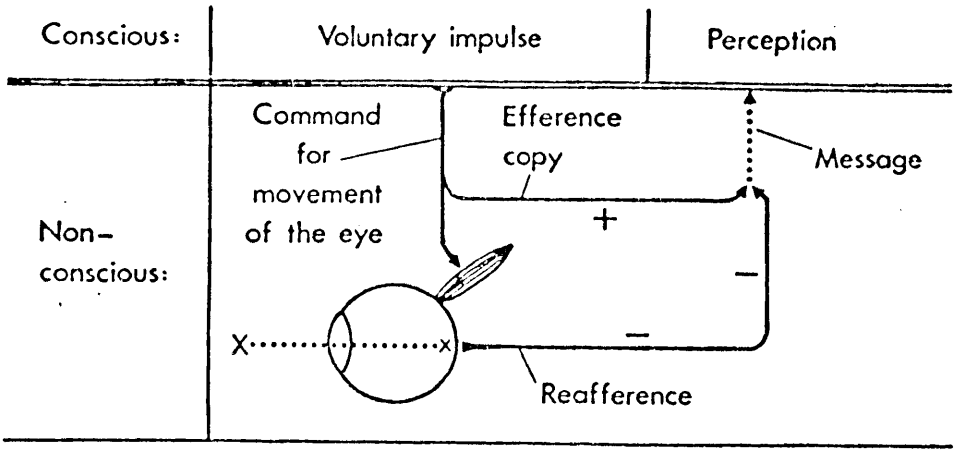


Figure 2. The efference copy - reafference mechanism, as applied to the eye: re-drawn from von Holst (85).

or too small, as a result of some external influence acting on the effector, either a + or a - remains as a residue ... this residue (the exafference) is transmitted upwards, sometimes to the highest centres." Figure 2 is taken from von Holst's (85) work, and depicts this system as it might apply to stabilizing visual perception during voluntary movements of the eye.

One of the most demanding requirements of the efference copy - reafference system is that of translating one or both elements into comparable neural formats or dimensions so that the proposed subtractive process can be carried out. This would mean generating from the motor command a precise match of the reafferent signal to be cancelled, from the reafferent inflow a match for the motor command despatched, or from both command and reafference, parameters amenable to subtraction (127). Temporal disparities of the signals to be cancelled would present a further difficulty.

It must be stressed that "efference copy" as envisaged by von Holst is unlike "corollary discharges" in two important ways: first, the efference copy is required to cancel the reafference exactly, while corollary discharges provide internal "adjustment" of sensory centers without such cancellation of reafference necessarily occurring; and second, in contrast to corollary discharges which are proposed specifically to deal with perceptual stability, efference copy is proposed simply as a "mechanism for distinguishing reafference and exafference" (86) which can apply as much to which are not involved at all with perception centers as it can to higher, perceptual centers.

MacKay (121, 122, 123, 124, 125, 126) criticized the efference copy - reafference mechanism on the grounds of its requirement of cancellation of reafferent signals. He wrote that, "although the sensory mechanism cannot properly interpret sensory changes without some

information as to the activity of the motor system, from an information-engineering standpoint the need is not for the changes due to voluntary movement to be eliminated from the sensory input, but for them to be appropriately evaluated" (126). In MacKay's view we build up and store an internal representation, or map, of our environment, which we then assume to be stable. The sensory systems explore the environment looking for evidence of change. At any moment, therefore, we know about the stability of the environment by reference to the stored representation and to any signals which indicate change. MacKay's considers that his view differs from that of most theorists of perceptual stability who see sensory inputs, moment by moment, "albeit modulated by signals fed in, fed forward or fed back" as constituting "the internal representation of the world", and according to whom perceptual stability depends upon "extracting an unchanging residue from the sensory input by a process of continuous and elaborate 'modification' under the guidance of information from motor centres" (127).

MacKay believes that the purpose of corollary discharges is "to set criteria that determine whether and in what respect an input calls for readjustment of the internal 'map'." Thus, "if a signal to the oculomotor system controls the magnitude of a saccade with an accuracy of x% and signals from the retina indicate a jump of the retinal image, the question to be settled by the evaluative process is whether this jump of the image implies that the world is stable or demands a change in 'map co-ordinates'" - that is, "whether the image jump is significantly different from that which the saccade was calculated to bring about on the 'null hypothesis' of visual stability, i.e. different by more than x%" (126). This particular example might be saying only that the subtractive process in some efference copy - reafference system need not give an answer of zero if stability is to be deduced:

an answer of x% of efference plus x% of reafference could also indicate stability.

MacKay's ideas on the uses of corollary discharges are not in conflict with the hypotheses of Helmholtz (77), Mach (120), Wundt (207) and Sperry (187: see also 80), but they permit a less demanding role for the discharges than would be permitted in the efference copy - reafference theories of von Holst and Mittelstaedt. Similar approaches have been developed by others (35, 194). Such ideas have been slow to find acceptance in some physiological circles because of the difficulty of reducing them to simple neuronal models.

In the hypotheses advanced by von Holst and Mittelstaedt, by MacKay, and by others, regarding central actions of motor command signals, the aspect which is particularly stressed is the nature of central processing of sensory information. In at least some of these roles proposed for them, however, it now seems very doubtful that motor command corollaries participate at all (see below). Nevertheless, the arguments regarding the nature of central sensory processing remain important even if the roles originally proposed for motor command signals are filled by alternative mechanisms such as proprioceptive afferent signals.

TERMINOLOGY

This section on Terminology is necessary because /Considerable inconsistency now exists in the literature regarding the terminology applied to the various accessory actions of motor commands. In particular the terms "corollary discharges" (187) and "efference copy" (86) are often used interchangeably, and both terms have been loosely applied to almost any internal neural correlate of a motor signal, and even to some peripheral (i.e. outside the central nervous system) accompaniments of motor commands. The historical

introduction given above indicates that the terms were introduced in connection with distinctly different hypotheses. The terminology used in this review attempts to preserve these distinctions.

All neural signals which are derived from motor commands and which remain wholly within the central nervous system, whether or not they involve sensory perception, will be referred to here simply as "internal command collaterals". They are examples of "central irradiation" by the motor commands.

> The term 'irradiation' has a long history in physiology. It was used, for example, in 1913 by Krogh and Lindhard (105) (see also 65, 156, 211) who postulated that, during muscular exercise, elements of the descending motor command 'irradiate' the cardiovascular and respiratory control centers within the central nervous system evoking changes in blood pressure, heart rate and breathing. Another prominent usage of the term is to describe the internal neural effects of the respiratory command so that, for example, the central inspiratory drive is said to 'irradiate' vagal and sympathetic centers involved in the control of heart rate, so contributing to sinus arrhythmia, the waxing and waning of heart rate during normal breathing (see 3, 4, 32, 103).

In all these associated functions of motor commands the internal command collaterals could be regarded as consequences or "corollaries" of the motor commands themselves, in that they arise from, or together with them within the central nervous system. Nevertheless, for historical reasons (see above), the term "corollary discharges"

should be reserved for those internal consequences of motor commands which affect sensations, either by central modification of the processing of sensory signals generated peripherally, or by their own independent actions. Where corollary discharges, acting in their own right, and independently of incoming sensory signals, evoke sensations, these are "sensations of innervation" (77, 207).

An "efference copy" is a special type of internal command collateral: its function is specifically to cancel reafferent signals and it may or may not influence perception. An efference copy does not simply suppress afferent transmission, as its function is to preserve 'exafference' while cancelling the contraction-evoked 'reafference'.

There are strong arguments against the use of the terms 'afferent' and 'efferent' without further qualification for connections and activities within the central nervous system. In a simple two-neuron reflex arc there is clearly one 'afferent' and one 'efferent' limb. If even a single interneuron is interposed, however, it is not unambiguously 'afferent' or 'efferent'. The problems are compounded in more complex systems. Thus, in considering a term like 'efference copy' one must ask how many synapses prior to the ultimate efferent channel (the α-motoneuronal pathway) can be regarded as transmitting efference rather than afference? When von Holst and Mittelstaedt (86) enunciated their views on efference copy and reafference they set themselves clearly against what they called 'classical reflex theory', which they saw as implying that actions are always initiated by stimuli, and that stimuli always evoke responses unless inhibited. They noted that central activities, such as the rhythmic outflow from the respiratory centers, can operate without sensory inputs, and so advocated a different approach. "Rather than asking about the relationship between a given

afference and the evoked efference (i.e. about the reflex)", they wrote, "we set out in the opposite direction from the efference, asking: What happens in the CNS with the afference (referred to as the 'reafference') which is evoked through the effectors and receptors by the efference?" (86). From the viewpoint of von Holst and Mittelstaedt, therefore, the problem of what to call 'efferent' and what 'afferent' did not exist - 'efferent' activity was generated centrally (not in response to an afferent input), and 'afferent' activity was generated peripherally. It is only within these constraints that the terms 'efferent' and 'afferent' can be used for wholly internal neural functions. Choice of such terminology would, however, make doubtful the use of 'efferent' to describe reflexly induced motoneuronal activity. The terminology is avoided here in connection with internal neural actions except where the concepts of von Holst and Mittelstaedt are specifically considered.

A similar problem arises when one considers 'motor commands'. Already this term is incorporated into the definitions given above, so its meaning in the context of this chapter should be made clear. Physiologists would not usually regard as a 'motor command' any neural discharge which gives rise to discharge of spinal α-motoneurones - otherwise, in the simplest case, the firing of muscle spindle primaries evoked by a tendon tap would constitute a 'motor command'. Whatever the logic of such a usage, it is so far from current practice in physiology that it cannot be recommended. Nevertheless, if the term is forbidden for one reflex it must be forbidden for all, for the same reasons. Thus, a 'motor command' is taken here to be a discharge or pattern of discharge which is generated within the central nervous system, and which leads to the excitation of spinal α-motoneurones. By this definition a 'motor command' would cause what von Holst and Mittelstaedt (86) called 'efference' (see above).

[Clearly, the proposal that any neural signal can be actually generated entirely within the central nervous system may pose problems for some physiologists, psychologists and philosophers - but a working definition is required. This Chapter deals mainly with what a layman would call 'voluntary' contractions (and others in this Handbook will grapple with defining that!). Other centrally-generated commands, such as those for respiratory movements (cf. 86) are also considered briefly.]

One particular feature of motor behavior which is relevant to much of what will follow, and to the question of terminology here, is the phenomenon of α-γ co-activation. This is the parallel activation of skeletomotor (α) and fusimotor (γ) fibers which occurs in most, perhaps all, voluntary muscular activity. The phenomenon is reviewed elsewhere (e.g. 69, 133, 141, 158, 188) and in other chapters of this volume/ (e.g. Matthews). Because of this co-activation, and because of the actions of (β fibers: 37), fibers which innervate both extrafusal and intrafusal muscle fibers/ a discharge of muscle spindle afferents is possible in any muscular contraction. This discharge will depend on the relative amounts of shortening of the extrafusal fibers (which would unload the spindles and reduce their firing), and the intrafusal fibers (which would increase spindle firing). It follows, as Granit has pointed out, that a "spindle component in excitation is included in the expectations related to the accomplishment of motor acts commanded by the will", and that, "the periphery itself is 'corollarized' by α-γ linkage" (70). This important point will be taken up again in the sections which follow for, in every case where an effect is attributed to a corollary discharge, the possibility must first be excluded that the effect is due to the discharges of sensory receptors, particularly intramuscular receptors. With respect to terminology two points should be noted. First, the discharges of α, β and γ motoneurons / cannot be regarded

as any kind of "central irradiation", "internal command collateral", "efference copy" or "corollary discharge" according to the terminology recommended above, because they are not internal to the central nervous system (- wholly internal collaterals of these axons, such as the collaterals of α axons which go to Renshaw cells, would however, be "internal command collaterals", and these might be used as corollary discharges). Second, discharges evoked in afferents of muscle spindles and tendon organs by the firing of α, β or γ motoneurons cannot be regarded as "central irradiation" because they also are not wholly internal to the central nervous system: such discharges are a form of "reafference" (see above).

COROLLARIES OF MOTOR COMMANDS TO LIMB AND TRUNK MUSCLES

If an irradiating motor command invades the 'sensorium' and evokes sensation, that sensation might be one of movement or of altered position of the part to which the command was directed, or of force generated by the muscular contraction in the part. Direct perceptual effects (sensations of innervation) of both kinds have been proposed and are now considered. Possible roles for corollary discharges in modifying the perceptual effects of proprioceptive afferent signals are also considered. Sensations associated with contractions of the oculomotor muscles are dealt with separately in the section following this.

Sensations of movement

Three reasons have been advanced to support the proposition that sensations of innervation for the limb and trunk musculature may manifest themselves as sensations of movement. First is the phenomenon of the 'phantom limb' (149), an illusion experienced by amputees that the amputated part still exists and can change its perceived position in space in response to motor commands despatched to it; second, is the ability of animals and man to recover control of complex movements after

de-afferentation of a part; and, third, is the claim that human subjects perceive that they successfully execute movements attempted during anesthesia of the moving joints and skin, even when such movements are mechanically obstructed (96, 144). These claims are now reviewed together with other evidence and the conclusion is reached that sensations of movement are not generated by centrifugal mechanisms.

PHANTOM LIMBS. "Natural" phantoms occur in about 95% of cases of amputation (17, 78). "Experimental" phantoms can also be produced by local anesthetization, after which they appear in about 30 minutes (142). Phantoms also occur commonly in paraplegics (15, 17, 162), and during spinal anesthetic blocks. Unfortunately, much of the literature on this topic is purely anecdotal and very few critical scientific studies have been reported A comprehensive review of much of the early literature on phantom limbs is given by Bradley (17). Typically, a phantom is associated with a mild tingling sensation, and is strongly perceived as having a position in space. More distal parts of a phantom are more clearly perceived, so that the intensity of referred sensation is roughly proportional to the central representation of the part in either the somatosensory or motor cortex (157). There have been reports of abolition of natural phantoms by lesions of the post central cortex (30, 76, 192), although not all post-central cortical excisions have this result (17).

It has been frequently noted that phantom limbs are perceived to move in response to motor commands despatched to them (10, 17, 68, 78, 142, 162). It is said that Admiral Lord Nelson, who remained conscious of his ability to move the phantom fingers of his amputated arm, took this as proof of the existence of his soul (17). Clearly the ability to make such movements must be considered in any account of sensations of innervation.

Not all perceived movements involving phantom limbs are relevant, for many of them involve no more than the perception of an entirely

stationary phantom carried by the movement of its mobile stump. Such perceptions reveal nothing about sensations of innervation, for the phantom merely holds its fixed position on the moving stump and this need not imply any change in its internal neural representation nor any new signals related to it (62).

More relevant here are the less common experiences of movements occurring within a phantom in response to motor commands - movements which result in changes in the perceived position of one internal component of the phantom relative to another (10, 17, 78, 142, 162). Movements of this kind are typically more difficult to make and cannot be finely graded. Often the attempts to make such movements are accompanied by gross twitching in the stump (10, 78, 162). During the second world war Henderson & Smyth studied the phenomenon in more than 300 cases of major amputations (78). They found that internal movements of a phantom were always accompanied by contraction of some muscles in the stump and that when such contractions were abolished by cutting the nerves in the stump, then the ability to make internal movements with the phantom was lost. They concluded that "appreciation of willed movements depends on afferent impulses from muscles which normally move that part".

Melzack & Bromage (142) made an investigation of experimental phantoms induced by paralysing the arm with a local anesthetic block of the brachial plexus. They recorded electromyographic activity in the affected arm while each subject made repeated attempts to move. The subject gave a running account of his sensations. They found that "total loss of voluntary movement of the phantom limb was reported at about the time that emg activity no longer appeared on the records". These findings, like those for natural phantoms described above, suggest that afferent impulses generated peripherally during attempts to move lead to the sensations of movements. Both sets of findings

provide strong evidence against sensations of innervation being sensations of movement.

The mere existence of a phantom limb and its static position in space do not appear to depend on peripheral inputs as they persist after denervation of the stump (17, 78) and after nerve block (142). From this it would follow that the sense of static position can be generated, or at least maintained, by nervous activity which is wholly internal to the central nervous system (61, 142). This internal representation of position, or 'body scheme' (76), can continue to be influenced by sensory inputs: thus, irritation of the stump may awaken awareness of a phantom which has faded from consciousness, or may cause spontaneous changes to occur in the relative positions of parts within the phantom (17). Spontaneous changes in the perceived static position of a phantom can occur without any awareness of movement between positions, and such changes are especially likely to occur when, in experimental phantoms or in the phantoms of paraplegics, the position of the real limb is seen - in such cases, the phantom suddenly "fuses" with the real limb (15, 17, 142).

In long-existent phantoms, mere concentration by the patient is said sometimes to cause the phantom to adopt a given position (17). Where paraplegic patients have been reported to have acquired an ability to "move" their phantoms, this ability was acquired only after many months (15), and seems as likely to have been a manifestation of a high-level interference with the body scheme similar to that acquired through concentration, as it was to have been any kind of a sensation of innervation.

It can be concluded, therefore, that superficially persuasive data on phantom limbs provide no firm evidence in favour of motor commands influencing perception.

DE-AFFERENTATION. Early experiments on de-afferentation of limbs by cutting the dorsal spinal roots failed to demonstrate any remaining ability to perform or to re-learn purposive movements (109, 152, 200). Later experiments, however, have amply demonstrated that recovery

of voluntary movements can follow such procedures in animals (16, 57, 196), and in man (43, 155; see also 197). However, the retrained movements are not normal. They "remain permanently ataxic and dysmetric" and "the elegance of normal movements is lost" (16). Retraining of movements under vision is very important, although retraining in deafferented monkeys without visual feed-back has been accomplished by Taub and his associates (196, 197; see also, Taub, this Volume). When only one forelimb is de-afferented in a monkey, it is simply neglected unless the opposite, normal, limb is restrained; with bilateral de-afferentation, however, both limbs are used spontaneously and develop, over a period of weeks or months, co-ordination in walking, the ability to grasp (as, for example, during climbing), and, occasionally, the ability to pick up small objects between the thumb and forefinger (196).

The gross recovery of movements, however inelegant and dysmetric, and the ability to co-ordinate and grade them even in a coarse way after transection of the dorsal roots suggests that these abilities can exist in the absence of afferent kinesthetic inputs. It is now known that afferent information carried by both myelinated and unmyelinated axons can enter the ventral spinal roots (28, 29), so that the possibility that some afferent kinesthetic inputs survive transection of the dorsal roots cannot be entirely excluded. Nevertheless, the failure of even very large electrical stimuli to evoke a cortical response when applied to the central cut ends of nerves in animals with acute and chronic de-afferentations (195), counts against this.

If afferent feedback is unnecessary for the re-acquisition of coarse motor skills a strong case can be made for some form of perceived internal feedback acting in its stead. Unfortunately, as Nathan & Sears (155) have pointed out in their review of accounts of deafferentations in man: "the observations on man are few, and they do not include accounts of subjective observations by the patients; such information is likely to be illuminating in a condition with such

deprivation of sensory information." One can, of course, only guess what de-afferented monkeys might base their adjustments of motor behaviour upon. Even if some form of perceived corollary discharge does contribute guiding sensations after de-afferentation, however, there is no need to suppose that these sensations are perceived as movements. It would be necessary only for the de-afferented individual to learn to identify, by wholly central mechanisms, that degree and pattern of command signals which will lead to success. It will be argued below that sensations of perceived muscular force can be sensations of innervation. One could, therefore, suppose that the re-acquisition of coarse motor skills after deafferentation might depend on an association of perceived commands for muscular force with the variously rewarded or observed movements which result from those commands - and all this without the de-afferented subject ever feeling that he moved.

DIMINISHED KINESTHETIC AFFERENT INPUT. Local anesthetization of the fingers or thumb leaves unaffected the long flexor and extensor muscles which move those digits, but causes kinesthetic sensibility in the anesthetized digits to be considerably blunted (26, 47, 62, 63, 96, 136, 144, 145, 151, 160). It was originally claimed that movements made with the anesthetized digits could be made "with much the same accuracy" as before anesthesia and, importantly, "if the movement is restrained ... the subject believes he has made it just the same" (144). This claim was subsequently modified (146), although, in its original form it had gained some prominence in the physiological literature. In a direct examination of this question, Goodwin, McCloskey & Matthews (62) repeated the experiment and reported that "subjects could readily detect for both the fingers and the thumb when the course of a large movement was manually obstructed by an experimenter". For smaller movements it was found that subjects were barely aware of moving at all even when their movements were unobstructed, and it was suggested that the earlier confusion had arisen because small movements were tested

which may have been undetectable by the prevailing, blunted, muscle sense. Such movements it was said, may have been trained under vision but not otherwise perceived at all as movements, either when they were executed properly or when they were obstructed - they were simply assumed to have occurred in response to each attempt to move.

These considerations also appear relevant to observations by Kelso (96) on subjects with anesthetized digits. These subjects made quite large active movements but failed to detect when these were unexpectedly obstructed. Nevertheless, kinesthetic sensibility in these subjects was considerably blunted, and they could not detect comparable large passive displacements of the same digits. Therefore, it is doubtful whether they ever perceived, as movements, their active contractions. Again it is likely that they simply assumed that commanded, but kinesthetically unperceived, movements proceeded on each attempt. Kelso's subjects did, however, demonstrate good accuracy in reproducing unobstructed active movements in these conditions, which indicates that they could reproduce the motor commands they needed without implying that those commands were sensed as movements.

It is of interest that human subjects can make movements which they do not perceive kinesthetically. With visual guidance under a microscope very fine movements can be made which cannot be perceived as movements when repeated without such guidance (144, 158, 175). When kinesthetic afferents are disturbed, even larger movements may be executed but not perceived, as suggested above. An example of this is shown in Figure 3, which illustrates what a blindfolded subject perceives upon attempting to extend all the digits of one hand when the index finger of that hand has been anesthetized by an injection of local anesthetic at its base. The subject successfully accomplishes the movement he attempts but perceives that the extension of the proximal interphalangeal joint of the anesthetized finger is incomplete. Clearly, for the very fine, imperceptible movements for which one needs visual guidance, and for the coarser movements which can occur unperceived when some of the

Figure 3 near here

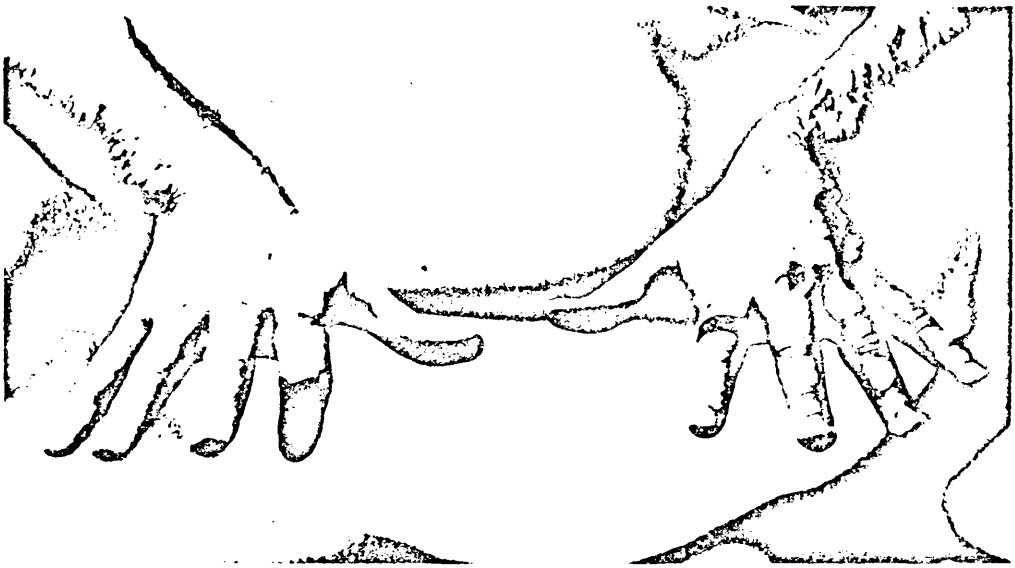


Figure 3. The index finger of the left hand (marked with circle) had been ring-blocked by the injection of lignocaine at its base. The blindfolded subject was asked suddenly to extend all the digits of the affected hand starting from a position of flexion, and then immediately afterwards to put the fingers of his other hand in the position into which he felt he had moved the affected hand. His position was then voluntarily 'frozen' and photographed. The insentient finger was felt to have failed to extend itself at all joints, though it actually succeeded in doing so. From Goodwin, McCloskey and Matthews (62).

relevant kinesthetic receptors are anesthetized, there is no sensation of movement and so no need to propose a sensation of innervation.

In the special circumstances which prevail for a minute or two during the development of 'pressure' or 'ischemic' nerve block in man afferent kinesthetic inputs are blocked (- at least, in their access to consciousness), while the ability to move survives. During this brief period a subject, when blindfolded, can move but remains unaware of any movement which he achieves (62, 110). See figure 4. Presumably, the phenomenon occurs because sensory fibers are blocked slightly before motor fibers. Such nerve block is almost certainly not selective (8, 58, 97) and considerable motor impairment exists by the time that afferent kinesthetic impulses are blocked. This presents difficulties for studying motor skills in this 'kinesthetically-deprived' state (110, 111, 112, 113, 114, 115). For the present analysis, however, the phenomenon shows that movements can be commanded, and even executed, without causing sensations of movement: thus, it provides a further argument against sensations of movement arising as perceived corollary discharges.

Figure 4 near here.

PARALYSIS. The final, and most conclusive, evidence on the matter of whether corollary discharges are perceived as movements comes from perhaps the most straightforward experiment. When various muscle groups or the whole body are paralysed and then the subject attempts to move the affected parts, no sensation of movement accompanies the attempt. This is so whether the paralysis is accompanied by anesthesia of the part, as in local anesthetic or ischemic nerve block (62, 110, 112, 142) or whether normal peripheral sensation is preserved, as in neuromuscular blockade (62, 140). In all these instances a perception that the paralysed part is extremely heavy accompanies the failure of the motor command to evoke any consciousness of movement, and this

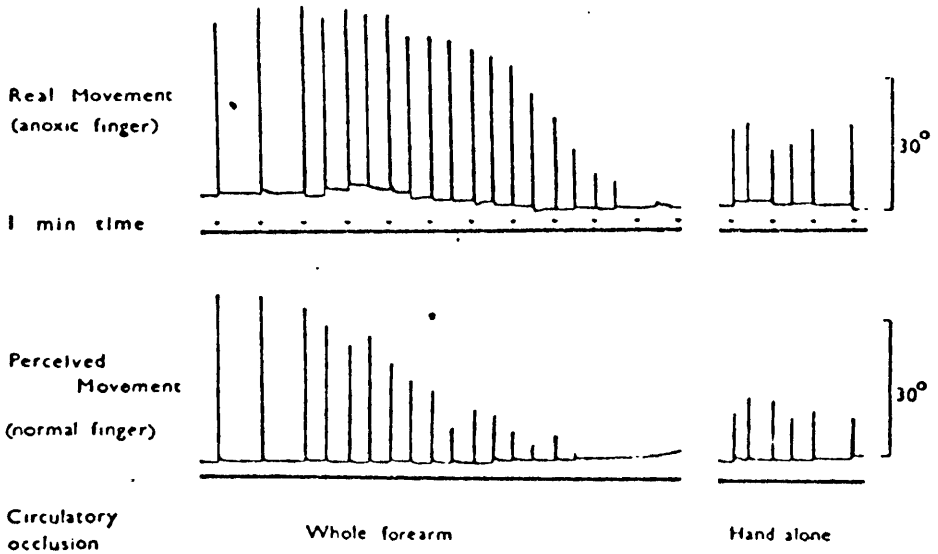


Figure 4. Records demonstrating that on progressive paralysis of a limb the perception of movement may be more severely impaired than the actual ability to move, making it unlikely that perception of movement can depend primarily on sensations of innervation. Top trace shows movements at the metacarpophalangeal joint of the index finger of one hand at a time when circulation to the arm was occluded; interphalangeal joints were fixed in full extension by strapping. Periodically, the subject was asked to raise his finger to full extension and then to lower it again; in between the finger lay partly flexed under the action of gravity. Immediately afterward he was asked to make an equivalent movement with the index finger of his other hand, thus providing an objective measure of his perception of the extent of the movement that was being paralyzed. Left: circulation to the whole of the forearm and hand was occluded by a pressure cuff above the elbow, which eventually led to complete paralysis of all the muscles involved and to complete loss of sensation. Even when paralyzed the subject still continued to attempt the movement at half-minute intervals. Right: pressure cuff had been shifted to the wrist so that the hand remained anesthetized, but the muscles of the forearm had been able to recover. Upper cuff was inflated for 13 min before the beginning of the records shown. There was an interval of 14 min between the left and right sets of records. Recordings were made by connecting the fingers to freely moving potentiometers. Subject could not see either his hands or the recordings. [From Goodwin, McCloskey, and Matthews (62)]

phenomenon is dealt with below.

An argument which will be considered below concerning the oculomotor muscles is that corollary discharges associated with those muscles might not evoke sensations referable to the eye itself, but instead might evoke only sensations referable to the visual world which the eye sees. Similarly it might be argued here that corollary discharges of motor commands to the limb muscles do not evoke sensations of movement of the relevant part, unless those sensations can be related to inputs from the peripheral sensory fields of that part. On this argument the absence of sensations of movement accompanying attempts to move parts which are both paralysed and anesthetized could be held to be inconclusive because anesthesia removes the inputs through which corollary discharges manifest themselves. It could also be said that simple paralysis by neuromuscular blockade is an inadequate test of the matter if peripheral sensory inputs are minimal when the unsuccessful attempts to move are made. The argument cannot be sustained, however, as it has been shown that even when peripheral cutaneous inputs which are consistent with success of an attempt to move are provided during neuromuscular blockade, no sensation of movement accompanies that attempt (140). Nor does an attempt to move a paralysed part cause any sensation of movement of a stationary cutaneous stimulus located on the paralysed part (140).

From all of the foregoing /it can be concluded that, at least for the limb and trunk musculature, motor commands do not evoke sensations of innervation in the form of sensations of movement.

Interactions between corollary discharges and kinesthetic afferent inputs

For some years conventional physiological opinion held that the discharges from intramuscular mechanoreceptors have no access to consciousness. Proprioceptive sensations were said to depend on the

activity of receptors in the joint capsules and ligaments. Later studies forced a revision of this view and it is now clear that muscle receptors contribute to kinesthetic sensibility (for review see 61, 62, 134, 136).

One argument against muscle spindles making any contribution to kinesthesia was that these receptors do not give a discharge which unambiguously signals muscle length or rate of change of muscle length. This is because muscle spindles fire not only in response to passive stretching of the whole muscle in which they lie, but also in response to contraction of their own striated muscular ends caused by discharge of fusimotor (γ-efferent) fibers (e.g. see 69, 133, and other chapters of this volume). Merton (143) observed that, "no doubt the absolute length of a muscle could be worked out indirectly if the rate of discharge of the γ efferents were taken into account", but like others who argued against a kinesthetic role for the spindles he felt that this was "a long way round", and not likely. There is now, however, considerable evidence that muscle spindles do contribute to kinesthesia, and it seems likely that corollary discharges provide the mechanism by which a useful kinesthetic signal is extracted from their total discharge. The proposal of such a role for corollary discharges comes from experiments on vibration and loading of muscles in man.

When high frequency vibration is applied through the skin over a muscle or its tendon, the vibrated muscle contracts involuntarily in a "tonic vibration reflex" which is usually attributed to excitation of the primary endings of muscle spindles (33, 73). The subject whose muscle is vibrated experiences an illusion of movement at the joint about which the vibrated muscle operates (62, 64), and this illusory movement occurs in the direction which would normally stretch the vibrated muscle. Illusory movements occur in opposite directions when vibration is applied to agonists and to antagonists, but none are experienced when the vibration is applied over the joint. This provides important evidence that muscle receptors rather than joint receptors give the signals that cause the illusions. Even when

all the joints and skin of the hand are anesthetized, vibration of the long flexor tendons within the anesthetized hand causes illusory sensations of extension of the fingers and thumb. Thus, although there is every likelihood that paciniform corpuscles and other mechanoreceptors within the skin and joints of the region normally would be excited by vibration, the kinesthetic illusions depend not on these but on the excitation of receptors within the muscles. Discharges seen in multifiber recordings from joint nerves during vibration (148) are likely to be due to the excitation of paciniform endings and in any case are not relevant to kinesthetic illusions. The vibration-induced illusions are predominantly illusions of movement - of velocity of joint rotation (62, 107, 135) - and continue for as long as vibration is applied.

It seems virtually certain that the spindle primaries are involved because of their high sensitivity to vibration (13, 22, 23, 24) and because of the appropriateness of illusory movement as a sensation arising from a receptor-type normally more sensitive to dynamic than to static stimuli. Nevertheless, considerable excitation of spindle secondaries and Golgi tendon organs is also caused by muscle vibration in man (23, 24).

If activity of muscle spindles is responsible for vibration-induced kinesthetic illusions, why do not similar illusions occur when the same spindles fire in response to the activity of fusimotor fibers? It is known that fusimotor activity increases with increasing strength of isometric voluntary contraction, so that the level of fusimotor-induced spindle activity increases too (24, 74, 75, 201, 202, 203) - so why are there no illusions? An answer to these questions could be that corollary discharges are used within the nervous system to distinguish the spindle firing which is 'appropriate' for any level of voluntary isometric contraction, from that which is 'inappropriate' and therefore of kinesthetic significance. One simple way for this to occur would be for the corollarydischarges to act as an 'efference copy' (86, see 'Terminology' section, above), and for the fusimotor-induced activity of spindles to act as 'reafference'. Then, by appropriate cancellation, only those spindle discharges with kinesthetic significance ('exafference') would proceed to a conscious level.

(It should be noted that on such a 'subtractive' scheme the efference copy should carry a negative sign and spindle activity a positive sign, so that only an excess of afferent activity and not an excess of 'efference' could impinge on consciousness as movement - it has already been indicated above that corollary discharges to limb muscles are not perceived as movements.) Alternatively, corollary discharges might be used to make the distinction between fusimotor induced and kinesthetically significant activity by 'evaluative' processes of the kind envisaged by MacKay (see Historical Development, above).

Muscle vibration probably causes an increase of spindle firing from its pre-existing level to some constant level - in the simplest case, by 1 : 1 entrainment, to the vibration frequency (133). It would, therefore, be expected that the kinesthetically significant proportion of vibration-evoked spindle firing would decrease as the force of muscular contraction (and so, fusimotor-induced spindle firing) increases. Such a process was proposed by Goodwin, McCloskey and Matthews (62) to explain the failure of vibration to cause kinesthetic illusions when applied to a strongly contracting muscle. A similar argument applies to the findings illustrated in Figure 5. When the velocity of a vibration-induced illusory movement is observed, it is found to decrease as the load borne by the vibrated muscle increases (135). This would be expected if only part of the spindle discharge - that part in excess of the level 'appropriate' or 'expected' for the prevailing contraction - were perceived. In a very strongly contracting muscle vibration would be expected to add little or nothing to the prevailing level of spindle discharge, and so no illusions would occur. Results such as these (62, 135; Figure 5) therefore indicate that some central process sorts and transmits only the kinesthetically significant portion of receptor firing.

The experiments so far described do not distinguish between muscle

Figure 5 near here

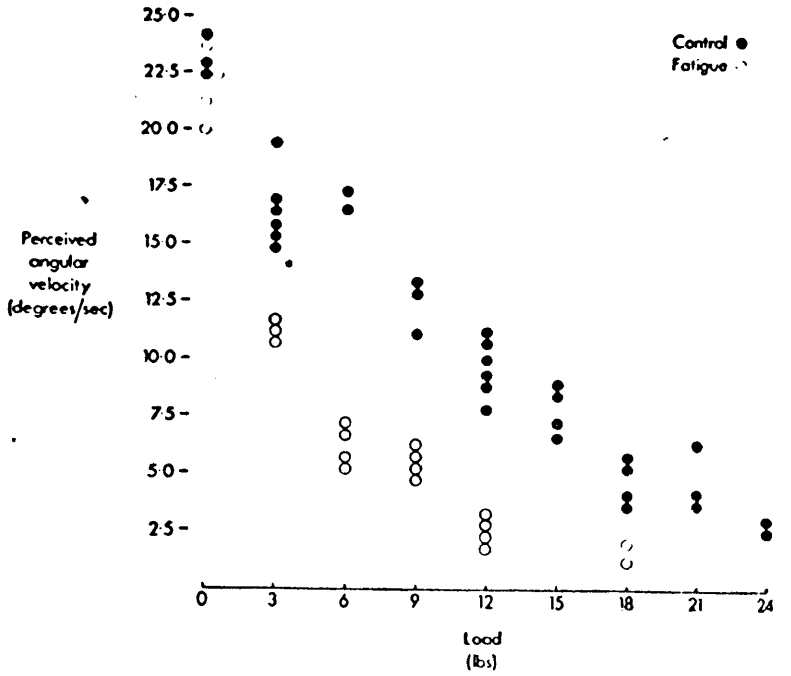


Figure 5. Angular velocity of the illusory movement of elbow extension induced by vibration of biceps brachii at 100 Hz, is plotted against the load at the wrist borne by tensing the vibrated biceps. Closed circles are points obtained when biceps carried its loads only briefly, and so was not fatigued. Open circles are points obtained when biceps was fatigued through a period of prolonged and continuous weight-bearing. From McCloskey (135).

spindles and tendon organs as the receptors involved in the illusory sensations which are processed as described. Certainly tendon organs are excited by vibration (23) and during active contractions (133) so that arguments similar to those just outlined could be marshalled to implicate tendon organs rather than muscle spindles in these processes. Observations made with vibration and loading during muscular fatigue, however, count against this alternative. As is shown in Figure 5, vibration applied to a fatigued muscle induces illusory movements of slower velocity at any load than it does when applied to a normal muscle (135). While the level of fusimotor-induced spindle firing could be expected to increase at any load during fatigue because of the greater command, or effort, needed to bear the load, there is no reason to expect the level of discharge from tendon organs to increase in the same circumstances. This is because tendon organs respond to intramuscular tension (see 133), which should remain the same at any load in fatigue. Thus, during fatigue, vibration would be expected to add a smaller increment than usual to spindle discharge, but to act similarly on tendon organ discharge. The slower illusory movements induced by vibration during fatigue therefore point to the spindles rather than the tendon organs as the receptors responsible.

Corollary discharges would clearly provide the simplest mechanism through which only the kinesthetically significant portion of discharge from intramuscular receptors is permitted to reach consciousness. Matthews (134) has recently suggested, without favoring, an alternative, entirely afferent mechanism by which the same result could be achieved: it is, however, considerably more complex than that involving corollary discharges.

If a certain level of spindle discharge is 'appropriate' or 'expected' at any level of muscular contraction, failure of extrafusal muscle fibers to achieve their normal level of force in response to a

motor command should lead to spindle discharge becoming inappropriately high (- if, that is, the intrafusal fibers do not at the same time fail to achieve their normal level of tension). According to the arguments above such inappropriately high spindle discharge should cause illusions of movement in the direction opposite to that which would normally be caused by the attempted contraction. Such circumstances might arise during the use of neuromuscular blocking agents when extrafusal but not intrafusal blockade (133) might occur, and perhaps also during muscular fatigue. However, no illusory movements are experienced (62, 137, 140). Possibly, therefore, some further internal 'scaling' mechanism is involved in cooperation with corollary discharges in the process of evaluating which level of spindle discharge is 'appropriate' to the circumstances - a signal of achieved muscular tension might be of value in this regard. This important aspect of perceptual evaluation requires further study.

It can be concluded that corollary discharges probably participate in the interpretation for kinesthetic purposes, of discharges from intramuscular receptors.

Corollary discharges and somatosensory afferents

It is generally accepted that many sensory discriminations, such as those concerning the textures of surfaces or the shapes of objects, are aided by movement of the exploring fingers or hands (e.g. see 56, 67). A role for corollary discharges is therefore easy to imagine, and many electrophysiological studies have demonstrated possible avenues for such participation (20, 66, 153, 172, 199, and see below). No definite perceptual effects of irradiation by motor commands have yet been demonstrated, however. In the discrimination of textures, for example, active exploratory movement is said to give no advantage over passive movement (106).

Many electrophysiological studies (66, 172, 199) have shown inhibitory effects by centrifugal 'motor' signals on ascending sensory pathways, and psychophysical thresholds for detection of tactile stimuli appear to be raised, not lowered, during active movement (31, 36). Possibly

corollary discharges play a part here. These findings might suggest that, contrary to general expectation, tactile acuity should be diminished during movements, although this need not be so. Gordon (67) has noted that "Improved acuity is not inconsistent with a raised detection threshold," and has proposed a simple scheme by which descending influences could act by lateral inhibition at a sensory relay station to 'sharpen' a stimulus. On such a scheme perceptual thresholds could increase while, above threshold, acuity improves. This observation provides an important warning for future experiments in this area.

In brief, therefore, there is little evidence on the matter of a possible role for corollary discharges in the 'interpretation' or perception of somatosensory afferent signals.

Sensations of muscular force, or heaviness

If one carries some load for long enough to cause the muscles which support it to become fatigued, one notices that it seems to become "heavier", and ultimately may become "too heavy" to support any longer. This phenomenon can be demonstrated objectively (137) by asking a subject to support a weight with one arm for a prolonged period, and to choose at various intervals through that period weights which seem to him to be as heavy as the continuously supported one. These matching weights are lifted with the corresponding muscles of the opposite arm, and are supported only intermittently so that this arm does not become fatigued. The subject chooses successively larger weights to match the one borne by the gradually fatiguing arm, showing that the perceived heaviness of the continuously supported weight does, indeed, increase. Figure 6 illustrates an experiment of this kind.

What gives rise to the sensation of the heaviness of a lifted object? In the Introduction to this Chapter, Wundt (207) and Muller (154) were quoted suggesting that this sensation might arise

Figure 6 near here.

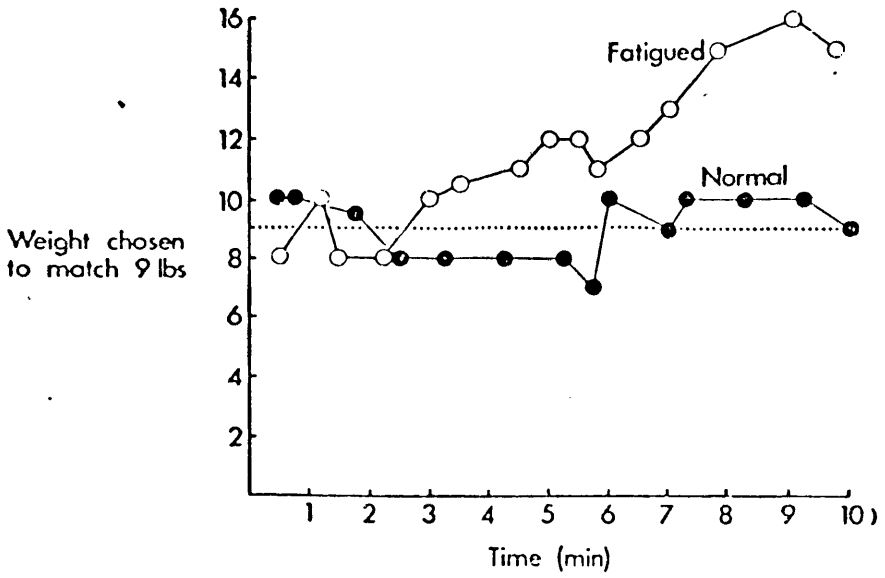


Figure 6. A subject was given a weight of 9 lbs (4.09 kg) to support by contraction of biceps-brachialis of one arm and, in a series of trials, chose apparently equal weights supported in the same way by the other arm. When the reference arm was rested between trials, the subject chose weights close to the reference weight to match it (closed circles). When the reference arm supported its weight continuously, it became fatigued, and heavier weights than the reference weight were chosen to match it. From McCloskey, Ebeling and Goodwin (137).

from a knowledge of the effort employed in lifting or supporting a weight. The same argument is adopted by many today. Thus, for example, Henneman (79) noted in a recent textbook account of motor control that, "in many paretic limbs, weights feel heavier than they actually are because of the greater effort involved in all performance". This argument, that heaviness is known because of effort, or command, employed rather than through results achieved, carries the assumption that one can perceive, in some way, the motor command. In considering this argument, therefore, we clearly must consider a role for corollary discharges.

Before proceeding to this, however, the alternative view should be examined - that one depends in judgements of muscular force or heaviness, as in judgements regarding other sensory modalities, upon afferent discharges arising peripherally in various sensory receptors. In a wide variety of experimental and neurological conditions (see discussion below), there is a constant association of weakness and increases in perceived heaviness. It is difficult to propose a mechanism for this which depends upon changes in peripheral afferent discharges for it seems likely that sensory receptors in skin, joints, tendons and muscles would continue to provide signals of the actual pressures and tensions involved during weakness. This seems a reasonable expectation, for example, in muscular fatigue. An exception might be the muscle spindles because when a centrally-generated effort increases (as it must, to maintain tension in a fatigued or otherwise weakened muscle), fusimotor drive could also be expected to increase with a resultant increase in the activity of muscle spindles. This possibility is the point of Granit's (70) observation about "the periphery itself" being "'corollarized' by alpha-gamma linkage" (see also 'Terminology' section, above).

Such reafferent discharges from muscle spindles cannot, however,

be responsible for sensations of muscular force or heaviness. This conclusion follows from the results of experiments using high-frequency (approx. 100 Hz) vibration of muscle. Vibration applied over the tendon of a muscle in normal human subjects powerfully excites the primary endings of muscle spindles, and also causes significant increases in the discharges of spindle secondaries and Golgi tendon organs (23, 24). An involuntary reflex contraction of the vibrated muscle occurs and has been attributed to this excitation of spindle endings (33, 73). Hagbarth and Eklund (73) were the first to note that "a subject gets a feeling of relief or lessening of tension", not a feeling of heaviness or increased force, when a muscle contracts involuntarily in response to vibration. Similarly, it has been shown that subjects perceive themselves to be exerting a smaller muscular force than normally when a given isometric tension is achieved with the assistance of a 'tonic vibration reflex' (137). Not only do these observations provide evidence against the participation of muscle spindles in sensations of muscular force (- and, against participation of tendon organs, for these are also excited by vibration, as noted above -), but they argue in favor of an awareness of the descending motor command being the basis of the sensation. This is because the involuntary reflex assistance provided by vibration permits a reduction in the centrally-generated voluntary motor command required to achieve a given muscular tension. This argument is summarized diagrammatically in Figure 7.

Figure 7 near here

The normal relations between motor commands and evoked muscular contractions can be disturbed in many ways, and whenever this is done the perception of muscular force or heaviness maintains, at least qualitatively, its relation to the motor command rather than to the tensions and pressures generated. Demonstration of this has usually

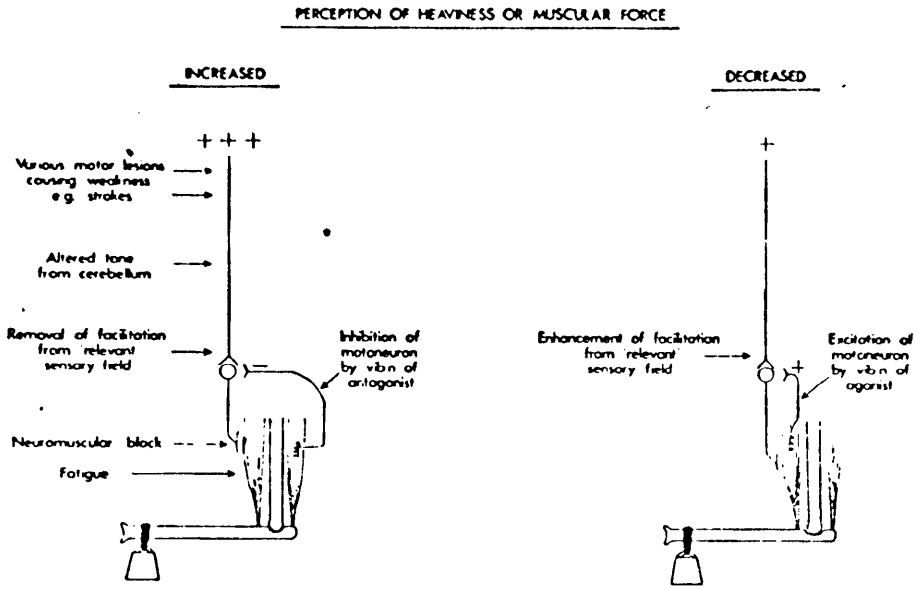


Figure 7. Summary of factors affecting perceived muscular force or heaviness. See text.

depended upon having a subject lift a weight or exert a reference tension with a muscle group on the affected side, and to match the apparent heaviness or force involved by choosing a similar weight, or by exerting an apparently similar force, with the corresponding muscle group on the other, unaffected, side. In this way it has been shown that when a muscle is weakened by fatigue (48, 137), or by partial neuromuscular paralysis (49, 50, 51), then weights lifted by that muscle feel heavier than normal and forces exerted by it feel greater than normal. Alternatively, muscular contraction can be inhibited through the neural pathways which contribute to its excitation: this can be done by vibrating the antagonist of the contracting muscle, and thereby eliciting a muscle spindle discharge which is inhibitory to the motoneurons of the contracting agonist. Again a sensation of increased muscular force or heaviness accompanies the weakness (65, 137). See Figure 7.

The association of weakness with perceived heaviness was recognized as a general neurological principle by Sir Gordon Holmes (82, 83). Holmes drew attention to disturbances of the appreciation of weight in patients with unilateral cerebellar lesions, noting that weights lifted on the affected, or "hypotonic", side of the body seem heavier than when lifted by muscles on the normal side. Such disturbances of sensation occur without any other - "conventional" - sensory loss. Holmes pointed out that the "hypotonicity" of the affected side would mean that unusually large motor commands would be required to achieve any given level of muscular force. Here, then, is another instance of increased voluntary motor command being associated with an increase in perceived heaviness or muscular force. See Figure 7.

Other neurological conditions provide further examples of the association between heaviness and weakness. Perhaps the simplest example is the simple "stroke" which results in hemiparesis. Samuel

Johnson (90, and see 49), for instance, took as evidence of his recovery from a "paralytick stroke" that, "This day I watered the garden and did not find the watering pots more heavy than they have hitherto been ...".

Most "strokes", of course, cause disturbances of conventional sensory modalities as well as motor power and so do not necessarily force the conclusion that the perceived heaviness is related to the increased motor outflow required for any task. Some strokes, however, are purely motor ones (42) and involve no conventional sensory loss. In these purely motor strokes, the symptom of increased heaviness is still common (21, 42, 49, 120), and increased perceived heaviness can be demonstrated objectively in matching tasks of the type described above (49, see Figure 7). Brodal (21), writing of his own purely motor stroke, which produced weakness but not paralysis, described his awareness of the "force of innervation" required to achieve muscular contractions.

Not all disturbances of the relation between central motor commands and achieved muscular tension result in increases in perceived muscular force. The "assistance" of a contraction by a tonic vibration reflex, as described above, reduces the centrally-generated motor command required in a contraction, and the perceived muscular force is reduced (see Figure 7). Another instance of "assistance" to the motor command is seen in muscle groups where inputs from the 'relevant' skin or joints of the moved parts seem to facilitate the motor command: examples of this are inputs from the thumb or index finger for the long flexor muscle of the thumb, and inputs from the hand for the elbow flexors (49, 50, 138). For such muscle groups enhancement of the neural facilitation from these 'relevant' sensory fields is associated with a reduction in the perceived heaviness of objects they lift (see Figure 7). When the tonic level of facilitation from these same inputs

is abolished, however, as in local anesthesia of the 'relevant' sensory field, perceived heaviness increases (49, 50, 138: see also Figure 7). [A suggested alternative explanation for these latter effects (129) cannot be sustained (54).]

It should be noted here that these many instances of an association between motor commands and perceived muscular force should not be taken as evidence that actually achieved muscular tension cannot be perceived. Indeed, when instructed carefully, normal subjects can demonstrate an ability to perceive intramuscular tension regardless of the effort or command required to achieve it (137, 169, 170): almost all normal subjects, however, appear to ignore the available afferent signals of intramuscular tension in favor of signals related to motor commands when estimating muscular force or heaviness (136). That normal subjects usually ignore these directly 'relevant' and demonstrably available afferent signals makes one time-honored objection to the involvement of corollary discharges appear much less likely. This is the idea introduced by Ferrier (40), and strongly supported by William James (89) that the magnitude of the motor command is perceived through afferent impulses set up by the activity of other muscles which are called into graded contraction at the time of the effort (-Ferrier specifically suggested the respiratory muscles). The objection seems even less likely when one tries to invoke it to explain judgements such as those described above, where subjects make comparisons between muscular efforts exerted simultaneously by muscle groups on each side of the body.

Clearly, a simple and convenient explanation for all the instances of association between commands and perceived muscular force would be that the motor commands irradiate sensory centers. Electrophysiological and anatomical studies have shown so many internal connections within and between major motor and sensory structures that little purpose would be served here by enumerating all

the possible sites for such irradiation. Certain general points can, however, be made. First, the corollary discharges involved would have to arise before the spinal motoneurones in the motor pathway. This follows from the observations outlined above and illustrated in Figure 7. Spinal motoneuronal output would be increased only in the instances of fatigue and partial neuromuscular blockade amongst the causes of motor weakness and heaviness: in the other causes of these conditions, in which the excitability of the motor pathway is depressed by experimental means (vibration of antagonist, removal of sensory facilitation), or by neurological deficits (altered cerebellar tone), the output of the spinal motoneurons could be assumed not to be altered. Similarly, in motor "strokes", the motor signals "upstream" of the spinal motoneurons would alter together with perceived heaviness, but the spinal motoneuronal output would not change.

A second point to consider is that the increases in perceived heaviness associated with motor strokes might suggest that the corollary discharges responsible arise before, or "upstream", even of the affected cortical cells. This need not be so, however, if corticofugal pathways are only partially interrupted by the stroke, because surviving pathways might then be expected to carry extra neural traffic to compensate for the loss, and this extra traffic might provide the relevant irradiation by the command. If this were so, one could expect that in at least some motor strokes which cause complete paralysis, all relevant corticofugal traffic would halt, and no sensations of heaviness would ensue. In the account by Ernst Mach of his own motor stroke, published in 1886 in 'The Analysis of Sensations', just such an experience is described. Mach wrote, "During the period of complete paralysis ... I felt no effort, but that it was impossible for me to bring my will to the point of executing the movement ... During the phases of imperfect paralysis ... my arm and leg seemed to

me enormous burdens which I could only lift with the greatest effort". (120: see also 136). One cannot, of course, be sure that Mach's paralysis was caused by the interruption of corticofugal pathways: it is possible, for example, that his 'stroke' involved the cortex itself. Nevertheless, this important matter deserves further study because the quoted account does suggest a post-cortical origin of the corollary discharges which are involved in perception of heaviness, effort, or muscular force. Certainly, when total paralysis is caused peripherally, by nerve block (62, 142) or by use of a neuromuscular blocking drug (140), the perception persists of a large effort accompanying every attempt to move.

Another finding which suggests that the motor signals for heaviness are provided at a relatively 'low' level comes from studies on patients in whom the cerebral hemispheres have been surgically disconnected. In such patients Gandevia (45) found that weights can be matched by lifting with corresponding muscles on opposite sides of the body and that, if a muscle on one side is fatigued by period of prolonged weight-bearing, the matching weight chosen by the unaffected side is larger than before. Thus, the signals for heaviness cross the mid-line even when the corpus callosum is divided, although heaviness still seems to depend on the size of the motor command.

Where corollary discharges have been considered up to this point the simplest role for them - that they act independently, and produce sensations of innervation - has been implied. The arguments advanced, however, including those concerning the possible sites in the motor pathway at which the corollary discharges could arise, would also apply if the discharges act on incoming sensory signals and produce their effects on consciousness not directly, but through altering the perception of these sensory inputs. During total paralysis and anesthesia of a part, motor commands remain associated with sensation of increased muscular force (62, 142), so one would have to propose that the sensory inputs which are affected in this way arise outside the

region to which the motor commands are directed. Very many possibilities for such interactions are known from electrophysiological and anatomical studies (66, 172, 199; and see below), and this more complex role for corollary discharges cannot be disregarded.

While corollary discharges could be used directly or indirectly to provide sensations of muscular force or effort, their use in judgements of the heaviness of a lifted object are more complicated. One can only judge the heaviness of an object if one can lift or support it: if the object cannot be lifted or supported by a muscular effort one can only say that it is heavier than some other object which can be lifted or supported by that effort. Therefore, when muscular tension increases in response to increasing command or effort some signal must be available to indicate which command or effort actually succeeds in generating enough tension to lift or support the object. A simple experiment in which the "lifted" object is rapidly unloaded from the lifting muscle as soon as a certain isometric tension is achieved shows that crude peripheral afferent inputs are sufficient for this purpose: it is not necessary for the weight to be "carried" or accelerated, but simply for some signal to be provided that the object has moved at a certain level of effort (52). It is as if the peripheral signal acts like an "event marker" to indicate to the central nervous system the level of effort or command which succeeds in moving or supporting the object - that is, the level of effort or command which is relevant to the required judgement of heaviness.

A similar view to this was given by Lewes in 1879. He believed that force, but not movement, sensations arise internally. "Suppose that I am suffering from cutaneous anaesthesia," he wrote, "I shall feel the effort, but not the effect; so that unless I am looking at my fingers, I shall be unable to say whether I have moved them or not" (116). (Lewes was extravagant in his support of the idea that

sensations of force arise internally. "Independent of and antecedent to all experience, we know the degree of Force, or Effort, which a movement demands: this is a birthright of the Soul", he wrote (116).)

Quantitative aspects of the relation between motor commands and sensations of force or heaviness are complex. Changes in perceived force or heaviness frequently do not bear a simple inverse proportional relation to the changes in muscular strength which they accompany. Indeed, this has been taken as evidence against sensations of force arising from motor commands (170). During partial neuromuscular paralysis, for example, perceived force and heaviness increase but rarely exceed twice their control levels even when the tension attainable in maximal voluntary efforts is reduced below 20% (49, 51). The situation appears to be similar in fatigue (137; and see Figure 5), and after motor strokes (49). When the excitability of relevant motor pathways is altered, however, as with vibration-induced changes in muscle spindle activity (137) or with altered inputs from associated sensory fields (46, 50, 138), maximal voluntary strength is rarely affected although forces exerted in submaximal contractions are perceived to be unusually high.

There is no reason to assume that the relation between motor command and perceived force should be a linear one. Nor can a linear relation between centrally-generated motor commands and achieved tension be assumed. Thus, some of the apparent discrepancies of proportionality between command and perceived force may reflect non-linearities in the relation between command and achieved tension. In particular, a changing level of reflex assistance to a voluntary motor command may occur at different output levels, and so contribute to such non-linearities. For example, Marsden, Merton and Morton (128) have described changes in the gain of load-compensating reflexes in the

human thumb, and have related the gain to "the effort made by the subject rather than the actual pressure exerted by the thumb". Motor activity evoked through such variable reflex mechanisms might contribute significantly to achieved force but not, as voluntarily-generated activity does, to the perception of force (see also, 51). Further quantitative work on the relations between motor commands and perceived muscular force is required.

In rapid movements an additional role for corollary discharges appears to exist: it seems likely that they provide perceived signals which can be acted upon before relevant kinesthetic afferent signals can be. For example, Angel (2) has described experiments in which subjects were induced to make numerous false moves when the directional relation between the movement of the hand and movement of a response marker was changed from time to time through a series of visual tracking tasks. In a significant number of trials 'false' moves were corrected in a shorter time than a simple reaction time, even when visual feedback could not have been involved. Figure 8 shows an example of this. Angel has suggested that corrections of this kind may be based upon perceived motor command signals. It should be noted that it would not be necessary in such a mechanism for anything more than direction of the false moves to be perceived: the experiment gives no information on whether sensations of force, or other sensations, were involved.

Figure 8 near here.

In summary, it can be concluded that corollary discharges participate in kinesthetic sensibility by generating sensations of muscular force or heaviness but not sensations of movement. They can also provide important sensations used in the timing of motor performances. Such sensations may provide important guiding signals for individuals deprived of kinesthetic afferent inputs. The extent to which normal, intact individuals might also use such signals instead of some available afferent inputs is an important matter which has not been investigated.

COROLLARY DISCHARGES AND EYE MOVEMENT

Much of the historical development of ideas regarding corollary

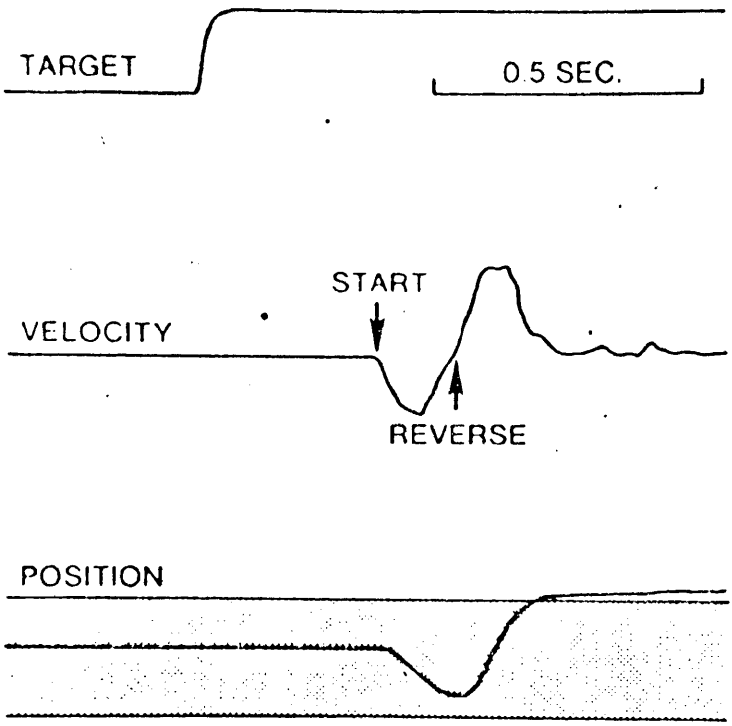


Figure 8. A false move corrected without visual feedback. At the time indicated on top line, a visible target jumps to left. Subject responds by moving hand to left. This causes marker to move in wrong direction. While the marker is still behind screen, and so is invisible (shaded area), subject reverses direction of movement. Marker then becomes visible at left (correct) side of screen. This response was classified as a false move, reversed while marker was invisible. The reversal was commenced in a shorter time than a kinesthetic reaction time. From Angel (2).

discharges concerned eye movements and stability of the perceived visual world. The major landmarks in this development were outlined above (see Historical Development, and Figure 1 and 2). In the more detailed consideration which now follows a role for corollary discharges will be considered in answering two questions. The first question is, 'Are positions and movements of the eye perceived in the absence of visual cues?' - and, if so,' 'Do corollary discharges provide or affect these kinesthetic sensations in the eye?' The second question, which may well be related to the first, is 'Do corollary discharges influence the perception of visual signals?' Wider implications of these questions are reviewed elsewhere (34, 147).

Corollary discharges and kinesthetic sensibility in the eye

In 1936 Irvine and Ludvigh reported that if the eye is passively moved in the dark by grasping its anaesthetized surface with forceps "no sensation of movement is aroused and the observer cannot state the position of his eye" (87). In 1960, Brindley and Merton (19) reported similar experiments in which one or both eyes were occluded with opaque corneal caps and moved with forceps. Passive movements of one occluded eye through tens of degrees were not detected, whether the other eye was occluded or whether it could see. Passive movements of the occluded eye did not cause detectable reflex movements of the other eye, nor did they cause apparent movements of things which the other eye could see. Brindley and Merton were aware that William James (89) had criticized Helmholtz's arguments regarding perceptual stability during eye movements on the grounds that sensory information from the opposite eye had not been considered (see below). Therefore, they occluded both eyes of a subject and imposed rotations on them both simultaneously, and in the same direction. Again, the subject did not detect deviations of up to 30^{o} from the mid-position.

Experiments of this kind led to the conclusion that the eye has

no afferent source of information regarding its position and movements. Thus, if the eye has any kinesthetic sensibility it would follow that this must arise from efferent sources. This point of view has been argued in detail by Merton (144, 146).

A re-examination of this question was made necessary by the findings reported by Skavenski in 1972 (178). In a carefully-controlled study using trained subjects Skavenski showed that rotations of about 10^{o} imposed on anesthetized, occluded eyes could be reliably detected. The same subjects were able, on instruction, to maintain the direction of the visual axis against forces which would otherwise have displaced the eye through about 5^{o}; again visual and non-proprioceptive cues were excluded as providing the basis for the correction. It was suggested that in the earlier, similar experiments of Irvine and Ludvigh (87) and Brindley and Merton (19) rather subtle proprioceptive sensations might have been missed because the subjects were untrained and were "distracted or under some degree of discomfort or duress" (178). As the surface of the tested eye was anesthetized and as the eye has, of course, no articular sense, the afferent signals responsible for the detections made in Skavenski's study are most likely to have arisen in the oculomotor muscles, (although unidentified retro-orbital receptors must also be considered). This conclusion means no more than that oculomotor muscle receptors behave like muscle receptors elsewhere, as it has now been repeatedly demonstrated that muscle receptors in the limbs can provide perceived kinesthetic inputs (61, 62, 134, 136).

One further aspect of the kinesthetic sensibility of the eye was investigated by Brindley and Merton (19): this was the perceptual consequence of impeding a voluntary movement of an eye in the absence of vision. Unfortunately, this matter is not entirely clear. The

original descripton had it that, in these circumstances, "the subject could not tell whether the eyes were held or not; he regularly had the impression that he succeeded in moving them through a large angle." Such an experience would be consistent with the view that "non-visual knowledge of the position of the eyes depends exclusively on judgement of the effort of will employed in attempting to move the eyes" (19). (Brindley and Merton attributed this view to Helmholtz, but it is not at all certain that Helmholtz believed that the effort of will gave kinesthetic sensations in the eye when vision was excluded - his arguments seem all to have dealt with visual sensations). Merton later described the same experiments (144, 146) rather differently: "When the subject attempted to make a voluntary eye movement, he could not tell if he succeeded or if his eye was restrained" (144).

It might be argued that kinesthetic sensibility of the eyes is inappropriately tested if it is required to reveal itself in the absence of vision. Afferent signals from intramuscular receptors in the limb muscles produce sensations referable, not to the muscles themselves (c.f. 55), but to the joints moved by the muscles (see 61, 62, 134, 136). Somewhat similarly, it could be that the signals of eye position and movement (whether of "outflow" or "inflow" origin) do not evoke sensations referable to the eye itself, but affect instead sensations regarding the visual world seen by the eyes. This cannot be entirely true for it is well known that normal subjects can direct the eyes with fair accuracy in the dark (72, 143, 176). Nevertheless, sensations of eye position and movement may be weak by comparison with sensations evoked when visual cues are available.

Appreciation of direction of the gaze in the dark is a phenomenon which Sherrington felt "must be attributed to muscular sense" (176). Merton (143) took the opposite view and noted: "There is no reason why we should not be able to judge the size of motor volleys

leaving the brain as accurately as we can judge the size of sensory volleys arriving". Gurevitch (72) studied 2,000 electro-oculographic records from 6 subjects who were trained to respond to an auditory stimulus by turning their eyes in total darkness and then maintaining them in the direction of formerly visible points. The subjects performed accurately in this task. Interestingly, the movements which ultimately carried the eyes to their final alignment differed from trial to trial in the number of saccades involved, the size of the individual saccades, and in the duration of pauses between the component saccades. See Figure 9. Gurevitch observed that "eye movements of equal total size and direction, just like motor acts of the organism as a whole, are generally produced by essentially variable sequences of innervation impulses" (72), and felt that, because of this, corollary discharges could not be important for performance. There is no reason, however, why a summed integration of the command signals delivered could not have been responsible. (See also (174).

Figure 9 near here

With respect to purely kinesthetic sensibility of the eye, therefore, one can conclude only that it exists. Available evidence does not clearly indicate its underlying mechanism, although afferent signals can participate.

Corollary discharges and visual perception

When we make judgements regarding the position and movement of a visual target relative to the body, three classes of signals must be available: (1) the position and angular velocity of the target relative to the axis of the eyes, (2) the alignment and velocity of the eyes relative to the head, and (3) the alignment and velocity of the head relative to the body. See Figure 10. The first of these classes of signals is of retinal location and movement. The third is proprioceptive, probably containing components common to all kinesthetic sensibility

Figure 10 near here

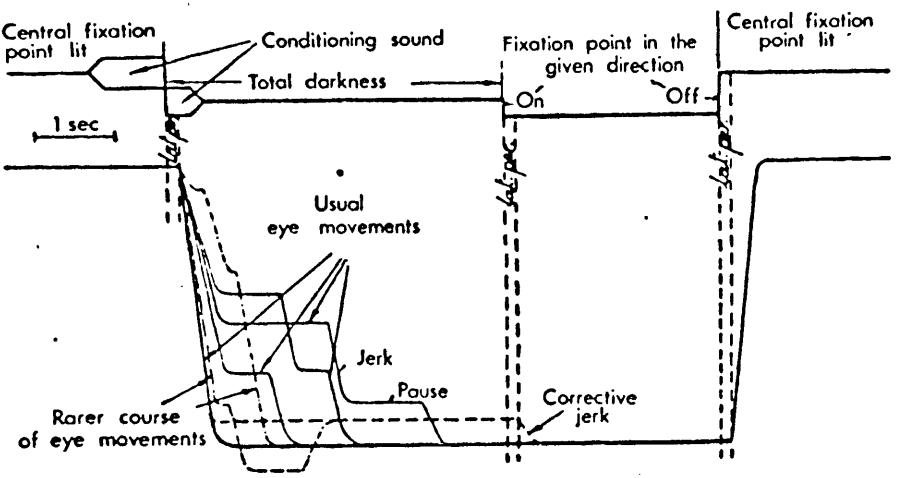
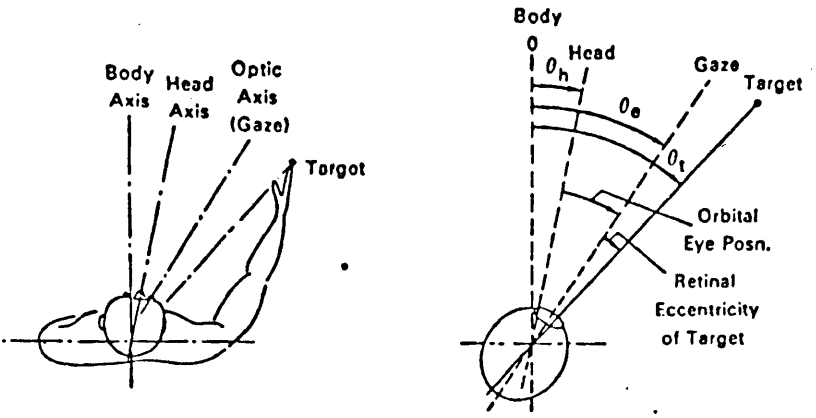


Figure 9. Representative scheme showing typical variability of equally directed precise (———) or imprecise (----) conditioned eye fixation movements in successive trials. Abscissa, time; ordinates, eye displacement during trials. In response to an auditory signal the subjects turned their eyes towards a fixation point of which they had learnt the location when it was visible some time before. From Gurevitch (72).



$$\text{Absolute Target Posn.} = \left[\begin{array}{c}\text{Target Posn. re Eye}\end{array}\right] + \left[\begin{array}{c}\text{Eye Posn. re Head}\end{array}\right] + \left[\begin{array}{c}\text{Head Posn. re Body}\end{array}\right]$$

$$\theta_t = \underbrace{[\theta_t - \theta_e] + [\theta_e - \theta_h]}_{\text{Gaze}} + [\theta_h]$$

Figure 10. Neural reconstruction of target position relative to the body. Neural reconstruction of target velocity must be based on velocity signals related to the same angles. From Miles and Evarts (147).

(61, 134, 136) plus a contribution from vestibular mechanisms. The remaining class of signal, that of eye position and movement, was considered in isolation above: it may be derived from extraocular ("inflow") sources, or from central irradiation by motor commands ("outflow"). It is possible that signals of eye position and movement are difficult to perceive on their own but manifest themselves more clearly when interacting with a visual input of some kind.

Some of the arguments used in supporting a role for corollary discharges in visual perception were outlined above (see Historical Development, and Figure 1). The essential argument concerns how retinal image displacements due to changes of eye position can be distinguished from similar displacements caused by changes in the position of visible objects - that is, how we know whether the eye or the viewed object has changed its position. Corollary discharges are invoked as the source of information about changes of eye position because extraocular kinesthetic signals have not been demonstrated to affect visual perception.

An important question concerns the type of eye movement for which corollary discharges might be important. The traditional arguments in favor of their participation concern voluntarily executed shifts of fixation, and how these differ from imposed movements of similar size. It is known that voluntary shifts in fixation are executed only by the fast saccadic system (161). Smooth eye movements, such as those used in tracking a moving target or those generated by the vestibular system, are evoked reflexly (165, 166), and stabilize the retinal image of a target when that target moves or when the head turns. Traditional arguments in favor of the use of corollary discharges for perceptual stability, therefore, concern voluntary fixations (see also 91, 93, 95, 147). A simple experiment illustrates this. With the head held still, extend both arms together and place the thumbs alongside each other.

Fixate the two thumbnails. Now slowly move one arm laterally, while keeping the other still. If one fixates the stationary thumb, the moving thumb is seen simply to move away, and the visual background stays still. If the moving thumb is fixated, however, both the visual background and the other thumb appear to move in a direction opposite to the tracked target. Finally, if the thumbs are separated and held still, and one fixates first one and then the other, neither of the thumbs seems to move nor does the background. The apparent movements seen during the tracking movement indicate that the perceptual stability for which corollary discharges are proposed to account does not occur for this type of movement. This need not indicate that eye position is not known during tracking movements, but only that the rules for perceptual stability are different. When a luminous target is tracked in the dark to a given position a subject can point to that position, although less accurately than when the target is located at the given point by a voluntary shift in fixation (41).

When a movement is imposed on the eye by an external force, visible objects seem to move (e.g. 19, 77, 80, 87, 179). This can be readily confirmed by pressing or tapping a finger against the corner of the eyelid while observing one's surroundings with that eye. When the visual axis is displaced and then held displaced by an external force, visible objects appear to be shifted. This can also be confirmed if one maintains a pressure against the corner of the eyelid: here the degree of apparent visual displacement can be roughly assessed by striking quickly at a visible target with a hand which is moved from a starting point that is initially out of the field of view. A refined experiment of this kind carried out in carefully controlled circumstances by Skavenski, Haddad & Steinman (179) confirmed this experience. These demonstrations of apparent shifts in the visual world accompanying imposed displacements of the visual axis indicate that, at least for

passive rotations of the eye, kinesthetic afferent inputs are insufficient to signal that the eye rather than the visual scene has changed its position. It is important to note that this argument applies as much to the static position of the eye as it does to movements imposed on it - when alternatives to extraocular afferent mechanisms are sought to account for visual stability they must work for both position and movement of the eye.

It is conceivable that afferent inputs are more effective during active, voluntary rotations of the eye than they are during imposed rotations. The mechanical state of the extraocular muscles, the background of contraction-induced proprioceptive reafference, and the central neural "context" into which afferent impulses would flow, could all be expected to be different in active and imposed eye movements. One possibility would be that corollary discharges 'gate' relevant kinesthetic inputs, allowing them access to perceptual mechanisms only during voluntary movements or fixations. These matters have not been studied. It is worth noting that, in the human finger, proprioceptive acuity dependent on muscle afferents is considerably improved during active contraction of the relevant muscles (47).

Central irradiation by motor commands was first proposed to play a part in the maintenance of perceptual stability in vision when the apparent inadequacy of kinesthetic afferent inputs to signal eye position was noted (77, 80). Positive evidence for its involvement came from observations on patients in whom the oculomotor muscles suddenly became weak (usually it was said that the oculomotor muscles were 'paralysed' in these patients, but complete absence of any muscular response to motor commands seems not to have been confirmed). On attempting to turn the eye in a direction in which it could not move, or could move only slightly, these patients saw apparent shifts in the visual world in the direction of the attempted movement. This

was illustrated in Figure 1. The "effort of will" (77) to move the eye, it was argued, had given the sensation that the eye did move, so that the unchanged position of retinal images made it seem that the visual world had shared the supposed movement of the eye (19, 27, 68, 77, 88, 117, 144, 198, and see 206).

Another observation which has been accounted for in terms of corollary discharges is similar to the findings in 'paralysis'. An early account of it was given by Mach (120) who restrained movements of his eyes to the right by pressing lumps of putty against the right side of each eyeball and noted that "the bare will to look rightwards gives to all images on the retina a greater rightwards value". Similar results were later reported by von Holst (85) and by Brindley and Merton (19). The phenomenon is depicted diagrammatically in Figure 13, and has usually been interpreted as indicating that movements of the eye are calculated from corollary discharges rather than according to any afferent signals which might indicate its true position.

A similar observation has been given a similar explanation in connection with position rather than movement of the eye. Skavenski, Haddad and Steinman (179) described an experiment in which subjects fixated a red target with one eye (the other eye was closed) and then moved a white target to a position they perceived to be "straight ahead". The viewing eye was pulled either to the right or left by various loads applied through a scleral contact lens, but was not displaced by the pull because it continued to fixate the red target: the subject simply opposed the pull by a more forceful contraction to achieve this. Thus, with various loads, subjects could be forced to use different motor commands to hold the position of the eye constant. When the subjects estimated the direction of "straight ahead" they thereby indicated their estimations of the location of the red fixation target relative to this.

Figure 11 shows the results obtained. The estimations of target position were in all cases close to the positions the target would occupy relative to the eye if the unloaded eye had been permitted to rotate in response to the particular command required: that is, target position was estimated as if by reference to the motor command employed rather than according to the true position of the eye. Skavenski et al., (179) claimed that this experiment required alterations in command, or 'outflow', while proprioceptive afferent input ('inflow') was kept constant. It is most unlikely, however, that 'inflow' was kept constant just because the eye did not move: the discharges of intramuscular receptors in the contracting oculomotor muscles are likely to have altered in parallel with the motor commands delivered (see below).

Figure 11 near here.

William James (89) did not accept arguments of these kinds. He believed that interpretations based on judgements made while one eye was displaced or weakened neglected to take into account the influence of the other eye. Sherrington (175) shared this view. An ingenious clinical investigation by Hughlings Jackson and Paton (88) suggested that there was no substance in James' objection. Moreover, Merton (144) proposed a simple experiment which provides further evidence against the objection. He noted that if James were correct it would follow that during imposed movements of one eye we judge the direction of the visual axis by reference to the other eye. That this is not the case, he argued, is shown by the fact that when both eyes are moved simultaneously "objects seen by both eyes appear to move, and do so independently of each other" (144: see also 19, 150). A similar experiment was performed by Skavenski et al., (179) who pulled on a thread attached to the occluded right eye of a subject while that subject fixated a target with his other eye: the target "appeared stationary no matter what was done to his right eye, which rotated freely". In addition, Merton (144) showed that passive displacements of the eye were associated with apparent visual shifts in a subject who had lost one eye in childhood, and who "may therefore be presumed to have come to disregard any sensory messages from the muscles of the empty orbit."

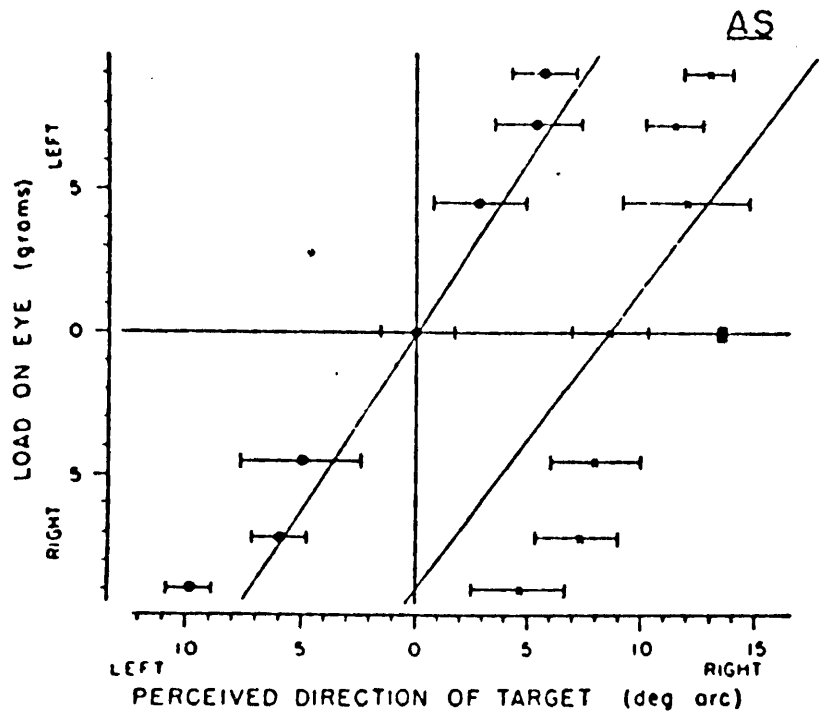


Figure 11. Mean shifts in the perceived direction of a fixation target for various loads applied to the left and right of subject A.S.'s right eye. A.S.'s mean straight-ahead position (based on trials when no load was applied) is shown as the intersection of the axes. Mean shifts in perceived direction are plotted as circles when the fixation target was present straight ahead and as crosses when the target was presented 13.5 deg of arc to the right. The rectangle on the right shows the objective position of the displaced fixation target. Oblique lines indicate the perceived shift in target direction predicted from "outflow" theory. Each data point is the mean of 10 position measures. Error bars show one standard deviation on each side of the means. From Skavenski, Haddad and Steinman (179).

The case against James' argument, therefore, seems sound. It should be noted, however, that it depends largely on excluding a role for extraocular kinesthetic afference from an eye which is not actively rotated (in this case, the proposed reference eye, the opposite eye). As was noted above, it is conceivable that afferent inputs have quite different significance during active, voluntary displacements and fixations of the eye. Cautious interpretation is advisable here because of a recent, brief report from Steinbach and Smith (189), who studied patients who had undergone surgery for correction of horizontal strabismus. The surgery involved detachment and re-attachment of extraocular muscles in order to re-align the visual axes. The patients were assessed on their ability to point with an unseen hand at a small light in an otherwise dark room: the target was viewed with only one eye. Remarkably, they mis-pointed when viewing with only the normal, unoperated eye, as if relying on inputs from the operated, non-viewing eye to reconstruct the position of the target.

The observations on patients with oculomotor 'paralysis' were confirmed in experiments in which severe weakness of the oculomotor muscles was induced in normal subjects by the injection of local anesthetic or by systemic or retro-orbital injections of low doses of curare (18, 19,104, 191). In the subjects of these experiments large apparent displacements of the visual world in the direction of intended but weakly executed movements occurred.

In 1954, however, Siebeck (177) reported that normal subjects who were <u>completely</u> paralysed with high doses of neuromuscular blocking drugs experienced <u>no illusions</u> of spatial displacement on attempting to move their paralysed eyes. The subjects noted only the subjective sensation that their eyes would not move. This surprising finding is in direct contradiction to the theory that corollary discharges are involved in the maintenance of perceptual stability in the visual system. Siebeck's findings on complete paralysis were subsequently

confirmed by Brindley, Goodwin, Kulikowski and Leighton (18) and by Stevens, Emerson, Gerstein, Kallos, Neufeld, Nichols and Rosenquist (191). No movement of the environment was seen with a wholly unsuccessful attempted movement of a paralysed eye "even when only those muscles actually needed for the attempted movement were completely paralysed" (17). This was only so for complete paralysis: during those stages of the experiments in which oculomotor paralysis was incomplete, apparent movements of the visual world accompanied attempts to move, just as Helmholtz and others had described.

Usually subjects were aware of making a very strong effort in attempting to move their completely paralysed eyes. In one of the studies one subject (Stevens, one of the authors of the paper) noted that, "when I looked to the right I felt that if I had to touch anything ... I would have had to reach over to the right." (191). He also reported, however, that this feeling was not "visual in nature" so that it may have been irrelev ant to the present discussion. Subsequently, this effect of spatial mislocation was documented more fully by Stevens (190). His extra-ocular muscles had been paralysed with retro-orbital injections of a mixture of curare and local anaesthetic and he then made attempts to point with his finger at targets within his visual field. He erred in these attempts in the ways shown in figure 12: he mispointed always in the direction that would have carried his gaze to the target had he attempted to fixate it, and the errors were greater the further the target was from the center of his visual field. Clearly, both aspects of the mispointing could be attributable to corollary discharges of commands to the fully paralysed extra-ocular muscles. In the later report Stevens again stressed the "non-visual" nature of his experience:" ... I felt that I would reach to the right in spite of the fact that it [a target] <u>appeared to be straight ahead</u>", he wrote. His descriptions suggest that it was not so much that the visual world had appeared displaced as it was that different movements seemed necessary for orientation within it. This fascinating subjective report is mentioned and illustrated here because it is the only remaining

Figure 12 near here.

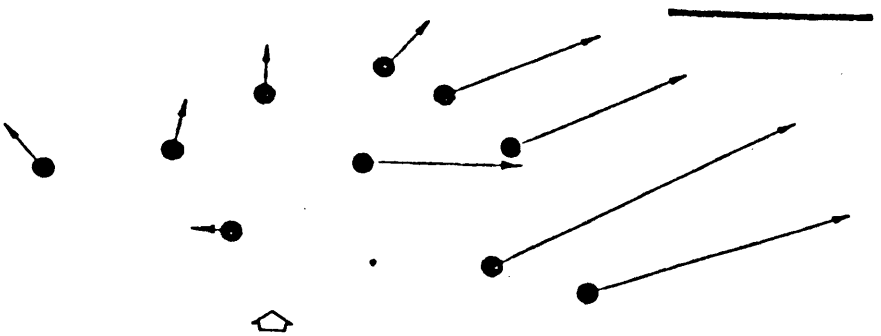


Figure 12. Pointing overshoot errors associated with complete oculomotor paralysis caused by retrobulbar injection of curare and local anesthetic. The subject was seated and his head was fixed with a bite bar. An experimenter placed his finger on the table in front of the subject. The subject then attempted ballistically to touch the experimenter's finger. The right eye was paralyzed and the left eye was occluded. Each black circle represents a target point and the length of the arrow leading from it represents the approximate error range for the normal subject. The black bar at the top of the figure corresponds to one foot, and the open arrow at the bottom is the subject. These same results were obtained under a wide variety of conditions (e.g., no bite bar, no visual feedback, etc.) in the one subject illustrated here (190). Other subjects did not demonstrate these effects (18). From Stevens (190).

indication of a role for corollary discharges in the once powerful array of evidence on visual perception during paralysis. It must be stressed, however, that Stevens himself was "the only person who could be certain of these results" (190) in his series of experiments (191). Moreover, other subjects (18) specifically denied any experiences of this sort.

Helmholtz (77) originally supported his arguments for sensations of innervation with the observation that after-images appear to move with voluntary movements but to stay still during imposed movements, and so Brindley et al., (18) extended their study to include observations on after-images. With one eye paralysed by retro-orbital injection of curare, they observed after-images formed in the paralysed eye and in the non-paralysed eye. In a significant number of trials on themselves as subjects they found that after-images formed in the non-paralysed eye moved with voluntary eye movements but those formed in the paralysed eye failed to move.

The observations made during complete oculomotor paralysis remove the strongest positive evidence of a role for corollary discharges in visual stability, and provide instead compelling evidence against such a role.

Clearly, the traditional arguments in this area must be carefully re-assessed. More experiments must be done. Figure 13 illustrates

Figure 13 near here.

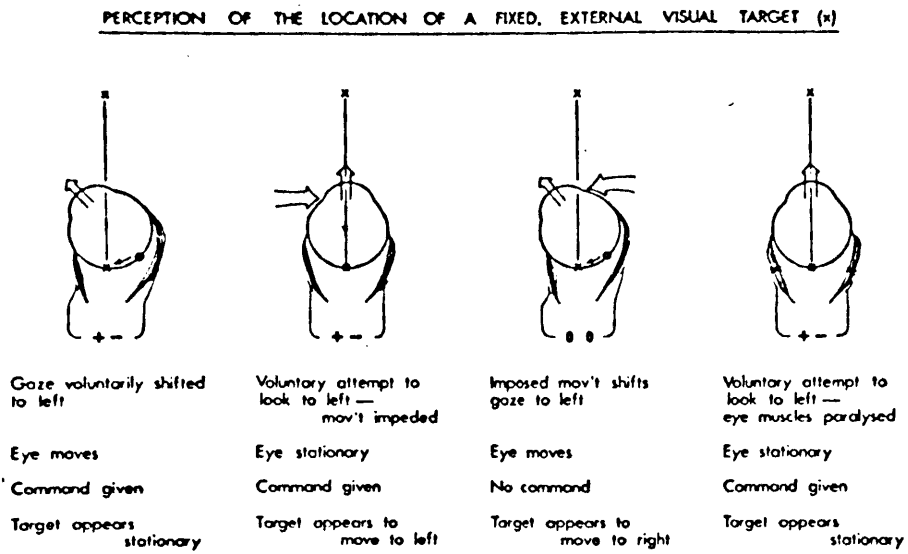


Figure 13. This figure summarizes current knowledge on several aspects of visual stability which are relevant to consideration of corollary discharges. The diagrams show actual positions of eye, viewed target and retinal image: the bottom line under each diagram summarizes what appears to the subject to be happening. This figure should be contrasted with Figure 1 in which historically important observations were depicted.

the findings which must now be accounted for, and should be contrasted with Figure 1 where the traditional case for corollary discharges was outlined. In particular, the role of the major alternative to corollary discharge - kinesthetic afference - must be re-examined. Possibly kinesthetic inputs have been inappropriately tested in the past, as suggested above. Or, possibly, certain 'telltale' features of the retinal signals themselves are sufficient to distinguish self-generated from imposed movements (although this has been considered, and found wanting, previously - see MacKay, 126).

The point of Granit's remark about the "periphery being 'corollarized' by alpha-gamma linkage" (see 'Terminology', above) might be relevant here. If the oculomotor muscle spindles are particularly sensitive to fusimotor drive, so that they achieve increased levels of firing even during shortening of the muscles in which they lie, the possibility should be considered that spindle discharge is the relevant discharge for perceptual stability: that is, that spindle discharges are responsible for what has previously been attributed to corollary discharges. If the oculomotor spindles have a relatively low sensitivity to passive stretch, the failure of imposed eye movements to affect visual perception could be explained. Furthermore, the apparent visual shifts which accompany attempts to move a loaded eye (see Figure 13) could be accounted for by the greater spindle discharge accompanying (through α-γ coactivation) the greater efforts involved. A relative sparing of fusimotor efferents or spindle afferents could explain the visual shifts seen in clinical 'paralysis', or during incomplete experimental paralysis. It is known that curare is usually less effective in blocking intrafusal than extrafusal transmission (132, 133) so that 'inappropriately' high levels of spindle firing should accompany attempts to use incompletely curarized eye muscles. When

paralysis is complete, however, spindle firing should cease, together with the perceptual illusions which accompany attempts to move. Barker's (8) suggestion that extraocular muscle spindles receive their motor innervation from collaterals of motor fibers to the extrafusal fibers - that is, that their innervation is of a 'β' rather than a 'γ' type - should not influence any of these considerations. Granit's important note, therefore, merits careful consideration with respect to the mechanisms underlying perceptual stability during eye movements (see also 147).

The discussion above concerned the role most frequently attributed to corollary discharges in the visual system - that of maintaining perceptual stability during eye movements. Whether corollary discharges are eventually found to have this role or not, it is possible that they may be important in other perceptual processes. Possibly they participate in the moderate, but incomplete, suppression of visual sensitivity which accompanies saccadic eye movements - although a part, and includes the phenomena of "blurring" and "masking" at least, of such suppression is peripheral in its origin (see 95, 126, 130, 131, 163, 204, for discussion). Possibly they are involved in 'gating out' the optokinetic reflex to permit rapid transitions from slow movements to voluntary saccades (127), or even for 'gating in' relevant kinesthetic afferent signals of eye position and movement as suggested above. Indeed, they might be implicated in any number of possible central mechanisms controlling "the sensitivity or the operating point or the resolving power" (127) of various sensory channels. These possibilities remain to be investigated, and should be kept in mind when central neural accompaniments of motor commands are demonstrated electrophysiologically (see below).

ELECTROPHYSIOLOGICAL CORRELATES OF MOTOR COMMANDS

There have been many demonstrations of central neural activity which is related to motor commands and which appears in circumstances that make it either impossible or highly unlikely for it to have an afferent basis. Frequently such activity has been called a 'corollary discharge' without evidence for its participation in perceptual processes, or an 'efference copy' without evidence for a specific suppression of only 'reafference', but not 'exafference'. Terminology is important here and such usages cannot be recommended because of the implications which they contain. Clearly, however, these examples of internal command collaterals could be corollary discharges or efference copies.

Neurons which carry corollary discharges have been sought in the visual system, and possible candidates have been described by Bizzi (14) in the frontal eye fields of the monkey and by several groups in the superior colliculus of the cat (193) and monkey (167, 171, 182, 209). In recordings made in the superior colliculus of the monkey Robinson and Wurtz (168) found cells which responded to stimulus movement in front of the eye but not to stimulus movements generated by eye movements across a stationary stimulus. The authors suggested that these differentiations were made possible by the participation of irradiant motor commands. Similar units have been sought, but not found, in the striate cortex (208).

Apart from effects within the visual system, central irradiation has been demonstrated to affect various sensory relay neurons in the spinal cord. An example is illustrated in Figure 14 taken from an experiment (5) in which the neural events of the scratch reflex were elicited by spinal stimulation, but actual scratching was prevented because the experimental animal, a decerebrate cat, had been given a neuromuscular blocking agent. The central events of scratching

Figure 14 near here

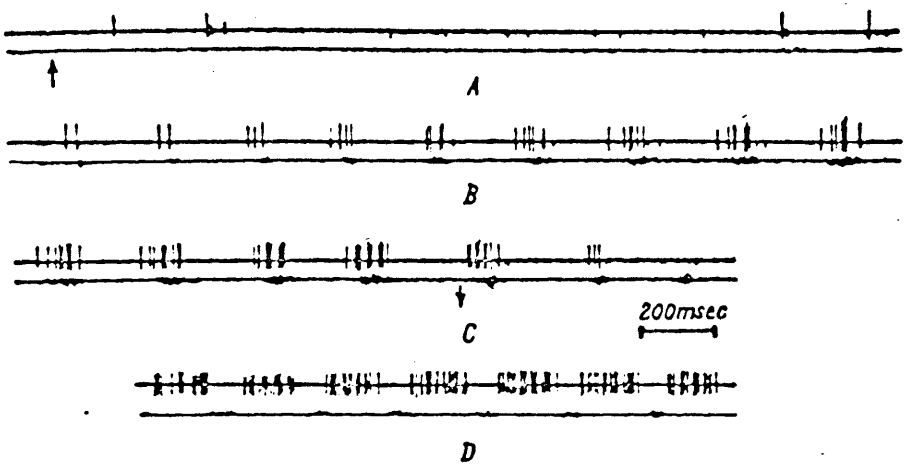


Figure 14. Activity of neurones of ventral spinocerebellar tract during 'fictive scratching' - i.e. animal paralysed. A-C, decerebrate cat: each line of recording is a direct continuation of the preceding one. Arrows denote start and end of stimulation of 1st cervical segment of spinal cord. D - decapitated cat. Upper part of each oscillogram gives extracellular recording of neurone of ventral spinocerebellar tract; lower, activity in nerve activating gastrocnemius muscle. From Arshavskii, Gel'fand, Orlovskii and Pavlova (5).

unaccompanied by actual movement are termed "fictive scratching". During such "fictive scratching" sensory relay neurons in the ventral spinocerebellar tract discharged in time with the motor impulses leaving the nervous system. As the experimental animal was motionless this modulation of sensory relay neurons could not have had an afferent basis - the 'driving' must have been central. Such results support Lundberg's (119) hypothesis that some ascending pathways might transmit central as well as peripheral feedback. Further evidence of central driving of sensory relays comes from studies in which inhibitory interneurons impinged upon by Ia afferents were shown to be driven by central signals associated with walking, but in circumstances where afferent inputs could not have contributed (39, and see 147 for further discussion: see also 71).

Other examples of effects attributable to irradiation by motor commands have been described in lower animals (92, 164, 210, - see 98, for review).

Electrophysiological evidence of internal command collaterals abounds and some, such as the several examples given above, concerns the involvement of such collaterals with sensory processing of various kinds. However, care must be taken in assigning a role for such collaterals in perceptual processes or in applying to them terms such as 'corollary discharges' or 'efference copies' which have very definite, and limiting, connotations.

OTHER INSTANCES OF CENTRAL IRRADIATION BY MOTOR COMMANDS

The term 'irradiation', which has been used in this Chapter to describe internal neural effects of motor commands, was given in 1913 by Krogh and Lindhard (105) to a proposed mechanism by which stimulation of the cardiovascular and respiratory systems could occur during muscular exercise. The idea was that in the course of their descent from higher centers to the spinal cord, motor command signals are tapped off along collateral pathways to 'irradiate' cardiovascular and respiratory control centers in the brainstem. In the original proposal the mechanism was called 'cortical irradiation', although no evidence was offered for cortical involvement. Many years later it was shown that when human subjects are weakened by partial

curarization, greater than normal changes occur in pulmonary ventilation, heart rate and blood pressure at a given level of exercise (6, 156). That is, cardiovascular and respiratory responses are greater when the motor command increases, even when achieved muscular work does not change. These effects, which have subsequently been shown in other circumstances and by other methods (44, 65) can confidently be ascribed to central irradiation. The alternative explanation, that the responses are evoked through muscle spindles as a result of "greater activation of the gamma loop" (6), has been specifically excluded (65, 81, 139). This demonstrable involvement of motor commands in evoking autonomic responses indicates that, to some extent at least, somatic and autonomic control mechanisms overlap within the central nervous system - it therefore provides a convenient explanation for many instances of the ability to 'control' autonomic responses voluntarily (see 180, for discussion).

Brainstem respiratory neurons generate activity which leads to contraction of the muscles of respiration and which irradiates other areas of the central nervous system. In 1936 Anrep, Pascual and Rossler (3,4) showed that sinus arrhythmia, the normal variation of heart rate in phase with breathing, is caused partly by reflexes evoked through intrapulmonary receptors and partly by irradiation of cardiovascular control centers by the central respiratory command (see Figure 15). The effect has since been shown to involve irradiation of both vagal and sympathetic centers (32, 53,103). Not only does the central irradiation impose a respiratory rhythm on the resting heart rate, but it also controls the access of various visceral afferent signals to cardiovascular control centers. Figure 15, for example, shows how stimulation of arterial baroreceptors or chemoreceptors evokes changes in heart rate only when it is delivered during the expiratory phase of breathing: during inspiration, central irradiation

Figure 15 near here

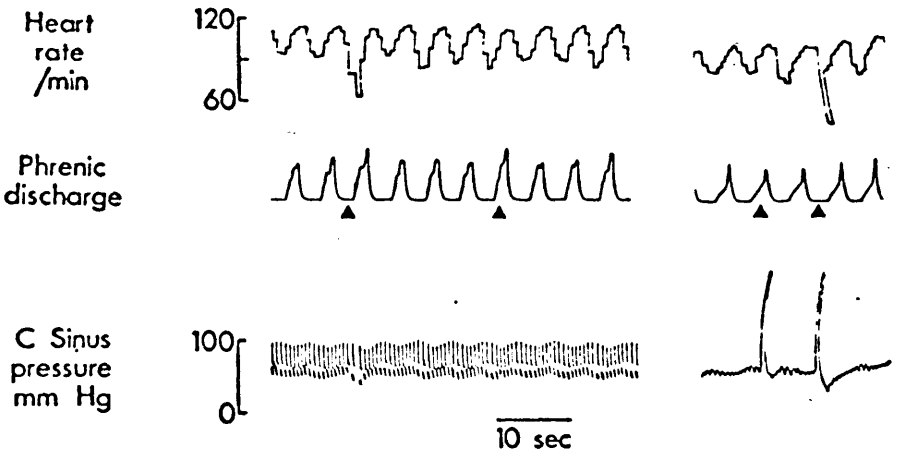


Figure 15. Paralysed anesthetized dog: during period of recording respiratory pump was temporarily stopped, so animal was completely motionless. Record of phrenic nerve discharge ("leaky" integrator) shows timing of central inspiratory activity. Note that heart rate is in phase with central inspiratory cycle. Left panel shows two brief, selective stimuli delivered to the arterial chemoreceptors at markers; right panel shows two brief, selective stimuli (pressure pulses) delivered to arterial baroreceptors at markers. In each panel the stimulus given during the expiratory phase of the central respiratory cycle (i.e. during phrenic inactivity) is shown to evoke a reflex slowing of the heart; the stimuli given during the inspiratory phase of the central respiratory cycle fail to slow the heart. From Gandevia, McCloskey and Potter (53).

by the respiratory command makes the relevant cardiovascular centers refractory to the stimulation (53,101).

Irradiation of brainstem sympathetic centers is largely responsible for the well-known respiratory grouping of sympathetic efferent discharges (e.g. 1,102). A respiratory rhythm is thereby imposed on many physiological variables, such as pupil size or muscle blood flow (see 100 for discussion). The functional significance, if any, of some of these effects is obscure. Furthermore, not at all instances of imposed respiratory rhythms necessarily involve autonomic effects as it has also been noted that the size of the tendon jerk fluctuates with a respiratory rhythm (99, 173).

None of the instances of irradiation by respiratory commands appears to involve corollary discharges, for in none has an effect on perceptual processes been described. Commenting on his own subjective experiences when completely curarized Campbell has noted: "I did not know what my inspiratory center was doing; I felt no rhythmic or continuous sensation of any sort in my chest or my head" (25). The sensation of 'breathlessness' does not occur when artificial ventilation is halted in a conscious, but curarized subject (59), although periodic lung inflation does seem necessary to avert all discomforts (181). The central cycling of respiratory command neurons continues in such circumstances, however, as can be seen in Figure 15. Even when ventilation of a paralysed subject is stopped for considerably longer than the maximal duration of voluntary breath-holding, the acutely distressing discomfort which terminates a voluntary breath-hold does not occur (59).

CONCLUSIONS

The development of modern neurophysiology has depended greatly on studies of responses which the investigator can trigger or stimulate to suit his purposes. The tradition, and indeed the philosophy, of the reflex response has thus grown up. The notions of corollary discharges from centrally generated activity, and of central irradiation in general, fit uneasily into this tradition and philosophy, and so are unwelcome in some physiological circles. Nevertheless, electrophysiological and anatomical observations indicate that there are very many pathways and mechanisms where centrifugal influences are likely to be at work, and the participation of central generators in locomotion and in breathing are not doubted (see Grillner, Sears, this Volume).

The present review has concerned one aspect of centrally-generated activities - their intrusion, through corollary discharges, into perceptual processes. Most of the relevant evidence here has dealt with experiments on human subjects.

While it is clear that remarkably little is yet known about the perceptual consequences of motor commands, this may well be because relatively little effort has been made to study them. If this is so, progress in this area will depend on more neurophysiologists being prepared to study conscious human subjects and to abandon the philosophy that the study of perceptual centrally-generated processes constitutes a "dead-end of research" (70).

Summary

This Chapter reviews the role in perception of internal collaterals from centrally-generated motor commands. Such internal irradiation is called a corollary discharge (187) when it influences perception, which it may do either by modifying the processing of incoming sensory signals, or by acting in its own right and independently of incoming sensory signals. The historical development of ideas in this field is first considered: this serves to introduce the major questions to be analysed subsequently,

and to document the definitions of various relevant terms. Corollaries of motor commands to limb or trunk muscles and to oculomotor muscles are then considered. For motor commands directed to muscles in the limbs corollary discharges do not themselves evoke sensations of movement. In this respect studies on 'phantom limbs', on de-afferentation, and on muscular paralysis are analysed. However, corollary discharges do influence the central processing of kinesthetic signals which arise peripherally in intramuscular receptors. In particular, they appear to be involved in enabling the central nervous system to distinguish, for perceptual purposes, muscle spindle activity which relates to length and velocity of movement of particular muscles, from spindle activity which is due to fusimotor drive to those muscles. Corollary discharges are also responsible for the perception of muscular force or effort - they thus participate in sensations of the heaviness of unloaded limbs or of lifted objects. For motor commands to oculomotor muscles an important role has long been attributed to corollary discharges in stabilizing visual perception during voluntary eye movements and in the perception of direction of the gaze. The traditional case for this is presented here together with later evidence which calls it seriously into question. In particular the demonstration of proprioceptive sensations from the eyes in normal human subjects, and the failure of complete neuromuscular paralysis to be associated with apparent shifts of the visual world, count strongly against the traditional view. The review concludes with a section on electrophysiological studies which may be relevant to consideration of perceptual processes and a section on some non-perceptual consequences of motor commands.

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