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THE EFFECTS OF BARORECEPTOR AND CHEMORECEPTOR STIMULATION ON SHIVERING

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When small or new-born animals are exposed to a cold environment (i.e. below the critical temperature) they often shiver and their consumption of oxygen always increases. When they are given low-oxygen mixtures to breathe, shivering stops and the rate of oxygen consumption decreases (Cross, Dawes & Mott, 1959; Hill, 1959). In 1958 von Euler & Söderberg observed that an intravenous injection of lobeline arrested shivering in cats. They suggested that this effect might be due to excitation of the systemic arterial chemoreceptors. Is is, however, known that in other species, such as the rabbit, lobeline excites other types of sensory receptors as well as the chemoreceptors (Dawes & Mott, 1959). The first object of the present paper was to test the validity of von Euler & Söderberg's hypothesis.

It was found that interpretation of the results was confused by changes in the arterial blood pressure. Ishii & Ishii (1960*a*) described experiments in which baroreceptor stimulation *enhanced* shivering. To facilitate description of the effect of chemoreceptor stimulation on shivering, the effect of baroreceptor stimulation is described first. A preliminary account of some of these experiments has already been given (Fagan & Mott, 1961).

METHODS

Sixty-five adult rabbits of 1·8–4·4 kg body weight, nine adult cats of 2·3–3·9 kg body weight and one lamb of 10·8 kg body weight were used. The lamb was anaesthetized with chloralose 30 mg/kg; the rabbits were given sodium pentobarbitone 30 mg/kg I.V. and the cats intraperitoneal sodium pentobarbitone 24–38 mg/kg. The anaesthesia was increased when necessary by intravenous injection of sodium pentobarbitone 12–24 mg I.V. or by inhalation of ether (e.g. during dissection of the sinus nerves). Ether in sufficient concentration stops shivering and was not administered immediately before or during observations on the effects of manoeuvres employed to influence the intensity of shivering. Arterial blood pressure (from a catheter in either a carotid or an axillary artery) and oesophageal pressure (from a saline-filled catheter with the tip at the level of the heart) were measured by Elema Inductance manometers and recorded on Evershed Quick Response Recorders, Type QU/CRD 19. These recorders give faithful reproduction up to 20 c/s, but this paper is only concerned with changes of mean arterial pressure; in some experiments

(e.g. that of Fig. 5) the arterial pressure pulse was integrated electrically, the device incorporated in this Elema manometer unit being used for this purpose. The pulse pressure was used to operate a heart rate meter (Wyatt, 1957) and the heart rate was recorded on one of the Evershed Quick Response Recorders in a few experiments. Solutions of drugs were made up in NaCl solution, 0·9 g/100 ml., were injected intravenously and washed in with 2 ml. 0·9 % NaCl. Doses of adrenaline and noradrenaline are expressed in terms of base, nicotine as the hydrogen tartrate and lobeline as the hydrochloride.

Shivering was induced by cooling. A 10–15 cm wide band around the rabbit's or cat's trunk was shaved and some rabbits and cats then started to shiver. Those which did not were further cooled by the draught from a fan and ice bags were sometimes applied. A mercury thermometer was used to measure rectal temperature; this usually fell 1–2° C or more before shivering occurred in rabbits, but shivering began after a lesser fall of body temperature in some cats. Electrical records of skeletal muscle activity during shivering were obtained from chlorided silver plates 12 × 36 mm in area inserted beneath the skin of the buttocks. The electrical activity was amplified and displayed on an oscilloscope. The rectified output was integrated (with a time constant of 0·5–10 sec as convenient) and recorded on an Evershed Quick Response Recorder as described above. These records gave a fair representation of the increases and decreases of shivering observed in the whole animal but are not to be regarded as accurately quantitative. Closing the jaws stopped shivering in the rabbit (but not in the cat) and proved a convenient means of determining the level of the record in the absence of visible shivering (see Figs. 2, 7 and 8).

Perfusion of the vascularly isolated carotid body was carried out in rabbits by means of an apparatus similar to that described by Joels, Neil & Vaughan Hudson (1961), modified to permit variation of the perfusion pressure. The carotid bifurcation was exposed, the internal carotid, occipital and all branches but one of the external carotid arteries were tied, as were also the branches of the common carotid between the entry of the cannula of the perfusion apparatus and the carotid bifurcation. The branch of the external carotid left open was occluded during perfusions. The water jacket of the perfusion column was kept at 37 ± 0·1° C. This was higher than the rectal temperature of most shivering rabbits and allowed for some cooling of the perfusate between the delivery cannula and the perfused area. The perfusate was Krebs–Henseleit solution equilibrated with 5 % CO_2 in either O_2 or N_2. The oxygenated solution had a pH of 7·4 and sometimes caused hyperpnoea. It was then found that the arterial pH of seven rabbits measured within 7 min of the induction of anaesthesia ranged from 7·58 to 7·73 and remained in this range for several hours. The bicarbonate content of the perfusate was therefore adjusted to give a pH of about 7·6. The pH of blood and of buffer solutions was measured with a glass electrode in a Stadie system at 35° C with a Model 23 A Direct Reading pH Meter (E.I.L., Richmond, Surrey), with an accuracy of ± 0·01 pH units. This temperature was selected as being close to the rectal temperature of a rabbit shivering under the conditions of these experiments.

Nerve stimulation was carried out with rectangular constant-current pulses of known frequency and duration.

RESULTS

The effect of baroreceptor stimulation on shivering

Rise of pressure in the vascularly isolated carotid sinus. During experiments in which the isolated carotid sinus and body of the rabbit were perfused with Krebs–Henseleit solution, it became clear that changes of intrasinusal and of systemic arterial pressure could influence the intensity of shivering. Figure 1*a* shows augmentation of shivering elicited in a rabbit by raising the pressure in the isolated sinus (from the level maintained by

retrograde auto-perfusion of the vessels through a branch of the external carotid artery) to 132 mm Hg. The shivering was intensified whether the perfusate was equilibrated with 95 % N_2 or 95 % O_2, though the increase was somewhat better maintained with the oxygenated solution. This response was abolished by cutting the ipsilateral carotid sinus nerve (Fig. 1*b*). Figure 2 illustrates an experiment in another rabbit in which raising the pressure in the isolated sinus to 130 mm Hg diminished shivering concurrently with the reflex fall of arterial pressure. After the depressor nerves had been cut a similar rise of intrasinusal pressure augmented

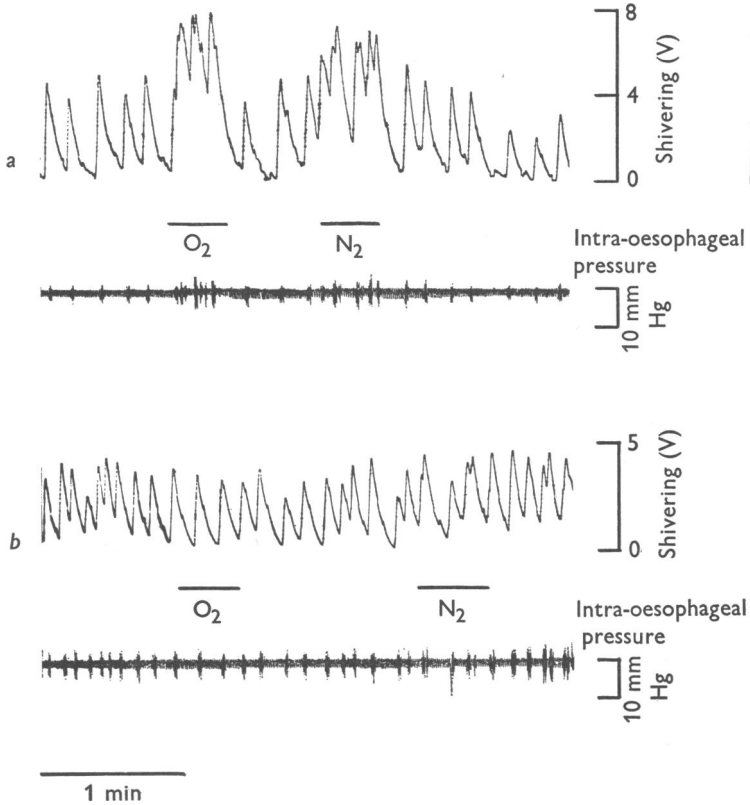

Fig. 1. Rabbit no. 53, 2·9 kg body wt., anaesthetized with sodium pentobarbitone. Upper record of each section, shivering; lower record of each section (inspiration downwards) oesophageal pressure. The left carotid sinus nerve was cut and the perfusion pressure in the vascularly isolated right carotid sinus and body was raised to 132 mm Hg during the bars causing the increase of shivering shown in *a*; O_2, perfusate equilibrated with 32 mm Hg CO_2 in O_2, pH 7·55; N_2, perfusate equilibrated with 36 mm Hg CO_2 in N_2, pH 7·39. The observations of the upper record were repeated in the reverse order with similar responses and the right carotid sinus nerve was then cut, which abolished the response as shown in *b*. Rectal temperature 34° C. Record retouched.

shivering, although the fall of systemic pressure was then greater than when the depressor nerves were intact.

Electrical stimulation of the central end of one depressor nerve. Stimulation of the cut central end of the depressor nerve in eight rabbits with other baroreceptor nerves intact never elicited or increased shivering. If the stimulation was sufficiently strong shivering stopped. Although the possibility existed that this reduction of shivering might be due to a fall in total

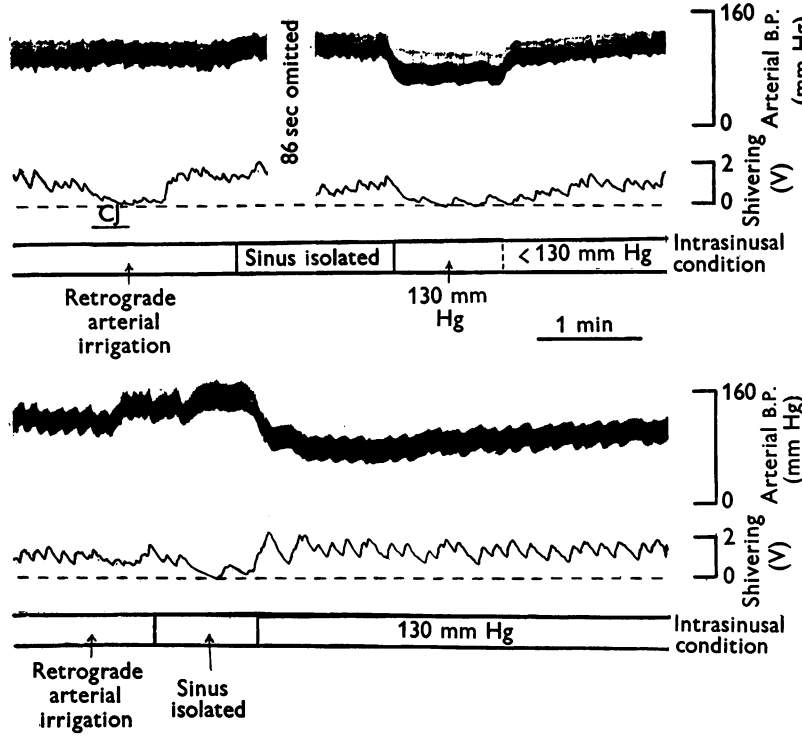

Fig. 2. Rabbit no. 60, body wt. 1·9 kg anaesthetized with sodium pentobarbitone, left sinus nerve cut, perfusion of vascularly isolated right carotid sinus. Upper record of each section, systemic arterial pressure; lower record of each section, shivering. Closing jaw (CJ) reduces shivering with little change of arterial pressure. Between upper and lower sections, depressor and cervical sympathetic nerves cut. Note that fall of arterial pressure due to raising pressure in sinus reduces shivering when depressors are intact, but not when they have been cut. Rectal temperature 36·7° C. Record retouched.

baroreceptor stimulation occasioned by the reflex decrease in arterial pressure, this decrease was usually small. In five rabbits intra-oesophageal pressure was recorded, and it was possible to induce increases of respiratory rate and/or depth in all of them by stimulating the central end of a depressor nerve, provided the respiratory rate was not already very high,

although no rise of arterial pressure occurred (Fig. 3). The increase of respiratory rate was, however, accompanied by more pronounced bradycardia than when the stimulus was insufficient to elicit an increase of respiratory rate but still produced a fall of arterial pressure.

The central end of the depressor nerve was also stimulated in seven rabbits with the opposite depressor nerve and the sinus nerves cut; in five the vagi were also cut. These rabbits, deprived of their baroreceptor innervation, shivered poorly or not at all, but shivering could be elicited in all by stimulation of the central end of the depressor nerve. In five rabbits

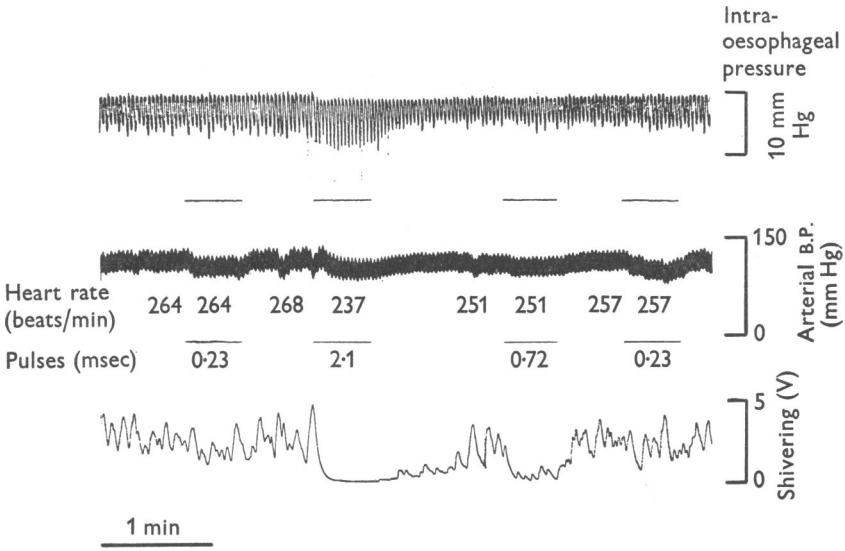

Fig. 3. Rabbit 131, 3·0 kg body weight, anaesthetized with sodium pentobarbitone, vagi cut, rectal temperature 34° C. Records from above downwards of intra-oesophageal pressure (inspiration downwards), arterial blood pressure, heart rate and shivering. During the periods indicated by the bars the cut central end of the right depressor nerve was stimulated electrically with rectangular pulses 0·7 mA at 33/sec. The duration of the pulses was varied from 0·23 to 2·1 msec, as indicated. The upper row of figures indicates the heart rate.

intraoesophageal pressure was recorded, and the generation of a shiver was associated with absence of tachypnoea or sometimes with slowing of breathing and was elicited by stimuli of shorter duration than those required to evoke tachypnoea and pronounced bradycardia. Figure 4 illustrates this point and also shows a slightly smaller fall of arterial pressure during the stimuli which increased the respiratory rate. Considerable persistence was necessary to demonstrate such differential responses to stimuli of differing strength, and it seemed possible that the precise level of anaesthesia was important.

These observations were consistent with the conclusions of Ishii & Ishii

(1960*a*, *b*) from experiments under urethane anaesthesia, that rabbits shiver more vigorously when the total baroreceptor stimulation is increased; but they also indicate the presence in the depressor nerve of fibres through which shivering can be inhibited. It followed that the best chance of demonstrating inhibition of shivering by perfusion of the carotid body with an hypoxic solution would be in a preparation in which the perfusion pressure was kept constant and was insufficient to stimulate too many of the baroreceptor fibres of the perfused sinus, and in which all other afferent baroreceptor nerves were cut.

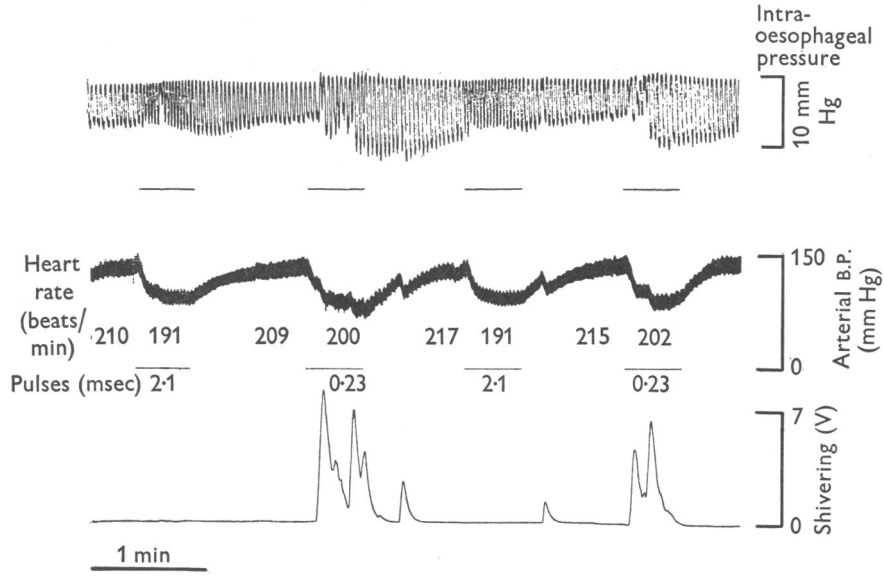

Fig. 4. Rabbit 132, 2·0 kg body weight, anaesthetized with sodium pentobarbitone; vagi, carotid sinus, depressor and cervical sympathetic nerves cut, rectal temperature 32·3° C. Records from above downwards of intraoesophageal pressure (inspiration downwards), arterial blood pressure, heart rate, and shivering. During the periods indicated by the bars the cut central end of the left depressor nerve was stimulated electrically with rectangular pulses 0·7 mA at 33/sec. The duration of the impulses was changed from 2·1 msec to 0·23 msec as shown. The upper row of figures indicates the heart rate.

The effect of chemoreceptor stimulation on shivering

Perfusion of the carotid sinus and body with an hypoxic solution. In four rabbits the depressor nerves were cut, the carotid arteries were stripped of adherent tissues, and the contralateral carotid sinus nerve was cut before preparing the rabbit for perfusion of the carotid body and sinus. Shortly before the perfusion was begun the branch of the external carotid artery, which had been left open to irrigate the otherwise isolated preparation, was occluded. The solution equilibrated with 95 % O_2 was then

allowed to run into the sinus. After a control period of 1–2 min the flow of the oxygenated solution was stopped and that of the solution equilibrated with 95 % nitrogen was begun, *the perfusion pressure remaining the same.* When the O_2-free perfusion had continued for $\frac{1}{2}$–$1\frac{1}{2}$ min, the oxygenated solution was again allowed to run into the sinus (Fig. 5). Stimulation of breathing during the perfusion of hypoxic solution was considered to indicate that the chemoreceptors were being stimulated; this response was obtained once in one rabbit, twice in two rabbits and three times in the

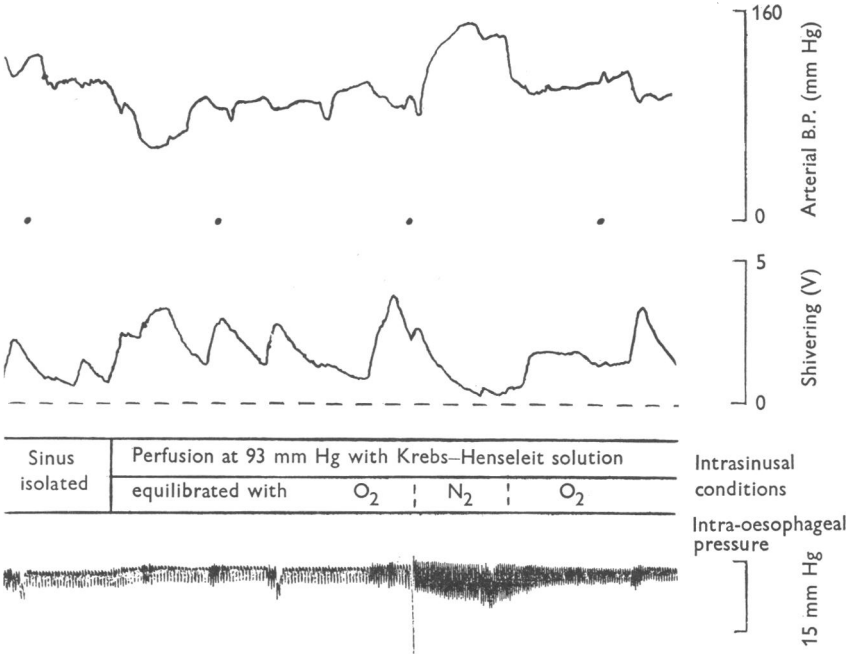

Fig. 5. Rabbit no. 65, 2·5 kg body wt. anaesthetized with sodium pentobarbitone. Left carotid sinus nerve and both depressor nerves cut; common carotid arteries cleaned. Perfusion of vascularly isolated right carotid sinus and body. Upper record, systemic arterial pressure; middle record, shivering; lower record, oesophageal pressure (inspiration downwards). Branch of external carotid irrigating the preparation occluded before record begins. Perfusion pressure 93 mm Hg; oxygenated perfusate equilibrated with 33 mm Hg CO_2 in O_2, pH 7·63; hypoxic perfusate equilibrated with 37 mm Hg CO_2 in N_2, pH 7·54. Rectal temperature 36·4° C. Time marker, 1 min. Record retouched.

fourth. Only in the latter rabbit was the stimulation of breathing not accompanied by a reduction of shivering on two occasions when the perfusion pressure was 130 mm Hg. When the perfusion was repeated in this rabbit at a pressure of 99 mm Hg a decrease of shivering accompanied the stimulation of breathing. This suggested that if the perfusion pressure was too high it might be difficult to reduce the level of shivering maintained by

the activity of the baroreceptors of the perfused sinus, even though the increased breathing indicated that chemoreceptors were being stimulated.

These experiments were not satisfactory, as vigorous shivering was difficult to obtain, presumably because all the nerves from the baroreceptor areas other than that of the perfused sinus were cut, and it was hoped that other methods of stimulating the chemoreceptors, involving less interference with the rabbit, might prove more instructive.

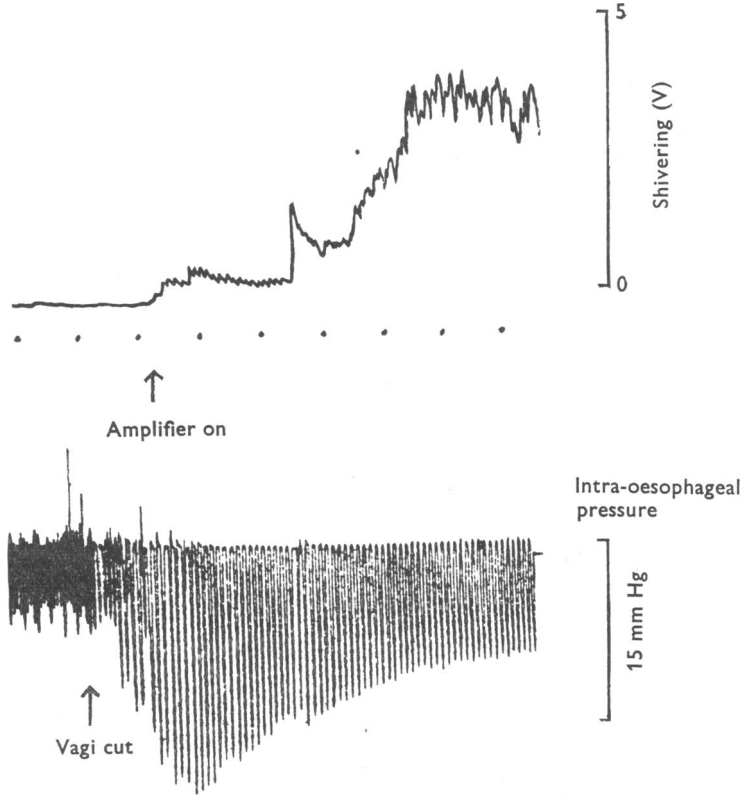

Fig. 6. Rabbit 69, 1·9 kg body wt. anaesthetized with sodium pentobarbitone. Resumption of shivering, after vagotomy. Upper record, shivering (amplifier switched on just after third time mark); lower record, intra-oesophageal pressure (inspiration downwards); rectal temperature 34° C. Time marker, 30 sec. Record retouched.

Intravenous injection of sodium cyanide. Injections of sodium cyanide (95–432 μg/kg I.V.) reduced or stopped shivering in twelve of thirteen rabbits (rectal temperatures 33·6–36·8° C). Repeated administrations of the same dose produced the same effect. In some rabbits rather more than the minimum quantity of sodium cyanide necessary to increase the rate and depth of breathing was required before there was a clear reduction

of shivering. The arterial pressure was recorded in eight rabbits; in seven of these the intravenous injection of sodium cyanide caused only trivial changes of blood pressure, but in the eighth a very brief rise of arterial pressure was followed by profound bradycardia and hypotension.

Vagotomy reduced or abolished shivering for 2–3 min. The return of shivering as the extreme hypernoea immediately following vagotomy subsided is shown in Fig. 6. Intravenous injection of the dose of sodium cyanide which had elicited an increase in breathing and reduction of shivering in the intact rabbit still did so after the vagi were cut in eight

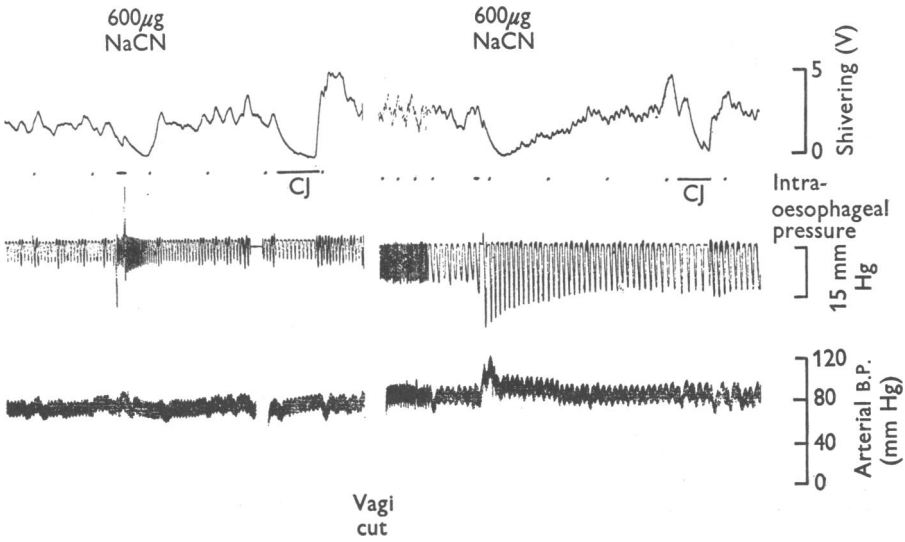

Fig. 7. Rabbit 69, 1·9 kg body weight anaesthetized with sodium pentobarbitone. The effect of intravenous injection of sodium cyanide 600 μg before and after cutting the vagi. Top record, shivering; middle record, intra-oesophageal pressure (inspiration downwards); bottom record, arterial blood pressure. Note that when shivering is stopped by closing the jaw (CJ), breathing is slowed; also that after vagotomy sodium cyanide causes a rise of arterial pressure and the inhibition of shivering is prolonged. Rectal temperature 34° C. Time marker, 30 sec.

rabbits (rectal temperature 33·6–36·4° C), and in four of these the inhibition of shivering lasted longer than before vagotomy. Arterial pressure, measured in five of the eight rabbits, rose on the injection of sodium cyanide (Fig. 7).

The carotid sinus nerves were cut in four vagotomized rabbits (rectal temperature 33·6–36° C). The dose of sodium cyanide which had both stimulated breathing and stopped shivering when the sinus nerves were intact now failed to do so. In three additional vagotomized rabbits, which had received hexamethonium 15 mg/kg, sodium cyanide also stopped

shivering and stimulated breathing, and these responses were likewise abolished by cutting the sinus nerves. Hexamethonium itself caused only a temporary arrest of shivering while the blood pressure was at its lowest. Cutting the carotid sinus nerves in three rabbits with intact vagi (rectal temperature 34–35·6° C) abolished the hyperpnoea elicited by sodium cyanide and in two of them the inhibition of shivering was also abolished (Fig. 8). In the third subsequent vagotomy also did not abolish the inhibition of shivering. Little change of arterial pressure occurred on injection of sodium cyanide in rabbits with the sinus nerves cut.

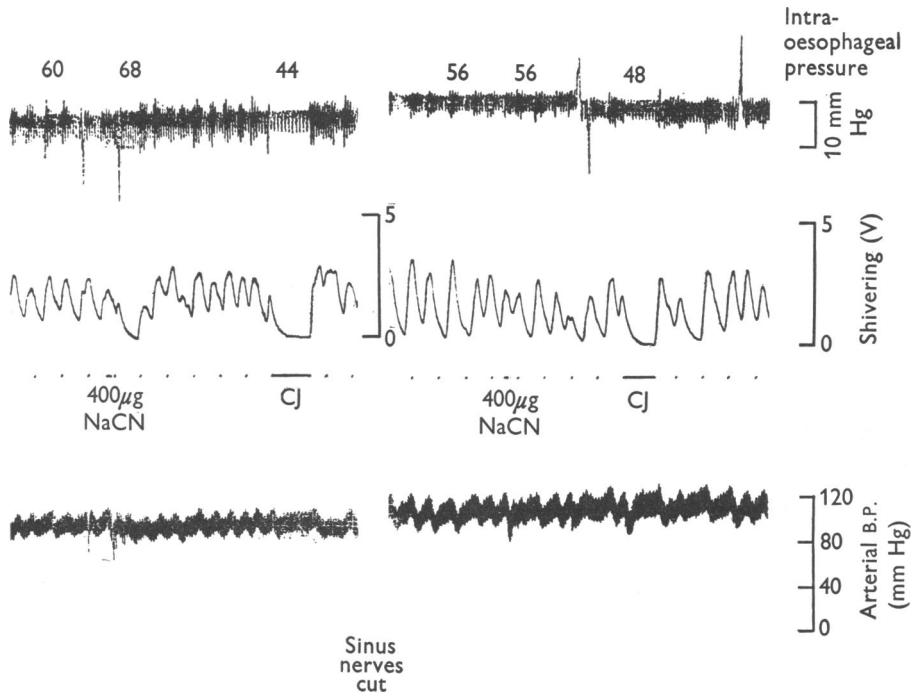

Fig. 8. Rabbit 79, 2·1 kg body weight, anaesthetized with sodium pentobarbitone, cervical sympathetic nerves cut. The effect of intravenous injection of sodium cyanide 400 μg before and after cutting the sinus nerves. Top record, intra-oesophageal pressure (inspiration downwards); middle record, shivering; bottom record, arterial blood pressure. The cessation of shivering induced by closing the jaw (CJ) is still present after cutting the sinus nerves, whereas that due to sodium cyanide is abolished. Figures denote breaths/min. Rectal temperature 35·6° C. Time marker, 10 sec.

Sodium cyanide (127–170 μg/kg I.V.) had similar effects in one intact and five vagotomized cats to those observed in rabbits, except that the intensity of shivering was reduced for a longer period. The initial abrupt diminution of shivering was associated with the stimulation of breathing

and a rise of arterial pressure as in the vagotomized rabbit. The blood pressure of the cat, however, unlike that of the rabbit, fell substantially for 1–2 min after the initial rise, and the prolonged inhibition of shivering caused by sodium cyanide in the cat coincided in duration with this fall. The administration of hexamethonium (15 mg/kg I.V.) did not abolish these responses to sodium cyanide in two cats. After cutting the sinus nerves in all five cats, however, the initial abrupt diminution of shivering, the increase of respiratory rate and depth and the initial rise of arterial pressure were abolished, though the fall of arterial pressure persisted. In two of the cats, tissue adhering to the carotid arteries had been stripped off at the beginning of the experiment in an attempt to ensure that subsequent vagotomy and sinus nerve section would eliminate all baroreceptor nerves. These two cats shivered poorly after cutting the sinus nerves, but sodium cyanide had no effect at all on the shivering although the arterial pressure fell. The shivering of the other three cats sometimes slowly diminished a little after intravenous injection of the dose of sodium cyanide which had previously produced an abrupt reduction of shivering. It is probable that this small reduction was attributable to the fall of arterial pressure reducing the baroreceptor stimulation in surviving portions of the aortic nerves cephalad of the point of vagal section (cf. Iggo & Vogt, 1962).

Intravenous injection of nicotine. Attempts to utilize acetic acid or ammonia to prevent the stimulation of chemoreceptors by nicotine or sodium cyanide were unsuccessful, so it was decided to see if hexamethonium would antagonize the stimulation of chemoreceptors by nicotine, as has been shown in the cat (Douglas, 1952). Because nicotine excites pulmonary vagal endings, thereby causing rapid shallow breathing in the rabbit (Dawes & Mott, 1959), these experiments were carried out after cutting the vagi. Injections of nicotine (140–525 μg/kg) regularly stopped shivering and increased the rate and depth of breathing in four vagotomized rabbits, in one of which the depressor nerves had also been cut. Administration of hexamethonium 15 mg/kg abolished the respiratory stimulation elicited by nicotine, and shivering then continued uninterruptedly. Nicotine caused small slow falls of arterial pressure in three of the four rabbits before administration of hexamethonium. Such minor falls of arterial pressure as occurred were unlikely to have been responsible for the abrupt inhibition of shivering seen on injection of nicotine. On some occasions nicotine caused bradycardia which was greatly reduced after hexamethonium.

Since stimulation of baroreceptor endings by nicotine and its antagonism by hexamethonium has been reported (Diamond, 1955) it was of interest to see what action nicotine had in rabbits with the vagi and sinus nerves cut but the depressor nerves, generally believed not to contain

fibres arising from chemoreceptors in this species, intact. In four such rabbits nicotine 263–540 μg/kg I.V. stopped shivering, and a small fall of arterial pressure was observed in three. There was sometimes a slight increase in respiratory rate but not of depth.

Intravenous injection of lobeline. Von Euler & Söderberg (1958) found that lobeline 300 μg/kg I.V. stopped shivering in cats. Larger doses of this drug (615–850 μg/kg) were required to diminish the shivering of three vagotomized cats, and the decrease of shivering was followed by an increase above the pre-injection level in two of the cats. The doses of lobeline effective in reducing shivering caused a much larger rise of arterial pressure than did those of nicotine, and the time course of events suggested that the delayed increase of shivering sometimes observed after the injection of lobeline was due to baroreceptor stimulation. When the sinus nerves were cut, shivering was poor and no abrupt changes of shivering followed injection of the doses of lobeline employed.

The central end of one carotid sinus nerve was stimulated electrically in six rabbits and one lamb. In one rabbit the opposite sinus nerve had been cut but the depressor nerves of all were intact. In the lamb the opposite sinus nerve and both vagi had been cut. When hyperpnoea was elicited by stimulation of the central end of the sinus nerve, shivering diminished. In one rabbit this diminution was not well sustained until after the vagi had been cut. In one of the rabbits arterial pressure was recorded and this fell during stimulation of the carotid sinus nerve. The stimuli effective in causing hyperpnoea and reduction of shivering in the rabbits were pulses of 0·7–45 msec duration at 19–33 c/s and 0·12–1·2 mA. In the lamb stimulation of 50 msec pulses at 15 c/s and 5·4 mA elicited tachypnoea and cessation of shivering, whereas stimulation at lower current strength had caused slowing of or no change in breathing and did not stop shivering. The arterial pressure fell in the lamb at all current strengths used.

Intravenous injection of adrenaline and noradrenaline

A few observations on the effect of these drugs were made, since an apparent contradiction existed between the evidence indicating that baroreceptor stimulation augments shivering (Ishii & Ishii, 1960*a* and this paper) and reports that intravenous injection of doses of adrenaline, sufficient to raise the arterial pressure considerably, inhibited shivering in rabbits (Ishii & Ishii, 1960*a*) and cats (Hall & Goldstone, 1940).

In six of seven rabbits in which both the vagi and carotid sinus nerves had been cut, injection of adrenaline (2–10·5 μg/kg I.V.) or noradrenaline (3·4–6·8 μg/kg I.V.) caused an increase in the intensity of shivering as the arterial blood pressure rose. The seventh rabbit was probably already shivering maximally, since after its shivering had been reduced by in-

jection of sodium pentobarbitone 12 mg I.V. shivering was increased on four occasions by adrenaline 9·6 μg/kg I.V. When the depressor nerves were cut only two of the seven rabbits continued shivering. Injection of the same doses of adrenaline as those given previously caused similar or more prolonged rises of arterial pressure, but failed to increase or generate any shiver (Fig. 9).

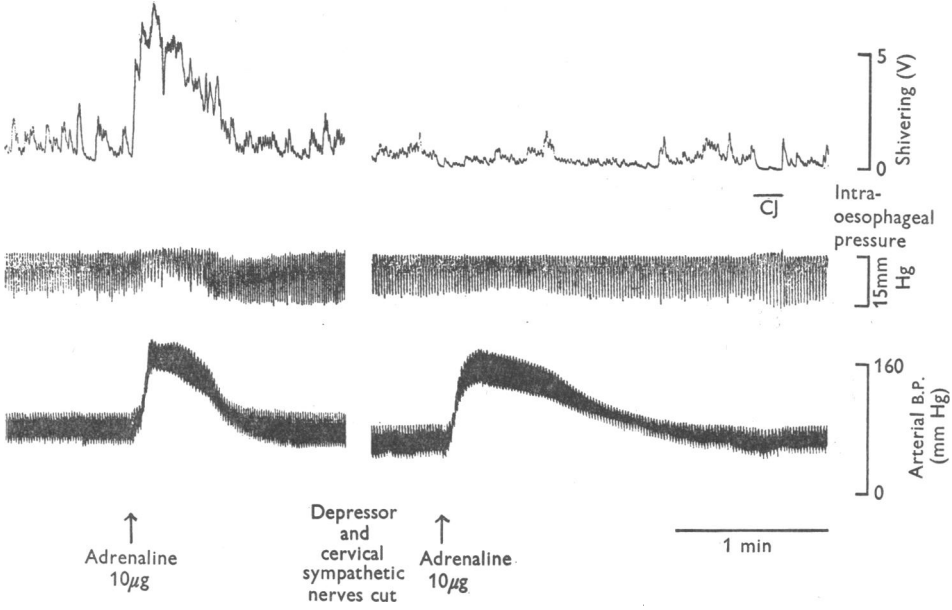

Fig. 9. Effect of injection of adrenaline 10 μg I.V. in rabbit no. 59, 2·0 kg body wt. anaesthetized with sodium pentobarbitone, carotid sinus nerves and vagi cut. Between the two sections of record depressor and cervical sympathetic nerves cut. Top record shiver; middle record oesophageal pressure (inspiration downwards); bottom record arterial pressure. Rectal temperature 36·4° C.

However, when adrenaline (1·7–10·5 μg/kg) or noradrenaline (3·4–6·8 μg/kg) was injected intravenously in seven intact rabbits, no sustained increase in the intensity of shivering occurred, and in five of the seven rabbits shivering either stopped or was greatly diminished during the greater part of the rise of arterial pressure (Fig. 10). Vagotomy alone did not alter the response.

Adrenaline or noradrenaline (2·7–8·7 μg/kg) was injected intravenously in four intact cats. In all of them shivering increased as the blood pressure rose, but in one the increase lasted only about 10 sec. The increases of shivering were sometimes followed by some decrease in the shivering below the pre-injection level, but, in contrast to the response of most intact rabbits, shivering did not stop. After the sinus nerves had been cut in

three cats, the increase of shivering following injection of a small dose of pressor amine was unchanged in two but somewhat reduced in the third. Cutting first the aortic nerves and then the vagi of the latter cat progressively diminished the extra shivering evoked by injection of adrenaline or noradrenaline 5·4 μg/kg. In the other two cats the vagi were cut close to their junction with the superior laryngeal nerves, where the aortic nerves can be identified and spared. The increase of shivering induced by injection of adrenaline or noradrenaline was greatly increased and prolonged after this partial vagotomy. After the aortic nerves had been cut,

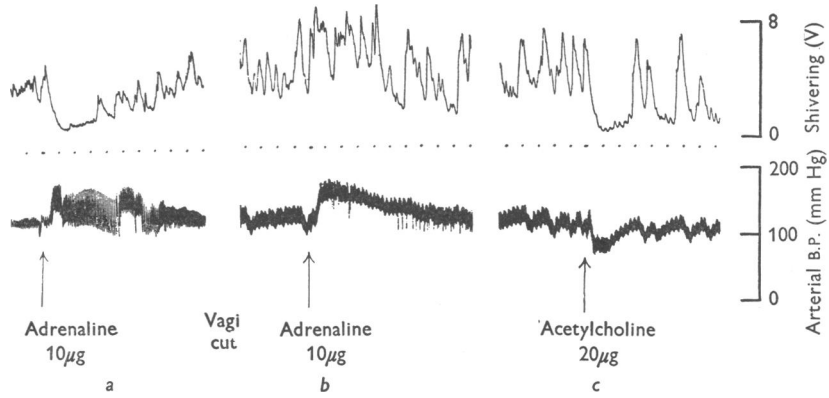

Fig. 10. Rabbit no. 78, 3·4 kg body wt., anaesthetized with sodium pentobarbitone, carotid sinus and cervical sympathetic nerves cut. Intravenous injection of adrenaline 10 μg (*a*) before and (*b*) after vagotomy; and of acetylcholine 20 μg (*c*) after vagotomy. 20 min interval between first and second sections of record and 2·5 min between second and third. Rectal temperature 33·3° C. Upper record, shivering; lower record, arterial B.P. Time marker, 10 sec.

however, shivering was much reduced and injection of the amount of adrenaline or noradrenaline previously effective in increasing shivering failed to do so in one cat and caused only a brief and minute increase in the other.

Breathing and shivering

Though the experiments already described demonstrated a clear association between the reflex stimulation of breathing and the inhibition of shivering through stimulation of the arterial chemoreceptors in anaesthetized animals, the possibility existed that more vigorous breathing might itself secondarily inhibit shivering. However, if this is so, vagal pathways cannot be involved, since the diminution of shivering induced by sodium cyanide in rabbits with the vagi cut was never less, and not infrequently greater, than that observed in the intact rabbit. Moreover, induced or spontaneous inspiratory gasps, often followed by a period of tachypnoea (Fig. 11), were frequently associated with increased shivering. Both

inflation and deflation of the lungs, sufficient to elicit strong Hering–Breuer reflexes so long as the vagi were intact, often stopped shivering; this response could still be obtained after vagotomy, and therefore cannot be attributed to pulmonary vagal receptors.

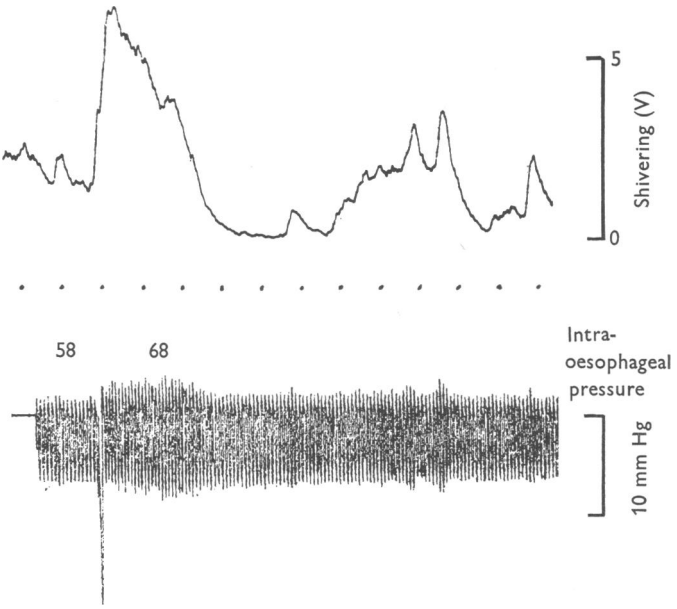

Fig. 11. Rabbit no. 91, 2·8 kg body wt., anaesthetized with sodium pentobarbitone; rectal temperature 36·6° C. Increase of shivering associated with increase of respiratory rate following a spontaneous inspiratory gasp. Upper record, shiver; lower record, intra-oesophageal pressure, inspiration downwards. Figures denote breaths/min. Time marker, 10 sec.

The temperature of the inhaled air. It seemed desirable to investigate whether administration of cold air to the lower respiratory tract caused shivering in rabbits, as reported by Cort & McCance (1953) in the piglet. Room air was cooled or heated and drawn at 5–15 l./min through a tube of 1·8 cm bore. The tracheal cannula was attached to a short side arm of this tube and the temperature of the flowing gas in the wide tube was measured by a thermometer inserted through another side arm. Some difficulty was encountered in delivering cold air to the trachea. The method adopted was to suck dried room air at 5–15 l./min through a brass manifold immersed in a mixture of methylated spirit and solid carbon dioxide in an insulated container. The tubes connecting the exit of the manifold from the cooling bath with the trachea were made as short as possible and lagged to retard the rewarming of the air before it passed the trachea and entered the suction pump. Hot air was obtained in a similar fashion from a wide

copper tube immersed in water at about 70° C. A two-way tap joined two of the sources of cold air, warm air or room air. The temperature of the inspired air of six rabbits was altered from room air to cold air, room air to warm air, or warm air to cold air by turning the tap. The negative pressure at the trachea did not exceed 1 cm H_2O. On twelve occasions three intact rabbits were switched from breathing room air at 18·4 to 24·5° C to cold air at +2 to −9·3° C. The greater part of the temperature fall was achieved within 1–2 min and the temperature fell more slowly thereafter. The cold air was administered when rabbits were not shivering, when shivering was imminent, when it was moderate and when it was well developed. There was never any spectacular change in the intensity of shivering that could be attributed to the stimulus of cold air entering the lower trachea. Shivering did increase on some occasions, but in a slow steady manner such as is liable to accompany lightening of anaesthesia and there were in any case small falls of rectal temperature (up to 0·3° C) on eight of the twelve occasions. Moreover, shivering never decreased when the cold air was replaced by room air. Another rabbit was switched from breathing room air at 21·6–23·2° C to warmed air at 32–33° C on three occasions without any change in shivering activity. Finally, on seven occasions in two rabbits the temperature of the inspired air was changed from 37·3–44° C (several degrees above the rectal temperature of the rabbit) down to −1·7 to −12° C, without any dramatic increase of shivering, even though falls of rectal temperature of up to 0·2° C were observed.

DISCUSSION

The observations described in this paper concern the tremor of mammalian somatic musculature induced by cold in lightly anaesthetized animals and colloquially termed shivering.

Baroreceptor stimulation caused by raising the pressure in the isolated innervated carotid sinus was shown by Ishii & Ishii (1960*a*) to elicit shivering in rabbits anaesthetized with urethane. This observation has been confirmed (Fig. 1), and further support for their conclusion that baroreceptor stimulation augments shivering is provided by the increase of shivering caused by intravenous injection of adrenaline in rabbits with the chemoreceptor nerves cut (Figs. 9 and 10), and by relatively weak electrical stimulation of the central end of the depressor nerve in rabbits with the vagi, sinus nerves and depressor nerves cut (Fig. 4). Moreover, adrenaline elicited larger increases of shivering in two cats with the aortic nerves intact than when the sinus nerves and vagi were also intact. Conversely, any manoeuvre causing a fall of arterial pressure, such as the injection of acetylcholine (Fig. 10), stimulation of the peripheral vagus or haemorrhage, reduces or stops shivering. In addition, rabbits and cats

with the majority of baroreceptor nerves cut shiver poorly, and shivering is not then evoked by a rise of arterial pressure. Ishii & Ishii (1960*b*) have shown that in rabbits selected as capable of maintaining their rectal temperature during restraint, the rectal temperature at which shivering began was inversely related to the arterial blood pressure, and they never observed rabbits to shiver when the arterial pressure was lower than 70 mm Hg (Ishii & Ishii, 1960*a*). While the evidence of this and other work (Mott, 1962) and the well known respiratory variation in the intensity of shivering show that the arterial pressure is not the only afferent source of stimulation influencing shivering, it is clearly important. It follows that if a stimulus causes a change in arterial pressure as well as a change in the intensity of shivering, the latter may be secondarily modified by changes in baroreceptor stimulation due to the former.

Chemoreceptor stimulation caused by perfusion of the carotid body in rabbits with an hypoxic solution (Fig. 5), by the intravenous injection of sodium cyanide (Figs. 7 and 8) or nicotine in rabbits and cats, and by the injection of lobeline in cats, diminished shivering. However, the inhibition of shivering by lobeline in vagotomized cats was brief and in two of three cats was followed by an enhancement of shivering above the resting level during the prolonged rise of arterial pressure caused by this drug. Conversely, the more prolonged inhibition of shivering induced by sodium cyanide in cats than in rabbits lasted throughout the late fall of arterial pressure caused by this compound in cats but not in rabbits.

Inhibition of shivering due to sodium cyanide was abolished by cutting the vagi and carotid sinus nerves in nine of ten rabbits. Since intravenous injection of sodium cyanide usually caused little change of arterial pressure in the intact rabbit (Figs. 7 and 8), the inhibition of shivering caused by this compound cannot be attributed to changes in the level of baroreceptor stimulation. Indeed, in the vagotomized rabbit sodium cyanide caused a rise of arterial pressure which would be expected to augment shivering, yet the inhibition of shivering was at least as great as in the intact animal. In cats, too, with the vagi cut the abrupt diminution of shivering elicited by intravenous injection of sodium cyanide was abolished by cutting the sinus nerves. These observations confirm the inference of von Euler & Söderberg (1958) that chemoreceptor stimulation inhibits shivering. The question arises as to whether this inhibition of shivering could be due to a secondary reflex initiated by the hyperpnoea resulting from chemoreceptor stimulation. Any such secondary reflex could only be non-vagal, since the inhibition of shivering elicited by chemoreceptor stimulation is not reduced in the vagotomized animal. The fact that shivering subsides immediately the hyperpnoea begins tends to exclude participation of a secondary reflex. Moreover, more vigorous breathing

is often associated with *increased* shivering (Fig. 11), and restriction of the tracheal inflow sufficient to cause an increase of respiratory rate did not stop shivering. It therefore seems reasonable to conclude that inhibition of shivering should be added to the list of primary effects due to chemoreceptor stimulation.

Electrical stimulation of the cut central end of the carotid sinus nerve in rabbits always caused a decrease of shivering if hyperpnoea was also induced. While this is consistent with the conclusion that chemoreceptor stimulation inhibits shivering, some baroreceptor innervation was intact in all these rabbits. Electrical stimulation of the carotid sinus nerves excites baroreceptor fibres as well as chemoreceptor fibres and causes a fall of arterial pressure (Neil, Redwood & Schweitzer, 1949). An increase of intrasinusal pressure also decreases γ motoneurone activity (Schulte, Henatsch & Busch, 1959), so that the interpretation of the reduction of shivering observed on stimulation of the carotid sinus nerve could be complex. However, in the lamb with both sinus nerves and the vagi cut, in which no decrease of shivering was seen on stimulation of the sinus nerve until the current strength was increased sufficiently to induce hyperpnoea, although the arterial pressure had fallen at lesser current strength, it is more difficult to evade the conclusion that chemoreceptor stimulation inhibits shivering. Inhibition of shivering caused by electrical stimulation of the carotid sinus nerve was described by Tournade & Malméjac (1929) in dogs. This phenomenon was probably due to stimulation of fibres from chemoreceptors, and the assumption of Ishii & Ishii (1960*a*) that this old observation is at variance with theirs on the effects of baroreceptor stimulation on shivering may be mistaken.

The depressor nerve of the rabbit has been generally believed not to include fibres arising from chemoreceptors, although there is evidence for the presence of two groups of baroreceptor fibres (Douglas, Ritchie & Schaumann, 1956). It seems probable that the generation of shivering elicited by relatively weak electrical stimulation of the central end of the depressor nerve is attributable to activity in the myelinated fibres from baroreceptors. Whether the inhibition of shivering or the failure to generate a shiver which follows rather stronger electrical stimulation of this nerve is attributable to the non-myelinated fibres from baroreceptors, or to previously undetected fibres arising from chemoreceptors, is not resolved by the observations of this paper. The fact that sodium cyanide always fails to cause any stimulation of breathing on injection into rabbits with the vagi and sinus nerves cut suggests that nerves arising from chemoreceptors may not be involved. If the inhibition of shivering caused by strong stimulation of the central end of the depressor nerve results from activity in non-myelinated afferent nerves of baroreceptors, it is of interest that

breathing is also stimulated, in contrast to the slowing of breathing sometimes evoked by weaker stimulation of the central end of the depressor nerve and generally considered characteristic of baroreceptor stimulation.

The relation of the vagi to shivering. Cutting the vagi stops shivering for a minute or two, and as Ishii & Ishii (1960*a*) suggested this is no doubt partly due to the accompanying fall of blood pressure. However, the resumption of shivering coincides with the subsidence of the extreme hyperpnoea that immediately follows vagotomy (Fig. 6) and this can take longer than the recovery of the arterial pressure. It is interesting that the inhibition of shivering elicited by sodium cyanide is sometimes more pronounced after vagotomy, and indeed in one rabbit could not be consistently obtained until the vagi had been cut. This could be interpreted as suggesting that some afferent vagal activity may augment shivering, as claimed by Cort & McCance (1953) from the results of experiments in which piglets breathed cold air through valves. They did not measure the temperature of the air entering the trachea and attempts to repeat their observations on piglets by making rabbits inhale cold air yielded no positive results. As with their piglets, the rectal temperature of rabbits tended to fall while breathing cold air but there was never any increase of shivering that could be attributed to stimulation by cold of the lower respiratory tract. They, too, found that shivering did not diminish on substituting room air for cold air until the animal was rewarmed. The interpretation of the fact that they failed to elicit a shiver by admission of cold air to the trachea after vagotomy (which in the pig presumably includes cutting most of the fibres from baroreceptors contributing to the aortic nerve) is now complicated by the demonstration that reduction of such sensory stimulation may itself reduce shivering.

Large inflations and deflations of the lungs stopped shivering in rabbits with the vagi cut; the afferent mechanisms responsible therefore cannot be vagal. While the fall of arterial pressure caused by inflating the lungs would be expected to contribute to the lessening of shivering, any gross movements of skeletal musculature, such as those involved in the extreme hyperpnoea immediately following vagotomy or dyspnoea caused by grossly restricting the tracheal inflow, and spontaneous movements of the limbs are also accompanied by a reduction or cessation of shivering.

The action of drugs on shivering

The results reported in this paper and elsewhere (Mott, 1962) make it clear that effects on shivering caused by drugs can be secondary to changes of systemic blood pressure or of chemoreceptor activity, or to a hypertonic stimulus reaching the brain.

It is interesting that large doses of hexamethonium did not prevent

shivering in rabbits and cats. However, hexamethonium largely or completely prevented the inhibition of shivering and stimulation of breathing caused by nicotine but not that caused by sodium cyanide. These observations are consistent with the conclusion of Douglas (1952) that in cats hexamethonium antagonizes the stimulation by nicotine of chemoreceptors but not that due to sodium cyanide. While there is evidence that hexamethonium reduces the response of chemoreceptors to sodium cyanide (Joels & Neil, 1962) the methods of recording employed and conditions of the experiments described in this paper were not necessarily suitable to detect such reduction. It has also been shown that baroreceptors in the isolated sinus preparation of the cat can be stimulated by nicotine and that such stimulation is likewise prevented by hexamethonium (Diamond, 1955). Nevertheless, since neither in the cat nor the rabbit does nicotine cause large falls of arterial pressure, as would be expected if it predominantly elicited baroreceptor rather than chemoreceptor reflexes, it is reasonable to suppose that the inhibition of shivering caused by nicotine is indeed due to stimulation of chemoreceptors. However, the possibility must be admitted that some of the sensory endings of the depressor nerve in the rabbit may be stimulated by nicotine, since this compound continues to stop shivering on intravenous injection after the vagi and the sinus nerves have been cut.

It is clear that adrenaline and noradrenaline may either increase shivering, leave it unchanged or decrease it. It would be expected that pressor amines would increase shivering, since they raise arterial pressure and should thereby increase the activity of baroreceptors. Shivering decreased on intravenous injection of adrenaline, however, in five of seven intact rabbits of this paper, in the rabbits used by Ishii & Ishii (1960*a*) and, with larger doses, in cats cooled in a bath (Hall & Goldstone, 1940). The inhibition of shivering by adrenaline in rabbits anaesthetized with urethane was abolished after cutting the vagi (Ishii & Ishii, 1960*a*) but in the rabbits of this paper persisted unless the sinus nerves also were cut. These observations and the similar ones in cats, together with the fact that noradrenaline can increase the rate of chemoreceptor discharge (R. A. Mayou & R. W. Torrance, personal communication), suggest that the inhibition of shivering sometimes caused by pressor amines is attributable to hypoxia of the glomus tissue following local vascular changes; the chemoreceptor stimulation thus produced can be sufficient to diminish the augmentation of shivering due to baroreceptor activity elicited by the rise of arterial pressure.

Connexion of the baroreceptors and chemoreceptors with the efferent pathway for shivering

The level at which arterial baroreceptor and chemoreceptor stimulation impinges on the efferent pathway for shivering (Birzis & Hemingway, 1956, 1957) remains to be determined, but many observations indicate that some effects of afferent stimulation of the ninth and tenth cranial nerves do reach the mid-brain (e.g. Bronk, Lewy & Larrabee, 1936; Chang, Chia, Hsu & Lim, 1937; Gellhorn, 1957; Bonvallet & Hugelin, 1961).

A full description of the mechanisms controlling shivering will also have to include an account of the parts played by α- and γ-motoneurones. Schulte, Busch & Henatsch (1959) and Schulte, Henatsch & Busch (1959) found that chemoreceptor stimulation increases, and baroreceptor stimulation decreases γ-motoneurone activity, and further that baroreceptor stimulation only decreased α-motoneurone activity if the γ-efferent innervation of the ventral root examined was substantially intact. These observations are consistent with older reports (summarized by Kaufmann (1938) and Heymans & Neil (1958)) that baroreceptor stimulation can decrease muscle tone. However, baroreceptor stimulation increases the tonic stretch reflex responses of the α-motoneurones of *de-efferented* muscle (Schulte, Henatsch & Busch, 1959). Thus if the conditions of the experiments of this paper were such as to minimize γ motoneurone activity, baroreceptor stimulation might well be expected to augment shivering through the α-motoneurones. Schulte, Henatsch & Busch (1959), however, also observed an increase of the tonic stretch reflex responses of the α-motoneurones of the de-efferented muscle during perfusion of the carotid body with cyanide by the *intra-arterial* route. The perfusion pressure is not stated and the possibility that baroreceptors were simultaneously excited certainly exists. It is therefore not clear whether α-motoneurone activity is modified in opposite directions by baro- and chemoreceptor stimulation as is the case with γ-motoneurone activity, but in the opposite directions. That it may indeed be so is suggested by the experiments of Kaufmann (1938), who observed that stimulation of the carotid body by sodium cyanide reduced the tone and/or reflex contraction of tibialis anterior evoked by stimulation of the posterior tibial nerve in anaesthetized dogs. On balance therefore it seems reasonable to suggest that the inhibition of shivering by chemoreceptor stimulation and its augmentation by baroreceptor stimulation may be due to effects on α- rather than on γ-pathways. The diminution of shivering due to inhalation of 100% O_2 in conscious man (MacCanon & Eitzmann, 1961) may be attributable to a reduction of γ-motoneurone activity. Likewise, the longer inhibition of shivering elicited by sodium cyanide in some anaesthetized

rabbits after vagotomy (Fig. 7) might depend on reduction of γ-motoneurone activity resulting from the rise of arterial pressure caused by sodium cyanide in the vagotomized, but not in the intact, rabbit.

In attempting any assessment of the contribution of baroreceptor and chemoreceptor stimuli to the thermal behaviour of the intact conscious animal, it must not be forgotten that the cerebral cortex can restrain reticular activity excited by hypoxia (Bonvallet & Hugelin, 1961). With this qualification in mind, it may, however, be suggested that reflex anoxic inhibition of shivering mediated by the arterial chemoreceptors could contribute to the fall of oxygen consumption observed in cold animals rendered hypoxic, in so far as this is not attributable to a simultaneous decrease of baroreceptor stimulation resulting from a fall of arterial pressure. Moreover, perhaps these effects would be more pronounced if γ-motoneurone function were undeveloped, as appears to be the case in the young kitten (Skoglund, 1960).

SUMMARY

1. It is confirmed that shivering can be intensified by baroreceptor stimulation. The development of shivering appeared to be largely dependent on the integrity of the baroreceptor nerves.

2. Weak electrical stimulation of the central end of the depressor nerve of the rabbit augmented shivering; but stronger stimulation stopped it and stimulated breathing but did not cause a rise of arterial pressure.

3. Stimulation of the chemoreceptors by perfusion of the isolated carotid body and sinus with Krebs–Henseleit solution equilibrated with 95 % N_2, or by intravenous injection of sodium cyanide, nicotine or lobeline, reduced or stopped shivering. Sodium cyanide failed to stop shivering in nine of ten rabbits after cutting the vagi and carotid sinus nerves.

4. When electrical stimulation of the central end of a carotid sinus nerve stimulated breathing shivering also stopped.

5. Administration of hexamethonium 15 mg/kg did not stop shivering in rabbits or cats. When the stimulation of breathing caused by nicotine in vagotomized rabbits was abolished by hexamethonium, the inhibition of shivering previously caused by nicotine was also abolished. The increased breathing and inhibition of shivering elicited by sodium cyanide persisted after the administration of hexamethonium.

6. Small doses of adrenaline or noradrenaline had variable effects on shivering. After cutting the nerves from chemoreceptors, however, shivering increased simultaneously with the rise of arterial pressure. This increase of shivering was abolished or greatly reduced after cutting the depressor nerves of the rabbit or the aortic nerves of the cat.

7. The hypothesis that chemoreceptor stimulation inhibits shivering in anaesthetized animals was confirmed, but it is pointed out that changes of arterial pressure during such stimulation may simultaneously influence the intensity of shivering.

8. It is suggested that the phenomena described are more likely to be due to changes in α- rather than in γ-motoneurone activity.

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