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RESPIRATORY AND CIRCULATORY CONTROL AT HIGH ALTITUDES

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SUMMARY

Hyperventilation is one of the most important features of acclimatization to high altitude. Resting ventilation at extreme altitudes increases up to fourfold and exercise ventilation for a given work level increases to the same extent. Hypoxic stimulation of the peripheral chemoreceptors is the chief mechanism for the hyperventilation but there is also evidence that central sensitization of the respiratory centres occurs. Permanent residents of high altitude have a blunted hypoxic ventilatory response compared to acclimatized lowlanders. Cardiac output increases in response to acute hypoxia but returns to normal in acclimatized lowlanders. Oxygen uptake at extreme altitudes is markedly limited by the diffusion properties of the blood gas barrier. As a consequence the maximal oxygen consumption of a climber near the summit of Mount Everest is near his basal oxygen requirements. Maximal oxygen consumption is so sensitive to barometric pressure that it may be that day-to-day variations will affect the chances of a climber reaching the summit without supplementary oxygen.

ACCLIMATIZATION TO HIGH ALTITUDE

Man and some other animals show a remarkable ability to adapt to living at high altitudes, a process known as acclimatization. Various factors participate in this acclimatization process including hyperventilation, increases in the red blood cell concentration of the blood and in the number of capillaries in peripheral tissues, and changes in the oxidative enzymes within the cells. Some people also believe that the rightward shift of the oxygen dissociation curve which sometimes occurs is also beneficial.

Of all these changes, probably the most important is the hyperventilation. As an example of the value of this we can consider a climber standing on the summit of Mt Everest (altitude 8848 m) who elects to maintain the same alveolar ventilation as he had at sea level. The result would be a fall in alveolar and arterial P_{O_2} to zero! Indeed, while the importance of hyperventilation is clear to see, many physiologists now question the roles of polycythemia and the rightward shift of the oxygen dissociation curve in the acclimatization process. For example, Winslow *et al.* (1979) showed that when some permanent residents of high altitude who had marked polycythemia were bled over a period of two or three weeks to reduce their haematocrit to normal sea level values, their exercise tolerance was substantially unaltered, or

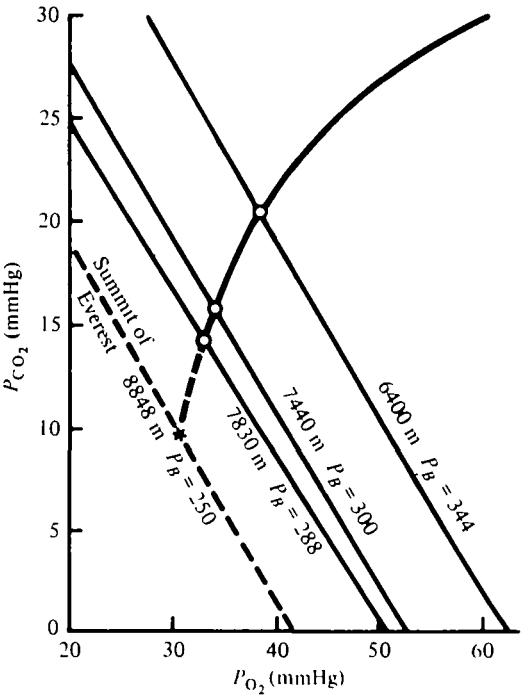

Fig. 1. Oxygen–carbon dioxide diagram showing alveolar gas composition at extreme altitudes (open circles). Extrapolation to the summit of Mt Everest (250 torr) gives a P_{O_2} and P_{CO_2} of approximately 30 and 10 torr, respectively. (From West & Wagner, 1980.)

even improved. Furthermore, during the American Medical Research Expedition to Everest which has just concluded, we found that reducing the haematocrit of some climbers at the end of the expedition by replacing whole blood with human albumin solution at an altitude of 5400 m did not appear to alter work capacity (as measured on a stationary bicycle) or psychological function.

Again the role of the rightward shift of the oxygen dissociation curve in acclimatization has recently been disputed. First, the extent of the shift in well-acclimatized subjects may be insignificantly small. But the most provocative relevant finding was reported by Hebbel *et al.* (1978) who showed that patients with haemoglobin Andrew–Minneapolis, who had a markedly left-shifted oxygen dissociation curve, apparently tolerated exercise better at medium altitudes than their siblings who had a normal oxygen dissociation curve. Theoretical studies of pulmonary gas exchange at high altitudes support this. Bencowitz *et al.* (1982) showed that a left-shifted oxygen dissociation curve results in a higher P_{O_2} in mixed venous blood during exercise at high altitude when oxygen transfer across the blood–gas barrier is partially limited by diffusion. Indeed, climbers may well exploit this leftward shifting at extreme altitudes. A common practice when climbing an 8000 m peak is to put in the high camps and then descend to a medium altitude for several days. Following this the climber moves as rapidly as possible to the summit. This procedure results in a partially compensated respiratory alkalosis at extreme altitudes which will cause a leftward shift in the oxygen dissociation curve and may well enhance oxygen transfer (West & Wagner, 1980).

Fig. 2. Christopher Pizzo, M.D., taking alveolar gas samples on the summit of Mt Everest during the course of the American Medical Research Expedition to Everest, 1981.

Thus, hyperventilation is one of the most important features of high altitude acclimatization. The extent of the hyperventilation that occurs is remarkable and is best considered under the headings of resting and exercise ventilation.

VENTILATION DURING REST

Measurements of ventilation at rest are notoriously unreliable because the experimental subject is distracted by the mouthpiece and other equipment. For this reason it is usual to report the alveolar or arterial P_{CO_2}; this is inversely proportional to the alveolar ventilation if carbon dioxide production is constant. Fig. 1 is an oxygen–carbon dioxide diagram showing alveolar gas composition at extreme altitudes (Gill *et al.* 1962). The data were obtained on the Himalayan Scientific and Mountaineering Expedition, 1960–1. The curve line at the top right of the diagram is essentially a continuation of the line drawn by Rahn & Otis (1949) for men acclimatized to high altitudes. Note that extrapolation of the line through the barometric pressure on the summit of Mt Everest predicts a P_{O_2} and P_{CO_2} of about 30 and 10 torr respectively. During the recent physiological research expedition to Everest, several alveolar gas samples were obtained on the summit by Dr Christopher Pizzo (see Fig. 2). These samples are still being analysed at the time of writing.

These data show the enormous degree of hyperventilation which occurs during rest at extreme altitudes. Since the normal sea level value for alveolar P_{CO_2} is 40 torr, the value of 10 torr predicted for the summit of Mt Everest represents a fourfold increase in resting alveolar ventilation.

VENTILATION DURING EXERCISE

Just as resting ventilation increases dramatically at high altitude, so does ventilation during exercise. In fact, at moderate levels of exercise, there is little or no change in arterial P_{CO_2} between rest and exercise. Since carbon dioxide production for a given work level is essentially independent of altitude, this means that ventilation measured at STPD is independent of altitude at a given work level. At work levels approaching maximal values at any altitude, alveolar and arterial P_{CO_2} fall compared with the resting level and exercise ventilation measured at STPD correspondingly rises. Naturally, if exercise ventilation is reported as BTPS which is the usual practice, the values for a given level of exercise increase markedly with altitude.

Very high levels of ventilation (BTPS) during maximal exercise are seen at altitudes of about 6000 m. Fig. 3 shows data obtained by Pugh *et al.* (1964) at sea level, 4650 m (440 torr), 5800 m (380 torr), 6400 m (340 torr), and 7440 m (300 torr). These data are shown by crosses on the diagram. The barometric pressure axis is non-linear for reasons which will be explained below. Note the very high values for maximal exercise ventilation at barometric pressures between 340 and 400 torr. Indeed, one measurement of maximal exercise at an altitude of 6400 m where the barometric pressure was 340 torr gave a value for ventilation of over 200 l/min BTPS (Pugh *et al.* 1964).

Fig. 3 also shows that at even higher altitudes (lower barometric pressures) maximal exercise ventilation falls off. Thus, at an altitude 7440 m (300 torr) the mean value was only 120 l/min. Predictions based on a model of gas exchange for a climber on

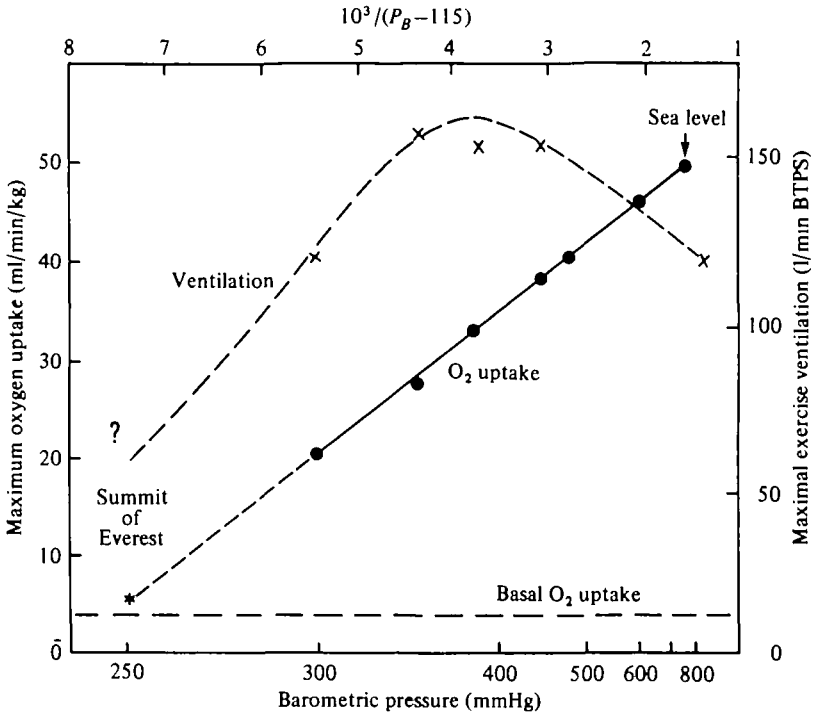

Figure 3. Maximal exercise ventilation and maximal oxygen consumption plotted against barometric pressure. The barometric pressure axis has been transformed according to the expression at the top of the graph so that the data for maximal oxygen consumption lie on a straight line. Note that maximal ventilation increases with falling barometric pressure up to a certain point and then decreases strikingly. The maximal oxygen consumption predicted for the summit is close to the basal oxygen requirements.

the summit of Mt Everest give values as low as about 50 l/min for maximal exercise ventilation there. Some measurements of ventilation during maximal climbing activity were made during the recent physiological expedition to Mt Everest at an altitude of about 8300 m (271 torr) but the results are not available at the time of writing.

The reason for the decline in maximal exercise ventilation at extreme altitudes is the reduction in maximal work level as indicated by the values for maximal oxygen uptake shown in Fig. 3. In this figure, data on maximal oxygen consumption at various altitudes reported by Pugh *et al.* (1964) are plotted on a non-linear barometric pressure axis which was chosen so that the data points lie on a straight line. The transformation is according to the hyperbolic function shown at the top of the diagram. Note that maximal oxygen uptake fell to approximately one third of its sea level value in a climber at an altitude of 7440 m (300 torr). A somewhat bold extrapolation of the data predicts a maximal oxygen uptake for a climber on the summit of Mt Everest of little more than his basal oxygen consumption. Since the work levels at these extreme altitudes are so low, the levels of maximal exercise ventilation are also reduced though, as stated previously , for a given work level, exercise ventilation (BTPS) continues to increase as the climber goes higher.

REGULATION OF VENTILATION AT HIGH ALTITUDE

If a resting subject at sea level is given a low oxygen mixture to breathe, ventilation generally increases through stimulation of the peripheral chemoreceptors. In acute hypoxia, the response is somewhat variable and is usually not seen until the alveolar P_{O_2} is reduced to between 50 and 60 torr corresponding to a simulated altitude of about 4000 m. With more severe degrees of alveolar hypoxia, increasing hyperventilation is seen though the levels of ventilation are considerably less than those observed in lowlanders acclimatized to high altitude. Not only is the resting ventilation increased in acute hypoxia but so is the ventilatory response to carbon dioxide as measured by the change in ventilation per unit rise in alveolar P_{CO_2} (Nielsen & Smith, 1952).

With chronic hypoxia such as caused by exposure to high altitude, ventilation initially increases as in acute hypoxia but there is a further increase which occurs over several days. The mechanism of this 'ventilatory acclimatization' is still obscure. One early explanation was that the initial hyperventilation increased the plasma pH, which tended to inhibit a further increase in ventilation until renal excretion of bicarbonate took place and returned the arterial pH to normal (Rahn & Otis, 1949). Another explanation was that similar acid-base changes occurred in the cerebral spinal fluid thus affecting the extra-cellular environment of the central chemoreceptors (Severinghaus *et al.* 1963). However, neither of these explanations is now accepted because the time course of changes in arterial blood pH and cisternal CSF pH are not consistent with the observed levels of ventilation (Forster *et al.* 1975). Physiologists working in this rather technical area now believe that some central sensitization of the respiratory centres occurs though the mechanism for this is far from understood. This explanation is consistent with the observation that if acclimatized lowlanders are given 100% oxygen to breathe at high altitude, while both resting and exercise ventilation for a given work level are reduced, they do not return to the sea level values (Pugh *et al.* 1964).

If we compare the hypoxic ventilatory response of acclimatized lowlanders with permanent residents of high altitude (including both the South American Andes and the Himalayas) we find that the native highlanders have a blunted hypoxic response. The response is still present as shown, for example, by the single or double oxygen breath test (Dejours *et al.* 1958) but it is less marked than in acclimatized lowlanders. The same phenomenon is seen in children born at sea level who have chronic arterial hypoxemia caused by cyanotic congenital heart disease. One consequence of the blunted hypoxic ventilatory response is that permanent high altitude residents have slightly higher alveolar P_{CO_2} values than acclimatized lowlanders at the same altitude.

CARDIAC AND CIRCULATORY FUNCTION

Acute hypoxia causes both an increase in cardiac output and heart rate. For example, when the arterial P_{O_2} is reduced to levels of approximately 35 to 45 torr, both cardiac output and heart rate are some 40 to 50% higher than normoxic control values (Kontos, *et al.* 1967; Vogel & Harris, 1967).

However after several weeks at high altitude, both the resting pulse rate and cardiac

output return to the sea level values, at least up to altitudes of about 6000 m. Above this altitude, resting pulse rate tends to increase. Very few measurements of cardiac output have been made above an altitude of 5000 m. However both Cerretelli (1976) and (Pugh (1964*a*) agree that cardiac output for a given work level at these high altitudes is similar to the sea level values. When oxygen is breathed by acclimatized lowlanders at high altitude, the heart rate for given work level decreases. However, the maximal heart rate increases because the maximal work level is so much higher. The fact that the cardiac output for a given work level at high altitude (during ambient air breathing) is essentially the same as at sea level suggests that the heart does not play a role in the acclimatization process. However, it should be pointed out that because of the associated polycythemia, the haemoglobin flow per unit time is actually increased at high altitude.

Changes in systemic arterial blood pressure are generally unremarkable in sea level dwellers acclimatized to high altitude. However, both they and high altitude natives show an increase in pulmonary artery pressure as a consequence of the hypoxic pulmonary vasoconstriction. The pulmonary hypertension is particularly marked on exercise, is accentuated by the increased viscosity of the polycythemic blood, and results in the characteristic changes of right heart hypertrophy in the electrocardiogram. High altitude pulmonary oedema which is occasionally seen is probably related in some way to the pulmonary hypertension though the mechanism remains obscure.

GAS EXCHANGE AT HIGH ALTITUDE

The changes in ventilation and cardiac output which occur at high altitude are part of the organism's response to oxygen deprivation. It is therefore pertinent to look at the overall picture of oxygen and carbon dioxide transport at high altitude. Our own recent preoccupation has been with extreme altitudes, stimulated in part by the remarkable physiological event which occurred just three years ago when Messner and Habeler reached the summit of Mt Everest for the first time without the help of supplementary oxygen. That this is very near the limit of human tolerance is supported by Fig. 4 which shows the greatest heights attained by climbers this century. Note that although men had ascended to within 300 m of the summit of Everest as early as 1924, the mountain was not climbed until 1953, and then only with supplementary oxygen. It was not until 1978 that climbers were successful breathing ambient air. Thus, the last 300 m took 54 years!

Recently we have analysed the gas exchange which is predicted to occur in a climber resting on the summit of Mt Everest. We were stimulated in part to do this by the climb of Messner and Habeler and by data such as those shown by the circles in Fig. 3 which suggest that the available maximal oxygen uptake at the summit is very close to the basal oxygen consumption. This theoretical analysis was partly made to identify the most important measurements that could be made during the recent physiological expedition to Mt Everest.

One of the most critical pieces of data needed for such an analysis is the barometric pressure on the summit. There has been some uncertainty about this but fortunately Dr Pizzo (Fig. 2) managed to make a measurement confirming that it is between 250

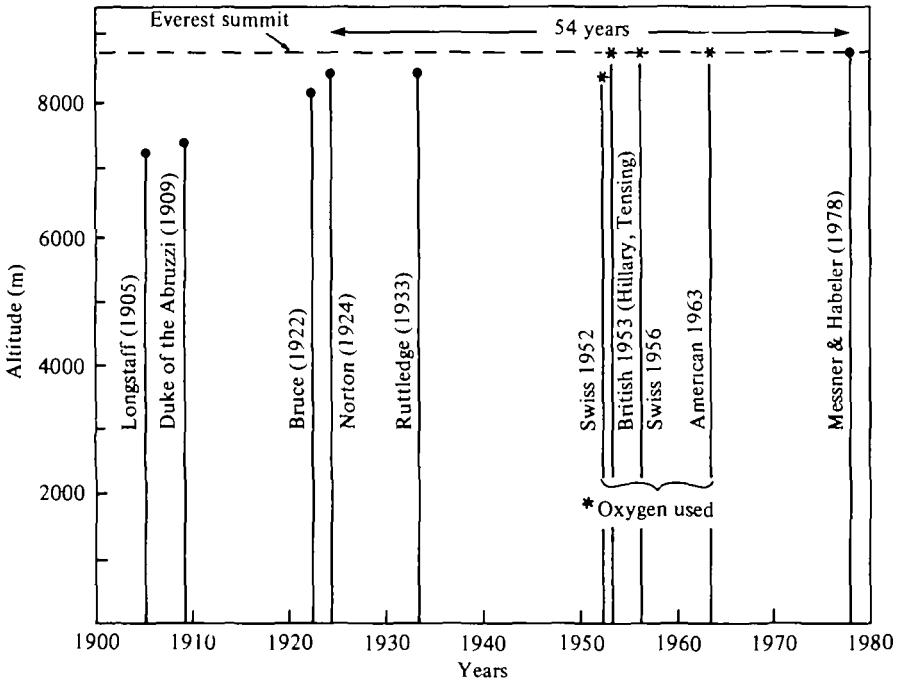

Fig. 4. Highest altitudes attained by climbers during this century. Note that as early as 1924 climbers ascended to within 300 m of the summit of Mount Everest. However the mountain was not climbed without supplementary oxygen until 54 years later. (From West & Wagner, 1980.)

and 253 torr. Incidentally, this is substantially higher than the pressure predicted from the ICAO Standard Atmosphere because the pressure at a given altitude is higher near the equator than the poles as a result of the presence of a large mass of cold air in the stratosphere above the equator. Many physiologists in the past have used the standard atmosphere which gives a pressure of only 235 torr at the altitude of Mt Everest. One conclusion of our analysis is that if the pressure were that low it would certainly be impossible to climb the mountain without supplementary oxygen.

Another critical variable is the alveolar P_{CO_2}. The extrapolation from data already obtained up to altitudes of 7830 m (288 torr) shown in Fig. 1 gives a value at rest of 30·5 torr and we have used this. We have also assumed that the alveolar P_{CO_2} remains constant as the exercise level is increased. This was found to be the case (Pugh *et al.* 1964) for oxygen consumptions of up to about 1 l/min at an altitude of 5800 m (380 torr). However, note that as the respiratory exchange ratio increases from about 0·8 to 1 during exercise, there is a gain in alveolar P_{O_2} of approximately 2 torr.

Other data needed for this analysis include the haemoglobin concentration, cardiac output, and diffusing capacity of the blood–gas barrier. For haemoglobin concentration we have assumed a figure of 20·5 g/dl, a mean value reported for acclimatized climbers during Himalayan expeditions (Pugh, 1964*b*) although measurements on the recent physiological expedition to Everest give a slightly lower value. Both cardiac output and diffusing capacity were assumed to be the same as at sea level for the same work level as was the case in measurements at 5800 m (Pugh, 1964*a*; West, 1962).

Based on these considerations, we have calculated the time-course of oxygenation along the pulmonary capillary by the method of forward integration using Runge–Kutta technique (Wagner, 1977). Reaction times for both oxygen and carbon dioxide were taken into account. Fig. 5A shows a typical result for a climber resting on the summit of Mt Everest, and Fig. 5B shows the normal time course of P_{O_2} in the pulmonary capillary at sea level for comparison. The oxygen uptake and carbon dioxide are constrained to be 250 and 200 ml/min respectively, giving a respiratory exchange ratio of 0·8. A striking finding of the calculations at extreme altitude is that even under these essentially basal conditions, there is marked diffusion limitation of oxygen transfer resulting in an alveolar end-capillary difference of approximately 6 torr. This is about 60% of the P_{O_2} difference between alvaolar gas and mixed venous blood. Thus even under these extreme resting conditions, the arterial P_{O_2} is only 25 torr while the alveolar P_{O_2} is 31 torr and the P_{O_2} in mixed venous blood is only 21 torr.

Additional calculations show that the situation rapidly worsens if the oxygen consumption is increased. This results in a further fall in the P_{O_2} of mixed venous blood. If we assume that there is a value of mixed venous P_{O_2} below which increases in oxygen consumption will not be tolerated, this places a limit on the oxygen consumption of the climber. Using reasonable values for diffusing capacity and the other variables, the analysis concludes that the maximal oxygen uptake can only be increased to about 700 ml/min before the P_{O_2} of mixed venous blood falls below 15 torr. This very low work capacity is consistent with the account of the extreme difficulties of reaching the summit of Mt Everest without supplementary oxygen (see for example Messner, 1979).

FACTORS LIMITING WORK AT EXTREME ALTITUDES

In view of the very restricted maximal oxygen consumption at extreme altitude, it is pertinent to ask what are the most important limiting factors. One way of answering this is to calculate the percentage increase in maximal oxygen consumption for the same percentage change of various parameters as shown in Fig. 6. To prepare this graph, calculations were made by changing only one variable at a time, all others being kept the same for the appropriate work level. Maximal oxygen consumption was assumed to occur when the P_{O_2} of mixed venous blood fell to 15 torr.

Fig. 6 shows that barometric pressure is by far the most critical variable. Thus, only a 6% fall in barometric pressure from 250 to 235 torr (the value predicted from the ICAO Standard Atmosphere) results in a decrease in predicted maximal oxygen uptake of 45% (from 470 to 260 ml/min). Indeed, it may be that even day-to-day variations in barometric pressure are significant. Radiosonde data indicate that a decrease of up to 4 torr can be expected in May or October (the preferred climbing months) as a result of daily changes in weather. A decrease of barometric pressure of 4 torr is predicted to result in a fall in calculated maximal oxygen consumption of about 10%, and this may well be sufficient to determine whether a climber is successful or not. Thus, a climber who plans to ascend to the summit of Mt Everest without supplementary oxygen might do well to consult his barometer first.

Fig. 6 also emphasizes the sensitivity of maximal oxygen consumption to the diffusing capacity of the blood–gas barrier. This is not surprising since Fig. 5A

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CENTRAL NERVOUS INTEGRATION OF CARDIOVASCULAR CONTROL

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SUMMARY

In this account an attempt has been made to identify integrative interactions in the control of the cardiovascular system. Three main sites of such interaction have been considered, the nucleus of the tractus solitarius (NTS), the vagal preganglionic supply to the heart and sympathetic preganglionic neurones.

In the case of the NTS the extent and range of afferent inputs from cardiovascular and respiratory receptors have been reviewed. In addition the interactions of these inputs on the activity of NTS neurones have been indicated although the details are as yet vague. With respect to the baroreceptor reflex, it is clear that its relay through the NTS permits the action of intrinsic drives, such as inspiratory activity, and extrinsic drives, for example the defence reaction, to modify to a greater, or lesser, extent the efficacy of the reflex. In the case of respiratory activity, changes in transmission of baroreceptor activity through the NTS are minimal, since a baroreceptor effect can be shown to exert itself on CVM activity throughout the respiratory cycle under appropriate experimental conditions (McAllen & Spyer, 1978*b*). The effectiveness of this excitatory input is, however, 'gated' by a direct inspiratory control of CVM activity. This indicates an essentially integrative role of vagal preganglionic neurones. The role of inputs from the lungs themselves evoked during inspiration, which also contribute to the respiratory modifications of the baroreceptor reflex, in the control of CVM activity is as yet uncertain although evidence is accumulating to suggest that they act by a mechanism different from that of inspiratory drive.

The influence of the defence reaction on transmission through the NTS has yet to be fully documented, but it appears as if there may be the potential for a marked modification. However, it is now certain that an inhibitory control of CVM activity can be evoked from the hypothalamus which is independent of any modification of the baroreceptor input at that level of the NTS and acts rather through an inhibitory synaptic influence directly onto CVMs.

In much the same way the baroreceptor influence on sympathetic preganglionic neurones is determined by their excitability, an excitability which is dependent on the balance of activity in several bulbospinal inhibitory and excitatory pathways, as well as segmental inputs. The role, if any, of direct hypothalamo-spinal pathways and the nature and organization of the descending pathways involved in the defence reaction requires elucidation. Existing data, however, make it clear that the thoracic intermediolateral cell column is an important site in the integration of cardiovascular control.

INTRODUCTION

The role of the nervous system in the regulation of the cardiovascular system is a subject of considerable medical and scientific interest. In recent years much has been learnt concerning the effects of cardiovascular reflexes and the elaboration of central patterns of cardiovascular response appropriate to changing behaviour. Unfortunately, our knowledge of the neural mechanisms involved in the interactions between these different drives and control processes is limited. Indeed, for much of this century those investigating the nervous control of circulation have given little thought to site and manner of these interactions since it was believed that this regulation was the concern of a circumscribed medullary 'vasomotor' centre. This model, which was convenient for its simplicity, has proved to be irreconcilable with the results of recent neurophysiological and neuroanatomical studies, but has been sufficiently influential, if not stifling, as to prevent a general exposition of our present understanding of the nervous organization of cardiovascular control. Some notable attempts have been made to redress this deficit (Hilton, 1975; Wurster, 1977) and the present account is intended to continue this re-evaluation. It will attempt to identify certain of the sites of integration within the neuraxis, concentrating on the processing and modifications in performance of the baroreceptor reflex (Spyer, 1981).

The role of the autonomic preganglionic neurones in the integration of control of the heart and circulation will receive particular attention in this account. An attempt will also be made to establish how the main medullary sensory nucleus receiving information from peripheral cardiovascular and respiratory receptors, the nucleus of the tractus solitarius (NTS), functions in elaborating outputs that regulate cardiovascular activity.

I. THE AFFERENT INPUT TO THE NTS

The NTS receives a marked afferent input from a range of receptors whose activity influences both the cardiovascular and respiratory systems. Since there is a close functional relationship between the respiratory and cardiovascular systems, which has been the subject of a recent review (Koepchen, Hilton & Trzebski, 1980), all these inputs may ultimately influence heart rate and blood pressure. At present the organization of the baroreceptor, chemoreceptor and lung stretch receptor inputs to the NTS are best understood and particular emphasis in the present account will be laid on the first of these. The question of the extent and organization of the baroreceptor input to the NTS has been reviewed in detail elsewhere (Spyer, 1981) and it is probably sufficient in this account to refer only to the major contributions and, in particular, to details of the most recent investigations.

Using the anterograde and transganglionic transport of the enzyme horseradish peroxidase (HRP), the central projections of sinus (SN) and aortic (AN) nerves, which in most species contain both baroreceptor and chemoreceptor afferents, have been illustrated (Berger, 1979, 1980; Panneton & Loewy, 1980; Wallach & Loewy, 1980; Ciriello & Calaresu, 1981; Ciriello, Hrycyshyn & Calaresu, 1981; Davies & Kalia, 1981). Figure 1, taken from the study of Ciriello *et al.* (1981), illustrates the

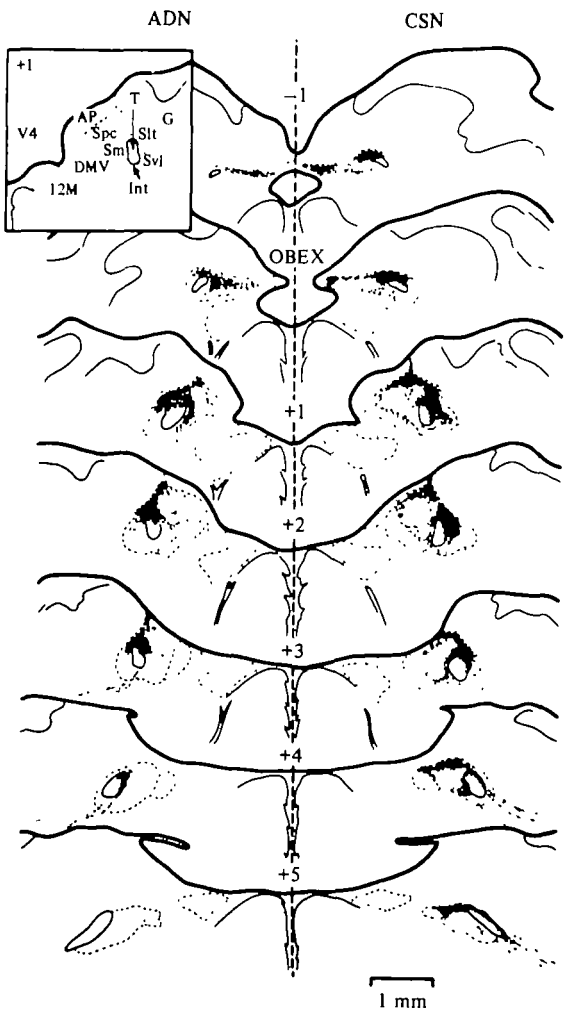

Fig. 1. Representative transverse sections of the dorsal medulla of the cat at intervals of 1 mm (from 1 mm caudal to 5 mm rostral to obex) showing the distribution of labelling following application of horseradish peroxidase (HRP) to the left aortic depressor nerve (ADN) and right carotid sinus nerve (CSN). Stippling indicates the presence of HRP reaction product. Box in upper left hand corner shows transverse section through region of the nucleus of the solitary tract. 12M, Hypoglossal nucleus; AP, area postrema; DMV, dorsal motor nucleus of the vagus; G, nucleus gracilis; Int, intermediate solitary nucleus; Slt, lateral solitary nucleus; Sm, medial solitary nucleus; Spc, parvocellular solitary nucleus; Svl, ventrolateral solitary nucleus; V_4, fourth ventricle; T, solitary tract. (Ciriello & Calaresu, 1981.)

distribution of SN and AN afferents and their terminals within the NTS of the cat, as shown, using this technique. As a generalization it would seem that all the major subnuclei of this complex receive some innervation but the quantitative aspects of the distribution appear to differ depending on the particular research group involved in the study. Although the medial solitary nucleus, commissural and lateral solitary nucleus appear to be densely innervated (Berger, 1979, 1980; Ciriello & Calaresu, 1981; Ciriello *et al.* 1981), the ventrolateral appears only weakly but

distinctly innervated (Davies & Kalia, 1981; Ciriello & Calaresu, 1981). These observations do not, however, resolve whether the dorsomedial aspect of the nucleus represents a 'cardiovascular' nucleus (Seller & Illert, 1969) and the ventrolateral a 'respiratory' nucleus (Baumgarten & Kanzow, 1958) since no distinction on the basis of such studies can be drawn regarding the specific distribution of chemoreceptor and baroreceptor afferents. The use of neurophysiological techniques, however, is beginning to reveal something of the specific central projections of individual baroreceptor afferents (Donoghue, Garcia, Jordan & Spyer, 1982*a*).

These electrophysiological studies have been undertaken in both cat and rabbit and mainly concern the central projections of the aortic baroreceptors. In the rabbit the AN is considered to be solely barosensory, which has facilitated these studies. Briefly, the activity of the cell bodies of aortic baroreceptor afferents are recorded from the *nodose ganglion* using microelectrodes, their central projections being identified by stimulating within the *medulla oblongata* using microelectrodes and mapping the points from which an *antidromic* action potential can be evoked in the ganglion cell under investigation (Donoghue *et al.* 1982*a*). Fig. 2 illustrates some aspects of the technique and Fig. 3 shows the results of an investigation into the central projection of a single aortic baroreceptor neurone with a myelinated axon, recorded in the cat nodose ganglion. By analysing both the latency of the response and the threshold for evoking the antidromic response during multiple penetrations through the dorsomedial medulla, it is possible to infer the course of the axon and its points of branching, and probably also its sites of termination (Donoghue *et al.* 1982*a*, *b*). Our data indicate that the aortic baroreceptor afferents project to either medial or lateral, including ventrolateral, subnuclei or both, in the cat, but predominantly to lateral, including ventrolateral, subnucleus in the rabbit, although in one case an exclusive and extensive projection to the medial subnucleus has been seen (Donoghue *et al.* 1982*a*). Experiments are currently proceeding in the cat in which the pattern of projection of individual carotid sinus baroreceptor afferents are being studied (Donoghue, Felder, Jordan & Spyer, 1982 and in preparation). The activity of their cell bodies in the petrosal ganglion is recorded and the antidromic stimulation procedure described above is employed. Preliminary observations indicate that those baroreceptor afferents with both myelinated and unmyelinated axons also have widespread projections throughout much of the NTS with a pattern of branching and probable terminations that closely resembles that of AN baroreceptors, described above (Donoghue *et al.* 1982*a*). In addition, data have been obtained regarding the projections of carotid body chemoreceptor afferents, with unmyelinated axons, which have a different and more restricted distribution within the NTS. There are considerable other data available in the literature concerning the projections of myelinated and non-myelinated AN fibres in the cat (Donoghue, Fox, Kidd & McWillam, 1981*a*) and non-myelinated fibres from the heart and lungs (Donoghue *et al.* 1981*b*), all of which relay to areas of the NTS shown to receive baroreceptor inputs.

These observations have extended the data obtained from previous neuroanatomical and neurophysiological studies (for review, see Spyer, 1981) and indicate a considerable overlap of the inputs from the AN and SN, and more specifically the

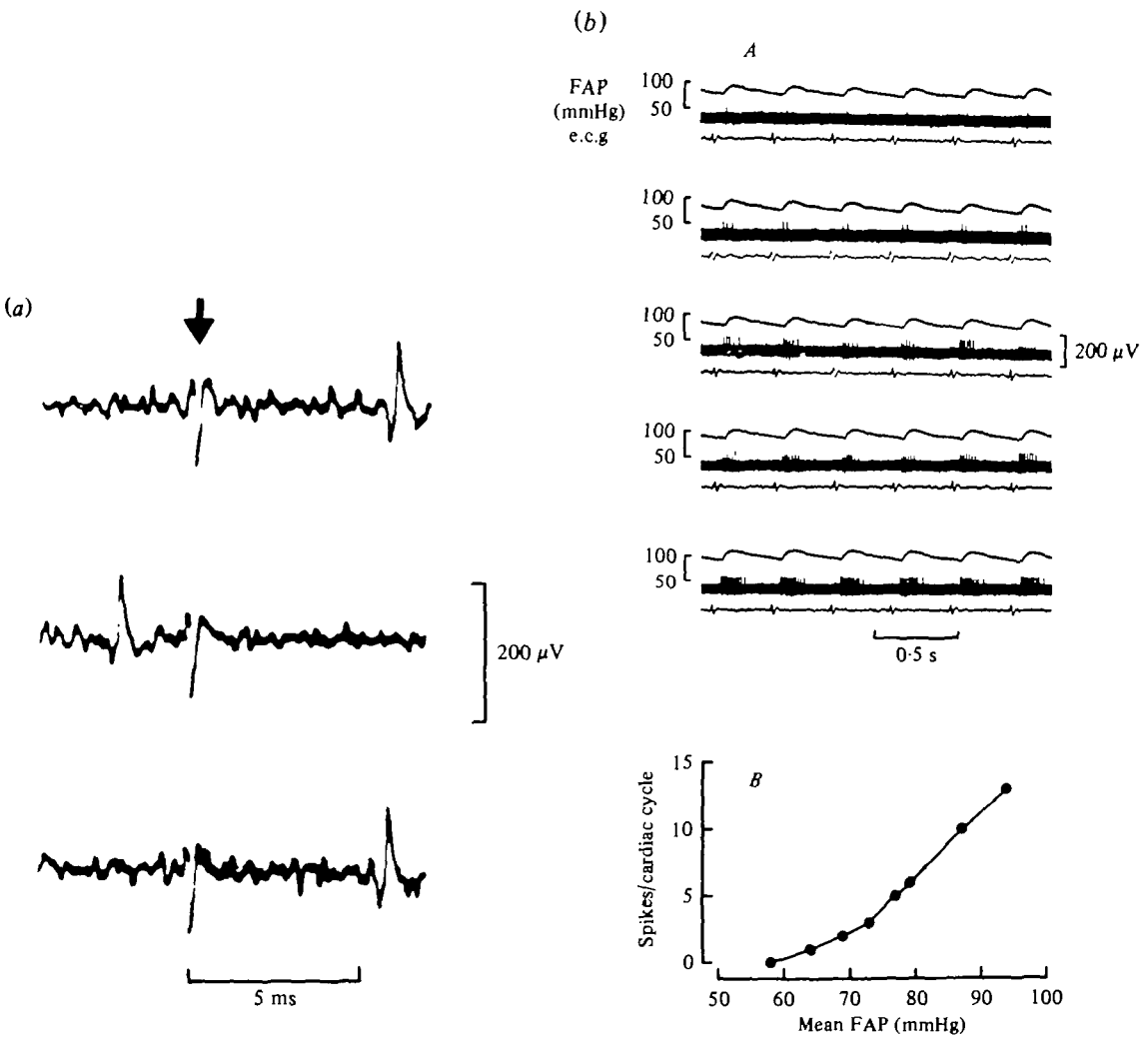

Fig. 2. (*a*) Cat: baroreceptor afferent. Oscilloscope traces showing three consecutive responses of the afferent shown in Fig. 5 to medullary stimulation. Stimulus artifacts are indicated by the arrow. In the top and bottom traces the stimuli each produce one antidromic action potential with a latency of 5·7 ms. In the middle trace a spontaneous action potential occurring 2·1 ms before the stimulus 'collides' with the antidromic potential, so cancelling it.

(*b*) Cat. (A) Original records of femoral arterial blood pressure (FAP), electrocardiogram (e.c.g.) and spontaneous activity of the aortic baroreceptor afferent, identified in (*a*) showing the relationship between FAP and afferent activity. (B) A graph of number of spikes/cardiac cycle (average of ten cycles) against mean FAP. (Donoghue *et al.* 1982*a*.)

baroreceptor afferents contained in these nerves. The immediate question is whether this implies a convergence of these inputs onto neurones in the various subnuclei, a convergence which might underline the interaction between baroreceptor inputs which has been readily demonstrated (see Spyer, 1981 for references). As yet the answer is uncertain. A lack of convergence of inputs from SN and AN in the NTS has been claimed although it was readily demonstrated beyond the confines of the nucleus (Biscoe & Sampson, 1970; McAllen, 1973). In a more recent study, Ciriello

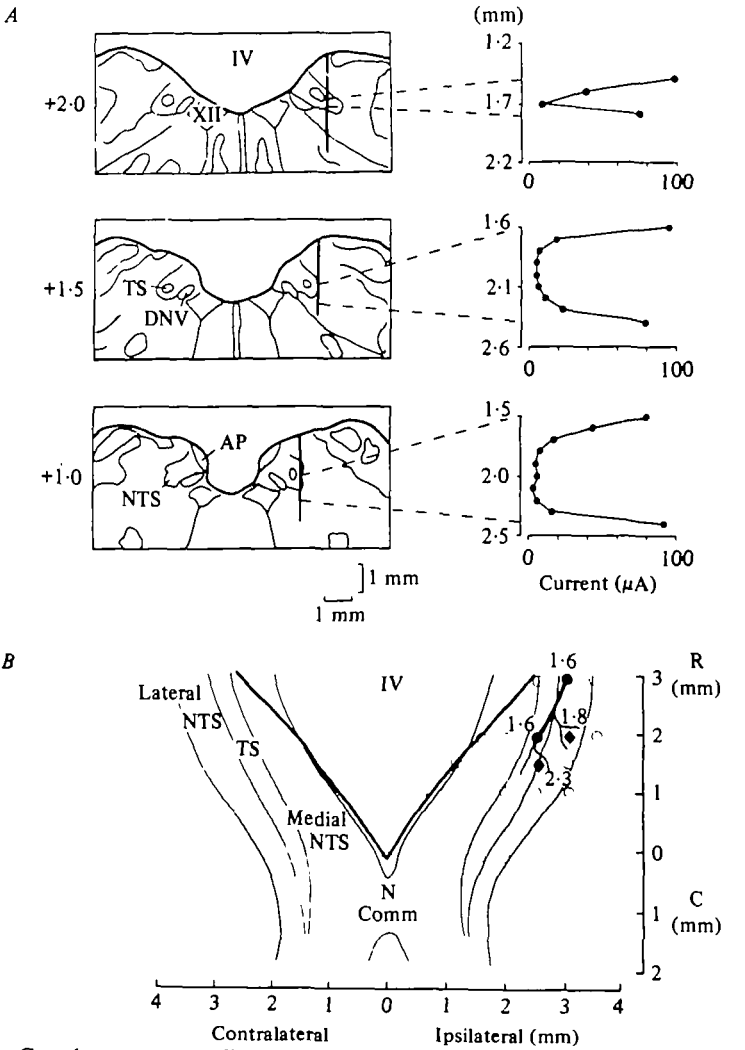

Fig. 3. Cat: baroreceptor afferent. (A) Cross-sections of the dorsomedial region of the medulla oblongata at 0·5 mm intervals from 1 mm rostral (+1) to 2 mm rostral (+2) to the obex. The thick vertical lines each represent a stimulating electrode penetration. On the right are shown depth-threshold curves corresponding to the penetrations. That at the top is of the 'point' type, the lower two of the 'field' type. (B) A schematic view of the dorsal surface of the medulla oblongata, showing the fourth ventricle. Superimposed on this is the medial and lateral extent of the tractus solitarius and its nucleus. Scales indicate distances (in mm) rostral (R), caudal (C) and lateral to the obex (O). Sites of stimulating electrode penetration are indicated, classed according to the type of depth-threshold contour obtained from the penetration, i.e. point (●), field (◆) or no response (○). The main axon is shown by the thick line connecting point types, and regions of branching by the thin lines. Abbreviations: Area postrema (AP), dorsal motor nucleus of vagus (DNV), nucleus commissuralis (NComm), nucleus tractus solitarius (n.t.s.), tractus solitarius (t.s.), hypoglossal nucleus (XII) and IVth ventricle (IV). (Donoghue *et al.* 1982*a*.)

& Calaresu (1981) have provided convincing evidence of convergence of these inputs onto neurones located within the medial, parvocellular, ventrolateral and intermediate subnuclei, but more specifically in areas adjacent to the nucleus.

In addition to the data from extracellular recording studies, Donoghue, Felder, Jordan & Spyer (unpublished material) have found evidence in intracellular recordi

studies that some NTS neurones receive convergent excitatory inputs from AN and SN but the majority appear to respond to one or the other input. In only a few cases was it clear that the cells responded to baroreceptor inputs specifically as shown by changes in membrane potential and spike discharge closely correlated to the e.c.g. In addition, a powerful inhibitory input from both SN and AN was seen in several NTS neurones. The localization and morphology of these different categories of neurones remain to be resolved.

This relative paucity of information concerning the specific organization of the baroreceptor reflex from these recent studies is fortunately supplemented by earlier observations. Lipski, McAllen & Spyer (1975) described neurones grouped mainly in the lateral and ventrolateral portions of the intermediate NTS of the cat's medulla, but with some in parvocellular and commissural subnuclei, that were excited by both SN stimulation and specific baroreceptor stimulation. Some neurones with this pattern of input were also shown to have axons which descended at least as far as the cervical spinal cord (Lipski & Trzebski, 1975). Using a rather different approach, Miura & Reis (1972) have described baroreceptor sensitive neurones in both medial and parvocellular portions of the NTS; the pulse rhythmic discharge of these cells was abolished by bilateral carotid occlusion. Similarly, Langhorst and his colleagues (Stroh-Werz, Langhorst & Camerer, 1977*a*, *b*) have described neurones in this general area of the NTS of both cat and dog, that have both cardiac-related activity and also respiratory modulated discharge. In no case was conclusive evidence provided that the cardiac rhythm was dependent on inputs from the aortic and carotid sinus baroreceptors.

Together this information has led to a controversy as to whether 'medial' or 'ventrolateral' portions of the NTS represent the primary integrative 'centre' in the baroreceptor reflex (see Spyer, 1981). The extensive projections of individual baroreceptor afferents described here may provide an explanation for this apparent dichotomy. There seems no doubt that both general areas receive an input from the arterial baroreceptors, and in fact a single baroreceptor afferent may innervate both areas. This underlines the importance of establishing the physiological properties of neurones in these areas and their functional connections both within and beyond the NTS.

Modifications of transmission of baroreceptor information within the NTS

Respiratory influences. The NTS contains one of the major groups of brainstem respiratory neurones (Richter, 1982) and receives a marked innervation from vagal lung stretch afferents (Donoghue *et al.* 1982*b*). This has led to speculations that at least part of the modifications of the efficacy of the baroreceptor reflex (and chemoreceptor reflex) that occur during the respiratory cycle might be accomplished by changes in either the excitability of NTS neurones or their afferent inputs (Koepchen, Wagner & Lux, 1961; Gabriel & Seller, 1970; Jordan & Spyer, 1979). This possibility has wider implications since if it were proven it would emphasize the integrative role of this nucleus in cardiovascular control.

One mechanism that has been considered as a possible factor in these changes is a presynaptic 'gating' of the afferent input to NTS neurones. Studies so far indicate, however, that baroreceptor and chemoreceptor afferents terminating within the NTS

are not amenable to modulation of their terminal excitability. This is based on the observations that the threshold for evoking antidromic discharge in nodose ganglion AN neurones and the membrane potential of AN afferents recorded within the NTS showed no fluctuations in phase with respiratory activity (Ballantyne *et al.* 1981).

This, however, does not eliminate a role for the NTS in modifying the performance of the baroreceptor reflex. There is plentiful evidence that the activity of many neurones in the NTS, which are not within the category of classical 'respiratory' neurones as discussed by Richter (1982), may show alterations in discharge related to respiratory activity as well as cardiac related discharge (Stroh-Werz *et al.* 1977*b*). Were these cells interneurones, receiving respiratory influences and baroreceptor inputs, their output would depend on the summation of these inputs. The data available so far are hardly compelling since neurones with cardiac-related rhythmicity may either show maximal or minimal discharge in phase with inspiration (Stroh-Werz *et al.* 1977*b*). The absence of an homogenous pattern of convergence underlines the need to identify the individual neuronal connections of these cell types. There is most certainly no evidence for an 'all or nothing' gating of the reflex input within the NTS, and any 'gating' would seem to act by synaptic processes remote from the primary afferent terminals.

The defence reaction. During the defence reaction evoked by electrical stimulation within a circumscribed region of the hypothalamus, the baroreceptor reflex may be totally suppressed, and this suppression is affected within the central nervous system (Coote, Hilton & Perez-Gonzalez, 1979). There is evidence for descending connections from the hypothalamus, arising probably in the vicinity of paraventricular nucleus, which contain neurophysins and terminate in several sites in the medulla, including the NTS (Saper *et al.* 1976; Swanson, 1977). As both cardiac and vascular components of the reflex appear to be blocked, and both arterial pressure, particularly pulse pressure, and heart rate rise, it has been proposed that the reflex may be blocked at an early stage in its processing, namely within the NTS (Coote *et al.* 1979).

The excitability of the baroreceptor afferent terminals is not heightened during stimulation of the hypothalamic defence area (Jordan & Spyer, 1979). There is, however, evidence that the excitatory effect of baroreceptor afferents on the NTS neurones is blocked by a conditioning stimulus to the hypothalamus (McAllen, 1976). Similar effects on the excitatory influence of SN stimulation have also been described (Adair & Manning, 1975; McAllen, 1976) although in one of these studies the stimulus to the hypothalamus had not been shown to affect the baroreceptor reflex, and the NTS neurones had not been shown to be sensitive to baroreceptor stimulation (Adair & Manning, 1975).

Together these data indicate that both peripheral and centrally arising inputs to the NTS can modify the performance of the baroreceptor (and chemoreceptor) reflex. This is certainly strong evidence for an integrative role of the NTS but as yet we have little data on the basis of the processing undertaken within the NTS that results in appropriate outputs to modify cardiovascular activity. In a general neuroanatomical sense much has recently been discovered concerning the *efferent* connections of the NTS (see Loewy & Burton, 1978; Spyer, 1981 for review). These

involve ascending pathways to the pons and diencephalon and descending connections to the spinal cord, as well as diffuse connections within the medulla. The significance of many of these connections in the physiology of cardiovascular control remains only poorly resolved. To obtain a clearer picture one must move to the output side of the CNS – the preganglionic sympathetic and vagal neurones – to obtain a critical appreciation of the role of the central nervous system in cardiac and vascular control.

II. REGULATION OF PREGANGLIONIC VAGAL ACTIVITY

The major regulation of cardiac activity, particularly chronotropic, is exerted by the vagal efferent innervation of the heart (Heymans & Neil, 1958). The mechanisms and neural pathways mediating this regulation have been the subject of intense study over the last two decades. The physiological properties of the vagal supply to the heart are now partially understood, and the baroreceptor–cardiac reflex offers some exciting opportunities for further study.

Considering the importance of this innervation, it is perhaps surprising that little was known of the site of origin of these neurones until recently. This subject has been reviewed in detail (Spyer, 1981) and a brief review is probably sufficient for the present discussion.

In birds, there is a single vagal motor nucleus in the medulla, the dorsal vagal nucleus (DVN), and there is good neurophysiological and neuroanatomical evidence that the vagal motoneurones that innervate the heart originate there (Cohen *et al.* 1970; Schwaber & Cohen, 1978*a*, *b*). In mammals, the situation is complicated by the presence of two motor nuclei – the DVN and N ambiguus (NA). Recent neurophysiological studies have shown the cardiac vagal motoneurones (CVMs) responsible for chronotropic control are located exclusively in the NA in the cat (McAllen & Spyer, 1976, 1978*a*, Fig. 4) and in both NA and DVN in the rabbit (Jordan *et al.* 1979). In the dog, CVMs have been identified in the NA but as yet there are no indications as to whether such neurones are also found in the DVN (McAllen & Spyer, unpublished observations). CVMs have small myelinated axons and there is evidence also that efferent neurones with unmyelinated axons may also innervate the heart, although their function remains uncertain (McAllen & Spyer, 1976). In a recent study, Geis & Wurster (1980) have suggested that in the cat the NA is responsible for chronotropic control, the DVN for inotropic control, presumably mediated by those vagal neurones with unmyelinated axons (McAllen & Spyer, 1976). Such a division of function seems surprising, since it is well established that any change in heart-rate produces *pari passu* a change in inotropic state. Additional claims for a wider distribution of vagal cardioinhibitory neurones in the medulla of the cat (Ciriello & Calaresu, 1980) should be viewed with caution, since a detailed analysis of the discharge pattern is necessary before neurones can be classified with certainty as cardiac in function (McAllen & Spyer, 1978*a*). Such a detailed analysis of the firing pattern in establishing a cardioinhibitory function has been undertaken in both cat and rabbit, and a general pattern of discharge has been revealed which conforms to that described for vagal fibres (McAllen & Spyer, 1978*b*; Jordan *et al.* 1979).

The pattern of discharge. Vagal efferent fibres supplying the heart have been

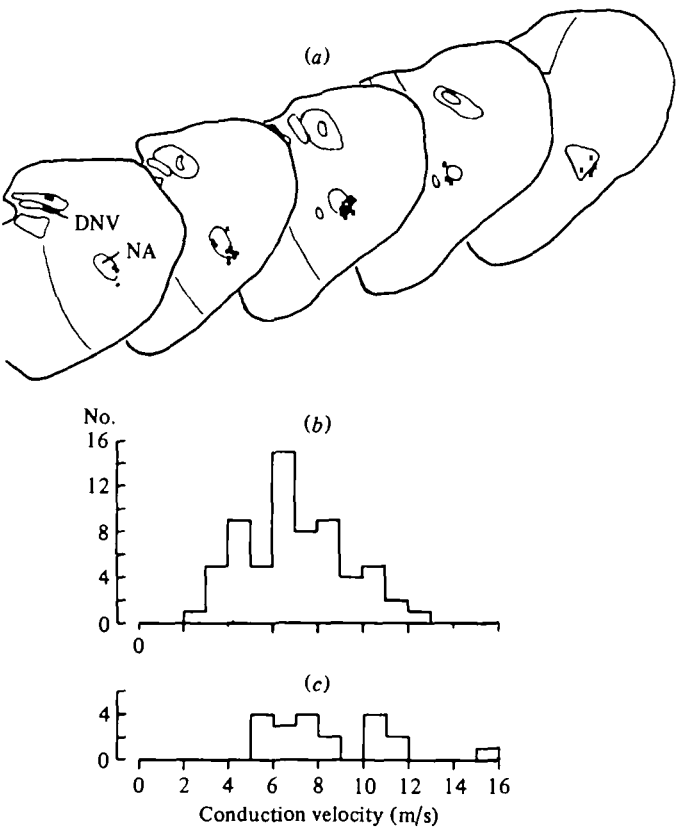

Fig. 4. Cat. (*a*) The position of 21 cardiac vagal motoneurones (CVMs) (●) and nine broncho-constrictor vagal motoneurones (BVMs) (×) on five standard sections of the medulla taken at obex level, 1, 2, 3 and 4 mm rostral to the obex. DMN dorsal motor nucleus of the vagus; NA nucleus ambiguus. (*b*), (*c*) Histograms of the conduction velocities of cardiac and bronchomotor units, respectively. (McAllen & Spyer, 1978*a*.)

shown to fire primarily during expiration and to have a conspicuous cardiac-related rhythm (see Spyer, 1981 for references). This discharge depends largely on excitatory inputs arising from the arterial baroreceptors (Heymans & Neil, 1958). Whilst this form of discharge is readily observed in the anaesthetized dog, such activity is less apparent in the anaesthetized cat, which is notorious for having a low 'vagal tone'. Recordings from CVMs made in cat, rabbit and dog have just such a pattern of discharge (McAllen & Spyer, 1976, 1978*a*, *b*; Jordan *et al.* 1979) but ongoing activity is rare in the cat, although a normally subliminal fluctuation in excitability underlining such a pattern can be revealed using the microiontophoretic application of the excitant amino acids DL-homocysteic acid (DLH) or glutamate to raise the cell's excitability above firing threshold (McAllen & Spyer, 1978*b*).

Baroreceptor inputs to CVMs. The baroreceptor influence on CVMs is conducted by way of both SN and AN and is mediated via the NTS (see above). Stimulation of the SN has been shown to excite cardiac efferent fibres recorded in the vagal branches supplying the heart after 26–90 ms (Kunze, 1972). CVMs have been excited by SN stimulation and the effects of carotid sinus baroreceptors can be

assessed by measuring the time between the SN afferent volley and the onset of CVM activity. The latency of the reflex appears to be from 20–110 ms with some distribution into two peaks (McAllen & Spyer, 1978*b*). The input from the AN to CVMs in the rabbit acts with a latency of 6–25 ms (mean 13 ms) for neurones recorded in both DVN and NA (Jordan *et al.* 1979).

The relatively short latency influence of the arterial baroreceptors on the activity of CVMs, and the well-documented connections from the NTS to the NA in the cat (Loewy & Burton, 1978) have indicated that the baroreceptor–cardiac reflex might be mediated over a relatively direct medullary pathway. This may indeed be partially true, but the longer latency influences manifest in the study of McAllen & Spyer (1978*b*) are compatible with an additional long-circuited component in the reflex (Spyer & Jordan, 1980; Spyer, 1981). It has been speculated that this might involve the hypothalamus (Spyer, 1979, 1981) since the anterior hypothalamus is known to participate in the baroreceptor reflex (Hilton & Spyer, 1971; Spyer, 1972). Recent studies in the rabbit have shown that stimulation within regions of the diencephalon that elicit bradycardia and receive an innervation from the NTS, excites CVMs at short latency (Kaufman *et al.* 1979). Stimulation within the hypothalamic depressor area excites CVMs with a latency of 10–20 ms, although this input is only effective if timed to occur during expiration (Jordan *et al.*, unpublished observations). There is plentiful anatomical evidence for pathways descending from the hypothalamus to the vagal preganglionic neurones although their relevance to these electrophysiological data remain to be resolved (Loewy & McKellar, 1980).

Respiratory influences. As shown above, CVMs when active discharge usually during expiration. They are usually totally or partially refractory to excitatory inputs, such as those arising from the arterial baroreceptors or the hypothalamus during inspiration (see for example, McAllen & Spyer, 1978*b*; McCloskey & Potter, 1981). In the cat, McAllen & Spyer (1978*b*) have shown that if the excitability of CVMs is raised by the direct effects of iontophoresed amino acids, a baroreceptor and SN influence can be revealed during inspiration which is qualitatively identical to that seen during expiration (Fig. 5). McCloskey & Potter (1981) have studied the influence of both lung inflation and central inspiratory activity independently in more detail (Gandevia, McCloskey & Potter, 1978) and indicate that the latter exerts a more potent inhibitory control of CVM activity, since it blocks both phasic and tonic components of baroreceptor excitatory responses (Potter, 1981). It is worth stressing that in many of the studies cited the animals were either paralysed or had thoracotomies, so that central inspiratory activity was desynchronized from lung inflation, which was driven by a ventilator. The inability of lung inflation inputs to affect the more tonic components of baroreceptor-induced discharge is suggested to indicate a separate site of action of this respiratory input to that of central inspiratory drive (Potter, 1981).

The overall observations relating to modifications of the efficacy of the baroreceptor reflex with respiration, vagal activity and heart rate cited above coincide with other observations in an expansive literature (see for example, Daly, 1972). They account well for the experimental studies of Anrep, Pascual & Rössler (1936*a*, *b*) which outlined the factors responsible for sinus arrhythmia.

The neural mechanisms underlying the changing responsiveness of CVMs to

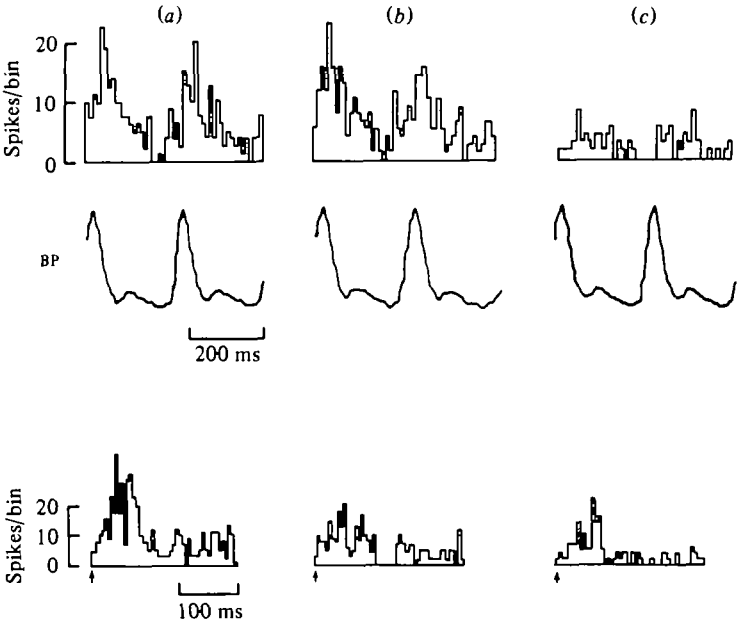

Fig. 5. Cat. Cardiac rhythm of a cardiac vagal motoneurone (CVM) and its response to stimulation of the sinus nerve. Trace from top downwards: pulse-triggered histograms of CVM activity (120 cycles, 10 ms bins) with femoral pulse wave (BP) on same time scale, histograms of response to sinus nerve stimulation (0·1 ms pulse at 2 V, 128 cycles, 5 ms bin width). (*a*) Analysed throughout the respiratory cycle; (*b*) analysed in expiration; (*c*) analysed in inspiration. Unit firing in response to 60 nA DLH. (McAllen & Spyer 1978*b*.)

their inputs, such as those from the arterial baroreceptors and chemoreceptors, have been the matters of much speculation (Lopes & Palmer, 1976*a*; McAllen & Spyer, 1978*b*; Spyer, 1981; Potter, 1981). As yet there is relatively little direct information although Garcia, Jordan & Spyer (1978) have provided neuropharmacological data to support a role of a cholinergic inhibition of CVMs in phase with the inspiration as the basis for this phenomenon. The pattern of firing of CVMs does not resemble the recruiting pattern of discharge of central expiratory neurones, a fact that has been used as an argument against an excitatory input from medullary expiratory neurones to CVMs (Spyer, 1979, 1981). As described in Spyer (1981) acetylcholine applied iontophoretically onto CVMs firing in response to DLH produces a dose-dependent inhibition, which is antagonized by the iontophoresis of atropine (Garcia *et al.* 1978). Atropine alone evokes an increase in CVM discharge, causing the neurone to fire during inspiration when it is normally silent. There is only a minor increase in the ongoing expiratory discharge, which suggests that atropine is blocking a phasic inhibitory input. Fig. 6 illustrates a schematic representation of the neuronal mechanisms that may account for these observations, which suggests that neighbouring inspiratory neurones may directly innervate and inhibit CVMs. This proposal of an inhibitory cholinergic synapse has received additional support from a neuropharmacological study on the interactions between medullary respiratory neurones (Jordan & Spyer, 1981). Since it is widely accepted that expiratory neurones are actively inhibited during inspiration (Richter, Heyde & Gabriel, 1975) it seemed

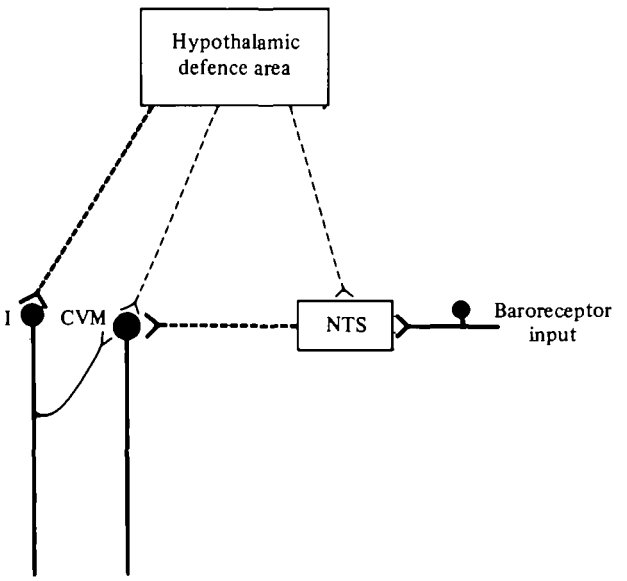

Fig. 6. Diagram illustrating the control of the baroreceptor input to cardiac vagal motoneurone (CVM). Inspiratory neurones of the NA (I) exert an inhibitory control of CVM. This inhibitory mechanism is sensitive to atropine. The hypothalamic defence area may inhibit CVM activity and block their baroreceptor input through this mechanism, but also by an alternative mechanism. This may involve a direct inhibitory control of CVM, or via a modification of transmission through the *NTS*. See text for further details. *Dotted lines* represent pathways of unknown synaptic complexity, excitatory pathways are shown by *thick lines*, inhibitory by *thin lines*. (Modified from Spyer, 1981.)

a reasonable suggestion that a common transmitter would mediate the inspiratory silencing of CVMs and expiratory neurones (Jordan & Spyer, 1981). The iontophoretic application of ACh to CVMs (Garcia *et al.* 1978) and expiratory neurones (Jordan & Spyer, 1981) evokes inhibition, an effect which is antagonized by atropine but not β-dihydroerythrodiene (Jordan & Spyer, 1981). Since the iontophoretic application of atropine alone evokes firing in both classes of neurone during inspiration, it appears that this action of ACh is likely to be direct rather than via an inhibitory interneurone which is excited by ACh; inspiratory firing neurones in the NA are not excited by ACh (Jordan & Spyer, 1981).

On the basis of this evidence it appeared that the excitability of CVMs was largely determined by this inspiratory related mechanism. It has been postulated that the inhibitory effects of lung inflation could be accounted for by the involvement of the Rβ group of inspiratory neurones (Lopes & Palmer, 1976), neurones that are located in the NTS and are excited by both central inspiratory drive and afferent vagal inputs driven by lung inflation (Baumgarten & Kanzow, 1958). These neurones most certainly project to the NA (Merrill, 1974) but there are differences in the efficacy of central inspiratory activity and lung inflation in modifying CVM discharge and the baroreceptor–cardiac reflex (Potter, 1981). This indicates that two independent processes may be involved.

Centrally evoked modifications. In addition to the respiratory related influences on CVM activity and their reflex inputs, it is known that heart rate changes mediated

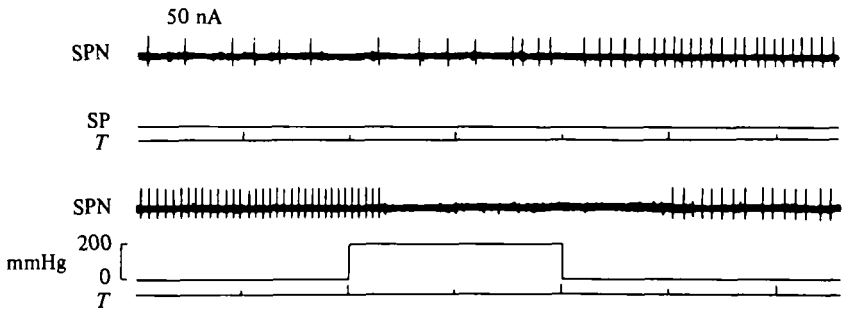

Fig. 7. The effect of an abrupt rise in sinus pressure (SP; redrawn) on the high-frequency (31 Hz) discharge of a single sympathetic preganglionic neurone (SPN) produced by the microelectrophoretic application of glutamate (50 nA) at beginning of top trace. Time trace *T*, 1 s. Records retouched. (Coote *et al.* 1981*a*.)

by alteration in vagal efferent activity can be elicited by stimulating several sites in the central nervous system. The synaptic processes underlying these responses are poorly illustrated, but in the case of the defence reaction evoked by stimulating within the hypothalamus certain possible mechanisms are emerging.

It has long been known that the cardiac component of the baroreceptor reflex is susceptible to central resetting (Spyer, 1981). With respect to the defence reaction both cardiac and vascular components appear susceptible to central inhibition (Coote *et al.* 1979). Since changes in respiratory activity accompany such centrally evoked cardiovascular responses the respiratory modifications of the baroreceptor reflex which have been summarized above might contribute significantly, if not totally, to the apparent resetting of the baroreceptor–vagal reflex.

With respect to defence reaction elicited by stimulating within the hypothalamus, there is clear evidence that this produces a suppression both of CVM discharge and of the excitatory response to AN stimulation (Jordan *et al.* 1981). This influence of hypothalamic stimulation could be observed at low frequencies of stimulation (i.e. 1·5 Hz) at which minimal cardiovascular changes, and no respiratory effects, were noted and the responses were not modified by the iontophoretic application of atropine on to the CVM under investigation, although this had its typical effect on respiratory fluctuations in discharge (Jordan *et al.* 1981). These observations lend support to the contention of Lopes & Palmer (1978) that there is a tonic hypothalamofugal inhibitory influence on CVMs, which is independent of respiratory activity (see Fig. 6). This pathway may be important in modifying the level of CVM activity with respect to arousal, in which the defence 'regions' of the brainstem may exert a profound influence.

III. REGULATION OF PREGANGLIONIC SYMPATHETIC ACTIVITY

In considering the role of preganglionic sympathetic neurones in the organization of cardiovascular control, one must account for the factors responsible for their ongoing discharge, which largely determines vasomotor tone, and their regulation by central structures. The traditionally accepted view has been that sympathetic tonic activity is dependent on the activity of a medullary 'vasomotor' centre

(Alexander, 1946) or 'oscillator' (Gebber & Barman, 1977). This concept has received considerable criticism over the last decade (Hilton, 1975; Hilton & Spyer, 1980), although some more recent data have indicated that a circumscribed region on the ventral surface of the rostral medulla might contribute significantly to 'vasomotor' tone (Feldberg, 1980; Guertzenstein *et al.* 1978; Hilton, 1982), as well as mediating hypothalamic and mid-brain excitatory drives to the sympathetic preganglionic neurones (Donoghue *et al.* 1981). Since relatively little is known of the neuronal inputs to and connections of the neurones of that area (Loewy, Wallach & McKellar, 1981), little discussion of its role in the integration of cardiovascular control will enter this report.

Implicit in the hypothesis of a 'vasomotor' centre was the idea that baroreceptor regulation of sympathetic activity was mediated by an active suppression of a descending excitatory drive emanating from this level of the brain which was responsible for the tonic discharge of these neurones. There is plentiful evidence of common rhythms of discharge in brainstem, and particularly medullary, reticular neurones and sympathetic preganglionic discharge (Langhorst *et al.* 1975; Gebber & Barman, 1977). The commonest is a 2–6 Hz rhythm, related to the cardiac cycle which is considered to be an intrinsic brainstem rhythm to which the baroreceptor input becomes entrained (Gebber & Barman, 1977, 1980). This rhythm appears commonly in neurones of the *N. reticularis gigantocellularis* (Barman & Gebber, 1980), which is known to contain bulbospinal neurones. As yet the neural connections between these brainstem 'oscillators' and sympathetic preganglionic neurones have not been studied experimentally.

Regarding the pathway for excitatory control of sympathetic neurones, there is evidence of a descending pathway passing through the dorsolateral funiculus of the cervical spinal cord (Coote & Macleod, 1974*a*, *b*, 1975; Geis, Barratt & Wurster, 1978). Whether this is directly related in the mediation of the patterns of excitatory control described above is not certain, but lesions in this specific region of cervical spinal cord severely modify the normal excitatory responses observed on hypothalamic and cerebellar stimulation (Achari, Al-Ubaidy & Downman, 1978).

Lesions in this same region of the cervical spinal cord also modify or partially abolish the baroreceptor control of sympathetic discharge (Coote & Macleod, 1974*b*, 1975). This does not appear to be a consequence of simply removing a tonic excitatory drive but rather represents the removal of a descending inhibitory control (Coote & Macleod, 1975). This suggestion had been considered controversial since its demonstration depended on rather small changes in spinal mediated reflexes into sympathetic nerves (Coote & Macleod, 1974*b*) but recent studies have shown that the activity of single sympathetic neurones recorded with microelectrodes in the intermediolateral cell column and firing in response to iontophoretically applied glutamate is silenced by baroreceptor stimulation (Coote *et al.* 1981*a*). Further, this glutamate-evoked discharge, or ongoing firing in these cells, was inhibited by the iontophoretic application of noradrenaline; adrenaline and dopamine were also effective (Coote *et al.* 1981*b*). Previous studies had indicated that the A1 group of noradrenaline-containing neurones, located in the region of the lateral reticular nucleus, had connections with the intermediolateral cell column of the spinal cord via a pathway

through the DLF of the cervical spinal cord (Coote & Macleod, 1974*a*; Fleetwood-Walker & Coote, 1981). Other reports question whether this pathway is truly nor adrenergic (Blessing, West & Chalmers, 1981; West, Blessing & Chalmers, 1981) but there appear compelling reasons to consider that this is likely and that this pathway is a major means by which the baroreceptors exert their control of sympathetic discharge.

In this same study Coote *et al.* (1981*b*) showed that serotonin, applied iontophoretically to preganglionic sympathetic neurones, evoked an excitatory response. Serotinergic neurones are grouped in several regions of the brainstem including the raphe complex but the electrical stimulation of this area evokes sympathoinhibition (Coote & Macleod, 1975). This inhibitory action is not concerned with the baroreceptor control of sympathetic activity (Coote & Macleod, 1975). In addition, the B3 group of serotinergic neurones, which may correspond to the ventral medullary 'vasomotor' neurones, have been shown to have a spinal projection (Loewy, Wallach & McKellar, 1981). This may well provide the first detailed description of an excitatory bulbospinal pathway to sympathetic neurones.

It would appear from the previous discussion that a specific inhibitory pathway, and two excitatory pathways (amongst several other possible pathways, both inhibitory and excitatory) have been identified which influence the pattern of discharge of sympathetic neurones (reviewed by Spyer, 1981). To this must be added the segmental and suprasegmental connections mediating somatic and visceral afferent reflex control of sympathetic discharge (Wurster, 1977; Coote, 1978). These data imply an important integrative role of the preganglionic neurone in the moment-by-moment regulation of cardiovascular system (Spyer, 1981). It may well be that most interactions between reflex inputs and centrally elaborated drives can be explained on the basis of summation at this level. It is known that intrinsic properties of these preganglionic neurones contribute to a narrow firing range so that saturation at one end and silence at the other can readily be evoked by additive influences (Polosa, 1967, 1968; Polosa, Mannard & Laskey, 1979).

This suggestion may well argue against 'gating' being involved in either the defence area suppression of the baroreceptor reflex, or the modifications of the reflex during the respiratory cycle. The available evidence makes it unlikely that either influence exerts an *all or nothing* 'gating' of the baroreceptor input at the level of the NTS (see above), although modifications may well occur. There is as yet no neurophysiological evidence relating to the interactions of baroreceptor inputs and the 'defence' pathway at other sites within the brainstem, except in the case of cardiac vagal motoneurones (see above), but this must be considered likely in view of studies on the patterns of discharge of neurones in the 'common brainstem' system which have multi-sensorial inputs (Langhorst *et al.* 1980). Depending on the balance of the two drives, one excitatory (defence) and one inhibitory (baroreceptor), it is possible to imagine changes in the efficacy of many of the descending pathways, culminating in a final output, sympathetic discharge, that is dominated by one or other. Essentially this is an example of summation and is very much the pattern of interaction that is responsible for the respiratory modifications of baroreceptor control of the heart mediated by sympathetic efferents. It is firmly established

that just as the baroreceptor–vagal reflex is modified by inspiration, so the baroreceptor–sympathetic component of the reflex is similarly affected (Seller *et al.* 1968; Seller & Richter, 1971; Davis, McCloskey & Potter, 1977). The duration of the silencing of sympathetic activity evoked by the baroreceptors was shown to be minimal in the middle of inspiration, i.e. peak of the phrenic nerve discharge, and maximal shortly after the cessation of inspiration (Seller & Richter, 1971). As it is believed that inspiratory neuronal discharge provides an excitatory drive to sympathetic neurones, at the end of inspiration the baroreceptor input would be timed to arrive at a 'disfacilitated' neurone, and hence a neurone readily affected by an inhibitory input. The respiratory influence does not, however, appear to be as powerful in effect as the inspiratory 'gating' of vagal efferent discharge described above.

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REFERENCES

ACHARI, N. K., AL-UBAIDY, S. S. & DOWNMAN, C. B. B. (1978). Spinal sympathoexcitatory pathways activated by stimulating fastigial nuclei, hypothalamus and lower brain stem in cats. *Expl Neurol.* **62**, 230–240.

ADAIR, J. R. & MANNING, J. W. (1975). Hypothalamic modulation of baroreceptor afferent unit activity. *Am. J. Physiol.* **229**, 1357–1364.

ALEXANDER, R. S. (1946). Tonic and reflex functions of medullary sympathetic centers. *J. Neurophysiol.* **9**, 205–217.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936*a*). Respiratory variations of heart rate. I. The reflex mechanism of the respiratory arrhythmia. *Proc. R. Soc. Lond.* B **119**, 191–217.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936*b*). Respiratory variations of the heart-rate. II. The central mechanism of respiratory arrhythmia and the inter-relationships between central and reflex mechanisms. *Proc. R. Soc. Lond.* B **119**, 218–230.

BALLANTYNE, D., DONOGHUE, S., JORDAN, D., MEESMANN, M., RICHTER, D. W. & SPYER, K. M. (1981). Respiratory influences on vagal afferent endings in the medulla: a study on baroreceptor and lung stretch neurones. *J. Physiol., Lond.* **312**, 28*P*.

BARMAN, S. M. & GEBBER, G. L. (1980). Sympathetic nerve rhythm of brainstem origin. *Am. J. Physiol.* **239**, 42–47.

BAUMGARTEN, R. VON & KANZOW, E. (1958). The interaction of two types of inspiratory neurones in the region of the tractus solitarius of the cat. *Archs ital. Biol.* **96**, 361–373.

BERGER, A. J. (1979). Distribution of carotid sinus nerve afferent fibers to solitary tract nuclei of the cat using transganglionic transport of horseradish peroxidase. *Neurosci. Lett.* **14**, 153–158.

BERGER, A. J. (1980). The distribution of the cat's carotid sinus nerve afferent and efferent cell bodies using the horseradish peroxidase technique. *Brain Res.* **190**, 309–320.

BISCOE, T. J. & SAMPSON, S. R. (1970). Responses of cells in the brainstem of the cat to stimulation of the sinus, glossopharyngeal, aortic and superior laryngeal nerves. *J. Physiol., Lond.* **209**, 359–373.

BLESSING, W. W., WEST, M. J. & CHALMERS, J. (1981). Hypertension, bradycardia, and pulmonary edema in the conscious rabbit after brainstem lesions coinciding with the A1 group of catecholamine neurones. *Circulation Res.* **49**(4), 949–958.

CIRIELLO, J. & CALARESU, F. R. (1980). Distribution of vagal cardioinhibitory neurons in the medulla of the cat. *Am. J. Physiol.* **238**, 57–64.

CIRIELLO, J. & CALARESU, F. R. (1981). Projections from buffer nerves to the nucleus of the solitary tract: an anatomical and electrophysiological study in the cat. *J. auton. Nerv. Syst.* **3**, 299–310.

CIRIELLO, J., HRYCYSHYN, A. W. & CALARESU, F. R. (1981). Horseradish peroxidase study of brain stem projections of carotid sinus and aortic depressor nerves in the cat. *J. auton. Nerv. Syst.* **4**, 43–61.

COHEN, D. H., SCHNALL, A. M., MACDONALD, R. L. & PITTS, L. H. (1970). Medullary cells of origin of vagal cardioinhibitory fibres in the pigeon. I. Anatomical structure of peripheral vagus nerves and the dorsal motor nucleus. *J. comp. Neurol.* **140**, 299–320.

COOTE, J. H. (1978). Afferent input as factors in aberrant autonomic, sensory and motor function In *The Neurobiologic Mechanisms in Manipulative Therapy* (ed. I. M. Korr), pp. 91–127. New York Plenum.

COOTE, J. H., HILTON, S. M. & PEREZ-GONZALEZ, J. F. (1979). Inhibition of the baroreceptor reflex on stimulation in the brainstem defence centre. *J. Physiol.* **288**, 549–560.

COOTE, J. H. & MACLEOD, V. H. (1974*a*). The influence of bulbospinal monoaminergic pathways on sympathetic nerve activity. *J. Physiol., Lond.* **241**, 453–457.

COOTE, J. H. & MACLEOD, V. H. (1974*b*). Evidence for the involvement in the baroreceptor reflex of a descending inhibitory pathway. *J. Physiol., Lond.* **241**, 477–496.

COOTE, J. H. & MACLEOD, V. H. (1975). The spinal route of sympatho-inhibitory pathways descending from the medulla oblongata. *Pflügers Arch.* **359**, 335–347.

COOTE, J. H., MACLEOD, V. H., FLEETWOOD-WALKER, S. M. & GILBEY, M. P. (1981*a*). Baroreceptor inhibition of sympathetic activity at a spinal site. *Brain Res.* **220**, 81–93.

COOTE, J. H., MACLEOD, V. H., FLEETWOOD-WALKER, S. & GILBEY, M. P. (1981*b*). The response of individual sympathetic preganglionic neurones to microelectrophoretically applied endogenous monoamines. *Brain Res.* **215**, 135–145.

DALY, M. DE B. (1972). Interaction of cardiovascular reflexes. In *Scientific Basis of Medicine Annual Review*, pp. 307–332.

DAVIES, R. O. & KALIA, M. (1981). Carotid sinus nerve projections to the brain stem in the cat. *Brain Res. Bulletin* **6**, 531–541.

DAVIS, A. L., MCCLOSKEY, D. I. & POTTER, E. K. (1977). Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate through the sympathetic nervous system. *J. Physiol., Lond.* **272**, 691–703.

DONOGHUE, S., FELDER, R. B., JORDAN, D. & SPYER, K. M. (1982). Brain stem projections of carotid baroreceptors and chemoreceptors in the cat. *J. Physiol., Lond.* (in the Press).

DONOGHUE, S., FOX, R. E., KIDD, C. & KOLEY, B. N. (1981*a*). The distribution in the cat brain stem of neurones activated by vagal non-myelinated fibres from the heart and lungs. *Q. Jl exp. Physiol.* **66**, 391–404.

DONOGHUE, S., FOX, R. E., KIDD, C. & MCWILLIAM, P. N. (1981*b*). The terminations and secondary projections of myelinated and non-myelinated fibres of the aortic nerve in the cat. *Q. Jl exp. Physiol.* **66**, 405–422.

DONOGHUE, S., GARCIA, M., JORDAN, D. & SPYER, K. M. (1982*a*). Identification and brain-stem projections of aortic baroreceptor afferent neurones in nodose ganglia of cats and rabbits. *J. Physiol., Lond.* **322**, 337–352.

DONOGHUE, S., GARCIA, M., JORDAN, D. & SPYER, K. M. (1982*b*). The brain-stem projections of pulmonary stretch afferent neurones in cats and rabbits. *J. Physiol., Lond.* **322**, 353–363.

DONOGHUE, S., HILTON, S. M., SMITH, P. R. & TIMMS, R. J. (1981). Inputs from the brain stem defence areas to ventral medulla neurones in the cat. *J. Physiol., Lond.* **319**, 116*P*.

FELDBERG, W. (1980). Cardiovascular effects of drugs acting on the ventral surface of the brain stem. In *Central Interactions Between Respiratory and Cardiovascular Control Systems* (ed. H. P. Koepchen, S. M. Hilton and A. Trzebski), pp. 47–55. Berlin: Springer-Verlag.

FLEETWOOD-WALKER, S. M. & COOTE, J. H. (1981). The contribution of brain stem catecholamine cell groups to the innervation of the sympathetic lateral cell column. *Brain Res.* **205**, 141–155.

GABRIEL, M. & SELLER, H. (1970). Interaction of baroreceptor afferents from carotid sinus and aorta at the nucleus tractus solitarii. *Pflügers Arch.* **318**, 7–20.

GANDEVIA, S. C., MCCLOSKEY, D. I. & POTTER, E. K. (1978). Inhibition of baroreceptor and chemoreceptor reflexes on heart rate by afferents from the lungs. *J. Physiol., Lond.* **276**, 369–381.

GARCIA, M., JORDAN, D. & SPYER, K. M. (1978). Studies on the properties of cardiac vagal neurones. *Neurosci. Lett.* (Suppl). **1**, S16.

GEBBER, G. L. & BARMAN, S. M. (1977). Brainstem vasomotor circuits involved in genesis and entrainment of sympathetic nervous rhythms. *Prog. Brain Res.* **47**, 61–76.

GEBBER, G. L. & BARMAN, S. M. (1980). Basis for 2–6 cycle/s rhythm in sympathetic nerve discharge. *Am. J. Physiol.* **239**, R48–56.

GEIS, G. S., BARRATT, G. & WURSTER, R. D. (1978). Role of descending pressor pathway in conscious and pentobarbital-anaesthetized dog. *Am. J. Physiol.* **234**, H152–156.

GEIS, G. S. & WURSTER, R. D. (1980). Cardiac responses during stimulation of the dorsal motor nucleus and nucleus ambiguus in the cat. *Circulation Res.* **46**, 606–611.

GUERTZENSTEIN, P. G., HILTON, S. M., MARSHALL, J. M. & TIMMS, R. J. (1978). Experiments on the origin of the vasomotor tone. *J. Physiol., Lond.* **275**, 78–79*P*.

HEYMANS, C. & NEIL, E. (1958). *Reflexogenic Areas of the Cardiovascular System*. London: Churchill.

HILTON, S. M. (1975). Ways of viewing the central nervous control of circulation – old and new. *Brain Res.* **87**, 213–219.

HILTON, S. M. (1982). (This meeting.)

HILTON, S. M. & SPYER, K. M. (1971). Participation of the anterior hypothalamus in the baroreceptor reflex. *J. Physiol., Lond.* **218**, 271–293.

HILTON, S. M. & SPYER, K. M. (1980). Central nervous regulation of vascular resistance. *A. Rev. Physiol.* **42**, 399–411.

JORDAN, D., KHALID, M. E. M., SCHNEIDERMAN, N. & SPYER, K. M. (1979). Preganglionic vagal cardiomotor neurones in the rabbit; location and properties. *J. Physiol., Lond.* **296**, 20–21.

JORDAN, D. & SPYER, K. M. (1979). Studies on the excitability of sinus nerve afferent terminals. *J. Physiol., Lond.* **297**, 123–134.

JORDAN, D. & SPYER, K. M. (1981). Effects of acetylcholine on respiratory neurones in the nucleus ambiguus-retroambigualis complex of the cat. *J. Physiol., Lond.* **320**, 103–111.

KAUFMAN, M. P., HAMILTON, R. B., WALLACH, J. H., PETRIK, G. K. & SCHNEIDERMAN, N. (1979). Lateral subthalamic areas as a mediator of bradycardia responses in rabbits. *Am. J. Physiol.* **236**, H471–479.

KOEPCHEN, H. P., HILTON, S. M. & TRZEBSKI, A. (Eds) (1980). *Central Interactions between Respiratory and Cardiovascular Control Systems*. Berlin: Springer-Verlag.

KOEPCHEN, H. P., WAGNER, P. H. & LUX, H. D. (1961). Über die Zusammenhänge zwischen zentraler Erregbarkeit reflektorischen Atemrhythmus bei der nervösen Steuerung der Herzfrequenz. *Pflügers Arch.* **273**, 443–465.

KUNZE, D. L., (1972). Reflex discharge patterns of cardiac vagal efferent fibres. *J. Physiol., Lond.* **222**, 1–15.

LANGHORST, P., SCHULZ, B., LAMBERTZ, M., SCHULZ, G., CAMERER, H. & STROH-WERZ, M. (1980). Dynamic characteristics of the unspecific brain stem system. In *Central Interactions between Respiratory and Cardiovascular Control Systems* (ed. H. P. Koepchen, S. M. Hilton and A. Trzebski), pp. 30–41. Berlin: Springer-Verlag.

LANGHORST, P., STROH-WERZ, M., DITTMAR, K. & CAMERER, H. (1975). Facultative coupling of reticular neuronal activity with peripheral cardiovascular and central cortical rhythms. *Brain Res.* **87**, 407–418.

LIPSKI, J., MCALLEN, R. M. & SPYER, K. M. (1975). The sinus nerve and baroreceptor input to the medulla of the cat. *J. Physiol., Lond.* **251**, 61–78.

LIPSKI, J. & TRZEBSKI, A. (1975). Bulbospinal neurones activated by baroreceptor afferents and their possible role in inhibition of preganglionic sympathetic neurons. *Pflügers Arch.* **356**, 181–192.

LOEWY, A. D. & BURTON, H. (1978). Nuclei of the solitary tract. Efferent projections to the lower brainstem and spinal cord of the cat. *J. comp. Neurol.* **181**, 421–450.

LOEWY, A. D. & MCKELLAR, S. (1980). The neuroanatomical basis of central cardiovascular control. *Fedn Proc.* **39**, 2495–2503.

LOEWY, A. D., WALLACH, J. H. & MCKELLAR, S. (1981). Efferent connections of the ventral medulla oblongata in the rat. *Brain Res.* (Reviews) **3**, 63–80.

LOPES, O. U. & PALMER, J. F. (1976). Proposed respiratory 'gating' mechanisms for cardiac slowing. *Nature, Lond.* **264**, 454–456.

LOPES, O. U. & PALMER, J. F. (1978). Mechanism of hypothalamic control of cardiac component of sinus nerve reflex. *Q. Jl exp. Physiol.* **63**, 231–254.

MCALLEN, R. M. (1973). Projections of the carotid sinus baroreceptors to the medulla of the cat. Ph.D. thesis, University of Birmingham.

MCALLEN, R. M. (1976). The inhibition of the baroreceptor input to the medulla by stimulation of the hypothalamic defence area. *J. Physiol., Lond.* **257**, 45–46*P*.

MCALLEN, R. M. & SPYER, K. M. (1976). The location of cardiac vagal preganglionic motoneurones in the medulla of the cat. *J. Physiol., Lond.* **258**, 187–204.

MCALLEN, R. M. & SPYER, K. M. (1978*a*). Two types of vagal preganglionic motoneurones projecting to the heart and lungs. *J. Physiol., Lond.* **282**, 353–364.

MCALLEN, R. M. & SPYER, K. M. (1978*b*). The baroreceptor input to cardiac vagal motoneurones. *J. Physiol., Lond.* **282**, 365–374.

MCCLOSKEY, D. I. & POTTER, E. K. (1981). Excitation and inhibition of cardiac vagal motoneurones by electrical stimulation of the carotid sinus nerve. *J. Physiol., Lond.* **316**, 163–175.

MERRILL, E. G. (1974). Finding a respiratory function for the medullary respiratory neurons. In *Essays on the Nervous System* (ed. R. Bellairs and E. G. Gray), pp. 451–486. Oxford: Clarendon Press.

MIURA, M. & REIS, D. J. (1972). The role of the solitary and paramedian reticular nuclei in mediating cardiovascular reflex responses from carotid baro- and chemoreceptors. *J. Physiol., Lond.* **225**, 525–548.

PANNETON, W. M. & LOEWY, A. D. (1980). Projections of the carotid sinus nerve to the nucleus of the solitary tract in the cat. *Brain Res.* **191**, 239–244.

POLOSA, C. (1967). The silent period of sympathetic preganglionic neurons. *Can. J. Physiol. Pharmacol.* **45**, 1033–1045.

POLOSA, C. (1968). Spontaneous activity of sympathetic preganglionic neurons. *Can. J. Physiol. Biochem.* **46**, 587–896.

POLOSA, C., MANNARD, A. & LASKEY, W. (1979). Tonic activity of the autonomic nervous system: functions, properties, origins. In *Integrative Functions of the Autonomic System* (ed. C. McC. Brooks, K. Koizumi and A. Sato), pp. 342–354. Japan: University of Tokyo Press.

POTTER, E. K. (1981). Inspiratory inhibition of vagal responses to baroreceptor and chemoreceptor stimuli in the dog. *J. Physiol., Lond.* **316**, 177–190.

RICHTER, D. W. (1982). Generation and maintenance of the respiratory rhythm. (This meeting.)

RICHTER, D. W., HEYDE, F. & GABRIEL, M. (1975). Intracellular recordings from different types of medullary respiratory neurons of the cat. *J. Neurophysiol.* **38**, 1162–1171.

SAPER, C., LOEWY, A. D., SWANSON, L. W. & COWAN, W. N. (1976). Direct hypothalamo-autonomic connections. *Brain Res.* **117**, 305–312.

SCHWABER, J. S. & COHEN, D. H. (1978*a*). Electrophysiological and electron microscopic analysis of the vagus nerve of the pigeon, with particular reference to the cardiac innervation. *Brain Res.* **147**, 65–78.

SCHWABER, J. S. & COHEN, D. H. (1978*b*). Field potential and single unit analyses of the avian dorsal motor nucleus of the vagus and criteria for identifying vagal cardiac cells of origin. *Brain Res.* **147**, 79–90.

SELLER, H. & ILLERT, M. (1969). The localisation of the first synapse in the carotid sinus baroreceptor reflex pathway and its alteration of the afferent input. *Pflügers Arch.* **306**, 1–19.

SELLER, H., LANGHORST, P., RICHTER, D. & KOEPCHEN, H. P. (1968). Über die Abhangigkeit der pressorezeptorischen Hummung des Sympathicus von der Atemphase und ihre Auswirkung in der Vasomotorik. *Pflügers Arch.* **302**, 300–314.

SELLER, H. & RICHTER, D. W. (1971). Some quantitative aspects of the central transmission of the baroreceptor activity. In *Research in Physiology* (ed. F. F. Kao, K. Koizumi and M. Vasalle), pp. 541–545. Bologna: Gaggi.

SPYER, K. M. (1972). Baroreceptor sensitive neurones in the anterior hypothalamus of the cat. *J. Physiol., Lond.* **224**, 245–257.

SPYER, K. M. (1979). The baroreceptor control of vagal preganglionic activity. In *Integrative Functions of the Autonomic Nervous System* (ed. C. McC. Brooks, K. Koizumi and A. Sato), pp. 283–292. Japan: University of Tokyo Press.

SPYER, K. M. (1981). Neural organisation and control of the baroreceptor reflex. *Rev. Physiol. Biochem. Pharmacol.* **88**, 23–124.

SPYER, K. M. & JORDAN, D. (1980). The baroreceptor input to vagal pre-ganglionic neurons: the neural pathway and physiological control. In *Arterial Baroreceptors and Hypertension* (ed. P. Sleight), pp. 238–243. Oxford: University Press.

STROH-WERZ, M., LANGHORST, P. & CAMERER, H. (1977*a*). Neuronal activity with cardiac rhythm in the nucleus of the solitary tract in cats and dogs. I. Different discharge patterns related to the cardiac cycle. *Brain Res.* **133**, 65–80.

STROH-WERZ, M., LANGHORST, P. & CAMERER, H. (1977*b*). Neuronal activity with cardiac rhythm in the nucleus of the solitary tract in cats and dogs. II. Activity modulation in relationship to the respiratory cycle. *Brain Res.* **133**, 81–93.

SWANSON, L. W. (1977). Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. *Brain Res.* **128**, 346–353.

WALLACH, J. H. & LOEWY, A. D. (1980). Projections of the aortic nerve to the nucleus tractus solitarius in the rabbit. *Brain Res.* **188**, 247–251.

WEST, M. J., BLESSING, W. W. & CHALMERS, J. (1981). Arterial baroreceptor reflex function in the conscious rabbit after brainstem lesions coinciding with the A1 group of catecholamine neurons. *Circulation Res.* **49**, 959–970.

WURSTER, R. D. (1977). Spinal sympathetic control of the heart. In *Neural Regulation of the Heart* (ed. W. C. Randall), pp. 211–246. New York: Oxford University Press.

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CONTROL OF THE FOETAL CIRCULATION

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SUMMARY

Foetal cardiac output is high, and the heart has not been shown to have the sustained reserves demonstrated in the adult heart. About 40% (~ 200 ml.kg body weight^{-1}.min^{-1}) of the combined output of both ventricles (CVO) in unanaesthetized foetal lambs in late gestation is directed to the umbilical circulation. At least one-half of the systemic flow (~ 300 ml. kg body weight^{-1}.min^{-1}) goes to skin and carcass. About 50% of the remainder (10% CVO) is shared by brain, heart and kidney and the rest by other viscera; less than 6% CVO perfuses the lungs. Hypoxaemia, acidaemia and various vasomotor agents influence the partition of cardiac output between systemic and umbilical circulations, with or without relatively small changes of blood pressure, which is low by adult standards. In general, the conductance of systemic circuits is more susceptible to change than that of the umbilical. Both cerebral and myocardial blood flow increase several-fold during hypoxaemia. The additional volume flow of blood demanded by such vasodilatation in organs forming a relatively small proportion of body weight is more than accounted for by concurrent vasoconstriction in muscle (which contributes a substantial fraction of body weight) and other tissues. Both humoral and reflex neural mechanisms are involved in these adjustments.

INTRODUCTION

The foetal circulation works under conditions very different from those found in adult mammals. Arterial pressure is low (see Table 3) and similar in all circuits and systemic arterial blood gas tensions are asphyxial by adult standards; average values reported for control foetal lambs (Tables 1 and 3) were P_{a,O_2} 20–24 mmHg and P_{a,CO_2} 40–48 mmHg while pH was 7·31–7·39.

Quantitative information about the foetal circulation has been acquired almost entirely from the foetal lamb in the last one-third of gestation (full term ~ 147 days). Unlike the adult, the foetal cardiac ventricles pump in parallel and their combined output (CVO) is about 0·5 l.kg body weight^{-1}.min^{-1}. About 60% of this goes to the oxygen-consuming circuits of the foetal body and 40% to the umbilical circulation (Table 1).

Table 2 lists the effects on cardiac output of various stimuli. The responses were for most procedures relatively small and the foetal heart does not seem to have a great deal of reserve.

The changes of conductance in systemic and umbilical circuits do not necessarily parallel one another following the application of any particular stimulus. A change of arterial pressure (Table 3) may or may not accompany a change of gross distribution

Table 1. *Partition of combined output of both ventricles (CVO) between umbilical and systemic circulation. Mean control values from 9 investigations on unanaesthetized foetal lambs*

Gestation age (days)	Umbilical	Systemic	Umbilical flow as % CVO
	ml.kg body weight^{-1}.min^{-1}		
100–147 Toubas *et al.* (1981)	264	340	43
122–142 Cohn *et al.* (1974)	191	273	41
	195	302	39
125–135 Lorijn & Longo (1980)	177	361	33
123–140 Iwamoto *et al.* (1979)	190	284	40
125–135 Lorijn *et al.* (1980)	191	363	34
120–131 Iwamoto & Rudolph (1981)	210	316	40
115–133 Iwamoto & Rudolph (1979)	239	302	44
139 Creasy *et al.* (1973)	158	248	39
Mean ± S.E.	202 ± 11	310 ± 13	Mean 39·2

Table 2. *Percentage change from control values of cardiac output (CVO) in foetal lambs subjected to various stimuli*

	Decrease (%)	Increase (%)
*Blood volume +10%		11
−10%	21	
Haemorrhage	27	
Hypoxaemia	5	
Acidaemia	23	
Noradrenaline	Unchanged	
Vasopressin	13	
Tri-iodothyronine		22
Angiotensin II		17
Saralasin	1	
Placental embolization	9	40
†Uterine ischaemia −50%		40
−75%	40	

References as in Tables 1 and 3 with the addition of
* Gilbert (1980)
† Yaffe *et al.* (1982)

of cardiac output. In any system of parallel circuits any change in one circuit will, other things being equal, affect all other circuits. In general, the conductance of the umbilical circulation seems somewhat less susceptible to alteration than that of the systemic circulation. Hypoxaemia, acidaemia, noradrenaline and vasopressin cause larger reductions of systemic than of umbilical flow but raised plasma (T_3), angiotensin II and saralasin (sar-1, ala-8 angiotensin II; a competitive inhibitor of angiotensin II) increase systemic more than umbilical conductance (Table 3).

Table 3. *Vascular conductance (ml.kg body weight $^{-1}$.mmHg arterial pressure^{-1}) of umbilical and systemic circulations in foetal lambs*

Gestation age (days)	Condition	Conductance			Δ Conductance (%)			Mean arterial pressure (mmHg)
		Umbilical	Systemic	Total	Umbilical	Systemic	Total	
100–147	Control	5·18	6·67	11·85				51
Toubas *et al.* (1981)	Haemorrhage	4·15	5·48	9·63	−20	−18	−19	46
122–142	Control	3·35	4·79	8·14				57
Cohn *et al.* (1974)	Hypoxaemia	3·28	3·52	6·8	−2	−28	−16	65
	Control	3·10	4·79	7·89				63
	Acidaemia	2·70	2·30	5·0	−13	−52	−37	76
125–135	Control	3·93	8·02	11·95				45
Lorijn & Longo (1980)	Noradrenaline	3·90	5·83	9·28	−1	−33	−23	58
123–140	Control	4·04	6·04	10·08				47
Iwamoto *et al.* (1979)	Vasopressin	3·59	3·73	7·32	−11	−38	−32	56
125–135	Control	4·06	7·72	11·78				47
Lorijn *et al.* (1980)	Tri-iodothyronine	4·53	9·98	14·51	+11·6	+29·3	+23	47
120–131	Control	4·57	6·87	11·44				46
Iwamoto & Rudolph (1981)	Angiotensin II	3·73	7·27	11·0	−18	+6	−4	56
115–133	Control	5·09	6·42	11·51				47
Iwamoto & Rudolph (1979)	Saralasin	4·82	8·29	13·11	−5	+29	+14	41
139	Placental embolization				−31	+2		•
Creasy *et al.* (1973)								

• Pressures similar in control and experimental animals.

Umbilical circulation

Umbilical cord

Under control conditions in the unanaesthetized foetal lamb, the umbilical vessels which are widely patent *in utero* transport blood at ~ 200 ml.kg^{-1}.min^{-1} at an arterial pressure of 40–50 mmHg (Tables 1 and 3).

Placenta and foetal membranes

Some 27% of the foetal blood has been estimated to be within the umbilical circulation in goats (Novy & Metcalfe, 1970). When the blood volume of foetal lambs was either reduced or increased (Faber *et al.* 1973), flow in the infra-renal abdominal aorta changed in the same direction according to the equation

$$\text{flow } \% = -70{\cdot}8 + 1{\cdot}71 \times \text{volume } \%. \quad (1)$$

Although both femoral arteries were tied in this preparation, 16% of the flow measured by the electromagnetic flowmeter was shown by microsphere injections to be extra-placental. The fraction of umbilical blood flow perfusing the intercotyledonary chorion found in sheep and goats, estimated from the distribution of radioactive microspheres, is ~ 6·2 ± 0·8% (Makowski *et al.* 1968). This shunt is large enough to be of importance in relation to the maternal–foetal oxygen gradient (Campbell *et al.* 1966).

Umbilical vascular conductance is little affected by hypoxaemia (as in exteriorized preparations; Dawes, 1968) or by infusions of noradrenaline. It is reduced by haemorrhage as might be expected from equation 1, and by acidaemia, vasopressin and angiotensin II. The only situation in which increased conductance has been observed was in lambs receiving T_3 (Table 3). These had a high cardiac output (Table 2) but arterial pressure was in the normal range. Blood volume was not measured but packed cell volume was in the normal range.

In the unanaesthetized foetus the umbilical fraction of cardiac output was significantly raised in hypoxaemia in chronically catheterized foetal lambs (Cohn *et al.* 1974; Sheldon *et al.* 1979). Much of the increase may result from accompanying rises of arterial pressure which in turn have been attributed to increased levels of circulating catecholamines (Jones & Robinson, 1975). Infusion of noradrenaline (1 μg^{-1}.kg^{-1}.min^{-1}) (Lorijn & Longo, 1980) and of vasopressin (6·8–36·4 μu.ml^{-1}) (Iwamoto *et al.* 1979) have been shown to increase the proportion of cardiac output perfusing the umbilical circuit. A small decrease in umbilical vascular resistance has been found at excessively high P_{a,CO_2} (> 80 mmHg (Walker *et al.* 1976)).

Umbilical blood flow increases with gestational age and the driving pressure required for any given flow tends to increase. Reduction of pressure by aortic constriction in exteriorized lambs (Dawes, 1968) or by haemorrhage in chronically catheterized lambs (Toubas *et al.* 1981), reduced umbilical flow. There was little effect of changes in blood gas tensions on the umbilical vascular bed in such experiments (Dawes, 1968). In unanaesthetized foetal lambs placental blood flow was not systematically related to O_2 content (Peeters *et al.* 1979). The balance of evidence suggests that placental circulation does not act as a collapsible circuit in which the

surrounding tissue pressure is determined by the uterine circulation. It has been proposed (Faber & Green, 1972; Longo & Power, 1973) that umbilical blood flow is regulated by change of cardiac output caused by variation in the transplacental flow of water and electrolytes. The theoretical basis for these propositions assumes that the foetal placental capillary follows Starling's Law, and that small changes of foetal systemic arterial pressure are transmitted to the capillaries of the exchanging area. Thus if arterial pressure falls, with a resulting decrease of umbilical blood flow, the fall of capillary pressure on the foetal side of the placenta would favour an increased flow of water and electrolytes from mother to foetus, resulting in an increased foetal blood volume. This would then lead to an increased venous pressure and increase of cardiac output, restoring arterial pressure and umbilical blood flow. While much of this proposal remains theoretical the appropriate relationship has been demonstrated (Faber *et al.* 1973) between blood volume and placental blood flow in chronically catheterized foetal lambs.

Lack of complete pressure–flow curves in whole animal preparations requires that concurrent observations of instantaneous changes of umbilical pressure and flow be assessed in relation to any other accompanying cardiovascular changes. Isoproterenol, dopamine, histamine and tolazoline do not change umbilical flow or resistance. Adrenaline, noradrenaline and acetylcholine do not change calculated umbilical vascular resistance but are accompanied by alterations of blood pressure and/or foetal heart rate. However, doses in the μg range of angiotensin II, 5-hydroxytryptamine, bradykinin and prostaglandins E_1, E_2 and $F_{2\alpha}$ reduce umbilical blood flow and increase calculated vascular resistance (Berman *et al.* 1978). Membrane flow as well as placental was substantially reduced following PGE_2 injection.

The umbilical circulation is unusual in that neither bradykinin nor E series prostaglandins are vasodilatory. The reduction of umbilical flow following infusion of saralasin is the consequence of an increase in foetal vascular conductance and a small fall of umbilical conductance.

Regional circulations

Cerebral circulation

Simultaneous measurement of carotid blood flow with an electromagnetic flow transducer and by microspheres showed that in the mature foetal lamb at normal blood gas tensions, 42–87% of the carotid blood flow was distributed to extra-cerebral structures (Dunnihoo & Quilligan, 1973). Distribution of cerebral blood flow is not uniform (Ashwal *et al.* 1980; Johnson *et al.* 1979; Palahniuk *et al.* 1980); as measured by the microsphere method the deeper structures receive up to double the blood flow per unit volume of the cortex. The average cerebral flow in foetal lambs at normal oxygen tensions is high (100–200 ml.100 g^{-1}.min^{-1}), compared with those accepted for adult humans (53 ml.100 g^{-1}.min^{-1}) and goats (45 ml.100 g^{-1}.min^{-1}) (Dunnihoo & Quilligan, 1973). Hypoxaemia increases cerebral blood flow as measured by microspheres by about 7–10 ml/100 g.min^{-1} mmHg P_{a,O_2}^{-1} in unanaesthetized foetal lambs.

The relative weight of the brain is large in primates compared with other mammals. This accounts for the larger share of cardiac output and total O_2 consumption taken by the primate brain compared with relatively smaller ones. Tissue O_2 consumption is

Table 4. *Cerebral blood flow in foetal sheep and primates*

Species	% CVO	ml.100 g^{-1}.min^{-1}	
Sheep	3	132	Rudolph & Heymann (1970)
Rhesus	15·7	60	Behrman & Lees (1971)
Baboon	13·6	40	Paton *et al.* (1973)

however higher in sheep than in monkeys (Table 4). Perhaps this reflects the larger ratio of basal to cortical tissues in sheep.

Cerebral blood flow also increases with hypercapnia. Widely varying figures have been reported for this response. The figure of 3·6 ml.100 g^{-1}.mmHg P_{a,CO_2}^{-1} from a particularly careful investigation may be representative (Jones *et al.* 1978). A value as low as 0·6 ml.100 g^{-1}.mmHg P_{a,CO_2}^{-1} was obtained using a method which measures mainly cortical flow (Kjellmer *et al.* 1974).

It seems probable that blood pH and oedema may also influence cerebral vascular conductance in addition to the vasodilator actions of falling P_{a,O_2} and rising P_{a,CO_2} in asphyxia. Such multiple actions probably account for failure to observe any hypercapnic hyperaemia in foetal lambs at P_{a,O_2} below 20 mmHg (Kjellmer *et al.* 1974). Cerebral blood flow increased in isocapnic hypoxaemia ($P_{a,O_2} \sim 15$ mmHg). Blood pressure only rose 17% but brain flow ~ 88%. Cortical blood flow increased by ~ 79% and brainstem flow by 119% of control values. Thus only a minor part of the increased cerebral flow during hypoxaemia can be accounted for by the accompanying increase of arterial pressure. Control levels of flow were regained 2½ h after the end of a 90 min period of hypoxaemia. In asphyxia the brain stem and other non-cortical parts have been found to attract proportionately larger increases of blood flow than the cortex (Johnson *et al.* 1979; Ashwal *et al.* 1980).

Halothane anaesthesia of the ewe when the foetus was already very acidotic led to a further fall of cerebral O_2 delivery in all regions, some of which must be attributable to the accompanying fall of arterial pressure in these extreme circumstances (Palahniuk *et al.* 1980).

Coronary circulation

In foetal lambs (120–140 days gestation) with chronically implanted catheters coronary blood flow in normoxia is about 150–200 ml.100 g^{-1}.min^{-1}. Reduction of the P_{a,O_2} to ~ 12 mmHg more than doubled blood flow (Ashwal *et al.* 1981; Cohn *et al.* 1974; Peeters *et al.* 1979). Similar hypoxaemia in foetal monkeys but under N_2O/halothane anaesthesia (Behrman *et al.* 1970) caused a non-significant increase of coronary tissue blood flow, but this response was complicated by accompanying hypercapnia and severe acidaemia. However, in both sets of experiments the coronary share of combined ventricular output was significantly increased from 2·7 to 4·9% in monkeys and from 2·5 to 6·8% in lambs.

When foetal cardiac output was raised after several days administration of triiodothyronine (T_3) coronary flow increased absolutely and also as a percentage of the increased cardiac output (Lorijn *et al.* 1980).

The enlarged hearts found in foetal lambs with raised blood pressures seven days

Table 5. *Myocardial blood flow in foetal lambs with normal and raised blood pressure* (*Fore*, 1982)

	Heart weight (g)	Blood flow	
		ml. 100 g^{-1}. min^{-1}	% CVO
Control lambs	24·0	253	3·1
Hypertensive lambs	35·9	530	9·7

following bilateral nephrectomy not only received an increased proportion of a cardiac output within the normal range but had a raised tissue flow (Table 5; Fore, 1982).

Renal circulation

The kidney receives approximately 1·9% of the cardiac output in foetal lambs (Rudolph & Heymann, 1970) and 2·7% in foetal rhesus monkeys and baboons (Behrman *et al.* 1970; Paton *et al.* 1973). Renal vascular resistance is high and GFR low when expressed in terms of kidney weight (Loggie, Kleinman & Van Maanen, 1975). In foetal lambs GFR does not change between 90 and 130 days gestation when expressed in terms of kidney or body weight (Robillard *et al.* 1977; Robillard, Weismann & Herin, 1981), in spite of the concomitant rise of arterial pressure, cardiac output and structural maturation within the kidney. After 135 days there is a large increase in absolute GFR but not renal plasma flow (Hurley *et al.* 1977). In those species where nephrogenesis is still continuing at birth (e.g. rat, rabbit and pig) incomplete development of the vasculature may contribute to the high resistance to flow. However, resistance remains high in lambs until after birth, even though nephrogenesis is complete some time before parturition (Robillard *et al.* 1981).

Renin-like granules have been described in the juxtamedullary apparatus of foetal kidneys of several species including the human (see Mott, 1979; Smith *et al.* 1974). However, it is doubtful if angiotensin II is responsible for the normally low renal blood flow since infusion of the angiotensin II antagonist saralasin into conscious foetal lambs did not alter renal blood flow or vascular resistance (Iwamoto & Rudolph, 1979).

The changes of renal blood flow which follow hypoxaemia, hypercapnia and haemorrhage have been attributed to sympathetic vasoconstriction (Beguin, Dunnihoo & Quilligan, 1974; Campbell *et al.* 1967*a*; Dunne, Milligan & Thomas, 1972). Using microspheres to measure the distribution of cardiac output at an arterial P_{O_2} of first 20 and then 12 mmHg in unanaesthetized foetal lambs, it was observed that renal blood flow was reduced by 25% during hypoxaemia, and by 50% during asphyxia (Cohn *et al.* 1974). Peeters *et al.* (1979) found that renal blood flow was independent of arterial P_{O_2} values above 20 mmHg and that vasoconstriction occurred abruptly below this. The decrease of renal blood flow in foetal lambs was larger when the hypoxaemia was induced after inhibition of prostaglandin synthesis by foetal infusion of indomethacin (Millard, Baig & Vatner, 1979). Thus prostaglandins may be responsible for mitigation of foetal renal vasoconstriction following hypoxaemia.

Renal vasoconstriction during hypoxaemia can arise reflexly from stimulation of the aortic chemoreceptors (Campbell *et al.* 1967*a*; Dawes, 1968). However, hypoxaemia also increases the circulating concentrations of catecholamines and vasopressin (Jones

& Robinson, 1975; Rurak, 1978; Robillard *et al.* 1981). Infusion of either hormone at rates which produce plasma levels comparable to those observed during hypoxaemia does not alter renal blood flow (Robillard & Weitzman, 1980; Walker, 1977) although absolute GFR is increased. These observations suggest that both hormones preferentially increase post-glomerular resistance.

Hence the effects of hypoxaemia on the foetal renal circulation appear to involve the competing effects of neurogenic vasoconstriction and the relative maintenance of renal blood flow and GFR by the increase of arterial pressure and the intra-renal actions of prostaglandins, catecholamines and vasopressin.

The mature foetal kidney has a considerable capacity for the synthesis and excretion of prostaglandins from at least 0·5 of gestation (Pace-Asciak & Rangaraj, 1978; Mitchell, 1982). Despite the presence of high concentrations of these potent vasodilator substances (Challis *et al.* 1978), the kidney maintains an apparent high vascular resistance. Prostaglandins appear tonically to decrease resistance somewhat, since renal blood flow decreases after prostaglandin synthetase inhibition in unanaesthetized foetal lamb (Heymann & Rudolph, 1976, 1978). However, the direct effect of prostaglandins on the renal vasculature may be secondary to their influence on the intra-renal action of other hormones, such as vasopressin and angiotensin, and on the effects of sympathetic nerve activity (Millard *et al.* 1979).

Gastro-intestinal tract

Estimates of normal blood flow through the gut of unanaesthetized foetal lambs range from 52 to 288 ml.min^{-1} 100 g^{-1} (2·8–5·8% CVO) (Charlton, Reis & Lofgren, 1979; Cohn *et al.* 1974; Gilbert, 1980; Iwamoto & Rudolph, 1979; Peeters *et al.* 1979). Some of this variation may be due to differences of procedure. Peeters *et al.* (1979) showed that flow to the ileum and jejunum was greater than that to the stomach and colon.

Intestinal blood flow in foetal lambs fell sharply when the P_{a,O_2} was less than 20 mmHg (Cohn *et al.* 1974; Peeters *et al.* 1979). It also fell following small (10%) increases or decreases of foetal blood volume (Gilbert, 1980).

Blood flow to the liver of unanaesthetized foetal lambs is high on account of the large contribution from the umbilical vein. It is clear that flow in the region of the portal sinus must be complex, and may be influenced by rhythmic changes in inferior caval pressure related to the cardiac cycle and foetal breathing movements.

The total blood flow through the liver of unanaesthetized foetal lambs, and the proportion received from the umbilical, hepatic and portal supplies, was not changed when the umbilical vein P_{O_2} was reduced from 32 to 20 mmHg for 5–9 min. When umbilical blood flow was reduced 25–50% by partial occlusion of the dorsal aorta the umbilical contribution to liver and blood flow was reduced in proportion, but the hepatic and portal contributions and their distributions within the liver were unchanged. Further evidence also suggested that the partition of flows between the liver substance and ductus venosus was determined purely by the pressure differences across, and vascular resistance within, the liver and ductus venosus (Edelstone *et al.* 1980).

Vasoactive agents

Isolated mesenteric vessels from foetal lambs of 115–130 days gestation were more sensitive to both noradrenaline and 5-hydroxytryptamine than at ages nearer to term (Su *et al.* 1977). This similar change, with growth, in response to two different agonists suggests that maturational changes of the contractile elements of the muscle occur which are unrelated to the innervation. Intravenous infusions of noradrenaline (Lorijn & Longo, 1980) and angiotensin II (Iwamoto & Rudolph, 1981) into conscious foetal lambs which produce an elevation of arterial pressure of 8–12 mmHg did not alter intestinal blood flow as measured with microspheres. Infusion of the angiotensin II competitive inhibitor saralasin was also without effect although blood flow to other regions (e.g. skin, muscle, adrenals) increased (Iwamoto & Rudolph, 1979).

Adrenal gland

Measurement of blood flow by venous collection from adrenal glands in anaesthetized foetal foals (Comline & Silver, 1972) led to the important observation that both splanchnic nerve stimulation and anoxia increased adrenal blood flow, although the possibility that this may have been partly due to the accompanying increases of blood pressure was mentioned.

Recent application of the microsphere technique has provided measurements of flow in normal and experimental situations in foetal sheep, but since the glands receive only about 0·1% of the cardiac output (Cohn *et al.* 1974) the number of spheres trapped is small. This limits the precision of some results, but in unanaesthetized sheep and monkeys adrenal blood flow is as great as in the adult. In foetal lambs this flow ($\sim$ 300 ml.100 g^{-1}.min^{-1}) appears to represent a minimum, since several dissimilar experimental manoeuvres all increase blood flow. Plasma angiotensin II may regulate adrenal blood flow since infusion of the hormone decreased flow (Iwamoto & Rudolph, 1981), whereas infusion of the antagonist saralasin increased flow (Iwamoto & Rudolph, 1979). Adrenal blood flow was increased during hypoxaemia, but this may only be secondary to the rise of blood pressure (Cohn *et al.* 1974). However, in this situation the increased flow might enhance the clearance of catecholamines and other hormones from the gland, and hence lead to a further increase of blood pressure and adrenal blood flow. Infusion of noradrenaline (Lorijn & Longo, 1980) and of vasopressin (Iwamoto & Rudolph, 1979) into unanaesthetized foetal lambs at relatively high rates did not alter adrenal blood flow. Presumably sufficient vasoconstriction occurred to counter the accompanying increase of arterial pressure. The small effects that vasoconstrictor substances and sympathetic nerve stimulation appear to have upon adrenal blood flow, in both the foetus and adult, suggest that this organ does not participate in these generalized compensatory reactions. This is perhaps appropriate, since maintenance of adequate blood flow through the gland would be required.

Thyroid

The fraction of cardiac output distributed to the thyroid of the foetal lamb ranged from 0·06 to 0·11% of the combined output of both ventricles (Iwamoto & Rudolph,

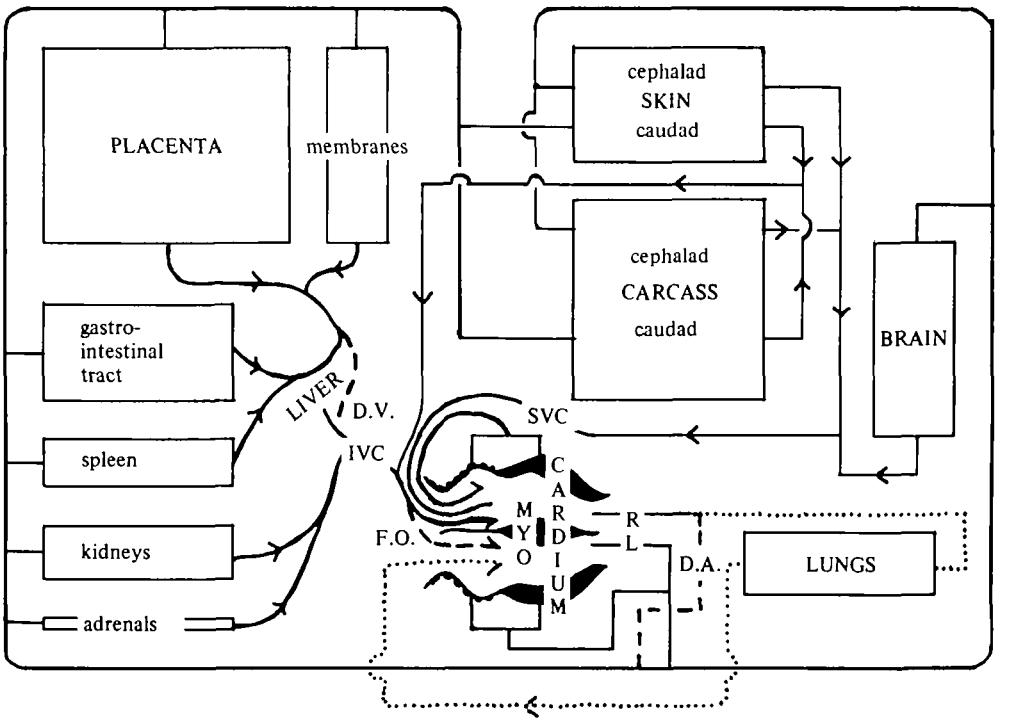

Fig. 1. Diagram to illustrate distribution of the foetal cardiac output in the lamb. The conductances of the principal vascular beds (other than the liver) are represented by rectangles of equal length and of width proportional to the square root of the flow (Table 6). 6·2 % of the umbilical flow (Makowski *et al.* 1968) is shown as supplying the foetal membranes. Arrows indicate the direction of venous return to the heart. The pulmonary circuit is dotted · · · · and the vascular shunts shown by dashed lines – – –. R, right ventricular outflow; L, left ventricular outflow; D.V., ductus venosus; F.O., foramen ovale; D.A., ductus arteriosus; IVC, inferior vena cava; SVC, superior vena cava.

1981; Lorijn *et al.* 1980). Administration of saralasin increased tissue blood flow from 170 to 329 ml.100 g^{-1}.min^{-1} despite a small fall of arterial pressure. Infusion of angiotensin II increased arterial pressure but decreased thyroid blood flow from 147 to 84 ml.100 g^{-1}.min^{-1}. Foetal lambs treated with tri-iodothyronine (2 ng. l^{-1} plasma) had arterial pressures in the normal range, but thyroid blood flow was little more than half that in untreated lambs despite a large increase of cardiac output (Lorijn *et al.* 1980). Whether this last response is due to increased sympathetic activity or increased concentration of circulatory vasoconstrictor substances is unknown.

Skin, skeleton and skeletal muscle

Less than one-fifth of the foetal cardiac output is accounted for by blood flow to the brain, heart, kidney and gastrointestinal tract. Moreover, these organs jointly receive less than one-third of the arterial flow to the foetal body. Detailed information is lacking about the circulation to the remainder, which comprises mainly skin, skeletal muscle, fat, bone and spinal cord. Many studies have calculated flow to the foetal body after removal of the viscera, and as such the carcass appears to receive at least

Table 6. *Distribution of blood flow to systemic vascular beds in foetal lambs (I. M. Fore, unpublished)*

	Cardiac output (CVO) (%)		Systemic flow (%)
Brain	4·3		
Heart	3·1		
Kidney	2·1		
G.I. tract	6·5		
	—	16·0	28·4
Liver (arterial)	0·4		
Spleen	1·4		
Adrenals	0·1		
Lungs	2·6		
	—	4·5	8·1
Skin	8·6		
Carcass	27·1		
	—	35·7	63·2

Table 7. *Change of blood flows (ml.kg body weight^{-1}.min^{-1}) during hypoxaemia (P_{a,O_2} 12–15 mmHg) in foetal lambs estimated from distribution of microspheres introduced into the arterial system or the umbilical vein*

	(*a*) Arterial system		(*b*) Umbilical vein	
Tissue	(−)	(+)	(−)	(+)
Myocardium		18·5		8·9
Brain		10·7		7·4
G.I. tract	1·5		1·5	
Kidneys	3·8		0·2	
Lungs	9·7		4·2	
Carcass	45·7		17·7	
	60·7	29·2	23·6	16·3

(*a*) Cohn *et al.* (1974).
(*b*) Reuss & Rudolph (1980).

20% of the cardiac output, or over 50% of the flow to the foetal body (Rudolph & Heymann, 1970). Since muscle may account for only about half of the weight of a carcass (Creasy *et al.* 1973), a considerable fraction of this flow is probably directed to bone and skin (Fig. 1, Table 6). In adult animals, blood flow to the skeleton accounts for 3–7% of the cardiac output (Copp & Shim, 1965; Tothill & McCormick, 1976), and the bone of growing animals may reasonably be expected to receive at least this proportion.

In unanaesthetized foetuses microsphere studies have shown that blood flow to the carcass decreased during acute hypoxia, and this was greater when acidaemia accompanied the hypoxaemia (Cohn *et al.* 1974). Flow to the carcass only fell at P_{a,O_2} < 20 mmHg (Peeters *et al.* 1979). However, since the carcass accounts for about a half of the systemic blood flow even moderate vasoconstriction is adequate to divert a considerable fraction to other regions which dilate during hypoxaemia (see Table 7).

Blood flow to the soleus (a slow) and gastrocnemius (a fast) muscle was found to be

12·1 and 14·0 ml.100 g^{-1}.min^{-1} respectively (Molteni *et al.* 1980), and this similarity shows that the higher basal flow rate of slow muscle, which is characteristic of the adult (Hilton, Jeffries & Vrbova, 1970), is not present in the foetus. During non-breathing periods flow to the foetal diaphragm was comparable to that of adult sheep during quiet breathing, whereas foetal intercostal muscle flow was three times greater than the adult. During vigorous breathing induced by intravenous infusion of acid (NH_4Cl or HCl 20–25 mM.kg^{-1}) to the foetal lamb, blood flow to the diaphragm and chest wall increased 6–12 times (Molteni *et al.* 1980), exceeding the changes occurring in adult sheep during heat stress (Hales, 1973).

In foetal lambs delivered by Caesarean section under light chloralose anaesthesia, section of the sciatic nerve resulted in an increase of femoral flow, indicating that in these circumstances the hind-limb circulation was under a degree of vasoconstrictor control (Dawes *et al.* 1968). The hind-limb vascular resistance increased progressively from 90 to 140 days of gestation. Asphyxia and hypoxia caused vasoconstriction which was considerably attenuated by section of the vagi, and the response was thus attributed to stimulation of the aortic chemoreceptors. After a careful search for any contribution from carotid chemoreceptors, their participation in reflex hypoxic vasoconstriction was concluded to be minimal or absent (Dawes *et al.* 1968, 1969). Variations of arterial blood gases produced by ventilating the foetal lambs with gas mixtures of various compositions had also shown that femoral flow was sensitive to changes of arterial P_{O_2} within the normal range (Campbell *et al.* 1967*a*). Reflex vasoconstriction of the hind-limb vasculature could be demonstrated from about 105 days gestation and was larger in older lambs. This provides a mechanism for the diversion of blood flow away from skeletal muscle during hypoxaemia and asphyxia (see Table 7).

Pulmonary circulation

The central feature of the circulatory transition accomplished at birth is a dramatic increase in pulmonary vascular conductance with reversal of the direction of blood flow through the ductus arteriosus (Dawes *et al.* 1953).

In the lamb *in utero*, although pulmonary blood flow can vary and is reduced in hypoxaemia it does not exceed 5–6% of the combined output of both ventricles as measured by microsphere techniques in conscious preparations with chronically implanted catheters.

Direct effects of blood gas changes on pulmonary blood flow have been examined by perfusion of a non-ventilated (foetal) lung with blood equilibrated with appropriate mixtures of O_2, CO_2 and N_2 by a donor lung. Blood gas tensions (P_{a,CO_2} 27 mmHg, P_{a,CO_2} 42 mmHg) representative of those normally found in foetal lungs, can be attained by equilibration with a gas mixture containing 3% O_2 and 7% CO_2 in N_2. The dilatation achieved by hyperoxia and hypocapnia in the foetal condition is still far short of that attained with ventilation with gas (Dawes, 1969). Asphyxial vasoconstriction has been demonstrated as early as 0·5 term and is not dependent on innervation of the lungs (Campbell *et al.* 1967*b*). This is analogous to the principal vasoconstrictor action of hypoxic ventilation in the adult. While reflex vasoconstriction could be blocked with hexamethonium (Campbell *et al.* 1967*b*), α and β adrenoceptor blockers were found not to influence the pulmonary vascular response to hypoxaemia in

chronically catheterized foetal lambs (Lewis *et al.* 1976). This suggests that the direct effects of hypoxaemia on the pulmonary vasculature are of predominant importance in the intact foetus.

During maternal hypoxaemia the fraction of cardiac output going to the foetal lungs was reduced from 10·7 to 3·2% in monkeys and from 3·9 to 1·9% in lambs (Behrman *et al.* 1970; Cohn *et al.* 1974).

Nervous control of the pulmonary vasculature

Electrical stimulation of the peripheral cut end of the vagus causes pulmonary vasodilatation, and stimulation of the cardiac sympathetic nerves to the foetal lung causes vasoconstriction (Colebatch *et al.* 1965). Although the sympathectomized lung is more vasodilated than the intact lung nevertheless pulmonary ventilation with 3% O_2 and 7% CO_2 (which avoids change of gas pressures in the perfusing blood) still substantially increases pulmonary conductance (Dawes, 1969).

Stimulation of the sympathetic supply to the left lung causes profound pulmonary vasoconstriction as early as 0·6 term. By 0·68 of term it has been shown that pulmonary vasoconstriction can be reflexly activated in a foetal lung itself perfused with normal foetal blood (Campbell *et al.* 1967*b*).

Vasoactive substances

The high vascular resistance of the foetal lung is reduced by acetylcholine in μg doses which have minimal effects on the circulation of a ventilated lung. In chronically catheterized foetal lambs sensitivity to acetylcholine increases with age (Lewis *et al.* 1976). Histamine (Dawes & Mott, 1962), bradykinin (Cassin *et al.* 1964*a*) and isoprenaline (Cassin *et al.* 1964*b*) also cause pulmonary vasodilatation in anaesthetized exteriorized preparations.

Angiotensin II increases and saralasin decreases pulmonary vascular conductance in foetal lambs (Iwamoto & Rudolph 1979, 1981). It has been suggested that angiotensin II might release vasodilator prostaglandins in the pulmonary vessels. However, it is possible that systemic venous and hence pulmonary arterial O_2 are increased as a result of increased systemic blood flow (Table 3) with the net result of vasodilatation in the lung circulation. Indeed, in some species it has been found that angiotensin II is necessary for hypoxic vasoconstriction (Berkov, 1974). Nevertheless foetal pulmonary blood flow can increase dramatically above 2 mM O_2 ($\sim P_{a,O_2}$ 13 mmHg; Peeters *et al.* 1979). It is also significantly raised during prolonged treatment with tri-iodothyronine (Lorijn *et al.* 1980).

Prostaglandin E_1 is a potent vasodilator of the goat foetal pulmonary circulation, with 50% of maximal response obtained by infusion of 1·6 $\mu g.kg^{-1}$ (during 1 min) (Cassin, Tyler & Wallis, 1975). However, administration of indomethacin (an inhibitor of prostaglandin synthetase) did not significantly affect the pulmonary vascular resistance of foetal goat lung perfused at constant flow.

The mechanisms of hypoxic vasoconstriction (which do not depend on neural mediation) remain a matter of contention even in the adult (Barer, 1981). By adult standards the normal foetal lung is vasoconstricted and is far more sensitive to vasodilator agents, as mentioned earlier, than the adult lung. Prolonged reactive

hyperaemia follows pulmonary arterial occlusion (Dawes, 1968). Ischaemia must exacerbate an already asphyxial situation and yet prolonged vasodilatation ensues. Various other manoeuvres also prevent pulmonary hypoxic vasoconstriction (e.g. injection of cyanide). No consensus as to a final common pathway for pulmonary hypoxic vasoconstriction has been achieved.

Vascular shunts and redistribution of cardiac output

Ductus venosus

In some species a half or more of the umbilical venous return bypasses liver tissue either, as in the lamb, through a relatively large vessel (Edelstone *et al.* 1978) or, as in the pig, through channels which permit passage of microspheres 15 μm in diameter which would be trapped by capillaries. In contrast no extrahepatic channel has been demonstrated between the umbilical vein and inferior cava in the foal (Barnes *et al.* 1979). There is no evidence that the ductus venosus, when present, regulates blood flow to the liver (Edelstone *et al.* 1980).

Foramen ovale

This passage in the foetal lamb allows well-oxygenated inferior caval blood to reach the left atrium directly without passing through the lungs. The fall of inferior caval and rise of left atrial pressure caused by increased pulmonary blood flow when breathing begins presses the semi-cylindrical membranous valve of the foramen against the crista dividens, thus preventing right-to-left shunting at this level in the newborn animal (Dawes *et al.* 1955). The progress of anatomical closure varies with the species (Dawes, 1968).

Ductus arteriosus

This short but wide remnant of lateral dorsal aorta forms a direct continuation of the pulmonary trunk which discharges into the descending aorta. Flow through it is from right to left in foetal life, with diversion of blood from the relatively high-resistance pulmonary circulation. The pressure drop along the ductus is small ($\sim$ 2 mmHg) but increases when constriction is induced by the prostaglandin synthetase inhibitors indomethacin or acetylsalicylic acid (Heymann & Rudolph, 1976; and see Mott, 1980). At birth blood flow through the ductus reverses following the fall of pulmonary artery pressure consequent upon pulmonary vasodilatation due to ventilation.

Redistribution of blood flow

Reduction of P_{a,O_2} from 21 to 12 mmHg reduced cardiac output from 464 to 442 $ml.kg^{-1}.min^{-1}$ and systemic conductance by 28% (Table 3). Arterial blood flow to the heart and brain were increased by $\sim$ 29 ml.kg body $weight^{-1}.min^{-1}$, which was only half the fall of flow measured in the gut, kidneys, lungs and carcass combined (Table 7*a*). In another investigation in which P_{a,O_2} fell from 24 to 15 mmHg, cardiac output was reduced from 505 to 414 $ml.kg^{-1}.min^{-1}$ and systemic/umbilical flow ratio from 1·06 to 0·69, a corresponding redistribution of umbilical venous blood

occurred (Table 7*b*). It is clear that provision for increased perfusion of heart and brain (which together form ~ 2% body weight) can be accommodated by a very limited degree of vasoconstriction in an organ such as skeletal muscle which constitutes a significant proportion of body mass (Campbell *et al.* 1967*a*; Dawes *et al.* 1968).

It is probable that the aortic chemoreceptors play a part in the redistribution of cardiac output in the foetus during hypoxia (Campbell *et al.* 1967*a*; Dawes *et al.* 1968). The threshold for foetal baroreceptor stimulation appears to be above the normal range of arterial pressures (Dawes *et al.* 1980). The small increases in arterial pressure which accompany hypoxaemia or asphyxia would not *per se* be expected to lengthen the heart period.

Experimental procedures designed to retard foetal growth in lambs have produced deviations from normal of cardiovascular function. Placental embolism caused by repeated doses of non-radioactive microspheres reduced placental conductance substantially but systemic conductance was unchanged. However, flow to the carcass was 27% lower, while that to the brain and heart were, respectively, 65% and 89% higher than in control animals (Creasy *et al.* 1973). These differences are probably largely due to the low P_{a,O_2} (17 mmHg) in the embolized lambs compared with 23 mmHg in the control lambs. The redistribution of flow resembles that caused acutely by hypoxaemia (Table 7), though the cardiac output per kilogram was comparatively lower than that seen during acute hypoxaemia. Comparable hypoxaemia accompanied by polycythaemia and hypoglycaemia were found in lambs conceived in ewes previously subjected to carunculectomy (Robinson *et al.* 1979).

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REFERENCES

Ashwal, M. D., Majcher, J. S. & Longo, L. D. (1981). Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia: studies during the posthypoxic recovery period. *Am. J. Obstet. Gynec.* **139**, 365–372.

Ashwal, S., Majcher, J. S., Vain, N. & Longo, L. D. (1980). Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia. *Pediatr. Res.* **14**, 1104–1110.

Barer, G. R. (1981). The physiology of the pulmonary circulation and methods of study. In *International Encyclopedia of Pharmacology and Respiration* section 104, 345–374 (ed. J. Widdicombe). London: Pergamon Press.

Barnes, R. J., Comline, R. S., Dobson, A. & Silver, M. (1979). On the presence of a ductus venosus in the fetal pig in late gestation. *J. Devl Physiol.* **1**, 105–110.

Beguin, F., Dunnihoo, D. R. & Quilligan, E. J. (1974). Effect of CO_2 elevation on renal blood flow in the fetal lamb *in utero*. *Am. J. Obstet. Gynec.* **119**, 630–637.

Behrman, R. E. & Lees, M. H. (1971). Organ bloodflows of the fetal newborn and adult rhesus monkey. *Biol. Neonat.* **18**, 330–340.

Behrman, R. E., Lees, M. H., Peterson, E. N., de Lannoy, C. W. & Seeds, A. E. (1970). Distribution of the circulation in the normal and asphyxiated fetal primate. *Am. J. Obstet. Gynec.* **108**, 956–969.

Berkov, S. (1974). Hypoxic pulmonary vasoconstriction in the rat: the necessary role of angiotensin II. *Circulation Res.* **35**, 256–261.

Berman, W., Goodlin, R. C., Heymann, M. A. & Rudolph, A. M. (1978). Effects of pharmacologic agents on umbilical blood flow in fetal lambs *in utero*. *Biol. Neonat.* **33**, 225–235.

Campbell, A., Dawes, G. S., Fishman, A. & Hyman, A. (1967*a*). Regional redistribution of blood flow in the mature foetal lamb. *Circulation Res.* **21**, 229–236.

Campbell, A. G. M., Dawes, G. S., Fishman, A. P. & Hyman, A. I. (1967*b*). Pulmonary vasoconstriction and changes in heart rate during asphyxia in immature foetal lambs. *J. Physiol.* **192**, 93–110.

CAMPBELL, A. G. M., DAWES, G. S., FISHMAN, A. P., HYMAN, A. I. & JAMES, G. B. (1966). The oxygen consumption of the placenta and foetal membranes in the sheep. *J. Physiol.* **182**, 439–464.

CASSIN, S., DAWES, G. S., MOTT, J. C., ROSS, B. B. & STRANG, L. B. (1964*a*). The vascular resistance of the foetal and newly ventilated lung of the lamb. *J. Physiol.* **171**, 61–79.

CASSIN, S., DAWES, G. S. & ROSS, B. B. (1964*b*). Pulmonary blood flow and vascular resistance in immature foetal lambs. *J. Physiol.* **171**, 80–89.

CASSIN, S., TYLER, T. & WALLIS, R. (1975). The effects of prostaglandin E_1 on fetal pulmonary vascular resistance. *Proc. Soc. exp. Biol. Med.* **148**, 584–587.

CHALLIS, J. R. G., HART, I., LOUIS, T. M., MITCHELL, M. D., JENKIN, G., ROBINSON, J. S. & THORBURN, G. D. (1978). Prostaglandins in the sheep fetus: implications for fetal function. *Adv. Prostaglandin Thromboxane Res.* **4**, 115–132.

CHARLTON, V. E., REIS, B. L. & LOFGREN, D. J. (1979). Measurements of carbohydrates, amino acids and oxygen across the intestinal circulation in the sheep fetus. *J. Devl Physiol.* **1**, 329–336.

COHN, E. H., SACKS, E. J., HEYMANN, M. A. & RUDOLPH, A. M. (1974). Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am. J. Obstet. Gynec.* **120**, 817–824.

COLEBATCH, H. J. H., DAWES, G. S., GOODWIN, J. W. & NADEAU, R. A. (1965). The nervous control of the circulation in the foetal and newly expanded lungs of the lamb. *J. Physiol.* **178**, 544–562.

COMLINE, R. & SILVER, M. (1972). Catecholamine secretion by the adrenal medulla of foetal and newborn goats. *J. Physiol.* **216**, 659–682.

COPP, D. H. & SHIM, S. S. (1965). Extraction ratio and bone clearance of Sr^{85} as a measure of effective bone blood flow. *Circulation Res.* **16**, 461–467.

CREASY, R. K., DE SWIET, M., KAHANPAA, K. V., YOUNG, W. P. & RUDOLPH, A. M. (1973). Pathophysiological changes in the foetal lamb with growth retardation. In *Foetal and Neonatal Physiology* (*The Barcroft Centenary Symposium*) (ed. R. S. Comline, K. W. Cross, G. S. Dawes and P. W. Nathanielz), pp. 398–402. London: Cambridge University Press.

DAWES, G. S. (1968). *Foetal and Neonatal Physiology*. Chicago: Year Book Publishers, Inc.

DAWES, G. S. (1969). Control of the pulmonary circulation in the fetus and newborn. In *The Pulmonary Circulation and Insterstitial Space* (ed. A. P. Fishman and H. H. Hecht), pp. 293–304. University of Chicago Press.

DAWES, G. S., DUNCAN, S. L. B., LEWIS, B. V., MERLET, C. L., OWEN-THOMAS, J. B. & REEVES, J. T. (1969). Cyanide stimulation of the systemic arterial chemoreceptors in foetal lambs. *J. Physiol.* **201**, 117–128.

DAWES, G. S., LEWIS, B. V., MILLIGAN, J., ROACH, M. & TALNER, M. (1968). Vasomotor responses in the hindlimbs of foetal and newborn lambs to asphyxia and aortic chemoreceptor stimulation. *J. Physiol.* **195**, 55–81.

DAWES, G. S. & MOTT, J. C. (1962). The vascular tone of the foetal lung. *J. Physiol.* **164**, 465–477.

DAWES, G. S., MOTT, J. C. & WIDDICOMBE, J. G. (1955). Closure of the foramen ovale in newborn lambs. *J. Physiol.* **128**, 384–395.

DAWES, G. S., MOTT, J. C., WIDDICOMBE, J. G. & WYATT, D. G. (1953). Changes in the lungs of the new-born lamb. *J. Physiol.* **121**, 141–162.

DAWES, G. S., JOHNSTON, B. M. & WALKER, D. W. (1980). Relationship of arterial pressure and heart rate in fetal, newborn and adult sheep. *J. Physiol.* **309**, 405–418.

DUNNE, J. T., MILLIGAN, J. E. & THOMAS, B. W. (1972). Control of the renal circulation in the fetus. *Am. J. Obstet. Gynec.* **112**, 323–329.

DUNNIHOO, D. R. & QUILLIGAN, E. J. (1973). Carotid blood flow distribution in the *in utero* sheep fetus. *Am. J. Obstet. Gynec.* **116**, 648–656.

EDELSTONE, D. I., RUDOLPH, A. M. & HEYMANN, M. A. (1978). Liver and ductus venosus blood flows in fetal lambs *in utero*. *Circulation Res.* **42**, 426–433.

EDELSTONE, D. I., RUDOLPH, A. M. & HEYMANN, M. A. (1980). Effects of hypoxemia and decreasing umbilical flow on liver and ductus venosus blood flows in fetal lambs. *Am. J. Physiol.* **238**, H656–H663.

FABER, J. J., GAULT, C. F., GREEN, T. J. & THORNBURG, K. L. (1973). Fetal blood volume and fetal placental blood flow in lambs. *Proc. Soc. exp. Biol. Med.* **142**, 340–344.

FABER, J. J. & GREEN, T. J. (1972). Foetal placental blood flow in the lamb. *J. Physiol.* **223**, 375–393.

FORE, I. M. (1982). Cardiac output and its distribution in hypertensive fetal lambs. *J. Physiol.* (in the Press).

GILBERT, R. D. (1980). Control of fetal cardiac output during changes in blood volume. *Am. J. Physiol.* **238**, 80–86.

HALES, J. R. S. (1973). Effects of exposure to hot environments on the regional redistribution of blood flow and on cardiorespiratory function in sheep. *Pflügers. Arch. ges. Physiol.* **344**, 133–148.

HEYMANN, M. A. & RUDOLPH, A. M. (1976). Effect of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs *in utero*. *Circulation Res.* **38**, 418–422.

HEYMANN, M. A. & RUDOLPH, A. M. (1978). Effects of prostaglandins and blockers of prostaglandin synthesis on the ductus arteriosus: animal and human studies. *Adv. Prostaglandin Thromboxane Res.* **4**, 363–372.

HILTON, S. M., JEFFRIES, M. G. & VRBOVA, G. (1970). Functional specialization of the vascular bed of the soleus. *J. Physiol.* **206**, 543–563.

HURLEY, J. K., KIRKPATRICK, S. E., PITLICK, P. T., FRIEDMAN, W. F. & MENDOZA, S. A. (1977). Renal responses of the fetal lamb to fetal or maternal volume expansion. *Circulation Res.* **40**, 557–560.

IWAMOTO, H. S. & RUDOLPH, A. M. (1979). Effects of endogenous angiotensin II on the fetal circulation. *J. Devl Physiol.* **1**, 283–293.

IWAMOTO, H. S. & RUDOLPH, A. M. (1981). Effects of angiotensin II on the blood flow and its distribution in fetal lambs. *Circulation Res.* **48**, 183–189.

IWAMOTO, H. S., RUDOLPH, A. M., KEIL, L. C. S. & HEYMANN, M. (1979). Hemodynamic responses of the sheep fetus to vasopressin infusion. *Circulation Res.* **44**, 430–436.

JOHNSON, G. N., PALAHNIUK, R. J., TWEED, W. A., JONES, M. V. & WADE, J. G. (1979). Regional cerebral blood flow changes during severe fetal asphyxia produced by slow partial umbilical cord compression. *Am. J. Obstet. Gynec.* **135**, 48–52.

JONES, C. T., & ROBINSON, R. O. (1975). Plasma catecholamines in foetal and adult sheep. *J. Physiol.* **248**, 15–53.

JONES, M. D., SHELDON, R. E., PEETERS, L. L., MAKOWSKI, E. L. & MESCHIA, G. (1978). Regulation of cerebral blood flow in the ovine fetus. *Am. J. Physiol.* **235**, H162–H166.

KJELLMER, I., KARLSSON, K., OLSSON, T. & ROSEN, K. G. (1974). Cerebral reactions during intrauterine asphyxia in the sheep. I. Circulation and oxygen consumption in the fetal brain. *Pediatr. Res.* **8**, 50–57.

LEWIS, A. B., HEYMANN, M. A. & RUDOLPH, A. M. (1976). Gestational changes in pulmonary vascular responses in fetal lambs *in utero*. *Circulation Res.* **39**, 536–541.

LOGGIE, J. M. H., KLEINMAN, L. I. & VAN MAANEN, E. F. (1975). Renal function and diuretic therapy in infants and children. *J. Pediatrics* **86**, 485–496.

LONGO, L. D. & POWER, G. C. (1973). Long-term regulation of fetal cardiac output: a hypothesis on the role of carbon dioxide. *Gynec. Invest.* **4**, 277–287.

LORIJN, R. H. & LONGO, L. D. (1980). Norepinephrine elevation in the fetal lamb: oxygen consumption and cardiac output. *Am. J. Physiol.* **239**, R115–R122.

LORIJN, R. H., NELSON, J. C. & LONGO, L. D. (1980). Induced fetal hyperthyroidism: cardiac output and oxygen consumption. *Am. J. Physiol.* **239**, H302–H307.

MAKOWSKI, E. L., MESCHIA, G., DROEGMUELLER, W. & BATTAGLIA, F. C. (1968). Measurement of umbilical arterial blood flow to the sheep placenta and fetus *in utero*. *Circulation Res.* **23**, 623–631.

MILLARD, R. W., BAIG, H. & VATNER, S. F. (1979). Prostaglandin control of the renal circulation in response to hypoxemia in the fetal lamb *in utero*. *Circulation Res.* **45**, 172–179.

MITCHELL, M. D. (1982). Prostaglandin synthesis, metabolism and function in the fetus. In *Biochemical Development of the Fetus and Neonate*, vol. 1. Amsterdam: Elsevier North-Holland Biomedical Press, (in the Press).

MOLTENI, R. A., MELMED, M. H., SHELDON, R. E., JONES, M. D. & MESCHIA, G. (1980). Induction of fetal breathing by metabolic acidemia and its effect on blood flow to the respiratory muscles. *Am. J. Obstet. Gynec.* **136**, 609–620.

MOTT, J. C. (1979). The renin-angiotensin-aldosterone system in pregnancy and its relation to that of the fetus and newborn. In *The Influence of Maternal Hormones on the Fetus and Newborn* vol. 5, (ed. M. Nitzan), pp. 126–145. Basel: Karger.

MOTT, J. C. (1980). Patent ductus arteriosus: experimental aspects. *Archs Dis. Childh.* **55**, 99–105.

NOVY, M. J. & METCALFE, J. (1970). Measurements of umbilical blood flow and vascular volume by dye dilution. *Am. J. Obstet. Gynec.* **106**, 899–906.

PACE-ASCIAK, C. R., & RANGARAJ, G. (1978). Distribution of prostaglandin biosynthetic pathways in organs and tissues of the fetal lamb. *Biochim. biophys. Acta* **528**, 512–514.

PALAHNIUK, R. J., DOIG, G. A., JOHNSON, G. N. & PASH, M. P. (1980). Maternal halothane anesthesia reduces cerebral blood flow in the acidotic sheep fetus. *Anesth. Analg.* (Cleveland) **59**, 35–39.

PATON, J. B., FISHER, D. E., PETERSON, E. N., DELANNOY, C. W. & BEHRMAN, R. E. (1973). Cardiac output and organ blood flows in the baboon fetus. *Biol. Neonat.* **22**, 50–57.

PEETERS, L. L. H., SHELDON, R. E., JONES, M. D., MAKOWSKI, E. L. & MESCHIA, G. (1979). Blood flow to fetal organs as a function of arterial oxygen content. *Am. J. Obstet. Gynec.* **135**, 637–646.

REUSS, M. L. & RUDOLPH, A. M. (1980). Distribution and recirculation of umbilical and systemic venous blood flow in fetal lambs during hypoxia. *J. Devl. Physiol.* **2**, 71–84.

ROBILLARD, J. E., WEISMANN, D. N. & HERIN, P. (1981). Ontogeny of single glomerular perfusion rate in fetal and newborn lambs. *Pediatr. Res.* **15**, 1248–1255.

ROBILLARD, J. E., SESSIONS, C., KENNEDY, R. L., HAMEL-ROBILLARD, L. & SMITH, F. G. (1977). Interrelationship between glomerular filtration rate and renal transport of sodium and chloride during fetal life. *Am. J. Obstet. Gynec.* **128**, 727–734.

ROBILLARD, J. E. & WEITZMAN, R. E. (1980). Developmental aspects of the fetal renal response to exogenous arginine vasopressin. *Am. J. Physiol.* **239**, F407–F414.

ROBINSON, J. S., KINGSTON, E. J., JONES, C. T. & THORBURN, G. D. (1979). Studies on experimental growth retardation in sheep. The effect of removal of endometrial caruncles on fetal size and metabolism. *J. Devl Physiol.* **1**, 45–66.

RUDOLPH, A. M. & HEYMANN, M. A. (1970). Circulatory changes during growth in the fetal lamb. *Circulation Res.* **26**, 289–299.

RURAK, D. W. (1978). Plasma vasopressin levels during hypoxaemia and the cardiovascular effects of exogenous vasopressin in foetal and adult sheep. *J. Physiol.* **277**, 341–357.

SHELDON, R. E., PEETERS, L. L. H., JONES, M. D., MAKOWSKI, E. L. & MESCHIA, G. (1979). Redistribution of cardiac output and oxygen delivery in the hypoxemic fetal lamb. *Am. J. Obstet. Gynec.* **135**, 1071–1078.

SMITH, F. G., LUPU, A. N., BARAJAS, L., BAUER, R. & BASHORE, R. A. (1974). The renin-angiotensin system in the fetal lamb. *Pediatr. Res.* **8**, 611–620.

SU, C., BEVAN, J. A., ASSALI, N. S. & BRINKMAN, C. R. (1977). Regional variation of lamb blood vessel responsiveness to vasoactive agents during fetal development. *Circulation Res.* **41**, 844–848.

TOTHILL, P. & MCCORMICK, J. (1976). Bone blood flow in the rat determined by the uptake of radioactive particles. *Clin. Sci. Mol. Med.* **51**, 403–406.

TOUBAS, P. L., SILVERMAN, N. H., HEYMANN, M. A. & RUDOLPH, A. M. (1981). Cardiovascular effects of acute hemorrhage in fetal lambs. *Am. J. Physiol.* **240**, H45–H48.

WALKER, A. M., OAKES, G. K., EHRENKRANZ, R., MCLAUGHLIN, M. & CHEZ, R. A. (1976). Effects of hypercapnia on uterine and umbilical circulations in conscious pregnant sheep. *J. appl. Physiol.* **41**, 727–733.

WALKER, D. (1977). Renal function and micturition in fetal lambs, and the effects of hypoxia. *Ann. Rech. Vet.* **8**, 497–498.

YAFFE, H., PARER, J. T., LLANOS, A. & BLOCK, B. (1982). Fetal hemodynamic responses to graded reductions of uterine blood flow in sheep. 29th Annual Meeting of the Society of Gynecological Investigation.

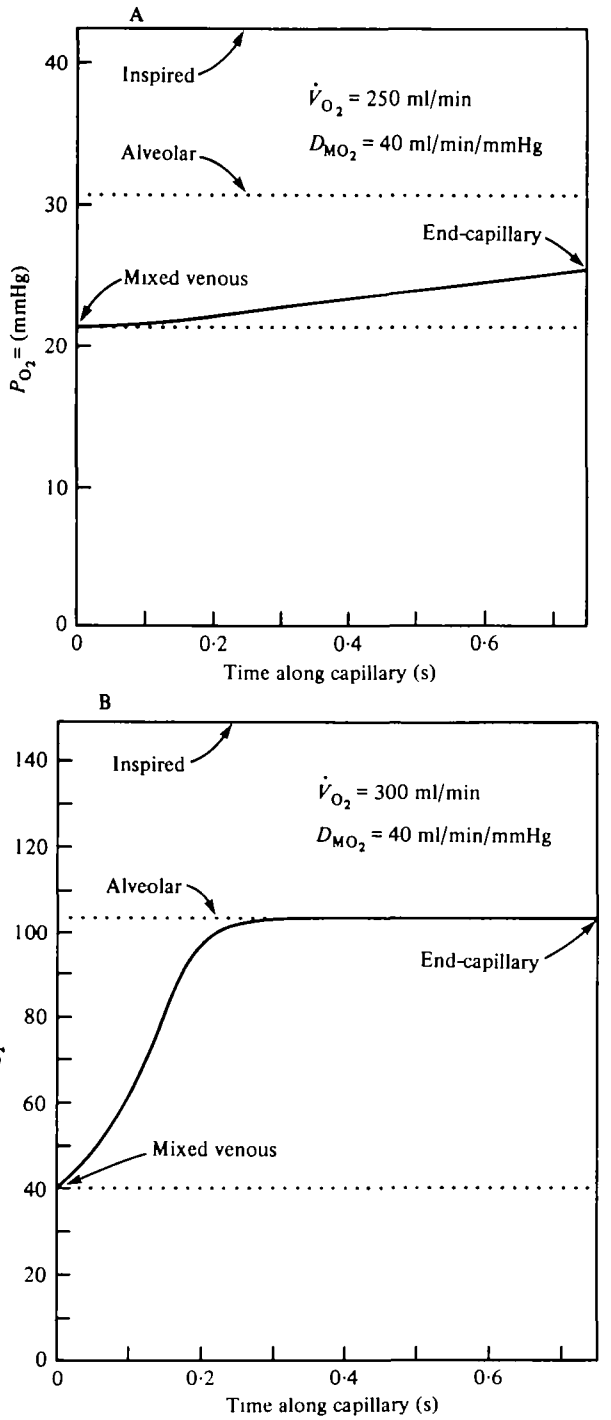

Fig. 5. (A) Shows the calculated time course of the P_{O_2} in the pulmonary capillary of a climber at rest on the summit of Mt Everest. Note the very slow rate of rise of P_{O_2} and the marked difference in P_{O_2} between alveolar gas and in capillary blood. (B) Shows the normal time course at sea level for comparison. (From West & Wagner, 1980).

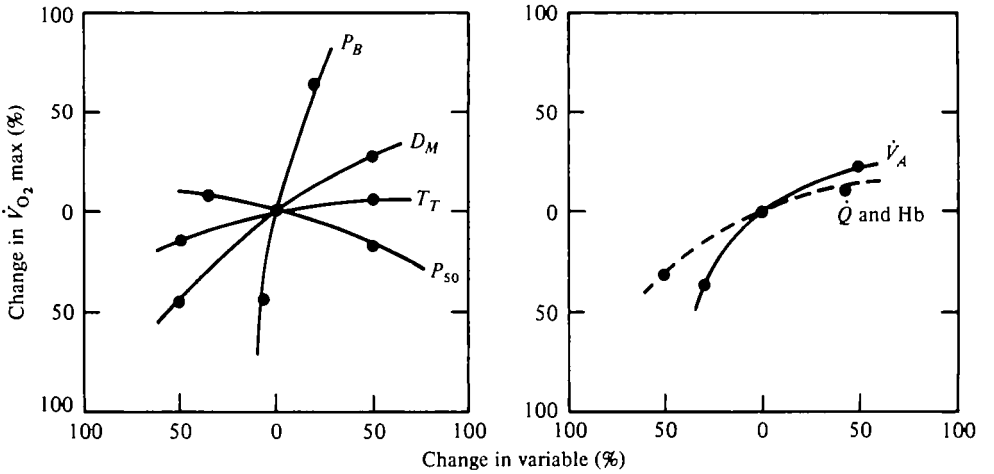

Fig. 6. Analysis of factors limiting maximal oxygen uptake at a barometric pressure of 250 torr. Note the extreme sensitivity to barometric pressure (P_B). The membrane diffusing capacity (D_M) is also a critical variable. Other parameters studied are capillary transit time (T_T), P_{50} of the oxygen dissociation curve, total alveolar ventilation (VA), haemoglobin concentration (Hb) and cardiac output (Q). (From West & Wagner, 1980).

emphasizes the extent to which oxygen transfer is diffusion-limited under these very hypoxic conditions. The reason for the marked diffusion limitation is the steepness of the slope of the blood–oxygen dissociation curve expressed as ml O_2/dl blood/torr. This steep slope can be ascribed to two factors: first, the capillary P_{O_2} is very low on the oxygen dissociation curve during the entire oxygenation process along the capillary, and second, the haemoglobin concentration is much increased.

How valuable would increases in ventilation and cardiac output be in improving maximal work capacity under these conditions? The right panel of Fig. 6 shows that both an increase in alveolar ventilation, and an increase in total pulmonary blood flow or haemoglobin would provide useful gains. This raises the question of why the climber does not increase his maximal exercise inflation which, as Fig. 3 shows, is restricted to low values at these extreme altitudes. One possibility is that the oxygen cost of additional ventilation would steal a significant portion of the total oxygen available. Another is that the action of the respiratory muscles themselves is limited by hypoxia.

The situation with cardiac output is equally puzzling. Pugh (1964*a*) showed that the relationship between cardiac output and work rate was the same at an altitude of 5800 m (380 torr) in acclimatized subjects as at sea level. It is known that acute exposure to altitude increases cardiac output at a given work level (Alexander *et al.* 1967) but apparently with acclimatization the relationship reverts to that seen at sea level. Why this should be when an increase in cardiac output would clearly improve oxygen delivery to the exercising muscles is obscure. However the answer to this paradox may have to wait until we understand the control of cardiac output at sea level which, as far as I can determine, is far from the case at the present moment.

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REFERENCES

ALEXANDER, J. K., HARTLEY, L., MODELSKI, M. & GROVER, R. F. (1967). Reduction of stroke volume during exercise in man following ascent to 3100 m in altitude. *J. appl. Physiol.* **23**, 849–858.

BENCOWITZ, H. Z., WAGNER, P. D. & WEST, J. B. (1982). Effect of change in P_{50} on exercise tolerance at high altitude: a theoretical study. *J. appl. Physiol.* (in the Press).

CERRETELLI, P. (1976). Limiting factors to oxygen transport on Mount Everest. *J. appl. Physiol.* **40**, 658–667.

DEJOURS, P., GIRARD, F., LABROUSSE, Y. & TEILLAC, A. (1958). Stimulus oxygène de la ventilation chez l'homme acclimaté à l'altitude (3613 m). *J. Physiol., Paris* **50**, 237–238.

FORSTER, H. V., DEMPSEY, J. A. & CHOSY, L. W. (1975). Incomplete compensation of CSF (H^+) in man during acclimatization to high altitude (4300 m). *J. appl. Physiol.* **38**, 1067–1072.

GILL, M. B., MILLEDGE, J. S., PUGH, L. G. C. E. & WEST, J. B. (1962). Alveolar gas composition at 21,000 to 25,700 ft. (6400–7830 m). *J. Physiol., Lond.* **163**, 373–377.

HEBBEL, R. P., EATON, J. W., KRONENBERG, R. S., ZANJANI, E. D., MOORE, L. G. & BERGER, E. M. (1978). Human llamas: Adaptation to altitude in subjects with high hemoglobin oxygen affinity. *J. Clin invest.* **62**, 593–597, 599–600.

KONTOS, H. A., LAVASSEUR, J. E., RICHARDSON, D. W., MAUCK, H. P. JR. & PATTERSON, J. L. (1967). Comparative circulatory responses to systemic hypoxia in man and in unanesthetized dog. *J. appl. Physiol.* **23**, 281–386.

MESSNER, R. (1979). *Everest: Expedition to the Ultimate*, trans. A. Salkeid, pp. 174–180. London: Kaye and Ward.

NIELSEN, M. & SMITH, H. (1952). Studies on the regulation of respiration in acute hypoxia. With an appendix on respiratory control during prolonged hypoxia. *Acta physiol. scand.* **24**, 293–313.

PUGH, L. G. C. E., GILL, M. B., LAHIRI, S., MILLEDGE, J. S., WARD, M. P. & WEST, J. B. (1964). Muscular exercise at great altitude. *J. appl. Physiol.* **19**, 431–440.

PUGH, L. G. C. E. (1964*a*). Cardiac output in muscular exercise at 5800 m. (19,000 ft.). *J. appl. Physiol.* **19**, 441–447.

PUGH, L. G. C. E. (1964*b*). Animals in high altitudes: Man above 5,000 meters – Mountain exploration. In: *Handbook of Physiology*, Sect. 4: *Adaptation to the Environment* (ed. D. B. Dill), pp. 861–868. American Physiological Society, Washington, D.C.

RAHN, H. & OTIS, A. B. (1949). Man's respiratory response during and after acclimatization to high altitude. *Am. J. Physiol.* **157**, 445–449, 460–462.

SEVERINGHAUS, J. W., MITCHELL, R. A., RICHARDSON, B. W. & SINGER, M. M. (1963). Respiratory control at high altitude suggesting active transport regulation at CSF pH. *J. appl. Physiol.* **18**, 1155–1166.

VOGEL, J. A. & HARRIS, C. W. (1967). Cardiopulmonary responses of resting man during early exposure to high altitude. *J. appl. Physiol.* **22**, 1124–1128.

WAGNER, P. D. (1977). Diffusion and chemical reaction in pulmonary gas exchange. *Physiol. Rev.* **57**, 257–312.

WEST, J. B. (1962). Diffusing capacity of the lung for carbon monoxide at high altitude. *J. appl. Physiol.* **17**, 421–426.

WEST, J. B. & WAGNER, P. D. (1980). Predicted gas exchange on the summit of Mt. Everest. *Respir. Physiol.* **42**, 1–16.

WINSLOW, R. M., STATHAM, B., GIBSON, C., DIXON, E., MONGE, C., MOREN, O. & DEBROT, J. (1979). Improved oxygen delivery after phlebotomy in polycythemic natives of high altitude. *Blood* **54**, suppl., 1, 61A.