Review article

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Onset of respiration at birth*

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The mechanisms which underlie the onset of respiration at birth are of common interest to the paediatrician, the obstetrician, and the physiologist. If respiration does not start shortly after birth, then the newborn is in a precarious position with a rapidly falling placental gas exchange and a not yet developed pulmonary gas exchange. And if this insult is added to that of a difficult labour and delivery, it is scarcely surprising that if the fetus survives, it does so with some form of neurological deficit. Thus the discovery of how the fetus resists hypoxia and of how breathing starts at birth is not simply a problem of interest to physiologists; rather, it can be considered a part of a wider strategy of research aimed at reducing the incidence of crippling diseases in children.

There are two widely held hypotheses which are invoked to explain the events at birth. The first suggests that the central respiratory neurones are shielded from the normal, i.e. newborn or adult, range of internal or external stimuli either because these stimuli are absent or attenuated by the congenital uterine environment, or because the receptors which detect and relay such information are themselves inhibited, or because a not yet fully organized system of synapses in the central nervous system effectively prevents this information from reaching and stimulating the respiratory neurones. Then, at birth there is a flood of new information from peripheral receptors and in some way this activates the central rhythm generator and the fetus starts to breathe. In this view, the fetus does not breathe before birth, or breathes for only part of the time because of insufficient respiratory and non-specific sensory input, and this view has additional interest since it implies that in the newborn and in the adult respiration is in part maintained by an adequate sensory input.

The second hypothesis was proposed by Barcroft (1946) on the basis of experiments carried out by Barron and himself in the 1930s (Barcroft and Barron, 1937a, b) in which the pattern of stimulation necessary to provoke respiration had been traced throughout gestation. It was Barcroft's view that respiration was actively inhibited in the mature fetus and that in some way this inhibition was lifted at birth and so the fetus was 'allowed' to breathe. It may be remarked in passing that this concept rests heavily on evidence that breathing was easily induced in the young fetus and not only has this not been confirmed (Dawes et al., 1972), but many observers have commented on the difficulty of distinguishing respiratory from nonspecific movements at this age, a point which will be discussed in a later section. Neither of these hypotheses is very precise about the mechanisms involved, but for the purposes of this discussion they are convenient points of departure.

One way in which the first hypothesis could be tested would be to draw up a list of the factors which are known to affect respiration in the adult and then to see whether or how far these factors are known to operate in the fetus. This has been done in Fig. 1., and from this it can be seen that the main respiratory excitatory activity arises from the peripheral arterial chemoreceptors, and the main inhibitory activity from the pulmonary stretch receptors and from various groups of receptors in the upper respiratory passages. To these receptors must be added a large variety of receptors whose afferent discharge acts upon respiration in a nonspecific way, e.g. from joints, skin, and viscera; and, since respiration is known to be under voluntary control, there must be provision for excitatory and inhibitory influences from the cortex. Finally, we must add the more direct actions of hypoxia, CO₂ and H⁺ upon the brain and various circulating substances, such as catecholamines. It will be apparent from the review which follows how little systematic work has been carried out in this field and in consequence how uncertain we remain about many of the factors which could influence respiration in a fundamental way.

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could be profound, is Purves, and sensitive to carotid body chemoreceptors to drive afferent in chemoreceptors Purves, Pao2 (Parker mmHg 50 respiration in numerous and- on the large changes arterial fetus affects this action of H+ upon the respiratory complex in the medulla, and numerous receptors including autonomic (ANS) receptors mediated in the spinal cord and cerebral cortex. Inhibitory (-) pathways arise from cortex, pulmonary stretch receptors, and upper respiratory passage receptors carried in the superior laryngeal nerve (SLN).

Arterial chemoreceptors and fetal response to hypoxia

It is clear that the fetus is protected in a number of ways from the harmful effects of hypoxia, whether this affects primarily the mother or the fetus itself. In the first place, the arrangement of blood vessels on the maternal and fetal side of the placenta ensures, as shown in Fig. 2, that in the face of large changes in maternal arterial oxygen tension, fetal arterial changes are comparatively small. Thus, if maternal Pao2 falls from normal levels by 40 or 50 mmHg, the fall in fetal Pao2 will be <10 mmHg (Parker and Purves, 1967). This fall in Pao2 would be detected by the peripheral chemoreceptors in the adult (Biscoe, Bradley, and Purves, 1970), and by increasing the receptor afferent discharge would constitute an increased drive to ventilation. In the fetus, however, the carotid body chemoreceptors do not appear to be sensitive to changes in Pao2 of this order (Biscoe, Purves, and Sampson, 1969) and so, unless hypoxia is profound, respiration will be unaffected. This could be considered as evidence supporting the first hypothesis, i.e. that the central respiratory neurones are unaffected because the peripheral receptors are themselves inhibited.

The second way in which the fetus is protected from the effects of hypoxia follows from the fact that, in contrast to the carotid body chemoreceptors, the aortic group is tonically active in the fetus and that its discharge increases with hypoxia and hypercapnia (Ponte and Purves, 1973). One of the consequences of its activation, e.g. by the asphyxia which accompanies occlusion of the umbilical cord (Fig. 3.), is a widespread increase in sympathetic discharge, and this rise in sympathetic activity has at least three important effects. First, there is evidence that as activity in the cervical sympathetic nerve increases, blood flow to the carotid body falls, chemoreceptor afferent discharge rises from its very low levels, and subsequently the receptors become sensitive to chemical changes in arterial blood as they are known to be shortly after birth (Biscoe and
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Fig. 3.—The consequences of occlusion of the umbilical vessels in a mature sheep fetus. Cord occlusion leads to a rise in systemic arterial pressure (BP), in venous pressure (VP), in arterial CO₂ pressure (Paco₂) and a fall in Pao₂. Activation of the aortic receptors brings about a second order excitation of the carotid body chemoreceptors and rise in activity in the sinus nerve (SN) through vasomotor neurones (VMN) in the brainstem.

Purves, 1967). This is a remarkable example of one group of receptors being activated by another, and as a consequence the carotid body chemoreceptors are able to contribute to the increased drive to ventilation after birth when under other circumstances, i.e. adult life, their afferent discharge would decline as arterial oxygen tension slowly rises. Secondly, it is known that a rise in sympathetic activity causes a fall in blood flow to a number of peripheral vascular beds, e.g. the hind-limb (Dawes et al., 1969). This means on the one hand that the amount of oxygen which is extracted from arterial blood will diminish and so assist in oxygen conservation, and on the other hand this relative ischaemia of a number of vascular beds will ensure, despite a fall in cardiac output (Rudolph and Heymann, 1973), that the level of umbilical blood flow to the placenta is maintained and that in consequence there is no drastic fall in the oxygen available to the fetus.

Activation of the aortic group of chemoreceptors is also likely to lead to another important component of the integrated vascular response of the fetus to hypoxia. It is known in the adult that the cerebral blood vessels are regulated in part by intrinsic mechanisms, and in part by the action of extrinsic nerves derived from the superior cervical ganglion (Kajikawa, 1969) and the VIIth cranial nerve (Chorobiski and Penfield, 1932). It is also known that stimulation of the peripheral arterial chemoreceptors brings about marked vasodilatation in the adult of cerebral blood vessels (Ponte and Purves, 1974), and it is very probable that this mechanism operates in the fetus, for it has been shown that the cerebrovascular dilatation which takes place in response to asphyxia is abolished if the vagi (which carry the afferent fibres from the aortic chemoreceptors) are cut (Purves and James, 1969). Excitation of the aortic chemoreceptors associated with a fall in arterial oxygen tension therefore brings about a widespread co-ordinated vascular response which has the overall effect of redistributing left ventricular output in favour of placenta and cerebral vessels. There is, however, a further bonus for the brain because, as shown in Fig. 4., the peculiar arrangement of blood flow through the right and left sides of the heart ensures that not only does the brain receive more blood but that this blood has the highest oxygen content and tension in the body.

The combination of all these factors, placental and fetal, thus ensures that the fetal brain which has only a limited capacity to respire anaerobically (Chesler and Himwich, 1944) is protected within limits from the harmful effects of hypoxia, which is probably the commonest hazard which the fetus faces in utero and at birth. It should be emphasized that in the fetus, unlike the adult, the response to hypoxia is entirely a vascular one and we know of two circumstances in

Fig. 4.—Showing the flow pathways of high P0₂ blood from umbilical vein and low P0₂ blood (hatched) from inferior and superior vena cavae (IVC, SVC). The aortic chemoreceptors (AC) are considered as altering vascular resistance in cerebral and aortic vascular beds. The diagram (lower right) shows how, with a fall in Pao₂, an increase in blood flow (a constant rate of metabolism) causes a narrowing of the A-V O₂ difference and maintenance of a normal tissue and venous P0₂.
which this vascular response fails or is inadequate. The first is when, as mentioned above, the vagi have been cut and when the cerebrovascular response to hypoxia is abolished. It is also probable that the same will happen if the reflex pathway from aortic chemoreceptors to cerebral vessels is interrupted at any other point, e.g. in the brainstem by trauma or haemorrhage. Secondly, the cerebral response to hypoxia does not occur or is attenuated if there is any sign of circulatory failure as shown by a spontaneously falling blood pressure, PaO₂, pH, and a rise in Paco₂. There may very well be other situations in which the cerebral response is inadequate or fails: but whatever the precipitating factor the effect is the same, namely increased vulnerability of the brain and in particular those parts having a high oxygen uptake, i.e. cortex and basal ganglia. In the absence of an adequate oxygen supply, the stage is then set for irreversible brain damage.

Pulmonary stretch and other receptors

It might be thought that since respiratory activity is so slight in the fetus, activity from pulmonary stretch receptors which respond to inflation of the lungs would be correspondingly scanty. This is not so and in fact these receptors discharge remarkably regularly (Fig. 5) and with a frequency which is close to that observed at peak inflation in the spontaneously breathing newborn lamb. Since it is known that these receptors inhibit respiration in the adult of most species and even more powerfully in the newborn, it is natural to inquire whether they have a similar effect in the fetus. There is some evidence which suggests that they do in fact have such an effect. First, it has been shown that if the fetuses are sufficiently aroused, deflation of the lungs (by withdrawing fluid from the trachea) causes a fall in receptor discharge and the onset of respiratory movements. If spontaneous movements are present, they can be abolished or reduced in frequency by inflating the lungs, which increases the receptor discharge. Secondly, if conduction in the vagus nerves is temporarily blocked by the application of a small direct current, respiratory movements are induced (Bystrzycka, Nail, and Purves, 1973). Thirdly, it has been shown that if the umbilical cord is temporarily occluded, activity from these pulmonary stretch receptors at first increases and then falls rapidly to zero at or about the time of the first breath (Ponte and Purves, 1973). Another important point is that if respiratory movements occur, the changes in intrathoracic pressure are accompanied by only trivial changes in receptor discharge when compared to the changes seen with air-filled lungs. It is presumed that the inertness of the fetal lung and the relatively high viscosity of tracheal fluid limit the amplitude of the fluctuation of receptor discharge, and this means that even with respiratory movements a high level of inhibitory discharge is maintained. The observation that this discharge falls to zero with the first breath is a remarkable example of an inhibitory process itself being inhibited at birth, and this would provide some support for Barcroft's hypothesis.

Another possible source of respiratory inhibition is from receptors in the upper respiratory passages which are known to inhibit respiration when stimulated with fluid (Angell James and Daly, 1972).

Fig. 5.—On the right (a) the discharge from a pulmonary stretch receptor in a mature sheep fetus measured in the vagus nerve at normal intrapulmonary pressure, and (b) one higher level to show an increase in frequency. On the left, interval histograms from 3 such receptors firing at different frequencies to show the regularity of the discharge. (Reprinted with permission from Ponte and Purves, 1973.)
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This possibility must be taken seriously because in utero the fetal trachea is full of fluid and its face is surrounded by amniotic fluid. It has certainly been confirmed that respiratory movements in the fetus can be reduced or inhibited if the fetal snout is placed in a stream of flowing water (Tchobrousky, Merlet and Ray, 1969) or if water is caused to flow through the fetal larynx (Fig. 6), and it has further been shown that this last manoeuvre in both fetus and newborn is associated with abolition of phrenic and medullary inspiratory unit discharge and enhancement of medullary expiratory unit discharge (Bystrzycka et al., 1973). However, these workers also noted that the fall in discharge was transient despite longer term application of the stimulus, and this might suggest that the receptors involved adapt quickly and are therefore unlikely to be responsible for long-term respiratory inhibition in the fetus. This possibility is reinforced by the observation of Johnson, Robinson, and Salisbury (1973) that whereas water and to a lesser extent 0.9% NaCl, placed near the laryngeal inlet in the newborn lamb, do inhibit respiration, tracheal or amniotic fluid have no such effect. On balance, therefore, the presence of fluid in the fetal trachea or around its face is unlikely to cause respiratory inhibition. However, the presence of water or saline in the larynx of the newborn could be a potent source of respiratory depression.

Of the other nonspecific reflexes which might affect fetal respiration, virtually nothing is known with one exception. This is the effect of altered environmental temperature. It has been shown by Dawes (1968) that if the skin of an exteriorized sheep fetus is cooled, respiratory movements can be elicited with ease and they disappear when the skin is rewarmed. Similarly it has been shown that if babies (Oliver, 1963) or newborn lambs (Harned, Herrington, and Ferreiro, 1970) are placed in warm water (38–39 °C), which not only stimulates skin temperature receptors but also prevents evaporative cooling, respiration is reduced by large amounts. We have confirmed this point and a typical response obtained in a newly born lamb immersed in warm water up to its neck is shown in Fig. 7. The rapid fall in ventilation with immersion and reappearance of respiration when the lamb was removed from water is obvious. Possibly of equal interest was the observation that when the lamb was placed in water it went limp and atonic and it failed to make any

![Figure 6](http://adc.bmj.com/figures/6.png)

**FIG. 6.**—Effect of flowing tap water at 21 °C retrogradely through the larynx in an 18-hour-old lamb (A and B) and in a sheep fetus, 147 days' gestational age (C). In each trace water flowed for the period indicated by arrows. In the lamb, the effect of water is shown upon medullary unit and phrenic nerve activity and in B, in addition, conduction in the vagi was blocked by a small DC, indicating that the enhancement of expiratory unit activity was not mediated by receptors whose afferents run in the vagi. In C, the effect of water is shown upon tracheal pressure and phrenic nerve discharge during a period of spontaneous respiratory movements.
withdrawal response to a mildly painful stimulus, i.e. pinching the hind foot. This indicates that the reduction in ventilation was not selective but formed part of a much wider motor and sensory depression. From these observations it may be concluded that the warm wet womb could well contribute to the long-term inhibition of fetal respiration and that the birth of the animal into the larger (and colder) world with a wet skin must constitute a powerful stimulus to breathing. In this connexion, the otherwise pointless reflex consisting of an involuntary gasp in the adult when the skin is suddenly cooled with water (Keatinge and Nadel, 1965) could be the vestige of a very important reflex at birth.

**Fig. 7.—Tracings of respiration in 2 lambs shortly after birth showing the changes which occurred when the lambs were immersed up to their necks in water at 38 to 39 °C as indicated by the ‘in’ and ‘out’ marks. Trace B shows, in addition, the lack of any response when the foot was pinched.**

### Central respiratory activity

It would be ideal if activity in brain stem units and in peripheral nerves could be recorded continuously in the fetus while in the uterus because this would confirm beyond doubt the medullary origin of thoracic respiratory movements, and would also allow a careful analysis of the organization of medullary respiratory units and the changes at central level which occur at birth. Indeed, the moment of birth may prove to be a unique opportunity to study the nature of the respiratory rhythm generator in the brainstem. At the moment, however, this type of study is not possible, for though there have been important developments in the techniques for recording from cortical units in awake cats and transmitting by telemetry, it is likely to be some time before units in the brainstem of the fetus can be held and activity recorded for hours or days in the latter part of gestation.

However, a start has been made in the exteriorized fetus and though the results of this study in which medullary activity was recorded in parallel with phrenic nerve activity before and after birth (Bystrzycka *et al.*, 1973) may not be totally applicable to the fetus in utero, the results are of interest and may be summarized thus. During a systematic study of an area rostral and caudal to the obex, the number of active units encountered was not less than that observed in comparable experiments in the newborn lamb and adult cat. For the greater part of the time, these units discharge tonically, there being neither discernible rhythm nor any discharge in the phrenic nerve. However, when respiratory thoracic movements were present spontaneously or after occlusion of the umbilical cord, these movements were invariably accompanied by phasic discharge in the phrenic nerve and in the medulla, groups of units which had hitherto been silent now started to discharge in phase with the phrenic, while other units which had been firing tonically were now phasically inhibited. From their relation to the phrenic nerve discharge, these units were identified as being inspiratory and expiratory, respectively. A third group of tonically active units were unaffected by the onset of respiratory movements.

These observations are important for a number of reasons. First, they indicate that any suppression of respiratory thoracic movements is not likely to be due to an inhibitory process at spinal level: on the contrary, the suppression of the rhythm generator or other fundamental part of the respiratory circuit appears to be at medullary level or above. Secondly, the pattern of respiratory inhibition, that is the inhibition of inspiratory units and the apparently uninhibited discharge of the expiratory units, is very similar to that seen during severe hypocapnia (Bystrzycka *et al.*, 1969) or during barbiturate narcosis (Robson, Houseley, and Solis-Quiroga, 1963) and in the experiments cited above where respiration in the fetus and newborn was inhibited transiently by the presence of water near the laryngeal inlet. In all these situations it appears that the respiratory rhythm generator is switched off in the 'expiratory' position. By itself, this does not indicate whether the suppression of respiration is due to activation of a specific inhibitory pathway, e.g. that from pulmonary stretch receptors, or whether it is due to the absence of adequate excitatory activity.

These experiments were extended to show that if the umbilical cord was occluded permanently, the pattern of discharge of medullary units underwent a slow progressive change which was reflected in the discharge from phrenic motor neurones. The first respiratory discharges were abrupt, lasting 4/500 msec with activation of inspiratory units in the medulla and phrenic neurones, and a corresponding phasic inhibition of expiratory neurones, which, however, continued to fire tonically throughout the lengthy expiratory pause of 1·5 to 2·0 seconds. By
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stages, the inspiratory unit discharge became less abrupt with a more even inter-spike interval and the inspiratory duration gradually increased so that by 30 to 60 minutes after the first breath, inspiration occupied just less than half the respiratory cycle. At the same time, respiratory frequency gradually increased from 10 to 15 to 30 to 40 per minute. This sequence follows very closely, in neurophysiological terms, the meticulous description of the onset of respiration in the sheep given by Barcroft (1946); and it may well represent the modulation of a rather primitive medullary rhythm by integrating activity from the upper medulla and pons, and it may be assumed that during this period shortly after birth the medullary respiratory neurones are for the first time experiencing and having to accommodate to activity from the carotid body chemoreceptors, phasic activity from pulmonary stretch receptors, and activity from the cortex and numerous peripheral receptors. It should be emphasized that this transition from the "gasping" type of respiration, seen in the fetus and immediately after birth, to the smoother and integrated type is essential from the point of view of adequate pulmonary gas exchange and the mechanisms which are involved will require careful analysis over the next few years.

Respiratory movements in the fetus

There is a large body of literature on fetal respiratory movements, but it has to be said that much of it—particularly the earlier papers—is of limited value since the authors failed to indicate how they distinguished respiratory from nonspecific movements and they rarely defined the chemical condition of mother or fetus. Thus, it is possible to conclude from this literature that maternal hypoxia excites, depresses, or has no effect upon fetal respiratory movements. It should be emphasized at this point that there are real difficulties in the recognition and interpretation of fetal respiratory movements. Thus in experiments which rely entirely upon the visual observation of the fetus and its chest wall, it may be difficult if not impossible to distinguish contraction of intercostal muscles and diaphragm from the more general writhing and jerky movements of the fetus, and this difficulty becomes more acute the younger the fetus. A second difficulty arises in those experiments where contraction of respiratory muscles is inferred from pressure or flow measurements of tracheal fluid. Here, fluctuations of the pressure/flow record due to genuine respiratory muscle contraction have to be distinguished from contractions of abdominal or scalene or other muscles, and the faithfulness with which pressure fluctuations can be transmitted in fluid-filled lungs can be shown simply by flicking the chest wall or abdomen in the exteriorized fetus and observing the damped oscillatory response in a tracheal pressure transducer—the analogue of a test which every medical student learns for the detection of excess peritoneal fluid.

With these qualifications in mind, there appear to be two types of respiratory movement in the fetus. The first has been observed many times in the exteriorized fetus. Typically, such movements are regular but poorly maintained, having a frequency of 3 to 15 per minute and are associated with large intrathoracic pressure fluctuations of \( \geq 20 \) mmHg. These movements are invariably associated with phasic discharge in phrenic motor neurones whose characteristics are those described in the previous section for inspiratory units in the medulla. Because the phrenic discharge is so abrupt, these movements of the chest wall are associated with equally abrupt changes in tracheal pressure and because of this, they have been labelled as "gasping". As has been described in a previous section, they can be affected by vagal activity and by changes in skin temperature, and possibly their most striking feature is the close relation to the degree of arousal of the fetus. Thus, when the fetus is first exteriorized it is clearly aroused, as is shown by frequent spontaneous limb movements, swallowing, and a brisk withdrawal response to a mildly painful stimulus. During this phase respiratory movements are common and relatively well maintained. In our experience, the fetus then becomes progressively more difficult to arouse; there are few spontaneous movements, little evidence of sensibility; respiratory movements are rare and can be elicited with a relatively long latent period with occlusion of the umbilical cord. This pattern of response is not due to deterioration of the fetus as judged by measurements of systemic arterial pressure and blood gas tensions and can easily be reversed with prolonged occlusion of the umbilical cord.

The second type of respiratory movement in the fetus was described by Merlet et al. (1970) and by Dawes et al. (1970), and the features of this type of movement have been amplified by Dawes et al. (1972) and Dawes (1973). Unlike the first type of movement, this type of respiratory movement is more difficult to observe in the exteriorized fetus, particularly if it is restrained, which means in effect that it will be impossible to investigate the neural sequences except in utero. Even in utero this type of movement can be abolished by manipulation, so that hours or days have to elapse after placement of transducers before reliable recordings can be made. From measurements of flow/pressure of tracheal
fluid made in utero, it appears that movements are maintained for periods of up to an hour at a time and that they occur for 40% or more of the 24 hours. In human fetuses, where such movements have been inferred from external ultrasonic probe measurements, they may occur for 80% of the time (Boddy, Dawes, and Robinson, 1973).

This type of movement, as shown in Fig. 8, almost exactly coincides with the arousal type of electrocorticogram which is commonly seen in the adult during rapid eye movement sleep. From the published records it appears that the frequency of this second type of movement is considerably greater than the first, i.e. up to 4 Hz has been recorded; it is less regular in both depth and frequency and there has not yet been any demonstration of how this pattern of movement merges with that after birth. These movements are not affected by activity conducted in the vagus nerves and so far there have been no parallel measurements of respiratory muscle electromyography, and in the only study in which phrenic nerve activity has been measured in utero (A. Bahoric and V. Chernick, personal communication, 1973) no discharge comparable to this type of movement has been observed.

The importance of this observation cannot be overestimated because if with further investigation these movements can be shown to be respiratory in origin beyond reasonable doubt, then the whole question of how respiration starts at birth has to be looked at in a new way. Instead of asking why or how respiration starts at birth, it is necessary to assume that it simply continues but with a new pattern, and those newborn animals who failed to breathe could then be considered as showing severe depression of established respiration. But just because it is such an important question, it is necessary to be cautious about the origin and physiological significance of the second type of respiratory movement. For example, in the absence of any direct evidence about the neural origin of these movements, it could be that these movements represent irregular activation of α-motor neurones in general as part of brainstem irradiation and of which the arousal type of electrocorticogram is also an index. It would therefore be interesting to see whether an electromyogram of a non-respiratory muscle, e.g. temporalis, exhibits a similar rhythm, and a simple correlation procedure would show whether the muscle activation was random or whether the activation was phasic and co-ordinated, suggesting a rhythmic phrenic and medullary drive.

**Respiration and arousal**

Despite the differences between the two types of respiratory movement outlined in the last section and the uncertainty about their origins, it should be emphasized that a feature common to both types is their manifest relation to the arousal of the animal. In this connexion it is important to realize that there are two quite separate components to the regulation of respiration. The one is automatic in the sense that we are largely unaware of it; it persists in sleep, in hypnosis, and down to all but the deepest levels of anaesthesia. This component is largely concerned with subserving the metabolic requirements of the body and assisting in acid-base homeostasis. The second component may be defined as behavioural in that it comprises the respiratory responses to cortical stimuli, special sensory stimuli, e.g. auditory, vocalization requirements, and a wide variety of emotional situations, e.g. anxiety, preparedness for exercise, sexual arousal. It is important to distinguish these components since there is clear evidence that they are served by different pathways.

![Fig. 8](image_url)

*Fig. 8.* From above down, tracings of electrocorticogram, tracheal pressure, tracheal flow, rectified and integrated flow to give the volume of tracheal flow. *t = 10 min.* From a fetal sheep, 140 days' gestational age, 9-10 days after implantation of recording instruments and 3-4 days before labour. (Courtesy of G. S. Dawes and Cambridge University Press.)
and therefore are likely to be affected separately in disease (Plum, 1970). Furthermore, it is likely that in real life (i.e. outside the respiratory physiological laboratory) respiration is more obviously affected by nonspecific stimulation—or lack of it—than by changes in blood gas tensions. For example, external stimulation such as noise or pain may override the metabolic respiratory component. On other occasions the two components may be affected together and potentiate one another as in the respiratory response to active voluntary exercise where, in addition to chemical factors, there is activation of nonspecific pathways from muscles and joints, a rise in temperature, and most probably a cerebral arousal component. Conversely, in such states as 'transcendental meditation' there is not only a fall in overall metabolic rate as is shown by the fall in O₂ uptake and CO₂ output, but there is evidence of motor depression, shown by atony, limpness, and disappearance of the residual electromyogram in limb muscles; it is to be presumed that all these features follow from the lack of external stimulation which the practiced meditator can exclude (Wallace, Benson, and Wilson, 1971).

The relevance of this to the fetus and newborn should be obvious. Not only have examples been given above which indicate the very close relation between respiratory activity and arousal of the fetus, but it is probable that at the moment of birth respiration is maintained more by nonspecific external and internal stimuli and specific 'respiratory' stimuli. That being so, the most important question for the physiologist is how such nonspecific afferent activity affects the central respiratory neurones. One suggestion has been given by Burns (1963) on the basis of experiments by Burns and Salmoiraghi (1960) that such nonspecific afferent activity provides important 'noise' which in some unspecified way maintains a rhythmic discharge in respiratory neurones. It is not immediately obvious how such a concept arises from these experiments which, in any case, can be otherwise interpreted; nor do they suggest how such a proposed relation might be tested experimentally. An alternative approach is to consider the involvement of the reticular formation which, as shown in Fig. 9, acts as an important relay between cortex and spinal cord. The available evidence suggests that the reticular formation acts in parallel and receives innervation from the more direct corticospinal and spinothalamic tracts and the peculiar arrangement of its cells allows very marked convergence, i.e. the discharge from different types of receptors and from different parts of the body can impinge upon and drive one cell. Further, as a result of this arrangement, the reticular formation can affect wide areas of the sensory and motor cortex rather than discrete parts of it and so gives rise to arousal or inhibition. It is this last property of the reticular formation that gives it such importance in sleep and allied states.

What is not known and what would be the most important single experiment to carry out is to determine how or whether activation of the reticular formation affects respiratory neurones, for it will be observed from Fig. 9 how intimate is the relation between respiratory neurones and the reticular formation. The results of such an experiment would be important not only for the immediate question of how respiration is affected at birth, but also the more general question of how respiration is affected in any state of arousal.

There is one final point which is related to respiration shortly after birth and which is often overlooked. It is often assumed that because a process is automatic—whether it be respiration or the control of the heart beat—no learning is involved. Not only is this untrue with respect to many processes controlled by the autonomic nervous system (DiCara and Miller, 1968), but it is unlikely to be true with respect to respiration in the newborn. Thus, whether the fetus has been making respiratory movements for 5 or 85% of the time in utero, at the moment of birth the respiratory system has to accommodate to a completely new set of respiratory

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**Fig. 9.—Representation of the pathways involved between motor (M) and sensory (S) cortex, spinal cord and facilitator (rostral), and inhibitor (caudal) parts of the reticulo-activating system (RAS). The distribution of respiratory neurones is indicated by .**

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and nonrespiratory inputs. While it is perfectly true that the newborn responds as does the adult to changes in its internal chemical environment (Burns, 1966b, b, c), and that there are closely defined relations between respiration and both metabolism and temperature (Cross, Dawes, and Mott, 1959), this evidence does not by itself indicate whether the respiratory system is stable, i.e. whether the learning process is complete. On the contrary, there is evidence which suggests that it is not, for example the frequency of apnoeic spells and the relative ease with which periodic respiration can be induced (Cross and Oppé, 1952). This question has scarcely been tackled, though a start has been made by Hathorn (1973) using a form of spectral analysis. This question cannot be considered simply as a form of academic curiosity for there is a real possibility that a proportion of babies do have a learning defect and in consequence a somewhat unstable respiratory control system. This might normally pass unnoticed, but when the system is faced with a certain but as yet unidentified set of circumstances, it fails and the baby dies. That this should happen in an otherwise healthy baby which has successfully negotiated the other hurdles placed before it during delivery and at birth is true tragedy. And this appears to be one of the many areas where collaboration between paediatrician and physiologist would be very profitable.

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References


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Purves, M. J. (1966a). Respiratory and circulatory effects of breathing 100% oxygen in the newborn lamb before and after denervation of the carotid chemoreceptors. *Journal of Physiology, 185*, 42.


