

Hypoxic Apnea and Gasping

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ABSTRACT We have tested the hypothesis that severe hypoxia causes apnea, regardless of the arterial CO_2 and pH, and that extreme hypoxia causes gasping. Acute experiments with airway occlusion and with low inspired oxygen (FIO_2) were performed on anesthetized adult dogs and monkeys. Arterial oxygen saturation was recorded continuously with fiberoptic oximetry, and PCO_2 by an electrode catheter. In addition, blood samples were obtained for PO_2 , PCO_2 , and pH. Apnea was induced regularly when the PaO_2 fell below 10 torr, whether the Paco_2 was high with asphyxia (63 torr) or low (26 torr) with low FIO_2 . Similarly, the PaO_2 at apnea was the same whether the pH was 7.17 with asphyxic hypoxia or 7.46 with hypoxic hypoxia. Gasping occurred at even lower PaO_2 (below 5 torr) after 1 or 2 min of apnea. Gasping promptly restored the PaO_2 to levels of moderate hypoxia (over 30 torr) which permitted resumption of regular respiration, with gradual elimination of the gasping. Fetal monkeys at term were studied in a similar manner from the moment of cord clamping. Their blood gases with apnea were quite similar to adult values in the narrow range of PaO_2 and the wide range of Paco_2 and pH. In the fetus, gasping was less immediately effective in improving arterial oxygen, but more persistent than in the adult. Regular respirations would not develop in the absence of oxygen in either the fetus or adult animal.

INTRODUCTION

Apnea is a universal phenomenon in mammals, before birth and with dying. Gasping is also nearly universal at the beginning and end of life. Although these phenomena are literally of vital interest to human physiology and clinical medicine, they have rarely been studied in man, except for posthyperventilation apnea (1, 2). Animal studies of apnea and gasping are infrequent as well, and usually include experiments on fetuses, in-

volving the first breath. The basis for apnea before birth has not been proven; the first breath at birth has been thought to involve either hypercarbia or hypoxia or both (3, 4).

Asphyxiation involves hypoxia and hypercarbia, but a primary role for hypoxia in apnea has received little study. Perhaps this stems from the concepts of negative feedback inherent in most models of ventilatory control (5-7). These models are based on a linear relationship between Paco_2 and ventilation. When PaO_2 was included in the quantitative description of ventilation by Gray (8), or in subsequent computer-based models (9, 10), that relationship was also a conventional negative feedback: the lower the PaO_2 , the greater the ventilatory response, mediated through the carotid body (11). Only in the first few days after birth in the preterm infant has a potentially positive feedback mechanism been demonstrated (12): a mildly reduced inspired oxygen content (FIO_2 of 15%) failed to stimulate respiration, and occasionally caused transient apnea. Until 1975, there were only nonquantitative references to the depressing effects of hypoxia on the respiratory center (13), and apnea during asphyxia was described merely as exhaustion or "failure" of the system by Milhorn (7). This year, Morrill et al. reported that 19 torr is the level of alveolar PO_2 at which depression of ventilation occurs, but they did not continue to the point of apnea (14).

In our recent studies in animal models of crib death, incidental observations suggested the possibility that severe hypoxia could produce apnea in mature rats, and that gasping occurred at an extreme stage of asphyxia (15, 16). The present study was designed to test the hypothesis that severe hypoxia causes apnea, profound hypoxia causes gasping, and restoration of an adequate PaO_2 is crucial to the restoration of regular respiration.

METHODS

25 adult dogs of unselected breed and sex, 4 adult *Macaca mulatta* monkeys, and 5 neonatal monkeys were studied. The dogs were anesthetized with morphine, 2 mg/kg i.m., fol-

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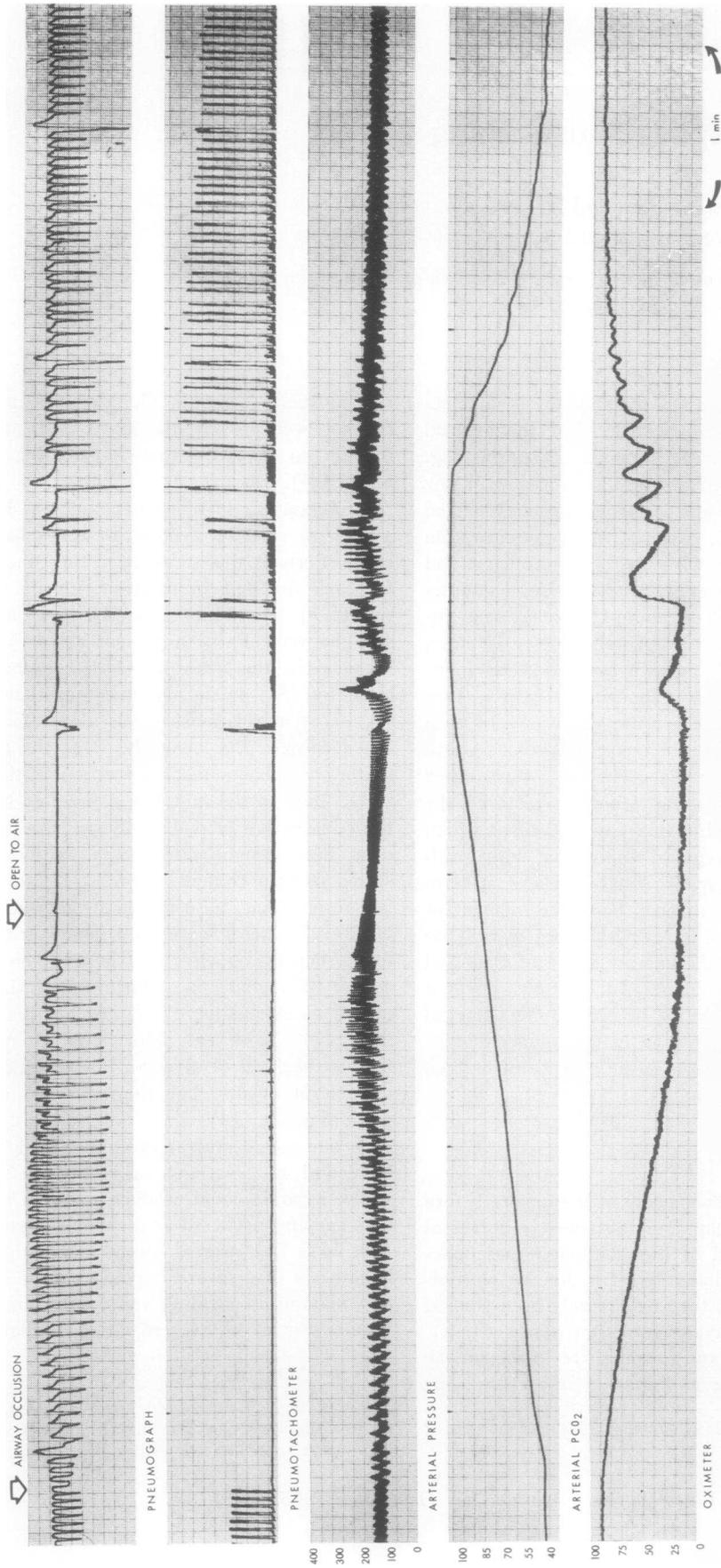


FIGURE 1 Record of respiration with a pneumograph, airway flow with a pneumotachometer, arterial pressure (torr), P_{aCO_2} (torr), and arterial oxygen saturation (percent) in a dog subjected to airway occlusion. After apnea occurred, the airway was opened to room air. Apnea was interrupted after 80 s by spontaneous

gaspings, which produced an increase in saturation, and after two further apneic episodes, regular respirations resumed when the oxygen saturation had reached a level of 40–50%. High amplitude gasps gradually decrease in frequency but are still occurring when the arterial saturation has returned to normal.

lowed in 30 min by pentobarbital, 15 mg/kg i.v. (one-half the full dose). An additional five dogs were premedicated with fentanyl and droperidol (Innovar-Vet), 0.1 ml/kg i.m., and anesthetized with chloralose, 75 mg/kg i.v., to investigate the effects of different anesthetics. The adult monkeys were premedicated with 0.1 mg atropine and anesthetized with 7.5 mg/kg ketamine. In all of these animals, the femoral arteries were exposed; one artery was cannulated with a 5.5-Fr fiberoptic catheter (Edwards Laboratories, Santa Ana, Calif.); the contralateral artery was catheterized with a flexible CO₂ electrode (General Electric Co., Milwaukee, Wisc.). One-half of the diameter of the fiberoptic catheter consists of fibers and one-half in a lumen, permitting pressure recording and blood sampling. P_{O₂}, P_{CO₂}, and pH were measured with an Instrumentation Laboratory pH/Gas Analyzer (Instrumentation Laboratory, Inc., Lexington, Mass.). Respiration was recorded with a pneumograph around the mid-thorax, and airway flow was measured with a Monel screen pneumotachograph. An electrocardiogram was also recorded, usually from transthoracic electrodes.

To investigate apnea and gasping in the fetal and neonatal state, we delivered five monkeys (*M. mulatta*) at term by cesarean section. The mother was premedicated with atropine and anesthesia induced with pentothal i.v. A light level of general anesthesia was maintained with halothane. The infant monkey was extracted, and a condom filled with warm saline was immediately placed over its head. Cooling was avoided by the use of radiant heat, which permitted easy access for introduction of catheters. The infant monkey was placed immediately adjacent to the mother, avoiding kinking of the umbilical vessels and any stimulation that might lead to spontaneous respiration. The groin was gently infiltrated with a local anesthetic and the femoral arteries were exposed. A 4-Fr fiberoptic catheter was inserted in one artery and a polyethylene cannula in the other. In two of the infant animals, the larger 5.5-Fr fiberoptic catheter was placed in the abdominal aorta, which required a midline incision and a purse-string opening for catheter insertion. Because of the limitation of size, it was not possible to place an intra-arterial CO₂ needle, but arterial blood sampling was performed for P_{O₂}, P_{CO₂}, and pH determinations.

The P_{CO₂} electrode catheter has a lag time with an abrupt change in P_{CO₂} of 1 s, and the rise time to 90% of full response was 2 s. The fiberoptic oximeter (Physio-Control, Seattle, Wash.) uses the reflectance method, and the light source is a photodiode. The reflectances for total hemoglobin and oxyhemoglobin are continuously compared and the ratio is converted to percent saturation, expressed digitally and with analog-output for a recorder. The instrument has a choice of two time constants; for our experiments we utilized the shorter time constant which allowed a 90% response time in less than 1 s. Both oximeter and CO₂ catheter electronic amplifiers produce linear recordings. Calibration of both was done for each animal experiment by using the results from the Instrumentation Laboratory Analyzer.

Two forms of hypoxia involving opposite trends in P_{CO₂} were alternated as the initial intervention: hypoxic hypoxia and asphyxic hypoxia. Inhalation of gas with low oxygen stimulated hyperventilation, resulting in a decrease in P_{CO₂} and a rise in pH. The hypoxic gas mixture was continued until apnea occurred. Arterial blood samples were obtained at the moment of apnea for P_{O₂}, P_{CO₂}, and pH. At that point, room air was substituted to study the effectiveness of subsequent gasping. The asphyxial method involved occlu-

sion of the airway until respirations had ceased. In the adult animals, a cuffed endotracheal tube was utilized, with the cuff inflated. Once apnea had occurred, the airway was opened, allowing spontaneous gasping to resuscitate the animal, if possible. Finally, apnea was produced, either through asphyxia or hypoxia, followed by a low F_{I_{O₂}} until death occurred.

After cannulation and a period for control recordings, the protocol for the fetal monkeys was removal of the condom from the head, and after 1 min, abrupt clamping of the umbilical cord. Results were complete in four of the five; the fifth monkey began spontaneous respiration before preparations were complete.

In the statistical analysis, only the results from discrete blood samples were used. The means and SEM were tabulated. The data from adult dogs and adult monkeys were combined since there were no detectable differences in the two groups. The comparison of means for different anesthetic combinations is based on a separate set of 10 animals, 5 in each category. The means between groups with different treatments were compared for significance with the Student's *t* test.

RESULTS

When the airway was occluded (Fig. 1), increased ventilatory effort was followed by relatively abrupt apnea after 127±13 s (mean and SE) in the adult animals. At the onset of asphyxic apnea, the P_{aO₂} was 8.1±0.9 torr, the P_{aCO₂} was 63±3.1 torr, and the pH was 7.17±0.02 (Table I). The airway was reopened as soon as apnea occurred, but no respirations occurred for a mean interval of 151±23 s. Gasping, characterized by infrequent, high amplitude inspiratory efforts, occurred in all but one dog, and in three of four adult monkeys. The gasp usually produced a sharp increase in arterial saturation, but two or three episodes of gasping were required to reestablish regular, more frequent respirations. Although gasping occurred with very few exceptions, successful autoresuscitation occurred in two-

TABLE I
Arterial Blood Gases at Onset of Apnea

	<i>n</i>	P _{aO₂} *	P _{aCO₂} *	pH*
Apnea with asphyxiation (adult animals)	21	8.1±0.9 <i>P</i> > 0.1‡	63±3.1 <i>P</i> > 0.1	7.17±0.02 <i>P</i> > 0.1
Apnea with low F _{I_{O₂}}	23	7.8±1.3 <i>P</i> > 0.1	26±1.6 <i>P</i> < 0.01	7.46±0.02 <i>P</i> < 0.01
Fetal state apnea	4	13.5±2.4 <i>P</i> > 0.1	79±13 <i>P</i> > 0.1	7.13±0.09 <i>P</i> > 0.1
Neonatal asphyxiation	5	8.4±1.5	64±11	7.19±0.07
Adult asphyxiation				
Morphine/Pentobarbital	5	9.5±1.6 <i>P</i> > 0.1	71±3.9 <i>P</i> > 0.1	7.21±0.03 <i>P</i> > 0.1
Innovar/Chloralose	5	10.6±2.1	66±5.4	7.18±0.03

* Mean ±SE.

‡ The *P* values for significance relate to successive vertical entries in the table (e.g. 7.8 compared to 8.1; the difference is not significantly different). Significant differences are generally defined as those with a *P* value less than 0.05.

thirds of the dogs, three of four adult monkeys, and all fetal monkeys.

Administering low FIO_2 (less than 6%) produced initial hyperventilation and then abrupt apnea at a mean PaO_2 of 7.8 ± 1.3 torr, a $Paco_2$ of 26 ± 1.6 torr, and a pH of 7.46 ± 0.02 (Table I). There was no significant difference from the PaO_2 found with asphyxic apnea, although the differences for $Paco_2$ and pH were highly significant ($P < 0.01$). After the occurrence of apnea, the animals were switched to room air. Apnea persisted for 1-3 min, usually terminated by a gasp. With a gasp, there was a steep rise in arterial oxygen saturation, the level achieved depending on how many gasps occurred. As in the asphyxiation experiments, regular respiration usually resumed after one to three episodes of gasping, but would not resume at all if the FIO_2 remained low.

The fetal recordings began with apnea (in four of the five experiments) in contrast to the adult animals in which apnea was induced with hypoxia. The resting arterial blood gases in the fetal monkeys demonstrated a wide range of Pco_2 and pH, but a relatively narrow range for PO_2 . The PaO_2 ranged from 9 to 20 torr, with a mean of 13.5 ± 2.4 . The pH varied from 6.95 to 7.34,

with a mean of 7.13 ± 0.09 ; the $Paco_2$ mean was 79 ± 13 , ranging from 51 to 104 torr. Although some of the fetuses could be considered compromised according to values found in chronic fetal monkey studies (17) none of the animals were gasping and all appeared stable. There were no significant differences upon comparison of the means with the means of PaO_2 , $Paco_2$, and pH from the adult animals with asphyxiation. After abrupt clamping of the umbilical cord, gasping occurred within 1-5 min (average of 3 min). Unlike the adult animals, there was no change in the arterial saturation after gasping for several minutes (Fig. 2), reflecting the presence of fluid in the fetal alveoli. Similarly, regular abdominal-type respirations did not develop in any of the fetal monkeys until there was an appreciable increase in the oximeter levels, requiring up to 30 min after gasping commenced. As the regular lower amplitude respiratory movements increased in frequency and amplitude, there was a corresponding decrease in frequency of gasping respirations. Discrete arterial samples, obtained at the time that there were infrequent gasps and regular abdominal breathing, yielded a mean PaO_2 of 43 torr, and ranged from 31 to 58. The $Paco_2$ again

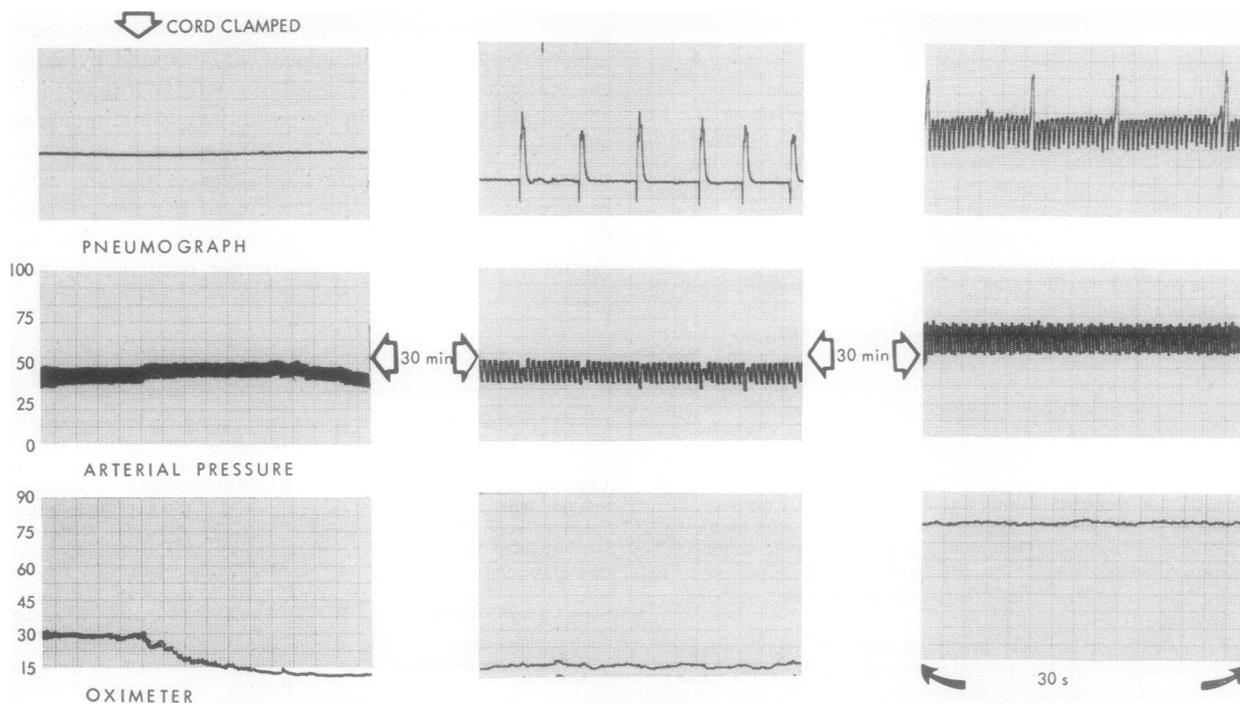


FIGURE 2 Record from a term monkey fetus delivered by section, after clamping of the umbilical cord. Arterial pressure is in torr and oxygen saturation is in percent. The first gasp occurred after 4 min. Regular, abdominal respirations are not evident until the last panel, by which time there was an appreciable increase in oxygen saturation. There was a gradual increase in amplitude of the regular respirations and a decrease in frequency of gasping.

showed a very wide range of 22-105 torr, with an average of 68.

The five fetal monkeys, with clamped cord and regular respirations, were then subjected to asphyxiation by nasal occlusion. Apnea occurred at a mean P_{aO_2} of 8.4 ± 1.5 torr, a P_{aCO_2} of 64 ± 11 , and a pH of 7.19 ± 0.07 . There were no significant differences when these means were compared with the means obtained in adult asphyxiated animals. When the airway was opened, gasping was quite effective in promptly raising the arterial oxygen saturation, in contrast to the earlier gasping after cord clamping in the same animal.

In all of the animals studied, fetal and adult, the animal was finally terminated by providing 100% nitrogen for inhalation after the primary apnea had occurred. Gasping occurred as before, but since the FIO_2 was unchanged, there was no improvement in the arterial saturation, and no regular respirations ever occurred subsequent to gasping. Gasping ceased within 1 min in the adult animals, followed soon by cardiac arrest, but gasping persisted for as much as 30 min in the neonatal animals. This was the only major difference between the neonatal and the older animals relative to apnea and gasping.

DISCUSSION

Sustained apnea was produced in our experiments at the same P_{aO_2} , with either asphyxiation or hypoxic hypoxia. With asphyxiation, the mean P_{aCO_2} was 63 and the pH was 7.17, in contrast to 26 and 7.46, respectively, for low FIO_2 . The nearly identical levels of P_{aO_2} at onset of apnea for the two groups thus suggests hypoxia as the primary basis for the apnea. This is in contrast to the claim by Honda et al. (18) that in dogs, even "during intense hypoxia, respiratory drive continues to be attributable to P_{CO_2} or CH , even when they have been reduced far below normal."

In either situation, with high or low CO_2 and hypoxic apnea, there was a period of apnea (after the cessation of breathing of 2-3 min duration) during which time the circulation was maintained with bradycardia and hypertension, a situation reminiscent of the dive reflex (19, 20). During the dive reflex, vasoconstriction and bradycardia conserve the oxygen for the cerebral and coronary circulation. As illustrated in Fig. 1, the arterial oxygen saturation changes very little during the apneic period; with discrete sampling, the P_{O_2} drops only 2 torr, and the P_{aCO_2} rises 4 torr. During this period of apnea, resuscitation may be readily accomplished, indicating that this form of apnea is not an irreversible "failure" of the system.

The situation in the fetus before birth is quite similar to this 2-min period of hypoxic apnea in the adult animals, except that the placental circulation permits sta-

bilization of the blood gases at that level. In our neonatal monkeys, the P_{aO_2} was not significantly different from the adult level at apnea, although in some of our monkeys, the P_{aO_2} was significantly below that reported in unanesthetized, chronically catheterized fetuses (17).

The most striking aspect of a gasp in the adult animal is seen in the continuous recordings of oxygen saturation and P_{aCO_2} : even one or two gasps are effective in restoring the arterial oxygen saturation, as long as the circulation is functioning, although there is little observable change in CO_2 . The presence of vasoconstriction makes the improvement in P_{aO_2} even more effective since the two vascular beds which are not constricted, and thus beneficiaries, are the cerebral and coronary circulations (19). The effectiveness of gasping in the fetus is greatly reduced in terms of oxygen rise, reflecting the fluid-filled lung. However, the durability of the gasp in the fetus is much greater than in the adult. When no inspired oxygen was supplied, the fetus continued to gasp for as much as 30 min before the cardiovascular system failed.

Whether gasping is successful in autoresuscitation may depend on the maturity of the subject, and also on the species. Adult rats were observed to revive themselves repeatedly (15), whereas adult dogs and monkeys were less successful. Whether permanent neurological deficits would have occurred in the older monkeys and dogs that successfully resuscitated themselves is a question unanswered by our experiments. Resuscitation by gasping in the human, other than in the neonate, is rare, and gasping is generally regarded as simply an agonal event; the gasp occurs too late for resuscitation due to either circulatory failure or to massive neurological insult from hypoxia. The human neonatal resistance to hypoxia, permitting successful autoresuscitation, may be pertinent to crib death. The first 3 or 4 wk of life are spared in that syndrome. It seems plausible that the neonatal resistance to hypoxia persists for that period in the human, and allows the apneic infant (20, 21) to revive after gasping occurs. The autopsy findings of victims of sudden infant death syndrome confirm their prior experience with hypoxic episodes (22).

There are few studies which have attempted to characterize or localize a center for gasping. *Dorland's Medical Dictionary* does not even list gasp. The Glossary Committee of the International Union of Physiological Sciences defined a gasp as "an abrupt, sudden transient inspiratory effort" (23). Legallois in 1812 (24) demonstrated gasping in a wide variety of animals, and the longer persistence of gasping in the drowning newborn, compared to older animals of the same species. Using a guillotine for sectioning, he con-

cluded that the mechanism for gasping was in the caudal portion of the medulla oblongata. Lumsden performed successive brain stem sections in cats in 1923, and could produce apneustic respirations by sectioning below the pons, gasping by sectioning in the upper or middle medulla, and complete cessation of all respirations by sectioning low in the spinal bulb (25). Hukuhara and colleagues found gasping could be produced in dogs by transecting the brain stem just caudal to the acoustic striae (26). Based on their electromyographic recordings, they felt that the gasping type of respiration could be identified by a sustained increase in neural activity to the expiratory muscles, which was abruptly interrupted by inspiratory activity. In our experiments, gasps were distinguished by a slower frequency, a higher amplitude, and a more prolonged expiratory phase.

Gasping in the fetus after interruption of the umbilical cord is not dependent upon peripheral chemoreceptors (27-29). Woodrum and Hodson, using sinoaortic denervated fetal lambs, have produced gasping with central perfusion of hypoxic, normocarbic blood.¹ Sodium cyanide is also capable of stimulating gasping in the apneic fetus with denervated peripheral chemoreceptors (30). Jansen and Chernick were able to localize the response to cyanide to the ventral medulla (31).

Gasping, once initiated by extremely low P_{O_2} , persists for some time after regular respirations resume, and gradually decreases in frequency, but not in amplitude. Although the P_{aO_2} may be restored, apparently there is a longer interval required for cellular recovery. Hukuhara et al. (26) suggested that there was neural inhibition of the gasping center by the normal respiratory center, based on the appearance of gasping with appropriate brain stem transection. From our studies, it seems more likely that the gasping center is relatively independent, and its threshold and subsequent frequency of firing are related to cellular P_{O_2} . If neural competition was effective, the long apneic interval (well over 60 s) before gasping in the asphyxiated adult is difficult to explain (Fig. 1). Similarly, the persistence of frequent gasping in the neonate (third panel of Fig. 2) in the face of a high frequency of regular respiration argues against neural inhibition.

Two forms of anesthesia were compared, and no difference was found between morphine-barbiturate anesthetic and chloralose, as far as the blood gases at the onset of apnea are concerned. We were reluctant to attempt these experiments without anesthesia, although the absolute blood gas values may have been different in the unanesthetized animal. Anesthesia does substan-

tially reduce hypoxic ventilatory drive (32), although chloralose does not change the P_{aO_2} at which central respiratory depression occurs in the dog, approximately 19 torr (14). This low threshold for depression may account for the brief interval we observed between slowing of respiration and apnea, and for the effectiveness of a gasp in restoring normal respiration, since restoration of a P_{O_2} over 20 would be effective.

The effects of hypoxia, viewed as three functionally and anatomically separate mechanisms, may resolve the apparent conflict between the reports of both depression and stimulation by hypoxia, and may explain the onset of breathing in the newborn, without requiring a control system unique to the fetus. Beginning with a normal P_{aO_2} and down to a P_{aO_2} of 20 torr, there is conventional negative feedback; i.e., the lower the P_{aO_2} the greater the stimulus from the sinoaortic chemoreceptors (11). At a level below 20, central hypoxic depression occurs, with a potentially positive feedback mechanism. At approximately 10 torr, apnea may occur, with relatively little transition between hyperpnea and cessation. Finally, with even more extreme hypoxia, gasping may originate from an extraordinarily hypoxia-resistant medullary center. Gasping persists until the arterial oxygen is sufficient to restore normal respiration, or until circulatory failure ends life.

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