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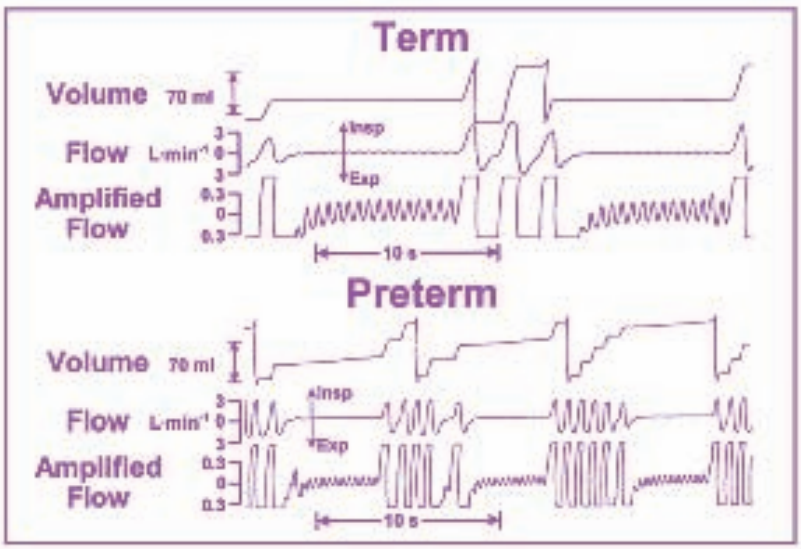
Respiratory Control and Disorders in the Newborn



edited by
Oommen P. Mathew

RESPIRATORY CONTROL AND DISORDERS IN THE NEWBORN

Edited by

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I want to note with sadness the passing of my former colleague, Giuseppe Sant'Ambrogio, M.D. He was not only an inspiration to many but, above all, a friend in the truest sense. His presence in the scientific community will be sorely missed. I dedicate this book to his memory.

INTRODUCTION

Newborn and infant mortality has been a plague of public health for centuries. However, during the 1900s, an extraordinary effort began to correct this disgraceful situation. Especially remarkable have been the accomplishments of the last 30 years or so. Although many challenges remain, very noticeable progress has been made relative to some specific causes of death in babies.

In the United States, neonatal respiratory distress syndrome (NRDS) was one of the main causes of death in premature newborns. However, an intensive research effort led to a major reduction of the number of deaths due to this condition—from about 55,000 per year in the 1960s to less than 5000 per year at the end of the twentieth century—and the number is still going down.

Paralleling the NRDS epidemic was that of sudden infant death syndrome (SIDS). Although some successes had occurred during the twentieth century, we really had to wait for a public health campaign, the "Back to Sleep" campaign, to witness more rapid declines.

In a way, NRDS and SIDS have some commonalities. NRDS relates to lung development and its respiratory function (i.e., gas exchange), whereas SIDS is one expression of dysfunction of the respiratory control system.

The respiratory machinery is one of the most complex of the human body. It has fascinated philosophers, teleologists, and biologists for a very long time, maybe beginning with the Chinese as far back as 2000 B.C. Erasistratus (around 304 B.C.) and then Gallen (around 130 A.D.) were the first to connect the lungs to the brain through "hollow" nerves, in which the blood was charged with "animal spirit." Since then, a long line of biologists have studied this machinery and its control. All this work led to the realization that the "hollow" nerves were not blood conduits at all, but "real" nerves conducting commands from the brain in response to stimuli from various parts of the body.

The first chapter of this new volume gives a panoramic view of respiratory control in the newborn. It is only the beginning of a journey that will show the reader how this control works and what it does in health and disease—from gasping to apnea, from feeding to gastroesophageal reflux, and many more newborn respiratory control disorders. This is a book for investigators, but also for clinical practitioners.

As the Executive Editor of the Lung Biology in Health and Disease series, I cannot overstate how enthusiastic my response was to Dr. Oommen Mathew's expression of interest in editing this volume. I knew this would be an important contribution, as well as a source of invaluable information and inspiration, for researchers and for clinicians. I am grateful to him and to the contributors for the opportunity to introduce this volume to the readership of the series.

Claude Lenfant, M.D.
Bethesda, Maryland, U.S.A.

PREFACE

Since the inception of this series, several volumes have been devoted to respiratory control. These contributions have critically reviewed the experimental evidence (beginning with the observation by LeGallois) that the respiratory center is located in the medulla. Until now, respiratory control in the newborn has been a small part of the general discussion of respiratory control. In recent years, the increasing interest in developmental neurobiology—more specifically, our quest for understanding the cellular mechanisms involved in the control of breathing—has put our knowledge of respiratory control disorders on a firmer footing. These cellular events are complex and often show marked developmental changes. Interpretation and integration of these cellular events into the system levels are necessary for better understanding of the pathophysiology of various respiratory control disorders, and, in turn, targeted therapeutic interventions can be developed. An excellent example of this undertaking is the discovery of surfactant deficiency as the underlying cause of respiratory distress syndrome in premature infants, and the subsequent development of natural and synthetic surfactants to treat this "developmental disorder." We hopefully anticipate the development of drugs specifically targeted to enhance maturation of respiratory control in premature infants and the rectification of abnormal cellular properties through molecular genetics technology.

This volume is devoted to the disorders of respiratory control in the newborn. To refresh and enhance our understanding of respiratory control, the first part deals with respiratory control in the normal newborn. Several chapters in this section address the relevant topics critically, in the fetus and the newborn, at both the system and cellular levels. These include chapters on development of respiratory control, gasping, and neural and chemical control of breathing. This section also features chapters on development of sleep states and metabolism—two vitally important factors in determining respiratory output.

The second part, which focuses on respiratory control disorders, begins with an overview. The diagnosis of these disorders in the neonate often begins with cardiorespiratory monitoring in the neonatal intensive care unit. An examination of the pros and cons of the cardiopulmonary monitoring techniques used in the neonate follows. The main focus of this part is apnea of prematurity; several chapters are dedicated to this clinically important topic. Congenital central hypoventilation and neuromuscular syndromes are examined next, followed by chapters on control of breathing in acute and chronic respiratory failure. A discussion of the maturational aspect of the respiratory control mechanisms sets the stage for the final chapter, which addresses modifiable risk factors in sudden infant death syndrome.

I would like to thank this outstanding group of international contributors for their comprehensive, critical, and up-to-date chapters.

Oommen P. Mathew

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CONTENTS

1

Respiratory Control in the Newborn

Comparative Physiology and Clinical Disorders

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I. Introduction

The control of respiration is one of the most fascinating phenomena in physiology, along with the genesis of heart pacing and rhythm, diurnal rhythm, and other cyclical phenomena. Indeed, there are amazing short-term and long-term cyclic phenomena that take place in nature from plants to humans. Consider, for example, the diurnal cyclicity of gene expression that occurs in plants being activated in the morning to protect plants from the heat of the sun and others being activated in the evening to protect them from cold temperatures and freezing! Cyclic phenomena are clearly intriguing, and it is well recognized that cyclic phenomena occur in all tissues of the body, whether they are related to regions of the brain that are responsible for diurnal rhythms (suprachiasmatic nucleus) or not. Respiration is a short-term cyclical phenomenon that involves the brain, lungs, heart, circulation, carotid bodies, and other sensors and interconnections among these various organs. This is clearly a crucial act for air-breathing mammals; hence its regulation is of paramount importance.

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The control of respiration is not mature at birth in full-term infants, and it is certainly not mature in premature infants. Keeping in mind that ~10% of births in the United States are premature, the basic understanding of respiration in the immature infant takes on added significance. Although there are a number of elements of the control system that are likely to be immature in the newly born, especially in the premature infant, the aims of this chapter will be [1] to review some of the salient features of respiratory control in the mature individual, [2] highlight some of the major differences between the newly born and the mature subject, and [3] illustrate how certain defects and/or abnormalities in the control system lead to disease and clinical manifestations.

II. Overall Concepts of Respiratory Control

To describe the respiratory control system and highlight its main features, I present below six concepts or main ideas that characterize the respiratory control system. These concepts constitute a distillation of a considerable amount of work done over more than two centuries, ever since LeGallois's experiments. In these experiments, done at the turn of the 19th century, he described the *noeud vital* in famous rabbit experiments when he discovered that no breathing efforts occurred when he severed the spinal cord from the *noeud vital*, located at the level of "origin of the nerves of the eighth pair" (1).

> **CONCEPT I:** *Respiration is controlled via a negative feedback system with a controller present in the central nervous system (CNS) and a controlled organ composed of respiratory muscles and lungs.*

Animal models and humans have been studied extensively and these investigations have clearly shown that the CNS integrates the drive and generates the oscillatory respiratory motor pattern, depending on inputs from a variety of feedback elements. This controller then adjusts the output of the system such as to optimize the function desired. Inputs from the carotid bodies, airway receptors, muscle receptors, and other sensors converge onto the CNS, which integrates and formulates the output to the respiratory muscles. Therefore, this feedback loop depends on several elements including sensors, comparators, integrators, and effectors. With every disturbance sensed, the feedback system tries to change its output to minimize the effect of the disturbance on the overall function of the system and to attempt to return it to baseline.

> **CONCEPT II:** *The central neuronal processing and integration in the brainstem is hierarchical in nature.*

This idea is important from the point of view of neuronal network as well as the "decision-making process" in the CNS when faced with competing inputs. For example, many experiments have shown that the laryngeal afferent input into

the brainstem is an extraordinarily potent inhibitory reflex to breathing and its effect on the CNS integrator/pattern generator is instantaneous, taking place in milliseconds (2,3) (Fig. 1)! This reflex is even more powerful during anesthesia, when cortical input onto the brainstem is attenuated. We and others have performed a variety of experiments in animal models and shown that, although there is a major interplay between anesthesia and this reflex, laryngeal input overwhelms other inputs coming to the brainstem (2,3).

> **CONCEPT III:** *The respiratory rhythm generation in central neurons is most likely a result of an integration among network, synaptic, cellular, and molecular characteristics of brainstem and other neurons involved.*

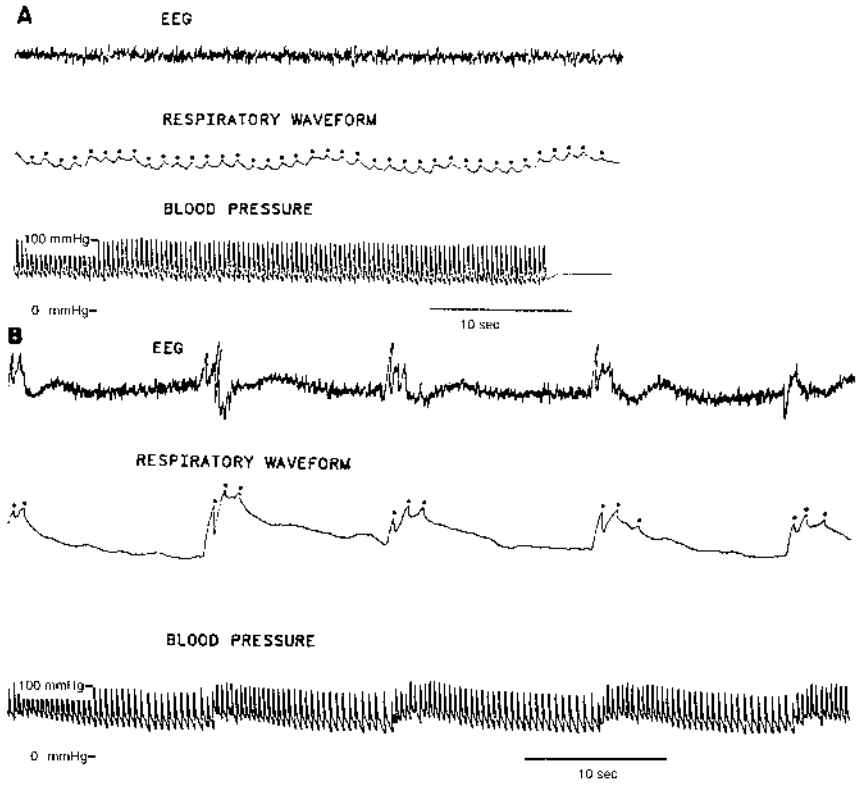

Figure 1 Original record in an experiment in which the superior laryngeal nerve (SLN) was chronically instrumented and the animal (piglet) was awake and unrestrained. Note the potent respiratory inhibition (compare A, which is at rest, with B, 10 min after the stimulation of the SLN) and the intermittent breakthough or respiration when the SLN was stimulated.

This idea has been developed in the past decade, as we have been able to utilize reduced preparations and study the membrane properties of individual neurons (4–6). The nature of the rhythm generator is not well delineated, but there are two potential scenarios. The respiratory controller may be a group of neurons that either form an *emergent network* or are *endogenous* or *conditional burster* neurons. In the first case, respiratory neurons would not have any special inherent membrane properties (e.g., bursting properties) that would make their membrane potential spontaneously oscillate (6). Rather, the output of the network they form would oscillate because of the special synaptic interactions among these respiratory neurons (6). In the second case, respiratory neurons, similar to those forming the sinus node of the heart, would have properties that make them individually "burst" or oscillate, even if they are *not* connected to any other neuron. This is termed an endogenous burster, or pacemaker neuron. A conditional burster is a neuron that oscillates only when exposed to certain chemicals (e.g., neurotransmitters). The properties of these neurons are also very critical in shaping the output of the network itself, irrespective of the properties of the respiratory network as a whole.

Although the exact nature of how these respiratory neurons operate is not known, more recent data have suggested that the respiratory rhythm is generated by an oscillating network in the ventrolateral formation of the medulla oblongata (7). The region that seems to be essential for the rhythm is the pre-Botzinger complex, as all cranial nerve activity ceases totally after this region is separated from lower brainstem levels (7–9). A number of questions clearly remain to be answered: [1] what are properties of individual neurons in this area? [2] how interconnected are these with others? and [3] what is the nature of their synapses with neurons in the brainstem and other more rostral regions? Recently, Feldman and colleagues have attempted to answer a number of these questions. For example, we know now that glutamatergic receptors (AMPA) and glutamate as a ligand play an important role in inducing the respiratory rhythm (10–12).

We and others have discovered a number of impressive membrane currents that may shape their repetitive firing activity (6). These include not only the classic sodium and potassium currents responsible for the action potential, but also an A-current, two types of calcium currents, calcium-activated potassium currents, inward rectifier currents, ATP-sensitive K^+ currents, and other currents (6,13). There seems to be little disagreement about the presence of these channels in respiratory neurons, since after their initial demonstration in brain slices, many of these channels were studied in identified respiratory neurons in vivo (6). Although the evidence is still insufficient, it has been suggested that delayed excitation may be responsible for the firing activity of "late" inspiratory neurons in the dorsal respiratory group (DRG) (6). If this is true, it is possible that the A-current in these neurons works in conjunction with processes, such as synaptic facilitation, to shape a ramp excitatory drive to phrenic motoneurons. Assignment

of a role for this current in forming the activity of the dorsal group (DRG) neurons is subject to study and speculation, and will ultimately require further investigation in vivo. However, we should emphasize that one of the important observations of the past several years is that these pre-Botzinger neurons do not seem to have special membrane properties. They seem to have receptors, ion channels, and transporters similar to those in other neurons in the CNS. Neurons in the brainstem do not seem to have properties similar to those that oscillate by themselves, i.e., oscillate by virtue of specific membrane properties, without the need of input from surrounding neurons. It is therefore very likely that the oscillations of brainstem respiratory neurons are based not on membrane properties alone but also on the integration of membrane, synaptic, and network properties.

CONCEPT IV: *Afferent information to the CNS is not essential for neuronal rhythmicity but is important for modulation of respiration.*

A considerable number of afferent messages converge on the brainstem at any one time. For example, chemoreceptors and mechanoreceptors in the upper airways constantly sense stretch, air temperature, and chemical changes over the mucosa and relay this information to the brainstem. Afferent impulses from these areas travel through the superior laryngeal nerve and the 10th cranial nerve (vagus). Changes in O_2 or CO_2 tensions are also sensed at the carotid and aortic bodies, and afferent impulses travel through the carotid and aortic sinus nerves. Thermal or metabolic changes are sensed by superficial receptors or by hypothalamic neurons and are carried through spinal tracts to the brainstem. Furthermore, afferent information to the controller in the brainstem need not be only formulated and sensed by the peripheral nervous system. As an example, sensors of CO_2 lie on the ventral surface of the medulla oblongata and constitute a major feedback regarding CO_2 homeostasis.

It is well known that afferent information is not a prerequisite for the generation and maintenance of respiration. When the brainstem and spinal cord are removed from the body of the rat and maintained in vitro, rhythmic phrenic activity can be detected for hours (7). Other experiments on chronically instrumented dogs in vivo in which several sensory systems are simultaneously blocked (cold vagal block, 100% O_2 breathing to eliminate carotid discharges, sleep to eliminate wakeful stimuli, and diuretics to alkalinize the blood) indicate that afferent information is not necessary to generate the inherent respiratory rhythm. However, both in vitro and in vivo studies demonstrate that, in the absence of afferent information, the inherent rhythm of the central generator (respiratory frequency) is slowed down considerably. Hence chemoreceptor afferents can play an important role in modulating respiration and rhythmic behavior. Furthermore, cortical and other central inputs are important afferent inputs onto the brainstem. They have a major impact on the regulation of

respiration, although they do not participate in rhythmogenesis. Consider for example, the effect of emotions, the wake state, sight, hearing, etc., on breathing (14).

> **CONCEPT V:** *The efferent limb of the respiratory control system (i.e., respiratory musculature) is a possible site of respiratory failure due to neuromuscular failure.*

Ventilation requires the coordinated interaction between the respiratory muscles of the chest and those of the upper airways and neck. For example, the activation of upper airway muscles occurs prior to and during the initial part of inspiration; the genioglossus contracts to move the tongue forward and thus increase the patency of the airways; and the vocal cords abduct to reduce laryngeal resistance. Indeed, we have learned considerably about the efferent limb and the respiratory muscles and the neuromuscular junction as potential sites for failure of the whole system. Extramuscular (e.g., respiratory nerves, neuromuscular junction) and intramuscular (e.g., ionic homeostasis, energy stores, fiber types, blood flow in the muscle) factors can play major roles in either contributing to or precipitating the failure of ventilation (15).

> **CONCEPT VI:** *The output of the respiratory control system is distributed among a number of respiratory muscles located in the airways, chest wall, and abdomen.*

This is an important idea since it is often considered that the diaphragm is the only muscle of respiration. Whereas the diaphragm is the major muscle, the best illustration for the importance of the other respiratory muscles, such as those in the upper airways, is related to the pathogenesis of upper airway obstruction/hypoventilation during sleep (OSAH) in children as well as in adults. The coordination, tone, and activation of upper-airway muscles are very important because it is the "uncoordinated" interactions between the diaphragm and upper airway muscles that can lead to hypoventilation or obstruction in the upper airways during sleep. It is therefore very essential to consider the functional state of all respiratory muscles and their synchronization; it is their coordinated activation that keeps the airways patent, especially under stress.

III. The Newborn's Respiratory Control in Perspective

A. Peripheral Sensory Aspects

In this section, I shall review data on the primary O_2 sensor in the body, the carotids. I will show that there are major differences between the newborn and the adult vis-à-vis the response of the carotids to low O_2 and with respect to the importance of this organ in overall respiratory function and survival in early life.

Recordings from single fiber afferents have demonstrated major differences between the fetus and the newborn and between the newborn and the adult (Fig. 2). Chemoreceptor activity is present in the fetus and a large increase in

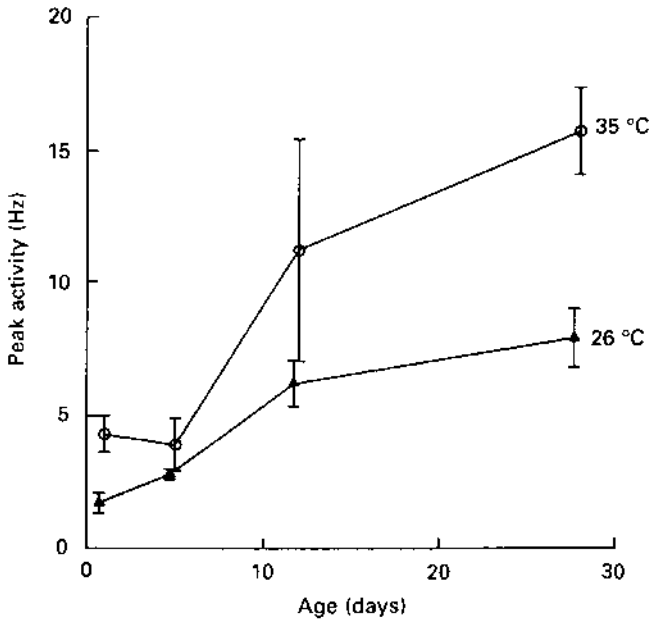

Figure 2 Peak discharge from single units of a carotid body in vitro. Note the effect of age on peak activity.

activity may be evoked by decreasing the PO_2 of the ewe (16). The estimated response curve was left-shifted such that PaO_2 values below 20 torr were required to initiate an increase in carotid sinus discharge. Furthermore, the large increase in PaO_2 at the time of birth virtually shuts off chemoreceptor activity. However, this decreased activity does not last long, and a normal, adultlike sensitivity is achieved after a few weeks (16,17). The mechanisms for the maturation of these peripheral sensors are not all worked out, but there are a number of factors, external or endogenous, that probably play a role in this process. For example, arterial chemoreceptors are subject to hormonal influences, which may affect the sensor or alter tissue PO_2 within the organ. Neurochemicals may also play a major role as they modulate chemosensitivity. For example, endorphins decrease in the newborn period, and the effect of exogenous endorphin is inhibition of chemoreceptor-mediated hypoxia sensitivity (18).

Even in studies in which hormonal or neural effects are minimized such as in in vitro experiments, the chemosensitivity of the newborn carotid is less than the adult. Nerve activity of rat carotid bodies, in vitro, following transition from normoxia to hypoxia is about fourfold greater in carotid bodies harvested from 20-day-old rats as compared to 1 to 2-day-old rats (19). This corresponds well

with the maturational pattern of the respiratory response to hypoxia in the intact animal (20) and suggests that major maturational changes occur *within* the carotid body itself. For example, the maturational increase in chemosensitivity may be attributed to a maturational change in the biophysical properties of glomus cells. In one model, it seems that hypoxia directly inhibits a membrane-localized K^+ channel which is active at rest, and the resulting depolarization leads to calcium influx, secretion of neurotransmitter, and increased neural activity in adult carotid cells (21). In comparison, glomus cells harvested from immature rats show a decrease in whole-cell K^+ current during hypoxia but the decrease in K^+ current is attributed to a decreased activation of a Ca^{+2}-dependent K^+ current rather than to a specialized K^+ channel sensitive to PO_2 (22). How this leads to reduced sensitivity and reduced firing is not well understood.

What role do the carotid bodies play in growing animals? And is this role tied to O_2 sensing? In comparison to the adult, peripheral chemoreceptors are believed to assume a greater role in the newborn period. Peripheral chemoreceptor denervation in the newborn results in severe respiratory impairments and high probability of sudden death. This has been demonstrated in a number of animal models. Lambs following denervation fail to develop a mature respiratory pattern (23,24) and suffer 30% mortality rate, days, weeks, or months following surgery. In other species, denervation also leads to lethal respiratory disturbances (2,25). For instance, denervated rats suffer from severe desaturation during REM sleep (25), and piglets suffer from profound apnea during quiet sleep (3). Of particular interest is that these lethal impairments only occur during a fairly narrow developmental window. Denervation before or after this window period in early life results in only relatively minor alterations in respiratory function (3).

B. Central Neurophysiologic Aspects

Although recent studies in the neonatal rat in vitro (whole brainstem preparation) were not targeted at understanding the neonate in particular, these studies have shed light on basic fundamental issues pertaining to control mechanisms of respiration in the newborn (7). In fact, we know now from several such studies that the young rat (in the first week of life) does not need any external or peripheral drive for the oscillator to discharge. The inherent respiratory rate (as judged by cranial nerve output) is markedly downregulated. These studies corroborate the idea that peripheral or central (rostral to the medulla and pons) inputs are needed to maintain the respiratory output at a much higher frequency.

Another interesting observation is that the discharge pattern of each neuronal unit in the neonate seems, from extracellular recordings, to be different from that in the adult in two major ways. First, the inspiratory discharge is not ramp in shape, but increases and decreases very fast within the same breath. The second is that it is extremely brief, sometimes limited to even a few action

potentials (26). In addition to differences in inspiratory discharge, expiratory units discharge weakly and appear often only after the imposition of an expiratory load (27,28).

Since the discharge pattern of central neurons in the adult or neonate (as discussed above) is affected by peripheral input, including input from the vagus nerve, one question that has been raised is whether the lack of myelination in the neonatal nerve fibers affects function. This is indeed the case, because of lack of myelination and potential delays in signaling. It is also because inspiratory and expiratory discharge periods are so fast or short that they preclude the effect of peripheral information on the CNS within the same breath. Therefore, one important issue that can be raised is whether breath-by-breath feedback is as potent in the young as in the adult.

Differences between neonates and adults are also observed in response to neurotransmitters or modulators. Young animals respond differently to neurotransmitters than adult animals do; this has been mostly documented by work on the opossum (29). Glutamate injected in various locations in the brainstem, even in large doses, induces respiratory pauses while it is clearly stimulatory in the older mature animal (29). Inhibitory neurotransmitters such as GABA have also been used, and these have age-dependent effects in the opossum. GABA has also been shown to be an excitatory neurotransmitter (Fig. 3) in the newborn but an inhibitory one in the mature adult neuron (30). These differences between newborns and adults are not quite understood at the fundamental level since there are many variables that have not been controlled for such as the size of the extracellular space, receptor development, and ability for sensitization, to name a few.

C. The Efferent System

There is a multitude of neuromuscular and skeletal changes that take place early in life. These include alterations in muscle cells, the neuromuscular junction, the nerve terminals and synapses, and the chest wall properties. Therefore, since muscle and chest wall properties change with age, it is likely that neural responses can be influenced by pump properties, especially that these muscles execute neural commands. One of the important maturational aspects of respiratory muscles is their pattern of innervation. In the adult, one muscle fiber is innervated by one motoneuron. In the newborn, however, each fiber is innervated by two or more motoneurons, and the axons of different motoneurons can synapse on the same muscle fiber; thus, the term polyneuronal innervation. Synapse elimination takes place postnatally, and in the case of the diaphragm, the adult type of innervation is reached by several weeks postnatally, depending on the animal species. The time course of polyneuronal innervation of the diaphragm in the human newborn is not known (15).

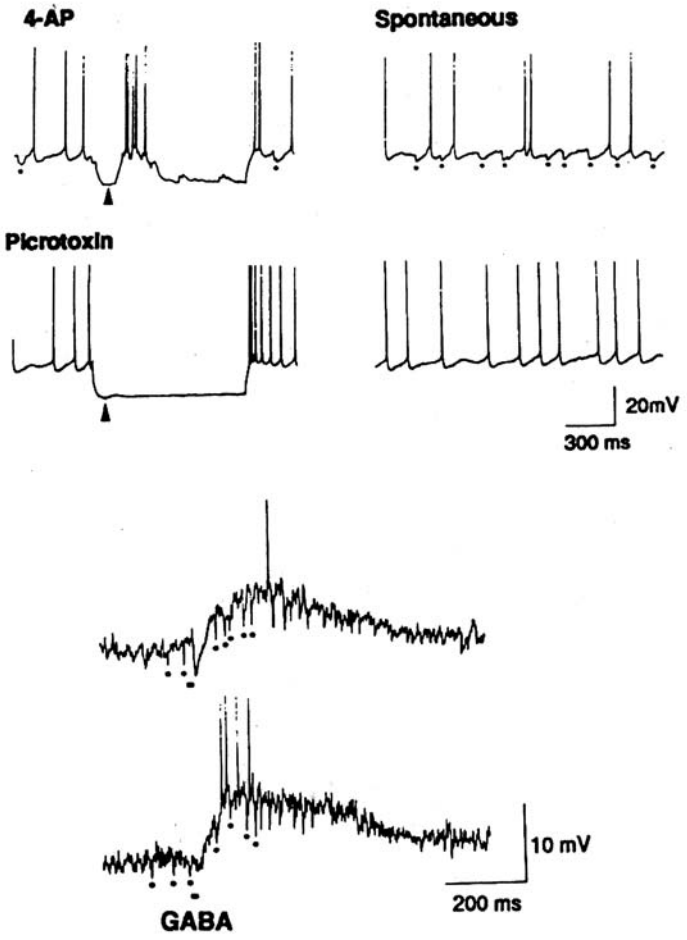

Figure 3 *Top panel of four records.* Left, above and below: Compare action potential discharge from one nerve cell in vitro after a hyperpolarization in the presence of 4-AP (I_A current blocker) or picrotoxin ($GABA_A$ receptor blocker). Note the lack of excitatory discharge in the presence of picrotoxin. Right panel shows spontaneous discharge. *Bottom panel*. Action potential discharge with depolarization with and without GABA agonist.

The neuromuscular junctional folds, postsynaptic membranes, and acetylcholine receptors and metabolism undergo major postnatal maturational changes. The acetylcholine quantal content per end plate potential is lower in the newborn than in the adult rat diaphragm (15). The newborn diaphragm is also more

susceptible to neuromuscular transmission failure than that in the adult, especially at higher frequencies of stimulation (15). The reason for this is not clear.

IV. Disease States

A. Respiratory Pauses and Apneas

Although there are numerous studies on apnea in the newborn and adult human, there are still major controversies. The length of the respiratory pause, usually defined as apnea, varies and has been subject to debate. Statistically, apnea can be defined as a respiratory pause that exceeds 3 standard deviations of the mean breath time at any particular age. This definition requires data from a population of subjects, lacks physiologic value, and does not differentiate between relatively shorter or longer respiratory pauses. This definition may therefore not be the best from a functional viewpoint. Alternatively, the definition of apnea may be based on the sequelae of pauses, such as associated cardiovascular or neurophysiologic changes. Such definition relies on the functional assessment of pauses and is therefore more relevant clinically. It is important to note here that, because infants have a higher O_2 consumption (per unit weight) than the adult and relatively smaller lung volumes and O_2 stores, it is possible that relatively shorter (e.g., seconds) respiratory pauses, which may not be clinically important in the adult, can be serious in the very young or premature infant. Furthermore, independent of age, respiratory pauses are more prevalent during sleep than during wakefulness. And the frequency and duration of respiratory pauses depend on sleep state. Respiratory pauses are more frequent and shorter in REM than in quiet sleep, and more frequent in the younger than in the older child or adult.

Although there is a controversy regarding the pathogenesis of respiratory pauses, there is a consensus about certain observations. Normal full-term infants, children, and adult humans exhibit respiratory pauses during sleep. It is also believed that the presence of respiratory pauses and breathing irregularity is a "healthy" sign and that the complete absence of such pauses may be indicative of abnormalities. This parallels well the concept of heart rate variability, and a lack of short-term or long-term variability in heart rate can be a sign of disease or immaturity. Prolonged apneas, however, can be life-threatening, and the pathogenesis of these apneas may relate to the clinical condition of the patient at the time of the apneas, associated cardiovascular (systemic or pulmonary) changes, the chronicity of the clinical condition, and whether the etiology is central or peripheral. Prolonged apneic spells require therapy, but optimally, treatment should be targeted to the underlying pathophysiology.

The pathogenesis of apneas can vary considerably. The etiology can be in the CNS, in the periphery, such as in the airways, or in the coordination between peripheral and central events. Upper-airway obstruction (UAO), for example, is an entity that is characterized by having lack of normal airflow (or complete lack

of airflow) not because of lack of phrenic output but because of obstruction in the airways. This is very different from abnormal (or lack of) airflow on the basis of absent phrenic impulses coming to the diaphragm. One reason for distinguishing the two conditions is to provide the optimal form of therapy.

Upper-airway obstruction during sleep is recognized with increasing frequency in children and adults. In contrast to adults with UAO in whom the etiology of obstruction often remains obscure, many children have anatomic abnormalities. A common cause of UAO in children is tonsillar and adenoidal hypertrophy, partly due to repeated upper respiratory infections. Other associated abnormalities include craniofacial malformations, micrognathia, and muscular hypotonia from a variety of causes. The usual site of obstruction of UAO in both infants and adults is the oropharynx, between the posterior pharyngeal wall, the soft palate, and the genioglossus. During sleep (especially REM sleep), upper-airway muscles, including those of the oropharynx, lose tone, and trigger an episode of UAO.

B. O_2 Deprivation and Cell Injury

A number of pathophysiologic conditions lead to respiratory failure with hypercapnia and tissue O_2 deprivation. Practically, all cardiorespiratory diseases can potentially produce failure of this system. This outcome may be deleterious to other organs because of the ensuing acidosis and hypoxia. However, it is the hypoxia that should be avoided at all cost since human tissues, especially the CNS, have relatively low tolerance to a microenvironment that is devoid of O_2 (31,32).

In the past decade, we have learned a great deal about the effect of lack of oxygenation on various mammalian and nonmammalian (vertebrate and non-vertebrate) tissues and at various ages, including fetal, postnatal, and adult. There is a vast array of cellular and molecular responses to lack of O_2. From an organismal point of view, the carotid bodies would seem to discharge and have an effect on ventilation when the PaO_2 reaches below 50 torr. It is probably the case that, in general, other tissues in the body do not respond or react to PaO_2 above 50 torr. Indeed, most tissues would start "sensing" a decrease in PaO_2 only below 35–40 torr. For example, the brain, which is one of the very sensitive tissues to lack of O_2, has a resting (no hypoxia induced) interstitial O_2 tension probably in the range of 20–35 torr depending on age, area (white vs. gray matter), neuronal metabolism, temperature, proximity to blood vessels, etc.

Although advances have been made in understanding the effect of lack of oxygenation on tissue metabolism, excitability, and function, major questions remain unanswered with respect to the mechanisms that lead to injury or those that protect tissues from it. This area of research is very complex, and we and others have focused on it for a number of years. In the case of the nervous system,

for example, a number of mechanisms are activated during O_2 deprivation. Membrane biophysical events such as those pertaining to Na^+ and K^+ channels, and others such as increased anaerobic metabolism, increased intracellular levels of H^+ and Ca^{2+}, increased concentrations in extracellular neurotransmitters (e.g., glutamate and aspartate), radical production, activation of kinases, protease, and lipase; injury and destruction of important cytoskeletal proteins; gene regulation of a number of proteins (e.g., c-fos, NGF, HSP-70, -actin) are just some events that take place during lack of O_2 (32–40).

V. Summary

The newborn seems to have either different mechanisms of control of respiration or an immature set of mechanisms that, with differentiation, arrive at the adult respiratory mechanisms. However, it is important to stress that it is not clear from studies that have been done at either the sensory limb, the central controller, or the efferent limb that the newborn is at an overall increased risk for injury. In fact, there is a considerable amount of data to demonstrate that the young are at an advantage from the viewpoint of stress-related hypoxic injury.

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Gasping and Autoresuscitation

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I. Introduction

Gasping is the first and last breaths of life. At birth, initial breaths appear to represent the brief and maximal inspiratory efforts characteristic of gasps. Such maximal inspiratory efforts, which may be induced by the asphyxia present at birth, serve to inflate the lungs. With the establishment of adequate oxygenation, gasps are superseded by normal eupneic ventilatory activity. The supersedure of gasping by brainstem mechanisms which generate eupnea is so complete that gasping may not again emerge for many years, with the agonal gasping prior to death being the extreme for reemergence. However, gasping may also reemerge at any time when a failure of eupnea results in severe hypoxia or when severe hypoxia or ischemia has itself caused an elimination of eupnea (Fig. 1). Once recruited, gasping provides a powerful mechanism for "autoresuscitation," with a return to eupnea and normal cardiac function. Such autoresuscitation is much more effective in the neonate than in the adult (1,2).

Inherent to the above is the concept that neuronal mechanisms underlying the generation of the gasp may differ from those generating eupnea (3–5). If this concept is valid, then the question arises as to the status of these neuronal mechanisms for gasping during most of life. It appears improbable that these neuronal mechanisms would be quiescent for years and only emerge when

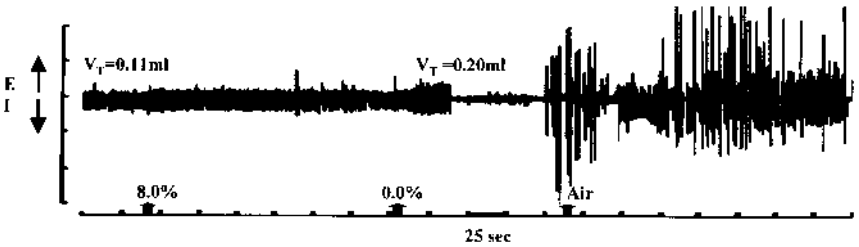

Figure 1 Autoresuscitation in the newborn. Tracing represents airflow from a plethysmograph in which an unanaesthetized 1-day-old rat had been placed. Animal was breathing 100% oxygen. At the first arrow, the inspired gas was altered to 8% oxygen in nitrogen. At the second arrow, 100% nitrogen was introduced. Note transient increase in ventilatory activity and then apnea. Apnea was succeeded by gasping, as evidenced by large excursions. Air was then re-introduced and the animal recovered a eupneic ventilatory pattern. (From Ref. 49.)

activated in severe hypoxia or ischemia. Rather, these neuronal mechanisms for gasping are incorporated into and function as part of the brainstem neuronal circuit generating eupnea. Severe hypoxia or ischemia suppresses components of this brainstem neuronal circuit and/or activates mechanisms for gasping. The mechanism of this activation and the relatively greater efficiency of "autoresuscitation" in the neonate than in the adult are also topics for consideration.

II. Elicitation of Gasping

A systematic comparison of gasping with normal eupneic ventilation was first performed by Thomas Lumsden in a series of papers in 1923 and 1924 (6–9). In addition to exposure to severe hypoxia or ischemia, Lumsden found that eupnea was replaced by gasping following a brainstem transection at the pontomedullary junction. Hence, hypoxia-induced gasping was envisaged to result from the suppression of mesencephalic and pontile components of the brainstem ventilatory control system and a freeing of mechanisms for gasping within the medulla.

Many subsequent investigators have confirmed and extended Lumsden's observations (see 3–5 for reviews). Concerning the elicitation of gasping in severe hypoxia, a stereotypical pattern of changes precedes the replacement of eupnea by gasping. Upon exposure to severe hypoxia, ventilatory activity increases, with tidal volume and frequency being progressively elevated. Both variables then decline to a "primary apnea" which is ultimately succeeded by the large, but somewhat infrequent inspiratory efforts of gasping. If hypoxia is

continued, the frequency and peak height of gasps ultimately decline to a "secondary" or "terminal" apnea (1–5). Importantly, however, periodic gasps may continue for minutes or, in neonates, for hours before terminal apnea (10). If during this extended period of gasping, hypoxia is removed and normoxia or hyperoxia is reintroduced, the frequency of gasps progressively increases and they are gradually replaced by eupneic ventilatory activity. This process is termed "autoresuscitation" (1,2) (Fig. 1).

Inherent to the above considerations is the observation that eupnea and gasping are distinctive patterns of automatic ventilatory activity from the day of birth. However, in the transition from eupnea to gasping, the duration of the period of "primary apnea" is exceedingly variable. In fact, this period may be entirely absent, with the augmented eupneic ventilatory activity being replaced by gasping. With such a transition, a distinction between the last eupneic inspirations and the first gasp is not obvious (11–15). This lack of distinction has led to the concept that eupnea and gasping might be variants of a single respiratory rhythm (11,14). While this concept remains possible, there is substantial evidence that different neuronal mechanisms underlie the neurogenesis of eupnea and gasping. Most prominent upon this evidence is the finding that destruction of neurons in a discrete region of medulla irreversibly eliminates gasping but not eupnea (see Sec. VI below). Mechanisms that may underlie the neurogenesis of gasping, and the relationship of these mechanisms to those generating eupnea, will be considered in Section IV.

In addition to exposure to severe hypoxia, eupnea is replaced by gasping following a brainstem transaction at the pontomedullary junction (see 3–5 for reviews) (Fig. 2). Hence, gasping represents the pattern of ventilatory activity which can be generated by the isolated medulla. Analyses of gasping resulting from brainstem transactions with hypoxia-induced gasping has revealed a virtual identity of characteristics; these characteristics are detailed in Section III.

III. Characteristics of Gasping

A. Neural Activities

Compared to eupnea, gasping might be considered as a greatly simplified pattern of ventilatory activity. As described in detail in a number of recent reviews (5,17,18), the eupneic ventilatory cycle consists of three phases: inspiration, and phases I and II of expiration. The eupneic inspiratory phase is typically defined as the "ramplike" rise of activity of the phrenic nerve. Bursts of activity, concomitant with that of the phrenic nerve, are recorded from spinal intercostals nerves and the facial, vagal, and hypoglossal nerves.

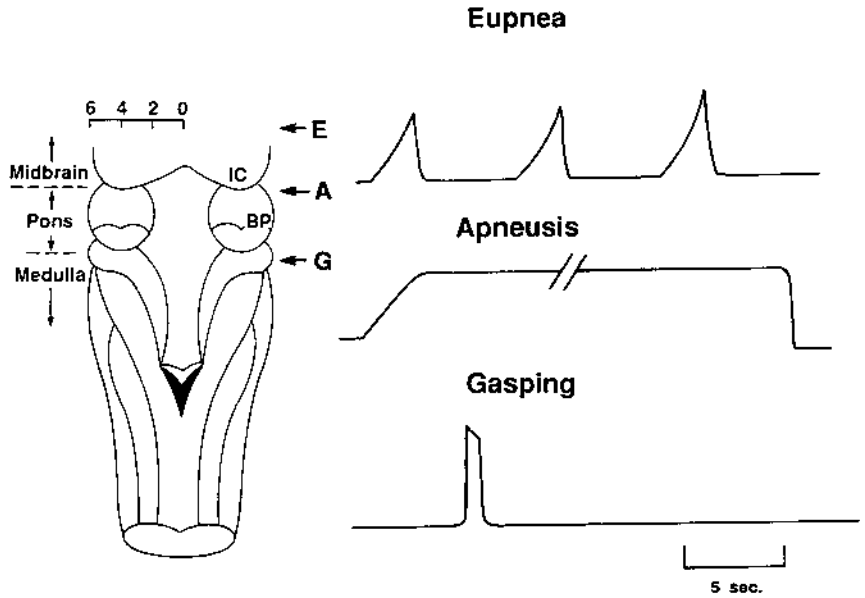

Figure 2 Patterns of automatic ventilatory activity after transections of the brainstem. Drawing is of the brainstem of the cat, with the cerebellum removed. IC, inferior colliculus; BP, brachium pontis; scale is in millimeters. Schematic records are of integrated activity of the phrenic nerve. Eupnea is recorded after a midcollicular transection (level E). After a rostral pontile transection (level A), apneusis is obtained. Gasping is recorded after a transection at the pontomedullary junction (level G). (From Ref. 4.)

Phase I of expiration is marked by the burst of activity of the branch of the recurrent laryngeal nerve innervating the thyroarytenoid muscle of the larynx (Fig. 3). Activity may also be recorded during phase I of expiration from the mylohyoid branch of the trigeminal nerve, as well as the facial and hypoglossal nerves. After phase I activities have terminated, activities of spinal nerves typically commence or augment greatly. These activities of spinal nerves define phase II of expiration.

The gasping ventilatory cycle consists of two phases: inspiration and expiration. In fact, the expiratory phase of gasping might be characterized as the "absence of inspiration" (Fig. 3).

A hallmark of gasping is the extremely rapid rise of inspiratory activity, as evidenced by the rate of rise of phrenic activity (see 3–5 for review). As opposed to the ramplike rise of phrenic activity in eupnea, phrenic activity in gasping reaches a peak value soon after onset and then declines. Hence, phrenic activity may be "decrementing" in gasping (Fig. 3).

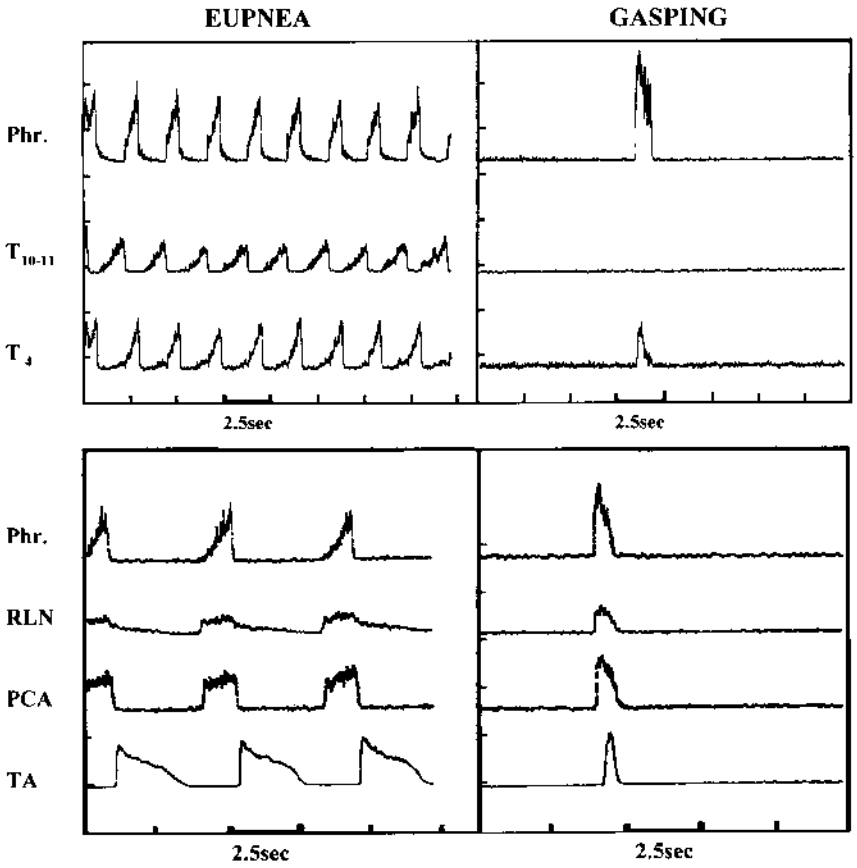

Figure 3 Activities of spinal and cranial nerves in eupnea and gasping in the adult cat. In upper panel, integrated activities of the phrenic nerve (Phr.), "expiratory" intercostal nerve (T_{10-11}), and "inspiratory" intercostal nerve (T_4) are shown. Note alteration of pattern of integrated phrenic activity from "incrementing" in eupnea to "decrementing" in gasping. Expiratory intercostal activity was eliminated. In lower panel, integrated activities of the phrenic nerve (Phr.), recurrent laryngeal nerve (RLN), and branches of the RLN innervating the posterior cricoarytenoid muscle (PCA) and thyroarytenoid muscle (TA) are shown. Note that activities during neural expiration of eupnea were eliminated in gasping. (From Ref. 28.)

Activities of spinal and cranial nerves are like that of the phrenic in gasping, with all exhibiting a decrementing discharge pattern. Compared to eupnea, activities during neural expiration, synonymous with the period between phrenic bursts, are greatly reduced or totally eliminated. Such a reduction of expiratory activities requires some clarification as, in recovery from severe

hypoxia or ischaemia, appreciable activities may be observed in the periods between gasps (19,20). This observation is perhaps not surprising since, as discussed below, eupnea and gasping share some common medullary neuronal circuits. However, this reduction or absence of expiratory activities in hypoxia-induced gasping strongly implies that a neuronal circuit, including expiratory activities, does not play an essential role in the neurogenesis of the gasp.

B. Response to Chemoreceptor Stimuli

Again, responses in eupnea and gasping differ fundamentally. In eupnea, it is well accepted that exposure to hypercapnia causes an increase in peak phrenic activity and the frequency of phrenic bursts and, hence, in both the tidal volume and frequency of ventilation. Both variables likewise increase upon exposure to hypoxia. This response is dependent upon the peripheral chemoreceptors. Following sectioning of the carotid sinus nerves and vagi, hypoxia causes a fall in eupneic ventilatory activity in decerebrate or anesthetized preparations (5,21).

In gasping, following transection of the brainstem at the pontomedullary junction, neither the peak height of phrenic activity nor the frequency of gasping is systematically altered in hypercapnia. In these preparations, hypoxia does cause a transient increase in the frequency, but not the height, of gasps. However, these transient changes in hypoxia are the same in preparations having intact and those with sectioned carotid sinus nerve and vagi (22). Hence, the characteristics of the gasping ventilatory pattern appear to be defined by conditions in the environment of the medulla. Fitting with this concept is the finding that, in paralyzed preparations, variables of hypoxia-induced gasping are independent of the concomitant levels of carbon dioxide (23). Moreover, in these same paralyzed preparations, various levels of hypoxia result in gasping having the same peak height and frequency (23).

C. Responses to Mechanoreceptor and Other Afferent Stimulation

A classic reflex in respiratory physiology is the Hering-Breuer reflex, in which inflation of the lungs causes a premature termination of the eupneic inspiration. Following bilateral vagotomy, the duration of the inspiratory and expiratory phases is greatly prolonged, the respiratory frequency is greatly reduced, and the tidal volume is augmented (24). Such changes following bilateral vagotomy are most marked in the neonate. Following vagotomy, the decline of respiratory frequency is so severe that some newborns are unable to maintain a level of

ventilatory activity which is sufficient for adequate oxygenation (25–27). Hence, feedbacks from mechanoreceptors of the lungs can markedly influence eupneic ventilatory activity.

Whether activation of mechanoreceptors of the lung alters the gasping ventilatory cycle has not been adequately examined. A number of investigators, beginning with Lumsden, have reported that the pattern of gasping appears the same before and after bilateral vagotomy and that lung inflation appeared not to alter the gasping pattern (6,27–29). Concerning Lumsden's work, the vagi were apparently inadvertently damaged during dissections in some of his preparations (see discussion in Ref. 4). In other studies, values before and after vagotomy or in the presence or absence of lung inflation were obtained during severe hypoxia or ischaemia (27–29). Hence, any influence of vagal mechanisms upon the gasping pattern may have been overshadowed.

Some reports do imply an influence, albeit subtle, of activation of pulmonary stretch receptors upon gasping. In one study (28), gasping was produced by ligation of the basilar artery, and the lungs were inflated by a servorespirator, in parallel with activity of the phrenic nerve. Phrenic activity was modestly altered when these lung inflations were withheld. However, given the modest frequency of phrenic bursts in gasping, withholding lung inflation would certainly cause an alteration in blood oxygenation. Two other studies (30,31) were performed using an in vitro mammalian preparation, which exhibits a pattern of rhythmic activity which is identical to gasping (4,5). In this preparation, with attached lungs, lung inflation did produce modest alterations in the duration of the phrenic burst and interval between bursts. The peak height of bursts was not altered (30,31). Using an in situ perfused rat preparation, we have reproduced the findings from the in vitro mammalian preparation during gasping (unpublished observation). Hence, in this preparation, in which oxygenation is maintained by an extracorporeal circuit, lung inflation alters the respiratory cycle in gasping, primarily by changing the period between phrenic bursts.

As in eupnea, gasping was markedly altered by stimulation of the superior laryngeal nerves (14). Such stimulation altered the duration of the gasp, its peak height, and the period between gasps. In this same context, gasping is inhibited by elicitation of a laryngeal chemoreflex, by placement of water or saline in the larynx (32).

It is perhaps not surprising that the activation of laryngeal and pulmonary receptors would alter both eupnea and gasping since afferents from both sets of receptors terminate in the region of the nucleus of tractus solitarius (33–35). It is well accepted that neurons in this region, termed the dorsomedullary respiratory nucleus, constitute a portion of the pontomedullary circuit responsible for defining activity of the phrenic nerve in eupnea and the medullary circuit which defines the gasp. However, neuronal activities in this region do not play a fundamental role in the genesis of either the gasp or eupneic inspiration. As

discussed in Section V below, eupnea is generated by a pontomedullary neuronal circuit and gasping is generated by a neuronal activities within a discrete region of the ventrolateral medulla.

IV. Effectiveness of Gasping in Autoresuscitation

In every mammalian species examined, gasping has been found to be a potent physiological mechanism for restoring ventilatory and also cardiovascular activity following a severe depression of these activities (1–6,10,11,13,36–38). Hence, gasping can be a critical mechanism for ensuring survival of the organism. Such survival mechanisms are most rigorous in the newborn. It is well established that, within the first few days after birth, many species can successfully "autoresuscitate" after being in an environment of complete anoxia for more than an hour. This maximal period of anoxia declines markedly with development such that, in the adult, this period is minutes or even seconds (2,10,36,39).

Without doubt, the major factor promoting the exceeding long survival of neonates in anoxia is the marked reduction in metabolic rate (see 40 for review). Concomitant with the onset of hypoxia, metabolic rate and, hence, consumption of oxygen and production of carbon dioxide fall dramatically in the neonate, but to a much lesser degree in the adult. Evidence of this marked reduction in metabolic rate is the reduction in core temperature. Also, during this period, cardiovascular activity is greatly altered with a profound bradycardia and hypotension (41–43). In addition, there is a redistribution of blood flow, with preferential maintenance of perfusion to vital organs, including the heart and brain, and a reduction in perfusion to skin and viscera. With this reduction of metabolism, gasps become infrequent, even in the newborn. However, if oxygen becomes available, gasps become more frequent, heart rate and arterial blood pressure rise, and eupnea gradually replaces gasping (37,41,44).

In addition to a single incidence of anoxia, gasping is very effective in promoting multiple autoresuscitations from multiple exposures to anoxia. Again, such autoresuscitation is more effective in the newborn, with animals surviving numerous exposures to anoxia over limited intervals (45).

V. Failure of Gasping in Autoresuscitation

The corollary of the above discussion is that gasping is ultimately unsuccessful in autoresuscitation, and such failure is more prevalent in the adult than the newborn. Since the metabolic energy during periods of anoxia is derived primarily from glycolysis, a depletion of energy substrates appears to represent the initial factor accounting for a failure of autoresuscitation. This depletion of energy substrates occurs in the cardiovascular system before the central nervous

system. Hence, even though the brainstem ventilatory control system may generate gasps, in terms of activities of the diaphragm and other "respiratory muscles," animals may not survive because of a failure of the heart to recover its normal functioning (2,42). In this context, such a failure of the cardiovascular system, before the brainstem ventilatory control system, is also observed in decerebrate, paralyzed, and ventilated preparation in which "fictive gasping" is monitored by activity of the phrenic nerve. Following a period of anoxia or asphyxia, the failure of heart rate to recover from bradycardia after the reintroduction of oxygen always precedes the failure to reestablish an eupneic pattern of phrenic activity (unpublished observation). Ultimately, however, the brainstem ventilatory control system fails and gasping ceases. Such a cessation is also observed in fictive gasping, recorded from activities of the phrenic nerve in paralyzed and ventilated preparations or, indeed, in a preparation in which the cardiovascular system has been replaced by an extracorporeal circuit (16,46). Again, such a failure of gasping doubtless reflects a failure to provide sufficient energy for maintenance of neuronal function.

This consideration of a "failure of gasping" should not obscure rigorousness of gasping, especially in the newborn. Indeed, it is difficult to induce a failure of gasping. In this context, a failure of gasping has been proposed as the basis of the "sudden infant death syndrome" (3,4,38,42,47). Based on this proposal, a number of risk factors for SIDS in humans have been reproduced in experimental preparations. Included in such risk factors are maternal use of nicotine and cocaine. However, even after prenatal exposure to relatively massive doses of nicotine and cocaine, newborn rats were still very successful in autoresuscitation in response to anoxia. The maximum number of successful autoresuscitations was reduced after exposure to nicotine, but multiple successes were still present (48–50).

VI. Critical Region for Neurogenesis of Gasping

Since gasping is expressed following a transection of the brainstem between pons and medulla (Fig. 2), gasping must be generated within the medulla. In a series of experiments, we found that gasping was irreversibly eliminated following physical lesions or injections of neurotoxins into a region of the rostral medulla. These lesions, which eliminated gasping following unilateral placement, did not disrupt the eupneic rhythm. This critical region for gasping has been termed the "gasping center" (2–5,51–56) (Fig. 4).

The gasping center lies medial and dorsal to the ventral medullary respiratory nucleus, in the region of the nucleus ambiguus. At its ventrolateral margin, the gasping center overlaps with a region of the ventral nucleus termed the "pre-Botzinger" complex (Fig. 4). Neuronal activities within this pre-

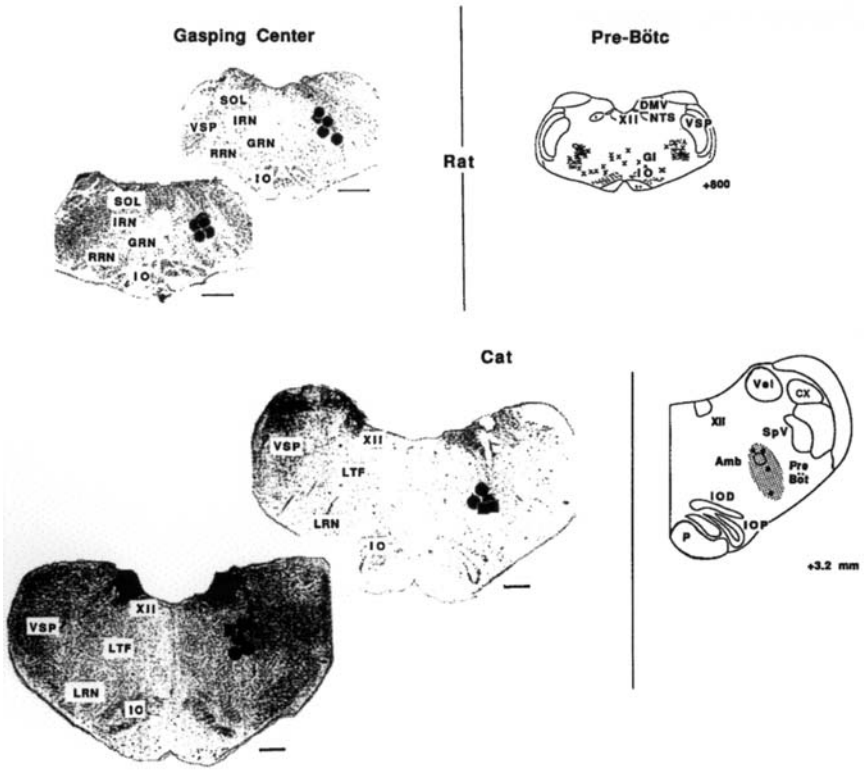

Figure 4 Locations of the gasping center and pre-Botzinger (pre-Botc) complex in adult rat and cat. Circles and squares in left panels designate regions in which injections of neurotoxins or physical lesions eliminated gasping, but not eupnea. Right panels show location of neurons—designated by cross, filled circles, and shading—taken to be within the pre-Botzinger complex. Scale is 1 mm. Amb, nucleus ambiguus; CX, nucleus cuneatus externus; DMV, dorsal motor nucleus of vagus; GI, gigantocellular reticular nucleus; IOD, nucleus dorsalis olivaris inferioris; IOP, nucleus principalis olivaris inferioris; IVN, inferior vestibular nucleus; NTS, nucleus of solitary tract; p and py, medullary pyramid; PP, nucleus prepositus; RFN, retrofacial nucleus; SpV, nucleus spinalis nervi trigemini; STN, spinal trigeminal nucleus; STT, spinal trigeminal tract; VeI, nucleus vestublaris inferior; VII, facial nucleus; XII, hypoglossal nucleus; 5SP, spinal trigeminal nucleus. (From Ref. 4.)

Botzinger complex have been shown to be responsible for the neurogenesis of rhythmic "respiratory" activities of in vitro preparations of neonatal rodents. However, as discussed in detail in a number of reviews, this "respiratory" activity in vitro differs markedly from eupnea in vivo but is very similar to gasping (4,5,56a). Indeed, it is very probable that these preparations are exhibiting

gasping and, as detailed in Section VII below, mechanisms of respiratory rhythm generation in vitro provide important insights into the neurogenesis of gasping in vivo.

Given the above, the question arises as to the relationship between the gasping center and pre-Botzinger complex. In a recent review, these regions are presented as two separate entities, both of which are essential for the neurogenesis of gasping (58). However, based on neuroanatomical and physiological evidence, it appears that these adjoining regions may contain elements of the same neurons, with soma in the pre-Botzinger complex and dendrites and/or axons in the gasping center. Anatomical evidence in support of this concept is the finding that filling of neurons of the pre-Botzinger complex with various dyes reveals extensive dendritic arborizations in the region of the gasping center (59,60). In a complementary study, injections of dyes into the region of the gasping center results in labeling of soma in the pre-Botzinger complex (61).

Physiological evidence that the gasping center and pre-Botzinger complex represent the same neurons is derived from studies involving injections of neurotoxins into the regions. Hence, as noted above, injections of such toxins into the gasping center irreversibly eliminates gasping (51–54). Similar injections into the pre-Botzinger complex, if performed bilaterally, transiently interrupt eupnea but irreversibly eliminate gasping (55,56). However, the volume of neurotoxin which must be injected into the pre-Botzinger complex to eliminate gasping is greater than if injected into the gasping center. This greater "efficiency" for the gasping center is perhaps reflective of the extensive dendritic arborizations of neurons of the pre-Botzinger complex into the gasping center. In any case, it appears probable that neurons of the gasping center–pre-Botzinger complex represent one component of the pontomedullary neuronal circuit which is necessary for the neurogenesis and expression of eupnea. However, these same neurons represent a unique source for the neurogenesis and expression of gasping.

VII. Mechanisms for the Neurogenesis of Gasping

A. Neuronal Activities Which May Generate the Gasp

Ablation of neurons in a circumscribed region of the rostral medulla irreversibly eliminates gasping in vivo and its analogue, the "rhythmic activity" of en bloc and slice preparations in vitro (see discussion in 4,5). Neuronal activities in this region must therefore be essential for the neurogenesis of gasping. An initial enigma arises concerning these neuronal activities which might generate the gasp. Since gasping is elicited only under conditions of extreme hypoxia or asphyxia, neuronal activities that generate the gasp might be quiescent for most of life. This concept of neuronal quiescence for many years seems improbable. More probable

is the incorporation of these neuronal activities which generate the gasp into the pontomedullary neuronal circuit responsible for the genesis and expression of eupnea. This pontomedullary circuit is reduced and reorganized in hypoxia, in ischemia, or following brainstem transactions at the pontomedullary junction, and neuronal mechanisms for gasping are released.

If a neuronal activity is responsible for generating inspiratory activity, its activity must commence before the start of activity of the phrenic nerve. For in vitro preparations, which exhibit gasping, a group of neuronal activities, termed preinspiratory, commence activity in late neural expiration and fire through the initial portion of the phrenic burst. These neuronal activities thus have a discharge consonant with generating the "burst" in vitro. The preinspiratory discharge of these neurons is by an intrinsic pacemaker mechanism (60–64).

During eupnea in vivo, the closest analogs to the preinspiratory activities in vitro are expiratory-inspiratory phase spanning neuronal activities (59,65). However, such activities cannot play an essential role in the neurogenesis of gasping, since, in fact, these activities cease in gasping. However, one group of neuronal activities, which discharge during all or the last portion of the phrenic burst in eupnea, acquires preinspiratory discharges in gasping (Fig. 5) (20,66). Thus, these neuronal activities, which have discharge characteristics that are compatible with generating the gasp, have markedly different discharges in eupnea. Such a change in discharge characteristics fits with the concept that neuronal activities that generate the gasp are superseded and captured by the pontomedullary neuronal circuit generating eupnea.

B. Release of Medullary Mechanisms for Gasping

The question obviously arises as to how severe hypoxia or ischemia or brainstem transactions between pons and medulla suppress components of the pontomedullary neuronal circuit for eupnea such that proposed medullary pacemaker mechanisms for gasping are released. Again, evidence as to the release of medullary mechanisms for gasping is derived from studies using in vitro preparations.

Evidence is now substantial that the rhythmic activity of in vitro en bloc or slice preparations is generated by the discharge of pacemaker neurons in the rostral medullary gasping center–pre-Botzinger complex. Fitting with a pacemaker mechanism for rhythm generation is the finding that in vitro rhythmic activities are only modestly altered following a blockade of inhibitory synaptic transmission within the preparation (61,62,64,67,68). This in vitro finding has been considered as enigmatic as a similar blockade of inhibitory synaptic transmission severely distorts the eupneic rhythmic activity of in situ preparations (69). Moreover, injections of blockers of inhibitory neurotransmitter into the region of the gasping center–pre-Botzinger complex of in vivo preparations

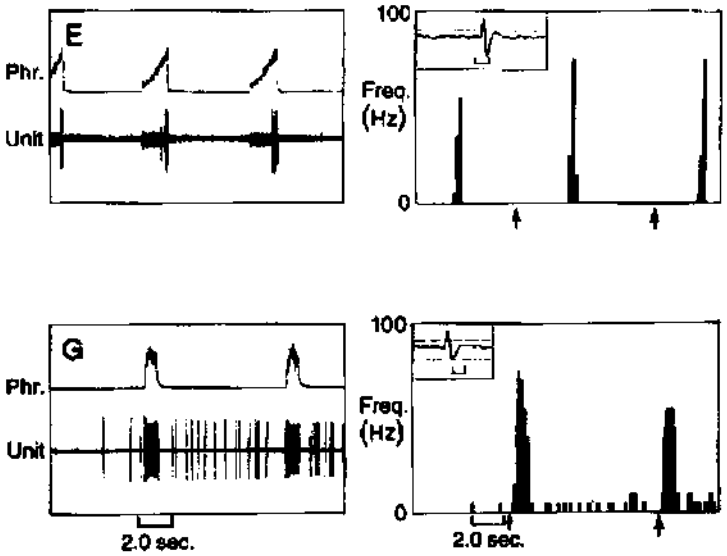

Figure 5 Neuronal activity of pre-Botzinger complex in eupnea and gasping. Left panels show integrated activity of the phrenic nerve (Phr.) and discharge of neuron (Unit) in eupnea (E) and gasping (G). Right panels show instantaneous discharge frequency of the neuron during ventilatory cycles of left panels. Arrows designate onsets of phrenic bursts. Insert is waveform of activity on extended time scale (1 msec). Note neuronal activity which commenced "late" in neural inspiration in eupnea began before the phrenic burst in gasping (From Ref. 20.)

causes an alteration of the eupneic rhythm to apneusis (70) or a "gasplike pattern" (57). This enigma concerning inhibitory synaptic transmission has been resolved by the finding that a blockade of this transmission causes a profound distortion of the eupneic rhythm of in situ preparations but only minimal changes of the gasping rhythm of this same preparation (71). The lack of sensitivity of medullary mechanisms for gasping to a blockade of inhibitory synaptic transmission fits with concept that, as in vitro, the discharge of pacemaker neurons in the gasping center–pre-Botzinger complex underlies the neurogenesis of the gasp.

Following the blockade of inhibitory synaptic transmission in situ, the eupneic rhythm was severed distorted but gasping was not elicited (71). However, as noted above, "gasplike" discharges have been recruited in some preparations following microinjections of bicuculline, a blocker of $GABA_A$ into the pre-Botzinger complex (57). Thus, in general, it would appear that a blockade of inhibitory synaptic transmission alone is not sufficient to release gasping. In this context, however, it is recognized that inhibitory synaptic transmission within the

brainstem fails in mild hypoxia (72). Likewise, pontile elements are recognized as one primary source of neurons whose discharge inhibits activities of medullary respiratory neurons (5,35,70,73,74). Thus, hypoxia or brainstem transactions would remove one element suppressing medullary mechanisms for gasping, the element being inhibitory synaptic transmission, largely of pontile origin.

In contrast to the reduction in inhibitory synaptic transmission, hypoxia is reported to cause an additional release of glutamate in some regions of the brain (57,75,76). Such a release might contribute to activation of persistent sodium channels of neurons in the gasping center–pre-Botzinger complex. As considered below, activation of these persistent sodium channels may be necessary to release pacemaker activities of these neurons. Such an activation by glutamate might underlie the finding that microinjections of the potent glutamate analog DL-homocysteic acid into the pre-Botzinger complex elicit an alteration from eupnea to gasping in some preparation (77).

Concerning ionic mechanisms underlying the release of medullary mechanisms for gasping, hypoxia causes an increase in the extracellular concentration of potassium (78). This augmentation probably results from the increased neuronal activity and occurs immediately prior to and immediately after the onset of gasping (14,78). In computational models, such an augmentation shifts the reversal potential for potassium to more positive values of voltage and, hence, reduces all potassium currents (79). This reduction of potassium currents is significant since computational studies have demonstrated that the activity of certain potassium channels may affect the conductance state of persistent sodium channels. Conductances through such persistent sodium channels are necessary for the intrinsic bursting behavior of some medullary neurons to be expressed (79), and are considered to play a major role in the generation of pacemaker-driven oscillations in vitro (80,81). Thus, reducing potassium currents may release intrinsic busting behavior in conditional pacemaker neurons and hence create necessary conditions, along with the elimination of inhibitory synaptic transmission, for pacemaker-driven gaspinglike oscillations in respiratory motor outflows (79).

The augmentation in the extracellular concentration of potassium is not the only mechanism by which conductances of potassium channels are reduced. Hence, hypoxia per se suppresses several types of potassium channels and activates low- and high-voltage calcium channels and also persistent sodium channels in neurons located in many brain regions (e.g., 82–91). The exact mechanisms intermediating the hypoxia-induced changes in the functioning of ionic channels and other intrinsic neuronal properties are not well defined. These mechanisms may involve signaling pathways, such as a change in nitric oxide (92), and second-messenger systems at the intracellular level. Moreover, hypoxia may modify channel conductances and neuronal firing properties through multiple cellular/intracellular mechanisms (92).

The hypoxia-induced processes, such as alteration of the ionic/metabolic extracellular environment, modulation of the intrinsic neuronal properties, and suppression of synaptic inhibition, cannot of course be limited to the region for neurogenesis of gasping in the rostral ventrolateral medulla. Rather, hypoxia-induced processes would be altered in many regions of the brainstem and, in intact animals, in the rest of the brain as well. However, recent studies have demonstrated that neurons in the rostral ventrolateral medulla have a high intrinsic chemosensitivity to hypoxia (87,93). It is unknown what intrinsic properties of these neurons define their special role in genesis of pacemaker-driven gaspinglike oscillations.

In summary, based on both theoretical and experimental studies, it is proposed that hypoxia or ischemia suppresses the pontomedullary neuronal circuit and releases medullary mechanisms for gasping by four interrelated changes: [1] a suppression of inhibitory synaptic transmission; [2] an augmentation in extracellular potassium concentration; [3] a decreased conductance through potassium channels; [4] an increased conductance through persistent sodium channels. These hypothesized mechanisms for the release of medullary mechanisms for gasping have been validated in an experimental study using an in situ preparation of the juvenile rat. In this preparation, a blockade of glycinergic transmission with strychnine, an augmentation in extracellular potassium concentration, and a block of potassium channels with 4-aminopyridine resulted in an elimination of eupnea and elicitation of gasping. Importantly, such an elicitation of gasping occurred under conditions of hyperoxia (94).

Gasping is also elicited under conditions of hyperoxia following microinjections of sodium cyanide into the region of the gasping center–pre-Botzinger complex (93). However, such injections would induce a region of localized "hypoxia" and thus might cause a release of gasping by mechanisms similar to those in generalized hypoxia or ischemia.

The basis for the release of gasping following several other perturbations is undefined. Hence, brainstem transactions at the pontomedullary junction would obviously remove any inhibitory synaptic transmission of pontile origin. Yet, as noted above, a blockade of inhibitory synaptic transmission alone is typically not sufficient to release gasping. For in vivo preparations, brainstem transactions result in a marked fall in arterial blood pressure and, of course, a varying region of tissue necrosis (22,95–97). Thus, the local environment in the region of the gasping center–pre-Botzinger complex might be hypoxic and/or acidotic following a brainstem transection. Yet, gasping also follows a transection at the pontomedullary junction of perfused in situ preparations of the neonatal and juvenile rat (46,94). In such preparations, perfusion of the brainstem should be relatively constant. Thus, in addition to inhibitory synaptic transmission, another "factor" of pontile origin appears capable of suppressing medullary mechanisms for gasping. In this context, removal of all pontile influences cannot reasonably be

equated simply with a removal of synaptic inhibition upon medullary neurons. As shown in many studies, apneusis follows removal of the rostral pontile pneumotaxic center whereas a complete removal of caudal pons is necessary to release gasping (see discussions in 3,4). Indeed, the pneumotaxic center alone exerts multiple functions in the control of ventilatory activity (98). It is obviously unknown whether removal of all pontile influences causes a switch to gasping by removal of synaptic inhibition upon neurons of the gasping center–pre-Botzinger complex, combined with depolarization of these neurons and activation of persistent sodium channels.

The mechanism by which another procedure releases gasping is undefined. Hence, under conditions of hyperoxia, eupneic ventilatory is replaced by gasping following elicitation of the "aspiration reflex" by stimulation of the pharyngeal mucosa (99). A series of studies have validated that gasping following pharyngeal stimulation is identical to that following brainstem transactions or exposure to severe hypoxia (54,100,101).

VIII. Summary

Thomas Lumsden's papers in 1923 and 1924 (6–9) formed the foundation for contemporary studies of the neurogenesis of automatic ventilatory activity. Lumsden considered that gasping was a "relic of some transitory primitive respiratory process" which "does not appear to influence true rhythmic breathing of normal type." Yet, presaging the concept of "autoresuscitation," Lumsden notes that he "feels no surprise that the facility has persisted in the evolutional struggle" since "gasping has been sufficient to revive animals whose higher respiratory centres have temporarily failed." Gasping represents the expression of a fundamental respiratory rhythm, generated by the discharge of pacemaker neurons in the rostral medullary gasping center–pre-Botzinger complex. For most of life, these pacemaker mechanisms are suppressed, and these rostral medullary neuronal activities are incorporated into the pontomedullary neuronal circuit responsible for the neurogenesis of eupnea. Under conditions of severe hypoxia or ischemia, many components of this pontomedullary neuronal circuit, including inhibitory synaptic transmission, are depressed. These depressions release the latent medullary pacemaker discharge and the gasp is generated.

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