The new biology has not so much uncovered basic principles as increased our appreciation of the complexity of the processes involved in oxygen sensing even at the cellular level. Nonetheless, new therapeutic targets have been identified that may become quite important for prevention and cure of diseases such as pulmonary hypertension and cancer.

PROBLEMS IN MEASURING HYPoxic VENTILATORY SENSITIVITY

Patients with lung disease and with sleep apnea and immature infants all may suffer adverse effects as a result of hypoxia. Because it was thought that poor sensitivity facilitated this, attempts have been made for many years to identify these susceptible individuals and develop therapeutic interventions that would improve ventilatory hypoxic responses. It is obviously crucial in such endeavors to be able to quantify the response to hypoxia (9). However, this is not easy to do and still remains largely unsolved.

HIGHLIGHTED TOPIC | Oxygen Sensing in Health and Disease

Oxygen sensing: applications in humans

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Cherniack, Neil S. Oxygen sensing: applications in humans. J Appl Physiol 96: 352–358, 2004; 10.1152/japplphysiol.00755.2003.—Our concepts of oxygen sensing have been transformed over the years. We now appreciate that oxygen sensing is not a unique property limited to “chemoreceptors” but is a common property of tissues and that responses to changes in oxygen levels are not static but can change over time. Respiratory responses initiated at the carotid body are modified by the excitatory and depressant effects of hypoxia at the brain and on the pathways connecting the carotid body to the brain. Equally important is that we are beginning to use our understanding of the cellular and molecular pathways triggered by hypoxia and hyperoxia to identify therapeutic targets to treat diseases such as cancer. We also have a better understanding of the complexities of the human respiratory responses to hypoxia; however, major deficiencies remain in our ability to alter or even measure human ventilatory responses to oxygen deficiency.

THIS PAPER WILL CONCENTRATE on the effects of hypoxia in humans and especially on the relevance and application of oxygen sensing to disease. It builds on the comprehensive review by Lahiri (30) 3 yr ago of the study of the sensing of hypoxia by the carotid body.

At the time of the Second World War, there was a resurgence of research on the effects of hypoxia, on oxygen sensing, and on the regulation of breathing in general for at least two reasons: 1) there was a need to develop ways of improving pilot performance to manage newly developed high-altitude aircrafts, and 2) there was a need to diagnose and treat chronic bronchitis and emphysema due to their being increasingly common diseases. The focus on “applications,” I suppose, was one reason for the appearance of the Journal of Applied Physiology at about the same time, with its emphasis on investigations on the study of the physiology of the common activities of humans. Although much was accomplished in the next 40 or so years, particularly in techniques of assessing the mechanical and gas-exchanging functions of the lung and in developing rapid methods of evaluating ventilatory responses to carbon dioxide, not as much progress was made in understanding human responses to hypoxia in health and disease.

The shift to studies of the actions of hypoxia at the cellular and molecular level has yielded an enormous amount of new information on oxygen sensing by the carotid body, which has been extensively reviewed (47). Perhaps even more importantly, studies have led to the recognition that oxygen sensing is a property of all tissues, that the response to hypoxia is multidimensional, that there is a complicated intracellular network concerned with the transduction of the response to hypoxia, and that the transducing pathways employed may depend on cell type (57).

The resurgence of research has also highlighted the even greater complexities of the neuropsychobiology of breathing in humans. The response to subnormal levels of oxygen on breathing involves long pathways and multiple organs, particularly the brain, and is not just dependent on the ability of the carotid body to sense oxygen. We now realize that hypoxia acts directly on the intercellular and interorgan relationships modifying carotid body signals. The response changes with time and can be affected at least transiently, volitionally, and by emotion. Despite the progress that has been made, huge gaps remain before the information gained from studies of cells and molecules can be applied to understanding human respiratory behavior.

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There are several sorts of problems. Some relate as much to measurements of the response to hypercapnia as to the response to hypoxia. In conscious humans, factors such as alertness, emotional states, and internal and external disturbances alter the level of ventilation and increase its variability to all stimuli (54). In addition, impaired lung mechanics will affect ventilatory responses. There is as yet no solution for the first problem. Various methods such as electromyograms, occlusion pressures, and so forth have been proposed over the years to overcome the second, but none has been completely successful (9, 37, 72).

Another set of problems is peculiar to the measurement of hypoxic responses. Attempts to develop a single number that would reflect ventilatory sensitivity to hypoxia have been frustrating. The ventilatory response to hypoxia is difficult to quantify because it is curvilinear, and there is uncertainty as to the exact effects of CO$_2$ on the hypoxic response (71). Some have considered the effects of hypoxia and CO$_2$ to be additive so that CO$_2$ responses measured at different constant levels of hypoxia form a set of parallel lines. Others, however, have considered the two stimuli to act purely as multipliers of one another so that CO$_2$ responses measured at different levels of hypoxia produce a fan of isoxic CO$_2$ response lines with the vertex of the fan resting on the zero ventilation axis. Both concepts require lengthy protocols that are rather taxing for the subject and for the measurer. In humans, hypoxic and CO$_2$ stimuli have both multiplicative and additive components and could be represented by a fan of isoxic CO$_2$ response lines meeting at negative levels of ventilation. This reflects interaction between CO$_2$ and O$_2$ occurring at the carotid body itself, additive effects of the peripheral and central chemoreceptors, and the additive effects of various neural drives (36).

Various solutions have been offered to simplify the quantifying of the hypoxic response. Severinghaus et al. (62) attempted to simplify the problem by proposing the hypoxic response be measured by the increase in ventilation when PO$_2$ was decreased from 200 to 40 Torr at resting levels of PCO$_2$. The development of rebreathing methods allowed CO$_2$ responses to be rapidly assessed, albeit in quite artificial circumstances, and led to the development of a similar method of evaluating the hypoxic response (51). Different methods of straightening the curvilinear ventilatory response to hypoxia have been proposed, but the most widely used involves plotting ventilation against oxygen saturation, even though it is recognized that PO$_2$ is the real stimulus to breathe. Because resting PCO$_2$ can differ considerably in conscious humans, there has been disagreement as to the correct PCO$_2$ for measuring hypoxic response by the rebreathing methods and, when the effects of acid-base changes are studied, whether PCO$_2$ or pH is to be kept constant. Single-breath responses to oxygen or nitrogen were developed to avoid having to control CO$_2$ changes with a corresponding loss in precision (13).

More recent studies have taken an even less rigorous approach to evaluating hypoxic response so that no attempt is made to maintain PCO$_2$ constant, allowing the natural decrease in PCO$_2$ to occur with hypoxic stimulation of breathing. Although this approach has simplicity as its advantage, it complicates the evaluation of changes that might occur with therapeutic interventions and hampers the interpretation of data comparing the effects of hypoxia in various species, both wild and mutant. It also tends to blur important physiological differences between changes in slope and changes in resting levels of ventilation, which theoretically have different effects on the stability of breathing.

**CENTRAL VS. PERIPHERAL ACTIONS OF HYPOXIA AND THEIR EFFECTS ON BREATHING**

Ventilation during exercise is reduced significantly in the few patients with asthma who have undergone bilateral resection of the carotid body but has a negligible effect on resting ventilation (22). Perhaps this is not as surprising as it may seem at first because normal arterial blood gases have been reported in adults with little response to CO$_2$ inhalation. For immature infants, the situation is quite different. Gozal et al. (17) have pointed out the potential clinical problems, such as sudden infant death syndrome (SIDS), that might be caused by inadequate carotid body function in the newborn.

Hypoxia has multiple effects that contribute to its action on breathing. Apart from its effects on the carotid body, it affects the brain’s release of neurotransmitters and its perfusion. It alters states of arousal and affects perceptions. It changes blood flow and its distribution through the lungs and the diameter of the airways, thereby altering the effectiveness of ventilation. It can alter the tone, strength, and endurance characteristics of the respiratory muscles, thus modifying the performance of the thoracic pump.

It is now clear that the ventilatory response to hypoxia changes over time, starting at birth, and is changed by experience with hypoxia (46). For example, birth under hypoxic conditions at altitude or with cyanotic heart disease diminishes or even obliterates the hypoxic response. In mature humans exposed to hypoxia at sea level for more than 5 min, ventilation falls off from its initial augmentation by hypoxia; in the newborn, ventilation may fall below prehypoxic levels (hypoxic ventilatory depression). On the other hand, sustained exposure in adults can lead to acclimatization with an increase in apparent hypoxic sensitivity (32). The various theories that have been proposed to explain these phenomena illustrate the problems that have plagued the understanding of hypoxia: with a stimulus having widespread and continuous effects on physiological systems, it is difficult to determine whether the breathing changes observed are due to an action of hypoxia at the carotid body or at the brain or elsewhere.

**Acclimatization.** Older arguments attributed acclimatization to the hypocapnia rather than the hypoxia occurring at altitude. Lowering of CO$_2$ levels produces alkalosis and brings into play mechanisms that reduce levels of bicarbonate in the blood via renal mechanisms and in the cerebrospinal fluid by a central process. The reduced bicarbonate allows greater increases in hydrogen ion to occur with increases in CO$_2$. This was considered in large part to explain acclimatization, but it is no longer believed to play an important role (44, 69).

More recent work suggests that direct effects of continuous hypoxia alter both the morphology and function of the carotid body, thus bringing about most of the changes that occur with acclimatization (3, 31, 32, 42, 70). However, despite the crucial importance of the carotid body, continuous intermittent hypoxia can produce acclimatization changes by central nervous system (CNS) actions (45).

Ou et al. (43) reported in a series of experiments that different areas of the brain exerted either inhibitory or facili-
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Itatory effects on breathing. These effects could be revealed in cats by removing parts of the brain and then exposing the animals to either acute or chronic hypoxia (68). Decortications of cats at sea level caused an exaggerated response to acute hypoxia principally as a result of an increase in breathing frequency; however, decerebrate cats had the same hypoxic response as intact cats. They concluded that the cortex exerted an inhibitory action on breathing, whereas the diencephalon had an excitatory action.

Both the excitatory actions of hypoxia on ventilation and the removal of a depressant effect of hypoxia have been implicated in the process of acclimatization, which is characterized by an increased response to changes in hypoxia and a shift of the CO₂ response curve to the left so that greater ventilations are observed at the same PCO₂. Neubauer et al. (40) proposed that hypoxic depression spreads rostrally to caudally in the brain and that altitude acclimatization might involve removal by hypoxic depression of a cortical inhibiting action on breathing. Hypoxia can have substantial effects on neuronal activity and on the mix of neurotransmitters released. An increase in the proportion of excitatory neurotransmitters may in part explain acclimatization (40). Ou and coworkers (43) described a facilitatory suprapontine mechanism in intact cats that contributed to high-altitude ventilatory acclimatization.

Hypoxic ventilatory depression. In humans with intact carotid bodies exposed to hypoxia, ventilation declines after 5 or 6 min from an initial peak, even if care is taken to prevent a decrease in arterial PCO₂ (40). This decline in ventilation (hypoxic depression) also seems to have both peripheral and central components.

Hypoxia increases both ventilation and cerebral blood flow. An increase in either brain blood flow or breathing lowers brain levels of CO₂ and has an inhibitory effect on ventilation, contributing to hypoxic depression. Although more intense hypoxia seems to have little stimulating effect after hypoxic depression has occurred, ventilatory responses to CO₂ changes are maintained even though with higher PCO₂ levels. This could be explained by the removal of an excitatory input from the carotid body itself rather than a general depressive effect on the CNS (52). However, in animals, hypoxic depression occurs even after carotid body denervation; thus the depression is obviously central. Robbins (52) claimed that, whereas hypoxia may act centrally to depress breathing in animals and perhaps those in the anesthetized state, in conscious humans the effect was mainly on the carotid body itself.

Studies by Neubauer and coworkers (41) suggested that hypoxic depression was caused by altered removal of inhibitory neurotransmitters like GABA during hypoxia perhaps secondary to an accumulation of lactic acid in the brain. Other studies suggest that, when it is present, the carotid body contributes to the occurrence of hypoxic depression. Tabata et al. (67) showed by microdialysis in freely moving rats that GABA levels in the nucleus tractus solitarius (NTS) increased with hypoxic depression and that a GABA antagonist injected into the NTS ameliorated the depression. Although this is consistent with a central hypoxic depression, they also found that, after carotid body denervation, the GABA increase with hypoxia no longer occurred and that the GABA antagonists had no effect. Carroll et al. (8) also demonstrated, using optical recording techniques, an inhibitory action of carotid body discharge on neuronal activity near the ventral surface of the medulla.

Recent studies indicate the importance of neurotransmitters in the brain in determining the size of the hypoxic response. The magnitude of a normal respiratory response seems to depend on an interaction between nitric oxide (NO) and glutamate and its N-methyl-D-aspartate (NMDA) receptors (19). Calcium transients resulting from activation of nitric oxide synthase (NOS) and NMDA receptors produce a mutually reinforcing cycle that augments the hypoxic response and diminishes the effects of hypoxic depression. S-nitrosothiols released from deoxygenated hemoglobin at the NTS are reported to play a major role in the hypoxic ventilatory response (35).

NOS is present in the medulla in both endothelial and neural constitutive forms, each having different effects on hypoxic response. These differences have been studied with knockout mice. Klime et al. (27) reported that mice lacking the gene for neural NOS had an exaggerated hypoxic response, whereas mice lacking the endothelial form of NOS had a diminished hypoxic response, but these differences may be due to effects either on carotid body function or on the pathways mediating the response to hypoxia or both. Both NO and CO act as neurotransmitters centrally as well as at the carotid body (48).

The actions of hypoxia on the systemic circulation may in some individuals contribute to ventilatory depression with hypoxia. Although the direct effect of hypoxia on the systemic blood vessels is dilating, hypoxia activates the sympathetic nervous system and produces a compensatory vasoconstriction. Edelman et al. (12) proposed that the inability of children with familial dysautonomia to tolerate hypoxia is not due to a loss of hypoxic sensitivity but occurs because there is sympathetic nervous system dysfunction. During hypoxia, systemic blood vessels fail to constrict as they normally do, allowing blood pressure and cerebral perfusion to fall so that ventilation is depressed (12).

CNS oxygen chemoreceptors. It is well established that the main effect of hypoxia on the CNS in anesthetized animals is to depress ventilation and excite sympathetic activity. The phenomenon of hypertension occurring with brain ischemia has been known for almost a century. More recently, it has been shown that, with severe hypoxia, respiratory excitation may also occur.

A number of investigators have reported tachypnea in chemodenerated animals with severe hypoxia that has been attributed to removal of suprapontine inhibition of breathing by hypoxic depression (68). More recent work has shown that severe hypoxia produces gasping in anesthetized animals by an action that involves the pre-Bötzinger area and perhaps other medullary sites. Solomon et al. (64) have proposed that gasping involves both a direct excitatory effect of hypoxia and the removal of a strong inhibition, which occurs during eupnea. Injection of minute amounts of cyanide in the pre-Bötzinger area causes gasping and increases in phrenic nerve discharge (39, 64).

NO also inhibits respiration, and the activity of NOS, which forms NO, is inhibited by hypoxia and thus is another possible mechanism for a central excitatory effect of hypoxia (48).

Systemic effects of tissue hypoxia. The explanation for the increase in breathing with exercise remains unclear. The relative lack of change in arterial PCO₂ with exercise hyperpnea suggests the possibility that the body can measure changes in
metabolic rate, and this in turn might occur if there were a chemoreceptor present in the mixed venous blood where changes in oxygen levels would reflect metabolism. However, the search for such a receptor has been unrewarding.

Recent studies in mutant mice with hemoglobin having subnormal affinity for oxygen have suggested that tissue levels of $P_O_2$ might be regulated and changes in tissue $P_O_2$ could initiate systemic responses; however, the tissues sites and mechanisms involved were not identified. Suzuki et al. (66), using a targeted knock-in strategy, generated mice with a mutation in the $\beta$ major locus of the globin genome. The half-saturation $P_O_2$ of this hemoglobin is 2 Torr higher than normal hemoglobin, which leads to chronically higher tissue oxygen levels (63). The hemolytic anemia, increased physical activity, and increased metabolic rate demonstrated by these mice and their elevation in arterial $P_CO_2$, due to decreased ventilation, were interpreted as adjustments aimed at reducing the elevated tissue $P_O_2$.

Mutations of $\alpha$- and $\beta$-globin genes have also been described that lead to an increased oxygen affinity of hemoglobin and decreased delivery of oxygen to the peripheral tissues; a decrease in tissue oxygen levels may produce a secondary polycythemia (28). A congenital deficiency of 2,3-bisphosphoglycerate that increases hemoglobin and oxygen affinity also produces polycythemia (28). There is no information on changes in ventilation or on ventilatory responses to hypoxia in this latter group of hemoglobin abnormalities. Changes since birth are perhaps required since Birchard and Tenney (4) reported no change in the hypoxic ventilatory response after rats were given sodium cyanate to acutely raise the oxygen affinity of their hemoglobin.

Hypoxia inducible factor-1 (HIF-1) is now recognized as the important element in determining erythropoietin levels. Through its action on renal peritubular cells, it is a potential link in a feedback system that uses changes in red blood cell mass as a method of regulating tissue $P_O_2$ (61).

OXYGEN SENSING IN DISEASE

Measurement of chemosensitivity in humans with lung disease is complicated by the systemic effects of hypoxia, particularly by its actions on the brain as well as by the reflex and central mechanisms triggered by the mechanical loading of the respiratory apparatus (18). The importance of ventilatory sensitivity to either hypoxia or hypercapnia in lung diseases in determining the natural history of the illness or its treatment remains an open question.

Obstructive lung disease. In the past, studies of the regulation of breathing in patients with chronic obstructive lung disease (COPD) focused on attempting to explain why some patients but not others develop hypercapnia. It was proposed that differences in pathology might account for the difference in behavior. Patients with $CO_2$ retention seemed more likely to have bronchitis, whereas those with emphysema seemed to be more likely to develop greater dyspnea and little if any hypercapnia (14). This notion was captured in the picturesque terms “blue bloater” (for the hypoxic hypercapnic bronchitic patient) vs. the “pink puffer” (for the patient with emphysema who had lost alveoli but desperately tried to maintain oxygenation). Sorli et al. (65) found that both hypercapnic and normocapnic patients had greater levels of ventilation than normal but that hypercapnic patients had a lower alveolar ventilation because they breathed with reduced tidal volumes and a faster frequency. Sorli et al. suggested that irritant receptors in the inflamed bronchi of bronchitic patients might be responsible for this pattern.

Because, for the same level of airway obstruction, some patients retained $CO_2$ but other did not, another idea was that depressed chemosensitivity contributed to hypercapnia. Altose et al. (2) reported low occlusion pressure responses to $CO_2$ in hypercapnic COPD patients, but others (21) did not. Altose et al. also showed that, although conscious healthy individuals when made to breathe through an external resistance increased their occlusion pressure, some hypercapnic patients did not, suggesting that they had an abnormality in load perception. No studies have looked at the strength of hypoxic-hypercapnic interactions in patients with obstructive lung diseases.

A blunted response to hypoxia may contribute to hypercapnia, but the evidence is not strong. Occlusion pressure responses to hypoxia were lower in patients who had experienced near-fatal asthma vs. those without asthma, suggesting that a decreased hypoxic sensitivity is a risk factor in causing life-threatening attacks (26).

It is possible that depressed chemosensitivity might reduce dyspnea in COPD patients and thus enhance exercise capabilities. No support for this was found by Robinson et al. (53) who reported that enhanced hypoxia and hypercapnia responses in patients with COPD led to greater maximum oxygen consumption during exercise and had no effect on dyspnea.

Hypoxia is the most serious consequence of COPD, producing pulmonary hypertension and heart failure, and is often treated by inhalation of oxygen-enriched gases. Because oxygen inhalation sometimes produces severe depression of breathing in patients with COPD, the contrary notion developed that those COPD patients who failed to respond normally to hypoxia survived because of their strong response to changes in the oxygen level. This also has been questioned, however, and the hypercapnia that occurs with oxygen breathing in COPD patients has been attributed to an enlarged dead space caused by the increased levels of oxygen in the lungs, which interfere with the adjustment of ventilation to perfusion (11).

Intermittent hypoxia and sleep apnea. Sleep apnea has only been recognized as an important disease that causes intermittent hypoxia in the last 30 yr.

Milhorn et al. (38) were the first to show in anesthetized cats that either episodic hypoxia or episodic electrical stimulation of carotid chemoreceptors produces a sustained increase in respiratory motor output (long-term facilitation) that could be prevented by serotonin depletion or the administration of serotonin antagonists. This increase in ventilation has been reported even in animals lacking neurally intact carotid bodies and seems to depend on changes in serotonin and on brain-derived growth factors within the CNS. However, the carotid body when intact may contribute to this phenomenon since an increase in its sensory discharge occurs with intermittent hypoxia (45).

Periods of hypoxia in animals interspersed among periods of normoxia simulating the pattern seen in sleep apnea can cause many of the same effects as chronic constant hypoxia, such as with pulmonary hypertension (49).

Intermittent hypoxia may affect human ventilatory responses to low oxygen. Katayama et al. (25) found increased hypoxic...
responses in six healthy volunteers at rest and during exercise who were exposed to a simulated 4,500-m altitude for 1 h/day for 7 days. Garcia et al. (15) reported an initial increase in hypoxic response in human volunteers who were subjected to intermittent hypoxia that later declined.

Both increased and decreased sensitivity to hypoxia have been reported in patients with sleep apnea (49). Prabhakar and Kline (49) suggested that there might be an increase in hypoxic sensitivity that occurs in early sleep apnea but that this increase disappears over time. Whether or not this occurs, the effects of changes in hypoxic sensitivity on the occurrence of apneas during sleep could be complex. Greater hypoxic sensitivity by increasing tendencies for periodic breathing might aggravate the numbers of apneas that occur during sleep, increasing the daytime feelings of sleepiness and fatigue that are important causes of disability in this syndrome.

Periodic breathing is a crescendo-decrescendo form of breathing that is interspersed with apneas or near apneas (10). Up until recently, this was perceived to portend imminent death occurring in patients suffering serious illnesses such as heart failure or stroke. Later, it was recognized as perhaps not quite as serious a sign as previously believed because it occurred at altitude and quite frequently during sleep. Recently, however, as a result of studies of patients with sleep apnea, it has been appreciated that the intermittent hypoxia that occurs with periodic breathing can have serious adverse consequences.

Hypoxia frequently brings on periodic breathing, whereas oxygen often eliminates it. The important factors in its genesis by hypoxia appear to be the increasingly greater changes in ventilation and sensitivity to CO₂ that result as hypoxia becomes more severe and the large changes in blood oxygen content that occur during hypoxia with even small changes in ventilation. All of these increase system gain and lead to instabilities in feedback control. Although there are adverse consequences to periodic breathing, Levine et al. (33), in a theoretical study, concluded that periodic breathing might actually improve oxygen delivery to the tissues.

The cellular effects of hypoxia can be significant in sleep apnea. For example, hypoxemia promotes tendencies for coagulation, probably by activating Egr-1, which in turn increases tissue factor in phagocytes and smooth muscle cells, leading to fibrin deposition (73). The intermittent hypoxia that occurs with sleep apnea may account for the increase in selectins seen in patients with that disorder, which promotes intracellular formation of clots and may be a factor in the increased incidence of hypertension and heart disease in sleep apnea patients.

SIDS. Hypoxia in utero produced for example by maternal smoking is now recognized as an important risk factor in SIDS. Some studies suggest that the depressed hypoxic ventilatory response of the infant is also important, but the evidence is far from conclusive.

Hunt et al. (23) compared the ventilatory responses to hypoxia and to hypercapnia in 36 near-miss SIDS infants with those in 23 control infants. Although baseline blood-gas values were the same during non-rapid eye movement sleep in the two groups, ventilatory responses to both hypoxia and hypercapnia were less in the near-miss infants. Subsequent siblings of SIDS victims were not aroused by hypoxia, although one-third of controls were, and the siblings were more likely to have periodic breathing with hypoxia (6).

Schiffman et al. (55) reported a depressed response to isocapnic hypoxia in SIDS parents. However, others found that parents of SIDS victims or near-miss infants had the same hypoxic and hypercapnic ventilatory responses as controls (34, 74). Also, no differences in the ventilatory or circulatory response to either hypoxia or hypercapnia were observed in school-aged SIDS siblings compared with siblings of healthy controls (16).

GENOMIC EFFECTS OF HYPOXIA

The techniques of cellular and molecular biology have revolutionized our understanding of the intracellular processes involved in the response to hypoxic stress and have identified several new possible therapeutic interventions for diseases such as cancer.

Only recently has it been appreciated that hypoxia has important immediate intracellular actions in many organs and tissues, which may be even more important for survival than the effects of hypoxia on ventilation (50, 60). Hypoxia has been shown to initiate changes in gene transcription that have long-time effects and can be beneficial or maladaptive. The number of genes known to be turned on by hypoxia is steadily increasing. A partial list of transcriptional activation by hypoxia includes AP-1, endothelin, NF-κB, Egr-1, and HIF-1 and indicates the widespread effects of hypoxia in modifying function (56). HIF-1 has been the transcription factor most studied. HIF-1 is continually formed but under euoxic conditions is rapidly inactivated by ubiquination, which in turn depends on the presence of Van Hippel Lindau protein and the enzyme prolyl-14 hydroxylase. HIF-1 is known to activate over 30 target genes, including erythropoietin and vascular endothelial growth factor. It stimulates the formation of glycolytic enzymes, inducible NOS, hem oxygenase-1, and non-insulin-dependent glucose transporter. It is also involved in apoptosis (56). Knockouts lacking the HIF-1 gene entirely have defective vascular and neural development and fail to survive (24).

It seems likely that hypoxia through its effects on HIF-1 is also involved in cancer progression (59). Many cancers have local areas of hypoxia and anoxia that might increase HIF-1 levels (50). Tumor cells without HIF-1 do not grow or develop new blood vessels as well as those that do, and HIF-1 may be involved in tumor spread (1). Studies in human pancreatic adenocarcinoma tissue showed increased production of vascular endothelial growth factor during hypoxia, which specifically activated HIF-1 (7). Xenografts grown from cancer cells exposed to a hypoxic environment had more rapid growth and spread more widely than xenografts grown in environments where oxygen was at normal levels (20). Bos et al. (5) found that high levels of HIF-1 in breast cancer cells predicted a poor prognosis. HIF-1 also upregulates the expression of genes that code a number of proteolytic enzymes and the cytokine tumor necrosis factor-α substances known to promote tumor invasion (29). It is likely that therapy targeted to neutralizing HIF-1 might be useful in cancer treatment (58).

CONCLUSIONS

There have been dramatic changes in our view of oxygen sensing. It was not very long ago that oxygen sensing focused on the “tasting” of oxygen levels by the carotid body. Appre-
cation of the pervasive effects of hyperoxia and hypoxia, both good and bad, has come rapidly during the past few years. With that has come the realization that the processes involved are intricate, and although each new discovery increases our understanding it has not as yet simplified our thinking.

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