Oxygen is the organizing influence of human biology and governs the aging process. In 2000, I began *Oxygen and Aging* with those words. Oxygen is a masterwork of nature — an enduring tribute to Nature’s preoccupation with complementarity and contrariety. It is an elixir of life and a hemlock for death — the ultimate molecular Dr. Jekyll and Mr. Hyde. Sometimes by its presence and sometimes by its absence, oxygen initiates signaling for cellular life as well as demise. In that context, it is important to recognize that oxygen drives chronic pain pathways primarily by its absence.

A large number of pain neurotransmitters are involved in clinical pain syndromes, including: substance P; enkephalins; neurokinin 1, 2, and 3; serotonin; adenosine triphosphate (ATP); nitric oxide; calcitonin; vasoactive intestinal peptides; epinephrine, norepinephrine, and related sympathomimetic agents; glutamic acid, aspartic acid, and related excitatory transmitters; and GABA, glycine, and related inhibitory transmitters. Some excitatory transmitters concerned with chronic pain include glutamic acid and aspartic acid, which are involved with dorsal horn sensitization through activation of NMDA receptors, while inhibitory transmitters participate in mechanisms that prevent or diminish pain. It seems safe to predict that future work will establish that, directly and indirectly, all those molecular species are triggered or influenced by oxygen deficit.

**Oxygen and Pain Neurotransmitters**

Neurotransmitters transmit information across synapses — regions separating neurons from adjoining neurons, as well as neurons from the muscle cells. These substances are stored in the bulbous ends of axons, and are released by electrical impulses traveling along the nerves to those ends. Upon their release, neurotransmitters either facilitate or inhibit continued electrical impulses along the nerve fibers on the other side of the synapse. Over 300 molecular species have been recognized to be involved in neurotransmission. Some of the best known of those over 300 neurotransmitters have been listed in a preceding section. It is regrettable that all neurologists and others in the headache industry I know limit their work only to serotonin and a few related neurotransmitters.

Next to oxygen and serotonin, substance P (SP) is the best examined of all the pain neurotransmitters, and its relationship with oxygen deficit has been most clearly delineated. It is an 11-residue peptide belonging to the tachykinin sub-family of G-protein-coupled receptors (GPCR). Those receptors form a class of integral membrane proteins. Serotonin in the mammalian brain and receptors of the olfactory epithelium that binds odorants are two other members of this family of receptors.

Oxygen deficit triggers the release of substance P. There are several lines of direct and indirect evidence for it. Direct evidence for that comes from experiments in which decreasing concentrations of oxygen were associated with the release of increasing amounts of SP. Specifically, the carotid bodies contain SP — in concentrations ranging from 1.4 to 1.6 ng/mg protein — that is released in response to tissue hypoxia. The amount of SP released from the carotid bodies increases in proportion to the severity of hypoxia. It is noteworthy that the release of SP by hypoxia is a calcium-dependent process, and is primarily mediated by N- and L-type Ca2+ channels.

Other lines of evidence for the fundamental role of oxygen deficit in the causation of pain include the following: (1) skin lactate levels are increased in complex regional pain syndromes; (2) SP increases protein extravasation in regional chronic pain states; (3) intradermal injection of epinephrine causes local pain (due to vasoconstriction and consequent oxygen deficit); (4) a tissue injury occurs in complex regional pain syndrome; (5) ascorbic acid reduces pain in reflex sympathetic dystrophy; and (6) certain other free radical scavengers also reduce pain in complex regional pain states — the mechanism of action of antioxidants being restoration of local oxygen homeostasis.

Substance P exerts varied effects on different tissues. It is excitatory to the carotid body. Release of larger amounts of SP in the lungs is associated with pulmonary hypertension, an effect that is attenuated by antioxidants. In the nasal mucosa, hyperbaric oxygen decreases immunoreactivity to substance P. Not unexpectedly in light of the oxygen/SP dynamics, oxyradicals under certain conditions also trigger the release of substance P. By contrast, antioxidants, such as ascorbic acid, inhibit the release of SP. However, the relationships between antioxidants and SP are complex. For instance, capsaicin increases regional perfusion — and oxygen delivery, inhibiting the release of SP — but is also known to increase SP release in the lung. Oxidants also have complex relationships with SP. For example, nitric oxide serving as an oxidant modulates histamine release from tissue mast cells and circulating basophils, and so contributes to pain caused by histamine. On the other hand, nitric oxide, through its vasodilator role, improves oxygen transport, decreases the release of SP, and mitigates some pain syndromes. (See *Nature's Preoccupation With Complementarity and Contrariety*, the first volume of The Principles and Practice of Medicine, for an in-depth treatment of the subject.)

Substance P also has complex relationships with certain other physiologic compounds, including enzymes and hormones. For instance, increased amounts of erythrocyte 2,3-diphosphoglycerate (2,3 DPG) caused by chronic hypoxia is associated with increased release of SP. Since chronic hypoxia increases the concentration of 2,3-DPG, this provides yet
another mechanisms by which oxygen deficit causes pain. Fascinating! How oxygen, by its absence, both triggers a mechanism for correcting that problem (by increasing 2,3-DPG production) and sends out messages to other cellular systems for participation in that effort (by inducing the production of SP). An example of the involvement of enzyme system with SP is that acute depressor actions of angiotensin II in the nucleus of the solitary tract are mediated by SP. An insight into the possible interactions between SP and hormones is provided by the complementary roles of SP and calcitonin gene-related peptide in the causation of phantom and ischemic pains.

An interesting aspect of the oxygen/substance P dynamics is revealed by the case of the East African naked mole-rats (Heterocephalus glaber). This rat species lacks substance P and does not appear to suffer pain when tormented.31 The rats feel no immediate pain when cut, scraped or subjected to heat stimuli. They only feel some aches. But when the rats get a shot of SP, pain signaling resumes working as in other mammals. One can only wonder about what other defense mechanisms exist in this rat species that compensate for substance P.

On the Nature of Pain

Pain is a sensory perception intricately linked to the emotional state of the person. Pain is not a disease, nor a discrete bodily state. That explains why pain in different cultures means different things to different people. This is a crucially important aspect of pain when considering the biochemistry of pain neurotransmitters presented above. I had certain ideas of pain during those three decades of my work as a surgeon and a pathologist. In those years, I suffered migraine attacks. Since vomiting accompanying migraine did not allow me to keep any painkillers down, I gave myself Demerol injection for relief. My work in integrative medicine changed all that. I taught myself control of migraine by assuring optimal hydration, preventing rapid hypoglycemic/hyperglycemic roller coasters and consequent rapid insulin shifts, addressing issues of mold and food allergy, and controlling vasospasms with self-regulatory methods - all measures that restore oxygen homeostasis, locally or systemically. I have not had to take Demerol during the last eight years. I have a prolapsed lumbar disc which sometimes caused disabling backache. During those years, I also taught myself control of that pain with limbic breathing32 - an energetic method of breathing with extended periods of exhalation (see Healing Miracles and the Bite of the Grey Dog for details of other effective self-regulatory methods). For years, I have controlled my back pain with limbic breathing, without any painkillers, manipulations, laser or other therapies.

I might point out here that direct oxygen therapies - oxygen by mask and hyperbaric oxygen - have been successfully used in controlling headaches and migraine attacks.34-37 Specifically, in one double-blind trial breathing 100% oxygen for 15 minutes or less during headache episodes controlled or significantly reduced the pain of acute cluster attacks in all subjects.34 Not surprisingly, one fourth of the study participants experienced cluster attacks soon after the treatment was stopped35 - since various elements jeopardizing oxygen homeostasis were not addressed. Administration of higher concentrations of oxygen during the postoperative period reduces or relieves the intensity of postoperative pain. It appears to both reduce the release of substance P and influence pain inhibitory pathways in the peripheral nerves. Correlation between urinary substance P and bladder pain has been documented.

Oxygen Homeostasis

Seeing Pain, Thinking Oxygen

In my clinical work, when I see pain, I think oxygen. I think about how dehydration in one person worsens functional oxygen deficits, and how incremental oxidative stress threatens oxygen homeostasis - locally and/or systemically - in another. I think about how hyperglycemic-hypoglycemic shifts trigger rapid insulin responses increasing the intensity of pain in yet others. I think about how undetected and unmanaged allergic triggers acting in the bowel and elsewhere cumulatively cause oxidosis, acidosis, dehydration, add to oxidosis, acidosis - and then all collectively threaten functionality of oxygen, increasing the degree of pain regardless of what the initial pain triggers might be. Then I ponder how often neurologists and anesthesiologists at pain centers think about the effects of total body burden of toxic metals and xenobiotics on pain neurochemistry - by feeding the frenzy of the three furies of pain - oxidosis, acidosis, and dysoxegenosis.

Following are some commonly observed clinical manifestations of biochemical interactions among the pain sensors and modifiers listed above:

1. Coronary chest pain is relieved or mitigated by the administration of oxygen, as are attacks of headache and migraine.33-35

2. Direct oxystatic measures - treatments that restore oxygen homeostasis, including oxygen, hydrogen peroxide, singlet oxygen, and related treatments - prevent, diminish or relieve diffuse tissue pain in fibromyalgia.35-39

3. Indirect oxystatic measures - treatments such as prolotherapy with injection of 50% glucose or other suitable agents that stimulate fibroproliferative responses - relieve trigger point pain by evoking local oxystatic inflammatory tissue response.40

4. Chronic back pain in many cases can be relieved by effective self-regulatory methods, especially with specific breathing methods (see limbic breathing in The Cortical Monkey and Healing).41

5. Pain syndromes accompanying reflex sympathetic dystrophy can be relieved with direct oxystatic therapies combined with indirect oxystatic measures, including restoration of bowel ecology and hepatic detoxification (personal unpublished observations); and

6. Cooling of forehead diminishes sympathetic tone, increases regional blood supply (correcting oxygen deficit), and relieves certain types of pain associated with dysautonomia.41

On deeper reflection, the pain-relieving roles of oxygen and oxyradicals can be recognized in most, if not all, empirically proven pain control therapies. Indeed, in my own clinical work I find that every chronic pain can be partially or completely controlled by effective direct and indirect oxystatic therapies. That, in essence, is the "oxygen view of pain" presented in this article.

Author's Priorities for Headache and Migraine: A Clinical Application of the Oxygen View of Pain

Headache and migraine patients must take the time to understand the true nature of their suffering, and not waste time worrying what type of headache and migraine they may or may not have. They must understand that drug therapies cannot be accepted as the full treatment of their suffering. They must know
Oxygen Homeostasis

that their suffering can be prevented by non-drug therapies, except in rare instances of pain associated with depression, anxiety, or drug dependence. It is mandatory to have tests done for antibodies for molds and this issue addressed. Mold sensitivity was present in nearly all of my patients with headache attacks. The same holds for uncovering and effectively managing food sensitivities. Even ordinary fluctuations in blood sugar levels can trigger headache attacks. So headache and migraine patients must not miss breakfast. Similarly, dehydration increases vulnerability to headache, and optimal hydration must be assured for optimal control of headache. In many instances, myofascial trigger points in the neck, shoulders, and scalp trigger headache attacks. Such trigger points require resolution by appropriate therapies. The author’s choice is prolotherapy with 50% glucose. Headache and migraine patients must become sensitive to problems caused by excess acidity.

Cellular oxidosis, acidosis, and dysoxigenosis resulting from nutrient deficits can trigger, perpetuate, or intensify headache. So, I consider nutritional therapies – magnesium, calcium, and potassium stand out in this context – as well as selected phytotherapies as important components of the program. And most importantly, headache and migraine attacks are commonly triggered by stress and perpetuated by chronic anger. Thus, such patients must learn effective self-regulatory methods for prevention and treatment of headache. (See Healing Miracles and the Bite of the Gray Dog.) Most importantly, persons with headache and migraine must learn to think oxygen when they experience pain. They need to recognize that self-regulatory, nutritional, and environmental measures enlighten and empower them, while drug therapies for headache disablepower the sufferers and keep them in the dark.

In closing, the crucial clinical importance of the “oxygen view of pain” presented here is this: It mandates that all relevant oxygen issues be diligently addressed in the clinical management of every patient with a chronic pain syndrome. How often do clinicians recognize the essential commonality of biochemical lesions – oxidosis, acidosis, and dysoxigenosis – that cause migraine and heart attack? How often do they see that commonality between the pain episodes of severe dysmenorrhea and myofascial trigger points? And that between arthritis and sympathetic reflex dystrophy? And that between pain of prolapsed vertebral discs and fibromyalgia? And that between pain of TMJ and renal colic? The oxygen view of pain provides a clear link. What might be required for managing ischemic coronary syndromes with the oxygen view of pain? The same approach as for controlling migraine attacks given above. Why? Because the oxygen issues that cause oxidative coagulopathy and so set the stage for coronary artery blockages are exactly the same as those that trigger migraine attacks. Cholesterol, I might add here, is an antioxidant and protects the coronary arteries until it gets oxidized, becomes rancid, contributes to oxidative coagulopathy, and sets the stage for atherosclerosis.

References


TOWNSEND LETTER for DOCTORS & PATIENTS – JANUARY 2005