Darwin Trilogy

THE PRINCIPLES AND PRACTICE OF INTEGRATIVE MEDICINE

VOLUME X

DARWIN, OXYGEN HOMEOSTASIS, and OXYSTATIC THERAPIES

THE THREE-LEGGED THRONE OF OXYGEN

Hydrogen Peroxide, Ozone, Oxygen and Related Protocols for Degenerative, Immune, and Neoplastic Disorders

10

MAJID ALI, M.D.

The Principles and Practice of Integrative Medicine
Volume X

Darwin, Oxygen Homeostasis, and Oxystatic Therapies

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The Principles and Practice of Integrative Medicine
Volume X

DARWIN, OXYGEN HOMEOSTASIS, AND OXYSTATIC THERAPIES

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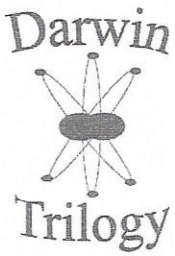

Oxygen in Public Discourse

2009 is the bicentenary of Charles Robert Darwin's birth and the 150th anniversary of the publication of his classic The Origin of Species. Anniversaries of cultural, sociologic, and religious events are usually celebrated with thinly disguised attempts to promote specific agendas. I am publishing Darwin and Dysox Trilogy with a clearly stated agenda: to underscore the central relevance of Darwinian tenets of competitive struggle for resources, natural selection, and ecologic connectedness. I assert that the element at the center stage of all elements that connect cellular populations—adjudicating all conflicts created by competitive struggle—is oxygen. So, I offer the Trilogy in 2009 to promote my fully declared agenda of bringing oxygen into the public discourse of medicine—for physicians, parents, public policy makers, teachers, and others.

The essence of a scientific model is that it is testable and, therefore, refutable. The core strength of the "oxygen simplicity" presented in the *Trilogy* is that it allows clinicians to effectively cope with enormous complexities of caring for the sick. This simple idea deserves broader testing—validation or refutation—than is possible for me in these three volumes.

Chemistry and medical textbooks describe oxygen as a substrate in biologic reactions. For example, hemoglobin is described to pick up oxygen in the blood. Oxygenases are said to add oxygen in reactions catalyzed by them. Hypoxia-inducible factors (HIFs) are supposed to sense the presence of oxygen. Mitochondria are considered to utilize oxygen. Chemoreceptors are assigned the roles of recognizing the concentrations of oxygen in blood and cells.

I do not consider oxygen as a substrate for enzymes, sensing proteins, mitochondria, or chemoreceptor cells. Oxygen is an organizer, not just a passive substrate. For reasons of crucial clinical significance in medicine, oxygen should be clearly seen for what it is: a mover, a shaker, an organizer. In this light, oxygen "rides" large protein complexes, such as hemoglobin. Oxygen rearranges protein complexes, such as those included in the HIF family. Oxygen drives electron and proton chain reactions in cellular organelles mitochondria. Oxygen awakens cells: chemoreceptors. Oxygen activates cells, such as glomus cells in the aorta and the carotid arteries.

The crucial clinical importance of the Dysox Model of Disease is that it requires an unfaltering focus on all relevant issues of oxygen homeostasis regardless of the diagnostic rubric used for a chronically unwell individual. For reversal of disease and lasting results, it is imperative to create conditions that foster restoration and recovery of all aspects of oxygen homeostasis.

What Is Oxygen Consciousness?

In the Darwin and Dysox Trilogy, I present unifying dysox models of inflammation, pain, diabetes, obesity, coronary artery disease, renal failure, asthma, adrenal dysfunctions, heavy metal toxicity, and other disorders. Why obsess with oxygen? I anticipate the question. Because if these models were understood and put into practice, billions of people worldwide would escape lifelong toxicity and the cost of prevailing drug therapies. A deep understanding of how oxygen sustains life on the planet Earth—oxygen consciousness is my term for it—sheds light on crucial issues of human habitat, animals, and plants.

Nature is mysterious. Nature is mystifying. Nature gives us our sense of wonderment, which brings together things that look different. This "togetherness" offers us the possibility of connecting the proverbial dots during the journey of life—seeing with clarity our oneness with all life around us. That is true enlightenment. In healing arts, I do not know of any other single element that can enlighten us more than oxygen. It is the unifying element that provides the glue that holds us together. For example, understanding oxygen to understand the nature of hypertension is also to have understood the beginning of all disease. This is the oxygen consciousness in medicine, a fascination with oxygen signals and oxygen energetics that begins with a struggle to control disease—normalization of blood pressure in hypertension without drugs, for instance—and turns into a lifelong search and love for understanding natural phenomena in biology. So begins a wondrous journey as mysterious and mystifying as anything known to me. I invite the readers to consider—then begin—this journey of an enlightened life.

THE DYSOX STATE

Dysox is the abbreviation of my term dysoxygenosis. In 1998, I introduced the term dysoxygenosis to refer to impaired oxygen homeostasis caused by a broad range of disruptions of oxygen signaling. Specifically, I included in the dysox state, the oxygen-related structural and functional abnormalities of:

- Mitochondria;
- Membranes; and
- Matrix

Mitochondrial abnormalities disrupt the Krebs cycle chemistry and cause complete or incomplete respiratory-to-fermentative shifts in ATP generation. Abnormalities in the membranes of cells and subcellular organelles disrupt functions of membrane channels, receptors, pumps, and related intelligence systems. Abnormalities of the matrix include impaired matrix signaling and diverse regulatory roles, and protease/protease inhibitor dynamics; included in this category are also the abnormalities of extracellular fluid compartments.

The dysox state is not an all-or-none phenomenon. Different cell populations in the various body organs of individuals undergo degradative shifts in oxygen homeostasis to varying degrees. Not unexpectedly, the range of symptom-complexes experienced by different individuals is broad. Needless to say, that occurs because the changing environmental, nutritional, and stress-related conditions affect the genetic, signaling, and enzymatic pathways in different individuals differently.

Why keep the dysox state in sharp focus at all times? Because the degrees of molecular derangements, tissue injury, and suffering caused by illness depend on the cumulative disruptions of oxygen signaling—whether caused by toxic environment, toxic foods, or toxic thoughts. Every step taken to improve oxygen homeostasis and signaling enhances the value of all others. This is the scientific basis of integrative medicine.

What Is Science?

A scientist has but one allegiance—to the truth in his observations. He grows when he continues to observe. A theory may be proposed to explain his observations, but first he must continue to observe. Once made, a valid observation stands on its own. The interpretations of that observation and conclusions drawn from it can—and should—be open to question. However, no valid observation, once made, must be discarded because it does not fit into any preexisting model or concept. This principle is as relevant to clinical medicine as it is to experimental sciences. Science neither claims nor accepts ownership. It recognizes neither gurus nor disciples. Science, simply stated, concerns itself with purity of observation

What Is Disease?

Chronic disease is a state of separation from one's nature. This is not a metaphysical notion. One's nature is the state of resonance with what is within and what is without. Humans evolved within the kaleidoscope of evolution of everything around them—geological formations, plants, and animals. Consequently, human health is the state of communion and coexistence with the human habitat.

What separates us from our nature are unhealthy foods, unhealthy environment, and unhealthy thoughts. Some readers might question why genes should be excluded from center stage. My simple answer: Hundreds, if not thousands, of genes are involved in the development of all chronic and dominant disorders. Effective gene therapies are not available for any of these disorders at this time. Nor does it seem likely that gene therapies for such disorders will be forthcoming in the near future. Beyond that, focus on genes is disempowering. Therefore, the true causes of disease at this time must be searched for in toxic foods, toxic environment, and toxic thoughts.

What Is Integrative Medicine?

In mid-1980s, I defined integrative medicine as a philosophy that requires physicians to offer all that is safe and effective without subservience to one or more schools of medicine.

Integrative medicine is not about popping zinc pills or omega-3 soft gels. It is about taking people with chronic disorders—Crohn's colitis, rheumatoid arthritis, multiple sclerosis, thyroiditis, asthma, failed coronary stents and bypasses, and others—and restoring their health while drug therapies are discontinued. The clinical craft of integrative medicine is to integrate therapies to enhance results beyond what is possible with individual therapies.

The Principles and Practice of Integrative Medicine

Volume I:
Nature's Preoccupation with Complementarity and Contrariety,
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Annual Pathology Review Series	1974-1986

Darwin, Dysox, and Our Fermenting Planet
Introduction to Darwin and Dysox Trilogy

No simplicity in clinical medicine—in my view—is as compelling as the simplicity of the "dysox model of disease," described and illustrated in the Darwin and Dysox Trilogy (the tenth, eleventh, and twelfth volumes of The Principles and Practice of Medicine). No simplicity allows me to more effectively cope with so many complexities of caring for ill individuals as the simplicity of three primary homeostatic mechanisms governed by oxygen: acid-base balance, redox regulation, and clotting-unclotting equilibrium (see chapter 2 entitled "Oxygen Homeostasis—Oxygen's Three-Legged Throne Model and The Sun-Soil Strategy for Healing" for details). In 1998, I introduced the term dysoxygenosis ("dysox" for short) for the states of respiratory-to-fermentative shift in ATP generation and disrupted oxygen signaling.[1-3] The core significance of the dysox model of disease is: All issues related to oxygen homeostasis must be diligently considered in caring for an ill individual regardless of the diagnostic rubric.

The great value of Darwin's seminal tenets of ecologic connectivity and natural selection is that in biology so little explains so much. The core importance of the dysox model of health and disease—in my view—is also that in clinical medicine so little explains so much. Darwin's theory of the origin of species continues to be rejected by some because they fail to see the range and rates of transition in the evolution of species. The significance of dysox is also not recognized by many clinicians because they fail to see the range and rates of transition in the evolving patterns of disrupted oxygen signaling and the respiratory and fermentative modes of cellular energetics in the evolution of various stages and forms of illness. I devote the Trilogy to an in-depth treatment of these crucial issues and related subjects.

Ecologic Thinking in Medicine

Darwin's essential message for biologists is that no part can be understood without understanding its relationship with the whole. The essential significance of the dysox phenomenon for physicians is that it explains foundational relationships between cellular injury and adverse effects of nutritional, environmental, and stress-related factors. I illustrate these crucial concepts with some clinical examples. A cardiologist prescribes Inderal for tachycardia. A dermatologist administers steroids for eczema. A neurologist uses Zomig for headache. A gastroenterologist treats gastroesophageal reflux disorder (GERD) with Nexium. How does Darwin inform these specialists? What should the phenomenon of dysox mean to them?

We doctors have not been ecologic thinkers. Darwin invites us to become clinical ecologists and understand how environmental, dietary, and stress-related triggers cause various symptom-complexes. In caring for chronically ill individuals, the dysox model of disease shifts the focus from the diagnostic terms chosen for them to detecting and addressing all factors that put oxygen homeostasis in jeopardy. It offers cardiologists, dermatologists, neurologists, and gastroenterologists not only a clear scientific basis of those relationships but also provides sound scientific basis for alleviating suffering and restoring health. These simple ideas call for a radical re-thinking of the prevailing medical philosophy.

Clinical Research

Who determines the long-term relative safety and efficacy of a drug—professors in medical schools or clinicians in the trenches of illness? Both groups know the answer. Clinicians focus on their patients as individuals and commonly treat concurrent problems in individual patients. Professors focus on a single drug made by a pharmaceutical company who pays for their "research" and disregaurd other co-exsisting disorders in people treated with that drug. Clinicans cope with clinical realities. Professors largely create artifical models. Some decades ago, I recognized a dire need for an integrative model of clinical research, in which teams of integrative clinicians, without any financial conflicts, collectively and openly, care for a large number of unselected patients with specific disorders, diligently maintaining detailed records. The outcome data are then published in-toto showing the clinical efficacy or inefficacy of the integrative management protocols. I wrote the Darwin and Dysox Trilogy to fulfill that need. The readers will recognize that these studies demonstrate the philosophy, principles, and practice of integrative medicine discussed at length in these and other volumes of this textbook.

Ethics in Medicine

Ethics, simply stated, is the study of the consequences of one's actions on others. Ethics is also the study of the consequences of one's failure to take the needed action on others. For example, it is clearly unethical for a nurse not to give a patient the prescribed medication. The relevance and significance of no action by a doctor, when action is required, is self-evident. It is clearly unethical when a doctor fails to do the necessary detective work to uncover the substances and/or elements that cause or contribute to the illness of a patient. In this light, how ethical is the use of Inderal for tachycardia without searching for and addressing the environmental, nutritional, and stress-related factors that create adrenergic hypervigilence? How ethical is the use of steroids for eczema while neglecting the underlying causes of mold allergy, mycotoxicosis, and adverse food responses? How ethical is the use of Zomig for headache without a diligent search for causes of headache? How ethical is the use of Nexium for blocking the acid pump when the real problem is gastroparesis? Indeed, is it ethical for any doctor to suppress symptoms with drugs without addressing the primary mechanisms of molecular and cellular injury—disruption of oxygen signaling and respiratory-to-fermentative shift resulting from impaired mitochondrial function? Is it ever ethical for a doctor to ignore the adverse effects of altered gut microbiota, impaired hepatic detoxification pathways, and environmental pollutants—industrial toxins, heavy metals, mycotoxins, and others—before prescribing any drug for a chronic disorder?

Humans Are Not the Apical Predators

Darwin and the dysox phenomenon have other important messages for physicians. Biology is an equalizer. We humans position ourselves at the top of the food chain and exult in that delusion. I do not see a food chain, only a food cycle in nature in which every species is both a predator and prey—in the eternal predator-prey dance of life and death, the predator often becomes a prey and the prey a predator. The human cells sometimes destroy invading microbes, and are sometimes killed by them. Based on extended clinical experience, morphologic observations, and biochemical findings in patients with diverse clinical disorders, I consider mold allergy, overgrowth of yeast species in the bowel, and mycotoxicosis to be the most significant threats to human health. The dysoxic effects of these factors—compounded by

those of toxic metals and synthetic chemicals— contribute significantly to the pathogenesis of autoimmune, environmental, degenerative, and neoplastic disorders. So, these "lowly" oxyphobic microbes can hardly be relegated to the bottom of the so-called food chain. Nor can humans be assigned the top position. I cite the case of Staphylococcus aureus to support my larger point here. In 1958, I learned that S. aureus was a nuisance, present on the skin of up to 40% of healthy individuals. In 2008, I learned that the microbial species killed more citizens of the United States than the HIV/AIDS complex.[4]

Dysox and Climatic Chaos: A Fermenting Planet Cannot Sustain Healthy Humans

Times are desperate for most forms of life on the planet Earth. In considering the predicted climatic changes, the focus is always on carbon issues, and oxygen-related issues are completely ignored. This, in my view, is a serious mistake. In reality, the biologic consequences of the oxygen-related issues (the "oxygen issues") are far more important. Below is text from my three-part article on the subject entitled "Dysox and Climatic Chaos: The Primacy of Oxygen Issues Over Carbon Issues.[5]"

Butterflies, bees, and bats are disappearing with accelerating rates.[6-8] Before the fall of these flyers, we witnessed large-scale extinction of amphibian species.[9,10] The world's best scientific sleuths used their best diagnostic technologies to uncover the underlying causes in fungi, viruses, pesticides, industrial pollutants, habitat destruction, and climatic changes. No specific cause was identified in any case. None of the investigators recognized the obvious: disruption of oxygen signaling and blockade of oxygen-driven bioenergetics caused by the cumulative effects of multiple oxygen disruptors—as is the case in all human deaths regardless of the initiating and complicating factors. The fundamental bioenergetics of butterflies, bees, and bats involve coupling of respiration with oxidative phosphorylation and mitochondrial ATP generation. Except during hibernation, the mitochondrial dynamics in these species are essentially identical to those of humans. In health, the products of metabolism of carbohydrates, fats, and proteins enter the Krebs cycle and, under optimal conditions, are broken down completely into water and carbon dioxide to generate "clean" energy. When the Krebs cycle is unimpeded, all of its intermediates (organic acids) are broken down to produce ATP.

As for oxygen-utilizing life forms, in my view, the planet Earth is fermenting. This view of dysox is a strong explanatory power not only for butterflies, bees, and bats, but also for humans.

The Future of Humankind Is Not a Zero-sum Game

In the context of the predicted climatic chaos, Darwin's message is: a gain of one people must not be equated with the loss of another—the future of humankind is not a zero-sum game. Nationalistic agendas for coping with projected climatic changes will not only be ineffective but also divisive and counterproductive. Humankind now faces different problems. If relentless global chemicalization, poisoning of human habitat, and fermenting of the planet continue unabated—global warming, without doubt, will explode the scale of oxygen crises—the threat to human health and survival will increase exponentially. Charles Robert Darwin developed his central ideas of ecologic connectivity and natural selection to define his theory of origin of species. Herbert Spencer hijacked that idea and introduced the expression survival of the fittest to advance his social manifesto—an unfortunate choice of words that fostered self-centeredness, abuse of power by the spiritually sclerosed, and oppression of people. Humankind now faces different problems. If

predictions about the looming climatic chaos are realized—evidence to the contrary is non-existent—there will not be a "fittest" left among us. What poisons some now will poison all with time. Is there a more compelling reason in support of the core notion of oneness of the human species—and, by extension, oneness of all planetary life? Is there a more cogent and forceful argument for accepting and fostering this notion of a shared planet? We physicians have important roles to play in the great environmental and social issues of our time. The Darwin and Dysox Trilogy is my attempt to engage that dialogue as well.

A fermenting planet cannot sustain healthy life.

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DEDICATION

We physicians do not invent wisdom—we only reflect the wisdom of the patients, who gain it through their pain and suffering. For five decades, I have tried to look at the problems of the sick through their eyes and through my eyes. So, I consider my patients my true teachers and dedicate this volume to them.

ACKNOWLEDGEMENT

I am most grateful to the physicians, nurses, nutritionists, patient counselors, and the administrative staff of the Institute of Integrative Medicine who have diligently worked for decades to create the environment in which I see my patients and conduct my basic and clinical research. In a larger sense, this volume reflects as much their work as it does mine.

Some of the previously published reports of long-term integrated clinical trials included in this volume describe results obtained with a team effort. The active participants in that team work were:

Alfred Fayemi, M.D.
Mahboob Baig, M.B.,B.S.
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Shara Resende, B.A.
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Talat, my wife, is always my enduring resource.

A Discipline of Wholeness

Human biology is a wondrous web of energetic-molecular happenings—a kaleidoscope brought to life by bursts of innate energy, colored by cellular mosaics, moved by paradoxes of complementarity and contrariety. When one thing moves in a web one way, everything in it moves in some way. Within the injury-healing-injury cycles in that web, life begets death and death begets life.

We physicians have not been ecologic thinkers. We need to be. To paraphrase Leonardo daVinci, every part is destined to unite with the whole so that it may escape its own incompleteness. In recent years, there have been astounding advances in the dissection of the molecular pathways of healing and dying. The clinician can now see *the whole* with increasing clarity. Health must be seen as harmony among the molecular and cellular ecosystems of the body — forms of sickness need to be recognized as ecologic disruptions caused by spiritual, nutritional, and ecologic elements. "I will speak of the functions of each part in every direction, putting before your eyes a description of the whole form and substance of man," da Vinci wrote. Today, that every direction must include not only the essential aspects of spiritual equilibrium—which da Vinci was acutely conscious of—but also the other fundamentally issues of oxidosis and disoxygenosis. It is not enough to speak of lymphocytic thyroids or renal lupus as 'diseases' nor is it sufficient to merely substitute echinacea for erthyomycin for recurrent infections or to replace hydrodiuril with hydrogen peroxide foots soaks for leg edema. We need a discipline of wholeness—a model of medical holism which would have brought smiles to Socrates, da Vinci, and Darwin.

Notwithstanding the possible virtues of controlled and blinded studies for evaluating the short-term efficacy of drugs, the prevailing pharmacologic blockade medicine for chronic disease is essentially flawed. Nutritional, ecologic, autoimmune, and degenerative disorders cannot be reversed by synthetic chemicals. It saddens me how often "control-crazed" clinicians deny the sick wonderful opportunities for healing with natural measures only because they think that it is not scientific. Those words may irk some readers, but if I succeed in raising a few discomforting questions in these volumes, my purpose would have been served.

From The Principles and Practice of Integrative Medicine
Volume 1: Nature's Preoccupation with Complementarity and Contrariety

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Preface to Volume X
Of Reason, Belief, and Oxygen

Physician continue to grow only to the extent that they continue to unlearn beliefs created in medical schools. Unlearning, of course, is much harder than leraning. So a life of continued growth and enlightenment of a physician is an arduous life.

A life of reason is based on the observable and the observed. A life of belief is based on the unobservable and the unobserved. Convictions in a life of reason grow stronger as one's power of reason strengthens. Convictions in a life of belief become sturdier as one's belief continues to deny what is plainly observed with passing years. It is a sad comment on contemporary medicine that so many physicians allow themselves to be led deeper and deeper into a life of belief.

Considerations of reason and belief bring us to the matters of freedom of speech and freedom of thought. The two are often lumped together but should not be. Two aspects of this subject seem important to me. First, the freedom of thought, not of speech, is what coaxed humankind to civility and civilization—whenever and wherever that happened. Second, the freedom of speech is a poor substitute for the freedom of thought. And it is the former, not the latter, which calls for true courage in an individual's journey of ideas and ideologies. It is the exercise of the freedom of speech minus that of the freedom of thought that sets the stage for confusion, conflict, and anger, at individual as well as societal levels. We Americans are the most strident proponents of freedom in general, and of the freedom of speech in particular. And yet—it seems to me—there is sparse enthusiasm for the freedom of thought. Seldom do we sufficiently challenge the presumed intellectual or moral superiority of those who presume to do our thinking for us. Flatearthers continue to thrive.

I address the matter of the primacy of the freedom of thought over the freedom of speech for three primary reasons. First, I believe that this primacy is worthy of consideration for all those who care for the sick and offer counsel for preserving health to the well. Second, the essential subject of oxygen homeostasis, to which this volume is devoted, has been misunderstood largely because medical practitioners have surrendered their right of the feeedom of thought to the editors of medical journals. Indeed, I consider the problem of compromised freedom of thought, so prevalent among physicians today, to be the central threat to the practice of civilized medicine. That problem has many facets. The first concerns a practitioner's inability to unlearn what clinical observations clearly hold not to be true—simply because it is contrary to the prevailing medical dogma. The second facet of that problem is a clinician's failure to trust her/his own clinical and intuitive perceptions, simply because the 'scientific' medical literature is silent on the issue. A common consequence of compromised freedom of thought is the ready dismissal by the practitioner of a sick person's sense of the illness.

One may pick up any issue of *The New England Journal of Medicine* or *JAMA* to see that there is much freedom of speech in those pages but little freedom of thought. I do not recall when those—or any other prestigious—medical journals last published any articles about how sugar overload and antibiotic abuse in children disrupt oxygen homeostasis and set the stage for chronic headache, recurrent infections, immune deficits, or behavior problems. Or, how exposure to environmental pollutants contribute to problems of mood, memory, and mentation in people of all ages. The sick continue to suffer because the clinician-readers of those journals have surrendered their freedom to thought to the editorial edicts in those publications.

But the problem of compromised freedom of thought is not confined only to the practitioners of medicine of drugs and scalpels. The practitioners of the so-called alternative, complementary, and 'holistic' medicines are just as likely to surrender their freedom of thought. The claims of cancer cures with exotic herbs and 'energy medicine' are readily accepted by them, without any inquiry as to how results might have been obtained. Remarkably, that happens even when it is quite evident that the person pretending to be a teacher is a mere marketer—albeit highly skillful—and has not actually treated diseases for which he sells miracle cures. The surrender of the freedom of thought persists among alternative practitioners.

Physicians have choice: They can choose a life of reason or that can allow themselves to be pulled into a life of belief. When they prefer a life of reason over that of belief, their patients an enormous price for that choice. In this third volume *The Principles and Practice of Integrative Medicine*, I challenge many of the prevailing assumptions—read belief—in clinical medicine. In support of those challenges, I marshall a large body of observations considering oxygen homeostasis in human biology.

Will my readers peruse the pages of this volume without surrendering their freedom of thought? I hope not. In the context of the "oxygen thinking" presented in this volume, below I succintly state several critical aspects of the functionality and pleurality of oxygen and oxygen homeostasis with which I challenge the readers' freedom of thought.

Oxygen is the organizing influence of human biology and governs the aging process. I arrived at this simplicity through my extended struggle with complexities in the fields of surgery, pathology, immunology, environmental medicine, nutrition, and self-regulation over a period of fifty years. Reductionistic simplicities seldom serve clinicians well in the long run. I devote this volume to that "oxygen simplicity" becauseI believe it has considerable clinical merit.

Oxygen is the primary "energy-nutrient" molecule of human biology. It is an exquisitely discriminating regulator of all developmental, metabolic, and detoxification mechanisms. It is the weapon of transcending importance in the man-microbe conflict.

In my view, the two primary threats to human health are unrelenting anger and relentless pollution of our environment. Both threats inflict damage through disrupting oxygen homeostasis. For all those considerations, I consider progressive oxygen dysfunction—dyshomeostasis caused by impaired function of oxyenzymes and altered expression of oxygenes—as the principal problem facing humankind and the animal kingdom alike.

Also for those reasons, I believe the primary focus of all clinicians managing chronic health disorders must be restoration of oxygen homeostasis. In acute illness, prompt attention to the specific lesion(s), of course, is essential. Focus on issues of oxygen homeostasis significantly improves clinical outcomes in those illnesses as well.

Oxygen is the ultimate molecular switch of human life. It causes cell death by its presence as well as by its absence. It is the primary energy-nutrient and the premium detox molecule of human biology. Oxygen is the spark for the furnace of human metabolism. It is the conductor of the whole orchestra of life. It drives all energetic-molecular pathways of cellular development, differentiation, and demise.

Oxygen is the elixir of life—and of death. Oxygen turns water into a lifegiver. It turns water into a lifetaker. From water, oxygen generates free radicals to usher life in. From water, it also produces free radicals to extinguish life. Oxygen sires hydrogen peroxide and deputizes it to protect molecules. It also cajoles hydrogen peroxide to do its dirty work of killing molecules. Oxygen spawns nitric oxide to sustain cells. Then it recruits it—and its progeny of nitroso radicals—to efficiently decimate them.

Oxygen is the ultimate molecular Dr. Jekyll and Mr. Hyde of human existencee—a spin doctor without peer. It turns DNA on to do its biddings in the good work of life. It also turns DNA off to starve life. Oxygen turns poisons into harmless materials and innocent substances into poisons. It is an acid former. It is an acid breaker. It is nature's primary antibiotic. Oxygen referees the match between a hunter immune cell and a microbe. Then, it determines who wins that match. In the same way, it referees the match between a hunter immune cell and a cancer cell, then determines who wins.

When called upon do so, oxygen turns into a messenger—accepting hormonal assignments by picking up an extra electron. It is a lifegiver in yet other ways and a lifetaker in just as many others. For all those reasons, I consider the fundamental oxygen order of human biology as the most elegant example of nature's order of economy.

From those considerations, I draw the rational and logical basis for advocating oxystatic therapies for restoring oxygen homeostasis included in this volume.

More importantly, my guidelines are based on the true- to-life clinical experience at the Institute of Integrative Medicine, which my colleagues and I have

diligently documented for several, but not all, clinicopathologic entities discussed.

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 master work 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.

Inflammation and Healing

Life is an unending injury-healing-injury cycle. Injury is inevitable in an organism's struggle for survival. *Healing is the intrinsic capacity of the organism to repair damage inflicted by that injury.* Inflammation—in my view—is one aspect of the *energetic-molecular mosaic* of that intrinsic capacity. This view of inflammation—that it is a *physiologic* component of the essential injury-healing-injury nature of life — extends far beyond the classical and wholly inadequate notion of it being a process characterized by edema, erythema, tenderness, pain, and infiltrate of inflammatory cells. Since oxygen is the organizing influence of human biology and governs the aging process in humans, it follows that inflammation, first and foremost, is one of the many face of oxygen homeostasis. In 1990, I also devoted a large part of *Oxygen and Aging* to this subject.

At the energetic-molecular level, the boundary between health and the state of absence of health is marked by oxidosis, acidosis, and dysoxygenosis (dysox). Microbial toxins and mercury are the most potent and common inciters of those three furies in the oral cavity. Regrettably, there is little, if any, appreciation of those crucial important causes of systemic disease among physicians. I have yet to meet a neurologist who seriously considers the role of mercury in the causation of multiple sclerosis, or a rheumatologist who searches for etiologic factors in oral microbiosis of a patient presenting with lupus erythematosus. Nor have I met a cardiologist who suspects oral microbiosis as the cause of cardiac arrhythmias. Later I present data about one such case to underscore the importance of this relationship.

Oxygen homeostasis has not been a consideration of immunologists and infectious disease specialists. It needs to be. Nor has oxygen been of interest to pediatricians, internists, and family practitioners who are the most frequent prescribers of antibiotics, since they take their cues from the specialists. I believe *this is the primary factors that leads to massive abuse of antibiotics.* In a chapter entitled "Oxygen Settles the Great Pasteur-BeChamp Debate" in *Oxygen and Aging*, I summarized my view of that matter with the following words:

> **When oxygen metabolism is optimal, Pasteur's microbes from outside play more important roles in causing infectious disease. When oxygen metabolism is dysfunctional, BeChamp's life forms multiplying from within the body become more important.**

The Man-Microbe Conflicts

Man-microbe conflicts are a legacy of microbe-microbe conflicts during the primordial period — long before humans appeared on the scene. Oxygen created and adjudicated microbe-microbe conflicts then, as it does the man-microbe conflicts now. I came to recognize that through my clinical work with persons who control microbial infections well — with or without antimicrobial drugs — as well as with those who cannot with *any* antimicrobial. A large body of personal phase-contrast microscopic and biochemical findings in those patients led me to the conclusion that the fundamental molecular derangement in the latter is disruption of the oxygen homeostasis, including respiratory-to-fermentative shift in ATP production described previously.

Oxygen adjudicates all man-microbe conflicts. In that matter, I draw the following two crucially important conclusions:

1. Physiologic inflammation becomes pathologic inflammation when oxygen homeostasis is in jeopardy; and
2. The status of oxygen homeostasis determines the outcome in man-microbe conflicts. In this context, oxygen also resolves the long-standing Pasteur-BeChamp controversy about whether disease is caused by microbes invading from outside or by microzyma proliferating from within.

Cancer

The central tragedy of oncology — in my view —is that it completely ignores the *crucially important* issue of the microenvironmental oxygen conditions ("oxyecology") of cancer and of non-cancerous tissues in its close vicinity. By oxyecology I refer not only to the glycolytic metabolic conditions within cancer cells that cause and perpetuate oxidosis, acidosis, and dysoxygenosis (dysox)—the three furies of cancer — but also to cancer-induced trio of oxidosis, acidosis, and dysoxygenosis in the matrix and non-cancerous cells cell surrounding cancer cells. Fortunately, researchers interested in molecular biology of cancer are beginning to recognize this critical issue.

I *Integrative Oncology*, the ninth volume of this textbook, I present a "cancerization-de-cancerization (can/de-can)" model of oxyecology. Specifically, I address three issues of paramount importance for understanding cancer biology — cellular multiplication, local growth, and formation of distant metastases—and for designing oxystatic protocols for integrative treatment of individuals with cancer:

1. How cancer cells induce metabolic (respiratory-to-fermentative) shift in non-cancer cells in their vicinity—recruit non-cancer cells to subserve them in their pursuit of growth and expansion, so to speak;
2. How non-cancer cells surrounding cancer cells not only resist that recruitment but also attempt to create oxyecologic conditions that coax cancer cells to relinquish their oxyphobic and destructive behavior; and
3. How concordant are the tenets of the cancerization-de-cancerization (can/de-can) model with known aspects of molecular biology of cancer — especially those tissue oxygen sensing, hypoxia-inducible factor(s), glycolytic ATP production, cancer-induced oxidative coagulopathy (with or without clinical phlebothrombosis), and oxygen-suppressor gene dynamics.

I consider the above three issues of crucial importance because my clinical work in treating cancer has convinced me that oxygen-adjudicated interactions between cancer and non-cancer cells determine the long-term outcome, except when an early cancer can be completely excised. Specifically, the long-term outcome with chemotherapy, radiotherapy, and the newer therapies based on interrupting or modifying cellular signalling in cancer depends more on oxyecologic status than any other elements.

All Chronic Pain Is Some Cells' Cries for Oxygen

It is important to recognize that oxygen drives chronic pain pathways *primarily* by its absence. 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 increases 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, acidosi— and then all collectively threaten *functionality* of oxygen, increasing the degree of pain regardless what the initial pain triggers might be. Then I wonder how often do 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 dysoxygenosis.

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.

Bone Homeostasis and Osteoporosis

As for bone homeostasis, osteopenia, and osteoporosis, the human anatomy and physiology evolved under the organizing influence of oxygen.[12]

Accordingly, oxygen not only provides signaling for all developmental, differentiative, and dying processes, it also serves as the *principal* nutrient for the body. Viewed in that light, bone homeostasis is but one face of oxygen homeostasis. Based on those considerations, I recently put forth the Oxygen Model

of osteoporosis that recognizes disturbances of oxygen homeostasis in the bone tissue as the *fundamental* energetic-molecular events that lead to bone loss clinically designated as osteopenia and osteoporosis.

Chronic fatigue, Fibromyalgia, and Other Chronic Energy Deficit States

Syndromes of persistent and debilitating fatigue—fibromyalgia, chronic fatigue syndrome, persistent fatigue following chemotherapy for malignant disorders, and others—may be properly designated "chronic energy deficit states." There is an enormous body of literature concerning clinical patterns, symptom-complexes, and putative etiologic agents. In 1994, in *The Canary and Chronic Fatigue*, I marshaled extensive evidence for my view that accelerated oxidative molecular injury is the common energetic-molecular pathway among all etiologic factors for chronic fatigue syndrome.

In this volume, I furnish evidence for the hypothesis that chronic disabling fatigue is caused by a respiratory-to-fermentative (RTF) shift in adenosine triphosphate (ATP) production. As a consequence, there is a drastic (over 93%) reduction in the available cellular energy currency (ATP) — only two moles of ATP per mole of glucose are generated in the fermentative mode as compared with approximately 30 moles of ATP per mole of glucose in the respiratory mode. In 1999, I introduced the term dysoxygenosis for this respiratory-to-fermentative shift in ATP production. I defined dysoxygenosis as a state of diminished cellular oxygen utilization resulting from function of enzymes involved in oxygen homeostasis (designated oxyenzymes) that leads to altered expressions of genes induced by hypoxic environment (designated oxygenes). The webs of oxyenzymes are vast, with each entity linked to every other through multiple pathways. The webs of oxygenes are seemingly far more complex. All such webs are exquisitely 'aware' of changes in oxygen availability in their microenvironment and vigorously respond to them. Some sense of the clinical significance of this may be obtained by considering the broad range of symptom-complexes of RTF shift in chronic energy deficit states.

Clear and unequivocal biochemical evidence for such shift can be readily established by measuring 24-hour urinary excretion of organic compounds (Tables 1). When the spectrum of organic acids included in the urinary profile is broad enough, not only is it possible to detect the presence of that shift, it is generally possible also to recognize defects in molecular pathways that set the stage for RTF shift.

Impaired Krebs Cycle

Of central importance in cellular energetics is the Krebs (citric acid, tricarboxylic acid) cycle. *In health, this cycle is the true crossroads of both anabolic and catabolic energetics.* It is the final common pathway for oxygen-driven breakdown of sugars, fats, and proteins for serving the energy needs of the body. It also provides for the oxygen-driven synthesis of the basic building blocks for structural and functional molecules of the body. All steps in this cycle of energetics are catalyzed by a variety of enzymes and their cofactors. Metabolic pathways of carbohydrates, lipids, and proteins enter the cycle via acetyl CoA derived from pyruvic acid, fatty acids, and amino acids respectively. Theoretically, blockages at various levels in the Krebs cycle can be produced when the enzymatic pathways of the Krebs cycle are:

1. Impaired or inactivated by incremental oxidative stress of endogenous and exogenous factors;
2. Hampered by intracellular acidosis resulting from chronic oxidosis;
3. Impeded by the quality and quantity of substrates (discussed below);
4. Rendered inefficient by deficiency of metal cofactors; and
5. Clogged by mitochondrial uncoupling.

In closing, I see the determinative hand of oxygen in *all* aspects of the health/dis-ease/disease continuum. That, indeed, has been my primary purpose in writing the eleven volumes o f *The Principles and Practice of Integrative Medicine.*

January 4, 2009

Preface To Volume I:
Nature's Preoccupation with Complementarity and Contrarity

This first volume of *The Principles and Practice of Integrative Medicine* is about five aspects of human biology. First, oxygen is the organizing influence of human biology and governs the aging process. It is also a molecular Dr. Jekyll/Mr. Hyde par excellence—ushering life with one sleight of hand and terminating it with another. Second, human biology is an enormous web of webs—a vast and intricate network of energetic-molecular pathways. Everything in that web is connected to everything else. Third, the webs of human biology form a panoramic kaleidoscope. When something in that kaleidoscope changes in one way, everything in it changes in some way. Fourth, spontaneity of oxidation in nature—sustained by oxygen above all else—provides the primary metabolic drive for all human life processes. It also assures that no oxygen-utilizing life form lives forever. Fifth, persistent and progressive oxidosis sets the stage for dysoxygenosis—a state of dysfunctional cellular oxygen metabolism resulting from an impaired function of enzymatic pathways involved with oxygen utilization. All clinical work of a practitioner of integrative medicine—in my view—should be based on a clear understanding of those five energetic-molecular aspects of human biology.

Two other issues in clinical medicine are of transcendent importance: (1) the spiritual serenity that is essential for long-term good health; and (2) chronic anger and sadness that fan the fires of oxidosis and dysoxygenosis. The so-called mind-body-trio is an artifact of thinking. Preoccupation with that trio, in reality, is an expression of our inability to sense, feel, and know the wholeness of the human condition. I have never seen anyone dissect a human and delineate where the body ends and the mind begins or where the mind ends and the spiritual begins. I address the issues of spiritual serenity and chronic anger as well as present the philosophic principles of integrative medicine in the second volume of this textbook.

Nature's preoccupation with complementarity and contrariety has created an enormous range of structural plasticity and multifunctionality of molecules.

That is as true of simple molecules—reactive oxygen species, nitric oxide, and others—as it is for very complex molecules, such as hemoglobin, thrombin, macrophage migration inhibition factors, and others. Equally relevant to the integrative model are the Dr. Jekyll/Mr. Hyde dynamics of cellular ecosystems in the body. In pharmacologic medicine, it is generally assumed that molecules and cells have fixed and unchanging roles. That assumption forms the putative rationale and/or basis of the prevailing drug therapies that essentially block cell receptors, channels, pumps, enzymes, or mediators of healing responses. It is my clear purpose in this volume to challenge that assumption. To do that effectively and defend my major themes in this volume, I have dwelled on the history and chemistry of oxygen and described at length the oxidative phenomena that set the stage for cellular dysoxygenosis. Some readers may find segments of my materials cumbersome. However, I believe the full validity of my challenge may escape some readers without a full treatment of those essential aspects of human biology.

The primary purpose of this volume, of course, is to serve as a textbook for the practitioners of integrative medicine. In subsequent volumes, I describe integrative therapies for various clinical states which my colleagues at the Institute and I have employed for nearly two decades. The primal issues for an integrative practitioner are the *long-term safety and efficacy* of his therapies. Those issues are addressed by including full texts of some large true-to-life long-term clinical outcome studies. In the pharmacologic model, the focus is on short-term results obtained in acute states with agents that block this or that cell receptor, channel, enzyme, pump, or mediator of inflammatory or immune response. That is distinctly different from the goals and objectives of an integrative physician for health preservation and disease reversal. The nurturing and restorative nutrient, herbal, detox, and self-regulatory measures generally take longer than synthetic drugs to yield desirable results. This essential point is often not fully appreciated. This volume, then, is written also to address the *scientific basis and rationale* for integrative therapies that must be administered for months and years before their full clinical benefits are realized.

Integrative Molecular Evolution

Molecular evolution was, is, and will continue to be an unending sequence of integrative phenomena. Every molecule acquires new functions only through its dialogues with its substrates. Every molecular