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*The central roles of acidosis, acidosis and dysoxygenosis can be recognized in all other risk factors of osteoporosis.

Table 1 – Commonality of Dysoxygenosis Among Known Factors of Osteoporosis

that cause bone loss – there would have been no need for anyone to propose the Oxygen Model of osteoporosis.

The primary prediction based on the Oxygen Model of osteoporosis is that restoration of oxygen homeostasis in bone should lead to restoration of bone homeostasis, without the use of any pharmacologic agents. The same should be the case for persons with osteoporosis who cannot accept hormonal therapies for fear of recurrence of breast and uterine cancers. Indeed, that prediction holds true. In my clinical work, I have seen patients, albeit limited in number, with a history of breast and ovarian cancer who did not respond to bisphosphonates and nutrient therapies (calcium, vitamin D, boron, others), but responded well to oxystatic therapies – direct oxygenative protocols and indirect measures for the restoration of the bowel, blood, and liver ecosystem – and rebounding exercise.

How consistent is the Oxygen Model of osteoporosis with the known experimental and clinical data concerning the pathobiology of bone and osteoporosis? What is the explanatory power of that model for the known aspects of the magnesium/calcium, calcium/calciferol, calciferol/phosphorus, phosphorus/parathormone, parathormone/hypoxia-inducible factor (HIF), and related interactions in the pathobiology of bone? What are the implications of this "oxygen view of osteoporosis" for the integrative clinician for the prevention and reversal of osteopenia and osteoporosis? I explore those questions in this column. But first, a few words about our dairy industry.

Calcium-Less Bones, Calcium-Loaded Arteries, and the Relentlessly Truthful Dairy Industry

These days it is impossible to escape the deep concern the dairy industry has about the bone health of Americans. In the milk-smeared upper lips of its celebrities, the industry reveals to us its grand design for curing osteoporosis. Every time I see such lips on TV or in print, my thoughts go to a frail lady I met in the hospital autopsy room nearly 40 years ago. It was then I had my first encounter with osteoporosis.

As a pathology resident, I performed an autopsy on a woman in her mid-seventies. In order to evaluate her bone morphology, I took out a large section of the front halves of her lumbar and thoracic vertebrae with an electric bone saw. Her porous bones had an egg-shell texture. Curious, I pressed my thumb into the cut surface of the vertebrae and saw a deep depression form there. How, on God's green earth, did she manage to walk on those bones?, I recall speaking out loud. My morgue assistant looked up, startled at my words. I smiled, said nothing, and proceeded with my dissection. Her aorta and other large arteries were nearly occluded by densely calcified plaques. How did she manage to live with those blocked arteries?, I asked under my breath that time. So, the

Oxygen Homeostasis
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The Oxygen View of Osteoporosis: Bone Homeostasis is But One Face of Oxygen Homeostasis

The human anatomy and physiology evolved under the organizing influence of oxygen. 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.

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poor lady was suffocated by calcium deposits in her arteries while there was little of the mineral in her eggshell-thin bones. What does that say about our “osteoporosis experts” who never tire of talking about calcium? In this context, I might add that one Swedish study showed a higher incidence of osteoporosis among postmenopausal women on a diet rich in calcium – milk fortified with retinol – than among the control group.6

Oxygen for Fractures? Of Course Yes! Oxygen for Osteoporosis? What For?

There is an interesting disconnect between the emphasis on the oxygen dynamics in discussions of healing fractures and in considerations of osteoporosis. The literature on the former is replete with references to the central roles of oxygen in those processes, whereas there is little, if any, reference to oxygen in the latter. For instance, every article on the relationship between smoking and fractures focuses on the underlying mechanism of oxygen deficit in the higher incidence and delayed healing of fractures in smokers compared with nonsmokers.7 And yet, there is seldom, if ever, any emphasis on preserving oxygen homeostasis in persons with osteoporosis and fractures. That should not be surprising since there is little money in selling oxygen at this time. When bottled oxygen begins to be sold the way bottled water is today, we can expect the men of money in medicine to rise to the occasion and loudly sing the praises of oxygen to sell their products.8

Oxygen Homeostasis

Oxygen Drives Osteoblasts and Bone Matrix

Diverse regulatory roles of oxygen in bone homeostasis have been delineated with various investigative methodologies.5-10

The effects of ambient oxygen on osteoblast function and bone modeling have been studied with in vitro studies employing osteoblast-enriched cultures from fetal rat calvariae. Effects of hypoxia were examined following exposure to 10% O2 and those of hyperoxia with 90% O2.17 Under low ambient oxygen tension, cellular proliferation increased, whereas the alkaline phosphatase activity, collagen synthesis, and the values of pO2 and pCO2 in the media decreased. Such observations clearly establish the existence of fundamental organizing influences of oxygen tension on osteoblastic function and bone modeling.

All microecologic cellular and macroecologic tissue-organ systems include a complex extracellular matrix that is intricately involved with signaling pathways that control cellular development, differentiation, and demise. Oxygen is the primary communication molecule in all cell-matrix and cell-cell transactions. The bone cells and matrix, of course, are not exceptions to that. Specifically, oxygen drives all those processes in osteoblast cultures grown on scaffolds of all soluble and insoluble factors – including those containing calcium phosphate, polylactide, and collagen. The oxygen

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Oxygen Homeostasis

> consumption rates have been used in those studies as indicators of osteoblastic proliferation and differentiation. Increased oxygen consumption also correlates well with augmented activity of alkaline phosphatase and increased DNA synthesis. The same holds for the growth and differentiation of malignant osteoblasts.

Oxygen Drives Bone Modeling Enzymes

Oxygen regulates the behavior of osteoblasts by driving their enzymes with crucial functions through many of its transcriptional, and does not require de novo protein synthesis.

dexamethasone, and mRNA stabilization have shown that in nature.

the oxygen-sensing mechanism in the bone tissue is bemelike in a similar time- and dose-dependent manner, it is likely that the binding domains of hypoxia-inducible factor have been established. In other studies, regulatory roles of HIF for preserving microenvironment in the bone marrow for effective hematopoiesis have been established.

The question of a link between the oxygen conditions and hypervascularity in the bone tissue is not of purely academic interest. If local dysoxygenosis is indeed the final molecular pathway in the pathogenesis of osteoporosis – the central tenet of the oxygen model of osteoporosis – one might speculate the following: Localized bone dysoxygenosis triggers hypoxia-inducible factor (HIF) and related molecular species and pathways to stimulate compensatory angiogenesis in order to correct deficit of functional oxygen. This line of reasoning may be pursued further by considering the possible molecular pathways involved in the prevention and reversal of osteoporosis by physical exercise. Exercise is a potent generalized vasodilator. It also increases tissue perfusion by a variety of mechanisms. Both factors are expected to alleviate local acidosis and dysoxygenosis. Finally, both oxidation and dysoxygenosis are expected to increase the rate of mutations in genes that code for proteins – matrix Gla, bone alkaline phosphatase, and others – with crucial metabolic roles in preserving bone homeostasis.

Oxygen Drives Hypoxia-Inducible Factor

During years of my work as a hospital histopathologist, I regularly observed a marked degree of hypervascularity in osteopenic and osteoporotic tissue. How does that morphologic characteristic of porotic bone fit into the oxygen model of osteoporosis? What, if any, relationship might exist between oxygen and hypervascularity of osteoporotic bone?

Hypoxia inducible factor (HIF) is a heterodimeric transcription factor. Under physiologic conditions, it is downregulated transcriptionally and at the protein level through degradation. Under hypoxic conditions, it is transcriptionally upregulated and the degradation of the protein is inhibited, allowing it to exert its biologic roles through translocation to the nucleus and facilitation of the transcription of an ever-growing number of genes that contain binding domains of hypoxia-inducible factor.

Studies with bone tissues from intact rat femurs and fracture callus after varying periods of repair response have shown that HIF-1α expression is upregulated in the tissue from fracture callus, the degree of upregulation increasing with time such that the peak value of 2.75-fold increase was seen after 21 days. In other studies, regulatory roles of HIF for preserving microenvironment in the bone marrow for effective hematopoiesis have been established.

The most pronounced degrees of osteoporosis encountered in cases of renal aciduria. In studies with osteoblast cultures, marked degree of inhibition of cellular proliferation and bone formation has been documented with increasing degrees of acidosis. The effects of pH conditions on bone homeostasis have been examined by...
measuring alkaline phosphatase activity, lactate production, proline hydroxylation, DNA content, and thymidine incorporation. In one set of experiments, as the pH of the osteoblastic culture medium increased to the value of 7.6, collagen synthesis, alkaline phosphatase activity, and thymidine incorporation increased. The changes in the DNA content showed a biphasic pattern, with increases seen from pH 7.0 to 7.2, a plateau effect observed from pH 7.2 to 7.6, and further increases encountered again from pH 7.6 to 7.8. Lactate production increased at pH 7.0, but remained constant from 7.2 to 7.8.

In clinical medicine, the primary regulatory influences of oxygen on acid-base equilibrium in the bone are rarely appreciated. That is odd in view of the well recognized detrimental effects of acidosis on bone homeostasis. Persistent acidosis is a metabolic precursor of oxidosis and dysoxygenosis. Acidosis is a member of the trio of metabolic furies — oxidosis, acidosis, and dysoxygenosis — which feed upon each other and collectively bring down the cellular houses of health. Thus, all the osteopenia- and osteoporosis-causing roles of all acidic and oxidizing risk factors fit well into the oxygen model of osteoporosis. The reader is referred to Nature's Preoccupation With Complementarity and Contrariety, the first volume of The Principles and Practice of Integrative Medicine for further discussion of the subject.

Oxygen Drives the Intracellular and Extracellular Lives of Phosphate

Since the earliest periods of the evolution of cellular life, phosphate has been assigned several key intracellular roles, including:

1. Structural components of nucleic acids and phospholipids;
2. Active moiety in high-energy bonds, such as adenosine triphosphate and guanosine triphosphate; and
3. Participation in cellular signaling through covalent phosphorylation of proteins and lipids.

The extracellular roles of phosphate appear to have evolved during later periods, evidently because the primordial cells had not acquired extracellular regulatory influences in the sense of the matrix of the multicellular organisms. Bone is the largest repository of extracellular phosphate. Phosphate is generally abundant in diet and is readily absorbed from the gut. The deposition and removal of phosphate from bone is considered to be under the influence of the parathyroid gland and 1,25-dihydroxyvitamin D3, the bioactive form of the vitamin. That is true. (However, before there was the parathyroid gland, there was oxygen driving the primordial energetic chemistry.) The phosphate shifts in and out of cells are profoundly influenced by energetic and metabolic events, such as when hyperglycemia evokes an insulin response.

Phosphorus is a critical element in the body for two major reasons: (1) for body energetics in which high-energy phosphate bonds (ATP) serve as the primary source of readily available energy; and (2) skeletal integrity. I have discussed diverse aspects of the essential drive of phosphate metabolism provided by oxygen in Dysoxigenosis and Oxystatic Therapies, the third volume of The Principles and Practice of Integrative Medicine.
There is seldom any emphasis on renal function in discussions of the treatment of osteoporosis. The kidney also plays crucial roles in phosphate homeostasis. It maintains serum phosphate levels within a narrow range by modulating clearance of phosphate. Phosphate is readily filtered in the glomeruli and is subsequently and efficiently reabsorbed in the proximal tubule — against an electrochemical gradient. The rate-limiting step in that reabsorption is the uptake of phosphate through a protein called 2a sodium-phosphate cotransporter (NPT2a). This transporter resides in the apical membrane of the proximal renal tubular cells.

NPT2a is the gene that encodes for NPT2a. Knockout NPT2a-negative mice exhibit low blood pressure, renal phosphate wasting, and dramatic reduction in transport of phosphate across the proximal tubular brush border membrane. Heterozygous mutations of this gene are associated with hypophosphatemia, increased urinary loss of phosphates, and bone demineralization, leading to osteopenia and osteoporosis.

**Oxygen Drives the Parathyroid Gland**

Oxygen is the organizing influence of all aspects of human biology. Needless to assert, the parathyroid gland, of course, is not an exception to that. There is, however, a singular aspect of the parathyroid gland that seems to have a special evolutionary twist to it.

For decades, the metabolic roles of calcium and vitamin D have been seen as inextricably intertwined. Calcium is a universal cellular messenger. It tells different proteins to do different things — as a warning shot might tell different sentinels guarding a castle to perform different functions. Its myriad biologic roles — the oxystatic influence being the common denominator among them in health — have been well-established for decades.

By contrast, the anti-inflammatory, anti-neoplastic, "anti-autoimmunity," and anti-arthritic roles of vitamin D — the oxystatic influence being the common denominator among all of them in health — have only recently been fully recognized. How may one then see calcium, vitamin D, and osteoporosis through the prism of oxygen homeostasis?

Population-based studies reveal a gradual increase in the levels of serum parathyroid hormone (PTH) from about 20 years of age, such that the maximum value at age 80 years may be as much as 50% higher than at the age of 30 years. This has been attributed to secondary hyperparathyroidism induced by diminishing intestinal calcium absorption with age. One could argue that decreasing exposure to sunlight with age in many communities could also contribute to such hyperparathyroidism by decreasing the production of vitamin D in skin. A more interesting question for me is this: Why do the serum levels of PTH continue to rise with age, while those of other hormones decrease? Could it be that the PTH production is preserved during the aging process for evolutionary reasons? Strong bones were essential for protecting fragile brain parenchyma and other soft organs. In that context, the nucleotide sequences coding for PTH would be expected to have appeared on the scene much earlier than those responsible for the later development of brain and other fragile tissues, and were selected for evolutionary advantage.

And since oxygen drove human evolution — molding its developmental, differentiative, and dying processes — it seems reasonable to deduce that oxygen selected parathyroid glands and parathormone for greater survival benefits.

Simply stated, I hypothesize that oxygen seeks to preserve bone homeostasis during later years of life by raising PTH levels to increase absorption of calcium, vitamin D, and most likely other nutrient factors. Cellular dysoxygenosis caused by our mindless destruction of oxyenzymes, of course, thwarts that order of oxygen. Shall we designate that as self-inflicted apoptosis of the whole being?

**Dysoxygenosis is the Common Denominator Among Known Risk Factors of Osteoporosis**

In Table 1, reproduced from *Pathobiology by Microecologic Cellular and Macroeologic Tissue-Organ Ecosystems*, the tenth volume of *The Principles and Practice of Integrative Medicine, 46* I list established risk factors of osteoporosis. The common underlying mechanism among all, except the lack of physical activity, is oxidative stress. In previous articles, I have shown data supporting my view that chronic oxidosis in all pathophysiologic states eventually creates acidosis, and together chronic oxidosis and chronic acidosis set the stage for local and/or systemic dysoxygenosis. Thus, the primary underlying pathogenetic mechanism in all of the known risk factors of osteoporosis is dysoxygenosis accompanied by respiratory-to-fermentative shifts of varying degrees. See *Townsend Letter August/September* for detailed descriptions of those phenomena.

**Dysoxygenosis Drives Oxidative Magnesium-Calcium Dissonance in Osteoporosis**

The paradox of calcium-less bones coexisting with calcium-loaded arteries cannot be understood except through an understanding of what I have designated as oxidative calcium-magnesium dissonance. In 1987, I wrote a monograph entitled *Leaky Cell Membrane Disorder. 56* The main point of that monograph was to underscore the clinical consequences of oxidative cell membrane injury that result in hemorrhage out of what is inside the cells and flooding the cell innards with what is outside them — matrix, lymph, and blood. I recognized then that calcium channel blockers were being prescribed for an ever-increasing number of symptom-complexes. Nutritionist-physicians were becoming increasingly liberal with their prescription for supplemental magnesium to treat an equally large number of symptom-complexes. I also recognized then that the common denominator in the pathogenesis of all those symptom-complexes was incremental oxidative injury — a subject I reviewed at length in *RDA: Rats, Drugs and Assumptions. 57* Calcium is a near-universal signaling element in cellular dynamics. Magnesium exerts strong regulatory influence over the movement of calcium in and out of the cell. It seemed useful to me to bring together the experimental and clinical observations concerning those two minerals under the heading of leaky cell membrane disorder.

In 2003, I introduced the term oxidative-dysoxygenative magnesium-calcium dissonance to further elaborate abnormal magnesium-calcium dynamics in clinical states resulting from local and/or systemic dysoxygenosis. That dissonance also sheds light on the questions under discussion:
Why is calcium not deposited in sufficient amounts in osteoporotic bones? Why are calcium deposits in arterial walls, where they serve no useful purpose? Specifically, why does osteoblastic alkaline phosphatase fail to facilitate deposition of calcium at the bone cell membrane in osteoporosis? Why does matrix protein Gla—so named for the carboxyglutamic acid residues that bind calcium—fail to prevent deposition of calcium in arterial walls in atherosclerosis? The answer: Functionalities of both proteins—the matrix Gla and osteoblastic alkaline phosphatase—are dependent on optimal pH, redox, and oxygen conditions. The concentrations of ionic calcium and phosphate in the extracellular fluid are at or slightly above the solubility product constant. That, of course, creates the need for strong controls to keep calcium and phosphate from precipitating in extraskeletal tissues. Thus, under physiological conditions, calcium and phosphate are deposited in the bone as hydroxyapatite under highly controlled conditions. The examples of two proteins are cited here to illustrate those controls. It seems highly likely that there are other enzymatic functions involved in keeping calcium in healthy bones and out of healthy arteries.

I might add here that while calcium has found a strong voice in the literature of osteoporosis, magnesium has been very low-key. That is peculiar since epidemiologic studies have clearly shown a direct correlation between Mg intake and bone density, thereby linking dietary Mg intake to osteoporosis. In the mouse model, diet-induced Mg deficiency reduces bone mass and increases skeletal fragility. Even moderate magnesium restriction (10% of the nutritional requirement [NR] for rats) leads to marked hypomagnesemia and up to a 51% reduction of bone Mg content.

In closing this section, I recognize that one aspect of my hypothesis—regulatory control of the matrix Gla and osteoblastic alkaline phosphatase—has not been tested with direct experimentation. However, evidence concerning the various osteoporosis risk factors listed in Table 1, when considered in aggregate—in my view—provides strong indirect support for my view. I refer the reader to Integrative Nutritional Medicine, the fifth volume of The Principles and Practice of Integrative Medicine, for an in-depth discussion of this subject. In that volume I also present strong explanatory power of oxidative magnesium-calcium dissonance for diverse clinical states, from Alzheimer's disease to chemotherapy-induced persistent fatigue to ulcerative colitis.

Rebounding, Vibrations, and Control of Osteoporosis
For several years, clinical experience has convinced me that the single most effective part of the oxystatic program for the prevention and control of osteoporosis is rebounding exercise on a trampoline with a safety bar to prevent injuries. For my elderly patients with arthritis—of knees, hips, and spine—I advise up-and-down motion on tips of toes rather than full-fledged rebounding. On the surface, this may seem at odds with the experience in space medicine in which continued bone....
Oxygen Homeostasis

loss at the rate of about 0.2% per month was observed in spite of extended daily physical exercise. There are, of course, two obvious differences between my patients and astronauts: (1) my patients do not face absence of bone-strengthening effects of gravity; and (2) they have years, not months, to strengthen their bones.

Some experimental observations are relevant to this discussion. In one study, rats whose hind legs were suspended all day exhibited severely depressed bone formation — down by 92% - while rats that spent ten minutes per day bearing weight still had reduced bone formation — 61% less. In another study, rats who were prevented from bearing weight on their hind limbs during the day and who were given a mere ten minutes per day of vibration therapy experienced restored near-normal rates of bone formation. In sheep studies conducted at the University of Colorado, the ewes whose hind legs were regularly exposed to the vibrations showed a three percent increase in bone density compared with the ewes that did not undergo treatment.

Based on experimental and limited early human studies, it seems likely that in the near future equipment will become available to administer low-intensity vibrational therapy while doing rebounding on a trampoline. Encouraging early results have been reported with the use of metal plates vibrating at 90 Hz (1 Hz = 1 cycle per second), with each brief oscillation imparting an acceleration equivalent to about one-third of Earth’s gravity.

Osteoclast Blockade with Bisphosphonates

Bisphosphonates are a class of drugs that are believed to work by blocking osteoclastic activity. These drugs are widely prescribed to treat osteoporosis (and bone disorders associated with accelerated bone resorption). Investigations of the mechanisms of action of these drugs have largely been limited to their effects on bone-resorbing osteoclast cells. It is sometimes implied that increase in bone mass observed with these agents also involves as yet uncharacterized paracrine factors of osteoblastic derivation. More importantly, the direct actions of bisphosphonates on gene expression, cellular proliferation, and bone modeling have been essentially inferred from studies with cultured human fetal cells. The bone homeostasis in the elderly, of course, varies widely from that in fetal bones. Thus, the conclusions drawn from observations with robust fetal bones cannot be considered as valid for porotic bones in the elderly or in diseased bones with failure of osteogenesis.

Beyond the above considerations, the osteoblastic proliferation was actually found to decrease with bisphosphate pamidronate (Aredia). Notably, that agent increased cytodifferentiation, total cellular protein, alkaline phosphatase activity, and type I collagen secretion in osteoblasts in a dose-dependent manner.

The actions of two other bisphosphonates, the weak-acting etidronate (Didronel) and the potent new analogue zoledronate (Zometa), have also been examined with immortalized human fetal osteoblasts (hFOB). Pamidronate and zoledronate decreased proliferation of hFOB cells equally, whereas such decrease was seen with etidronate only at much higher concentrations. Interestingly, EDTA potentiates the effects of some bisphosphonates by reducing free divalent ion concentrations. Based on those studies, it has been suggested that both pamidronate and zoledronate positively influence the bone-forming activities of osteoblasts.

The class of bisphosphonates currently includes the following drugs: etidronate (Didronel), alendronate (Fosamax), tiludronate (Skelid), risedronate (Actonel), pamidronate (Aredia), and ibandronate (Boniva, still in phase III trials).

Defining Osteoporosis

Osteoporosis is believed to be a preventable and treatable condition that affects an estimated 75 million people in the United States, Europe and Japan. Not surprisingly, it has drawn much attention in all developed countries. Yet, there is little consensus on how to define it, and its definitions remain conceptual. Consider the definition offered by a Consensus Development Conference: "A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture." By contrast, a Working Group of the World Health Organization attempted to assign a numerical value to its definition and proposed that osteoporosis be defined as bone mineral density (T score) that is 2.5 SD below the mean peak value in young adults. The limitations of this definition include:

- By focusing on mineral density, it ignores other important determinants of bone strength;
- It does not specify the methodology for determining mineral density;
- It fails to take into account increased vulnerability to fracture of bones of older women; and
- It does not address the important issue of wide variations in mineral densities in different bones of the same individual.

Another proposed method is to compare the value of the individual with the mean value in normal subjects of the same age and sex (Z score). For clinical use, a Z score below -1 at femoral neck or lumbar spine indicates a value in the lowest 25% of the mean value of the normal group, and a T score lower than -2.5 is considered an indication for pharmacologic intervention by the HRT proponents.

Oxystatic Therapies for Osteoporosis

The treatment plans for osteoporosis, whether comprising pharmacologic regimens or nutritional therapies, seldom, if ever, focus on issues of oxidation, acidosis, and dysoxygenosis arising from disruptions of the bowel, blood, and liver ecosystems. That, in my view, is the primary failure in the management of osteoporosis. In Dysoxygenosis and Oxystatic Therapies, the third volume of The Principles and Practice of Integrative Medicine, I have described at length therapies that have in common the goal of preserving or restoring oxygen homeostasis. I published an outline of those therapies in the last issue of the Townsend Letter. I refer the reader to those publications for detailed information on that subject.

What may be expected in real life with the therapeutic plans that are intended to arrest or reverse osteoporosis by achieving local and/or systemic oxygen homeostasis? In Tables 2 and 3, I present data for two women who were unwilling to take hormones and who failed to improve bone density with bisphosphonates. They responded well to oxystatic therapies. Needless to say, judicious use of hormonal therapies can be safely added to oxystatic therapies for improved results.
Oxygen Homeostasis


73. Sharp yield osteoporosis clues. news@nbc. com/link/1489025, Janurary 13, 2005.


