

21st Century Diets ~ Stone-aged Bodies

Submitted to:

Mr. Kevin Guest
Chief Marketing Officer
USANA Health Sciences

Submitted by:

Lyle MacWilliam, MSc, FP
MacWilliam Communications Inc.
7594 Klinger Road
Vernon, British Columbia
CANADA V1H 1H4

February 15th, 2010

21ST CENTURY DIETS ~ STONE-AGED BODIES

Introduction

Prevailing nutritional patterns of the late Palaeolithic Period, occurring 100,000 to 50,000 years ago, established epigenetic (genetically expressed) regulatory mechanisms for the human species that continue to be expressed today. These ancient dietary patterns prescribe a reference standard for the optimal health of modern-day humankind; deviation from this ancestral norm is believed to be a principal cause of the rising prevalence of degenerative disease in our modern world.¹

During the intervening millennia, genetic evolution selectively created many observable changes to the human genome (such as hair, eye and skin pigmentation, and immune defences against microorganisms); however, core biochemical and physiological processes have remained resolutely inviolate.² Anthropological data from Africa, humanity's mother continent, reveal a pre-historic dietary plant-to-animal ratio of close to 1:1, with fish and shellfish comprising much of the animal component.³ These diets, high in unprocessed plant fibre and indigenous fruits, would have been slightly alkaline, which remains the prevailing norm for modern human biology and physiology.

Archaeological evidence further reveals that, as a growing wave of humanity pressed outward from the East African plains, cultural and nutritional patterns began to diverge from this central norm. A growing discord between humankind's ancient genetic tapestry and the rapidly devolving cultural and nutritional patterns of early hunter-gatherer societies is evident in a recent worldwide study of 229 tribal societies. The findings reveal net acid loads of hunter-gatherer diets that reflect their particular geographic locations and that become progressively more positive as plant-to-animal dietary ratios decline.⁴

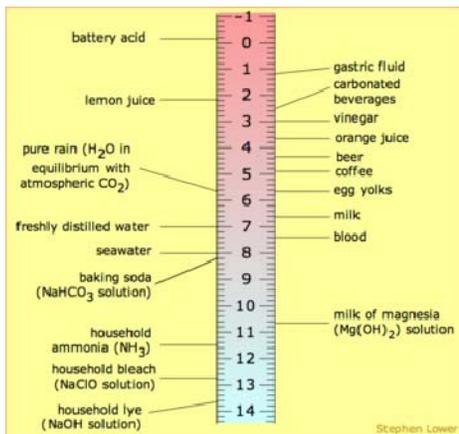
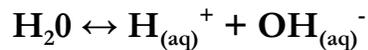
These profound changes in humankind's cultural and biological environments, enhanced by the introduction of agriculture and animal husbandry about 10,000 years ago, were further magnified with the arrival of the industrial revolution. According to Cordain and co-workers, such paradigm shifts occurred too recently and too swiftly on an evolutionary scale for the human genome to adapt.⁵ They contend that, in conjunction with this growing discord between our ancient biology and the prevailing nutritional and cultural patterns of contemporary populations, many of the so-called diseases of civilization have emerged⁶ — consequences of 21st Century diets and Stone-Age bodies.

Dietary Acid/Alkaline Balance

The Neolithic (9500 BCE) and industrial periods altered seven functional characteristics in our ancestral diets that have proved detrimental to the wellbeing of modern humankind. These include: glycemic load; fatty acid composition; macronutrient composition; micronutrient density; sodium-potassium ratio; fiber content; and acid-alkaline balance.⁵ This position paper will focus on a principal factor, the increased net acid load of modern diets and its health implications; within this context, the relevance of other dietary factors will be discussed. We will also review two disease processes, osteoporosis and cancer, and the role played by chronic acidosis in their etiology.

What is Net Acid Load?

The acidity or alkalinity of any solution is determined by the relative concentrations of hydrogen (H^+) and hydroxide (OH^-) ions within the solvent and is expressed as pH, meaning “**p**ower of **H**ydrogen.” The pH of a solution is a mathematical calculation based on a logarithmic scale from 0-14, where 7 is neutral ($pH = -\log [H^+]$). This is the pH of distilled water, where the relative concentrations of H^+ and OH^- are equal, as represented by the following chemical equation.



For every unit *below* pH 7.0, the concentration of H^+ increases by a factor of 10. Such solutions are said to be acidic. For every unit *above* 7.0, the concentration of OH^- is increased similarly. Such solutions are said to be alkaline. For example, a can of cola has a pH of about 2.5, over 10,000 times the acidity of the human cell. All living cells *must* operate within strict confines of a physiological pH that is slightly alkaline. Human blood, for example, has a pH of 7.365. If it drops below 7.0 (acidemia) or rises above 7.8 (alkalemia), coma and death can quickly follow.

Consequently, the human body does *everything* in its power to ensure that the pH of its tissues remains within stringent confines.

Net acid load is an expression that refers to the contribution of acid (H^+) to the cells of the body from foods that are consumed. As such, it represents the total *body burden* of dietary acid. A net acid load of zero would imply that the foods eaten were exactly balanced in their relative acidity and alkalinity. While our ancestral diets were slightly alkaline, today's modern Western diet has a high net acid load. This has severe implications for long-term health.

What is meant by acid-foods?

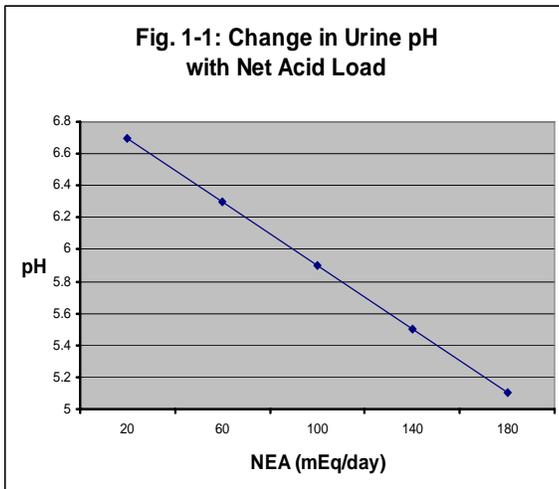
People frequently confuse the *acidity* of a food source with its *acid load*. It appears paradoxical, but a lemon (which is quite acidic) will actually *reduce* the body's acid load, once its mineral contents (generally found in the pulp) are absorbed into the body fluids. This is because the predominant minerals within the lemon (i.e. the electrically positive cations of calcium, potassium, sodium and magnesium) have an alkalizing (acid-reducing) effect on the body. They do this by forming mineral hydroxides and carbonates in our cells, which act like molecular sponges to “suck up” excess acidity. Most fresh fruits and vegetables are replete with health promoting alkali minerals, which is in part why countless epidemiological studies have substantiated their health promoting effects.⁷ Other minerals, including some found in the amino acids and proteins consumed in our diet, are *acid promoting*. These negatively charged anions (chloride, sulfate, phosphate, nitrate and some sulfur-containing amino acids) draw hydrogen into solution to form hydrochloric, sulfuric and phosphoric acids, and assorted weak organic acids in our cells. Foods that are predominant in these elements are commonly called acid-foods because they *contribute* to the body's net acid load. To determine

if a particular food is acid absorbing or acid yielding, the food is completely oxidized to collect its mineral ash, then mixed with water to measure the resultant pH. The ash consists of the combined mineral contents of the food.

When organic matter is consumed, digestive enzymes cleave the constituent proteins, carbohydrates, fats and nucleic acids into their basic building blocks for absorption from the gut into the blood. All materials absorbed into the blood pass through the liver for detoxification inspection,

ultimately reporting to the kidneys; it is here where the blood's pH is continually monitored and adjusted.⁸ At the cellular level, dietary constituents are further oxidized by complex respiratory pathways, or are used to manufacture other structural components for the cell. During these metabolic exchanges, compounds containing sodium, potassium, magnesium, calcium, nitrogen, sulfur, chlorine and phosphorus are formed that can also contribute to the net acid load of the cell.⁹

A more accurate means of calculating the net acid load of a diet consists of directly measuring the acid and ammonium in the urine, then subtracting the measured level of bicarbonate (HCO_3^-) to yield a NEA (net excreted acid) score.¹⁰ The NEA provides a measure of the *total* acid load of a *mixed* diet that is contributed to the body.



The NEA correlates closely with the pH of the urine as measured by narrow-range pH paper, something that can easily be done at home.

Figure 1-1, adapted from Remer and Mantz (1995),¹¹ shows how one can estimate the body's NEA by simply measuring the pH of the urine with narrow-range pH paper. Low protein diets or those high in vegetables and fruits will provide a low acid load, whereas high protein diets or those with a paucity of fruits and vegetables will have a high acid load. This is reflected in the milli-equivalents (mEq) of total acids excreted per day.

Another index, called PRAL (potential renal acid load), provides an estimate of the net acid excretion for an *individual* food source.¹² Using detailed charts, it is easy to identify the contribution of an individual food source to the total body burden of acid contributed from the diet. Table 1-2 provides a summary of PRAL values by food group, as reported by Remer and Manz.¹¹ Using the PRAL values, it is possible to estimate the acid load per 100 grams of an individual food or food group.

Chronic metabolic acidosis

The role of nutrition in pH homeostasis (balance) has been a subject of controversy for almost a century. Physiological research demonstrates that the prodigious capacity of the kidneys to excrete excess acid precludes any direct measure of changes to acid-base balance due to diet. In healthy individuals fed diets that create a 10-fold increase in their acid load, changes in blood pH are barely detectible, confirming the textbook knowledge of full compensatory balance.¹³ However, this tenacity of the blood not to deviate from its physiological norm does not preclude the possibility of a net retention of acid somewhere within the body, or the ability of the body to draw down its mineral stores in order to replace alkalizing minerals lost in the excretion of excess acid.

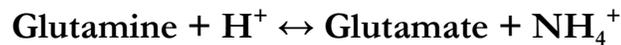
Table 1-2: Food group/100g	PRAL (mEq/day)
Processed Cheeses	31.5
Hard Cheeses	21.4
Soft Cheeses	10.0
Meats & Meat Products	9.5
Cottage Cheese	8.7
Eggs (whole)	8.2
Low Protein Cheeses	8.0
Fish	7.9
Pasta	7.2
Grain products (n/i pasta)	5.2
Nuts and Fruits	4.5
Yogurt	1.4
Sugars/sweets	0.8
Milk	0.7
Legumes	0.5
Fats and Oils	0.0
Vegetables	-3.2
As adapted from: Remer and Mantz, 1995 July;95(7):791-7.	

The pH of the blood and extracellular fluids bathing our cells is one of the most tightly regulated processes in human physiology.¹⁴ Even minute changes to the pH of these fluids invoke powerful regulatory responses necessary for our survival. In the blood, these responses involve the release of excess carbon dioxide (a volatile acid) from our lungs, the utilization of bicarbonate buffer (HCO₃) to mop up excess acid, and the formation and

removal of ammonia through our kidneys (urine) and skin (perspiration). Within the cells themselves, the buffering role falls principally to the phosphate (PO_4^{-3}) buffering system. About 85% of the phosphate ions used in intracellular pH buffering comes from potassium phosphate deposits on our bones and teeth.¹⁵

Normally, these homeostatic responses are more than sufficient to deal with the day-to-day production of acids from cellular metabolism and return our cellular fluids to a slightly alkaline pH. Even in situations of extreme metabolic stress, where the body is forced to generate large quantities of lactic acid (such as in running a marathon), these regulatory mechanisms will soon return the pH to normal. However, if excess acid is continually introduced — either through pathological conditions or through the diet — a state of low-grade, chronic metabolic acidosis will occur.

To preserve pH balance under conditions of chronic acid load, the body must continually draw on its alkaline reserves by releasing calcium, potassium and magnesium from the bone matrix to neutralize excess acid. In addition, the body begins to break down muscle protein in order to release the amino acid glutamine. In turn, glutamine is converted to glutamic acid (glutamate) by the liver and, in doing so, binds with excess hydrogen ions to generate ammonia (NH_4^+). The ammonia is then excreted in the urine, along with chloride (Cl) ions that are needed to balance the electrochemical charge.^{16, 17}



These two catabolic processes, if unchecked, result in the gradual loss of protein, calcium and related alkali minerals from the bone (osteopenia), and progressive muscle wasting (sarcopenia), both of which are age-related degenerative processes.

The fact is, low-grade (sub-clinical) chronic metabolic acidosis does exist normally in humans eating ordinary diets that yield normal net rates of endogenous acid production. Furthermore, this phenomenon has also been observed in other animal species.^{18, 19} The degree of acidosis increases with age, which explains the gradual decline in skeletal and muscle mass that occurs with aging.²⁰ If you have ever noticed the pungent aroma in a seniors' center, it is likely from the high levels of ammonia excreted in the urine of the acidotic residents.

Mainstream medicine has yet to recognize chronic metabolic acidosis, except as can occur through serious illness, such as diabetes and cancer. The heated debate amongst medical practitioners (who claim it is impossible to acidify the blood, except in the case of life-threatening disease) and the scientific research community (who finds otherwise) overlooks a simple misunderstanding. Acidosis is a *process*, not an end-game; like the voltage

potential of a charged battery, acidosis is the electrochemical force that attempts to *drive* the pH of the blood *toward* acidity. Only if not countered by the prevailing regulatory mechanisms of the body, will the end-game — *acidemia* (acid blood) — inevitably result.

As previously mentioned, compared to our ancestral diets, which were alkaline preserving, the modern Western diet is acid producing. Research by Sebastian and coworkers shows that the NEA of the ancestral diet was approximately -88 mEq/day, as compared to +48 mEq/d for the Western diet.²¹ While many proponents of alkaline (vegetarian) diets cite the high protein intake of the contemporary diets as the main contributor to acid load, the role of proteins in pH balance is exceedingly complex and dependent on the specific amino acid content of the protein(s) in question (plant protein vs. animal protein). A high protein intake *can* be acid forming, due to the phosphate and sulfur groups found in the amino-acid building blocks of animal proteins; however, protein degradation can also counteract some of its own acid load by increasing the renal capacity to excrete excess acid (as mentioned previously with glutamine). Thus, it appears that the shift from alkaline to acid load may come largely through displacing the bicarbonate-yielding fruits and vegetables with acid-yielding grains and dairy products.⁸ In other words, it may not be so much an *excess* of acid-producing foods, but a *paucity* of alkaline-yielding vegetables that tips the scale from a healthy alkaline diet toward one of chronic metabolic acidosis.²²

Chloride Balance

This paper reports another important regulatory mechanism that appears to have been largely overlooked in the ongoing debate about chronic acidosis: the significant contribution by sodium chloride — more specifically, the role of the chloride ion (Cl^-), itself — to the net acid load of the body. Evidence of such participation has been very recently reported by Frassetto and coworkers, of the University of California, who found that the concentration of NaCl in the blood can *independently* predict the acid-alkaline status of the body.²³ The authors contend that, depending on the level of dietary intake, the concentration of chloride in the blood can predict a startling **50-100%** of the acidosis-producing effect of the diet. This finding is supported by the earlier work of Kellum and others, whose investigations into the determinants of blood pH concluded that it was the relative concentration of chloride to other strong ions (known as the strong ion difference) — and *not* the level of bicarbonate (HCO_3^-) buffer — that determines the level of acidosis.^{24, 25} According to Kellum, the chloride ion can *singularly* act as a strong base, drawing hydrogen into solution. Consequently, as the level of chloride increases, so too does the level of acidity (pH decreases).

A typical American diet contains amounts of sodium chloride *far above* evolutionary norms and potassium *far below* those norms. It is estimated that our ancestral diet had a potassium/sodium ratio of 10:1, which has now been inverted to 1:3, reflecting a 30-fold

change.²⁶ This inverted ratio of potassium to sodium in our contemporary diet, compared to our ancestral diet, is known to adversely affect cardiovascular function and contribute to hypertension and stroke. The very recent finding that diets containing substantial sodium chloride and diets that are acid producing can act *independently* to induce and sustain increased tissue acidity suggests a potent “tag-team” combination, enhanced by increasing age and the kidney's impaired ability to excrete excess acidity.^{27, 28}

These findings have huge implications, considering the amount of salt in the human diet, and suggest that sodium intake may play a role *equal* to or *greater* than net acid load of *all* other nutrients in the process of acidosis.

Acidosis and Disease

The great French scientist, Louis Pasteur once said, “The germ is nothing, the inner terrain is everything.” Within this context, chronic metabolic acidosis represents a profound disruption of our inner biological terrain, and one that is consistently observed in most physical and mental degenerative diseases. According to some clinicians, chronic acidosis is a clinical barometer by which we can measure the degenerative process.²⁹

In animal and human studies, metabolic acidosis has been shown to:

- increase Reactive Oxygen Species (ROS), impair oxidative phosphorylation (energy transfer), and invoke oxidative damage;³⁰⁻³²
- create aberrations in intestinal absorption of minerals and other nutrients;^{33, 34}
- elevate insulin and cortisol levels;^{35, 36}
- cause derangements in endocrine hormone balance;^{37, 38}
- impair immunity and increase systemic inflammation;^{32, 36, 39-41}
- reduce skeletal mineral and protein content and impair the function of bone-building cells;⁴²⁻⁴⁹
- retard skeletal growth;⁵⁰⁻⁵²
- promote proteolysis of protein and age-related muscle wasting;^{42, 44-47, 53-55}
- induce hypertension and cardiovascular dysfunction;^{56, 57}
- decrease insulin sensitivity and promote obesity, and;^{22, 50, 51, 58}

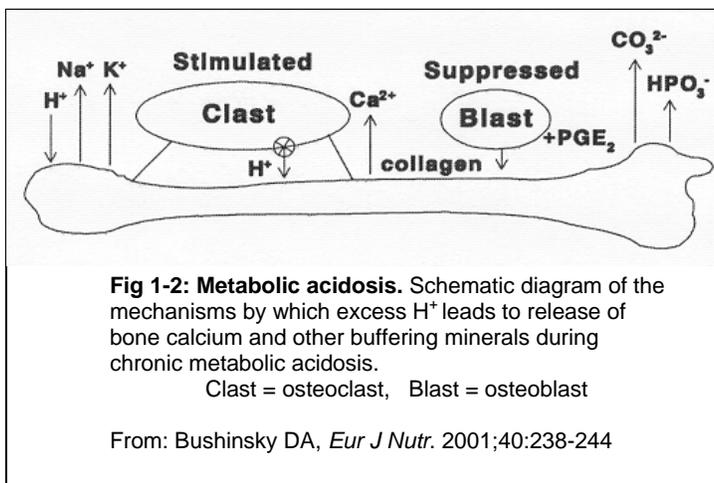
- activate critical cellular signalling molecules linked to inflammation and carcinogenesis.^{59, 60}

The *real* problem with chronic acidosis may not be so much one of excessive protein intake as it is one of chronic alkaline deficiency. It is well known that the standard North American diet falls woefully short of the daily intake of the fresh fruits and vegetables needed to supply the alkalizing minerals to effect pH balance. Several studies confirm that returning to an alkaline diet closer to our physiological norm will ameliorate the negative effects of excess acid load.⁶¹⁻⁶³

Too much acid, too much salt, chasing too few minerals. It is clear that today's dietary patterns are in serious discord with our genetically prescribed needs. As a society, we have neglected and abused our 'biological terrain' and degenerative disease is the consequence of our folly.

Osteoporosis

To protect at all costs the pH balance of the blood, the body sacrifices bone tissue through direct chemical dissolution of the bone surface, conscripting the minerals as buffers against the corrosive effects of excess acidity. As little as one week on a mildly acidic diet is sufficient to show a detectable drop in bone minerals from the bone surface.⁶⁴



Consequently, acid-producing diets can dramatically alter both bone structure and function. A high dietary acid load has been shown to both *increase* bone resorption (a process by which the bone structure is remodeled) and *decrease* bone formation.⁶⁵

In the process, calcium (Ca^{+2}) and carbonate (CO_3^{-2}) are released from the bone mineral matrix.^{65, 66} This release of calcium into the blood and its excretion

in the urine is *not* compensated by equivalent calcium uptake in the gut. Sodium (Na^+), potassium (K^+), and assorted phosphate (PO_4^{-3} and HPO_3^-) ions are also released from the bone surface to combine with the excess hydrogen (H^+) in the blood.⁶⁷⁻⁶⁹ Unchecked, this degradative process leads to thinner, weaker bones (osteopenia) and, if not corrected, osteoporosis (hollowed out bones).

It begins with the release of the alkaline minerals sodium and potassium from the bone surface, which the blood uses as its first line of defense against excess acid. Failure to restore pH balance then stimulates osteoclast (bone-destroying cells) activity and shuts down osteoblast (bone-forming cells) activity, precipitating the release of calcium and the carbonate/phosphate buffers from the bone mineral matrix and the increase of calcium (hypercalciuria) in the blood.⁶⁵ Arnett and coworkers have shown that bone resorption by osteoclasts is absolutely dependent on extracellular acidification; these cells are inactive at alkaline pH levels (above 7.3) and show maximum stimulation at a pH of about 6.9. Resorption is most sensitive to changes in acidity at a pH of about 7.1 (close to the interstitial pH in bone).⁷⁰ This cell-mediated response is likely affected through the release of the stress-related hormone cortisol, high levels of which are known to concurrently deplete muscle protein and accelerate mineral loss (a likely reason why prolonged stress, which raises blood cortisol levels, will accelerate bone loss).³⁵

Researchers with the massive Framingham Osteoporosis Study, published in 2001, contend that the consumption of fresh fruits and vegetables is a prudent means of interrupting this bone destroying process.⁷¹ Because fruits and vegetables metabolize to bicarbonate, investigation has recently turned toward supplementation of the diet with alkaline salts, such as potassium bicarbonate and potassium citrate.^{72, 73}

Maurer and coworkers (2003) were the first to demonstrate that even very mild diet-induced acidosis will lead to the destruction of precious bone mineral, an effect that could be immediately and significantly reversed with the administration of bicarbonate mineral salts.³⁵ The treatments are generally well tolerated and help replenish the body's alkaline reserves while also serving to reverse the dysfunctional potassium/sodium ratio characteristic of modern diets. In one study, neutralization of dietary acid load using potassium bicarbonate (KHCO_3) supplements improved calcium and phosphorus balances, reduced bone resorption, improved nitrogen balance (through reduced muscle wasting) and helped mitigate the normal age-related decline in growth hormone levels.¹⁹ Other investigations demonstrate the remarkable bone preserving effect of this simple mineral salt. Dietary intervention with potassium-rich and bicarbonate rich foods and KHCO_3 supplements confer striking protection against the bone-wasting effects of today's high-acid Western diet.⁷⁴⁻⁷⁷ KHCO_3 supplementation can also reduce hypertension and risk of stroke, prevent kidney stones by reducing calcium excretion, and protect against osteopenia and osteoporosis by increasing the retention of calcium and phosphorus, reducing bone resorption, and enhancing bone formation.⁷⁸ The dose of bicarbonate required to provide skeletal protection was found to be 60-120 mg/d, or about 1-2 teaspoons of potassium bicarbonate each day.⁷⁹

Cancer

In his elegantly written documentary, *Anticancer ~ A new Way of Life*, physician, researcher and cancer survivor, David Servan-Schreiber, paints a startling exposé of mainstream medicine's abject failure to address the true causes of cancer.⁸⁰ He contends that it is our modern Western diet and lifestyle that acts as a 'fertilizer' for cancer, helping to prepare our biological terrain for the incursion of this deadly process. According to Servan-Schreiber, the disease can best be understood as a breakdown in the balance between pre-cancerous cells that lie dormant in our bodies and our own natural defenses, which normally keep them at bay. By preparing the 'soil' with diets that are highly glycemic and highly acidic, these cancerous seeds germinate and morph into fast-growing clusters of mutated cells that soon become immortal and divide without end, spreading a growing tsunami of hyper-acidity that kills normal cells to make room for the new kids on the block. He argues that our best defense is a good offense, through simple and practical dietary and lifestyle changes.

Servan-Schreiber's arguments are well supported by a wealth of epidemiological and clinical studies, which confirm that more than 60% of cancer deaths can be avoided by simply adopting healthier lifestyles.⁸⁰⁻⁸² A very recent study demonstrated that women with breast cancer that had already spread to the lymph glands (metastasized), and whose treatment focused on diet, lifestyle change and stress reduction, saw their risk of dying from cancer drop a remarkable 66% compared to those women who chose the conventional treatments of "cut, burn and poison."⁸³⁻⁸⁶ As well, researchers at the Université de Montréal confirm that high fruit and vegetable intake diminishes the risk of breast cancer in genetically-prone, high-risk individuals by a stunning 73%. It seems that an alkaline diet confers the ability to down-regulate the cancer-causing genes that can lead to the development of this type of cancer.⁸⁷

In a study of 93 men with prostate cancer who refused conventional treatment and chose instead to modify their diet, exercise habits and stress levels, researchers found a marked reduction of their levels of prostate specific antigen (PSA), a blood marker for prostate cancer. Moreover, their blood was *7-fold* more capable of inhibiting cancer growth than those seeking conventional treatment.⁸⁸ In a very recent study, the same researchers found that such lifestyle changes modified the expression of more than 500 genes within the prostate, stimulating the cancer-protective genes and inhibiting cancer-promoting genes.⁸⁹

Such strong evidence begs the question: What is it about our Western diet that seems to kick-start the cancer process? While a growing volume of observational, clinical and epidemiological evidence points to the role of chronic tissue acidosis in the genesis and maintenance of cancer,⁹⁰ a review of the literature on acid-forming diets and cancer reveals a

paucity of research. The vast majority of cancer studies are looking through the *wrong* end of the microscope — focusing on treatment/cure rather than prevention and risk mitigation. Nobel Laureate James Watson (co-discoverer of the molecular structure of DNA), describes today's cancer industry as, “intellectually bankrupt, fiscally wasteful and therapeutically useless.” However, recent studies *have* emerged that provide an intriguing insight into the relationship between diet and cancer.

As previously mentioned, an acid-promoting diet initiates a broad cascade of biochemical and physiological changes to our inner terrain that appear to set us up for cancer. These include: chronic oxidative stress, enhanced catabolism (muscle wasting and destruction of skeletal reserves), elevation of insulin and cortisol, systemic inflammation, obesity, and impaired immunity. Each of these aberrations is known *singularly* to be involved with the genesis of the cancer process. Just imagine the implications when they are *all* pulling on the same rope.

Cancerous cells are formed continuously in the human body, with an estimated 10,000 cells active at any given time, their growth normally kept in check by an active, healthy immune system.⁹¹ Abnormalities in our acid/alkaline balance seem to play a major role in the genesis of cancer by knee-capping our immune response to allow cancerous growths to start.³² The glucocorticoid hormone, cortisol (responsible for the muscle wasting and bone depleting effects of chronic acidosis) is well known for its inhibitory effects on our immune system and is over-expressed in highly acidic tissues.³⁶ High levels of inflammation also block the body's natural defenses by disarming its natural killer (NK) cells (specialized white blood cells) and enhancing the production of chemical signalling molecules, such as prostaglandin E2 (PGE2), to further inhibit immunity and encourage unchecked growth.^{92, 93} Measuring the level of systemic inflammation can, in fact, predict a patient's survival time for several cancers.⁹⁴⁻⁹⁶

It was the father of modern pathology, Rudolph Virchow, who first observed that people often develop cancer at the exact spot where they had sustained an injury. Virchow advanced the hypothesis that cancer was a wound repair that had gone awry. The finding that cancer is most often directly related to a chronic inflammatory state adds support to Virchow's position, as inflammation is intricately related to the healing process.⁹⁷ Cancer, in fact, requires inflammation to both initiate and sustain its growth. For this reason, cancer cells secrete inflammatory proteins and other signaling molecules seen in natural wound repair, to fuel their growth.

Yet the unchallenged growth of cancer appears to rely principally on a single pro-inflammatory agent present in all cells but highly expressed in cancer cells — Nuclear factor

kappa- β (NFk β) — the ‘master switch’ that regulates inflammation throughout the body. Once activated, this cellular protein migrates to the nucleus of the cell, where it can switch on over 400 genes that control the body’s inflammatory cascade.⁹⁸ According to Albert Baldwin, of the University of North Carolina, almost every cancer agent known to pharmacology is an inhibitor of NFk β . In fact, the entire industry focus appears intent on finding an appropriate drug that will expressly inhibit this critical biochemical trigger.

Simply put, you could not find a better way to set us up for systemic inflammation and cancer than our acid-forming Western diet. Systemic tissue acidity (pH \sim 7.0 or less) has been shown to switch on NFk β and other inflammation-signaling chemicals, such as C-reactive protein.(CRP) and cyclooxygenase-2 (COX-2), an enzyme central to the manufacture of other important inflammation-signaling molecules.^{32, 99} At the same time, hyper-acidity within the tumor site (assisted by an already acidic condition) further cripples the immune system by knocking out of action the specialized white blood cells responsible for culling aberrant cells.¹⁰⁰⁻¹⁰² Acidification of tissues through imprudent dietary and lifestyle choices appears to tip the scales in favor of harm, *enslaving* our innate immune responses, which would normally swing into action to search out and destroy these invasive growths.³⁶

While the pH of cancer cells is neutral to slightly alkaline, the pH of the fluid surrounding these cells (extracellular fluid) is highly acidic due to acids secreted by cancerous cells, conferring upon them the ability to invade. Recent studies show that the administration of potassium and sodium bicarbonate salts can markedly enhance cancer kill rates and arrest cancer growths.¹⁰³⁻¹⁰⁵ Other investigations have shown that interfering with the over-expression of carbonic anhydrase, an enzyme responsible for acidification of the tumor through conversion of bicarbonate to carbon dioxide (thereby removing the buffering effect of HCO₃⁻), can attenuate the invasiveness of cancer.¹⁰⁶⁻¹¹⁰ Some practitioners are now beginning to use bicarbonate therapy in their clinics, with remarkable results,¹¹⁰ supporting the argument that it is a lack of bicarbonate and other alkalizing nutrients in the diet that predisposes us toward cancer and other degenerative processes.

Conclusions

Oxidative stress, insulin resistance, cortisol-induced catabolism, systemic inflammation — *all* are consequences of a diet and lifestyle out of sync with our genetically prescribed patterns. They work synergistically to alter the body’s ancestral biological terrain, defeat its natural defenses and dramatically increase our lifetime risk of cancer, osteoporosis, and other serious chronic diseases. The good news is that we can control these risk factors *ourselves*, with appropriate diet and lifestyle changes, so that the threat of these and other degenerative processes need not loom so large.

The following are some suggestions for kicking the ‘acid’ habit, returning your body to a healthy alkaline balance, and reducing your lifetime risk of degenerative disease, which unnecessarily cuts short so many lives today:

- 1) bring pH balance back to the dinner table by serving meals that consist of 60-80% alkalizing fruits and vegetables;
- 2) stir-fry or steam your vegetables to preserve mineral and vitamin content, which is usually lost from overcooking and boiling;
- 3) Reduce your reliance on acid-producing dairy products, particularly hard cheeses, which should be used as condiments only;
- 4) Seriously reduce your use of acid-promoting white flour and substitute with multi-grain flour;
- 5) Start each day with an alkalizing glass of lemon water by squeezing a fresh lemon (NO SUGAR) into pure water — and make sure you include the pulp;
- 6) Drink 6-8 glasses of water each day to help flush acidic wastes out of the body;
- 7) Choose fresh fish and organically grown chicken over red meats and limit your protein intake from meat to about 4 ounces a day (about the size of a deck of playing cards);
- 8) Throw out your sugar bowl — really;
- 9) Trade in your table salt (sodium chloride contains traces of over 60 chemicals from the refining process) and choose natural sea salt, which contains a mixture of alkaline mineral complexes;
- 10) Don’t drink sugary sodas (a single can of cola contains over 9 teaspoons of sugar and requires 32 glasses of water to neutralize its acidity);
- 11) Increase your intake of inflammation-reducing omega-3 fats, found in fish and flax seeds, and reduce your intake of inflammation-promoting omega-6 fats found in vegetable oils, fatty meats and dairy products;
- 12) Get some exercise every day, preferably aerobic exercise, to blow out excess acid-producing CO₂ from your tissues and help maintain muscle tone; and,

Lastly, learn to chill out, laugh and love a little more. Stress relief is now understood as a vital component of reducing tissue acidity and inflammation and protecting your long-term health.

Reference List

- (1) Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* 1985 January 31;312(5):283-9.
- (2) Smith E, Morowitz HJ. Universality in intermediary metabolism. *Proc Natl Acad Sci U S A* 2004 September 7;101(36):13168-73.
- (3) Eaton SB, Konner MJ, Cordain L. Diet-dependent acid load, Paleolithic nutrition, and evolutionary health promotion. *Am J Clin Nutr* 2010 February;91(2):295-7.
- (4) Strohle A, Hahn A, Sebastian A. Estimation of the diet-dependent net acid load in 229 worldwide historically studied hunter-gatherer societies. *Am J Clin Nutr* 2010 February;91(2):406-12.
- (5) Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005 February;81(2):341-54.
- (6) O'Keefe JH, Jr., Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. *Mayo Clin Proc* 2004 January;79(1):101-8.
- (7) New SA. Intake of fruit and vegetables: implications for bone health. *Proc Nutr Soc* 2003 November;62(4):889-99.
- (8) Berardi J. Covering Nutritional Bases. *ScienceLink* 2003; Available at: URL: <http://www.johnberardi.com/articles/nutrition/bases.htm>. Accessed February 2, 2010.
- (9) Acid and Alkaline in the Diet. *RawFoodExplained.com* 2010; Available at: URL: <http://www.rawfoodexplained.com/acid-and-alkaline-substances/acid-and-alkaline-in-the-diet.html>. Accessed February 8, 2010.
- (10) Remer T, Manz F. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr* 1994 June;59(6):1356-61.
- (11) Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc* 1995 July;95(7):791-7.
- (12) Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc* 1995 July;95(7):791-7.

- (13) Vormann J, Daniel H. The role of nutrition in human acid-base homeostasis. *Eur J Nutr* 2001 October;40(5):187-8.
- (14) Kellum JA. Determinants of blood pH in health and disease. *Crit Care* 2000;4(1):6-14.
- (15) Kim B. Essential Details on Acid and Alkaline-Forming Effects of Food and How Your Body Maintains a Healthy pH. *Dr Ben Kim* 2010; Available at: URL: <http://drbenkim.com/ph-body-blood-foods-acid-alkaline.htm>. Accessed December 2, 2010.
- (16) Frassetto L, Morris RC, Jr., Sebastian A. Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. *J Clin Endocrinol Metab* 1997 January;82(1):254-9.
- (17) Welbourne TC, Joshi S. Enteral glutamine spares endogenous glutamine in chronic acidosis. *JPEN J Parenter Enteral Nutr* 1994 May;18(3):243-7.
- (18) Riond JL. Animal nutrition and acid-base balance. *Eur J Nutr* 2001 October;40(5):245-54.
- (19) Frassetto L, Morris RC, Jr., Sellmeyer DE, Todd K, Sebastian A. Diet, evolution and aging--the pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. *Eur J Nutr* 2001 October;40(5):200-13.
- (20) Frassetto L, Morris RC, Jr., Sebastian A. Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. *J Clin Endocrinol Metab* 1997 January;82(1):254-9.
- (21) Sebastian A, Frassetto LA, Sellmeyer DE, Merriam RL, Morris RC, Jr. Estimation of the net acid load of the diet of ancestral preagricultural Homo sapiens and their hominid ancestors. *Am J Clin Nutr* 2002 December;76(6):1308-16.
- (22) Berkemeyer S. Acid-base balance and weight gain: are there crucial links via protein and organic acids in understanding obesity? *Med Hypotheses* 2009 September;73(3):347-56.
- (23) Frassetto LA, Morris RC, Jr., Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. *Am J Physiol Renal Physiol* 2007 August;293(2):F521-F525.
- (24) Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest* 2006 October;130(4):962-7.
- (25) Story DA, Morimatsu H, Bellomo R. Hyperchloremic acidosis in the critically ill: one of the strong-ion acidoses? *Anesth Analg* 2006 July;103(1):144-8, table.

- (26) Challem J. The pH Nutrition Guide to Acid / Alkaline Balance. *Natural News* 2010; Available at: URL: http://www.naturalnews.com/Report_acid_alkaline_pH_1.html. Accessed February 10, 2010.
- (27) Frassetto LA, Morris RC, Jr., Sellmeyer DE, Sebastian A. Adverse effects of sodium chloride on bone in the aging human population resulting from habitual consumption of typical American diets. *J Nutr* 2008 February;138(2):419S-22S.
- (28) Frings-Meuthen P, Baecker N, Heer M. Low-grade metabolic acidosis may be the cause of sodium chloride-induced exaggerated bone resorption. *J Bone Miner Res* 2008 April;23(4):517-24.
- (29) Philpott WH. Metabolic Acidosis and Degenerative Disease. *J Orthomol Nutr* 1987;2(4):211-2.
- (30) Bento LM, Fagian MM, Vercesi AE, Gontijo JA. Effects of NH₄Cl-induced systemic metabolic acidosis on kidney mitochondrial coupling and calcium transport in rats. *Nephrol Dial Transplant* 2007 October;22(10):2817-23.
- (31) Rustom R, Wang B, McArdle F et al. Oxidative stress in a novel model of chronic acidosis in LLC-PK1 cells. *Nephron Exp Nephrol* 2003;95(1):e13-e23.
- (32) Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Crit Care* 2004 October;8(5):331-6.
- (33) Charoenphandhu N, Wongdee K, Tudpor K, Pandaranandaka J, Krishnamra N. Chronic metabolic acidosis upregulated claudin mRNA expression in the duodenal enterocytes of female rats. *Life Sci* 2007 April 17;80(19):1729-37.
- (34) Wongdee K, Teerapornpuntakit J, Riengrojpitak S, Krishnamra N, Charoenphandhu N. Gene expression profile of duodenal epithelial cells in response to chronic metabolic acidosis. *Mol Cell Biochem* 2009 January;321(1-2):173-88.
- (35) Maurer M, Riesen W, Muser J, Hulter HN, Krapf R. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. *Am J Physiol Renal Physiol* 2003 January;284(1):F32-F40.
- (36) Lardner A. The effects of extracellular pH on immune function. *J Leukoc Biol* 2001 April;69(4):522-30.
- (37) Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on thyroid hormone homeostasis in humans. *Am J Physiol* 1997 May;272(5 Pt 2):F648-F653.
- (38) Wiederkehr MR, Kalogiros J, Krapf R. Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients. *Nephrol Dial Transplant* 2004 May;19(5):1190-7.

- (39) Krieger NS, Frick KK, LaPlante SK, Michalanka A, Bushinsky DA. Regulation of COX-2 mediates acid-induced bone calcium efflux in vitro. *J Bone Miner Res* 2007 June;22(6):907-17.
- (40) Yorio T, Page RD, Frazier LW. Prostaglandin regulation of H⁺ secretion in amphibian epithelia. *Am J Physiol* 1991 May;260(5 Pt 2):R866-R872.
- (41) Bushinsky DA, Parker WR, Alexander KM, Krieger NS. Metabolic, but not respiratory, acidosis increases bone PGE(2) levels and calcium release. *Am J Physiol Renal Physiol* 2001 December;281(6):F1058-F1066.
- (42) Ballmer PE, McNurlan MA, Hulter HN, Anderson SE, Garlick PJ, Krapf R. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Invest* 1995 January;95(1):39-45.
- (43) Disthabanchong S, Radinahamed P, Stitchantrakul W, Hongeng S, Rajatanavin R. Chronic metabolic acidosis alters osteoblast differentiation from human mesenchymal stem cells. *Kidney Int* 2007 February;71(3):201-9.
- (44) Kleger GR, Turgay M, Imoberdorf R, McNurlan MA, Garlick PJ, Ballmer PE. Acute metabolic acidosis decreases muscle protein synthesis but not albumin synthesis in humans. *Am J Kidney Dis* 2001 December;38(6):1199-207.
- (45) May RC, Masud T, Logue B, Bailey J, England B. Chronic metabolic acidosis accelerates whole body proteolysis and oxidation in awake rats. *Kidney Int* 1992 June;41(6):1535-42.
- (46) May RC, Bailey JL, Mitch WE, Masud T, England BK. Glucocorticoids and acidosis stimulate protein and amino acid catabolism in vivo. *Kidney Int* 1996 March;49(3):679-83.
- (47) Williams B, Layward E, Walls J. Skeletal muscle degradation and nitrogen wasting in rats with chronic metabolic acidosis. *Clin Sci (Lond)* 1991 May;80(5):457-62.
- (48) Wongdee K, Riengrojpitak S, Krishnamra N, Charoenphandhu N. Claudin expression in the bone-lining cells of female rats exposed to long-standing acidemia. *Exp Mol Pathol* 2009 December 24.
- (49) Frick KK, LaPlante K, Bushinsky DA. RANK ligand and TNF-alpha mediate acid-induced bone calcium efflux in vitro. *Am J Physiol Renal Physiol* 2005 November;289(5):F1005-F1011.
- (50) Goldberg R, Reshef-Bankai E, Coleman R, Green J, Maor G. Chronic acidosis-induced growth retardation is mediated by proton-induced expression of Gs protein. *J Bone Miner Res* 2006 May;21(5):703-13.
- (51) Green J. The physicochemical structure of bone: cellular and noncellular elements. *Miner Electrolyte Metab* 1994;20(1-2):7-15.

- (52) Green J, Goldberg R, Maor G. PTH ameliorates acidosis-induced adverse effects in skeletal growth centers: the PTH-IGF-I axis. *Kidney Int* 2003 February;63(2):487-500.
- (53) Ruggieri F, Caso G, Wegmann M et al. Does increasing blood pH stimulate protein synthesis in dialysis patients? *Nephron Clin Pract* 2009;112(4):c276-c283.
- (54) Garibotto G, Sofia A, Robaudo C et al. Kidney protein dynamics and ammoniogenesis in humans with chronic metabolic acidosis. *J Am Soc Nephrol* 2004 June;15(6):1606-15.
- (55) Baldwin DN, Spencer JL, Jeffries-Stokes CA. Carbohydrate intolerance and kidney stones in children in the Goldfields. *J Paediatr Child Health* 2003 July;39(5):381-5.
- (56) Zhang L, Curhan GC, Forman JP. Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension* 2009 October;54(4):751-5.
- (57) Murakami K, Sasaki S, Takahashi Y, Uenishi K. Association between dietary acid-base load and cardiometabolic risk factors in young Japanese women. *Br J Nutr* 2008 September;100(3):642-51.
- (58) Kopple JD, Kalantar-Zadeh K, Mehrotra R. Risks of chronic metabolic acidosis in patients with chronic kidney disease. *Kidney Int Suppl* 2005 June;(95):S21-S27.
- (59) Krieger NS, Bushinsky DA, Frick KK. Cellular mechanisms of bone resorption induced by metabolic acidosis. *Semin Dial* 2003 November;16(6):463-6.
- (60) Krieger NS, Frick KK, Bushinsky DA. Mechanism of acid-induced bone resorption. *Curr Opin Nephrol Hypertens* 2004 July;13(4):423-36.
- (61) Bell JA, Whiting SJ. Effect of fruit on net acid and urinary calcium excretion in an acute feeding trial of women. *Nutrition* 2004 May;20(5):492-3.
- (62) Frassetto LA, Todd KM, Morris RC, Jr., Sebastian A. Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable foods. *J Gerontol A Biol Sci Med Sci* 2000 October;55(10):M585-M592.
- (63) New SA. Intake of fruit and vegetables: implications for bone health. *Proc Nutr Soc* 2003 November;62(4):889-99.
- (64) Bushinsky DA, Chabala JM, Gavrillov KL, Levi-Setti R. Effects of in vivo metabolic acidosis on midcortical bone ion composition. *Am J Physiol* 1999 November;277(5 Pt 2):F813-F819.
- (65) Bushinsky DA. Acid-base imbalance and the skeleton. *Eur J Nutr* 2001 October;40(5):238-44.
- (66) Bushinsky DA, Sessler NE, Glens RE, Featherstone JD. Proton-induced physicochemical calcium release from ceramic apatite disks. *J Bone Miner Res* 1994 February;9(2):213-20.

- (67) Bushinsky DA, Levi-Setti R, Coe FL. Ion microprobe determination of bone surface elements: effects of reduced medium pH. *Am J Physiol* 1986 June;250(6 Pt 2):F1090-F1097.
- (68) Bushinsky DA, Wolbach W, Sessler NE, Mogilevsky R, Levi-Setti R. Physicochemical effects of acidosis on bone calcium flux and surface ion composition. *J Bone Miner Res* 1993 January;8(1):93-102.
- (69) Chabala JM, Levi-Setti R, Bushinsky DA. Alteration in surface ion composition of cultured bone during metabolic, but not respiratory, acidosis. *Am J Physiol* 1991 July;261(1 Pt 2):F76-F84.
- (70) Arnett T. Regulation of bone cell function by acid-base balance. *Proc Nutr Soc* 2003 May;62(2):511-20.
- (71) Tucker KL, Hannan MT, Kiel DP. The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. *Eur J Nutr* 2001 October;40(5):231-7.
- (72) Phend C. Counteracting Acidic Diet Reduces Markers of Bone Loss in Older Adults. *Medpage Today* 2008 December 3; Available at: URL: <http://www.medpagetoday.com/PrimaryCare/DietNutrition/12006>. Accessed February 13, 2010.
- (73) Marangella M, Di SM, Casalis S, Berutti S, D'Amelio P, Isaia GC. Effects of potassium citrate supplementation on bone metabolism. *Calcif Tissue Int* 2004 April;74(4):330-5.
- (74) Frassetto L, Morris RC, Jr., Sebastian A. Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women. *J Clin Endocrinol Metab* 2005 February;90(2):831-4.
- (75) Lanham-New SA. The balance of bone health: tipping the scales in favor of potassium-rich, bicarbonate-rich foods. *J Nutr* 2008 January;138(1):172S-7S.
- (76) Lutz J. Calcium balance and acid-base status of women as affected by increased protein intake and by sodium bicarbonate ingestion. *Am J Clin Nutr* 1984 February;39(2):281-8.
- (77) Mathur RP, Dash SC, Gupta N, Prakash S, Saxena S, Bhowmik D. Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. *Ren Fail* 2006;28(1):1-5.
- (78) Morris RC, Jr., Schmidlin O, Tanaka M, Forman A, Frassetto L, Sebastian A. Differing effects of supplemental KCl and KHCO₃: pathophysiological and clinical implications. *Semin Nephrol* 1999 September;19(5):487-93.

- (79) Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC, Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994 June 23;330(25):1776-81.
- (80) Servan-Schreiber D. *Anticancer: A New Way of Life*. 3rd ed. Toronto: Harper-Collins Publishers; 2009.
- (81) Stewart BW, Kleihues P. World Cancer Report. Lyon, France: World Health Organization (WHO); 2003.
- (82) Yatani R, Shiraishi T, Nakakuki K et al. Trends in frequency of latent prostate carcinoma in Japan from 1965-1979 to 1982-1986. *J Natl Cancer Inst* 1988 July 6;80(9):683-7.
- (83) Andersen BL, Farrar WB, Golden-Kreutz DM et al. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. *J Clin Oncol* 2004 September 1;22(17):3570-80.
- (84) Andersen BL, Farrar WB, Golden-Kreutz D et al. Distress reduction from a psychological intervention contributes to improved health for cancer patients. *Brain Behav Immun* 2007 October;21(7):953-61.
- (85) Andersen BL, Yang HC, Farrar WB et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. *Cancer* 2008 December 15;113(12):3450-8.
- (86) Thornton LM, Andersen BL, Crespin TR, Carson WE. Individual trajectories in stress covary with immunity during recovery from cancer diagnosis and treatments. *Brain Behav Immun* 2007 February;21(2):185-94.
- (87) Ghadirian P, Narod S, Fafard E, Costa M, Robidoux A, Nkondjock A. Breast cancer risk in relation to the joint effect of BRCA mutations and diet diversity. *Breast Cancer Res Treat* 2009 September;117(2):417-22.
- (88) Ornish D, Weidner G, Fair WR et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol* 2005 September;174(3):1065-9.
- (89) Ornish D, Magbanua MJ, Weidner G et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci U S A* 2008 June 17;105(24):8369-74.
- (90) Orive G, Reshkin SJ, Harguindey S, Pedraz JL. Hydrogen ion dynamics and the Na⁺/H⁺ exchanger in cancer angiogenesis and antiangiogenesis. *Br J Cancer* 2003 October 20;89(8):1395-9.
- (91) Roland-Mieszkowski M. Cancer - A Biophysicist's Point of View. *Digital Recordings com* 2004 July 21; Available at: URL: <http://www.digital-recordings.com/publ/cancer.html>. Accessed February 12, 2010.

- (92) Huang M, Stolina M, Sharma S et al. Non-small cell lung cancer cyclooxygenase-2-dependent regulation of cytokine balance in lymphocytes and macrophages: up-regulation of interleukin 10 and down-regulation of interleukin 12 production. *Cancer Res* 1998 March 15;58(6):1208-16.
- (93) Baxevanis CN, Reclos GJ, Gritzapis AD, Dedousis GV, Missitzis I, Papamichail M. Elevated prostaglandin E2 production by monocytes is responsible for the depressed levels of natural killer and lymphokine-activated killer cell function in patients with breast cancer. *Cancer* 1993 July 15;72(2):491-501.
- (94) Wallace JM. Nutritional and botanical modulation of the inflammatory cascade--eicosanoids, cyclooxygenases, and lipoxygenases--as an adjunct in cancer therapy. *Integr Cancer Ther* 2002 March;1(1):7-37.
- (95) Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. *Br J Cancer* 2006 March 13;94(5):637-41.
- (96) Al Murri AM, Bartlett JM, Canney PA, Doughty JC, Wilson C, McMillan DC. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. *Br J Cancer* 2006 January 30;94(2):227-30.
- (97) Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 1986 December 25;315(26):1650-9.
- (98) Goepf JG. What is Nuclear Factor kappa Beta? Life Extension , 31-40. 2006.
Ref Type: Magazine Article
- (99) Miyazawa K, Inoue K. Complement activation induced by human C-reactive protein in mildly acidic conditions. *J Immunol* 1990 July 15;145(2):650-4.
- (100) Severin T, Muller B, Giese G et al. pH-dependent LAK cell cytotoxicity. *Tumour Biol* 1994;15(5):304-10.
- (101) Loeffler DA, Juneau PL, Heppner GH. Natural killer-cell activity under conditions reflective of tumor micro-environment. *Int J Cancer* 1991 July 30;48(6):895-9.
- (102) Redegeld F, Filippini A, Sitkovsky M. Comparative studies of the cytotoxic T lymphocyte-mediated cytotoxicity and of extracellular ATP-induced cell lysis. Different requirements in extracellular Mg²⁺ and pH. *J Immunol* 1991 November 15;147(10):3638-45.
- (103) Robey IF, Baggett BK, Kirkpatrick ND et al. Bicarbonate increases tumor pH and inhibits spontaneous metastases. *Cancer Res* 2009 March 15;69(6):2260-8.
- (104) Raghunand N, Gillies RJ. pH and chemotherapy. *Novartis Found Symp* 2001;240:199-211.

- (105) Raghunand N, He X, van SR et al. Enhancement of chemotherapy by manipulation of tumour pH. *Br J Cancer* 1999 June;80(7):1005-11.
- (106) Winum JY, Rami M, Scozzafava A, Montero JL, Supuran C. Carbonic anhydrase IX: a new druggable target for the design of antitumor agents. *Med Res Rev* 2008 May;28(3):445-63.
- (107) Pastorekova S, Parkkila S, Zavada J. Tumor-associated carbonic anhydrases and their clinical significance. *Adv Clin Chem* 2006;42:167-216.
- (108) Thiry A, Dogne JM, Masereel B, Supuran CT. Targeting tumor-associated carbonic anhydrase IX in cancer therapy. *Trends Pharmacol Sci* 2006 November;27(11):566-73.
- (109) Rafajova M, Zatovicova M, Kettmann R, Pastorek J, Pastorekova S. Induction by hypoxia combined with low glucose or low bicarbonate and high posttranslational stability upon reoxygenation contribute to carbonic anhydrase IX expression in cancer cells. *Int J Oncol* 2004 April;24(4):995-1004.
- (110) Mac Farlane AB. Sodium Bicarbonate Lessons in Cancer and General pH Management. *International Medical Veritas Association* 2007 July 4; Available at: URL: <http://www.health-forums.com/alt-support-cancer/sodium-bicarbonate-lessons-cancer-long-read-but-worth-even-if-you-do-not-have-cancer-14887.html>. Accessed February 15, 2010.