2008: Another Year Older Or Younger?

What did we learn during the past year from anti-aging science?

By Bill Sardi © 2009

Based upon the alleged discovery four years ago that a single gene may control the rate of aging, many longevity seekers began to self experiment with a gene-controlling molecule called resveratrol, in an attempt to live longer, healthier lives. Have consumers of resveratrol pills been able to turn back the clock hands of biological time?

Research studies published in 2008 took longevity seekers on a wild ride of topsy turvy science as prior concepts about aging were dashed and others confirmed. The hope of an anti-aging pill approaches reality, but not for the reasons originally proposed.

One thing is for sure, humanity must race to save itself from the physical and economic ravages of aging. In developed countries, more than 88% of all newborns will live past age 65 and at least 44% will live beyond age 85. This dramatic extension of life has provided social and economic benefits, but also challenges. Albeit, increased healthcare costs associated with the care of longer-living adults threatens to thrust all Western societies into financial insolvency.

Have increases in life expectancy over the past century led to the untenable problem of prolonging life, only to live more unhealthy years, incapacitated by the curses of old age – memory loss, muscle shrinkage, heart failure, as well as loss of skin elasticity, skin wrinkling and hair loss that produces the physical appearance of being old?

The answer to the problem of chronic age-related disease must now move beyond rhetoric. There is no time to conduct more research. The *"best available evidence"* must be employed to stave off a global crisis beyond imaginable proportion.

Such an effort runs head on against the current disease-care system that allows chronic age-related disease to occur and then treat it.

The percentage of the population made up of elderly persons in the United States is projected to increase from 13 percent of the population in 2000 to 20 percent by 2030. The worldwide prevalence of chronic disease mortality in 2001 was 46% and is expected to rise to 57% by 2020. [Nutrition 2008 early online]

Total expenditures (in 1996 dollars) from the age of 65 years until death increase substantially with longevity, from $31,181 for persons who die at the age of 65 years to more than $200,000 for those who die at the age of 90. A substantial portion of this increase is attributed to nursing home costs. Keeping longevinarians mobile and active, and out of the nursing home, may be the most productive way to reduce health care spending among seniors. [The New England Journal Medicine 342: 1409-15, May 11, 2000]

Researchers are saying, if ageing is combined with extended years of healthy life, it could *"produce unprecedented social, economic, and health dividends."*

A report published in the July 19, 2008 issue of The British Medical Journal states:

"In recent decades, scientists have shown that the underlying biological processes of ageing, which give rise to most diseases and other age related health problems, can be delayed. We argue that a concerted effort to slow ageing would provide a broad strategy for primary prevention that would greatly enhance and accelerate improvements in health at all ages.

"It is possible—for example, by dietary intervention or genetic alteration, to extend life span and postpone ageing related diseases such as cancer, cataracts, cognitive decline, and autoimmune diseases. Investigating how genetic mutations influence the basic rate of ageing is likely to provide important clues about how to develop drugs that do much the same thing

"Attempts to develop preventive measures against individual conditions related to ageing have been, for the most part, frustrating and unsuccessful. But in striking contrast, all of these conditions, and more, can be ameliorated or postponed simultaneously by well validated interventions that slow ageing.

Leading researchers go on to say *"The most efficient approach to combating disease and disability is to pursue the means to modify the key risk factor that underlies them all—ageing itself. The time has arrived for national policies to support and develop practical interventions that slow ageing."* [British Medical Journal July 19, 2008, 337: 149-50]

Let's start reversing aging

Great! Just how do we get started? Can we reverse the biological clock-hands of time even after aging changes have already occurred? That is the zillion-dollar question.

Furthermore, are doctors onboard in this quest? It doesn't appear so. The masses are going to have to fend for themselves. In the end, less doctoring may be advantageous.

Is youthful aging possible?

We get a peek at what can be achieved by a paper published in the journal Neurobiology of Aging this past year. In a paper entitled *"What does it take to stay healthy past 100? Commentary on 'No disease in the brain of a 115-year-old woman',"* Joseph L. Price, of the Department of Anatomy & Neurobiology, Washington University School of Medicine, comments on the discovery of a 115-year old woman without dementia or Alzheimer's disease. The report is remarkable. Several similar cases have been reported before among adults age 85-105 years of age.

In this instance, *"not only was the subject the oldest known living human at the time of her death, but she also had very little mental decline, and her brain was found to be remarkably*

healthy, even for someone much younger than 115 years." Her mental test scores prior to her death were that of a middle-aged woman. Upon autopsy, she had no characteristic tangles or plaque in her brain tissue.

As the authors point out, this indicates that brain disease is not inevitable, even in super-centenarians. While this report provides no hint as to how this woman was able to maintain healthy brain function while living about 35 years longer than most long-lived adults, there is more than just hope for healthy super-longevity. *"Even in cases older than 90 years of age, about 20% do not have plaques,"* note researchers. [Neurobiology of Aging 29: 1140–1142, 2008] Senility is not inevitable!

The view from Okinawa

Drs. Bradley and Craig Wilcox, the doctors known for their investigation into the unusual longevity among residents of Okinawa, the most southern island prefecture of Japan, reported this past year on *"Secrets of Healthy Aging and Longevity From Exceptional Survivors Around the Globe: Lessons From Octogenarians to Supercentenarians."* Their report was published in the Journal of Gerontology. [Journal of Gerontology, Medical Sciences, 2008, Vol. 63A, No. 11, 1181–1185]

Drs. Wilcox say more comprehensive study of long-lived individuals who are free of major clinical diseases and disability, and who might be called *"exceptional survivors,"* is just now beginning. By studying *''healthy aging''* rather than focusing on specific diseases, *"we might find protective genetic or environmental secrets that will benefit both length and quality of life."*.

They go on to say that *"this has led to the discovery of so-called 'longevity genes' in model organisms and humans. Undreamed of advances in proteomes, metabolomes, and a plethora of other 'omes' are occurring."*

Drs. Wilcox say higher than expected prevalence of exceptional longevity has been found in unexpected locales such as the aforementioned Japanese island of Okinawa, as well as the Mediterranean island of Sardinia, and among Seventh-Day Adventist-rich Loma Linda, California, where a vegetarian diet is adopted.

These doctors also report on the autopsy study of a *"typical"* centenarian woman in Okinawa, found with absence of coronary artery disease, cancer, stroke, and little evidence for major damage in several organ systems.

Study healthy centenarians, not illness

Too much effort is directed towards the study of illness rather than health. Newly published studies are beginning to provide a profile of measurable parameters that characterize healthy aging.

For example, researchers reporting on data obtained from 208 centenarians living in Japan (age range 100-108 years) reveal that those subjects with the highest levels of inflammation, as measured as TNF, had much higher mortality rates. The lowest level of insulin-like growth factor (IGF-1) was also associated with increased mortality. [The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 63:1209-1218 2008] TNF and IGF-1 may serve as markers of biological aging.

Immunity and aging

Researchers surprisingly report that the immune systems of middle-aged adults in Spain were worse than those of young adults and centenarians. Their white blood cells, known as neutrophils, were sluggish, did not pursue pathogenic germs or tumor cells very well. [Journal American Geriatric Society. 2008 Dec; 56(12):2244-51] Centenarians, however, are remarkably able to maintain a healthy immune response, similar to those of young adults!

An understanding of how to maintain healthy neutrophil activity, and therefore a healthy immune system, may be within reach. It has long been known that humans with rickets (bone softening due to a lack of vitamin D) are prone to infections and have very sluggish neutrophils. [Acta Paediatrica Scandinavia 1976 Nov; 65(6):695-9]

One of the problems in activating neutrophils is the uncontrolled inflammation that results from the biological chaos caused by the neutrophils themselves in their pursuit of pathogenic bacteria, viruses or tumor cells. Not only does vitamin D, but also other small molecules, exert a controlling effect over neutrophils. When some lab dishes are pre-treated with quercetin, a small molecule commonly found in red wine, red apple peel and red onions, susceptibility of neutrophils to produce uncontrolled inflammation is greatly reduced. [Inflammation Research 2005 Dec; 54(12):500-7]

TNF and aging

A most miraculous discovery was made in August of 2008 when Edward Tobinick MD, a Los Angeles physician, administered an anti-inflammatory drug (Enbrel, generic name etanercept) into the brain of Alzheimer's patients via direct injection into neck veins. An almost immediate recovery of memory was achieved. Families of treated patients attest to the treatment online at YouTube.com. The problem is that the treatment effect only lasts 6 days or so and would cost about $10,000 to $40,000 a year. [BMC Neurology 2008 Jul 21; 8: 27; New Scientist, August 9, 2008]

But the anti-inflammatory treatment proves a point. It is not the tangles, or tau protein, or buildup of beta amyloid plaque that destroys the memory of older patients per se. It is the inflammation that interferes with the transmission of brain chemicals (neurotransmitters) across the gap between brain cells (the synapse) that impairs memory. Animal experiments conducted in 2007 also appear to confirm this recent finding in humans. [Journal Neuroscience 27 (20); 5394-5404, 2007]

However, there are problems with anti-inflammatory drugs, as attested by the premature death of an estimated 20,000 Americans taking Vioxx, a COX-2 anti-inflammatory drug. What was only discovered later is that Vioxx (refocoxib) tends to decrease COX-2 but increase TNF-alpha. [Clinical Experimental Rheumatology 24 (4): 361-65, 2006]

What is only now coming into scientific view is that TNF is master marker of inflammation in the human body (not C-reactive protein, not COX-2). Normally, TNF is produced in small amounts and acts to protect brain cells, for example, from invading viruses that may pass through the blood-brain barrier. But, as iron accumulates in the body, abnormally high levels of TNF are produced, resulting in uncontrolled inflammation. [Medicinski Pregled 2007; 60 Suppl 2:33-8]

This past year researchers showed that iron chelators (key-lay-torz) can reduce TNF. [Journal Immunology 2008 Aug 15; 181(4):2723-31] Iron chelation was also demonstrated to control TNF almost two decades ago. [Journal Immunology 1989 Aug 15; 143(4):1290-4]

Inflamm-aging

The master pathway for inflammation and regulation of insulin resistance that accompanies adult-onset diabetes, obesity and brain disease is the NF-kappaB pathway. [Cellular Molecular Life Science 65 (7): 1049-58, 2008] This same NFKappaB pathway is also the master regulator of the innate (first-responding) immune system (which dispatches or activates white blood cells known as neutrophils, macrophages and natural killer cells).

The age-related rise in TNF is the primary marker for what is called inflamm-aging. An array of natural molecules, all iron chelators, can be employed to inhibit NFKappaB. Among natural molecules tested (resveratrol (red wine), quercetin (apple peel, onion), EGCG (green tea), naringenin (grapefruit) and vitamin C), quercetin was able to reduce NFKappaB levels in a lab dish to almost non-inflammatory levels at low concentration. [Journal Medicinal Food 8 (2) 269-74, 2005] Ferulate (or ferulic acid), a constituent of fruits and wine, is also a potent NFKappaB inhibitor [Journal Nutritional Biochemistry July 2008 online]

Over-activation of innate immunity system during aging:

Researchers have noted that as the human body ages the adaptive immune response (delayed response, activating T-cells and B-cells) declines whereas the innate immune system (rapid immune response involving white blood cells- neutrophils, macrophages and natural killer cells) seems to be over-activated with advancing age to the point of creating a pro-inflammatory environment. Researchers also note that the NFKappaB pathway is the master regulator of the innate immune system. Researchers write that NFKappaB cell signaling seems to be the culprit of inflamm-aging, since this signaling system integrates the intracellular regulation of immune responses in both aging and age-related diseases." They note that *"some plant extracts have been used for centuries to alleviate inflammatory diseases and their effective compounds include, e.g. terpenes (example: eugenol from cloves, or d-limonene from orange peel oil, others in grape skin), lignans (example- from flaxseed)*

and flavonoids (example, from grape skin, berries, etc.), block the NFKappaB system." [Ageing Research Reviews 7 (2008) 83–105]

2008: Iron and aging

A criticism of modern anti-aging science is that it is too minimalist and is overly fascinated with genes. The mapping of the human genome has tantalized scientists into the idea of manipulating expression (protein production) of genes to treat disease or even stave off aging.

Regardless of which genes, or how many genes, are switched on or off, aged tissues and organs are characterized by mineral-overload, hardened and stiffened by calcification and rusted by iron and copper. This unhealthy, unyouthful condition must be addressed regardless of gene expression patterns.

Calcification and rusting must be reversed via a process called chelation (key-lay-shun). In fact, progressive overmineralization with advancing age actually alters gene expression patterns. In June of 2008 researchers in France reported that dietary iron influences the expression (activation or non-activation) of various genes in mouse liver. [Blood, June6, 2008 online]

Genes don't run the biological show, biological stressors like solar radiation, heat, cold, starvation, and progressive overmineralization do.

Since 1993 it has been known that inhibition of iron absorption prolongs the life span of fruit flies (*Drosophila melanogaster*). For more than a decade it has been known that lifespan is also proportional to the rate of iron accumulation for fruit flies, mice and humans. Furthermore, researchers report the total calcium content of fruit flies correlates with iron load. Moreover, iron content in fruit flies does not increase during growth and development.

Strikingly, it was demonstrated then that tea extracts, as an iron chelator, inhibit age-related accumulation of iron and prolong the lifespan of fruit flies by as much as 21.4%, which would be equivalent to adding another 14 years of life to humans. Researchers have known that *"iron accumulation is a significant factor contributing to senescence,"* but have largely failed to employ a strategy to prevent iron accumulation. [Mechanisms Ageing Development 67: 227-37, 1993] Had this discovery been announced years later, after the human genome had been mapped, and gene array studies performed, it would have caught the attention of anti-aging scientists and the public. But today it is a buried study.

In 2008 many research papers continued to confirm the overmineralization theory of aging.

Christiaan Leeuwenburgh, Professor and Chief Division of Biology of Aging, at the Department of Aging and Geriatrics, Institute on Aging, College of Medicine, University of Florida, published a landmark paper in August of 2008 showing that gastrocnemius muscle of 37-month old rats have 600% higher iron levels than 8-month old rats, which leads to the shrinkage (atrophy) of muscle seen in old age (a condition called sarcopenia). Calorie

restriction slows this process by limitation of iron intake. This is a landmark paper and further confirms the overmineralization theory of aging. [PLoS ONE Biology 3 (8); e2865, August 2008]

Then in October of 2008 these same researchers at the Department of Aging & Geriatrics at the University of Florida report that iron increases with advancing age in the mitochondria of liver cells. (Mitochondria are energy-producing bodies inside cells.) Iron then makes cells susceptible to damage by oxidation, which in part may explain aging. [Aging Cell 7: 706-16, 2008]

The most destructive of oxygen-derived free radicals is the hydroxyl radical. This free radical damages cells, proteins, fats and DNA. It is implicated in heart attack, stroke, cancer, age-related brain disease and aging itself. Iron-generated DNA damage by the hydroxyl radical is the primary cause of cell death under oxidative stress conditions.

Unbound iron can greatly increase inside cells. For example, E. coli, a pathogenic bacterium, normally has unbound (free) iron levels of 10-30 micromole concentration. However, if iron control is not maintained, free iron may increase to 80-320 micromole concentration. Even mildly elevated iron levels in humans are associated with cancer. [Nutrition 2008, early online]

An increased prevalence of iron overload, especially among healthy men, ostmenopausal women, and elderly individuals, has been widely described and attributed to changes in dietary habits, such us the consumption of more meat, alcohol, and iron supplements or fortification. This led researchers in Brazil to investigate the role of iron among aging adults. Their study is very revealing.

There were a total to 134 participants. The study was skewed. Iron depletion was defined as any ferritin (iron storage) number below 10 grams per liter of blood for women and 20 for men, while iron overload was defined as any ferritin score over 120 for women and 250 for men. This is nonsense. These are common reference ranges of ferritin, not healthy ranges. While men typically have higher iron storage levels than females, this should be no excuse to characterize ferritin levels in males that are double that of equally aged females as being *"normal healthy"* ferritin numbers. Females live longer and have lower ferritin (iron storage) scores.

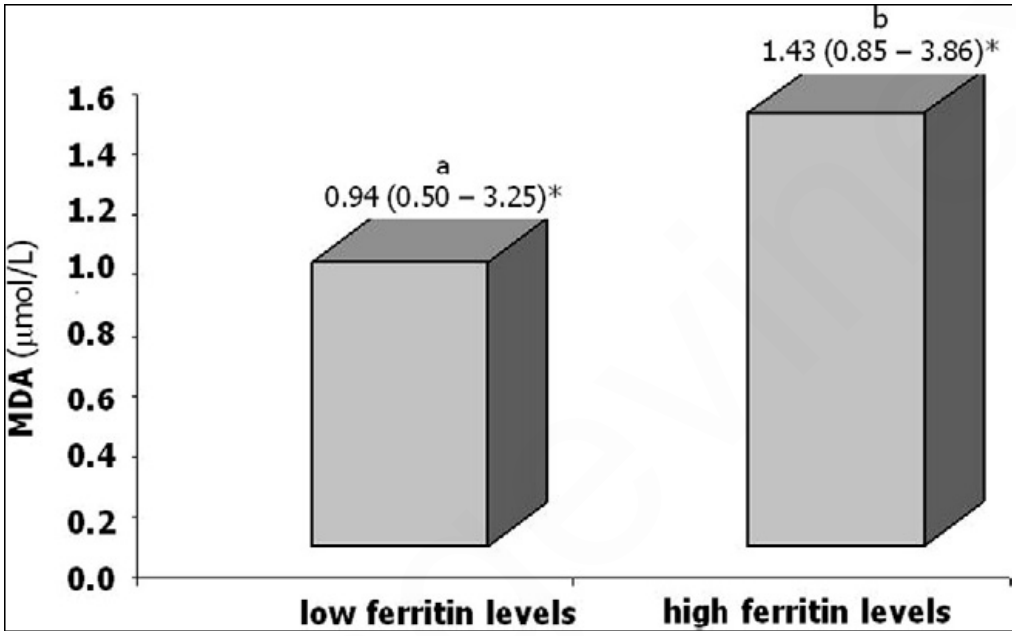
The intake of iron in the Brazilian diet, as exemplified in this study of 134 subjects, showed a wide range of iron intake.

Iron intake
Iron (milligrams per day) range: 2.4–29.5 mg
Men 17.8 (range 2.4–24.8 mg per day)
Women 10.9 (range 7.5–29.5 mg per day)

Iron storage (ferritin) levels were also wide ranging:
Blood serum ferritin (grams per liter)
Overall range: 1.3–355.9 ferritin

Men 95.0 (27.7–355.9)
Women 30.8 (1.3–183.0)

The Brazilian researchers used malonaldehyde (MDA), a marker of rancidity in foods and spoilage of fats (lipids) in the human body as an indicator of the effects of iron in aging adults. They correlated MDA with iron storage (ferritin) levels. The greater amount of iron that is stored in the body of adults, the greater the amount of undesirable MDA is produced. (See chart below.)



These researchers elaborate, that in countries that have adopted iron fortification in foods for 20 years, there are higher rates of iron overload than of anemia. In the United States, after the adoption of food iron fortification in the 1970s, the Framingham Heart Study (2001) found that the prevalence of high iron storage in healthy elderly American subjects was 13%, which exceeded the degrees of iron deficiency (2.7%) and anemia (1.2%). Could it be that the introduction of iron fortified foods in the 1970s spawned the diabesity epidemic now underway in the U.S.?

Researchers said: *"These results suggest that low levels of iron can promote a lower state of oxidative stress, and that iron fortification during the decades-long period of increasing life expectancy in Brazil may induce high iron storage in subjects who currently have a normal iron status. This may increase the risk of developing chronic diseases associated with oxidative stress."* [Nutrition 2008, early online]

Iron chelators and autophagy

Dr. Tino Kurz of Linkoping University in Sweden suggested the use of iron chelators to diminish the age-related accumulation of cellular debris in living cells called lipofuscin. In healthy young cells, cellular debris is removed in a cannibalistic action called autophagy.

The cell literally digests its own garbage by the action of enzymes produced inside cells by lysosomal bodies. [Rejuvenation Research 11 (2): 441-43, 2008]

Lead accelerates aging by 6 years

Iron is not the sole metallic metal involved in aging. In August of 2008 researchers reported that adults age 50-70 years with the greatest amount of lead deposited in their bones also exhibit greater mental decline, suffering from *"accelerated aging"* with a deteriorating ability to think, learn or remember. Adults with the highest amount of lead aged six years faster than those with the least. [Environmental Health Perspectives 2008 June; 116(6): 784–790]

Global gene effects

Changes in single gene expression, however, are per se not predictive enough to account for all metabolic changes.

Researchers are calling for a broader approach to understanding aging and genomic medicine. Rather than focusing on single genes, gene networks must be evaluated. As members of the European Nutrigenomics Organization write: *"The ultimate objective for nutritional systems biology is to understand the whole organism rather than a single cell type… Nutritional systems biology may be defined as the ultimate goal of molecular nutrition research, where all relevant aspects of regulation of metabolism in health and disease states at all levels of its complexity are taken into account to describe the molecular physiology of nutritional processes."*

In light of this author's assertion that genes can be controlled by mineralization, which describes progressive aging, these European researchers also concede that *"the role of trace elements (Zinc, copper, iron, selenium)…. has been almost completely neglected so far."* [Genes Nutrition 2008 Dec; 3(3-4):107-13]

The ongoing saga of Sirtuins

While the Sirtuin1 gene is oft mentioned in the lay press as an anti-aging gene, and purveyors of red-wine resveratrol pills often cite early research conducted at Harvard Medical School which showed that resveratrol activates the Sirtuin1 gene and may serve as a molecular mimic of a calorie restricted diet, recent data points in another direction.

In July of this past year Leonard Guarente of MIT revealed that calorie restriction does not universally up-regulate (activate) the Sirtuin1 gene in all tissues and organs. [Genes & Development. 2008 July 1; 22(13):1753-7] This threw an immediate cloud over the idea of a molecular calorie restriction mimic like resveratrol. This doesn't mean resveratrol is not a spectacular molecule, but it means Sirtuin1 activation may not be an adequate measure of its properties.

This past year numerous reports were published which show health benefits when the Sirutin1 gene is down-regulated (switched off). For example:

- Researchers at Harbor-UCLA Medical Center in California gave resveratrol to male rats that were also being fed alcohol (ethanol) for 1 month, in liver tissue the Sirtuin1 gene was down-regulated, but activated by alcohol alone. Resveratrol accentuated (worsened) scarring (fibrosis) and cell death (necrosis) in the liver. [Experimental Molecular Pathology 2008 Dec; 85(3):155-9]

- And the idea that Sirtuin1 gene activation promotes health and longevity got another blow when university-based researchers report that the down-regulation of the Sirtuin1 gene inhibits the growth of human prostate cancer cells in a lab dish and that stimulation of the gene encourages prostate tumor cell growth. The study, published in the Journal of Biological Chemistry, adds to the growing body of knowledge concerning the role of the Sirtuin1 gene in health and disease and runs contrary to the idea that stimulation of the Sirtuin1-gene is beneficial in all tissues. Sirtuin1 gene protein is not overproduced in normal prostate cancer cells and nicotinamide (niacin, vitamin B3), a known Sirtuin1 gene inhibitor, selectively blocks prostate cancer cell growth. [Journal Biological Chemistry 2008 Dec 15, online]

- Sirtuin1 gene activation was found to inhibit the FOXO1 gene, which contributed to the growth of prostate cancer cells. The researchers at the University of Wisconsin called Sirtuin1 an *"oncogene,"* that is, a gene that promotes cancer in prostate tissues. [Journal Biological Chemistry 2008 Dec 15, online] This report was preceded by a study, published in August of 2008 by researchers in Japan, which also show that up-regulation of the Sirtuin1 gene promotes prostate cell cancer growth. [Biochemical Biophysical Research Communications. 2008 Aug 29; 373(3):423-8]

By December of 2008 researchers at Williams College were showing that resveratrol treatment in laboratory mice does not elicit the same effects seen in calorie restriction. Namely, calorie restriction produces a slowed heart rate and a slightly lower body temperature. This was not found after mice were given supplemental resveratrol, and furthermore, these mice exhibited marked reduction in endurance on a treadmill test. [FASEB Journal Dec. 4, 2008, early online]

Again, this does not mean resveratrol is a useless molecule, but it does mean that it is not a molecular mimic of a calorie restricted diet.

University of Washington anti-aging researcher Matt Kaeberlein, in a paper entitled *"The Ongoing Saga of Sirtuins and Aging,"* writes that the inhibition of the Sirtuin1 gene, or completely knocking out the Sirtuin1 gene in calorie-restricted animals, fails to prolong life span. This is consistent with the idea that lifespan extension produced by CR is controlled by Sirtuin1. However, the inhibition of Sirtuin1 in animals may slow aspects of aging, at least in the brain.

So what are Sirtuin1-gene followers left to conclude? Kaeberlein: *"What's the 'take-home message' from all this? Is more SirT1 good, or is less SirT1 good? The answer, as is often the case in biology, is that there's no simple answer. Activating Situin1 is probably a good thing in some cells under some conditions and is probably a bad thing in other cells under other conditions. Sirtuin1 activators may be good for diabetes but may cause cancer due to p53 inhibition, Sirtuin1 inhibitors may protect against cancer but cause metabolic disease, and there is evidence supporting the idea that both activators and inhibitors of Sirtuin1 can confer protection against neurodegeneration in different contexts. The one thing that seems clear is that sirtuin activators are unlikely to be a 'magic bullet' for aging."* [Cell Metabolism July 2008 p. 4-5]

That health benefits are derived from resveratrol are not in question, as many users of resveratrol pills attest, but what is in question is the promise of long life and the dosage required to produce such an effect.

Dr. Sinclair conducted research, widely publicized in November of 2006, which showed that high-dose resveratrol (1565 milligrams human equivalent, or the amount of resveratrol provided in 750-1000 bottles of red wine) given to laboratory mice significantly extended their life. The sales of resveratrol pills skyrocketed at the time. But the catch was that this effect was accomplished by engorging the mice with an ultra high-fat diet (60% fat calories vs. 35% for humans) which was not a real-world test.

A lower dose of resveratrol was also used in this 2006 study, but researchers conveniently said they would report on the effect of a lower dose at a later date and advised to public that they would have to consume thousands of bottles of red wine, or hundreds of red wine pills, to achieve the same effect, and to wait for a more powerful resveratrol drug that was then being developed by Sirtris Pharmaceuticals, where Dr. Sinclair also serves on their scientific advisory board.

Subsequently, on April 24, 2008, GlaxoSmithKline, the worldwide pharmaceutical company, announced purchase of Sirtris Pharmaceuticals and its heralded resveratrol pill for $720 million.

Timeline of Resveratrol/Sirtuin1 Gene Research

Sept. 2003: Resveratrol identified as molecular mimic of calorie restriction and activator of Sir2 gene (akin to Sirtuin1 in humans) in yeast cells. Yeast cells lived longer when given resveratrol.

Nov. 2006: Mega-dose resveratrol given to laboratory mice fed a very high-fat diet lived longer and overcame fatty liver condition. Results using a lower dose of resveratrol were not reported.

August 2008: Mega-doses of resveratrol (360 mg and 1565 mg human equivalent) shortened the lifespan of laboratory mice compared to a standard calorie diet alone.

Four months later [August, 2008, journal of Cell Metabolism] researchers including Dr. Sinclair reported on the effects of Sirtris' SRT501 resveratrol pill in mice given a standard-calorie diet. The mice, while profoundly healthier, didn't live as long when given resveratrol in two different doses (360 mg and 1565 mg) compared to a standard-calorie diet alone. The higher dose shortened the life span more than the lower dose.

While in prior studies resveratrol had been found to prolong the life of yeast cells, fruit flies, roundworms, and cold-water fish, in the highest life form, warm-blood mammals (mice), in mega-doses, it failed as an *"anti-aging"* pill.

The lab mice largely succumbed to lymphoma, an indication of impaired immunity.

A possible pathway to explain this lack of longevity and impaired immunity may emanate from resveratrol's ability to inhibit a marker of inflammation called TNF (tumor necrosis factor). Over-inhibition of TNF in humans is associated with lymphoma. It's possible that mega-dose resveratrol over-inhibits TNF which could be deleterious.

Research conducted by University-based researchers in Wisconsin may help explain why. Resveratrol is reported to mimic the effects of a calorie restricted (CR) diet. Limiting caloric intake by ~50% about doubles the lifespan of all living organisms tested. The problem is that CR cannot be conclusively proven to prolong life in humans, nor a molecular mimic or CR like resveratrol, because such a study would require100-years, which is impractical.

So the Wisconsin researchers proposed using gene array studies to determine which interventions may genomically mimic the effects of CR rather than conducting lengthy longevity studies. The Wisconsin researchers reported a lower dose of resveratrol than previously reported, ~343 milligrams human equivalent, paralleled gene expression patterns seen in CR. [Public Library of Science PLoS ONE 2008 Jun 4; 3(6):e2264]

Then in September of 2008 the same Wisconsin researchers reported that a far lower dose of resveratrol, 17-320 times lower than prior published studies, exerted influence over far more longevity genes (1711) than plain resveratrol (225) or even calorie restriction (198), when accompanied by other small molecules (Longevinex® patent applied for matrix). [Experimental Gerontology 2008 Sep; 43(9):859-66] While it takes life-long adherence to calorie restriction to influence this many genes, Longevinex® accomplished this rapidly and earlier in life. A synergistic rather than additive effect was demonstrated here. The mainstream news media failed to report on this astounding discovery.

Subsequent other studies also confirm that the combination of resveratrol, quercetin and other small molecules produces a synergistic effect. [Journal Medicinal Food 2008 Dec; 11(4):773-83; Life Science 2008 May 7; 82(19-20):1032-9] Some of these studies show relatively lower rather than higher doses to be more beneficial. [Translational Oncology 2008 March; 1(1):19-27]

A more recent animal study conducted by researchers at the University of Connecticut shows resveratrol, in human equivalent doses of 175-350 milligrams, limits cardiac tissue damage caused by a heart attack, but at higher doses, 1750 and 3500 milligrams, it worsens the extent of heart damage following a heart attack. The higher doses would be more appropriate for cancer treatment, when cancer cell death is advantageous. [Journal Nutritional Biochemistry 2008 Sept 10 early online]

So, in summary, in the period 2004-2008, thousands of Americans heard they should take mega-dose resveratrol pills which were said to activate the Sirtuin1 gene, a gene that could slow aging. By the end of 2008 the Sirtuin1 gene was no longer a viable mimic of the effects of calorie restriction and therefore may not be a valid target of molecular calorie restriction mimics like resveratrol, and lower rather than higher doses of resveratrol, particularly when combined with other small molecules like those found in red wine (quercetin, ferulic acid, etc.), appear to produce superior effects.

The ongoing saga

In Science Magazine Sinclair announced that he had severed ties with Longevinex® (though he had never received any money or signed an agreement) after he said the company broadcast comments from him on its web site that were inaccurate. [Science 27 February 2004: Vol. 303. no. 5662, pp. 1276 – 1279] Disclaim relationship with the dietary supplement company or face never gaining tenure at the university. That was what Harvard demanded. Others had tried it and failed, Sinclair was told.

In 2004 Longevinex® filed a patent application describing an emulsified, stabilized resveratrol capsule with accompanying mineral-chelating (key-lay-ting) molecules. The patent is still pending. Sirtris later received acclaim for its SRT501 resveratrol pill which is an emulsified, stabilized, micronized resveratrol pill. The bragging rights certainly belong to Longevinex® (dba Resveratrol Partners LLC), and should a patent be issued, it may be valuable to GlaxoSmithKline which has no proprietary technology with its SRT501 developmental drug.

In fact, Sirtris says it won't be marketing a resveratrol pill by itself and intends to combine it with a prescription drug, like a statin cholesterol-lowering drug, or an anti-diabetes drug like metformin.

Clearing the air on dosage

On the dosage issue, Sinclair settled on a 100 milligram dose of resveratrol with accompany polyphenolic molecules in VIVIX, a dosage and assemblage of molecules very similar to that of Longevinex®. Sinclair never cleared the air on dosage after it was found mega-dose resveratrol didn't prolong the life of animals. Many who followed the advice to take mega-dose resveratrol experience avoidable side effects, namely Achilles heel tendonitis (inflammation), anxiety reactions, skin rash and flu-like symptoms, symptoms which appear to be more commonly experience by individuals who are anemic.

Sinclair found himself advising the public to hold their breath and wait for the second generation SRT1720 Sirtuin1 gene activator rather than take mega-dose resveratrol pills, all the while endorsing a dietary supplement that provided a far-lower dose which he had said would not be adequate. A June 7, 2007 edition of the Harvard Gazette quoted Dr. Sinclair as saying *"a person would have to drink more than 100 glasses of red wine a day to get the same amount of resveratrol as the mice."*

Red wine redux

In a November 2, 2006 New York Times report entitled *"Yes, Red Wine Holds Answer. Check Dosage"* by Nicholas Wade, it was said that a person would *"need to drink 750 to 1,500 bottles of red wine a day to get such a dose"* of resveratrol that lengthened the life of rodents who were engorged with fat in their diet. This was calculated at about 1.5 to 3.0 milligrams of reserveratrol per liter of red wine. But in the same article, David Sinclair indicated *"he has long been taking resveratrol, though at a dose of only five milligrams per kilogram"* (350 milligrams per 160-lb human). Recall, this is the same dose that shortened the lifespan of laboratory mice.

Instead, Sirtris has subsequently attempted to tantalize the public and investors with its SRT1720 drug, which is said to activate the Sirtuin1 gene 1000-fold, far greater than SRT501 which stimulated the gene by ~12-fold. Yet more than 7-5 fold greater Sirtuin1 gene protein was found to produce heart failure in animals. [Circulation Research. 2007; 100: 1512] SRT1720 is a synthetically produced molecule that has never been used in humans. Yet here again, the news media heralded SRT1720 as if it were the next weight loss pill. It may be years away from gaining FDA approval.

Roger Corder, Professor of Experimental Therapeutics, William Harvey Research Institute, London, and author of **"***The Red* Wine *Diet,"* first published in January of 2008, says there is no way the small amount of resveratrol in 3-5 glasses of red wine (about 3-5 milligrams at best) could be attributed to the unusual health benefits seen among wine drinkers. Dr. Corder

notes that red wine provides an array of molecules called polyphenols, about 60 milligrams per 5-ounce glass, and that would represent about 180-300 milligrams of these molecules.

So, as one would expect, after revelation that mega-dose resveratrol did not prolong the life of rodents, the news press jumped on the promoters of resveratrol pills as being nothing more than junk science. Had the public never been steered in the wrong direction, i.e. over dosage, the story would be different. But certainly, criticism is deserved. Sandy Szwarcz who writes for Junk Food Science offered a critical review of resveratrol pills. http://junkfoodscience.blogspot.com/2008/12/living-longer-with-resveratrol.html It's worth reading.

I offered this defense of red wine pills:

There are many published reports claiming resveratrol is not bio-available, but these are mistaken reports. It is already well established that oral resveratrol is biologically available in animal and human studies. Systemic effects are produced, not just local effects in the gut. Thomas Walle's work should be discredited. It is misleading and sponsored by a drug company. It is obvious from other studies that systemic effects are produced by resveratrol. Its effects are not limited to the gut. Yes, free (unbound) resveratrol is not commonly found in the blood circulation. Once it reaches the liver it is conjugated with glucuronate or sulfate, which are detox molecules. The res/glucuronate conjugate is too large to pass through cell walls and influence genetic machinery. However, glucuronidase is an enzyme that is abundant at sites of inflammation, infection and malignancy and it free resveratrol to be delivered at the right time and place.

http://www.ncbi.nlm.nih.gov/pubmed/19114588?

http://www.ncbi.nlm.nih.gov/pubmed/15349955?

Second, we cannot call for longevity studies in humans, this is impractical -- 99-year studies would be required. So researchers are forced to use animals. Even 3-4 year mouse studies are costly. Yes, some human trials are on the way, but would only prove what has already been observed in animals, they are profoundly healthier, but may die sooner. This is a bit of a paradox (explained below). Gene array testing may serve as a valid shortcut to longevity studies (see more below).

http://www.ncbi.nlm.nih.gov/pubmed/11238786?

http://www.ncbi.nlm.nih.gov/pubmed/10906510?

http://www.ncbi.nlm.nih.gov/pubmed/10464095?

Third, the positive health benefits of red wine molecules like resveratrol are observed and repeatedly demonstrated in animal studies and by epidemiology ONLY in relatively lower doses and when an array of molecules are employed. Aged, dark red wine provides ~60 mg

of polyphenolic molecules (resveratrol, quercetin, catechin, gallic acid, kaempferol, ferulic acid, etc) per 5 oz glass of wine.

A U-shaped consumption curve is revealed. Abstainers and over-imbibers exhibit no benefits. Consumers of 3-5 glasses of red wine, providing ~180-300 mg of total polyphenols, exhibit profound and repeated health benefits, i.e. 30% reduced cardiac mortality among French red wine drinkers.

http://www.ncbi.nlm.nih.gov/pubmed/8814971?

http://www.ncbi.nlm.nih.gov/pubmed/12965884?

Resveratrol appears to exert profound beneficial effects at very low concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/18234130?

The beneficial effects of red wine molecules are additive:

http://www.ncbi.nlm.nih.gov/pubmed/15740983?

Fourth, there are synergistic effects observed when polyphenolic molecules are combined.

http://www.ncbi.nlm.nih.gov/pubmed/19053873?

http://www.ncbi.nlm.nih.gov/pubmed/18495457?

http://www.ncbi.nlm.nih.gov/pubmed/18433793?

http://www.ncbi.nlm.nih.gov/pubmed/16935024?

http://www.ncbi.nlm.nih.gov/pubmed/16310197?

http://www.ncbi.nlm.nih.gov/pubmed/15670891?

http://www.ncbi.nlm.nih.gov/pubmed/12888656?

http://www.ncbi.nlm.nih.gov/pubmed/11743756?

Fifth, lower doses of resveratrol appear to genomically mimic calorie restriction:

http://www.ncbi.nlm.nih.gov/pubmed/18523577

Sixth, it has been shown that relatively lower doses of resveratrol when combined in a matrix of mineral-chelating molecules exerts a far greater genomic effect than plain resveratrol. At a dose of resveratrol 17-320 times lower than prior studies, a resveratrol/quercetin/rice bran IP6 matrix significantly affected 1711 genes, but only 225 genes as plain resveratrol alone.

http://www.ncbi.nlm.nih.gov/pubmed/18657603?

Seventh, the molecules in red wine are known TNF inhibitors. There are many other natural molecules that are TNF inhibitors (vitamin E, fish oil, vitamin C, curcumin, etc.). Over-inhibition of TNF is associated with increased risk for lymphoma.

http://www.ncbi.nlm.nih.gov/pubmed/18360633?

http://www.ncbi.nlm.nih.gov/pubmed/17654504?

The animals in the 2008 Cell Metabolism study did not live as long on 360 mg or 1565 mg human equivalent of resveratrol compared to a standard calorie diet alone. The animals tended to die of lymphoma.

http://www.ncbi.nlm.nih.gov/pubmed/18599363?

I believe it was the over-inhibition of TNF that shortened the lives of these lab animals. Dosage would then be critical in achieving health benefits, as over-inhibition of TNF may be deleterious.

Eighth, relatively lower doses of resveratrol (175-350 mg human equivalent) appear to protect the heart from damage should a heart attack occur, while larger doses (often provided in some mega-dose resveratrol supplements) may worsen the area damaged (scarred) by a heart attack (1750-3500 mg human equivalent). Mega-dose resveratrol is more appropriate to induce apoptosis (cell death), such as for cancer therapy.

http://www.ncbi.nlm.nih.gov/pubmed/18789672?

Ninth, provision of mega-doses of the molecules in red wine, as well as in bran, as mineral chelators, may induce anemia and resultant side effects. For example, resveratrol is a copper chelator and copper is needed for collagen synthesis. Achilles tendonitis is commonly reported among users of mega-dose resveratrol and may be due to weak collagen. Resveratrol and other mineral chelating molecules are not appropriate for menstruating females, growing children, or known anemics.

The beneficial effects of red wine may be safely replicated in a pill that provides a modest dose (180-300 mg) of red wine polyphenols or other mineral-chelating molecules, as provided in 3-5 glasses of aged, dark, red wine, and such a pill eliminates the hazards posed by alcohol, excess calories, sugar, heavy metals and sulfite preservatives found in wine. Such a pill would also be far more affordable than 3-5 glasses of red wine. The idea of a red wine anti-aging pill is still scientifically alive!