Ray Peat's Newsletter

Many a small thing has been made large by the right kind of advertising. Mark Twain

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Resveratrol, rate of living, CO2, and aging

A year ago GlaxoSmithKline bought Sirtris, a company focusing on the biological effects of resveratrol, for $720,000,000. Harvard Medical School's website, and broadcasts by Barbara Walters and Morley Safer have publicized resveratrol as a longevity-increasing drug, and millions of people are spending large amounts of money for resveratrol capsules.

The main claim being made about resveratrol is that it can mimic the anti-aging effects of calorie restriction, without having to restrict food consumption. This involves silencing genes, blocking their production of RNA and protein.

The mass media and some medical journals aren't giving a balanced description of the biological effects of resveratrol, but many biologists are being influenced too, by the same simple arguments that the television reporters summarized. The academic biology culture, the medical culture, and the basic American culture itself, are all permeated by the idea of genetic determinism, so when a DNA molecule in yeast is identified as the "anti-aging gene," and a molecule is found that activates it, that molecule, or something similar, seems to them clearly to be an anti-aging drug.

Part of the cultural framework that makes it easy to sell that idea is the old "rate of living" theory of aging, the idea that we have only so many heartbeats in a lifetime, that we can use only so many calories and so much oxygen in a lifetime, and that organisms with a low metabolic rate therefore live longer than those with a high metabolic rate. The rate of living theory is closely related to the "wear and tear" theory of aging, that our bodies are (except for our germ cells) made up of "post-mitotic cells," unable to continue dividing once growth is complete, and so must die when those cells are "worn out." By the middle of the 20th century, those ideas had been disproved in many ways, but in the 1960s Leonard Hayflick renewed for a time the doctrine of aging as the wearing out of unrenewable cells, with his doctrine that somatic cells (non-germ cells) have an absolute limit of 50 replications. Producing cloned animals from somatic cells, and the subsequent excitement about stem cells, made that theory obsolete (again).

The "longevity gene," named Sir2 in yeasts, worms, and flies (its equivalent in mammals is called SirT1), is activated by restricting calories, and caloric restriction is known to extend lifespan (though the restriction of certain nutrients can similarly increase longevity, without restricting calories). Both semi-starvation and increased activity of the Sir2 gene can prevent obesity, and obesity has some harmful effects. The promoters of the theory suggest that a resveratrol-like drug will be able to prevent obesity and cure type-2 diabetes. They are also suggesting that it could slow aging and increase longevity.

Talking about the "aging" of a single-celled organism such as yeast, and drawing conclusions about the aging of multicellular organisms and humans, from events in the life of yeast, is meaningful only to people who subscribe to the Hayflick doctrine, and who deny the reality of stem cells in mammals and other complex organisms. They are actually talking about the "fertility," the reproductive growth capacity, of the yeasts. The study of yeast metabolism and growth developed mostly in relation to the needs of the wine and beer industries, and that has biased ideas about the ways yeast adapts to changing ecosystems. Yeasts adapt their reproductive strategy to the perceived adequacy of their environment. An individual yeast cell coordinates its physiology with the surrounding cells, in ways

analogous to the ways individual cells in an animal participate in the coherence of the organism.

As in higher organisms, stress can accelerate the reproductive process in yeast. In animals, stress can cause precocious puberty, as if they were being exposed to an excess of estrogen. Resveratrol is a defensive fungicidal antibiotic, or phytoalexin, so it's reasonable that it would be perceived as a stressor by yeast. It is also a phytoestrogen, and for many years yeasts have been known to be responsive to estrogenic substances. To the brewing industry, these effects of phytoestrogens are known to influence the biomass, but when the rate of growth is considered to represent aging, then increased biomass is equivalent to increased longevity.

Anyone familiar with the last 40 years of yeast research would presumably know that phenolic phytoalexins are estrogenic, and that the growth of yeast is influenced by estrogenic substances, and also that estrogenic substances such as resveratrol could be very dangerous if consumed in exaggeratedly large amounts.

Resveratrol is a stilbene, similar in structure to diethylstilbestrol, DES, the famously toxic-carcinogenic pharmaceutical. Estrogens affect all of the systems affected by resveratrol, and for 67 years, the estrogen industry has been telling the public that whatever estrogen does is beneficial---more than 200 medical conditions have been benefited by estrogen treatment, according to the medical literature/pharmaceutical advertising.

Many people have been asserting that the reason calorie restriction can extend life is that it activates "the antiaging gene, Sir2." A recent publication (Carrano, et al., 2009) from the Salk institute proposes that two other genes are responsible for calorie-restriction longevity in the roundworm, C. elegans.

But restricting calories has a multitude of effects--Sir2 is only one of hundreds of genes that function differently in hunger-stressed animals. Calorie restriction is stressful, but the nature of that stress and the response to it depends on the whole situation, just as in any other challenging situation.

One problem with the Sirtris scheme is that increased Sir2 activity shortens the actual chronological lifespan of non-dividing yeast (Kennedy, et al., 2005; Fabrizio, et al., 2005). In animals, increasing the activity of SirT1 might contribute to the development of cancer (Liu, et al., 2009). It might also be involved in Alzheimer's disease, and the replacement of nerve cells in the brain with astrocytes or other glial cells. Gliosis can occur in normal aging, but inflammation can produce extreme degrees of fibrosis of the brain or spongy encephalopathy. Estrogens also have this effect of accelerating stem cell production of glial cells.

In a recent study, to determine whether resveratrol would slow the heart rate and lower the body temperature in mice (as expected according to the rate of aging doctrine), those metabolic indicators were depressed by resveratrol for one day, but then returned to normal. However, the endurance of the mice on a treadmill was reduced by the resveratrol treatment (Mayers, et al., 2009).

Going beyond the Sir2 gene-based argument, many researchers have examined resveratrol's effects on various other genes. Too often, it seems that the authors reason that whatever resveratrol does to those genes must be good for the organism. These arguments seem to be following the reasoning that has been systematically used to promote estrogen and polyunsaturated fats.

If we consider the effects of resveratrol in the context of the well established facts about the metabolic processes associated with long life, we will notice many things that should lead to skepticism about the claims being made by the advertisers.

A little stress can make an organism more resistant to subsequent stresses. However, resveratrol fails to extend the lifespan of normal mice, being effective only in a strain of mice that becomes abnormally fat on a normal diet.

About 40 years ago, when people first began promoting fish oil as a longevity factor, Alex Comfort watched the rats that were being given the fish oil in their food. The food smelled bad, and the rats ate it only when they were very hungry, so they ate less and were leaner than the animals that were getting the standard diet. Their increased longevity was the result of avoiding obesity.

In a long-term study at NIH, rhesus monkeys are being studied to learn whether calorie restriction extends the lifespan of primates, as it does certain (genetically fat) rodents. The monkeys are kept in small cages. Confinement causes severe stress. Rats that are allowed to bite something while restrained suffer less physical stress, fewer ulcers, and are more able to maintain normal body temperature. Restraint normally lowers body temperature, lowering thyroid and increasing cortisol.

Eating in response to stress ameliorates some of the hormonal changes, but the monkeys that are permitted to eat as much as they want during their life of confinement have become very obese. They look much less agitated than the low calorie monkeys, and their body temperatures are higher.

The rate-of-living doctrine causes the researchers to reason that the low-calorie diet is slowing the rate of aging by lowering their body temperature. However, their metabolic rate, per gram of non-fat tissue, hasn't decreased.

An important difference that has been observed is that the chromosomes of the calorie deprived monkeys have more defects.

Nitric oxide, which is promoted by resveratrol, according to numerous publications (Klinge, et al., 2008; Gresele, et al. 2008; Gan, et al., 2009), and estrogens (acting partly through nitric oxide), including some phytoestrogens, cause chromosomal damage (Banerjee, et al., 1994; Kulling, et al., 1999) which contributes to cancer and possibly to birth defects. Nitric oxide has been proposed to be a major factor in causing the degenerative diseases of aging.

If these monkey experiments have any relevance to human biology, it is to demonstrate that prolonged torture by confinement and food restriction causes bodily damage, in the form of chromosomal abnormalities. But unless the next generation of monkeys is examined for birth defects and other problems, the full meaning of the experiment won't be apparent.

In some of the publications claiming that resveratrol increases lifespan, it was reported that niacinamide had the opposite effect, suppressing Sir2, the longevity gene, and shortening the organism's lifespan. To put their claims into context, it's helpful to look at a variety of experiments involving treatment with niacinamide.

It protects nerves, vascular cells, insulin-producing cells in the pancreas, and a variety of other types of cell from cell death produced by lack of oxygen, excitotoxicity, endotoxin, and a variety of stressors and toxins. (Niacinamide acts in many ways as a negation of resveratrol; for example, resveratrol interferes with the ability of the beta cells to secrete insulin [Szkudelski, 2007]).

Niacinamide protects mitochondrial respiration from many of the age-related factors that can damage mitochondria and decrease energy production. Lipopolysaccharide, the bacterial endotoxin, increases the production of the free radical nitric oxide, leading to the secretion of inflammatory mediators and the suppression of energy production by the mitochondria. These effects are blocked by niacinamide (Fukuzawa, et al., 1997). Calorie restriction also protects mitochondrial respiration, in yeasts (Lin, et al., 2002) and rats (Broderick, et al., 2002)

The "replicative lifespan" of human cells in vitro is extended by treatment with niacinamide (Kang, et al., 2006).

In an experiment with human keratinocytes *in vitro,* resveratrol had the opposite effect, reducing their ability to divide (Blander, et al., 2009). By the definitions of "aging" used by the advocates of the rate-of-living theory, this experiment suggests that resveratrol causes premature aging. Estrogen has a similar effect on keratinocytes. Resveratrol, nitric oxide, and estrogen, unlike niacinamide, suppress mitochondrial respiration. Resveratrol inhibits the formation of progesterone (Chen, et al., 2007), which is synthesized in mitochondria.

The NIH researchers reported that the food deprived monkeys (contrary to their expectation) didn't have a lower rate of metabolism, but many experiments done with a variety of very different animals through much of the last century found that a ***higher*** metabolic rate corresponded to increased longevity. Within a given species of bird or mammal, the higher rate of metabolism is often associated with a higher body temperature, and a long life span.

But when different types of animal of very different sizes are compared, smaller animals may have a higher rate of metabolism, but a shorter lifespan, than a larger animal, as in the case of mice and elephants. This example was used recently by an endocrinologist, Martin Surks, to argue against treating "subclinical hypothyroidism." He suggests that hypothyroid people, who have a lower rate of metabolism than euthyroid people, are likely to live longer, because their metabolism is analogous to the slow metabolism of elephants, rather than the fast metabolism of mice.

Comparing animals of different species, such as birds, monkeys, and rodents, of similar sizes, those with the highest metabolic rate are likely to have the longest average and maximum lifespans.

The smaller an organism is, the more easily it loses heat to the environment. Most of a mouse's metabolic energy is spent simply maintaining its body temperature. Large animals have less surface area in proportion to their mass, so they spend relatively little energy in temperature regulation.

One of the ideas deeply associated with the rate-of-living theory of aging is that our metabolic energy is spent mainly for regulating the concentration of salts and other substances in cells, with a small amount used for secretion, movement, and--a relatively recent admission--for thought.

Gilbert Ling has demonstrated the falsity of the idea that "membrane pumps" regulate the concentratons of dissolved materials, and showed that the amount of energy needed to operate them constantly would be much greater than the metabolic capacity of any organism.

The fact that those "membrane-based" energy consuming processes don't exist leaves a lot of energy to be accounted for. One of the main energy-consuming activities of a cell is just being alive, that is, adapting, sensing, responding, anticipating, orienting itself to its environment. Except in very special circumstances, the substance of a cell is in constant motion, and the molecules are being consumed and reconstructed, in a process of continuous renewal. These intracellular streams of renewal of molecules and organelles are paralleled on the scale of tissues and organs by a process of renewal, in which new cells are born and unnecessary cells are dissolved.

Part of the "rate of living" relates to the rate of renewal of the organism. Another part relates to issues such as the loss of heat, that makes life shorter and harder for very small animals.

The end product of respiration is carbon dioxide, and it is an essential component of the life process. The ability to produce and retain enough carbon dioxide is as important for longevity as the ability to conserve enough heat to allow chemical reactions to occur as needed.

Carbon dioxide protects cells in many ways. By bonding to amino groups, it can inhibit the glycation of proteins during oxidative stress, and it can limit the formation of free radicals in the blood; inhibition of xanthine oxidase is one mechanism (Shibata, et al., 1998). It can reduce inflammation caused by endotoxin/LPS, by lowering the formation of tumor necrosis factor, IL-8 and other promoters of inflammation (Shimotakahara, et al., 2008). It protects mitochondria (Lavani, et al., 2007), maintaining (or even increasing) their ability to respire during stress.

The "replicative lifespan" of a cell can be shortened by factors like resveratrol or estrogen that interfere with mitochondrial production of carbon dioxide. Both of those chemicals cause skin cells, keratinocytes, to stop dividing, to take up calcium, and to begin producing the horny material keratin, that allows superficial skin cells to form an effective barrier. This process normally occurs as these cells differentiate from the basal (stem) cells and, by multiplying, move farther outward away from the underlying blood vessels that provide the nutrients that are oxidized to form carbon dioxide, and as they get farther from the blood supply, they get closer to the external air, which contains less than 1% as much CO2 as the blood. This normally causes their eventual hardening into the keratin cells, but when conditions are optimal, numerous layers of moist, translucent cells that give the skin the characteristic appearance of youth, will be retained between the basal cells and the condensed surface layers. (Wilke, et al., 1988)

In other types of tissue, a high level of carbon dioxide has a similar stabilizing effect on cells, preserving stem cells, limiting stress and preventing loss of function. In the lining of the mouth, where the oxygen tension is lower, and carbon

dioxide higher, the cells don't form as much keratin as the skin cells do. In the uterus, the lining cells would behave similarly, except that estrogen stimulates keratinization. A vitamin A deficiency mimics an estrogen excess, and can cause excessive keratinization of membrane cells.

Yeasts adapt their physiology and life cycle to their particular ecological situation. The cells within an animal behave analogously, but that is likely to be forgotten or denied, because of the culture of genetic determinism.

The cells in each organ and tissue of the body are arranged in ways that allow them to make their contribution to the function of the organism, while receiving oxygen, glucose, and regulatory substances in the blood, and maintaining and renewing themselves. Except for the skin, their situation amid other cells assures that they will live in a high concentration of carbon dioxide.

There are proteins (uncoupling proteins, UCP) that cause the mitochondria to increase their consumption of oxygen without increasing their synthesis of ATP. The synthesis of ATP is usually thought of as the main reason for the consumption of oxygen, so the UCP have been assumed to exist to increase heat production. The formation of carbon dioxide is usually thought of as just an unavoidable consequence. UCP proteins, however, exist in situations in which heat production doesn't seem appropriate (Borecký & Vercesi, 2005; Aguilera, et al., 2005; Gnanalingham, et al., 2005). For example, fasting or calorie restriction increases UCP, tending to cause tissues to consume energy more rapidly. Stress and hypoxia also can increase UCP, suggesting that these enzymes have protective functions.

Increasing the formation of carbon dioxide seems to me to be the essential function of the UCP. Thyroid hormone (T3) increases UCP, and UCP increases the formation of new mitochondria. Increased activity of the UCP is closely associated with increased lifespan. A decreased amount of T3 in tissues during aging corresponds to decreasing mitochondrial functon.

Increased CO2 inhibits the formation of lactate, decreases the lipolytic effect of adrenaline, and the lowered energy charge produced by the UCP would prevent the diversion of glucose into other uses.

According to the rate-of-living theory of aging, the "post-mitotic" organism ages and degenerates in proportion to the rate at which it metabolizes. Leonard Hayflick, to demonstrate that it is cell division, not the passage of time, that ages cells, put some cells in a freezer, while others, from the same batch, were kept in a warm incubator and allowed to go through their allotted number of divisions. When the warm, growing cells had approached 50 replications and began dying "of old age," the other cells were taken out of the freezer, and they were able to divide as well as they had before being frozen. The implication was that slowing metabolism was the only way to extend the lifespan.

These beliefs have allowed people to view the metabolism, the turnover of substance and cells, of a tissue such as bone, as indicating breakdown, weakening, and loss. For many years, it was impossible to show any beneficial effect of estrogen on the bones of experimental animals or people, but then it was discovered that it could slow the metabolism of the osteoclasts, reducing the rate of turnover in the bones. This was propagandistically effective.

The estrogen industry's funding greatly reinforced the rate-of-living theory of aging, and metabolic markers of bone turnover began to be used to measure the effects of treatment. Thyroid hormone (the active T3 hormone) increases the rate of turnover of all tissues, including bone, so by reference to the "bone protective effects of estrogen," the argument was made that thyroid supplementation should be reduced, to prevent osteoporosis (despite animal studies showing that T3 increases bone development). Since hypothyroidism usually involves increased thyroid stimulating hormone, TSH, the argument was extended by showing that TSH lowers bone turnover.

One factor involved in the increased production of TSH in hypothyroidism is that the low metabolic rate allows estrogen to accumulate, leading to increased serotonin production. Serotonin stimulates both TSH and prolactin. Serotonin and prolactin both happen to cause bone loss. They increase nitric oxide, which inhibits mitochondrial respiration. Serotonin increases a cytokine, osteoprotegerin, that inhibits osteoclasts, reducing bone turnover. However,

serotonin's other antimetabolic effects outweigh that effect, and it is a major factor in causing osteoporosis. The antimetabolic factors that slow the rate of living also slow the rate of renewal, and on balance lead to tissue atrophy, fibrosis, inflammation, and degeneration. Several decades after estrogen-induced prolactin might have been recognized as a cause of bone loss in aging, a few people are mentioning the mechanism in specific situations (Horner, 2009; Horner, et al., 2007).

With aging, metabolic activity and the turnover of biological substance decrease. Organelles such as mitochondria are renewed every day or two, much of the brain substance has a similarly fast rate of turnover, and other parts of the body are renewed more slowly. When conditions are optimal, the new structures are flawless, but under the wrong conditions, faulty repairs can accumulate, producing the degenerative problems of aging.

Our culture's understanding of biology has been shaped by a series of ideologies, and currently the drug industry is the main force shaping those ideologies, creating an attitude that's receptive to their products.

The huge marketing campaign for resveratrol will have direct effects on people's health, probably extending beyond the generation that uses it, but it is also polluting the culture by reinforcing the doctrine that torpor, slowing the life process, is beneficial.

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