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## On The COVER

### STAYING YOUNG FOREVER

Putting new research findings into practice

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Scientists believe that human beings are made for a life span of approximately 120 years. Why do so few of us achieve this potential? And would we want to be that old anyway?

Getting older is not the real problem- the diseases of aging are what we fear. So far, modern medicine has done relatively little to prevent the underlying disorders that tend to accelerate the aging process and bring the vulnerability, pain, and suffering that we associate with aging.

Aging involves a broad variety of factors: genetics, environment, nutrition, stress load and overall lifestyle. We now know that aging can be accelerated, slowed down or even reversed depending on these factors.

Longevity research has discovered that aging is accelerated by declining cellular energy production, free radical damage, the "browning" of proteins by glucose (glycation), and impaired immune defenses. We will examine some fascinating recent research on key compounds that have a strong potential for influencing these processes and keeping you young.

#### Preventing mitochondrial decay

Mitochondria are tiny structures within the cells that convert nutrients into energy through the process of cellular respiration. Mitochondrial decay-and the consequent decline in cellular energy production-may be one of the most important causes of cellular decline in aging.

This age associated mitochondrial dysfunction seems to a great extent to be due to cumulative free radical damage as well as a lack of important micronutrients in the cell. One co-factor that is critical for the transport of proteins in the mitochondria is a phospholipid called cardiolipin. Coenzyme Q10 is another cofactor that participates directly in energy production. Both of these mitochondrial cofactors decline with age (Hagen TM et al., 1997).

Cellular energy production itself produces free radicals that can damage cell structures, including the mitochondria, and ultimately lead to various diseases if the body's natural antioxidant capacity is inadequate. Acetyl-L-carnitine and lipoic acid are both endogenous (naturally present in the body) antioxidants that have been shown to restore mitochondrial function and reduce free radical damage. (Hagen TM et al., 1998; Lyckesfeldt J et al., 1998). Together with coenzyme Q10, they work to maintain the function of the mitochondria.

Acetyl-L-carnitine enhances energy production by facilitating the transport of fatty acids into the energy-producing units in the cells. In two animal studies from the University of California at Berkeley (Hagen TM et al., 1998) acetyl-L-carnitine significantly reversed age-associated mitochondrial decay. It increased cellular respiration, membrane potential and cardiolipin levels.

Acetyl-L-carnitine has been shown to improve energy production within brain cells and is considered a neuroprotective agent because of its antioxidant action and membrane stabilizing effects. Several controlled clinical studies in Europe show that acetyl-L-carnitine slows down the natural course of Alzheimer's disease in many important respects. (Calvani M et al., 1992)



Remarkably, a 1995 study of acetyl-L-carnitine provided the first demonstration that any drug or supplement could bring about both clinical and neurochemical improvements in patients with Alzheimer's disease (Pettegrew JW et al., 1995). Patients given acetyl-L-carnitine (3g/day for 1 year) fared significantly better than control patients on both the ADAS (Alzheimer's Disease Assessment Scale) and MMS (Mini-Mental Status) rating scales. The researchers used magnetic resonance spectroscopy to measure neurochemical activity in the patients' brains. They found that acetyl-L-carnitine normalized the levels of key neurochemicals involved in neural membrane function and energy metabolism (high-energy phosphates and phosphomonoesters).

## Lipoic acid

Alpha lipoic acid helps break down sugars so that energy can be produced from them through cellular respiration. In addition, recent research has discovered that alpha lipoic acid plays a truly central role in antioxidant defense. It is an extraordinarily broad spectrum antioxidant able to quench a wide range of free radicals in both aqueous (water) and lipid (fat) domains. Moreover, it has the remarkable ability to recycle several other important antioxidants including vitamins C and E, glutathione and coenzyme Q10, as well as itself! For these reasons, alpha lipoic acid has been called the universal antioxidant.

In addition to serving as the hub of the body's antioxidant network, lipoic acid is the only antioxidant that can boost the level of intracellular glutathione, a cellular antioxidant of tremendous importance. Besides being the body's primary water-soluble antioxidant and a major detoxification agent, glutathione is absolutely essential for the functioning of the immune system. Scientists have known for a decade that maintaining a high cellular level of glutathione is critical for life and crucial for health.

Raising glutathione levels has been shown to alter the cytokine balance in favor of a Th1 immune response mode (the anti-cancer and anti-viral mode of the immune defense-see sidebar, "The immune system"). (Peterson JD et al., 1998). Agents that deplete glutathione, such as ethanol, have been shown to impair the body's immune defense. TNF-a (tumor necrosis factor alpha), increased in many diseases of aging, has been shown to be involved in depletion of cellular glutathione. (Phelps DT et al., 1995). As we shall see later in this article, TNF-a is thought to be a major factor in the immune decline associated with aging.

People with chronic illnesses such as AIDS, cancer and autoimmune diseases generally have very low levels of glutathione. White blood cells are particularly sensitive to changes in glutathione levels, and even subtle changes may have profound effects on the immune response. It was shown that glutathione deficiency in HIV-infected individuals correlates with decreased survival (Herzenberg LA et al., 1997).

The practical problem for those who wish to maintain healthful glutathione levels is that taking glutathione itself as a supplement does not boost cellular glutathione levels, since glutathione breaks down in the digestive tract before it reaches the cells. Therefore, the discovery that lipoic acid can effectively boost glutathione levels has very important implications in the prevention and treatment of numerous diseases.

In a number of experimental and clinical studies, lipoic acid has now been shown to be useful in the treatment of such conditions as diabetes, ischemia-reperfusion damage, neurodegeneration, heavy-metal poisoning, radiation damage and HIV infection and may offer significant protection against stroke, heart disease and cataracts (Packer L et al., 1995). It is likely that much of the beneficial effect of lipoic acid may be attributed to its ability to increase levels of glutathione, chelate metals (such as iron and copper), quench diverse free radicals, and recycle antioxidants.

## Inhibiting glycation

Glycation is the name of a process in which glucose reacts with protein in an undesired way, resulting in sugar-damaged proteins (similar to browning food in the oven!) called advanced glycation end products (AGE). The formation of AGE happens in everyone and is a major factor in the aging process itself. These damaged proteins may lead to premature signs of aging (wrinkles and brown spots) and in the long run to damaging effects on most organ systems within the body. Glycation reactions are accelerated in the diabetic patient and contribute to the development of diabetic complications.

It has been observed that glycated proteins produce 50-fold more free radicals than nonglycated proteins. As a result of this, AGE exert multiple detrimental effects in the body. For example, AGE induced free radicals activate the proinflammatory cytokine TNF-a (tumor necrosis factor alpha), known to be elevated in the elderly. TNF-a has been shown to be particularly high in inflammatory diseases of the central nervous system (Alzheimer's disease, multiple sclerosis and ischemia) and is considered to promote neurodegeneration (Venters HD et al., 1999).

AGE formation is increased under conditions of oxidative stress, such as glutathione depletion that can for example be found in the substantia nigra in the brain of patients with Parkinson's disease. Glutathione is suggested to be the decisive factor that triggers the formation of Lewy bodies in pre-symptomatic cases of this disease.

The amino acid carnosine is a natural AGE inhibitor found in high concentrations in the brain, muscle tissue and the lens of the human eye. It is also known to be an antioxidant capable of protecting cell membranes and other cell structures. In vitro studies demonstrated that carnosine inhibits glycosylation and crosslinking of proteins induced by reactive aldehydes, and that it is effective in reducing AGE formation by competing with proteins for binding with the sugars. The authors suggest that this nontoxic compound should be explored in the treatment of such conditions as diabetic complications, inflammatory disorders, alcoholic liver disease and possibly Alzheimer's disease (Hipkiss AR et al., 1998).

Many additional functions for carnosine have been suggested, such as immunomodulator, neurotransmitter, metal ion chelator and wound healing agent. In a series of animal studies it was demonstrated that carnosine was effective in overcoming muscle fatigue, lowering blood pressure, reducing stress and hyperactivity and inducing sleep (Quinn PR et al., 1992). More recently carnosine was shown to delay senescence in cultured human fibroblasts (McFarland GA et al., 1994).

In an animal study on the effect of carnosine in the ischemic brain, carnosine had a protective effect, preserving nerve cells from damage and death, suggesting that this amino acid might be a promising treatment for patients with stroke (Stvolinsky, SL et al., 1998). In other studies carnosine was shown to be effective in the treatment of senile cataracts in dogs, suggesting the possible use of carnosine in the prevention and treatment of cataracts in humans (Halliwell B et al., 1985).

Along with carnosine, lipoic acid has been shown to control the formation of AGE and reduce protein damage from glycation in both humans and animals. This has proven to be of special value in preventing and treating diabetic neuropathy, which is believed to be due in part to glycation and protein oxidation by glucose (glycoxidation). Lipoic acid has been an approved treatment for this condition in Germany for 25 years.

### Preventing age-related senescence of the immune system

The immune system is an intricate network of interacting components. Its basic function is to discriminate and eliminate foreign and undesired entities in the body. Bacterial, viruses as well as cancer cells and super-antigens (toxins) are the targets for the immune system.

Immunological functions are known to decline with age, while the incidence of various age-associated diseases-such as infections, cancer, inflammatory bowel and vascular diseases-increases (McGee W, 1993). It has been observed that elderly people who have well functioning immune systems live longer (Samsoni P et al., 1993). What can we do to support the immune system and prevent its decline?

The thymus gland is of critical importance for immune function. This gland modulates many aspects of immunity, especially the development of "T" (thymus-derived) cells. A decline in thymic function begins, however, at the time of puberty, which results in a limited capacity for T-cell regeneration as early as young adulthood. Adult humans with severe T-cell depletion therefore must regenerate T-cells primarily via inefficient thymic-independent pathways. An indication of this decline was demonstrated in a study in which the recovery of T-cell numbers after exposure to the stress of chemotherapy treatment was retarded in older individuals compared with younger ones (Mackall CL et al, 1995).

An unexpected culprit in immune decline may be estrogen. In experiments, estrogens have been shown to be myelotoxic, i.e. suppress bone marrow (Fried WT et al., 1974), to reduce natural killer cell activity (Luster MI et al., 1984), to increase the incidence of autoimmune disease (Ahmed SA, 1990), to alter T-cell development (Screpanti I et al., 1989) and to induce thymic atrophy (Seiki K et al., 1997). The thymus appears to be one of the major targets of estrogen in the immune system.

New research suggests that the pronounced decline of thymic function in old age may imbalance the delicate mechanisms of immune-neuroendocrine regulation that have been hypothesized to trigger aging processes (Goya RG et al., 1999). Fortunately age related changes in the thymus structure and function can be partially corrected by mild oral zinc supplementation. Thus preservation of thymic function could have far-reaching consequences for longevity.

Aging of the immune system is characterized not only by thymic degeneration and consequent decline in functioning T-cells, but also by increased levels of tumor necrosis factor alpha (TNF-a) in the blood stream. TNF-a is a so-called cytokine, a messenger protein involved in the regulation of inflammatory and immunological responses. With aging, TNF-a becomes increasingly involved in the death of T-cells. It has recently been shown that T-cells from aged humans have an increased susceptibility to TNF-a-mediated apoptosis (programmed cell death/ cell suicide) as compared with cells from young subjects (Aggarwal S et al., 1999).

By playing a major role in the death of T-lymphocytes (Aggarwal S et al., 1998) this messenger molecule has a powerful impact on the development of various kinds of diseases. TNF-a is, for example, known to play a part in arthritis, Chron's disease, multiple sclerosis, HIV replication, malaria, sepsis and the wasting syndrome (cachexia) associated with cancer. It is also reported to play a

central role in the development of cancer as an endogenous tumor promoter (Gelin J et al., 1991; Wu S et al., 1993; Orosz P et al., 1993).

The results from a cell culture study (Suganuma M et al., 1996) showed for the first time that inhibition of TNF-a works as a cancer preventative. The authors strongly suggest that specific, non-toxic TNF-a inhibitors will be effective not only in cancer prevention but in the treatment of diseases related to elevated levels of TNF-a. A recent study of TNF-a deficient mice showed evidence that TNF-a is required for the development of cancer. After exposure to a potent cancer-inducing chemical, these mice proved resistant to the development of both benign and malignant skin tumors (Moore R et al., 1999).

Some experimental drugs are known to inhibit TNF-a, but are there any natural, non-toxic inhibitors of TNF-a?

Continuation of "Staying Young Forever"

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