Life Extension Update

New Information On Advanced, innovative Products For- Health And Longevity

November 1994

THE AGING CLOCK

Findings On Melatonin

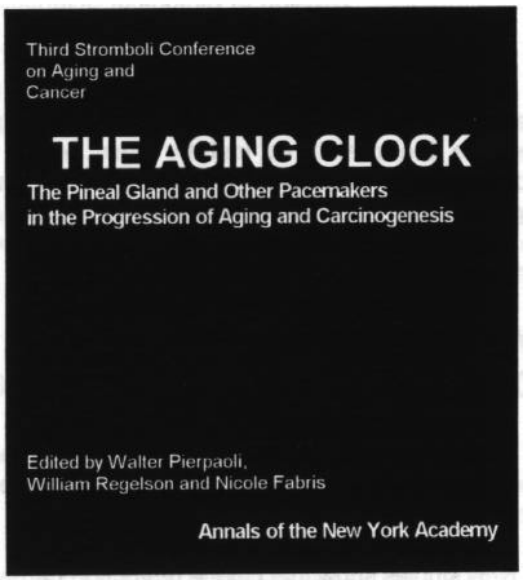
Third Stromboli Conference On Aging and Cancer

Annals Of The New York Academy Of Sciences (Vol. 719 - 1994)

The New York Academy of Sciences has just published a 588-page book of scientific papers presented at a June 1993 conference on Stromboli island, off the coast of Sicily, Italy, investigating current means of slowing aging and preventing cancer.

There were fifteen new papers on **melatonin** presented at the conference that help to clarify the potential role this hormone plays in preventing disease and extending lifespan. These new studies suggest that melatonin may be the single most important component of your life extension program. Fortunately, it is also the least expensive anti-aging supplement in the world.

This issue of **Life Extension Update** presents findings from this conference, which was called: **THE AGING CLOCK - The Pineal Gland and other Pacemakers in the Progression of Aging and Carcinogenesis.**



MELATONIN AS AN ANTIOXIDANT

Melatonin may be the most important antioxidant supplement you can take. The reason for this is easy to understand.

Most antioxidant nutrients have difficulty penetrating cell membranes. Melatonin, on the other hand, enters cells and sub-cellular compartments with ease.

One consequence of aging is a declining number of melatonin-producing cells in the pineal gland and a decline in the amount of melatonin secreted by surviving melatonin-producing cells. This phenomenon can be linked to a number of degenerative changes associated with normal aging.

The following quote from the paper **'Clocks, Cell Cycles, Cancer and Aging" :**

> Melatonin, *the* primary hormonal product *of the pineal g/and* — a *photoneuroendocrine* transducer and **biological** pacemaker *that* affects *the* seasonal adaptation **of** higher animals — *governs a variety* **of** reproductive *and immunoregulatory functions* **and may** *play a role in* cancer, *aging* and *senescence. Not only does melatonin production decline* clinically *with age, but administration of melatonin or the implantation of pineal tissue from young* donors *prolongs both median and absolute survival times of older mice.*
>
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These findings provide further evidence that most people over 40 should take melatonin every night to replace the melatonin lost by their bodies with advancing age. Melatonin is a critical, sleep-enhancing, antioxidant, and anti-cancer hormone that needs to be maintained at youthful levels for optimal health and longer life.

MELATONIN INCREASES DURING CALORIE RESTRICTION

Calorie restriction consistently produces radical increases in lifespan and reduction of cancers in animal studies.

New studies show that calorie restriction causes an increase in serum melatonin, and scientists are *speculating* that this may be one of **the** reasons why severe calorie restriction extends lifespan so dramatically.

A new study also confirms that melatonin is synthesized in parts of the body other than just the pineal gland. The retina in the eye, which is exposed to continuous ultraviolet oxidative damage, is the most acknowledged independent site of melatonin synthesis in vertebrates.

In this study, melatonin was found to be more abundantly produced in the gastrointestinal tract than even the pineal gland.

Here is an excerpt from the conclusion of the paper **"Melatonin & Gastrointestinal Tract" :**

> *Melatonin exerts direct and indirect beneficial effects* **in** *delaying developmental and aging processes. Because similar effects* are *elicited by dietary restriction, it may be assumed that the anti-*aging *effects of food restriction* are *mediated by an increased* **fonation** *of melatonin levels in experimental animals and maybe* also *in human subjects. Indeed, food restriction causes an elevation of* **circulating** *melatonin.* However, *this* increased **level** *of* **circulating** melatonin appears *not to be derived from the pineal g/and, but instead* **from a** *hitherto rather neglected extrapineal site of* melatonin *synthesis, the enterochromaffin cells of the gastrointestinal tract. The amount of melatonin found in the* **gastrointestinal tract is much** *higher than in* any *other organ including the* **pineal,** *and the* gut appears *to make* a *significant contribution in circulating* melatonin, *at* **least** *under certain conditions.*
>
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Several new studies indicate that melatonin supplementation could produce some of the beneficial lifespan-extending effects of calorie restriction.

MELATONIN AND ZINC RESTORE IMMUNE FUNCTION

it is well established that the age-related decline in immune function corresponds with the involution (shrinkage) of the thymus gland and the subsequent decline in the production of the hormones produced by the thymus gland **— the thymosins, thymopoetin, and thymulin.** All these factors are required for the proliferation and differentiation of vital T-cells.

Previous studies have shown that growth hormone and thyroid hormone replacement therapy can regenerate the thymus gland and induce the recovery of immune competence in the aged.

New studies indicate that melatonin may have a restorative effect on thymic function by inducing regrowth of the gland, increased production of T-cells, and recovery of immune efficiency. Among the measures of immune function improve by melatonin supplementation are: reduced mitogen responsiveness to PHA and Con A, increased production of spleen T-cells subsets, and increased thymosin and thymulin secretion.

Another factor in restoring thymic function is zinc. In numerous studies in animals and humans, zinc supplementation increased thymic activity and partially reconstituted immune function, even in old age. Zinc deficiency has been documented to cause thymic and lymph node atrophy along with impaired immunity. Zinc absorption is strongly reduced in the elderly, sometimes even in those who take supplemental nutrients. Melatonin supplementation enables older animals who are zinc deficient to absorb and utilize zinc more effectively and induces regrowth of the thymus gland with increased plasma levels of thymulin.

A specific example of zinc's effect on immune function is the fact that it is required to activate the thymic hormone thymulin, which plays a critical role in generating T-cells, especially those involved in protecting against slow-acting viruses such as the HlV (AIDS) virus. When thymulin is not bound to zinc it is inactive and as we grow older, the percentage of inactive thymulin in our bloodstream increases. Zinc supplementation leads to the complete disappearance of the inactive form of thymulin and an increase in the active form of thymulin comparable to that found in youth.

These observations clearly suggest that the age-dependent involution of the thymus is a reversible phenomenon and that both melatonin and zinc can be used to rejuvenate the thymus. The following table compares the restorative effects of zinc and melatonin on critical immune system functions,

TABLE 1. Immunological Consequences of Aging and Restorative Effect of Zinc or Melatonin

Scientists at the Italian National Research Centers on Aging have discovered that melatonin has a regulatory effect on zinc metabolism. Because of the similar rejuvenation effects on immune function of both melatonin and zinc, the Italian scientists have proposed a close interrelationship between melatonin and zinc in regulating the immune system.

Here are their conclusions in a paper entitled **"The Zinc-Melatonin Interrelationship":**

Taking info account all the findings reported above, *we may hypothesize that a melatonin-induced effect* on *the immune system is largely mediated by the adrenals. We know that* melatonin *modulates glucocorticoid production an/or release and that* glucocorticoids *modulate zinc turnover. We also know* that *zinc may influence thymus function.* On *the basis of these considerations, we may assume that melatonin treatment in old age induces* a *reduction of adrenal function, supported by the reduced adrenal weight,* and *through this action, increases zinc availability with consequent* higher *saturation of thymulin,* which, in *turn, favors thymocyte proliferation and* maturation.

With regard to the effect of zinc supplementation, we may hypothesize that zinc may *affect thymic function either directly- or indirectly through a reduced glucocorticoid secretion, and, possibly, and increased melatonin secretion.*

In this last case one should assume that zinc supplementation does not have a *direct effect on* the *thymus,* but an *indirect one mediated through normalization,* in *old age, of the neuro-endocrine profile. independently of these interpretations,* if *remains undetermined whether the action of both zinc and* melatonin should *be considered as directed towards* true *aging processes or* towards *age-associated stressful conditions.*

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TABLE 2. Effect of MEL on ***in Vivo*** Antibody Response. The MEL/Saline ratio measures the increase in the TNP PFC antibodies; eg, In experiment 1, the antibodies produced in 2-month-old mice given melatonin exceeded those in the saline controls by 3.6 times.

Age (months)	ET. No.	Treatment	Anti-TNP PFC (SE) per Spleen	MEL Saline	p
2	1	saline	22776(1.06)	3.08 (1.07)	<0.00005
		MEL	*86601(1.04)*		
	2	saline	11224(1.16)	1 .06(1.20)	<0.05
		MEL	18034(1.12)		
12	1	saline	3623(1.24)	I.9(1.30)	<0.05
		MEL	6503(1.09)		
	2	saline	618(1.08j	2.6(1.10)	<0.0002
		MEL	15.86(1.07)		

MELATONIN RESTORES IMMUNE FUNCTION IN AGED MICE

In a study testing the ability of melatonin to restore immune function *in* vivo, significant increases in immune function were observed in both young and old mice. Melatonin produced an increase in antibody response of 1.6 to 3.8 fold in young mice and 1.2 to 2.6 fold in old mice (see table 2).

In old mice only, melatonin produced an increase in the vital immune component Interleukin-2 (IL-2).

These studies also showed that melatonin restored immune function damaged by drugs. This indicates that cancer chemotherapy patients, whose immune system is ravaged by chemotherapy, could benefit from high-dose melatonin supplementation.

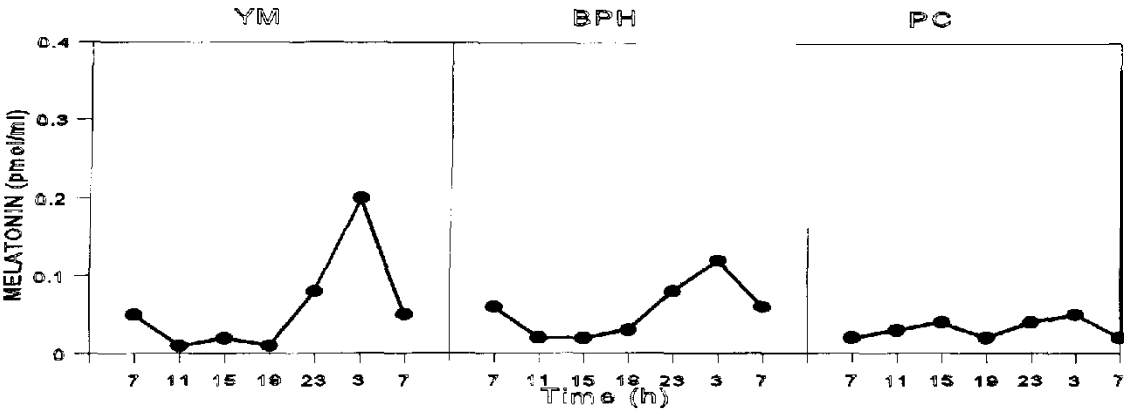

FIGURE 2. Circadian profiles of melatonin in serum of young men (YM), elderly men with benign prostatic hyperplasia (BHP), and patients with unoperated primary prostate cancer (PC).

Here is the summary of the paper **"Melatonin Restores Immunodepression on Aged and Cyclophosphyamide-Treated Mice":**

Melatonin, the main hormone *of the* pineal g/and, when *chronically injected into young* mice or *mice immunodepressed by aging or by cyclophopha*mide treatment, was *able to enhance the antibody response to a T-dependent antigen. The enhancement of antibody response was associated with increased induction of T helper Cell activity and IL-2 production as evidenced in mice immunodepressed by aging or by cyclophosphamide treatment. These observations suggest* that melatonin *may be successfully used in the therapy of immunodepressive conditions.*

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MELATONIN ENHANCES REGULATION OF LYMPHOCYTES

Healthy immune function requires a delicate balance of hundreds of different immune system components In several new studies, melatonin has been shown to have specific receptor binding sites on lymphocytes, suggesting a direct effect of melatonin on the regulation of lymphocytic immune function.

This means that, in addition to the numerous other mechanisms by which melatonin enhances immune function, a direct mechanism of regulation can be attributed to the binding of melatonin to immunocompetent lymphocytes. Additional research will have to be done to determine if melatonin will have a beneficial or detrimental effect as a treatment for lymphoma or Hodgkin's disease. Until more is known, **The Life Extension Foundation** cautions against the use of melatonin by those with immune system cancers (including leukemia).

Previous studies on the development, regulation, structure and function of the pineal gland have provided ample evidence that the pineal gland is an important component of the neuro-endocrine system. New studies corroborate the early studies and provide a better understanding of the role the pineal gland plays on a wide range of immune responses.

PINEAL GRAFTING AND MELATONIN SUPPLEMENTATION

Experiments in Russia have shown that melatonin supplementation or the grafting of young pineal glands to aging mice delays aging and prolongs youthful, disease-free life. **When l8-month old mice were given pineal gland transplants from young 4-month-old mice, they went on to live to an average age of 34 months, but when the younger mice received pineal transplants from the older mice, they only lived an average of 17 months... one month less than the age at which the older mice received their young pineal glands!** The results of these studies show the critically important role of the pineal gland in the aging process, and provide further evidence that the pineal gland functions as an "aging clock".

The following conclusion comes from a paper entitled: **"Pineal Cross-Transplantation as Evidence for an Endogenous 'Aging Clock"':**

Circadian *(night)* chronic administration *of* melato*nin and young-to-o/d pineal* grafting into *the thymus have provided* evidence for the existence *of an endogenous, primary* and *central "aging* clock" *in the* pineal *gland. The new model described* here serves *to* definifely demonstrate that

the replacement of the pineal g/and of an old mouse with the pineal from a young, syngeneic donor mouse remarkably prolongs its life and, conversely the "old" pineal transplanted into a younger *mouse will considerably shorten its lifespan. Pineal cross-transplantation thus provides* clear-cut evidence *for the central role of the pineal gland in the initiation and progression of senescence. It offers a novel basis for interventions into* the aging *process.*

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Additional studies *from* Russia confirm melatonin's ability to maintain and restore immune competence. The ability of melatonin to restore youthful sleep patterns are another youth-promoting mechanism studied by the Russian researchers. The Russian scientists speculate that a melatonin deficiency is one cause of Down's Syndrome in children, and that it may be correctable by melatonin supplementation.

Melatonin was first used to extend lifespan in Russia. In 1987, Dilman and coworkers administered melatonin to rats and produced a 25% increase in lifespan and an observable delay in the aging process.

The conclusion of an article published by the Institute of Experimental Medicine in Russia entitled **"The Pineal Aging Clock"** was that melatonin produced a **"striking aging-postponing effect hinting at a possible re-synchronization of cell cycle clocks..."**

MELATONIN AS A THERAPY TO PREVENT AND TREAT CANCER

Two well established facts are that aging results in a significant decline in melatonin secretion and that the incidence of cancer increases as people age.

Melatonin plays a well documented role in the prevention and treatment of breast tumors, whether or not they are estrogendependent. Until now, there was little documentation about the effect of melatonin on prostate cancer.

In a brand new study, prostate cancer patients were found to have no circadian melatonin rhythm due to obliteration of nighttime melatonin release (see figure 2). In a second study, prostate cancer patients showed a 65% decline in overall melatonin serum levels compared to age-matched controls. The reduction in melatonin in breast and prostate cancer patients is associated with a marked endocrine disturbance that weakens the patient's immune response to the tumor.

The hormonal changes in patients with advanced tumors show that endocrine disturbances caused by a decline in melatonin levels may be a predisposing factor that allows a small group of malignant cells to become a life-threatening tumor with metastatic potential.

In advising about the use of melatonin for cancer patients, the authors of the article entitled, **'Diminished Pineal Function Coincides with Disturbed Circadian Endocrine Rhythmicity in Untreated Primary Cancer Patients"** state:

The above considerations indicate that a substitutional therapy with melatonin may he/p to prevent if not *to restore central endocrine imbalances as described* in *cancer patients* with *depressed melatonin. In addition, this therapy may prove to be beneficial due to the* oncostatic as well as *immunoregulatory role of melatonin. First therapeutic attempts have been reported using melatonin alone or* in *combination with lymphokine* as *well as chemotherapy. Encouraging results were reported leading to a better tolerance of the* therapies *employed including* an *improved general well-being, and even signs of tumor inhibition. Melatonin may show even better therapeutic results* if *it* is administered *soon after tumor detection and prior to operation since a direct tumor-inhibitory activity at the* cellular level *is detectable if sufficient* estrogen receptors are *present and tumors are at an* ear/y *stage of development. Another possible therapeutic effect of melatonin may involve* stimulation *of the pineal* anti-tumor *activity (PATA) present in* low-molecular *weight ultra-membrane filtrates of sheep pineal* glands (500-1000 *d)* which effectively *inhibits a wide range of experimental* tumors *in vitro that* are unresponsive *to melatonin.*

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These new findings provide further evidence that melatonin is an effective adjuvant therapy for two of more of the most common cancers striking Americans today. Based upon these new findings, prostate cancer patients may consider supplementation with low doses (3-9 mg each night) of melatonin. Earlier studies failed to show an effect of melatonin on prostate cancer, but did show a significant benefit in preventing and treating breast cancer. Breast cancer patients may consider nightly doses of melatonin ranging from 10 to 50 mg.