

HOW TO STOP AGING?

By Walter Pierpaoli, M.D., Ph.D.

[Ed. Dr. Pierpaoli is one of the world's leading neuroendocrine researchers and it was his work that has made melatonin "common knowledge" throughout the world. However, as you will read in this article, Dr. Pierpaoli's research about melatonin goes far beyond its use just for sleep, jet-lag and as an antioxidant. In-fact, Dr. Pierpaoli's ground-breaking work suggests that melatonin is a crucial factor in the treatment for aging itself and these ideas formed the basis of his lecture at the Second Monte Carlo Anti-Aging Conference (tapes now available). We are therefore very pleased to print this article by Walter Pierpaoli, M.D. of Chronolife in Switzerland].

Melatonin and the pineal gland:

The answer to programmed neuroendocrine and immune aging, to its prevention and its reversal.

What is aging?

If we restrict our analysis to the vertebrates, and in particular to the mammalian species, we can clearly state that, notwithstanding the unforeseeable occurrence of traumatic accidents and the aging-accelerating effects of social distress, a large number of noxious environmental agents, poisons, bacterial or viral diseases, that aging is by itself a genetically programmed event for all species.

In homeotherms, (namely in warm-blooded vertebrates), we can in-fact predict a lifespan which is closely dependent on their genetic background. The question arises: why has a specific lifespan been established for a species? We may never be able to answer that question, but our curiosity concerns the nature and essence of the "programmed clock" for all mammalian species and the common pattern which characterizes the decay of biological functions which, in all species, is called "senescence." In other words, we do not deny its importance but we forget for a while, the evolutionary significance of aging, and restrict our attention to the nature of aging in order to delay, arrest or even reverse its course. There is no time for academic exercises!

I will limit my article to the evaluation of the scientific "hard-facts" that concern the known approaches to delaying aging in mammals : They are :

Restricted caloric diet

Exogenous administration of melatonin

Over the course of many years, we have progressively developed and analyzed the concept and experimental data to underly our claim that aging, (similar to somatic growth and fertility), is simply a pineal complex-driven neuroendocrine programme in the brain, that leads to progressive derangement and de-synchronization of fundamental neuroendocrine and hormonal regulation such as gonadal, thyroid, adrenal functions etc.

In other words, the aging conductor "the pineal" delivers untimely and chaotic, haphazard messages and therefore the whole orchestra gets deranged! There is a common

denominator for all the typical somatic and functional deficits of aging and the metabolic decay and dissociation of basic cell activities, such as the oxygen-dependent energy production inside the cells. We think that the "programme of aging," similar to the "programme of growth" is basically dependent on the close synchronic and mutually dependent relationship between, first the developing and later the aging neuroendocrine and immune systems. This is clearly exemplified in the course of aging by andropause and menopause. However, in the course of our studies, other elements have appeared which are in-fact a fundamental aspect of aging : the neuroendocrine-immune interactions both during development of the immune system and during aging. The "discussion" between the two systems is provided by the molecules to both the reproductive functions and to the maintenance of an efficient and self-monitoring immune network.

In recent years, the discovery of transferrins as key agents for the maintenance of "self" identity, has opened a new field for evaluation of the relevance of "self" integrity and for interfering with the programme of aging. In fact, one could speculate that aging is by-itself the progressive extinction of the capacity to distinguish between "self" and "non-self," namely to maintain self-tolerance. This is typically shown in the emergence of autoimmune diseases and cancer, which is progressive with aging. Here we can find an important link in the cross-talk between the neuroendocrine and the immune system, where we have identified some key elements which all contribute to an efficient functioning of neuroendocrine and immune functions. We can now start arguing about their role in the context of aging.

However, a restricted caloric diet (RCD) is the first historical approach to significantly retard aging, so the question is: Has melatonin a relation to a low calorie diet? In other words, does a low calorie diet modify melatonin and conversely does melatonin mimic a restricted caloric diet? Is there a common denominator which will affect the inherited longevity programme of each individual?

Life prolongation via a restricted calorie diet (RCD)

Since the first dramatic experimental evidence produced by McKay with rodents in 1934, an immense amount of literature is now available which documents the different methods used. All prove that a diminished calorie intake will significantly delay aging and the many aging related diseases and their metabolic dysfunctions. However, it took more than sixty years before the National Institute on Aging started to evaluate whether or not a RCD applied to non-human primates would also retard aging (sic!). There is now evidence that this is the case and many results begin to be available from this long-term trial. At the time when the thymus was considered to be, (thanks to its basic developmental functions in ontogeny), a kind of "clock" for aging of the immune system, we demonstrated long ago in a rather neglected publication, that the thymus does not deserve such a primary role for initiation and progression of aging (Table 1). Removal of the thymus at different times after birth in mice, did not significantly affect their life span (Table 2). However, it became clear that the thymus was deeply involved in the ontogenetic programming and maturation of the entire neuroendocrine system, and that

athymic-nude mice suffered a kind of precocious senescence, which could be completely prevented by thymic implantation. In-fact, thymus grafting resulted into a complete normalization of neuroendocrine functions. On the basis of those findings and the consequent observations of the ability of mature lymphocytes to restore growth, immunity and to prolong the life of dwarf mice, the idea evolved that a different hormonal regulation could be responsible for the aging-postponing effects of a RCD. In other words, we suggested that a decreased calorie intake would produce permanent changes in the central, hypothalamic-pituitary hormonal functions, thus maintaining the body at a more juvenile level of endocrine and metabolic regulation. This was particularly clear with regard to sexual functions of rodents maintained at a RCD.

We conducted some experiments in which we could demonstrate that if mice are kept at a RCD for a few weeks after weaning, and then fed again ad libitum, they maintain (in spite of this normal feeding) a permanently different pattern of hormonal regulation (Table 3). This data confirmed that the feeding behaviour (at a time when the neuroendocrine system is still immature), permanently affects maturation and function of the entire neuroendocrine system. This observation is of course very relevant with regard to the onset of obesity in overfed children and the consequent permanent derangement of their mature neuroendocrine and metabolic system and irreversible obesity. This environmentally induced obesity (which is now so dramatically evident in the affluent Western Society) is of course different from mild or severe fattening of "normal" metabolic aging in humans. Also, this environmentally acquired dietary obesity is different from genetically inherited obesity, which however afflicts a small number of families and individuals.

The clear answers from many studies all indicate that a RCD produces juvenility-oriented and permanent changes of neuroendocrine regulation and they are exactly the opposite outcome of environmentally induced and aging-accelerating dietary obesity. If endocrine and metabolic dysfunction are the expression of the programme of aging, and if the pineal gland is a "life and aging clock", consequently we must consider that a RCD affects mainly the pineal gland and its functional state. This seems to be the case. It has been reported that a RCD maintains juvenile levels of melatonin in rodents.

In a collaborative project with Dr. George Roth and Mark Lane at the National Institute on Aging, Baltimore, USA, in which large groups of primates have been under a RCD for several years, data is emerging that RCD very significantly maintains high levels of nocturnal melatonin in both male and female aging monkeys, comparable to the levels in young primates (see reference 16). Our conclusion is that a RCD, by setting the "neuroendocrine clock" at a more juvenile level, protects the pineal gland from aging and thus protects from aging the whole pineal-controlled hormonal, circadian and seasonal periodicity, whose progressive decay leads to aging. However, melatonin is only a signal from the pineal gland of an overall de-synchronization of the whole neuroendocrine network, leading to a progressive alteration of hormonal cyclicality and consequently, of the surveillance of the immune functions.

The anti-aging molecule melatonin

In spite of the political denigratory campaign against the anti-aging properties of melatonin, it is beyond any doubt that exogenous administration of melatonin to aging rodents postpones their aging and/ or prolongs their life (Figure 1). Unfortunately, for mysterious or tactical reasons, those experiments have not been properly replicated, while the deceptive behaviour against the anti-aging properties of melatonin continues. Of course, melatonin serves to indicate that the pineal gland is directly involved in the aging process. Pineal grafting experiments disclose a dramatic new approach for strategies to postpone aging. Also, these fundamental experiments have not been replicated, although they may soon, several years after their initial publication! The pineal grafting experiments also serve to indicate that the pineal gland, via its links to the entire neuroendocrine system, controls the "programme of aging" and that in-fact an aging pineal can accelerate aging even in a normal young animal carrying his own young pineal (Figure 2). These striking observations help to understand that other key mechanisms and/or molecules must be operative for the anti-aging and the aging-accelerating properties of pineal grafting. Whether or not the anti-aging and the pro-aging capacities of the young and old pineal gland depend on a unique mechanism, it is reasonably clear that pineal peptides play a basic role.

That melatonin could significantly postpone aging thanks to its anti-oxidative and hydroxyl radical-scavenging properties, (like those of vitamin E or glutathione), is not supported either by logic or by any serious in-vivo confirmation. It does not seem to me that the many receptor-mediated effects of melatonin and the myriad of affinity binding mechanisms can explain its anti-aging properties. The anti-stress, immunoprotecting effects of melatonin show a rather slow "buffer" mechanism. This reinforces our hypothesis that melatonin does not by itself exert the activities observed but rather protects the pineal gland from aging. But nocturnal melatonin supplements will not protect from aging when the age of the animals is too advanced! This has now been proven in another kind of placebo-controlled clinical trial, in which perimenopausal women aged 42 to 62 years, have been treated with melatonin. After six months the evidence emerges that younger women are more susceptible than older women to the anti-aging properties of melatonin. This fact strongly supports the view that the beneficial and pineal-protecting effects of melatonin are more pronounced at a time when the pineal is still relatively young. This unexpected finding indicates that melatonin can exert a more pronounced anti-aging effect if the administration starts rather early in life, in so-far as it protects the pineal from aging! This observation is fundamental for the preventive use of melatonin in anti-aging interventions and strengthens the suggestion that the mechanism of action of melatonin cannot be attributed to a "hormonal" effect on specific receptors, but rather to a relatively simple night saturation of melatonin content in the pineal gland, and consequent abrogation of night endogenous melatonin production (which is a rather energy consuming and complex two-phase enzymatic process).

If this suggestion is true, it must be possible to drastically reduce or abrogate aging-dependent endocrine and metabolic dysfunctions by the administration of exogenous melatonin in the early, post-pubertal life of mammals, (man included), as hinted by the emerging results in perimenopausal women.

Melatonin delays and reverses menopause in women
(Abstract from "Experimental Gerontology", 36, 297-310, 2001)

Night levels of melatonin in mammals and man decline progressively in the course of aging. Also, the function of the thyroid gland and of sex glands (ovaries and testes) decline steadily, while on the contrary in the hypophysis the production of gonadotropins (luteotropic hormone, LH and follicle stimulating hormone, FSH) constantly increase. Those hormones regulate the production of estrogens and progesterone in the ovaries and the menstrual cycle and testosterone in the testes. The increase of LH and FSH is a clear-cut aging signal for sexual and reproductive functions, both in males and in females (i.e. menopause and andropause).

Previous studies with laboratory animals had shown that evening administration of melatonin in senescent animals, as well as transplantation of a young pineal into old animals produces a true reversal of sexual decay. This has been shown by measuring (in that part of the brain that controls sexual organs and functions- the hippocampus), receptors which regulate the synthesis of LH and FSH (gonadotropins) in the hypophysis (Figure 3). This remarkable evidence induced us to evaluate the effects of melatonin in women from pre-menopausal and peri-menopausal age (from 42 to 52 years of age) until menopause (from 52 to 62 years of age). The question was: is pineal melatonin, whose blood levels decline in the course of aging in the sexual-reproductive tract of women, responsible for, or directly connected with the onset of menopause? Are we able to modify or eventually delay menopause by evening administration of melatonin?

Measurement of melatonin in saliva before the initiation of the study allowed us to select women with nocturnal low basal levels of melatonin, as well as women with medium night levels of melatonin and finally women with high night levels of melatonin. This served to verify if the possible effects of melatonin administration, depend only on a condition of individual endogenous melatonin deficiency.

Women were strictly divided into homogeneous groups (melatonin or placebo) according to age and also to their endogenous levels of nocturnal melatonin in the saliva. Before initiation, blood samples were taken for measurement of hormones and all women answered questions in a questionnaire, concerning mood, sleep, and all psychic problems and neurovegetative symptoms typical of women' climacteric. Half of the selected women started taking 3mg of highly pure melatonin while the other half took placebo, this was conducted with the classic double-blind method (neither the physician nor the patient know if the patient takes the active substance or not). After three and six months from the initiation of the treatment, hormonal measurements were repeated and all women answered again all the questions.

The results obtained after three and six months, (a period of time ethically acceptable for the administration of placebo), have shown that:

All women, in particular those who had shown individual low night levels of melatonin in their saliva, had a very remarkable improvement of latent and unsuspected conditions of low thyroid function (hypothyroidism). In-fact, we observed a significant increase of the active thyroid hormone triiodothyronin (T3) in all women independently from their night levels of melatonin and to a minor extent of its precursor thyroxin (T4) only in women with medium and low endogenous levels of melatonin (Table 4). The effect of melatonin does not depend on pituitary TSH (thyrotropin stimulating hormone) but on the direct effect of melatonin on the thyroid gland (conversion of T4 into T3, the active hormone).

In the course of six months, evening administration of 3mg melatonin produced a clear-cut decrement in blood of the pituitary hormone LH (which increases progressively in the course of aging). This was most noticeable in the younger women (43 to 49 years of age). Therefore, the recovery of pituitary function to a more juvenile pattern of regulation is more pronounced and rapid in younger women (Figure 4a and 4b). This equaled to an arrest and even a reversal of brain aging and restoration of reproductive functions in the women taking evening melatonin

As a confirmation of a restoration of thyroid and sexual functions consequent to the evening use of melatonin, seven women, at 2 and more years after onset of menopause (complete interruption of the menstrual cycle), have now reacquired a normal and physiological menstrual cyclicity.

Finally, 96% of women who had taken melatonin, declared a total disappearance of morning depression, which is typical in perimenopausal and menopausal women.

Our results demonstrate that a clear-cut, cause-effect relationship exists between the function of the pineal gland and night secretion of melatonin on one side, and aging of sexual functions on the other side. The decline of synthesis and release of pineal melatonin during aging, signals to us a central hypothalamic alteration of the control of the juvenile hormonal cyclicity and the progressive quenching of fertility in women. Our results show that nocturnal administration of melatonin produces a recovery of thyroid function (synthesis of T3 and T4) and pituitary (hypophysis) sensitivity to ovary regulation (decrease of LH and FSH) in the direction of a remarkable recovery of more juvenile sexual-reproductive functions. The effect of evening administration of melatonin is more pronounced in younger women and in women with lower melatonin levels in saliva (before initiation of oral melatonin treatment).

Women (and men), wake up!

Who is afraid of melatonin? Since the publication in New York in August 1995 of the American bestseller "The Melatonin Miracle" (Simon and Schuster, 1995, authors W. Pierpaoli and W. Regelson with Carol Colman) (Figure 5) which is now translated into 17 different languages, an oppressive air of suspicion and conspirational silence descended in old Europe upon the word "melatonin." This is only broken from time to time by isolated flashes of light, which in-turn are immediately clouded by untimely and

clumsy interventions of the "insiders" of the press and television. In-fact, the simple and clear scientific reality of the matter should not to be classed with day-to-day "disposable products." It took millions of years for Mother Nature to elaborate its logical strategy, which we are now really starting to perceive and interpret. Few people read and try to learn and understand before opening their mouth, particularly newsmen and reporters. They must produce an inexhaustible supply of exciting news daily, while Mother Nature, fortunately for us, does not measure time or regard fashions. As my mother, a woman of central Italy, used to say : "They open their mouth and give out breath!" (She was referring to politicians and their mental and personal deficiencies).

The basic question is : "Why do we age?" The answer is so simple to the point, that it sounds provocative and strange, and for many of my colleagues outrageous, as did the straightforward observation of Galileo to the Fathers of the Catholic Church in the Vatican: "And yet (the earth) it moves!" We age in a way similar to that in which we grow! But then, what is melatonin needed for? It inhibits aging. Why? Simply because it prevents aging of the remarkable "switchyard" in the pineal gland (which truly is not a typical gland!). Nocturnal administration of melatonin prevents the pineal from deteriorating, from decaying into a heap of scrap, and thus from becoming unsuitable to deliver the precise signals which regulate the natural rhythms of day and night. These precise messages keep us constantly synchronized through the hormonal system with the environment in which we live. If and when we stray from this natural pathway, we develop diseases and age more rapidly. The so-called reality of the world in which we live escapes our sensorial and psychological consciousness, simply because we are an integral part of it! We navigate in a dimension whose nature and boundaries we ignore. Our only reference marks are the rhythms scanned by day, night and the seasons. It would be like asking a fish to describe air, or a bird to say what life in the water looks like.

But is melatonin a true hormone? No! Can it induce damage? No! Melatonin is produced and secreted by different tissues and organs, but during night-time only by the pineal gland. Even at huge dosages and for very long periods, melatonin is totally harmless. Well documented data for this exists, but it is never mentioned ! However, a few milligrams (3mg) of melatonin suffices to put the pineal at "night rest" and thus to protect the pineal, our hormonal switchboard center, from aging! If the pineal does not age, we cannot possibly age, or at least the aging process will never again be as we have seen and experienced it until now.

Why do I address women?

I wish to speak to women because they are more adaptable and flexible and thus rightly live longer. They read more and are able to ponder what they hear and read. They are the vehicles of family, peace and serenity, the true basis of our daily life. They have endured the dominance of men for millennia and can thus better help destroy a world of ignorance, lies and egoism. For this reason, two years ago we started a long, expensive, wearisome and unannounced investigation under the guidance of Dr. Giulio Bellipanni and his co-worker Pierluigi Bianchi at the Menopause Center of the Madonna delle Grazie Clinic in

Velletri, near Rome. Using accepted strict scientific criteria we aimed at answering the most obvious and urgent question concerning the aging of women : What is menopause? Can it be prevented, delayed or modified? If melatonin is able to decelerate or even to stop aging, what more suitable model is there than menopause? We now have the answer, and it is extremely convincing.

Our findings have been elaborated and have recently been published. Nocturnal melatonin alone can deeply modify the hormonal and psychosomatic conditions in the perimenopausal years, which can extend from 40 to 60 years of age. Here we only mention what is published in an official scientific journal, to inform all women about it in order to alleviate the countless problems they face daily in family and society. Menopause is simply the end of the hormonal "fertility program" of women, but this program is perfectly amenable to modification. It is not true that "the ovaries are depleted!" They simply atrophy according to their "genetic program." But the expression of that program is purely hormonal, and we can restore the juvenile hormonal control of the ovaries. Certainly the juvenility and health of women are linked to the maintenance of a juvenile hormonal status, which can be supported with nocturnal melatonin administration. In perimenopausal women, melatonin in the most striking fashion, reconstitutes the juvenile hormonal conditions and produces a rapid regression of all the neurovegetative and psychic alterations of menopause, in particular the states of nervousness, anxiety and depression. In addition, we can now address the issue of an impressive combination of melatonin with zinc. Zinc is a basic mineral in the body and essential for the function of over 200 enzymes that are fundamental for the respiration of all cells in the body. The combination of melatonin and zinc dramatically accelerates the effects of melatonin and boosts a depressed immunity. This is all documented. The answer to our queries is clear, simple and strictly scientific. Nocturnal administration of melatonin can resynchronize the entire hormonal system and, by protecting the pineal from aging, can maintain the juvenility of the pineal and its capacity to synthesize other very remarkable molecules. We found another of these molecules 12 years ago, but it must be studied in more detail before being used. At the present time only melatonin is available, which according to our studies is better if taken with zinc. This is all published in excellent scientific journals. Nothing I have stated is casual or extemporized!

Enough of trivial reservations regarding jet-lag and sleep, together with threats of "hormonal side-effects" : Melatonin is, as I said recently in a BBC interview in London, a "gift of God" and can harm only those who do not take it! People (especially women), are now able to appreciate what hormonal and metabolic aging means and thus also prevent it. Others, let them wait to have "youth genes" inserted! At present, 3 milligrams of melatonin and zinc is sufficient for me and all those dear to me before switching off the light and sinking into refreshing sleep Who is right? We shall see in a few years!

[Ed- As can be gleaned from Dr. Pierpaoli's excellent and provocative article- he is passionate about Melatonin and his work (and rightly so). Dr. Pierpaoli also became annoyed at the low quality of melatonin on the market and has since devised his own formula. This version is "more" than just melatonin and contains "other" natural substances that work synergistically. We were all staggered at IAS to find that it is far

more potent than any other form of melatonin we've used! The new form is called TI-MELatonin® and details of it are outlined below].

TI-MELatonin®: Biological effects and scientific information

TI-MELatonin® expresses the best imaginable melatonin preparation available on the world-market and is now available as a food additive and dietary supplement to anybody wanting to take advantage of the extraordinary scientific observations of Dr. Walter Pierpaoli and his co-workers.

The basic experimental findings of 35 years of research, resulted in the discovery of the undeniable existence of a programmed "Aging Clock" in the pineal gland complex of the brain.

We have investigated the possible mechanisms and also the molecules which presumably cooperate and synergize with melatonin in the regulation and re-synchronization of the fundamental immunological and hormonal functions, (which are normally lost or deranged in the course of aging). In recent studies and long-term experiments with old rodents it has been observed that zinc can completely correct aging-dependent immunodepression and several other hormonal and metabolic alterations typical of aging. It has been found that the low zinc levels in aging animals can be restored to normal values with nocturnal administration of melatonin or transplantation of the pineal gland from young animals into older animals⁶⁻⁹. Zinc is an essential component of more than 200 enzymes and one of the most relevant trace elements in the body^{8,9}. It is therefore clear that additional zinc must be supplemented daily to the body of an aging organism with a low zinc balance, in-order that melatonin can better exert its anti-aging activities on the entire neuroendocrine and immune systems! This important and novel scientific observation of the powerful anti-aging and immunoenhancing activity of the combination of zinc and melatonin has now resulted into the development of TI-MELatonin®.

Furthermore, selenium is a fundamental trace element of the body and possesses powerful anti-cancer effects. But modern agriculture and alimentary habits have dramatically decreased the daily input of selenium from the diet. Selenium is essential for the enzymatic reaction responsible for the synthesis of glutathione, a powerful physiological molecule which constantly protects the body from oxidative damage. A lack of selenium will thus result in a loss of the detoxification capacity of the body, immunodepression and onset of degenerative diseases and cancer¹⁰. This is the reason why TI-MELatonin® combines, (in a unique synergistic combination), the three fundamental anti-aging molecules of melatonin, zinc and selenium. Whilst melatonin plays the master role for reactivation and restoration of its natural night peak to juvenile levels, (this resulting into normalization of all measurable immunological and endocrine functions in the course of aging), the positive age-postponing, metabolic and immunological effects of TI-MELatonin® can be measured easily by anybody with a normal periodic check-up! These restoring metabolic changes will become progressively more visible and remarkable over the course of years, after initiation of the treatment with TI-MELatonin®.

Further studies are now in progress and they will allow us to progressively add more elements suitable to further improve and accelerate the rejuvenizing effects of nocturnal melatonin. But the "programme of aging" can be slowed down now to a more acceptable rate with regular nocturnal use of TI-MELatonin®.

TI-MELatonin®: Composition of active components in each tablet

Melatonin (N-acetyl-5-methoxytryptamine), 3mg, synthetic, certified purity: (99.9 % (HPLC), Zinc-*orotate* x 2H₂O, 50mg corresponding to 8.7mg zinc. Selenium, 50mcg, from sodium selenite pentahydrate. TI-MELatonin® is produced in Switzerland in compliance with the severe international rules of Good Manufacturing Practise (GMP) and under licence of Swiss Health Authorities.

Contraindications and general suggestions

TI-MELatonin® should not be given to healthy children, pregnant women and lactating mothers unless specifically prescribed by a physician. There is no evidence that TI-MELatonin® could adversely influence the effects and activity of estrogens. On the contrary, melatonin increases the density of estrogen receptors in sensitive target tissues (mammary gland, womb, ovaries, etc.) and greatly improves their actions. There are no contraindications for dietary supplements containing melatonin, zinc and selenium. No ascertained, life-threatening, acute or moderate, short- or long-term side-effects have been scientifically demonstrated or reported.

Melatonin must be taken late in the evening at bedtime in order to mimic and restore the physiological night peak, which normally declines progressively during the course of aging. As mentioned in the literature reported above, the progressive abrogation of melatonin night-cyclicity during aging is considered to be a basic signal expressing the extinction of the most fundamental regulatory system in the body. This brain "clock" is genetically and evolutionary linked to the sun, the planetary system and the obvious dependence of our health from daily and nocturnal, rhythmic cyclicity. Every person expresses their own genetically inherited nocturnal peak of melatonin, with very large individual variability. However, in the majority of the population, the night elevation of melatonin declines and most of us become "flat" after 80 years of age. This is a basic aging message from the "clock" 11.

The dosage of melatonin is still rather empirical and based on animal and human studies. The blood night level generated by 3mg by far exceeds the normal night levels of healthy young persons. However, melatonin is rapidly metabolized and excreted by the kidneys with no consequences.

Use of beta-blockers in the evening may abrogate the night peak of melatonin. If they must be taken, it may be necessary to take them in the morning or to increase the dosage of melatonin. Circadian, night melatonin seems to produce a resynchronization of the entire neuroendocrine system and will certainly improve metabolic and hormonal

functions, including blood pressure, cholesterol levels, thyroid, gonadal and adrenal functions. These effects can be easily evaluated with a routine check-up. Melatonin will counteract the negative side-effects of corticosteroids and of di-stressful agents, thus protecting the immune system. Melatonin does not induce sleep but facilitates its onset and produces a sleep pattern which is typical of children or young persons. It greatly improves the quality of sleep and its restoring physical and psychological effects, with a clear improvement of morning mood and body muscle strength.

Melatonin is not a drug and it is not itself a cure for any disease! Melatonin is ubiquitous in nature, cells, plants, animals, tissues and any living organism. Milk, vegetables, cereals, rice, meat, etc., contain variable amounts of melatonin. Synthetic melatonin could be theoretically replaced by alimentary melatonin in the daily food, but its replacement would be problematic and difficult to achieve for everybody.

Melatonin produced by the pineal gland seems to be responsible for the night peak, while melatonin produced by the gut and the retina does not seem to affect the nocturnal levels. It is thus evident that the night peak of melatonin initiates a sequence of positive effects with a cascade of events which maintain the body systems synchronized with the physiological cyclicity of hormones and cells. This night "signal" is essential for the maintenance of immunity and the "surveillance" against the onset of tumors. Therefore melatonin is a fundamental element for prevention of aging-related diseases, including cancer, autoimmune and cardiovascular diseases. Melatonin cannot be considered a classical "hormone," although it is so-named. It does not possess any of the qualities of the classical hormones like growth hormone, cortisol, estrogens, thyroid hormones etc. It is rather a chemical mediator whose mechanism is still unknown. It modulates and controls the synthesis and secretion of all hormones within a circadian and seasonal periodicity and variability. It has been given at a huge dosage of grams daily for prolonged periods, and to 1500 women at the daily dosage of 300mg for years with no observed late side-effects and consequences. The administration of melatonin to restore the physiological adaptation of the body to circadian and seasonal periodicity is only the beginning of a new medicine based on the concept that nobody can escape the established laws of Nature within the solar-planetary system, in which man developed as a mammalian species. We must be able to restore and correct the derangements of this adaptation system and maintain it in its original juvenile conditions. These metabolic conditions can be perfectly measured and maintained under balance, not with a cumbersome and complex hormonal supplementation (e.g. testosterone, growth hormone, pregnenolone, etc.), but with a correction of the central regulatory system located in the "pineal complex" (pineal gland and the many anatomical and functional connections in the brain and the neuroendocrine-immune systems).

TI-Melatonin® is perfectly suitable to re-synchronize all neuroendocrine functions. TI-Melatonin® contains basic elements which will synergize in order to obtain more rapid effects and to compensate the loss of fundamental minerals, due to a wrong diet or to aging. The beneficial effects of melatonin in the normalization of zinc levels have been scientifically proven and constitute a basic tool for maintenance of hormonal and immune functions and to restore these functions during aging.

Common agents which antagonize synthesis and secretion of melatonin

Alcohol, corticosteroids, beta-blockers (especially in the evening), caffeine, nicotine and many chemical substances with pharmacological activity can antagonize the synthesis and secretion of Melatonin. But melatonin does not itself antagonize the activity of any drug and can be used in combination with any medical drug and pharmaceutical speciality. Nocturnal melatonin will in-fact improve the effectiveness and activity of drugs as a consequence of its synchronizing properties on the entire neuroendocrine and immune systems.

TI-MELatonin®: Suggested daily dosages as a dietary supplement

Between 40 and 50 years of age: 1.5mg to 3mg at bedtime (peremptorily at the same hour, with half an hour tolerance). After 50 years until 75 years of age: 3mg at bedtime- as above. From 75 years of age: 3-6mg at bedtime- as above.

Although not mandatory, it is indicated to take TI-MELatonin® for 5 months in summer (May-June-July-August-September) and for 5 months in winter (November-December-January-February-March). TI-MELatonin® can be safely taken without intervals after 50 years of age, in the presence of chronic, degenerative diseases and cancer, or as a protective agent under stressful conditions (night-work, exposition to poisons and noxious agents, time-zone travel etc.).

It is strongly recommended to take TI-MELatonin® for periods of weeks before and after surgical interventions to ameliorate general conditions (mood, immunity, etc.) and to accelerate immunological reconstitution, wound healing, tissue regeneration and recovery from anesthesia toxicity after the operation.

For jet-lag we suggest taking 3mg of TI-MELatonin® for four to five days at 10-11 PM, local time, on arrival at the place of destination and to repeat the same procedure after returning to the original place of departure.

Key-words (42)

Aging, andropause, anti-oxidant, autoimmunity, biorhythms, brain ischemia, cancer, cholesterol, cholangitis, coronary and cardiovascular diseases, depression, dietary supplement, eye diseases, fertility, heart infarction, hepatitis, humour, hypertension, immunity, insomnia, jetlag, libido, medical food, melatonin, menopause, multiple sclerosis, natural molecules, nervousness, osteoporosis, parkinson, pineal gland, prostata, selenium, senescence, sex power, sleep, stress, surgery, thyroid diseases, ti-melatonin, Walter Pierpaoli, zinc.

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Last Updated: Wednesday, February 20, 2002

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