

HEALTH AND STRESS

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MELATONIN MANIA

I have had to repeatedly update this Editorial because of the unprecedented plethora of publicity and propaganda pouring in from the popular press for the past few months. Melatonin mania is rampant, with sales exceeding all other supplements, including vitamin C, which itself increased 60% in 1994. The demand for the "Wonder Drug" here and abroad produced a global shortage, as many started to hoard it. Stores couldn't get enough of it, limited purchases, and advertised as soon as a new shipment came in. Much of the craze followed the publication of *Melatonin: Nature's Sleeping Pill*, and *The Melatonin Miracle*, claiming that melatonin could delay aging, combat cancer and other diseases, prolong or restore sexual vitality, and cure jet lag and insomnia. They were quickly followed by *Stay Young the Melatonin Way*, *Melatonin: Your Body's Natural Wonder Drug*, and *Melatonin: The Anti-Aging Hormone*. There have also been numerous magazine, TV, and other media promotions, predicting benefits for patients with Alzheimer's and Parkinson's disease, and other age related disorders.

Most stores sold out shortly after *Newsweek's* November 6 cover story. One melatonin marketer alone projected sales of more than 7 million bottles in 1995. Advertisements proclaimed that "Nightly melatonin supplement can boost the performance of immune systems compromised by age, drugs, or stress.", "it can slow the growth of tumor cells", or "control cholesterol, regulate blood pressure and modulate the release of heart-killing stress hormones". Although one correctly warned, "There is no assurance that you will have any beneficial effect from melatonin. We make no guarantees.", this was immediately followed by, "The only promise is: a good night's sleep, complete with dreams of a rip-roaring 105th birthday party."

All of this is quite amazing since there are few human studies that confirm most of these claims, and no information on the benefits or hazards of long term use in humans.

The Dracula Hormone

Since melatonin secretion occurs almost entirely at night, it has been referred to as "The Dracula Hormone", or "The Hormone of Darkness". The first clue of its presence came in 1958, when scientists noted that pineal secretions affected the melanin pigmentation of tadpoles. Others found that it could also speed up the metamorphosis of tadpoles into

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frogs. In 1963, melatonin was identified as a human hormone, and subsequent studies suggested that it was closely involved in circadian rhythms, or biological cycles like sleep, that tend to recur at 24 hour intervals. It was also found to be important for seasonal rhythms that affect sexual and behavioral habits. One example is seasonal affective disorder, where individuals become depressed and unusually sleepy, and experience carbohydrate craving and weight gain as the shorter days of winter approach.

Melatonin secretion rises during darkness and is suppressed by bright light. High levels cause drowsiness, which is why most of us get sleepy at night. They fall progressively as we get older, which may explain why almost half the population over the age of 50 have some sort of sleep problem. Insomnia is a common complaint in the elderly, probably because they tend to have the lowest levels of melatonin. About ten years ago, researchers wondered whether giving melatonin might simulate the soporific effects of darkness, or change the timing and rhythm of sleep cycles. By administering very small amounts between 3 and 6 P.M., they found that it could help some insomniacs to fall asleep around 10 or 11 P.M. instead of tossing around in bed until 2 or 3 A.M.

In humans, melatonin is manufactured almost entirely in the pineal gland. Its precursor is tryptophan, an amino acid which is a building block for serotonin. Serotonin is stored during the day, but with the onset of darkness, it is converted by enzymes into melatonin. The pineal has a very rich blood supply, and melatonin is readily released directly into the circulation as well as the spinal fluid. It is extremely soluble in fats and lipids, which is why it reaches such high concentrations in the brain, and diffuses so readily across cell membranes. How it exerts its various neuroendocrine and behavioral effects is still not clearly understood. Unlike other neurotransmitters and hormones, there do not seem to be specific receptors or target glands that account for this.

Under normal circumstances, levels of melatonin vary in a circadian rhythm, and concentrations are ten times higher at night than during the day. There are also seasonal changes which affect the magnitude of this dark-light ratio, and there is a marked decrease of up to 75% of nocturnal secretion just prior to and during puberty. It is believed that these variations allow melatonin to send signals that control both the timing of daily and seasonal rhythms. It also has significant hormonal effects on gonadal function in both sexes.

Why All The Hype?

Most of the current melatonin madness stems from animal studies by Walter Pierpaoli, an Italian researcher interested in aging, and co-author of *The Melatonin Miracle*. He found that nightly spiking of their drinking water with melatonin could prolong the life of elderly experimental animals by 25 per cent. Based on Russian research, he devised an experiment in which the pineal glands from 3-4 month old mice were grafted into 20 month old recipients of the same species. Compared to their litter mates, these aged animals with the youthful pineals, who would be the equivalent of 60 to 70 year old humans, began to show signs of rejuvenation, evidence of improved immune system function, and their life spans were extended by 30 to 40 per cent.

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Conversely, when aged pineals were substituted in very young animals, they seemed to age more rapidly, and there was a 20% decrease in longevity. The most logical explanation for these observations appeared to be the increased secretion of melatonin by the youthful pineal glands. It also suggested that many manifestations of aging might be due to a lack of melatonin, and that correcting this might slow down certain signs and symptoms of old age, and prolong life. Extrapolating from these animal studies, Pierpaoli and his co-author, William Regelson, Professor of Medicine at the Medical College of Virginia, predicted that taking small amounts of melatonin every night might very well allow people to live 120 years or more! They describe it as "nature's age-reversing, disease-fighting, sex-enhancing hormone". Who could ask for anything more?

Dr. Ray Sahelian, author of *Melatonin: Nature's Sleeping Pill*, had recommended melatonin to a few dozen patients with sleeping problems, aged 20 to 85, and was impressed with the results. Four out of five reported that they fell asleep faster, and woke up much less frequently. Not surprisingly, their energy levels and moods the next day were also significantly improved. Around 15% didn't notice any significant benefits, and 5% stopped taking it because of vivid dreams or nightmares. He also surveyed more than 200 individuals taking melatonin for insomnia, and found a similar response pattern. Most reported experiencing a deep and sustained sleep, without the next day grogginess or rebound insomnia often seen with prescription sleeping pills.

However, the dose they took each evening ranged from .3 to 10 mg, a 30-fold variation. Some patients experienced headache or other disturbing side effects if they began with a dose that was fine for others, but apparently too much for them. It therefore seems advisable to start with .3 mg the first night, and to increase this by .5 mg every evening until the desired results are achieved, or a dose of 6 mg is reached. Taking more than 6 mg doesn't seem to provide any additional benefits. During this period of progressive increase in melatonin intake, most insomniacs will find that they can

gradually decrease their use of sleeping pills, and eventually no longer need them. In some instances, once normal sleeping patterns are established, melatonin may not be needed every evening. As with other sleeping medications, younger baby boomer insomniacs should probably take melatonin only occasionally, while older individuals may require it more frequently. Melatonin seems to be quite safe based on the information currently available. In some studies, researchers have given 50-75 mg daily, a dose that produces 1,000 to 1,500 times the normal blood levels, without noting any toxic effects. Nobody has ever died from an overdose, even with amounts as high 6,000 mg.

According to the jacket of, *Stay Young the Melatonin Way*, melatonin is "the most exciting medical breakthrough of our time!". Not only does this "miracle hormone" provide a sturdier immune system, lower cholesterol, better sex, better sleep, and protection from cancer, but also states that "doctors now believe that we can actually *reset our body clocks, and reverse the effects of aging*" [their italics]. When questioned during subsequent interviews, authors tended to be much more restrained, claiming that the publishers were responsible for most of the hype, and they had little control over this. With respect to the sexual enhancement claim, Regelson also conceded, "We don't know whether what we've observed in animal studies, transfers directly to humans."

There can be little doubt that the leading expert in the field is Dr. Russel J. Reiter, Professor of Neuroendocrinology at the University of Texas. He has been studying melatonin for thirty years, and takes a dim view of some of these extravagant claims. As he points out, "there's a big difference between delaying aging and reversing it. It's not going to make a 60-year old into a 30-year-old." He also doubts that it will prove to be an aphrodisiac, noting, "I certainly don't think it will improve anybody's sex life or enhance orgasms or anything like that... if you get over your jet lag on the second day instead of the seventh and you feel better, so you're more interested in sex, well, I guess that's an indirect connection." He agrees that melatonin is safe, "The greatest danger to someone taking mela-

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tonin, is driving to the corner store to buy it", but believes that everyone should check with their physician. Health warnings could change.

Russ is a good friend, a member of the Board of Trustees of The American Institute of Stress, and has regularly reported on his research at our annual International Montreux Congress on Stress. He is a staunch, dyed-in-the-wool Texan, and starts every lecture off with a beautifully colored slide of the Seal of Texas, that completely fills the screen for at least a minute, just to let you know he is proud of where he comes from. Although he is totally devoid of any other of the braggadocio characteristics often associated with denizens of that great state, he is extremely enthusiastic about melatonin's potential, and takes it himself. That's important, since he is a very cautious and careful investigator.

His expertise is in cellular biology, and he has conducted a wide range of experiments. In one of these, he found that when he injected rats with a cancer-causing agent, those who were receiving melatonin had much less disruption of their DNA. In his first presentation at our Congress, he showed how melatonin could be suppressed not only by bright light, but also non-visible electromagnetic radiation, and that melatonin could protect against radiation induced chromosomal damage. This might have important implications for the current debate concerning the possibility that exposure to high power lines or cellular telephones could cause cancer. More recently, he has demonstrated that melatonin is five times more potent than anything else as a scavenger for the hydroxyl radical. It also enhances the activity of other protective natural antioxidants. This is the most toxic of all the oxygen free radicals, because it particularly damages vital brain and nervous system components. Many believe it plays an important role in Alzheimer's and Parkinson's disease, and other neurologic disorders.

Italian investigators have also reported that melatonin can restore the immune system deficiency seen in aged mice, and prevent the lowering of immune system defenses caused by immunosuppressant drugs, raising speculation that it might benefit some patients with AIDS.

Concerns About Melatonin

Most scientists concede that melatonin is probably quite safe, but believe that since it is a hormone, it should probably be subjected to the same scrutiny the FDA requires for these and all biologically active substances. Some animal studies show that supplemental melatonin administration decreases serotonin, which could be important for some patients. Serotonin is low in some types of depression, as well as other psychiatric and emotional disorders. One human study suggests that high doses of melatonin may worsen depression. There is little information about the effects of melatonin on the actions of serotonin reuptake inhibitors, like Prozac, which are used to treat depression and an increasing number of other complaints. We don't know about its possible interactions with other widely used drugs, or how it could affect pregnancy, lactation, and puberty.

There could also be problems with quality control, since while some products are synthesized, others are extracted from animal material. There is no federal control over the production process, because melatonin is sold as a dietary supplement. Therefore, manufacturers don't have to prove that it is either safe or effective. This could have disastrous consequences, as was experienced with tryptophan. This amino acid had long been a very popular dietary supplement sleeping aid, probably because it is the precursor of melatonin. Several years ago, at least 1500 people developed eosinophilic myalgia syndrome, a very rare disorder. There were over twenty deaths, and many others suffered permanent neurologic damage. Authorities were puzzled for months, since this occurred over a relatively short time period, until it was finally determined that the problem was due to batches of tryptophan that had been contaminated during their production. There was a public warning, all products were recalled, and it can now be obtained only by prescription.

Melatonin is also not regulated as a drug because the companies that produce it are very careful not to make any health claims. The information on one bottle, simply states that it "keeps the body in rhythm with the day and the season. The body

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naturally releases melatonin in response to changes in light, with melatonin levels rising at night. It is in this way that melatonin helps promote sleep.*” The asterisk refers to the following disclaimer: “This statement has not been evaluated by the Food and Drug Administration, this product is not intended to diagnose, treat, cure, or prevent any disease.” If they did claim that melatonin could be used to “treat” insomnia, instead of “helps promote sleep”, it would immediately have to be classified as a drug, and subjected to the usual rigorous FDA standards for proof of efficacy and safety. This would cost millions and take years.

The FDA regulates what can appear on the label, which does advise consulting a physician if you are taking any tranquilizers or sedatives, have an autoimmune or depressive disorder, and are pregnant or lactating. It emphasizes that it should be kept out of reach of children, and should not be administered to anyone under 12 years of age. The Federal Trade Commission (FTC) has jurisdiction over promotional advertising, but as noted above, there are ways to get around this by saying “promotes” sleep, rather than “prevents” or “treats” insomnia. In addition, there is no control over what store owners or the media might claim. To date, there have been relatively few adverse reactions reported, although this is not surprising, since most physicians do not prescribe dietary supplements other than vitamins, and are generally unaware of over the counter products being taken by their patients.

It is quite obvious that considerably more research in humans must be done, particularly with respect to long term studies. These are usually funded by pharmaceutical companies as part of the protocol required for FDA approval. But there is little incentive for them to do this for melatonin, because it is unlikely that they could apply for patents that would guarantee any commercial reward. Although federal research funding has been sharply curtailed, and there are other pressing priorities, the National Institutes of Health (NIH) is very interested in safety issues, and clinical indications. They currently support about 134 projects related to melatonin, and about 20% of these are

from the National Institute of Aging (NIA) to study its effects on sleep. They have encouraged any research proposal that could provide information important to physicians and patients, since their goal is learning how to improve the health and quality of life of older individuals, and to make them more productive. Melatonin might help keep the elderly out of hospitals and nursing homes, and also save the economy vast sums of money in other ways.

The FDA and governmental agencies are frequently criticized, but have been of great assistance in at least one previous similar situation. In 1987, a paper in the *New England Journal of Medicine* described a substance that was highly effective in reversing the symptoms of Alzheimer’s disease in 17 out of 18 patients. As it was in the common domain, drug companies could not obtain patents, and had little interest in funding further research. However, the NIH decided it was important to investigate this, and conducted the first major controlled clinical study. Researchers discovered that it was not as effective as reported in this most prestigious journal, and that it could also have unsuspected adverse affects on the liver. Nevertheless, it is now the only prescription medication that has been approved for the treatment of Alzheimer’s disease.

How Much Should You Take And Other Questions

When Richard Wurtman reported the first clinical studies in 1963 which identified melatonin as a hormone, he indicated that he had no idea what dosage to use. Based on animal studies, he decided that 240 mg would be appropriate. As he commented, although this made the people “verrry,verrrry sleepy”, it also gave them a hang-over the next day, and concluded that it would probably not be very useful as a sleeping pill. He recently reported that 1/800 of that dose, (.3 mg) could induce a restful sleep in many individuals without any side effects. The most widely available dose currently available, 3 mg, may be more than 10

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times the amount needed, and can actually cause insomnia in some people. Others may experience nightmares, headache and mental impairment, and according to one authority, affect the secretion of other hormones. Peak and low melatonin levels vary tremendously in apparently healthy people, from barely detectable, to concentrations 500 times the average. So how can you determine what dose is best for you, and when or how often it should be taken to promote sleep?

Following the administration of melatonin, its concentration in the blood stream reaches a peak in about 20 minutes, and then falls very rapidly, since it has a half-life of only 40 or 50 minutes. Therefore, it would presumably work best in those individuals who primarily have problems falling asleep. If your difficulty is that you wake up frequently and can't fall back to sleep, then you might need to take a much higher dose before retiring, or repeated small doses to insure significant levels that are maintained throughout the night. Some researchers have used a sustained release 2 mg tablet with good results. It's also important to emphasize that sleep problems may be due to many things other than melatonin deficiency. Chronic pain, shortness of breath, and urinary or gastrointestinal disorders are particularly common in the elderly, who are the prime candidates for melatonin. Drugs that cause sweating, itching or urinary frequency may also contribute to lack of sleep, and it is doubtful that melatonin would be very effective in such situations. On the other hand, benzodiazepines, the most common sleeping pills, and beta blockers, widely used for hypertension and heart disease, may inhibit melatonin synthesis and secretion, so it might prove helpful in promoting sleep in these patients.

There must be some reason why one third of our life is devoted to sleep, and while everyone agrees that sleep is very important, nobody seems to know why. The usual answer is that "you need time to recharge your batteries". But exactly how much sleep is optimal for each of us? It has been shown that sleep helps to improve immune system defenses against infection, but what is the minimum amount required to achieve this? There seems to be a great deal of individual variation, and some stud-

ies suggest that it is healthier to take a nap during the day, and perhaps sleep less at night. It has been proposed that one of the major purposes of sleep might be to allow melatonin to be produced, in order to neutralize free radicals that are so damaging to the immune and central nervous systems, and accelerate aging. These harbingers of havoc are the product of increased metabolic activities resulting from exertion and eating, or exposure to sunlight, environmental contaminants, and stress. But since all of these occur during the day, why should a powerful antidote like melatonin only be secreted while you are restfully sleeping at night? Perhaps the primary purpose of sleep may be to neutralize free radicals that have been generated during the day, and instead of charging our batteries, we are really putting out lots of little fires.

Melatonin rhythms are disrupted or delayed during the winter months, when there is less light, and are thought to be particularly disturbed in patients with Seasonal Affective Disorder, appropriately referred to as SAD syndrome. If SAD is due to this phase delay, some suggest that taking melatonin at specific times could help. On the other hand, since melatonin secretion increases in the winter, when SAD patients are most depressed, it might make this and other symptoms worse. Melatonin is high during childhood, starts a steady but slow decline after puberty, but like dehydroepiandrosterone (DHEA), tends to plummet after the fourth decade. In the great scheme of things, there must be some purposeful explanation for this. The body has its own wisdom, and the notion that artificially correcting such deficits in the elderly is always desirable, may be erroneous. Perhaps a concoction of these and other anti-aging antidotes will prove to be a modern fountain of youth, as suggested by Stewart Wolf's presentation at our 1996 Congress.

However, it is not likely that improved sexual prowess will prove to be one of these rewards. While Pierpaoli and Regelson reported this in mice, they never measured melatonin levels in their experiments to see if there was some correlation. More importantly, the particular strains of mice they used may not produce melatonin. Mice are not

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men, and there is a marked difference in response to melatonin in different experimental animals. Syrian hamsters gain weight, but Siberian hamsters lose weight. We really don't know very much about the pineal, and it may have been something else that these transplanted pineals were secreting. The Russians have isolated a pineal peptide they call epithalamin, but nobody seems to know what it is or what it does. Thyrotropin releasing hormone is also concentrated in the pineal, and there is preliminary evidence that pineal secretions could produce some of their effects by influencing thyroid function.

What Do We Really Know?

There seems to be little doubt that melatonin can be extremely helpful for many people suffering from insomnia, particularly the elderly. Israeli scientists were able to demonstrate that elderly patients with the poorest sleeping habits also had the lowest melatonin levels. In 12 of these men and women who were around 75 years old, and hardly producing any melatonin, half received .3 mg and half received a placebo every night for three weeks. Following a washout period of one week when they received nothing, the groups were switched, and took either a placebo or melatonin for another three weeks. They wore devices that recorded their sleep patterns, and the results confirmed that those taking melatonin fell asleep more quickly, and also slept 10% longer. In another placebo double blind study, .3 to 1 mg of melatonin induced sleep within one or two hours without any hangover. This was a healthy sleep pattern that preserved normal REM activity. However, finding the optimal dose of melatonin is best determined by careful titration. You can accomplish this by taking .5 mg (half of a 1 mg tablet), and increasing the dose every evening or two by .5 mg, until you achieve the desired results. The authors of these best seller books personally take between .1 and 2 mg, and Russ Reiter has been taking 1 mg nightly for years. Nobody recommends that people under 40 should take melatonin.

There are now over 100 placebo controlled studies suggesting that melatonin can alleviate jet lag, but this is much more difficult to measure scientifically. In one survey of over 400 subjects,

half were significantly improved subjectively on both eastward and westward flights. In another study of 52 subjects flying from the UK to Australia or New Zealand, which crosses at least ten time zones, most felt better, but 17 noted no effect and 4 said they were worse. This may be due to the difficulty in determining the proper dose, and precisely when to give it, since individuals vary with respect to their requirements and circadian rhythms.

The theory is that taking melatonin at your bedtime's destination will reset your body clock. If you're going east and losing time, take .5 mg for a few days before the trip at the bedtime for the new time zone. That should not make you sleepy, but will help adjust your body clock to the change in time. For east-west flights, take the same dose in the morning to delay the dawn. Another method is to take 1 mg for every time zone you cross (up to 10 or 12 mg) at bedtime, after you have reached your destination. When you return home, you can also take it at bedtime for the first few nights. This helps to prevent the usual routine of waking up at 4:00 a.m. and being unable to get back to sleep after coming back from Europe. Not much has been published on the benefits of melatonin for shift workers. However, anecdotal reports suggest it improves sleep and increases alertness at work, if taken at the desired bedtime (6-7 a.m.) after a night shift. Melatonin is generally not recommended for blind people, since its effects have not been carefully studied, but it may be useful in the free running sleep-wake cycles that trouble some individuals.

What Are The Possibilities?

There appears to be no limit. One researcher has invented a birth control pill that suppresses ovulation with 75 mg of melatonin, and also contains progesterone. It has been used in 1500 women for three years, with a success rate similar to standard oral contraceptives. There has been no water retention, loss of libido, or other significant side effects, and it also appears to relieve premenstrual tension. Despite the astronomical doses, there has been very little excess sleepiness. Another pill in the pipeline for postmenopausal women contains estrogen and melatonin, since this could reduce the

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likelihood of malignancy. Melatonin greatly enhances estrogen activities, so it is possible to use a much lower dosage of estrogen and reduce side effects. A study in China suggests it may prevent or improve macular degeneration. Early human trials in Italy claim that it slows the progression of far advanced cancer. In another recent report of 2 patients with sarcoidosis unresponsive to conventional therapy, lung and skin lesions disappeared on 20 mg/day, returned when melatonin was stopped, and regressed when it was resumed. As noted previously, there is good reason to suspect that melatonin might provide benefits for patients with AIDS, Alzheimer's, Parkinson's, Lou Gherig's disease, and other disorders for which there is no effective treatment. But we will never find out, unless the proper research is done. The major purpose of Russ Reiter's book, *Melatonin: Your Body's Natural Wonder Drug*, was to present a scientific approach, rather than one which was mostly speculative, or created unrealistic hopes because of the sensationalism generated by promotional advertising. Another goal was to generate greater interest in melatonin, so that the studies necessary to explore its intriguing potential could be funded.

The pineal, which Descartes called "the seat of the soul", may contain other important chemical messengers, and have other purposes. We will report on this in a subsequent Newsletter. Stay tuned.

Paul J. Rosch, M.D.

Editor

Book Review

Chronic Diseases, Stein, M., Baum, D., (eds.), Lawrence Erlbaum Associates, Mahwah, 1995. 303 pages, \$69.95.

During the past century, the major causes of death have shifted from infectious diseases that we could not control, to chronic disorders associated with the aging process. Many of these are often stress related, and all of them are significant sources of stress, not only to those afflicted, but also family, friends, and care givers. Several studies have shown that stress reduction strategies can remarkably reduce such problems. In some instances, such as certain cancers and coronary heart disease, reducing stress can also favorably influence the course of the illness.

The meaty book contains 15 chapters, and is divided into four sections. The first discusses the psychological and neurological aspects of chronic illness, with an emphasis on Alzheimer's Disease and AIDS. Section II, Stress and Psychosocial Aspects of Chronic Illness, contains chapters on what we can learn from models of stress in monkeys and other primates, and the role of psychosocial stress in herpes virus reactivation, but concentrates primarily on AIDS and cancer. Section III, Human Sexuality and Disease, reviews behaviors that contribute to sexually transmitted diseases, again with an emphasis on HIV/AIDS, and particularly the problems encountered in minority groups.

The last section provides a thorough analysis of possible mechanisms of action, based on recent advances in psychoneuroimmunology. The final chapter, which is written by the senior author, outlines the complex interactions between stress and the hypothalamic-pituitary-adrenal axis, and points to areas where future advances are most likely to take place.

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