Evidence That Melatonin Is An Anti-Aging Therapy

Recently, there's been an explosion of research studies on melatonin, which have generated an enormous amount of evidence in support of **Dr. Rozencwaig's** theory that melatonin plays a critical role in aging. The findings of these studies have uncovered several potential mechanisms of action to explain how melatonin affects aging and the diseases of aging.

The first and most basic piece of evidence that implicates melatonin in aging is that the production melatonin by the pineal gland (see page 2) falls drastically with advancing age. The startling age-related decline in melatonin levels in humans has been shown by scientists such as N.P.V. Nair of McGill University in Montreal and Russel J. Reiter of the University of Texas Health Science Center in San Antonio.

The data indicate that peak night-time levels of melatonin in humans are about twice as high in young people (21-25 years) than in middle aged people (51-55 years), and about four times as high in young people than in old people (82-86 years). The 24-hour secretion of plasma melatonin has been shown to be approximately twice as high in 20-year-old men and women as in 60-year-old men and women.

These findings suggest that the age-related depletion of melatonin may be a cause of the deficits and diseases associated with aging.

The Super Antioxidant

Dr. Denham Harman of the University of Nebraska in Omaha is the originator of the free radical theory of aging. Free radicals are molecules containing an unpaired electron in their outermost orbital ring, which makes them extremely reactive and short-lived. The interaction of oxygen and other chemicals is the primary source of free radicals within our bodies. In the past 50 years, there has been a huge, rapidly growing body of evidence linking uncontrolled free radical activity to aging and the degenerative diseases of aging.

Over the years, free radical scientists have identified a number of substances (called antioxidants) that counteract the damaging effects of excessive free radical activity. Among these are the enzymes **superoxide dismutase, glutathione peroxidase,** and **catalase,** and compounds such as **glutathione, vitamin E, vitamin C, selenium cysteine** and **methionine,** and **uric acid.** Scientists have also found antioxidant properties in drugs such **as deprenyl, hydergine,** and **centrophenoxine.**

A Better Hydroxyl Scavenger Than Glutathione

The knowledge that melatonin is one of the body's own natural antioxidants is of very recent vintage. It was first proposed in 1990 and experimental evidence of melatonin's antioxidant powers has only emerged since that time.

One series of experiments showing that melatonin is a highly potent antioxidant was conducted in Dr. Reiter's lab. In one study, the carcinogen, safrole, was administered to rats, either alone or in combination with melatonin. Safrole causes nucleic acid damage in DNA via the production of oxygen radicals.

The result of the study was that melatonin almost totally knocked out the DNA-damaging effect of safrole. The amount of DNA damaged by safrole (300 mg/kg) was reduced by 41% even when the dose of safrole administered was 1,500 times greater than the dose of melatonin (0.2 mg/kg). When the dose of melatonin (0.4 mg/kg) was doubled (but still 750 times less than that of safrole), DNA damage was reduced by 99%!

In an in vitro study, melatonin very significantly" reduced highly reactive hydroxyl (OH) radicals generated by ionizing radiation.

In another in vitro study, **melatonin's** ability as a free radical scavenger was compared to **mannitol** and **glutathione,** the most effective hydroxyl radical scavengers tested to that point. The concentrations of **melatonin, glutathione,** and **mannitol** required to reduce hydroxyl radical activity by 50% were, 21, 123, and 238 microns/M respectively. Thus, **melatonin was shown to be 5.9 times more effective than glutathione and 11.3 times more effective than mannitol in fighting hydroxyl radicals!**

The Dangerous Hydroxyl Radical

The uncontrolled action of hydroxyl radicals — the most damaging free radical by far — can have devastating effects within the body. The hydroxyl radical is a third generation species of radical which is derived from hydrogen peroxide (H^2O^2), which, in turn, is derived from the superoxide radical through the action of the enzyme superoxide dismutase.

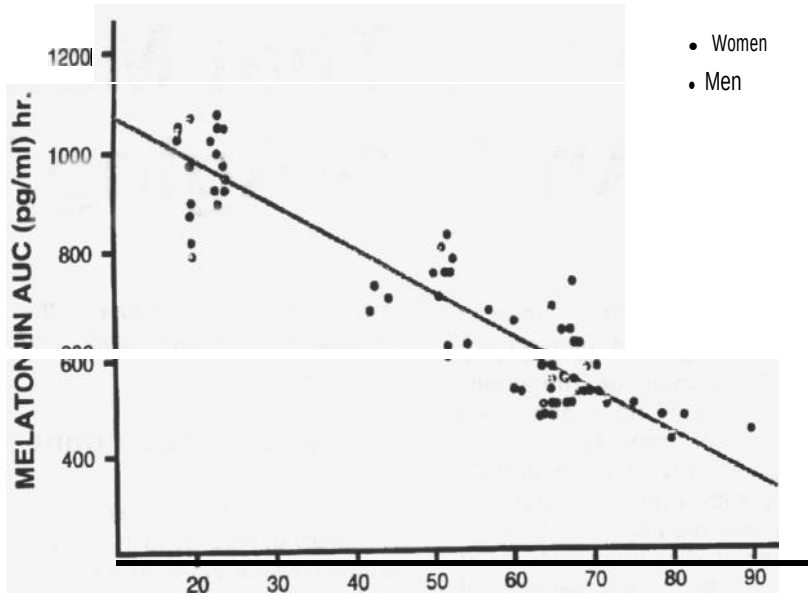


FIGURE 1

Correlation between age and 24-hour secretion of melatonin.

Hydrogen peroxide is reduced to hydroxyl radicals by the enzymes glutathione peroxidase and catalase in the presence of transition metals such as iron or copper. The dangers of the hydroxyl radical has been highlighted by Dr. Reiter:

"If the function of radicals is to destroy molecules and tissues, then the hydroxyl radical would be the radical's radical. It reacts at diffusion rates with virtually any molecule found in its path including macromolecules such as DNA, membrane lipids, proteins, and carbohydrates. In terms of DNA, the hydroxyl radical can induce strand breaks as well as chemical changes in the deoxyribose and in the purine and pyrimidine bases."

"Damaged proteins, many of them crucial enzymes in neurons, lose their efficiency and cellular function wanes. Protein oxidation in many tissues, including the brain, has been proposed as an explanation for the functional deficits associated with aging."

The fact that melatonin is so much better at scavenging hydroxyl radicals than any other antioxidant is persuasive evidence that melatonin protects us against a wide variety of

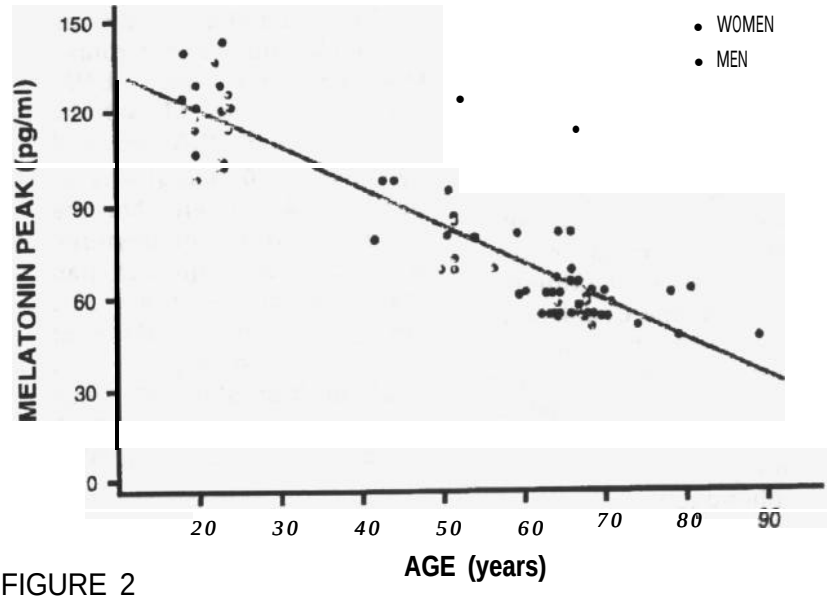


FIGURE 2

Correlation between age and peak levels of plasma melatonin.

diseases and that its progressive depletion with advancing age contributes to aging and the diseases and disabilities associated with aging.

Vitamin E As A Lipid Antioxidant

One of the byproducts of the clash between hydroxyl radicals and polyunsaturated acids (PUFA) derived from vegetable oils is the peroxyl radical (ROO.), which attacks enzymes, receptors, and other structures found in cell membranes. These radicals initiate a chain reaction within cell membranes called lipid peroxidation, which also takes place under the influence of **iron** and **copper.**

Until recently, it was thought that **vitamin E,** which is found in abundance within cell membranes, is the most important scavenger of lipid peroxides in the body. **Vitamin E** is a chain-breaking antioxidant that throws a monkey wrench into the lipid peroxidation process. What makes **vitamin E** an especially potent lipid anti-oxidant is that it can be recharged by **vitamin C** for additional antioxidant work before it degrades.

The critical importance of **vitamin E** for good brain function is evidenced by observations that patients with prolonged **vitamin E** deficiency due to fat absorption problems suffer from neurologic deficits. It is also true that adding **vitamin E** to neurons in tissue culture promotes the growth of neurites and the survival of the cell. A preliminary study of **vitamin E / vitamin C therapy** is being conducted in Parkinson's disease patients, but the results are not in yet.

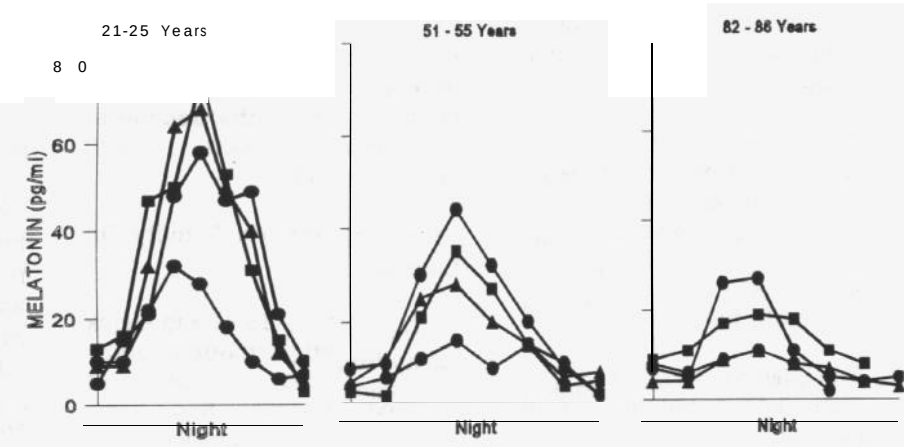


FIGURE 3
Nighttime melatonin levels in four individuals each in three different age groups.

A Better Lipid Antioxidant Than Vitamin E

As good as **vitamin E** is in fighting lipid peroxidation in the brain and other areas of the body, it appears as if **melatonin** is much better. A recent study showed that **melatonin is twice as good a scavenger of the peroxyl radical than vitamin E!**

The reason melatonin is a better lipid antioxidant than **vitamin E** is because **melatonin counteracts lipid peroxidation by preventing the initiation of the process as well as by breaking the lipid peroxide chain reaction** (which is the only method by which **vitamin E** acts).

Melatonin is thus the only antioxidant that has dual lipid antioxidant action in addition to its action as a hydroxyl radical scavenger!

Finally, there is evidence that **nitric oxide** may play an important role in causing damaging free radical reactions, and that melatonin is a potent inhibitor of **nitric oxide.**

The Total Body Antioxidant

To top it all off, melatonin is the only antioxidant that functions throughout our entire body... in every cell and in every part of every cell and in every bodily fluid. Melatonin is a non-toxic, natural hormone produced within the body that requires no binding sites or receptors to act. Melatonin is a small molecule that is highly diffusible and crosses every internal barrier within the body easily, including the blood-brain barrier.

Guardian Of The Brain

Because of melatonin's ability to cross the blood-brain barrier and penetrate into every type of cell, organelle, and membrane, as well as its extraordinary antioxidant properties, it is now becoming clear that melatonin may protect the brain better than any other substance in the body, and that the precipitous loss of melatonin with advancing age has especially serious effects within the brain.

Melatonin is of critical importance in the brain for four reasons:

1. The brain has the highest amount of free radical activity in the body because it uses far more oxygen than any other part of the body in carrying out its diverse and demanding metabolic functions.

2. The brain has an exceptionally high iron content, which increases the number and virulence of its free radical reactions.

3. The brain is relatively deficient in antioxidant defense systems, in part because the blood-brain barrier restricts the entry into the brain of antioxidant compounds.

Melatonin Stimulates Glutathione Peroxidase Activity

In addition to its formidable powers as an antioxidant, **melatonin** also protects the brain by stimulating glutathione peroxidase (GSH-Px) in neural tissue. GSH-Px converts **reduced glutathione** to its oxidized form and in doing so converts **hydrogen peroxide from H^2O^2 to H^2O, (water),** which stops the generation of dangerous hydroxyl radicals in its tracks, thereby preventing cell degeneration and death.

The major flaw in our antioxidant defense system as we grow older is the age-related accumulation of **hydrogen peroxide.** The increase in **hydrogen peroxide** occurs because superoxide dismutase, the initial free-radical-deactivating enzyme produced within the body is increased without a concomitant increase in the other key enzymes, catalase and glutathione peroxidase. **These deficiencies appear to be due in large part to the decline in melatonin levels with advancing age!**

Effect Of GSH-Px Activity On Lifespan

The ability of GSH-Px to knock **out hydrogen peroxide** (thereby preventing the generation of hydroxyl radicals) has been shown to be significant in determining lifespan. A recent comparison between the short-lived house mouse (Mus musculus) and the long-lived white-footed mouse (Peromyscus leucopus) showed **much higher GSH-Px activity in the long-lived mouse and a much higher amount of oxidative damage in the short-lived mouse!**

A recent study by scientists at the University of Texas Health Science Center in San Antonio showed that the administration of melatonin caused **a two-fold rise in glutathione peroxide within 30 minutes** in laboratory rats. They also found that GSH-Px activity within the rat brain is higher at night than during the day, which correlates directly with melatonin levels in the brain.

How The Aging Clock Works

Melatonin is the pacemaker for the circadian rhythms that maintain our health, strength, and youthful vigor through the neuroendocrine and immunologic control of vital functions such as sleep, appetite, heart rate, blood pressure, temperature, movement, coordination, pain and pleasure, sexual function, reproduction, and protection against invading bacteria, viruses, chemicals, and radiation.

Melatonin is the clock that governs the actions of the hypothalamus region of the brain, which produces releasing factors that trigger the pituitary gland to release peptide hormones such as prolactin and growth hormone which, in turn, stimulate the release of thyroid hormones, adrenal hormones such as DHEA and cortisol, and steroid hormones from the testes and ovaries such as testosterone, estrogen, and progesterone.

The healthy functioning of this intricate system requires a synchronized, rhythmic, cascading ebb-and-flow involving highly sensitive interactions among the neurotransmitters, hormones, and enzymes that affect every organ and life system in the body. A good example of the circulatory cascading nature of the system is the fact that estrogen is produced by the ovaries after a long series of signals or messages starting in the brain. After its release, estrogen travels throughout the body to help maintain strength and vigor and, finally, ends up in the brain, where it helps to maintain memory and other cognitive functions in the process of starting the cycle over again.

Sending Messages From One Cell To Another

In governing this system, melatonin acts as a neurotransmitter to help control the activity of neurons in the central nervous system. It does so by sending chemical messages via cyclic nucleotides — such as cyclic AMP (cAMP) and cyclic GMP (cGMP) -which travel from one neuron to another

within the brain, spinal cord, and peripheral nerves.

Studies at the University of Milan in Italy have shown that one of melatonin's primary functions, in conjunction with **GABA (gaba-amino-butyric-acid),** is to inhibit the neuronal firing rate in the cortex of the brain in order to synchronize activity within the neuroendocrine system. **Excessive or uncontrolled brain cell activity can contribute to movement disorders as in Parkinson's Disease and cognitive disorders in Alzheimer's Disease. It can also contribute to the time-dependent declines of normal aging, which leads to progressive deterioration, culminating in the death of the organism. Taking 3-6 mg. of melatonin at night on a daily basis helps to resynchronize the clock, which slows aging and helps to prevent some of the diseases of aging.**

Melatonin Extends Lifespan

The sine qua non of anti-aging research is the ability of a therapy to extend maximum lifespan in animals (It's not practical to study this in humans). In this respect, **melatonin** is highly promising, but the lifespan studies conducted with **melatonin** to date have been few and have been limited in size. As a result, the findings of these studies are far from definitive. They leave certain questions unanswered, the resolution of which will require future research.

Joint Lifespan Studies

Melatonin lifespan studies have been conducted in three different strains of mice as a joint venture of **Walter Pierpaoli** of the University of Ancona in Italy and **William Regelson** of Virginia Commonwealth University in Richmond. Drs. Pierpaoli and Regelson have written a recently published book entitled **The Miracle Of Melatonin** (Simon and Schuster, 1995) in which they describe these experiments. The results were published in their scientific paper:

"Pineal control of aging: Effect of **melatonin and** pineal grafting on aging mice: in the **Proceedings of the National Academy Of Sciences, USA,** Vol. 91, pp. 787-791, January 1994 (see **Life Extension Abstracts** in this issue).

Two Types of Experiments

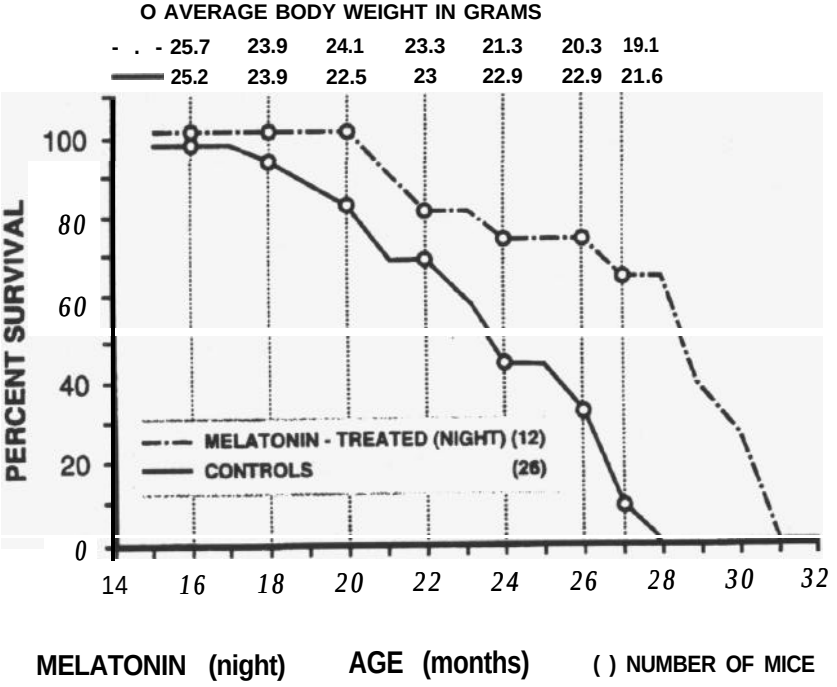
In these experiments, aging mice were given melatonin in their drinking water during a fixed circadian dark cycle, when melatonin is normally produced.

In a second set of experiments, the pineal gland, which is the body's prime source of melatonin, was transplanted from young (3-4 months) to old (16-22 months) mice.

In the transplant experiments, the pineal gland was not removed in the old mice. The site of the graft in the recipient mice was the thymus gland, which is believed to be similar to the pineal in its embryologic development.

Three strains of mice were used in these studies: BALB/c females; NZB females; and C57B/6 males, with the pineal transplants performed in the BALB/c and C57BL/6 females as well as in BALB/cJ-C57BL/6 hybrids. In the BALB/6 mice, melatonin administration was

Figure 4



Life prolongation in BALB/c female mice after nightly administration of melatonin.

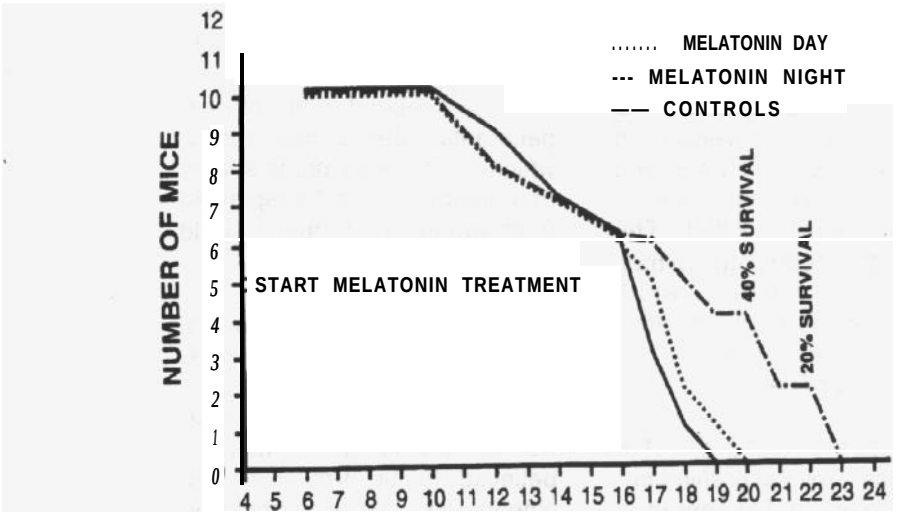


FIGURE S

Survival in New Zealand Blade (NZB) female mice given melatonin in their drinking water

started at 15 months of age with 12 experimental animals and 26 controls. In the NZB mice, melatonin was started at 5 months of age, with 10 experimental animals and 10 controls. In the C57BL/6 mice melatonin was started at 19 months of age, with 15 experimental animals and 20 controls.

Results Of Lifespan Studies

The results of these experiments demonstrated both median and maximum lifespan extension in all four experimental groups **(Figures 4-6, Table 1).** There were not significant differences in weight among any of the experimental and control groups, which rules out calorie restriction as the cause of the lifespan extension effects in these studies.

In the BALB/6 mice, the average survival of the control animals was 715 days compared to 843 days in the melatonin-treated mice. The median survival in controls was 23.8 months compared to 28.1 months in the melatonin-treated mice, and maximum survival in the controls was 28 months compared to 31 months in the melatonin animals.

In the **NZB** mice, maximum survival was 19 months in the control animals compared to 23 months in the melatonin-treated animals. The maximum survival in 10 NZB animals given melatonin during daylight hours was 20 months.

In the C57BL/6 mice, the melatonin-treated animals lived up to 6 months longer than the control animals.

The Pineal Transplants

Pineal glands from young (3-4 months) BALB/cJ female mice were transplanted onto the thymus glands of 3 22-month old BALB/cJ mice. Similar pineal transplants were put into 7 16-month-old C57BL/6 female mice as well as into 5 19-month-old BALB/cJ-C57BL/6 female hybrid mice. An identical number of control mice (of the same ages) from all three strains received similar transplants of pineal-sized, matched fragments of brain cortex tissue.

Results Of Transplant Studies

Every untreated control animal in all three groups was dead by 26 months of age, while at least one mouse in all three transplant groups was still alive at 31 months of age, and one hybrid mouse who received a pineal transplant survived until 33 months of age.

The three groups of aged mice receiving young pineal gland transplants lived 406 months longer than the control animals, which represents **a 17% increase in survival for the 16-month-old C57BL/6 mice, a 21% increase in survival for the 19-month-old hybrid mice, and a 27% increase in survival for the 22-month-old BALB/6 mice!**

In another experiment, 20-month-old C57BL/6 male mice receiving pineal transplants from 3-month-old donors lived 12% longer than controls.

Rejuvenation After Pineal Transplants

When autopsies were performed on the aged mice who had received young pineal glands, the scientists found striking rejuvenation effects in the organs of the transplant recipients.

The first evidence of rejuvenation in the transplant recipients was the pineal gland itself, which had normal, viable clusters of pinealocytes (pineal

gland cells) assembled within intact, youthful-looking structures.

Further evidence was the observations that both the thymus and thyroid glands had been rejuvenated in the experimental animals to a striking degree. After noting these effects, Pierpaoli and Regelson commented that:

"In the pineal-grafted animals, survival *data are reinforced by the apparent juvenile morphologic state of the thymus and thyroid and the immune status of recipients despite their age. The maintenance of thymic function is not surprising as melatonin and the pineal are known to enhance the immune response. This may we// delay the appearance of tumors and autoimmune disease as factors in age-related pathology...*

Thymic and thyroid morphologic restoration occurs at a time when the normal involution of age is demonstrable. Our exogenous use of circadian **melatonin** *and pineal engraftment of young pineals to the site of the thymus in aged mice suggests* that *there may be a firm relationship between the pineal, ifs products, and the thymus, providing a homeostatic control mechanism of significance for aging and survival."*

Questions About Lifespan Experiments

The most exciting finding of the Pierpaoli-Regelson lifespan experiments is that both **melatonin** and **pineal transplants** were able to achieve a significant prolongation of life and vigor, as well as organ rejuvenation in aging animals. Since most of us are already older than we'd like to be, it's encouraging to see evidence that a therapy can produce anti-aging and rejuvenation effects in middle-aged animals.

Can Melatonin Really Extend Maximum Lifespan?

Although the melatonin-treated animals in the Pierpaoli-Regelson experiments lived significantly longer than the control animals, the question of whether melatonin can extend *maximum* lifespan is still open to question none of the controls or the treated animals reached their maximum lifespan potential (MLP for the strain of mice under scrutiny.

In the case of the C57BL/6 mice, the MLP for untreated animals is about 40 months, but none of the melatonin treated animals lived beyond 29 months. In the case of the BALB/6 mice, the MLP is about 36 months, but none of the melatonin-treated animals lived beyond 31 months. And in the case of the NZB mice, the melatonin-treated animals did reach their MLP, but the strain itself has been genetically bred to die prematurely from autoimmune disease.

Larger Study Needed

However, the fact that most of the melatonin-treated animals failed to reach their maximum lifespan potential is not surprising because M L P represents the longest possible lifespan of a strain of mice under ideal living conditions, and its extremely rare for laboratory animals to come close to this ideal.

Since there were relatively few mice in the Pierpaoli-Regelson studies, and since their living conditions may not have been ideal, the results are far from definitive. What's needed is a larger study of the effects of melatonin on maximum lifespan in which the experimental animals are maintained under the best possible conditions. Such a study would help us learn a great deal more about melatonin's ability to slow aging and extend lifespan.

Other Pineal Hormones

Another unanswered question is whether other pineal hormones might add to melatonin's anti-aging effects. Since the animals receiving pineal transplants did even better than the melatonin-treated animals, in spite of the trauma of the operation, it seems reasonable that other hormones produced by the pineal gland may also be involved in aging in addition to melatonin.

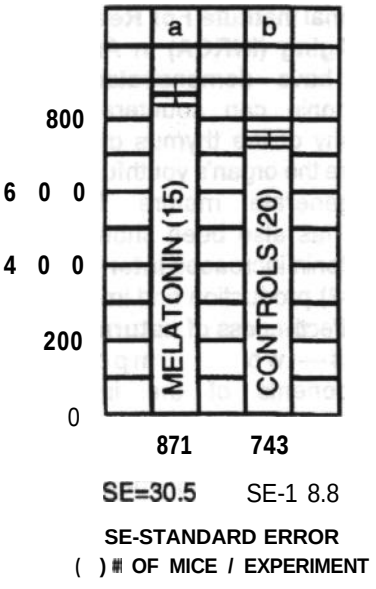


FIGURE 6

Survival in C57BL/6 male mice given melatonin at night beginning at 19 *months of age.*

At least one of these hormones - **epithalamine -** has been identified, characterized, and used in experiments (in Russia) to extend the lifespan of laboratory animals. It would be interesting to determine if the combination of melatonin and **epithalamine** extends lifespan more than just melatonin.

Melatonin Improves Immune Function

The pineal transplants showed that young pineal tissue could rejuvenate atrophied thymus glands in aging mice. Since the thymus is the master gland of immunity, this finding suggests that melatonin and other pineal hormones may be able to boost declining immune function in middle and old age animals.

Experiments In Italy

Further experiments at the **National Institute For Research On Aging (INRCA)** in Ancona, Italy have demonstrated that melatonin can counteract the atrophy of the thymus gland to restore the organ's youthful ability to generate mature T-cells.

It has also been shown that melatonin increases **interleukin-2** (IL-2) production and improves the effectiveness of **natural killer cells-two** important components of the immune system.

Among the mechanisms of action proposed for melatonin's immune-boosting effects have been that:

1. Melatonin has a direct stimulatory effect on immune system tissues;

2. Melatonin affects immune function indirectly through its effects on thyroid-stimulating hormone;

3. Melatonin influences zinc metabolism, which, in turn, plays a major role in strengthening immune function.

Links To Other Anti-Aging Therapies

Since melatonin plays such a central role in so many of the body's life maintenance processes, and is found so ubiquitously throughout the body, one wonders whether the health and longevity benefits of other therapies might be mediated through their interaction with melatonin.

Does Deprenyl Stimulate Melatonin Syntheses?

It's long been assumed that low doses of deprenyl - according to the rat experiments of Hungarian scientist Dr. Joseph Knoll - (injections of 0.25 mg/kg every other day) inhibit the enzyme monoamine oxidase-B (MAO-B) selectively, and that this selective inhibition is lost at higher doses, which also inhibit monoamine oxidase-A (MAO-A). It's also been assumed that deprenyl's ability as a selective inhibitor of MAO-B is at least partially responsible for its ability to extend lifespan in both laboratory animals and Parkinson's Disease patients.

This hypothesis is based upon 21-day studies of low and high doses of deprenyl in rats. However, a recent study at the Brown University School of Medicine in Providence, Rhode Island showed that, **after six months of low-dose deprenyl treatment in rats, deprenyl inhibited <u>both</u> MAO-B and** MAO-A!

This inhibition doubled the concentration of serotonin in the pineal gland of the deprenyl-treated rats, increased the levels of noradrenaline, and doubled the levels of the metabolic precursor to melatonin (N-acetylserotonin), although there was no evidence of increased melatonin levels. Since melatonin is manufactured from serotonin in the pineal gland triggered by noradrenaline, **these findings suggest that long-term deprenyl therapy may slow aging and extend lifespan by stimulating the synthesis of melatonin!**

Does Acetyl-l- Carnitine Stimulate Melatonin Synthesis?

Scientists at the University of Milan in Italy have found that injections of **acetyl-l- carnitine (ALC)** at doses of 10, 30, and 90 mg/kg lead to "remarkable *increases"* of pineal and serum melatonin one hour later in young (2 month-old) male rats, but that only the 90 mg/kg dose of ALC increases melatonin levels in old (24 month old) rats.

The scientists hypothesize that:

"Since both ALC and *melatonin are remarkable free radical scavengers, if is possible that ALC's ability to reverse certain aging processes may be due to ifs ability to promote melatonin production.* Another *reasonable hypothesis* that can be derived from *this study is that the body may lose ifs ability to utilize acetyl-l-carnitine and that we may need to* take higher doses *of ALC to compensate for this age-related change."*

Melatonin Increases Growth Hormone Levels

When scientists at the University of Manitoba in Canada gave hamsters daily injections of melatonin for 10 weeks they found a "substantial increase" of both **growth hormone** and **insulin-like growth-factor-I (IGF-1)** — a precursor to growth hormone. These findings suggest that one of melatonin's mechanisms of action in promoting longevity may be the stimulation of growth hormone release. Growth hormone is depleted with advancing age (just as melatonin is), and the administration of growth hormone to aging men has produced rejuvenation effects such as increased muscle mass, increased strength, greater flexibility, and better coordination.

Food Restriction And The Pineal Gland

The most dramatic lifespan extension seen to date in warm-blood mammals is food restriction, which has prolonged survival in dozens of studies in both rats and mice, starting with the pioneering studies of Cornell University nutritionist Clive M. McCay in the 1930's.

When started very early in life (just after weaning), severe food restriction has delayed physical and sexual maturation, and led to very large increases in maximum lifespan. The longest-lived, food-restricted animal to date was studied by Morris Ross of the **Institute For Cancer Research** in Philadelphia. This rat lived for 1,830 days, which is more than 5 years, and well beyond the world record for rat survival under natural conditions. In the 1980's Richard Weindruch and Roy Walford (of UCLA Medical Center) showed that the lifespan of middle-aged mice could be extended (moderately) by depriving them of food (with nutrient supplementation) gradually over an extended period of time.

Food restriction is accepted by virtually all gerontologists as a regimen that definitely extends maximum lifespan in rodents (and possibly in humans). Studies have shown that food restricted animals show many signs of retarded aging including delayed deterioration in connective tissues, hormone output, visual capacity, strength, coordination, and energy production. (Studies are currently underway to determine the effects of food restriction in monkeys).

However, the physiological mechanisms of action by which food restriction retards the aging process are not known, although there have been several credible hypotheses to explain it including reduced free radical activity and enhanced neuroendocrine stabilization.

The Pineal Gland In Food-Restricted Rats

In the late 1980's a research team, including scientists from the University of Texas at San Antonio working with scientists from Norway and Germany, studied the effects of food restriction on the pineal gland in very old male Fisher 344 rats (28 months old), roughly equivalent to 80 years of age in humans, and in young, normally-fed rats (3 months of age).

In this study, the experimental rats were divided into two groups when they were six weeks of age, with one group receiving 60% of the calories consumed freely (ad libitum) by the rats before the experiment was started. They were then individually caged and maintained until 28 months of age, when 5 old food-restricted rats and 5 old normally-fed rats

TABLE 1

group	Strain and Treatment	Age at implant or sham-operated. months	No.	No. of surviving mice (months of age) 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33
A	Implanted C57BL/6	16	7	7 7 7 7 7 6 6 5 4 3 3 2 1 1 1 0
B	Control C57BL/6	16	7	6 6 6 4 4 2 1 1 0 0 0 0 0 0 0
C	Implanted hybrids*	19	5	5 5 5 5 5 5 5 5 5 5 4 3 2 1
D	Control hybrids	19	6	6 6 4 3 2 1 0 0 0 0 0
E	Implanted BALB/cJ	22	3	3 3 3 3 3 3 3 3 1 0
F	Control BALB/cJ	22	5	5 5 5 2 0 0 0 0 0

• **C57BL/6 X BALB/cJ female hybrids. All donor and recipient mice used were inbred females.**

Implantation of pineal glands from young (3-4 year old) donors into the thymus gland of *old mice prolongs the lifespan of the recipients.*

were sacrificed, examined, and compared with 11 young rats.

Results Of Study

There were many striking differences between the old food-restricted and normally-fed rats. The normally-fed rats weighed 29% more than the food-restricted rats. They had overt pathological lesions - three with tumors and two with cataracts in both their eyes. Apart from one rat with a cataract, the food-restricted animals all appeared to be in good health.

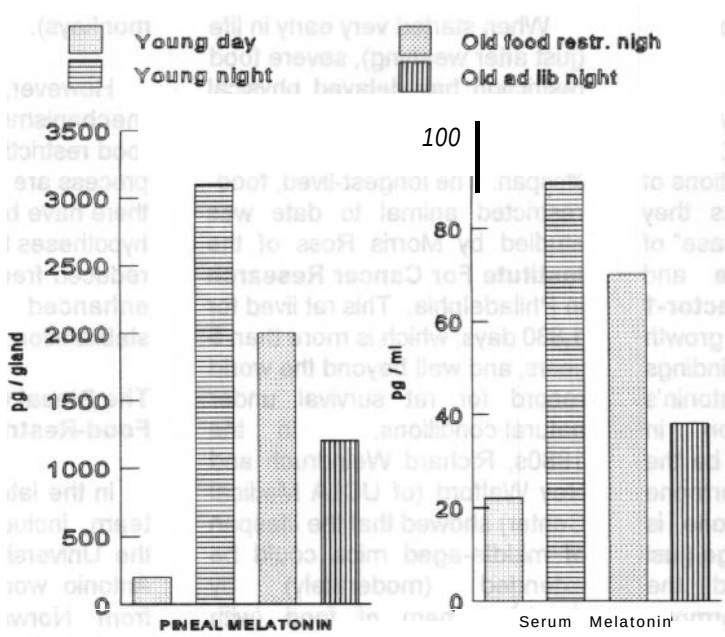


FIGURE 7

Pineal and serum melatonin levels in young and o/d, food-restricted and normally-fed male rats.

How Pineal Function Was Affected

The old food-restricted rats displayed **significantly higher pineal and serum (blood) concentrations of melatonin** (as well as higher levels of the enzymes involved in melatonin synthesis), although the melatonin levels were not as high in the old, food-restricted rats as in the young rats **(Figure 7).**

The condition of the pineal glands in the old, food-restricted rats was much better than in the old, normally-fed animals. They showed less cell loss, better structure, and more youthful function than the pineal glands in the normally-fed old animals, which were calcified and decrepit in comparison.

Does Food Restriction Work Through Pineal Action?

The scientists suggested that the anti-aging, lifespan-extending effects of food restriction in laboratory animals may occur because of the preservation of youthful pineal function. As they put it:

"Based *on* a positive correlation between the present findings of elevated pineal activity in old, food-restricted *rats and* a retardation of age-related *physiological* deteriorations, absence of *pathological manifestations and longevity in* such animals, we *propose that the* pineal *gland, through its secretion of melatonin, may be* regarded as *a possible neuroendocrine mediator between food restriction and some of the age-related changes. The present findings* are *similar* to those *in mice* which *were treated with melatonin."*

Melatonin and Body Temperature

Another method of extending lifespan is reduction of body temperature. In the 1960's, Liu and Walford (at UCLA Medical Center) were able to extend the mean and maximum lifespan of cold-blooded fish by reducing their body temperature by several degrees. This was accomplished by putting the fish in a cold water tank, and approach that is not possible in warm-blood animals whose thermoregulatory system attempts to maintain normal body temperature under all conditions. (Efforts by UCLA scientists to lower body temperature in warm-blooded mice with marijuana and other chemical agents only achieved transitory results).

We've already seen that melatonin enables us to recuperate, and be revitalized and rejuvenated at night by inducing deep, restful sleep. One effect of the high levels of melatonin that circulate throughout our body at night is reduced body temperature in the wee hours of the morning when we normally experience our deepest level of sleep. Considering the lifespan-extending effect of reduced body temperature in fish, it may be that melatonin helps to maintain

youthful function by lowering body temperature every night.

There have been studies in both men and women showing that body temperature is not lowered nearly as much during the night in older people, as their melatonin levels decline with advancing age. In a recent study by scientists at the University of California School of Medicine, San Diego, core body temperature was measured in 8 young women (22-32 years) and 6 older, postmenopausal women (54-62 years) by a sensor inserted into the vagina.

Age Differences In Temperature Descent

They found that the nightly temperature descent produced by elevated levels of melatonin at night was steeper in the younger women. The mean temperature descent in the young women was 2.1 ° F. (to 96.5" F.) compared to only 1.2° F. in the older women (to 97.4° F. (Figure 8). This difference in temperature descent correlates with the sharp decline in melatonin levels with advancing age, which may be one of the causes of aging.

Melatonin Supplementation And Body Temperature

Since supplemental melatonin improves the quality of sleep, it suggests that taking melatonin should also help to maintain the temperature descent of youth. In another part of the University of California study, 7 young (22-32 years) women and 7 older (54-62 years) women were put into two groups and given high oral doses (100 mg) of melatonin or placebo in an attempt to determine the effects of melatonin supplementation on body temperature.

Results Of Study

They found that in young women, melatonin reduced body temperature significantly in young women, but produced only slight and inconsistent results in the older women. The findings mean little, however, because the women took melatonin at 8 AM in the morning rather than at night when it acts to induce therapeutic sleep. Thus, we await another study to measure the effect on body temperature of the nightly administration of melatonin.

Combining Food Restriction And Temperature Reduction

When Liu and Walford were studying the lifespan-extending effects of temperature reduction in fish, they tried one experiment in which they restricted the food intake of the fish early in life and lowered their temperature late in life. **The combined effects of these two regimens enabled them to triple the lifespan of the fish!**

This experiment, which has never been repeated, suggests that the appropriate combination of existing lifespan-extending therapies could have synergistic effects exceeding that of any single therapy. What's needed is a major research program aimed at discovering the most effective combinations of anti-aging therapies.

Melatonin And Coronary Heart Disease

There has been file research about melatonin's effects on cardiovascular disease, but a recent study in **The Lancet** (Vol. 345, Jun. 3, 1995, page 1408) by scientists at the **Institute for Cardiovascular Diagnosis And Therapy** in Salzburg, Austria

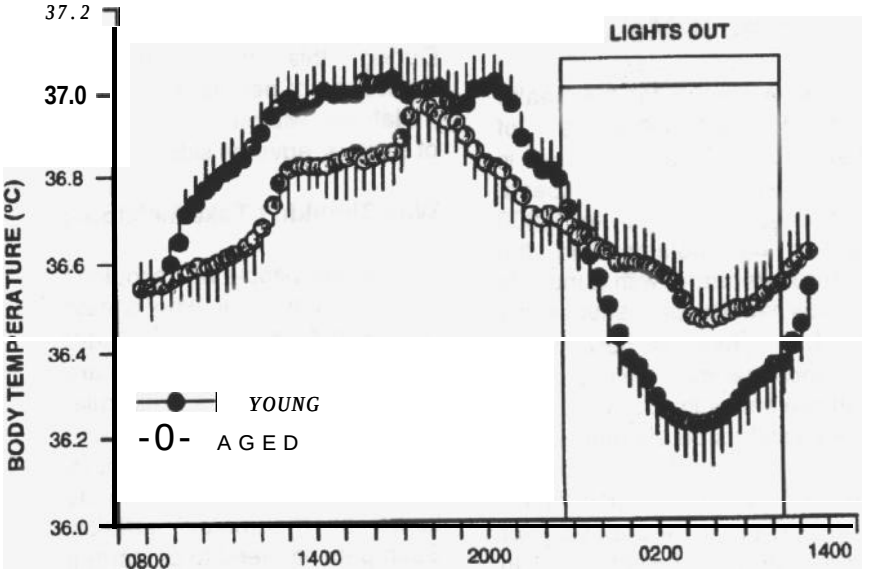


FIGURE 8

Core Body temperature in 8 young and 6 older women.

produced some eye-opening findings.

They looked at nightly melatonin levels in the serum of two groups of subjects: 2 women and 13 men with documented coronary heart disease (mean age 54) and 2 healthy women and 8 healthy men (mean age **53).** They measured serum melatonin levels in these subjects, both in the afternoon and at night.

Differences In Melatonin Levels

Melatonin was not detectable in either group during the afternoon. At night, when melatonin does its work, however, the results were very different. The scientists found that **melatonin levels in the coronary disease patients was five times lower than in healthy subjects (Figure 9)!**

They speculated that, since melatonin reduces noradrenaline, which may inflict damage in arterial walls, the lack of melatonin in individuals with coronary heart disease fails to keep their noradrenaline levels in check. It would be interesting to determine if individuals who suffer heart attacks have depleted melatonin levels before their heart attack.

What's very clear, however, is that replenishing the depleted melatonin levels in coronary heart disease patients could be a very effective therapy, and that maintaining youthful melatonin levels could be an effective way of preventing heart attacks, strokes, and other cardiovascular diseases.

The Austrian scientists agree about this in their conclusion to their paper:

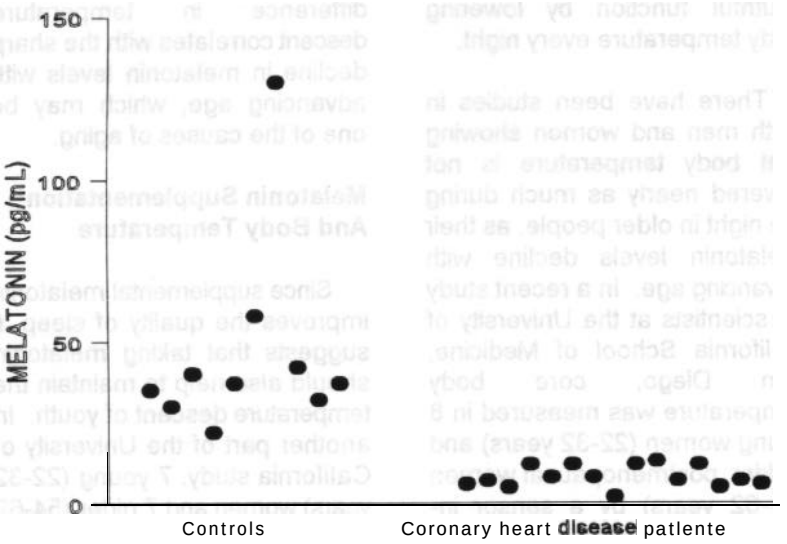


FIGURE 9

Melatonin concentrations at night in patients with coronary heart disease and in controls.

"Because melatonin concentrations can be increased by oral administration of melatonin, it would be easy to treat patients with coronary heart disease with melatonin to study effects on the development of atherosclerosis and coronary heart disease."

How Safe Is Melatonin?

The evidence for the health and longevity benefits of melatonin is enormous and is growing at unprecedented speed. There are now 4,000 -to- 5,000 studies on melatonin in the scientific literature, with hundreds of new studies published every month. There is now strong evidence that melatonin is an all-purpose anti-aging therapy. That melatonin has potent anti-cancer effects. That it can help to prevent and treat heart attacks. And that it may be beneficial for other chronic diseases. In addition to all this, the main reason most people take melatonin -to get a good night's sleep — makes it likely that millions of people will soon be taking melatonin on a daily basis for many years.

With such imminent popularity on the horizon, it's prudent to make sure that melatonin is safe to take on a long-term basis. **The Life Extension Foundation** has been offering melatonin to its members for several years. During this time, tens of thousands of people have taken melatonin, without any evidence of serious, adverse side effects.

Who Shouldn't Take Melatonin

The only people who shouldn't take melatonin, or who should only take it very carefully under the care of a physician, are patients with leukemia, lymphomas, or other immune system cancers, or who have autoimmune diseases such as lupus or rheumatoid arthritis. Such patients need to be careful about taking melatonin because it is a strong immune system stimulant, which is beneficial for most people, but can cause

problems in patients whose immune system has gone awry. There is also some evidence suggesting that patients with ovarian cancer should not take melatonin.

The only other people who should be careful about taking melatonin are women who are pregnant, or who want to become pregnant. The reason for this is that melatonin is involved in the control of reproductive function, and studies are underway to use it as a contraceptive. Even though much higher doses of melatonin are being used in these studies than are used for anti-aging purposes, caution should be exercised.

No Evidence Of Toxicity

For all others, it appears as if melatonin is as benign a therapy as can be found. None of the thousands of scientific papers on melatonin in the scientific literature have found any evidence of harm or risk of any kind in anyone taking melatonin for any reason at all.

To get some idea of how safe melatonin is, let's take a look at several clinical trials in which exceptionally high doses of melatonin were used. In one such study, 40 malignant melanoma patients were given up to 700 mg. a day of melatonin in 4 divided doses for up to 33 weeks. The toxicity encountered in this trial was 'minimal" and consisted primarily of fatigue in 17 of 40 patients.

In a study of melatonin's contraceptive action at **Dijkzigt University Hospital** in Rotterdam, Holland, 12 women received 300 mg. a day of melatonin for 4 months. The scientists commented on the lack of toxicity in these women as follows:

"No requests for study discontinuation were reported by the women. There were no complaints about altered night/day sleep, and *activity patterns, altered emotional well-being, or mood changes. The results of all hematological and biochemical determinations were normal before, during and after* treatment."

In a third study at the Yale University School of Medicine, five adult patients with hyperpigmented skin were given 1,000 mg. (one gram) of melatonin a day (in four divided oral doses) for 25-30 days. Because of the extraordinarily high doses of melatonin used in this study, there was extremely careful monitoring of the subjects. **The scientists found that, at this super-high dose of melatonin, which is 333.3 times higher than the most commonly used dose for anti-aging purposes, there was no evidence of toxicity!**

"All subjects were watched carefully for signs of toxicity. Slit lamp examinations, direct and indirect fundoscopy, visual acuity, and visual fields showed no evidence of retinal toxicity- Blood pressure and pulse rate were unchanged. Electrocardiograms were not affected. All hematologic tests including white blood cell counts, hemoglobin, hematocrit, platelet count, reticulocyte count, differential white counts were normal throughout the trials. All of the blood chemistry tests including urea nitrogen creatinine, uric acid, calcium, phosphorus, SGOT (serum glutamic oxalcetic transaminase) LDH (lactic dehydrogenase), bilirubin, total proteins and albumen, were normal. Urinalyses were normal."

In an article by Russel J. Reiter of the University of Texas Health Center in San Antonio in the **Annals Of The New York Academy Of Science it** was stated that:

"Melatonin, even when given in massive amounts (300 mg. daily) for prolonged periods (up to 5 years) to humans *does not produce untoward side effects."*