LIFE EXTENSION REPORT

The Insider's Report on Efforts to Prevent Aging and Rejuvenate the Aged

How Melatonin Combats Aging

A Pioneering Doctor's Ideas And Clinical Experience

By Saul Kent Founder, Life Extension Foundation

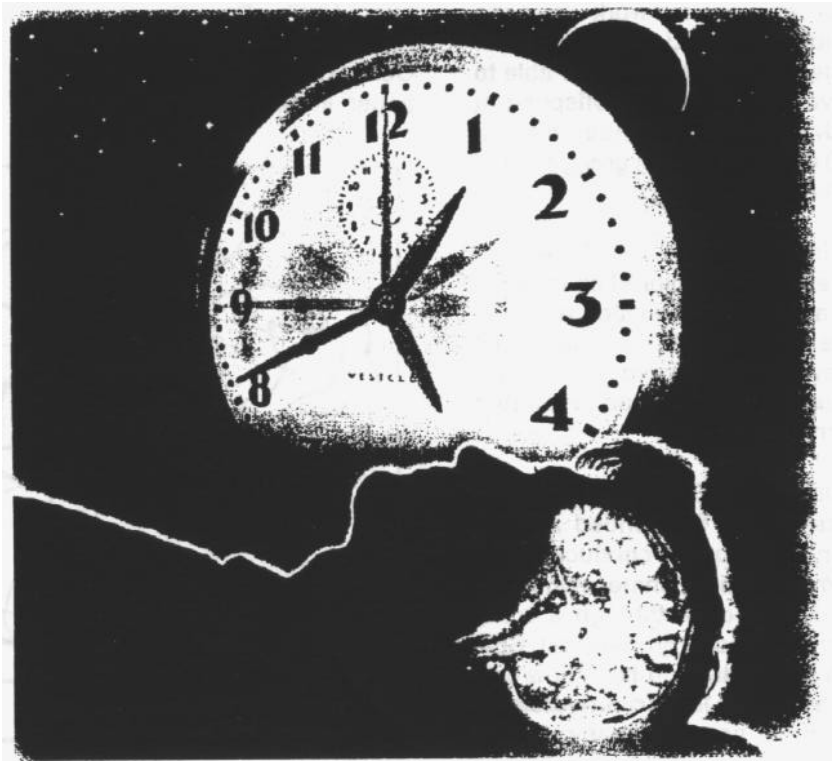
In the mid 1960's - in my early days as an immortalist - - I met a young scientist named Paul Segall who had decided to devote his life to research to extend the human lifespan. Paul was the first scientist I'd ever encountered who had confidence that safe-and-effective methods to control the aging process would be developed.

At the time, Paul's focus was on experiments by Dr. Richard Gordon at the Monsanto Chemical Company, in which the lifespan of both chickens and rats had been extended radically by feeding them a diet deficient in the amino acid **tryptophan.** These experiments were a variation of the groundbreaking food restriction experiments first conducted by Dr. Clive McCay at Cornell University.

Paul was fascinated by a small, mysterious organ at the center of the brain called the **pineal gland,** which he believed was involved in aging in some important way. This was shortly after it had been discovered that the **pineal gland** secretes a hormone called **melatonin,** which governs the circadian rhythms that help us adapt to changing environmental conditions.

A Biological Time Bomb

Paul believed that the human body is **a** biological time bomb with an intrinsic clock mechanism that causes us to grow old, suffer, and die with precision. He envisioned a genetically determined clock controlled within the brain through the action of the neurotransmitters, hormones, and enzymes of our neuroendocrine system.



In Paul's vision, the ticking of this clock is expressed through timing mechanisms that cause us to go through growth, puberty, and menopause at roughly the same time in the lifespan, and by the progressive deterioration of our cells and organs, leading inexorably to disability, decrepitude, degenerative disease, and death!

Dr. Segall's Research

Dr. Segall went on (in the 1970's) to explore the lifespan extension potential of **tryptophan deprivation (T-) experiments** in laboratory rats at the University of California at Berkeley. He found that T- rats were more youthful and lived longer than normally fed animals and that their extended youth could be shown by their improved ability to adapt to various types of stress, such as swimming in cold water.

The most dramatic illustration of youth prolongation in tryptophan deprived rats that came out of Segall's work was the finding that old (28 months of age) T- female rats were able to give birth to normal offspring at advanced ages, comparable to a 70 year old woman giving birth to a healthy baby.

In conduction his T- experiments Paul explored changes in brain neurotransmitter levels in his experimental animals, but never again focused on the **pineal gland,** which had fascinated him in the 60's.

In the 1980's Paul turned his attention to Suspended Animation - and began conducting low temperature experiments in hamsters and dogs through a company called **Cryomedical Sciences.** Paul and his fellow scientists soon left **Cryomedical** to form a new company called **BioTime,** which extended this work to non-human primates (baboons). **Biofime** is now a public company seeking to apply its research to clinical hypothermia in humans.

Dr. Rozencwaig Focuses On Melatonin

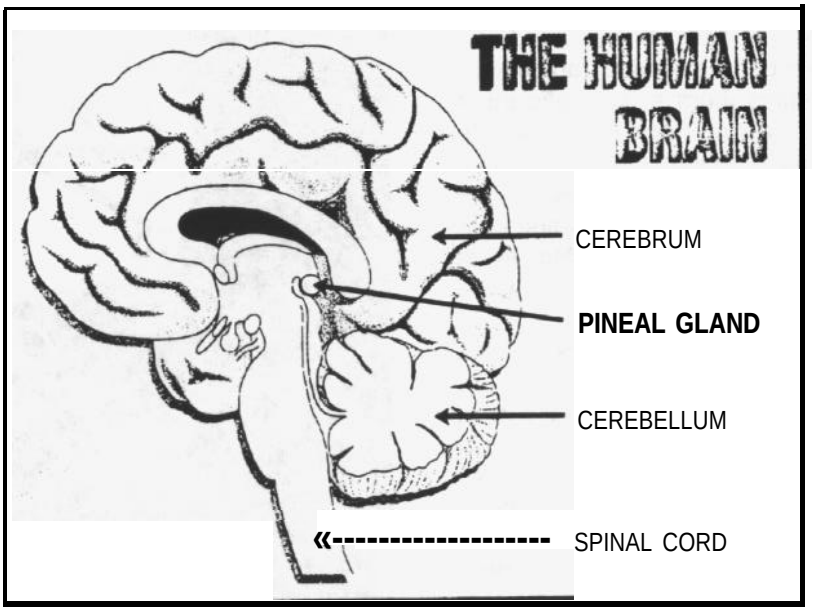
Around the time Dr. Segall was losing interest in the pineal gland, a pioneering **Canadian** medical doctor by the name of **Roman Rozencwaig** was beginning to focus his attention on **melatonin,** the primary hormone secreted by the **pineal gland.**

Dr. Rozencwaig was born in Odessa in the USSR in 1946. He moved to Canada at the age of 14. He later obtained his medical degree from **McGill University** in Montreal, where he began experiments, which led him to the realization, in the mid 1980's, that melatonin plays a critical role in aging and the diseases associated with aging.

In 1987, **Dr. Rozencwaig** (along with B. R. Grad and J. Ochoa) published a seminal paper in **Medical Hypotheses** (Vol. 23, pgs. 337-352) in which he expressed his theory that the progressive depletion of **melatonin** with advancing age is a primary cause of aging and age-related diseases such as heart disease, stroke, cancer, and Alzheimer's disease.

In 1987, **Dr. Rozencwaig** began to treat patients with **melatonin** (as well as a drug with similar effects called **Periactin** (see box on page 14). **Dr. Rozencwaig** recalls that:

"As a medical doctor, I first used melatonin in 1987 on a patient with lung cancer who had received all the standard therapies prior to the use of melatonin. Today, the patient is well, his metastasis has disappeared and he is leading a normal life. Since then many of my patients have benefited from melatonin and I have used it for various conditions with considerable success. Mainstream medicine is only now beginning to appreciate its value in treating various conditions. For my practice, it has certainly opened a new vista in health care and rejuvenation."



Like Lightning Striking

The impetus for **Dr. Rozencwaig's** use of **melatonin** in clinical practice came as a byproduct of his pioneering ideas about the role of the **pineal gland** in aging and his realization that supplemental **melatonin** would likely be able to restore many of the life functions lost because of the atrophy of the **pineal gland** as we grow older.

He recalls that suddenly he experienced a vision of the role of **melatonin** in aging and that he knew from that point on that he would devote the rest of his life to helping people live longer by further exploring the role of **melatonin** in aging. As he puts it:

*"It happened just like the popular view of how scientists make discoveries. It just came to me... without warning... like lightening striking! Immediate/y, I started scribbling my ideas on the wall, so that I could preserve them in their original form.**

Melatonin And Serotonin In Aging

Dr. Rozencwaig's hypothesis has been developed in several published papers. It was first expressed in his Medical Hypotheses paper entitled: **The Role Of Melatonin And Serotonin In Aging:**

"Aging is a pathological process originating (from gradual failure) of *the pineal g/and that results in a diminished out-put of melatonin, along with a diminished melatonin to serotonin ratio, leading to a decline in adaptive processes.... and subsequent death of the organism."*

Circadian Rhythms And The Pineal Gland

Dr. Rozencwaig believes that the **pineal gland** is both the primary clock and pacemaker of aging, and that the time dependent decline of our vital functions (aging) comes about as a result of the increasing disintegration of our neuroendocrine and immune systems. He believes that the harmony and consistency of these systems is maintained through biorhythms, most of which follow 24-hour, circadian cyclicity (on our rotating planet) under the control of the **pineal gland.**

Dr. Rozencwaig contends that the **pineal gland** is:

" *a primary clock because it measures, and is synchronized with, the most constant environmental cue which is the light-dark cycle. The pineal's function as a* pacemaker *is carried out through the production of neuro-hormones, which subsequent/y control the entire nervous system and endocrine axis and hence homeostasis. The effect is achieved through (the secretion of) very small concentrations of substances produced in the pineal, primarily serotonin and melatonin."*

Melatonin Is Produced From Serotonin

Melatonin is produced from **serotonin** with the help of several associated enzymes and cofactors, while **serotonin** is produced from the amino acid **tryptophan,** which is found in a wide variety of high-protein foods such as meat, fish, milk, and cheese. **Melatonin** is also found in small amounts in **bananas, tomatoes,** and other fruits and vegetables.

Melatonin also is produced in smaller amounts in the gastrointestinal (GI) tract and other **parts** of the body. The **pineal gland** contains the highest central nervous system concentration of **serotonin (Table 1)** in the body, and produces the largest amounts of **melatonin as** well as other neuroendocrine hormones.

Every day, as darkness sets in, **melatonin** production (from **serotonin)** in the **pineal gland** is rhythmically induced via **cyclic AMP** activation of beta receptors by the neurotransmitter **norepinephrine** through the action of the enzyme N-Acetyltransferase (NAT), which results in low levels of **serotonin** and high levels of **melatonin.**

TABLE 1

REGIONAL DISTRIBUTION OF SEROTONIN IN RAT BRAIN

Tissue	ug/g Net Wt.
Whole brain	0.62
Cerebral cortex	0.57
Hippocampus	0.53
Striatum	0.57
Hypothalamus	0.97
Pons and medulla oblongata	0.83
Cerebellum	0.07
pineal gland	73.00
Pituitary gland	0.56

The Serotonin/Melatonin Ratio

The **pineal gland** has weak regenerative abilities because its primary **cells (pinealocytes)** are of neuronal derivation. The number of pinealocytes in the **pineal gland** is genetically predetermined, and these non-dividing cells are not replaced when they are lost due to biological or chemical injury.

As we grow older, our **pineal gland** atrophies, eventually reaching a state of organ failure, as cells are constantly lost for **a** variety of reasons. The decline of the pineal is accelerated by the accumulation of **calcium deposits,** which cause the organ to harden and interferes with its activities.

According to **Dr. Rozencwaig,** the age-related decline of the **pineal gland** means that there are fewer and fewer pinealocytes available to produce **melatonin** from **serotonin,** which leads to lower levels of **melatonin** and higher levels of **serotonin,** and that the resulting change in the **serotonin/melatonin** ratio is responsible for much of the deterioration experienced throughout the body with advancing age.

He points to evidence that increasing levels of circulating **serotonin** may be responsible for the increased incidence of certain types of cancer, and that high levels of **serotonin** are associated with platelet adhesiveness leading to atherosclerosis, the primary causes of heart attacks and strokes.

He also points to Dr. Segall's tryptophandeprivation experiments, which, he believes, lowered only extra-pineal **serotonin** levels, leading to a major decrease in the incidence of cancer and other degenerative diseases, as well as extended lifespan and reproductive capacity in laboratory rats.

Dr. Rozencwaig's Periactin Therapy

Dr. Rozencwaig also uses a **serotonin** antagonist called **Periactin (Cyproheptadine)** to treat the diseases of aging. He says that the results he gets with **Periactin** are ***similar*** to those ***he*** gets ***with melatonin*** and that he, sometimes, uses both agents together (as in the case of Dora Lewenstein).

Dr. Rozencwaig owns **three** U.S. **patents** on **Periactin**. The **first** patent (No. 4,66 1,500) was issued on Apr. 28, 1987 fur the use of **serotonin** antagonists as anti-aging therapies for conditions such as "AIDS, multiple sclerosis, and Alzheimer's disease." The patent describes three patients with Alzheimer's disease:

"These patients were treated with a dose from 2-to-4 mg of cyproheptadine every evening. Four months after initiating the treatment, a test for recent memory has shown that there was an improvement by 50% and the general condition of the patient improved subjectively in all three cases. There was no further deterioration in any of these cases."

Dr. **Rozencwaig's** second patent (No. 4,77 1,056) was granted on Sep. 13, 1988 for the use of **serotonin** antagonists in the treatment of cancer. Among the cases cited in this patent was the following:

"Patient C, having lung cancer ~

This patient had inoperable lung carcinoma which was irradiated concurrently with cyproheptadine treatment (4 mg every evening). Ten percent of patients with lung carcinoma receiving radiation therapy survived one year. Patient C... is now ***free of cancer recurrence 18 months after*** the ***initiation of cyproheptadine treatment, which the patient continues to take*** every evening."

Dr. **Rozencwaig's** third patent (No. 5,081,129) was issued on Jan. 14, 1992 for the use of **serotonin** antagonists for the treatment of anemia. The research that this patent is based upon is a controlled study (to be published shortly) of women with cervical ***cancer.***

The study shows that cervical cancer patients treated with surgery or radiotherapy who were given 4 mg daily of cyproheptadine exhibited improved hemoglobin levels in addition to increased body weight, improved quality of life, and enhanced survival.

The Regenerative Ability Of Melatonin

In 1987, when **Rozencwaig,** et al. published their hypothesis about the role of **melatonin** in aging, there was relatively little evidence to support it. Yet the extent to which they anticipated future research advances is remarkable.

It was pointed out, for example, that night is the time of replenishment, when our bodies recuperate by regenerating our tissues and restoring our glycogen reserves. Since **melatonin** is the natural agent that prepares us for sleep and circulates in peak amounts while we sleep, it almost certainly plays a major role in the regenerative process. The fact

that **melatonin** is extremely effective at penetrating the blood-brain barrier indicates that it may be especially beneficial in the repair, regeneration, and rejuvenation of the brain during sleep.

Among the anti-aging effects of **melatonin** mentioned by Dr. **Rozencwaig** in the 1987 paper is the fact that **melatonin** stimulates natural antioxidant levels, improves DNA repair mechanisms, and enhances our neuro-endocrine and immune systems.

In a subsequent update in **Pscyhoneuroendocrinology** (Vol. 18, No. 4, pgs. 283-295, 1993) **Grad** and **Rozencwaig** discuss the evidence in support of their hypothesis. Among the **effects** of **melatonin** discussed in this paper is its ability to block pregnancy, boost immune function, improve the quality of sleep, regulate the endocrine system, protect against cancer, stimulate natural antioxidants, and protect against cardiovascular disease by inhibiting platelet aggregation and ischemia. (A review of the latest evidence for **melatonin** as an anti-aging therapy will follow this article).

The final paragraph in the paper is a cogent assessment of a theory of aging that time, and experimental evidence, is validating to a greater degree with every passing year.

'The Melatonin Deficiency Syndrome is perhaps the basic mechanism through which aging changes can be explained in terms of a sing/e causative lesion, a lesion that causes the progressive patterns of change seen in the older population. In addition, pineal rhyfhmicify is the on/y biological clock synchronized wifh a time dimension, which also has the capacity to repair and rejuvenate fhe organism. Since the pineal gland's action fo delay development is known, it is not surprising that if would also act to delay developmental senescent changes and extend tie lifespan. In addifion, if raises tie possibility of the reversal of senescence.... This may require replacement of melatonin along with other hormones in order to achieve a more youthful endocrine balance and homeostasis, and consequent/y a possi-b/e repair of the body as a who/e. "

The Melatonin Doctor

Dr. Rozencwaig has been treating patients with **melatonin** for about eight years. He's used **melatonin** for the treatment of cancer, inflammatory diseases, neurologic diseases, and viral diseases. He's had particular success with cancer patients, in conjunction with traditional treatments. Among the types of cancer he's treated are pancreatic, breast, brain, and lung cancer. When used as an adjuvant treatment for cancer, **melatonin** reduces the side effects of toxic

Figure : Dr. Roman Rozencwaig

therapies and boosts their effectiveness.

According to **Dr. Rozencwaig, 3-6** mg of **melatonin** a day is sufficient if there is no metastasis, but if cancer patients have metastatic lesions, he doubles or triples their does of **melatonin.**

The Case Of Dora Lewenstein

One **of Dr. Rozencwaig's** patients is Dora Lewenstein, a 69-year-old woman, who was diagnosed with thyroid cancer in 1989. When I visited **Dr. Rozencwaig** in July, I met Dora during a brunch at a restaurant in Montreal. Although she had some difficulty in talking because of the side effects of past radia-

Figure : Dr. Rozencwaig patient, Dora Lewenstein

tion therapy, she was clearly in good health and bursting with energy when I met her.

Dora told me that it had been quite depressing to deal with her previous doctors because they were so negative about her condition. In one instance, she recalled, she received bad news about her condition on her answering machine. After listening to a cold, hopeless message about her thyroid cancer spreading, and a new tumor on her lung the size of a peach, she felt like crawling into a corner to die.

But when she visited **Dr. Rozencwaig,** he gave her hope by telling her that he thought he

could help her, and made her feel important by treating her compassionately and spending enough time with her to establish a good relationship.

Even more important is the fact that **Dr. Rozencwaig** has helped her enormously with **melatonin** therapy, at a dose of 6 mg (along with **4** mg of **periactin) every** evening. When Dora started taking **melatonin,** she had metastatic lesions in her lungs as well as a new primary carcinoma of the lung. The lesions were not operable. The only treatment she was given was radiotherapy that paralyzed one of her vocal chords. She believed she was going to die and was very depressed.

Since she started taking **melatonin,** on the other hand, her depression has lifted and she is buoyant, hopeful, and delightful to be around. Her tumors have shrunk in size dramatically and her metastatic lesions have disappeared.

Today, Dora Lewenstein believes that **melatonin** (and **periactin)** therapy saved her life. She is a very enthusiastic proponent of melatonin and often discusses its use at cancer group meetings. She is happy to be alive and wants to tell her story to the world in order to help other cancer victims.

Melatonin As An Anti-Aging Therapy

Although **Dr. Rozencwaig** believes **melatonin** is highly beneficial for the treatment of a wide variety of diseases, his overriding interest is in **melatonin as** an anti-aging therapy, with the potential to help us all live longer in good health.

Dr. Rozencwaig has been prescribing **melatonin** for many of his patients, his friends, and for himself, ever since he realized that **melatonin** could be a key to the control of aging. As a result, he probably has more experience with the long-term use of **melatonin** for anti-aging purposes than any other doctor.

Although the results of his use of **melatonin** as an anti-aging therapy have not been quantitated, he reports that everyone taking **melatonin** has been feeing exceptionally good and have been aging quite well.

Perhaps his biggest fan is his

Figure 2: Mimi Fay and Dr. Roman **Rozencwaig**

friend Mimi Fay, a beautiful Eurasian woman who was born in France and who is a model, actress and businesswoman. Mimi first met **Dr. Rozencwaig** 10 years ago, when he was 35 years old and was very upset about the thought of growing old.

'When I *met Dr. Rozencwaig, I was very depressed. I saw the signs of aging in the mirror and thought my life would be all downhill from that point on. Then he told me about melatonin and my entire life changed. I've been taking melatonin for 10 years now. I fee/ better than I've ever felt before and I don't think I look a day older than I did ten years ago.* "

I don't know if Mimi Fay "hasn't aged" in 10 years because I just met her, but I do know she looks remarkably young and vigorous for her age, and that she's absolutely convinced that it's because she's been taking **melatonin** all these years! ▪

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