

REVIEW ARTICLE

THE PINEAL GLAND : ITS PHYSIOLOGICAL AND PHARMACOLOGICAL ROLE

V. SRINIVASAN

Institute of Physiology,
Madurai Medical College, Madurai - 625 020

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Abstract : Our perception of pineal gland function has attained new dimensions during the last decade. The gland is active throughout the life of an individual and secretes melatonin, the major pineal hormone, and many indoles and polypeptides. The secretion of pineal gland is regulated not only by sympathetic nerve fibers but by other central pinealopetal projections also. Many neurotransmitter-receptor sites have been identified recently in the pineal gland. The gland plays an established role in controlling reproduction and is involved in the control of sexual maturation. It has a major influence on the circadian organization of vertebrates including human beings. The hormone melatonin has a potential therapeutic value in treating disorders that are associated with biological rhythm disturbances like sleep disorders, "jet lag" phenomena and affective disorders. The gland is actively involved in the mechanisms controlling sleep-wakefulness cycle and human mood disorders. It actively participates in the neuroendocrine mechanism controlling stress and acts even as an oncostatic gland. The pineal gland may be considered an "equilibrating-tranquillizing gland" contributing to longevity.

Key words : pineal gland	neuroendocrine-transducer	pinealocyte
seasonal reproduction	sexual maturation	circadian rhythms
chronobiotic	sleep-wakefulness	affective disorder
psychotropic drugs	stress	longevity

INTRODUCTION

Once considered to be an organ of little functional significance, the pineal gland has now emerged as a major "neuroendocrine transducer" (a gland which converts a neural input into hormonal output) with specific effects on reproductive mechanisms, circadian organization, sleep mechanisms and control of human mood. The gland acts as "a general synchronizing, stabilizing and moderating organ" for several physiological processes (1) and its hormone melatonin has been designated as "equilibrating hormone" (2).

The pineal gland of vertebrates develops from the neural crest cells of the roof of the diencephalon. In human beings it is deeply situated in the midline of the brain below the corpus callosum. It is "ideally placed anatomically to collect, integrate and compare information from extra cranial sources and intracranial sites" (3). Calcification which occurs in the human pineal gland is considered to be a physiological process related to its past secretory activity rather than an indicator of present degeneration (4). Available evidence strongly indicates that the pineal gland is active throughout the life of an individual (5).

PINEAL GLAND STRUCTURE

The chief cellular component of the pineal gland is pinealocyte although other astrocyte like interstitial cells also have been identified recently (6). Pinealocytes are extremely modified photoreceptor cells that represent the last step in the phylogenetic evolution (7). The presence of opsin-retinal S-antigen in the pinealocytes suggests their close relationship to retinal photo-receptor cells (8). The cytological nature of pinealocyte still remains enigmatic although it contains the usual cellular organelles like endoplasmic reticulum, golgi complex, lipid droplets, mitochondria and different types of synaptic ribbons. Neuron specific enzyme enolase also has recently been demonstrated in these cells (6).

BIOSYNTHESIS OF PINEAL HORMONES

The pinealocytes of all vertebrates synthesize two different types of substances, namely, indoles and polypeptides. Melatonin, or 5-methoxy N-acetyl

tryptamine, the major hormone of the pineal gland, was first isolated by Lerner in 1958 (9). Subsequently many other hydroxy and methoxy indoles have been identified in the pineal gland. The biosynthesis of melatonin is given in Fig. 1-A. It begins with conversion of the amino acid tryptophan into 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. Decarboxylation of 5HTP by 5-HTP decarboxylase gives rise to 5-hydroxytryptamine (5-HT) or serotonin. Serotonin is N-acetylated to form N-acetylserotonin by the enzyme serotonin N-acetyl transferase (SNAT) which is the rate limiting enzyme in the bio-synthesis of melatonin. N-acetylserotonin is methylated to form melatonin by the enzyme hydroxyindole O-methyl transferase (HIOMT). HIOMT is almost exclusively found in the pineal gland, although recent studies have demonstrated the presence of this enzyme in retina also. The synthesis of melatonin involves many other cofactors like S-adenosylmethionine, S-adenosylhomocysteine, and pteridines (10). All other 5-hydroxyindoles present in the pineal gland can be methylated to form methoxy indoles like

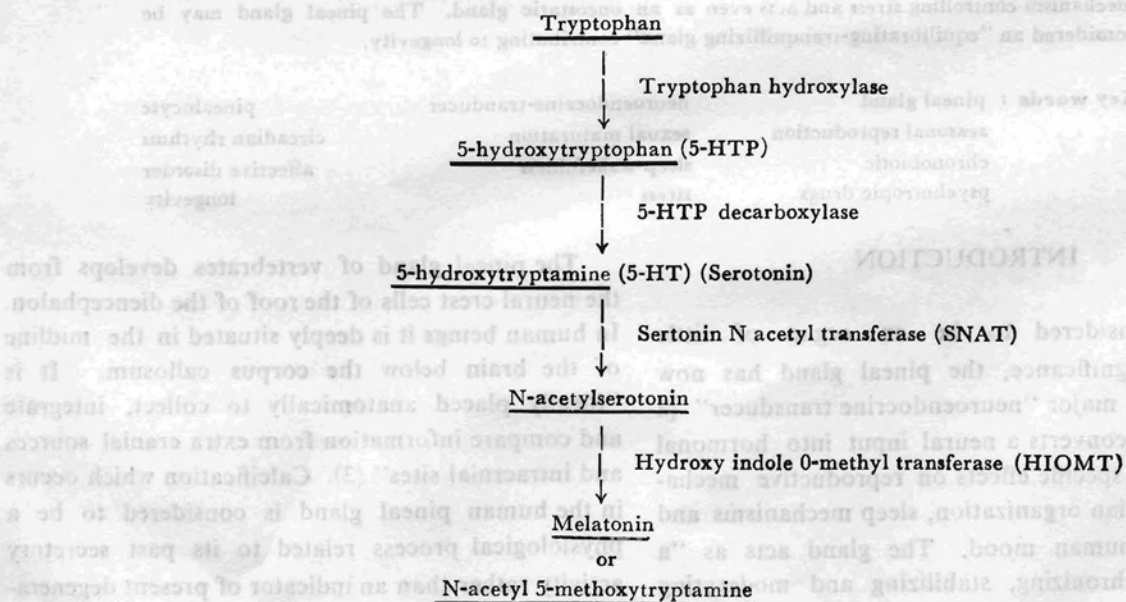


Fig. 1-A : Biosynthesis of melatonin - the major pineal hormone

5-methoxytryptophan, 5-methoxytryptamine, 5-methoxyindole 3-acetic acid and 5-methoxytryptophol. Figure 1-B gives the bio-synthetic pathway for the formation of all these methoxy indoles. The biologically active methoxy indoles include only melatonin and other two methoxy indoles like 5-methoxytryptophol and 5-methoxytryptamine.

Ultra structural and ultra cytochemical observations have shown that pinealocytes are capable of protein secretion (7). With the use of bioassay, RIA (radioimmunoassay) and immunocytochemistry many immunoreactive polypeptides have been identified in the pineal gland (11). Arginine vasotocin (AVT), a tripeptide threonine-serine-lysine, delta sleep inducing peptide (DSIP), S-antigen, and Calbindin 27 are some of the recently identified polypeptides in the pineal gland of vertebrates (10,12). Recently zinc-containing metallothionins also have been identified in the pineal gland of mammals (13). The principal route for the synthesis and secretion of proteins appears to be through endoplasmic reticulum, golgi complex and vesicular membrane bound compartments (11). The highly vascular pineal gland secretes their products directly into the cerebrospinal fluid, or into the perivascular spaces

to be transported by the blood (7) According to Wurtman (14) melatonin once formed is not stored within the pineal gland to any appreciable extent but is released into the circulation directly.

REGULATION OF PINEAL GLAND SECRETION

The secretion of melatonin, the major pineal hormone is rhythmic in nature, with high levels occurring in the night and low levels during the day. This rhythm persists even when animals or human beings are housed in constant environmental conditions (e.g. continuous darkness) suggesting thereby that the rhythm is largely endogenous in nature (14). The suprachiasmatic nucleus, the "master circadian clock", present in the hypothalamus, is largely responsible for this endogenous melatonin rhythm (15). It controls the activity of the pineal gland through the release of norepinephrine from the sympathetic nerve fibres, (Fig. 2). Increased release of norepinephrine from the sympathetic nerve fibres in night time increases the rate of synthesis of melatonin in the pineal gland (16). Light-dark cycle entrains the melatonin rhythm generated by the suprachiasmatic nucleus by acting through the

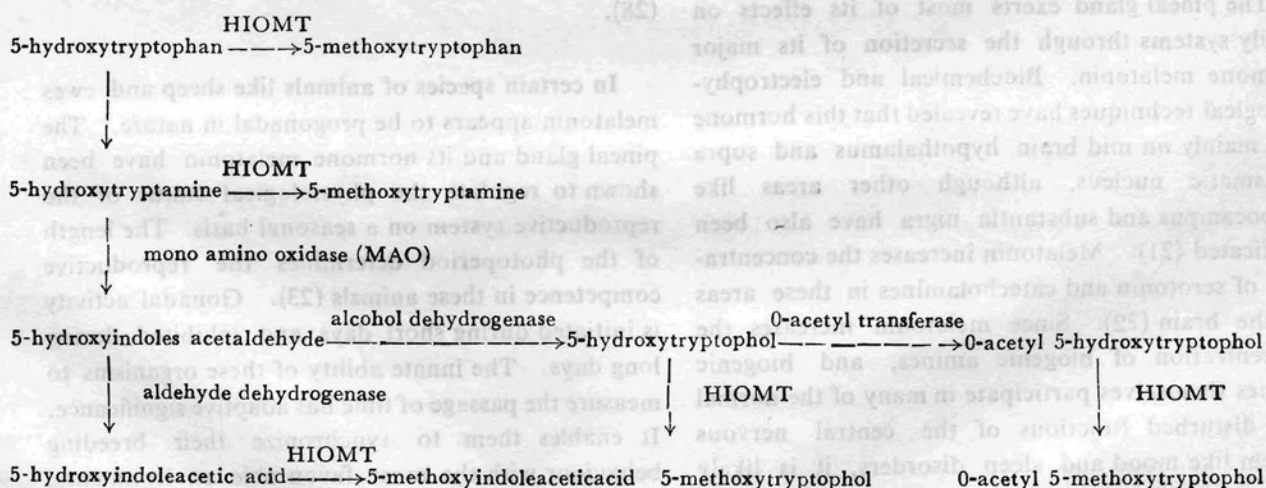


Fig. 1-B : Pathway showing the biosynthesis of hydroxy and methoxy indoles in the pineal gland

retinohypothalamic tract (17). The physiological significance of this mechanism is linked with the photoperiod control of melatonin secretion (14).

Electrophysiological and radioligand studies have shown that light impulses reach the pineal gland also through central pinealopetal projections (18). Many peptides like vasopressin, oxytocin, neurophysin, vasoactive intestinal polypeptide (VIP) have been identified in the central pinealopetal projections (11). Neurotransmitter receptor sites like beta adrenergic, alpha adrenergic, dopaminergic, serotonergic, GABAergic, glutamatergic, benzodiazepinergic, substance P-ergic, have been identified recently in the pineal glands of mammals including human beings. Extensive reviews on this aspect have been elegantly brought out by Ebadi and Govitrapong (19, 20). These pineal receptor sites are involved not only in the synthesis of melatonin and other methoxy indoles but also participate in the "biological expression of hitherto unknown functions of the pineal gland (21).

PINEAL GLAND FUNCTIONS

The pineal gland exerts most of its effects on bodily systems through the secretion of its major hormone melatonin. Biochemical and electrophysiological techniques have revealed that this hormone acts mainly on mid brain, hypothalamus and supra chiasmatic nucleus, although other areas like hippocampus and substantia nigra have also been implicated (21). Melatonin increases the concentration of serotonin and catecholamines in these areas of the brain (22). Since melatonin increases the concentration of biogenic amines, and biogenic amines themselves participate in many of the normal and disturbed functions of the central nervous system like mood and sleep disorders, it is likely that melatonin exerts some of its actions on bodily systems by influencing biogenic amine transmission in the central nervous system (21).

Melatonin, when administered in physiological doses, mimics the light dark cycle in the induction of photoperiod dependent responses (23). The hormone acts as a conveyor of photoperiodic information which is interpreted differently in different times of the year (24). Hence in recent years studies on pineal gland function have focussed mainly in seasonal cycles rather than on daily cycles (25).

Pineal Gland and Reproduction

The physiologic effects of melatonin on reproductive function in animals depend on the species, but suppression of gonadal function has been well documented as the primary effect of melatonin and related compounds in most of the species that have been studied (26). Initial studies carried out by Wurtman and his coworkers (27) showed that melatonin exerts a direct inhibitory action on gonads. Studies carried out on neuroendocrine-reproductive axis revealed that melatonin acts on the hypothalamic neurons where it reduces the amplitude and/or frequency of GnRH pulses and thereby exerts an inhibitory action on gonads through the inhibition of gonadotrophin secretion (28).

In certain species of animals like sheep and ewes melatonin appears to be progonadal in nature. The pineal gland and its hormone melatonin have been shown to regulate the physiological status of the reproductive system on a seasonal basis. The length of the photoperiod determines the reproductive competence in these animals (23). Gonadal activity is initiated during short days and inhibited during long days. The innate ability of these organisms to measure the passage of time has adaptive significance. It enables them to synchronize their breeding behaviour with the most favourable environmental conditions when the chances of survival of their young ones will be great (29, 30). The fact that melatonin rhythm changed as a function of season

was first shown by Arendt (31) who clearly demonstrated that longer nights were associated with more prolonged periods of high melatonin levels. The insertion of melatonin implants has been found to promote the onset of reproductive function in sheep even when they were exposed to inhibitory photoperiods (32, 33). The reproductive responses could reflect the presence of the "short day" produced by the constant elevation in circulating melatonin induced by melatonin implants (34). The induction of short photoperiod by careful administration of melatonin has been found to be of great commercial value in increasing either sheep breeding (35, 36) or growth of fur (37). Many studies also have pointed out that breeding in humans has two annual peaks and this has been attributed to the two distinct types of photoperiodic responses based on genetic heterogeneity (38).

Pineal Gland and sexual maturation

The occurrence of precocious puberty in a four year old boy with a pineal tumour was described as early as 1898 by O'Heubner. Studies carried out in recent years suggest that human pineal's secretory activity is associated with pubescence (14). Kitay and Altschule (39) on the basis of an extensive review of literature suggested that pineal gland has antigonadotropic effect on human sexual maturation.

In all mammals including human beings the onset of puberty has been attributed to the pulsatile secretion of gonadotrophin releasing hormone (GnRH) by the arcuate nucleus of the hypothalamus (40). Melatonin appears to have a direct and continuous regulatory action on gonadotrophin secretory pattern from infancy to the onset of puberty (41). In an extensive study carried out on human beings belonging to different age groups (1 to 80 years) they noted a steady decline in the nocturnal plasma melatonin levels from infancy to early adulthood and a steady maintenance of the levels thereafter. In summarizing the evidence for

the probable involvement of pineal gland in human puberty they have noted that melatonin deserves a very thorough examination for a possible action in the mechanism controlling human sexual maturation (42).

Pineal gland and circadian rhythms

Every organism exhibits certain kinds of biological periodicity which enable it to measure the passage of time. The most important one among these is the circadian rhythm which coincides with the 24-hour light and dark cycle. Under normal circumstances the endogenous rhythms are synchronized with or entrained to external events by environmental cues or zeitgebers (time givers) such as light-dark cycle (43). The daily rhythms such as rest-activity, temperature, REM sleep mechanism, electrolyte and cortisol excretion, have been well studied in man and other animals and are said to "free run" in the absence of any time cues when studied in specially constructed isolation bunkers (44, 45, 46).

Investigation on the control of these circadian rhythms has revealed the presence of an internal master biological clock in the supra chiasmatic nucleus (SCN) of the hypothalamus (43). Lesions of the supra chiasmatic nucleus abolish all known circadian rhythms in rodents (47).

Evidence for the possible involvement of pineal gland in the synchronization of circadian rhythms has come from the early observations of melatonin biosynthesis which exhibits a characteristic day and night rhythm. Melatonin is said to be one of the naturally occurring substances that affect circadian rhythmicity (48). A functional synchronizing role for the pineal gland was suggested by Armstrong et al (25) who administered melatonin in various physiological (10 microgram/kg body weight) and pharmacological doses (1 mg/kg body weight) and noted disruption of various behavioural rhythms in

experimental animals. In human beings, sudden rapid transfer across several time zones during intercontinental flights results in internal desynchronization, a phenomenon known as "jet lag". Short (49) first suggested that melatonin administration after an intercontinental flight would alleviate the jet lag phenomenon. Melatonin administration has been found to be really very effective in alleviating jet lag (24, 50). In an interesting study they also noted that late afternoon administration of melatonin has been shown to phase advance the fatigue-alertness rhythm (24). Melatonin is said to have a direct effect on the central rhythm generating systems and act as a circadian zeitgeber for darkness; hence the expression "darkness hormone". The function of the mammalian pineal gland is to adjust the phase and synchronize internal rhythms by periodic nocturnal release of melatonin. When administered in pharmacological doses, melatonin acts as a powerful chronobiotic maintaining synchronicity and preventing desynchrony within circadian systems (51). It has a potential value in treating external desynchronization that may occur in some categories of people such as astronauts, submariners and polar explorers and may be useful therapeutically in treating such diseases associated with biological rhythm disturbances (14, 24, 51). All these studies point out that pineal gland plays an important role in the physiology of circadian organization of vertebrates, although compelling evidence for the full involvement of this gland in the control of circadian systems is yet to be obtained.

Pineal gland and sleep mechanism

There is enough evidence to suggest that pineal gland and its hormone melatonin participate in the physiological regulation of sleep and sleepiness (52). Intrahypothalamic administration of melatonin induced sleep in cats (53). Studies carried out in other animals also supported the sedative like effect of melatonin. Following melatonin administration, sleep induction occurred in human beings also (54).

Vollroth et al (55) applied low doses of melatonin intranasally and found induction of sleep in healthy human volunteers. A number of other investigators also have noted that melatonin acted like the hypnotic agents (52). The hormone is believed to be released in pulses during light phases of human sleep and its probable physiological function is to induce deep sleep and to prevent awakening (56). Daily late afternoon administration of melatonin has been shown to phase advance the timing of sleep (35). The high rate of melatonin secretion during night hours and the induction of sleep by exogenous melatonin suggests that one of the physiologic functions of melatonin is to do with the timing of sleep (14). A clinical condition known as delayed sleep phase syndrome (DSPS) due to ineffective entrainment to zeitgeber (periodic events) such as light dark cycle, has been documented. In these patients the timing of sleep onset is abnormal. Since melatonin seems to be the natural chronobiotic it could be used effectively for correcting the sleep abnormality of these patients (51).

Melatonin and Human mood disorders

Depression, mania or hypomania are the commonest type of human mood disorders that are described in the literature. From psychiatric point of view depression covers a wide range of affective states which includes normal and abnormal mood swings. The etiology of morbid depression however remains unknown. Many biological theories have been put forward to explain the underlying causes of depressive illness.

Since some of these affective disorders are cyclic in nature, desynchronization of biological rhythms has been suggested as the cause for the precipitation of manic depressive diseases (57). With the recognition of pineal gland involvement in the control of various bodily rhythms, much attention has been paid in recent years linking pineal gland with affective disorders. Hypo-functioning of the pineal

gland as reflected by decreased levels of melatonin in body fluids was first noted in the year 1979 by Wetterberg (58). Many other investigators working in different parts of the world have also confirmed the presence of "low melatonin syndrome" in a group of depressives (59). These studies revealed certain forms of depressions could be due to biochemical defects in the synthesis, release and actions of melatonin (60). Supportive evidence for the involvement of melatonin in affective disorders came from the studies of psychoactive drug administration in experimental animals and in patients with affective disorders. The tricyclic antidepressants (imipramine) and monoamine oxidase inhibitor antidepressants increase the pineal melatonin content significantly in experimental animals (61, 62, 63, 64).

These drugs elevate the serum melatonin (65). Urinary melatonin (59, 66) or urinary 6 hydroxymelatonin levels (67). A schematic diagram depicting the probable mechanism of action of antidepressants in elevating melatonin concentration of the pineal gland is shown in Fig. 2. Both these drugs activate the beta receptors of the pineal gland by elevating the norepinephrine concentrations at the receptor sites. A specific disease known as seasonal affective disorder (SAD) with regularly occurring winter depressions was first noted by Rosenthal and his coworkers (68). Bright light was found to be very effective in treating such disorders and it seems to act by altering the profile of melatonin secretion in these patients (69).

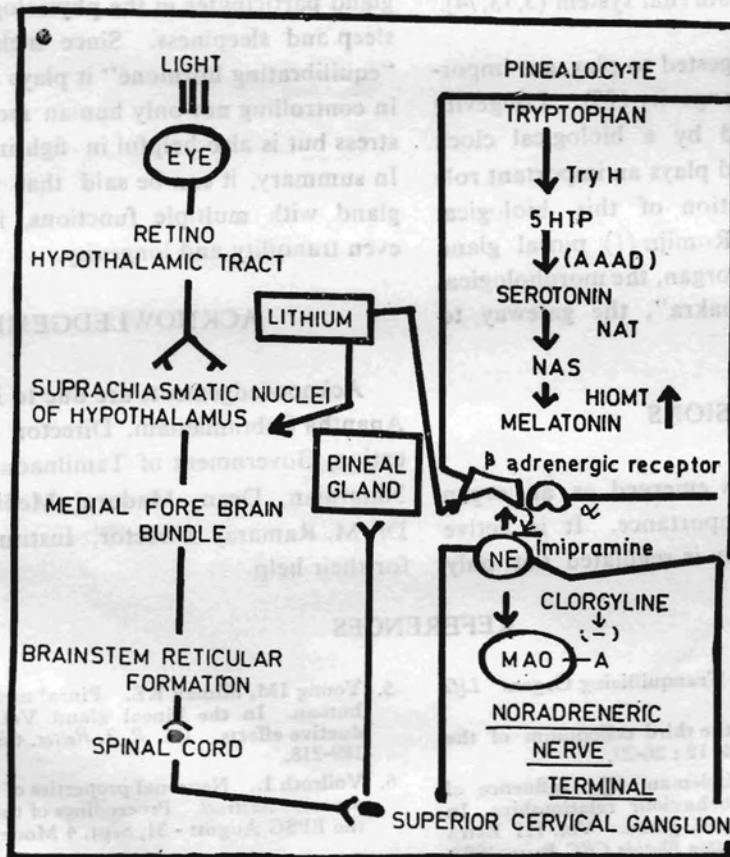


Fig. 2 : Effects of anti-depressants on pineal gland function.

Other miscellaneous functions of the pineal gland

Recently a great number of studies have been devoted to the study of pineal gland influences on cancer. Pineal gland extracts exert an inhibitory effect on tumour growth in experimental animals and this growth inhibitory effect seems to be related to melatonin only and not shared by other indoles (70). Melatonin exerts an inhibitory effect only where it is present in physiological concentrations (71) and the timing of melatonin administration seems to be crucial for arresting tumour growth (72).

The pineal hormone melatonin has been found to be antistressogenic in nature and it participates in the overall neuroendocrine mechanism involving hypothalamo-hypophyseal-adrenal system (3,73,74).

The gland has been suggested to play an important role in determining longevity (75). Longevity is believed to be regulated by a biological clock mechanism and pineal gland plays an important role in synchronizing the function of this biological clock (76). According to Romijn (1) pineal gland is the natural tranquillizing organ, the morphological substrate of the "seventh chakra", the gateway to perfect harmony and rest.

CONCLUSIONS

The pineal gland has now emerged as an organ of major neuroendocrine importance. It is active throughout life. Its secretion is regulated not only

by sympathetic nerve fibers but also by central pinealopetal projections. Many neurotransmitter-receptor sites have been identified in the pineal gland.

Melatonin, the major pineal hormone is responsible for most of the gland's effects on bodily systems. The pineal gland plays an established role in controlling reproduction. Though it is mainly antigonadotropic, it also has progonadal actions in some species of animals. In recent years there is growing evidence to suggest that pineal plays an important role in the mechanism controlling sexual maturation and puberty. Pineal hormone, melatonin, has a potential value in treating diseases associated with biological rhythm disturbances. The gland participates in the physiological regulation of sleep and sleepiness. Since melatonin acts as an "equilibrating hormone" it plays an important role in controlling not only human mood disorders and stress but is also helpful in fighting against cancer. In summary, it can be said that pineal gland is a gland with multiple functions, including possibly even tranquility and longevity.

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