Comprehensive Melatonin Profile

Overview

Determining the circadian analysis of melatonin can be a critical tool for accurately diagnosing endocrine dysfunctions, effectively treating mood and sleep disorders, and revealing contributing factors in the pathology of various diseases. It can also serve as a crucial chronobiological indicator of the aging process, gauging the body's natural protection against cell damage associated with oxidative stress.

Melatonin is the major neuroendocrine modulator of annual and circadian biorhythms in the body, and has a far-reaching biological influence over most of the autonomic, hormonal, and behavioral functions of the human organism. With its unique ability to pass through all blood barriers in the body, melatonin acts as the central hub of physiological function, orchestrating the complex interactions among the mind, the body, and the environment.

Melatonin's diurnal rhythm is synchronized by the light-dark cycle, and is strongly affected by day length, artificial illumination, electromagnetic energy, exercise, and other factors. Melatonin rhythms also reflect the biological process of aging. Secretion levels peak in childhood and diminish over an individual's lifespan. Since melatonin exhibits strong regenerative and integrative influences over the body, gradual decreases may explain the age-dependent weakening of immune function which can lead to malignancy, senescence, and eventually death.

Melatonin also has a pivotal role in regulating body temperature, the sleep-wake cycle, female reproductive hormones, and cardiovascular function. Hence disrupted secretion rhythms are widespread in many degenerative illnesses.

Great Smokies' **Comprehensive Melatonin Profile** is a convenient, reliable noninvasive test that analyzes the circadian secretion patterns of melatonin over a complete light-dark cycle. This profile can reveal imbalances of melatonin that may relate to physical and psychological symptoms and premature acceleration of the body's aging process. References ranges are based on a non-supplementing population and many not apply to individuals using certain forms of hormone replacement therapy.

Pineal gland

Located at the roof of the posterior portion of the third ventricle of the brain, the pineal gland is an endocrine organ with diverse roles. It has access to a rich supply of blood, and its hormonal products affect virtually every organ system in the body. The principle cellular components of the pineal gland are pinealocytes, which are arranged into cords or follicles separated by connective issue septa.

The pineal gland is innervated by the sympathetic nervous system, via the superior cervical ganglion. This innervation is essential for the rhythmic metabolism of indoleamines, such as tryptophan and serotonin and their derivatives, as well as the pineal gland's endocrine functions. Besides sympathetic innervation, the pineal gland also receives axons from the brain entering through the stalk. There is strong evidence to suggest parasympathetic, commissural, and peptidergic innervation as well.[1]

Melatonin Synthesis

Melatonin is the primary substance secreted by the pineal gland, which modulates the adrenal (HPA) axis during clinical illness, the serotonergic system in psychiatric disease, as well as the body's general response to stress.

Melatonin is synthesized within the pineal gland from tryptophan via the pathway shown in the figure above.[2] The secretion pattern is generated within the suprachiasmatic nucleus (SCN). Synthesis occurs upon exposure to darkness, with the increased activity of serotonin-N-acetyltransferase. By the action of hydroxyindole-O-methyltransferase (HIOMT), N-acetylserotonin is converted to melatonin. Melatonin is then rapidly secreted into the vascular system and, possibly, into the cerebrospinal fluid.[3]

Peripheral tissues, such as the retina and the gut, are also known to synthesize melatonin.[4]

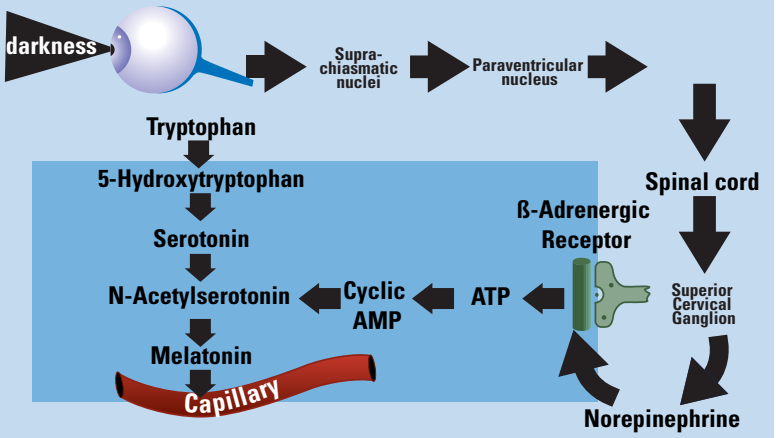
What this test does:

Analyzes Melatonin secretion pattern for imbalances that can lead to sleep disorders, SAD, infertility and compromised immune function.

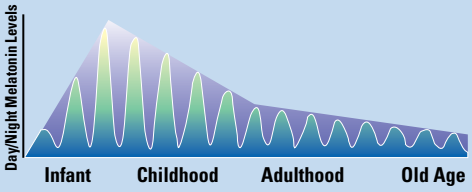
Turn-around Time 7 days

Great Smokies Diagnostic Lab

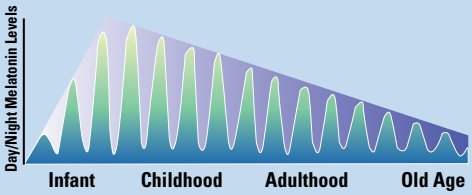
The Synthesis of Melatonin



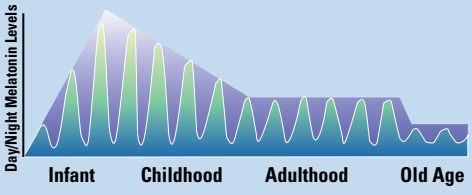
3 Patterns of How Melatonin Decreases with Age



A rapid drop in melatonin levels during childhood followed by a gradual decrease into adulthood and old age.



Gradual decrease starting in childhood and continuing into old age.



A rapid drop during childhood followed by a leveling off in adulthood. The sharp drop in melatonin during old age may be caused by a critical event in later life.

Aging

Melatonin production in humans begins at the age of approximately 3 months. Peak nocturnal levels occur between the ages of 1-3 years. Secretion levels decline as the individual develops sexual maturity, and drop 80% by the time adulthood is reached, diminishing even further with age.[5]

Light-Dark Cycles

Melatonin is synthesized and secreted during the dark phase of the day. The secretion rhythm is endogenous (internally generated), and generally persists in the absence of time cues, assuming a period that deviates only slightly from 24 hours. Thus, it is a true circadian rhythm.[6,7]

Melatonin secretion is related to the length of the night. The longer the night, the longer the duration of the secretion. If humans are kept strictly in darkness for 14 hours per day over a period of one month, the duration of melatonin secretion expands to cover almost the entire dark period. Conversely, if a subject is exposed to light for 14 hours per day, the duration of secretion shrinks to 10 hours, accompanied by concomitant changes in body temperature and sleep.[8]

Light Exposure

Light exposure of the retina alters the amount of serotonin metabolized to melatonin, via the neural pathways that connect the retina to the pineal gland.[9] The individual's visual system must be intact for proper synchronization of the melatonin rhythm. Blind persons commonly exhibit a pronounced lack of circadian rhythm, with free-running cycles generated internally despite the presence of other external time cues in their environment.[10,11]

Exposure to sufficient levels of light at night can rapidly reduce melatonin production.[12] One investigator found that after human subjects were exposed to one hour of light at midnight using 3000, 1000, 500, 350, and 200 lux intensities, melatonin levels dropped by 71, 67, 44, 38, and 16% respectively.[13]

The spectrum of light that most dramatically inhibits melatonin secretion is green band light (540nm), which corresponds to the rhodopsin absorption spectrum in humans.[14] This observation is of considerable importance, not only to understand the physiological effects of melatonin, but to effectively regulate circadian rhythms—a crucial component in the treatment of Seasonal Affective Disorder (SAD) and other health problems.[15]

Electromagnetic Energy

Laboratory studies with rats have consistently shown that exposure to electromagnetic fields can disrupt pineal function and circadian secretion patterns of melatonin.[16-19] One study on humans who used electric blankets concluded that periodic exposure to even low frequency electric or magnetic fields can significantly affect pineal gland function.[20] In an interesting study on electric power, pineal function, and breast cancer, investigators postulated that higher rates of breast cancer in industrialized nations may be due to increased light-at-night (LAN) and electromagnetic fields (EMF) suppressing human melatonin production.[21] Many modern occupations and conditions—including living near a power line—can drastically increase EMF exposure.[22,23]

Seasonal Variations

Seasonal changes can affect melatonin secretion patterns by advancing or delaying secretion phase shifts.[24,25] The exact nature of these variations is still not clearly understood, although factors such as length of photoperiod, temperature, and effect of seasonal changes on individuals may all be contributing factors.[26]

Effect of Drugs

Antidepressants and other psychotropic drugs affect the synthesis and release of melatonin. Some monoamine oxidase-inhibiting drugs such as clorgyline and tranyl-

cypromine seem to enhance plasma melatonin levels, while others, such as deprenyl, register no significant change.[27-30]

Tricyclic antidepressants that influence monoamine uptake and beta-adrenoceptors trigger a decrease in plasma melatonin in rodent experiments; however, human patients treated with the tricyclic desipramine show either no change, or a notable rise, in nighttime melatonin levels.[27,30] Although tricyclics and fluvoxamine are both associated with increases in melatonin secretion in humans, fluoxetine (commonly known as Prozac) reportedly lowers blood melatonin levels.[31]

One group of researchers conjectured that sleep disruption associated with some nonsteroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, and acetaminophen may be a result of decreased prostaglandin production, which can suppress melatonin secretion.[32] Both ibuprofen and indomethacin significantly reduce melatonin plasma levels and delay the nocturnal rise of the circadian rhythm.[33,34]

ß-blockers can also significantly alter melatonin levels. Hypertensive patients undergoing chronic beta-adrenoreceptor blocker treatment with propranolol and ridazolol showed considerably diminished melatonin secretion.[35] Propranolol hydrochloride also induced a noticeable decrease in serum melatonin levels in schizophrenic patients.[36]

Exercise

Research suggests that daytime exercise can increase melatonin levels. While some studies report that the increase occurs during or immediately after physical activity,[37-39] others point to a delayed rise that takes place in the second half of the dark phase.[40] One group of researchers found that nighttime exercise effectively blunts the nocturnal melatonin surge.[41] And, in a unique study undertaken by Swiss researchers, daily 1-hour morning walks outdoors were shown to phase advance the onset and/or offset of melatonin secretion, and were twice as effective as low dose artificial light therapy in relieving the symptoms of SAD.[42]

The Role of Melatonin

Mood and Behavior

Abnormalities of melatonin circadian function have been closely linked to a variety of behavioral changes and mood disorders. Determining the circadian secretion rhythm of melatonin can assist the clinician in diagnosing the type of mood disorder.

In general, studies have reported decreased nocturnal melatonin levels in patients suffering from depression.[43-45] One investigation of major depression in children and adolescents found that melatonin levels were significantly lower in depressed subjects with psychosis than in depressed subjects without psychosis.46 Subnormal levels of melatonin accompanied by a delayed circadian rhythm have also been reported in patients with panic disorder.[45]

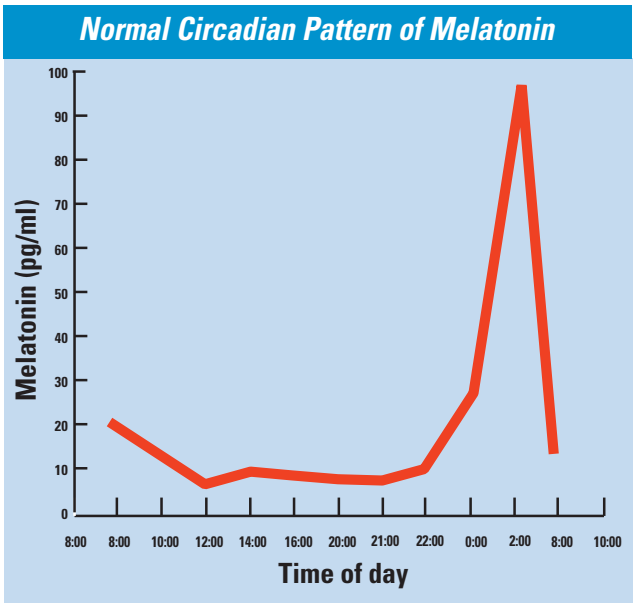
In a fascinating study on geomagnetic storms and depression, British researchers found that male hospital admissions with a diagnosis of depression rose 36.2% during periods of geomagnetic activity as compared with normal periods. The investigators hypothesized that this increase may have been caused by a phase advance in the circadian rhythm of melatonin production.[47]

In Seasonal Affective Disorder (SAD) melatonin secretion tends to be elevated. Since full spectrum light reduces the rate of melatonin secretion, light therapy can be very effective in treating patients with SAD.[48-49]

Body Temperature

In humans, melatonin is closely connected with changes in body temperature. The most striking example is the reciprocal relationship found in circadian profiles, where the lowest body temperature correlates closely with the peak level of melatonin. The ovulatory rise in temperature during the menstrual cycle is also associated with a decline in melatonin secretion levels. There is a possible causal relationship between the two phenomena, since exogenous melatonin can acutely depress body temperature in humans.[50]

Melatonin's effect on body temperature may be one of the keys of its ability to enhance sleep. Body temperature follows a circadian rhythm, rising during the day



and falling at night. The daily temperature variation in the human body is only about 1 degree, but this small difference has a dramatic influence on sleep. In general, a falling body temperature induces sleep, while a rising body temperature provokes wakefulness. It has been demonstrated that an individual will fall asleep most quickly and stay asleep the longest when lights are out, and the body temperature undergoes its most rapid decline.[51]

Sleep

Patients with delayed sleep phase insomnia cannot sleep until the early hours of morning, and often end up sleeping through much of the day. This condition has been treated successfully with exposure to bright light in the early morning to induce phase advances of the clock. An evening dose of 5 mg of melatonin at 11:00 p.m. has also been shown to advance sleep time significantly.[52] A combination of both methods—timed application of bright light in the morning and a dose of melatonin in the evening—seems to be the most effective therapy for treating melatonin rhythm disturbances.

Melatonin has not only been shown to advance sleep time, but to increase sleep duration as well.[53] It is also effective in reducing the symptoms of jet lag.[54] One study examined the effectiveness of melatonin in treating the sleep disorders in 100 children, who had a wide variety of physical problems including blindness, mental retardation, autism, and central nervous system diseases. Melatonin therapy was found to benefit over 80% of these children, and was lauded as a "safe, inexpensive, and very effective treatment of sleep-wake cycle disorders."[55] In general, smaller doses of melatonin appear to be just as effective as larger doses in inducing and sustaining sleep.[56]

Patients with sleep disorders are often given a prescription for a benzodiazepine, a family of drugs that includes Dalmane, Doral, Halcion, ProSom, Restoril, Valium, Xanax, and many others. Although these medications can be very effective, particularly in cases of anxiety-related insomnia, they have many limitations and adverse side affects, including anxiety, depression, and memory loss (anterograde amnesia).[57-59] Melatonin enhances REM and slow-wave sleep patterns with little or no adverse reactions.

Cancer

There is good evidence for photoperiod dependence and/or melatonin responsiveness in the initiation and evolution of certain cancers, particularly hormone-dependent cancers. Administration of melatonin significantly improved survival time and quality of life in patients with brain metastases due to solid neoplasms.[60] When used after first-line chemotherapy (cisplatin) for treating nonsmall cell carcinoma (NSC) of the lung, melatonin also successfully prolonged the survival time for patients with metastatic NSC lung cancer.[61]

Because of its powerful oncostatic effects and its estrogen-blocking ability, melatonin demonstrates particular promise in the treatment of breast cancer. Numerous studies have reported an inverse correlation between melatonin levels and the growth of estrogen-receptive positive tumors.[62-66] Used in conjunction with tamoxifen to modulate cancer endocrine therapy, melatonin shows marked ability to modulate estrogen receptor expression and inhibit breast cancer cell growth. Moreover, researchers surmised that melatonin may induce objective tumor regressions in metastatic breast cancer patients refractory to tamoxifen alone.[67]

Immune System

When properly administered, melatonin has general stimulatory effects on immune system functions; its positive anti-cancer effects may stem from this strengthening of the immune response.68 One theory is that melatonin acts as an anti-stress hormone via the brain opioid system, with consequent up-regulation of the immune system.[69,70]

Many researchers believe that T-derived cytokines are the main mediators of the immunological effect of melatonin. Specific high affinity binding sites for 125I-melatonin have been discovered on T-helper-type 2 lymphocytes in the bone marrow and in various lymphoid tissues.[71,72]

Multiple Sclerosis

Multiple Sclerosis (MS) is the most common of the demyelinating diseases of the central nervous system. The clinical course and prognosis of the disease is variable, although it typically tends to progress in a series of relapses and remissions. In most cases, a patient with MS undergoes a slow and steady deterioration of neurological function.

Recently, the pineal gland has been implicated in the pathogenesis and clinical course of MS. When melatonin levels decline, an exacerbation of MS symptoms is seen.[73,74] Remission effects in MS are thought to relate to the stimulatory influence of melatonin on the immune system.

In one study, [32] MS patients were randomly selected from patients consecutively admitted to a neurology service in a hospital for exacerbations of their symptoms. Nocturnal levels of melatonin and the activity of the pineal gland were monitored over the course of each patient's illness. The study revealed a progressive decline in melatonin levels over the duration of the illness. Since patients with chronic progressive MS had a lower mean melatonin level compared to those with a relapsing-remitting course of the disease, an analysis of melatonin levels may be crucial for understanding the pathophysiology of MS and, specifically, the course of its progression.[75]

Antioxidant Activity

Free radicals, especially the hydroxyl radical, can be extremely damaging to cells. Melatonin has both water and fat soluble properties, making it one of the only known antioxidants in nature that can protect all parts of a cell. Since melatonin has the unique ability to navigate any body barrier with ease—including the blood-brain barrier and the placental barrier[76]—it can protect virtually every cell in the body.

Recent evidence suggests that melatonin plays a critical role in free radical scavenging activity, preserving macromolecules such as DNA, protein, and lipid from oxidative damage.[77,78] In fact, melatonin has been proven more powerful than both glutathione and mannitol in neutralizing hydroxyl radicals and may protect cell membranes more effectively than vitamin E.[79,80] Remarkably, it is five hundred times more efficient at protecting cells from radiation than dimethyl sulfoxide (DMSO).[81]

Cardiovascular Disease

A decrease in melatonin causes increased nighttime sympathetic activity, which in turn appears to increase the risk for coronary disease. One study found that patients with coronary heart disease had nocturnal melatonin levels five times lower than in healthy controls. Investigators surmised that lower levels of melatonin may act to increase circulating epinephrine and norepinephrine, which have been implicated in damage to blood vessel walls. Atherogenic uptake of LDL cholesterol is accelerated by these amines at pathophysiological concentrations.[82]

Research conducted on laboratory rodents has shown that melatonin treatment exerts the beneficial effect of increasing the HDL/total LDL cholesterol ratio, perhaps by enhancing endogenous cholesterol clearance mechanisms.[83] Specific binding sites for the melatonin agonist 2-[125I] iodomelatonin have been discovered in the heart (and lungs) of various animals.[84] In addition, melatonin seems to inhibit platelet aggregation. Platelet aggregation plays a significant role in the progression of cardiovascular disease.[85]

Ovulation and Pregnancy

Recently melatonin has stimulated the interest of researchers for its potential use as an oral contraceptive. Researchers have established a negative correlation between melatonin and sex steroids, independent of gonadotrophin activity.[86] Increased secretion of melatonin in winter appears to suppress or inactivate the hypothalmic-pituitary-gonadal reproductive axis, which in many species results in a limited, seasonal period of reproduction.[87] This natural form of contraception occurs via the hypothalamic GnRH pulse generator. It is postulated that a melatonin/ovarian steroid contraceptive could re-activate this anovulation mechanism in humans, and one melatonin-based contraceptive is already undergoing Phase III clinical trials.[88] Long term use of such a contraceptive could reduce the risk of breast cancer by preventing the proliferation of epithelial breast cells caused by continuous ovulatory cycles.[89]

Significant increases in melatonin have been noted in women during the luteal phase of ovulation.[90] In animal studies, pharmacological doses of melatonin caused no harmful effects on developing embryos, suggesting that the administration of melatonin may be safe during pregnancy.[91]

Melatonin Rhythm Assessment

Melatonin secretion levels are low during the day and high at night, peaking at about 2-3 a.m. for most healthy individuals. This circadian rhythm makes melatonin one of the best markers for circadian rhythm disruption available at this time.

Scientific literature demonstrates excellent circadian plotting obtained by saliva analysis.[92-95] Since salivary and serum melatonin levels correlate well, Great Smokies' **Comprehensive Melatonin Profile** offers the patient a safe, economical, and non-invasive way of assessing pineal function and melatonin secretion patterns. Results can be useful in treating any of the wide variety of disorders associated with abnormal melatonin levels.

The profile plots melatonin activity based on 3 saliva samples taken at morning, evening and midnight. The figure below shows the normal circadian melatonin pattern for one patient over a 24-hour period.

Clinical Therapeutics

Once a diagnosis has been made, results can be used to design and implement successful therapeutic programs. Melatonin therapy has been shown effective in treating hormonal rhythm disturbances that aggravate symptoms of PMS, insomnia, fatigue, and mood disturbances. Patients with insomnia or disturbed sleep cycles frequently show a marked improvement in sleep patterns after being given carefully administered oral doses of melatonin. Ovarian problems resulting from the untimely secretion of estrogen and progesterone can also often be resynchronized with melatonin replacement therapy.

A dose of melatonin in the evening is often the most effective treatment for melatonin rhythm disturbances featuring subnormal melatonin secretion. The Comprehensive Melatonin Profile provides crucial information for the clinician to help determine appropriate dosage levels. References ranges are based on non-supplementing individuals and may not apply to patients using hormone replacement.

For abnormally elevated levels, application of bright light in the morning is helpful, particularly for mood disturbances such as Seasonal Affective Disorder (SAD). Exercise also holds great promise for treating melatonin imbalances, since physical activity may alternately raise or lower melatonin levels, depending on the time it is performed.

Related Tests to Consider

Bone Resorption Assessment

Melatonin is thought to regulate calcium metabolism by stimulating the activity of the parathyroid glands and inhibiting both calcitonin release and prostaglandin synthesis. Thus a decline in melatonin levels may be an important contributory factor in the development of postmenopausal osteoporosis. One investigator has even suggested using oral doses of melatonin combined with light therapy for prophylaxis and treatment of post-menopausal osteoporosis.[96] The Bone Resorption Assessment reveals current rates of bone loss with the most specific bone resorption analysis available.

Oxidative Stress Analysis

Numerous studies have reported on the remarkable antioxidant properties of melatonin, which may occur when melatonin supplies a cell with NADPH2-reducing equivalents.[97] Depressed levels of melatonin can be accompanied by an excess of free radicals, resulting in cellular damage, impaired detoxification and increased risk for many diseases. A sensitive assessment that utilizes acetaminophen and salicylate challenges, Great Smokies' Oxidative Stress Analysis thoroughly evaluates the body's oxidative stress and antioxidant potential. This analysis can be performed by itself or as part of the Comprehensive Detoxification Profile, an in-depth evaluation of the liver's ability to convert and clear toxic substances from the body.

Adrenocortex Stress Profile

A substantial body of research underscores melatonin's capacity to regulate the HPA axis. Patients with hypercortisolism often exhibit decreased melatonin levels with a disrupted circadian rhythm.[98] Melatonin has also been shown to greatly affect cortisol levels in post-menopausal women.[99] Additionally, interactive patterns of melatonin and cortisol secretion have been associated with behavior disorders such as depression and alcoholism.[100] Recent laboratory evidence reveals that melatonin also stimulates production and secretion of the adrenal hormone dehydroepiandrosterone (DHEA).[101] The Adrenocortex Stress Profile measures production of the major adrenal hormones cortisol and DHEA, which are actively involved in the body's development, growth, immune response, and cardiovascular function. Used in conjunction with the Melatonin Profile, this profile can provide the clinician with a more detailed, comprehensive picture of how endocrine function may be affecting patient symptoms.

Male Hormone Profile/Female Hormone Profile

The interdependent relationship between pineal function and sex hormones has been borne out it by several studies. One possible explanation is that sex hormones regulate melatonin production by modifying beta-adrenergic mechanisms.[102] Using the results from the Female Hormone Profile, a graph of ß-estradiol and progesterone activity can be conveniently compared with melatonin secretion patterns. Since melatonin is theorized to entrain the nocturnal secretion of testosterone,[103] the results of the Male Hormone Profile can also be crucial for a better understanding of how melatonin secretion may be influencing other basic hormone functions.

How do I order this test?

For Comprehensive Melatonin Profile kits or information, please call a GSDL Accounts Receivable representative at 888-201-8333 or use our secure web contact center at www.gsdl.com/billing.

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