human MFG membranes might be of some biological relevance
towards the prevention of infection in neonates and infants, even
though it remains unclear how much of the ingested human MFG
and MFG membranes serve solely nutritional purposes.

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EDITORIAL COMMENTS

The Use of Melatonin for Sleep

Melatonin (N-acetyl-5-methoxy-tryptamine), the major hormone
produced nocturnally by the pineal gland, serves as a signal of
darkness in the organism.1 This hormone has recently come to public
awareness as a miraculous therapeutic agent in a variety of maladies,
and the exaggeration of the beneficial effects attributed to melatonin
has already brought about intense criticism from the scientific world.2
Nevertheless, research on melatonin for over 40 years indicates that this
hormone is involved in a variety of physiological systems, suggesting
possible clinical implications and therapeutic interventions.

The circadian pattern of melatonin production and release is
controlled by an endogenous biological clock located in the suprachiasmatic nucleus of the hypothalamus. The primary natural
synchronizer of this hypothalamic oscillator is light perception by
the retina.3 Melatonin is released from the pineal gland soon after
its synthesis and, due to its lipid solubility and low molecular
weight, it is widely distributed in all body tissues including the
brain.4 Melatonin is metabolized in the liver and is rapidly elimi-
nated by the kidney, predominantly as 6-sulfatoxymelatonin.5
The average serum half life of melatonin in humans is 48 min.6
Nocturnal melatonin concentrations in serum and biological
fluids decrease with advancing age.7 This primary age-related
change is associated with disturbances in the sleep-wake cycle.8
Several clinical syndromes and drugs are associated with melato-
nin abnormalities. For example, patients with primary degenera-
tion of the autonomic nervous system and diabetic neuropathy,
coronary heart disease, ischemic stroke, and several types of
neoplasms may have a decreased nocturnal melatonin profile.9
10-12 β-blockers and clonidine, which are widely used for the treatment
of hypertension, naloxone, ibuprofen, and alcohol, may all decrease
serum melatonin concentrations.7 Benzodiazepines, which are the most commonly used drugs for the treatment of insomnia,
may paradoxically suppress the nocturnal rise in plasma melatonin
and shift its day-night rhythmity.
A large body of evidence indicates that melatonin output varies
with sleepiness in healthy individuals. Elevated serum endogenous
melatonin concentrations correlated with fatigue and sleepiness while
sleep deprivation was found to increase serum levels of melatonin.10
Both the duration of melatonin secretion and sleep have been found
to respond to changes in day length.12 Tryptophan, which has been
widely used as a natural sleep-promoting agent, increases circulating
serum melatonin. In hypertensive patients treated with β-blockers, the decrease in serum melatonin was significantly correlated with the percentage of nights with poor sleep. In addition, in middle-age and elderly subjects, 6-sulphatoxymelatonin levels were found to be significantly lower in poor compared to good sleepers.

Data on the effects of exogenous melatonin on insomnia have been inconclusive. Notably, in many of the studies where melatonin was given as a drug, previous measurements of endogenous melatonin concentrations in serum (or of its metabolites in urine) were not performed. In other words, various doses of exogenous melatonin were given to humans who might have initially had normal, shifted, or decreased production and secretion of the endogenous hormone.

Following intravenous, intranasal, and oral administration of melatonin, sedative effects have been demonstrated in healthy young individuals. In most cases these experiments were performed during daytime hours, when endogenous plasma melatonin concentrations are low. Apart from a direct hypnotic effect, exogenous melatonin can affect sleep through its phase-resetting action on the biological cycle. Administration of melatonin in the evening can advance sleep in patients with delayed sleep phase syndrome (who can fall asleep only very late at night) and synchronize sleep to the day-night cycles in blind subjects. The time of administration is of crucial importance in determining the phase-shifting effects of melatonin; exogenous melatonin may advance, delay, or not affect the endogenous melatonin rhythm, depending on the time of administration. It may be concluded from these data that melatonin administration may improve sleep by producing a short-term sedative effect, and by phase shifting a desynchronized circadian system.

Because of its fast clearance, regular melatonin formulations can produce physiological levels for only 2–4 h. Sustained-release formulations can circumvent the fast elimination of the hormone and produce peak serum concentrations that remain within the physiological range for the night period. Our group has compared controlled release with regular melatonin preparations (2 mg) in melatonin-deficient insomniacs. Sleep efficiency significantly improved following administration of controlled-release melatonin but not regular melatonin as compared to placebo. However, sleep latency (the time needed to fall asleep) was more improved with the regular compared to the controlled-release formulation. Sleep initiation and maintenance further improved following 2 mo of treatment with the 1-mg controlled-release melatonin formulation, indicating that tolerance had not developed. Sleep quality deteriorated again within 2 mo after cessation of treatment.

The effects of the aforementioned controlled-release melatonin on sleep quality were studied in elderly insomniacs who had been receiving various medications for chronic illnesses as well as in elderly subjects who had consumed benzodiazepines for sleep induction. In all of these subjects, the peak excretion of nocturnal 6-sulphatoxymelatonin was lower than normal and delayed, in comparison with elderly good sleepers. In both studies, sleep efficiency and wake time after sleep onset were significantly improved following 3 wk of treatment with controlled-release melatonin. In benzodiazepine users, controlled-release melatonin significantly improved sleep latency as well. Objective measurement of these parameters may show improvement in sleep as early as 1–3 wk following the onset of replacement treatment. In our experience, however, subjective improvement varies markedly between individuals and in some elderly insomniacs several months elapsed before a subjective improvement of sleep quality was reported.

The results of our studies are compatible with the hypothesis that melatonin deficiency plays a significant role in the pathogenesis of insomnia in the elderly population. These data also indicate that melatonin replacement therapy can improve sleep quality in elderly insomniacs to the level found in non-insomniacs of comparable age.

Based on the current scientific and clinical knowledge, there seem to be at least two clinical indications for melatonin therapy in sleep disorders:

1. Replacement therapy in subjects with low or absent nocturnal melatonin concentrations (hypomelatoninemia) of any cause (aging, disease, or drug therapy). In these patients the goal is merely to regain normal melatonin status, and is better met with the controlled-release melatonin formulation.

2. Phase-shift of the circadian rhythm. This may be the main objective in specific clinical settings such as blind people, jet-lag, or delayed sleep-phase syndrome. For phase resetting, regular release melatonin has proven efficacy.

The decision on whether to apply melatonin therapy and what preparation to choose would be more accurate if preceded by evaluation of the patient’s melatonin output. Assessment of 6-sulphatoxymelatonin in urine collections of 4 h intervals for 24 h, provides a good measure of melatonin output and profile. When both melatonin output and its peak time are within normal range, exogenous melatonin of any kind is less likely to improve the existing sleep disturbances. If total melatonin output is normal but its nocturnal pulse is delayed, regular melatonin given in the evening may help reset nocturnal sleep.

Melatonin is produced by the pineal gland of all vertebrates and can thus be extracted from pineal preparations of cattle, cows, etc. However, the amounts produced are small and a risk of contamination by deleterious agents exists. Hence, most if not all of the preparations presently used contain chemically synthesized melatonin. Recently, it has been found that melatonin is produced in edible plants such as tomatoes, bananas, and plants of the rice family. The consumption of plant materials that contain the hormone may theoretically serve as replacement therapy for melatonin deficiency. Yet, the bioavailability of plant melatonin in humans is yet unknown and the large quantity of plant material that has to be consumed makes this source of melatonin quite impractical. Furthermore, it is difficult to determine whether the ingested melatonin would achieve physiological levels of the hormone throughout the night.

Presently, no melatonin formulation has been approved for clinical use by any regulatory authority. Further clinical studies are still needed to determine the recommended doses, timing, and duration of melatonin use and long-term effects. Giving melatonin at the wrong dose or time of the day may incorrectly reset the body’s clock, thus altering a variety of physiological and endocrine rhythms. Other complications such as receptor down-regulation or unwanted side effects may become apparent at doses producing supraphysiological serum levels of the hormone. Therefore, physicians should gain full control of the use of melatonin and be the only discipline deciding on the indications for therapy, what preparation should be given, and when and how to use it.

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Mediterranean Diet in the Prevention of Coronary Heart Disease

The Traditional Mediterranean Diets

In 1986, in an editorial of the American Journal of Cardiology, Henry Blackburn described “the low risk coronary male,” documented to live on the Isle of Crete: “He is a shepherd or small farmer, a beekeeper or fisherman, or a tender of olives or vines. He walks to work daily and labors in the soft light of his Greek isle. . . At the end of the morning’s work, he rests and socializes with cohorts at the local cafe under a grape trellis. . . His midday, main meal is of eggplant, with large livery mushrooms, crisp vegetables and country bread dipped in the nectar that is golden Cretan olive oil. Once a week there is a bit of lamb. Once a week there is a chicken. Twice a week there is fish fresh from the sea. Other meals are hot dishes of legumes seasoned with meats and condiments. The main dish is followed by a tangy salad, then by dates, Turkish sweets, nuts or succulent fresh fruits. . .”

Although we are not against introducing poetry in Science and Medicine, it is clear that the traditional Cretan way of living and eating, as reported by Henry Blackburn, is actually not transferable to coronary patients living in the USA or France as it is; rather as it was, because, unfortunately, it is likely that few people are still living like this “low risk male,” even in Crete. This particular way of eating, however, should not be rejected (as being not applicable to the present European or US urban conditions) but adapted to each specific situation or country. We should not forget the lessons of the past.

In addition, it is important to recall that the Cretan diet is not the only Mediterranean diet associated with protection against coronary heart disease (CHD) and it could be useful to consider Mediterranean regions other than Crete, for instance South Italy or Spain. In fact, there are several types of traditional Mediterranean diets, quite different in terms of foods and dishes and dependent on historical and geographical characteristics. There are, for instance, non-negligible differences between Eastern (Greek, Turkish, Egyptian) and Western (Spanish, Portuguese, Sicilian, Tunisian) Mediterranean diets and between north and south of the Mediterranean Sea (North Africa versus the south of France, for instance) as dietary habits reflect cultural and religious differences.

In terms of nutrients, however, and in order to simplify the picture for non-Mediterranean readers, it could be said that apart from the intake of lipids (about 30% of total energy in the Western diet and