The Next Step in Sleep Dentistry:

Is There Anything We Can Do For The Ones Who Don't Have Apnea?

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Dentists have become involved in the treatment of sleep apnea for several reasons. An oral appliance is usually less uncomfortable than sleeping with a continuous positive airway pressure (CPAP) mask, so dentists offer a welcome alternative for CPAP intolerant patients. Also, the growth and development of the jaw and palate control airway function, therefore; dentists play an important role in the diagnosis and treatment of childhood sleep disorders. Now that we know that sleep plays an important role in health, dentists are asking about their patients' sleep and sleep-related medical problems. Often what they hear from their patients is that they sleep poorly, they're always cranky, or they wake tired and in pain. If the sleep study shows significant apnea, then the appropriate treatment is clear but what if there's no apnea? What if the patient is wearing an oral appliance or a CPAP mask but is still suffering effects of poor sleep? Is there anything else to offer?

Sleep Disorders Are More Than Just Apnea

Looking back on twenty years of treatment of sleep disorders reveals the unfortunate fact that we have concentrated on apnea to the exclusion of other sleep disorders because we know so little. We don't know why sleep disorders are epidemic in developed countries and are now spreading into undeveloped countries.[1-3] We don't know why our patients stop breathing. We don't know why some people have to move to their recliner to be able to sleep, even with their CPAP mask on. Because we don't know why, the best we can do is open the throat and force air in. We make up stories to explain why they stop breathing; "fat neck" or "fat tongue". But if the tongue is fat, it's fat all the time. The breathing difficulty occurs, by definition, during sleep. This suggests that the airway changes during sleep.

For those patients who can't sleep, it's even worse. We blame them for their disease. We give sleep medications that are addictive and only partially successful because we don't know what else to do. Those few who are lucky enough to still have normal, fully restorative sleep can't understand what all the fuss is about because they just lie down and go to sleep. But sleep experts now recognize that inadequate sleep, sleep that doesn't include deep sleep, and sleep interruption from any cause, all increase our risk of chronic disease.[4-12] Stated another way, I believe that many of our patients are sick *because* they are not healing in sleep.

I am a general neurologist who became interested in sleep in 2005 when one of my young, daily headache sufferers had complete resolution of her headaches by wearing a CPAP device. The link between daily headache and sleep is only now beginning to be reported[13,14] but because of her dramatic improvement I started to send all of my headache patients for sleep studies. I sent several hundred daily headache sufferers for sleep studies. They were all abnormal! The confusing part was that they didn't usually have apnea, and if they did have apnea they sure didn't look like what I'd been taught to look for. Most of them were young, healthy females and their sleep studies showed reduced or absent rapid eye movement (REM) sleep. Children showed the same. Why would these apparently normal young people have no REM sleep?

Once I started to ask my patients about their sleep it seemed that every patient in my practice had some sort of a sleep disorder. Children couldn't get up in the morning. Teenagers couldn't fall asleep. Young adults were tired every day and always had pain somewhere. My medications were only partially effective and "wore off" with time. Even the positive CPAP effects lessened over time.

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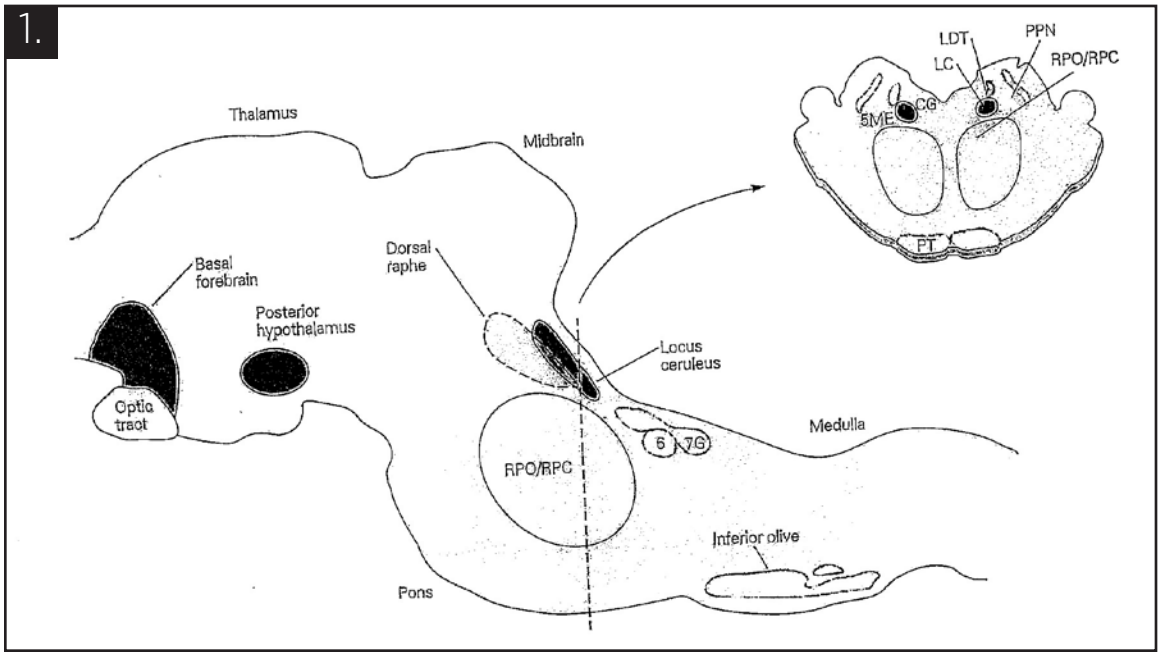

Brainstem anatomy of REM sleep. RPO/RPC: Reticularis Pontis Oralis/ Reticularis Pontis Caudalis. From: *Sleep and Dreaming.* Rechtschaffen A, Siegel J. Chapter 47, Kandel E and Schwartz J, Principles of Neural Science, 4th edition. McGraw-Hill;2000 ISBN 0-8385-7701-6

A recommendation of CPAP only made sense if they had apnea. What was I to do for the majority who did not stop breathing? They were just as depressed, headachy and forgetful as the ones who did stop breathing. The ones without apnea had no drops in oxygen, so the "not enough oxygen to the brain" explanation was clearly not the answer. Apparently the work of REM sleep was not being done. Maybe that was why they were also forgetful and cranky. Why was the REM sleep gone and how could we get it back again?

Brainstem Control Of The Airway During Sleep

Some of my young, healthy patients had sleep studies with more than one abnormality. I began to wonder about my eight-year-old patient with apnea *and* leg movements; his tonsils were out, his airway looked fine, why would he have one sleep problem, let alone two? Could his leg pain in the morning be related to those leg movements in sleep? To learn more I began to read about the brainstem control of sleep. There are specific brainstem nuclei, **(Figs 1 & 2)** the *nuclei reticularis pontis oralis and caudalis* that have connections to every muscle in the body. They paralyze us during deep sleep. What if they were malfunctioning and "wobbling" back and forth between two extremes? Could apnea be "too paralyzed" and leg movements "not paralyzed enough"? Could he have one brain malfunction that was producing both sleep study abnormalities? Other brainstem nuclei, right next door, allow us to switch in and out of the various stages of sleep. Was there something affecting this part of the posterior brainstem that could provide an answer and therefore a treatment for my patients?

Due to a series of fortunate accidents, in 2010, I stumbled on the clinical observation that all of the patients in my practice who had sleep disorders also had vitamin D deficiency. Since vitamin D deficiency is about as common as smartphone use, that observation would certainly not suggest a cause and effect. But a literature search about vitamin D and the brain led me to studies showing vitamin D receptors in the nuclei reticularis pontis oralis/caudalis and the other brainstem nuclei responsible for the transitions between sleep stages.[15-17]

Why Would There Be Vitamin D Receptors In The Brain?

In 1979, Dr. Walter Stumpf (working in the laboratory of Hector DeLuca, one of the major vitamin D laboratories of that time) published experimental results documenting the presence of vitamin D receptors in the intestinal tract, the stomach, kidney, skin, pituitary and parathyroid.[18] In the next ten years they published evidence of vitamin D receptors in multiple areas of the brain, the pancreatic islet cells, the thymus, the pylorus muscle, gastric endocrine cells, the salivary glands, the skin, the placenta, and the mammary glands.[19-31] Vitamin D was not a vitamin, it did not come from food, it

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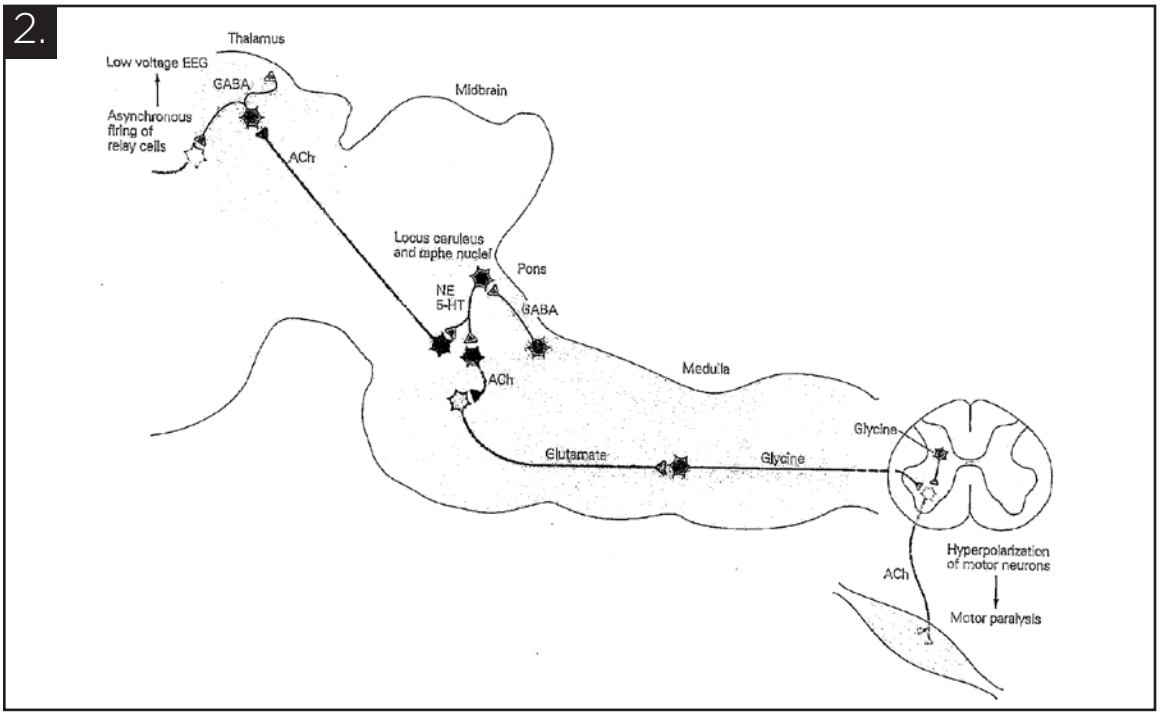


Neurotransmitters involved in the paralysis of REM sleep. From: *Sleep and Dreaming*. Rechtschaffen A and Siegel J. Chapter 47, Kandel E and Schwartz J, Principles of Neural Science, 4th edition (McGraw-Hill;2000 ISBN 0-8385-7701-6)

was a steroid hormone made on the skin from UVB light, the only wavelength not present in winter sunlight away from the equator. It was obviously *not* just about bones.

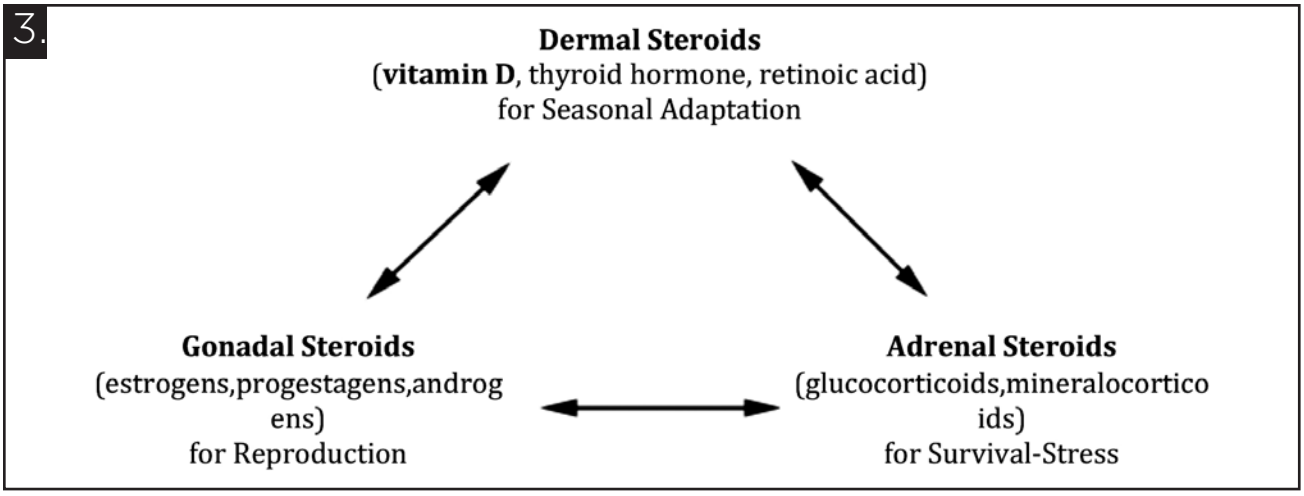
By the early 1980's, Dr. Stumpf had published a compelling theory that integrated hormone D into the rest of the endocrine system, the system that allows us to *adapt to change*. D hormone was responsible for "seasonal adaptation" and like all hormones, it had multiple effects on different parts of the body. Vitamin D receptors have been found in over thirty organs. Dr. Stumpf wrote extensively about the implications of these findings in mood disorders, infertility, immune system disorders, GI tract motility, skin disorders, and other related endocrine disorders such as hypothyroidism.[15,16,18-31]

If There Are Vitamin D Receptors On The "Sleep Switches" Could Vitamin D Be Used To Treat Sleep?

Because seasonal adaptation is clearly related to hibernation and therefore to sleep it seemed plausible that vitamin D supplementation might improve sleep. Two years of clinical observation in over 1000 patients showed that vitamin D supplementation to a vitamin D blood level of 60-80 ng/ml produced a definite subjective improvement in sleep. It worked in all types of sleep disorders including insomnia.[32] Based on my clinical observations and the documented D receptors in brainstem sleep nuclei, Dr. Stumpf and I published the hypothesis that Vitamin D deficiency was the underlying cause of the recent epidemic of all sleep disorders, not just apnea.[32] There are no confirmatory clinical trials as yet, though there is a clear epidemiologic link between sleep disorders and vitamin D deficiency.[33]

Why Didn't I Learn The "D Hormone, Seasonal Adaptation" Model In Dental School?

Despite mounting evidence to the contrary, the vitamin D scientific community remained tied to the "bone vitamin" dogma and fifty years of medical advances left vitamin D behind. The last ten years have produced numerous laboratory and clinical reports that corroborate Dr. Stumpf's publications.[34-43] A recent Pub Med search totals 65,000 articles about "vitamin D" published since the 1930's, 35,000 of them published in the last ten years. While the vitamin D scientific community argues about "vitamin vs hormone" the widespread use of air conditioning and sunscreen has changed our lives and produced a pandemic of D deficiency, the implications of which we are just starting to understand.



Vitamin D (soltriol) the steroid hormone for seasonal adaptation of growth, procreation and maintenance-survival. Interactions with gonadal and adrenal steroid hormones (incl. retinoic acid, thyroid hormone, melatonin. Stumpf WE. ref. 31).

Lack Of Understanding Produces Incorrect Use Of Vitamin D

Despite hundreds of articles showing epidemiologic links between vitamin D deficiency and chronic illness, despite bench research showing the varied effects of vitamin D receptor activation on many different cell types, those designing human clinical trials still grossly misunderstand the multilayered actions of this hormone. Most studies, both prospective and retrospective, are still designed with a study group on a specific dose of vitamin D (instead of a dose that achieves a specific blood level) compared to an untreated "control group" whose vitamin D blood level is not uniform or controlled.

Though hairless humans and pigs absorb this chemical through their skin most animals have fur or feathers and ingest the D3 that they make by self-grooming or preening. This means that it *is* usually taken orally by animals, birds, reptiles, and insects but it is not from food, *they are eating a product that they make on their own skin from sun exposure*. All animals have large amounts of D3 in their liver so eating raw liver does provide large doses of D3 but it was not meant to come from the food, it was meant to come from the sun.

The Vitamins D1 and D2 that were originally discovered and named in the 1930's were produced by fungus growing on grain given as food to laboratory rats. It appears that animals that are nocturnal must be able to effectively use D2 as their primary D source. But as the fossil record suggests that bacteria and fungi preceded the appearance of animals on this planet, D2, which is made by fungus and mushrooms, is probably a more primitive form of D3, and it is absolutely **not** identical. There is plenty of literature confirming the differences between Ergocalciferol, D2 and Cholecalciferol, D3.[44-46]

My patients experienced D2 very differently than D3. In my earliest use of D supplement, when I mistakenly thought that D2 had to be better because it was a prescription, my patients consistently reported that D2 had very negative effects on their sleep. Despite the fact that D3 is the animal chemical and D2 is the fungus chemical, it is still being recommended for treatment, and still being used in human clinical trials.

Vitamin D Did Not Fix Everything

There were two symptoms related to metabolism and the GI tract that never improved on D supplement; my obese patients did not lose weight. They slept better, exercised more, felt better but still didn't lose weight. Also, because irritable bowel syndrome (IBS) complaints were common, and D hormone has receptors in many parts of the GI tract, I expected the IBS symptoms to resolve and was disappointed when they did not improve.[47,48]

I continued to follow my patients' sleep and vitamin D levels for another five years. After two years the beneficial effect of a D level of 60-80 ng /ml began to wane. The patients' sleep complaints started to return and they began to report more and more pain. Something else was affecting their ability to sleep normally. Two young headache sufferers (on B12 supplement and on vitamin for two years) had a new, worrisome complaint of burning in the hands and feet.

Pantothenic Acid Plays A Role In Sleep

Serendipitously, a patient brought me a book about pantothenic acid (B5) and sleep. Eisenstein and Scheiner's book documented that 400 mg of B5 significantly improved pain and sleep in rheumatoid arthritis patients.[49] B5 is needed to make

coenzyme A, the cofactor required to make cortisol in the adrenal glands and acetylcholine in the brain.[50-52] Acetylcholine is a key neurotransmitter in REM sleep and paralysis during REM **(Fig. 2)**. The authors referenced studies done in the 1950's on convicts, that have never been repeated, showing that in a period of only two weeks a diet completely deficient in B5 produced burning in the feet, a puppet-like gait, abdominal discomfort and insomnia.[53-56] These were very interesting studies and I had several patients with unexplained gait disorders, but why would my patients be B vitamin deficient without a change in diet and why would it take two years to develop?

Hoping that my patients would return to sleeping better, and having nothing else to offer, I followed the recommendation of 400 mg of B5. Because I had no assurance that pantothenic acid was the only deficiency, and the B vitamins are very intertwined metabolically I also recommended B10057 (B100 is a non-proprietary B complex containing all 8 B vitamins 100 mg or 100 mcg of each except folate, 400 mcg). Importantly, my first attempt at supplementing pantothenic acid was very unsuccessful! Approximately 40 patients took part and the majority reported that the combined total of 500 mg of pantothenic acid made them agitated, "revved up" and unable to sleep immediately. Luckily, several of the patients stopped the 400 mg B5 supplement continued B100 alone and their sleep and pain were immediately much better. The two patients with the recent onset of burning neuropathy had immediate relief. This suggested that the patients had indeed developed a B vitamin deficiency after two years of D supplementation that was now affecting their sleep. The good news was that B100 returned their sleep to normal very rapidly. The bad news was that B5 acted like a neurotransmitter, had a very narrow dose range, and had no similar observations in the scientific literature. After three months of B100 most patients were able to stop the additional supplement and their sleep stayed better.[58] There was also improvement in weight loss and a dramatic improvement in IBS symptoms.

The Intestinal Microbiome, The B Vitamins And Sleep

In 2016, I published an hypothesis that attempts to explain why a secondary B vitamin deficiency might be induced by vitamin D supplementation, and why the combination of B100 plus D returned my patients intestinal function (and presumably the microbiome) back to normal, even though D supplementation alone did not).[58]

The normal intestinal microbiome is made up of four major species; Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria.[59] I believe they appear as a foursome spontaneously in our GI tract under the proper circumstances because they are commensal. They each provide one another at least one of the bacterial growth factors that we call the "B vitamins". Thus, the primary source of the B vitamins has probably always been the normal intestinal microbiome,[57,58] with the possible exception of niacin and B12. (All patients reported here were on separate B12 supplementation if blood levels were < 500 pg/ml as B12 is well documented to be related to sleep.)[60-62] This implies that anyone who has an abnormal microbiome also has a reduced ability to make B vitamins, regardless of their diet. Increased repairs during sleep appear to require more B vitamins, the building blocks of cellular repair. Thus, improved sleep might eventually result in depletion of B vitamin stores and produce clinical symptoms of B vitamin deficiency in someone who lacks the normal intestinal supply.

Some of the current beliefs about the B vitamins, such as "you can't overdose because we urinate out the excess" may be a misinterpretation of study results. My patients took months to years to develop what appeared to be B vitamin deficiency symptoms suggesting that there were body stores, at least of B5. In support of this interpretation are two studies that observed that large dose fluctuations in supplemented B5 did not result in significant changes in the B5 blood level but did result in changes in the urinary excretion. Both groups concluded that B5 has body stores and that the B5 blood level does not accurately reflect those stores (there are similar articles documenting the same for B6).[63,64]

Conclusions

Most sleep disorders can be more easily understood when grouped into two categories, both run by brainstem nuclei. The "clock" function governs the timing and time-locked progression of normal sleep stages. Patients with insomnia, inverted sleep phase syndrome and multiple unexplained awakenings without apnea may have malfunctions here. The "paralysis" function governs normal paralysis during deep sleep. This malfunction presents at the extremes as REM behavioral disorder (not paralyzed at all) or apnea (way too paralyzed), but also includes bruxism, chronic joint, neck and back pain, fibromyalgia, and sleep walking, just to name a few. These two categories often present together as a mosaic, probably depending on each individuals' ability or inability to make the correct neurotransmitters in the right place at the right time during sleep **(Fig. 2)**.

The type of sleep disorder is also dependent on the length of time the individual has been unable to repair their own "sleep switches". Normally functioning sleep switches have multiple, fail-safe, self-propagating and self-inhibiting connections that guarantee that we can ***never*** *be awake and asleep at the same time*.[65-67] The graphic representations of these multiple, mutually-inhibitory pathways are difficult to follow but they do convey the idea of signal redundancies.

Dr. Saper's group has used the term "flip-flop switch", stealing from the software industry where it describes an

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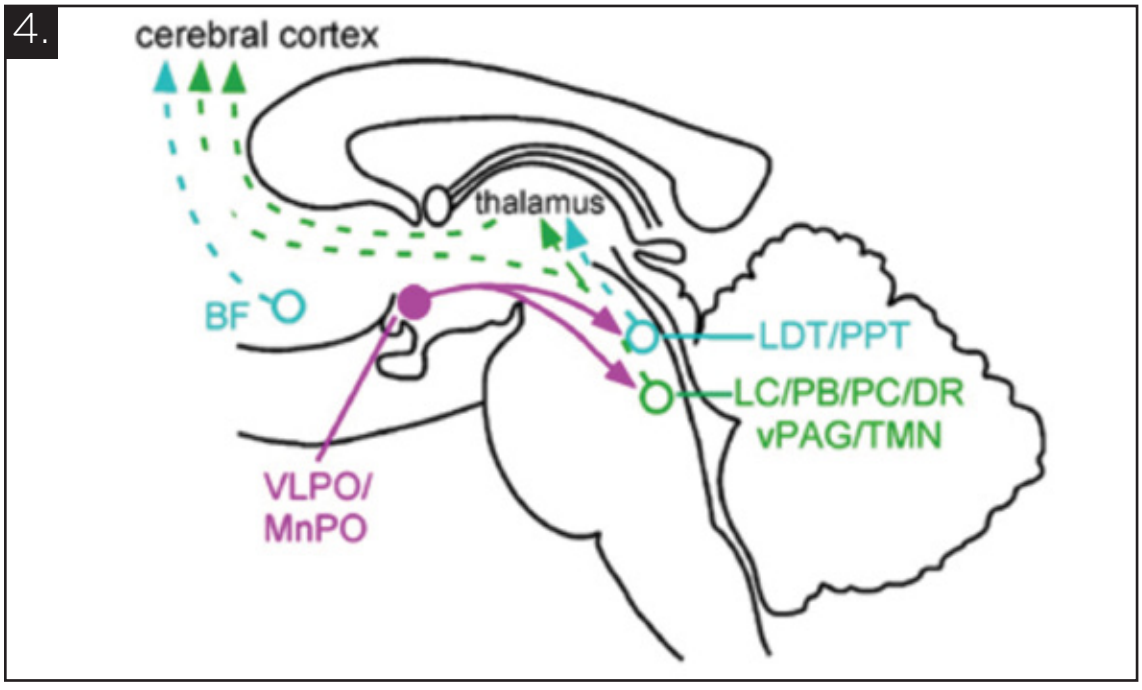

During sleep preoptic neurons inhibit the arousal system (from Saper C Ref. 67)

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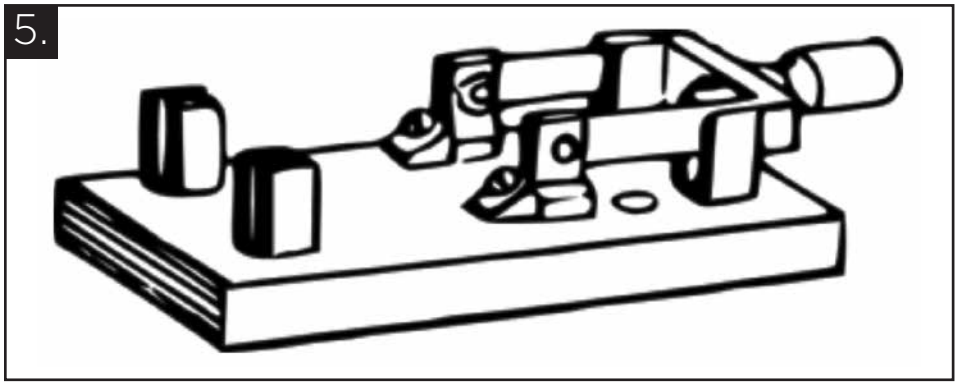

From Clipart Kid

intentional design that prevents states "A" and "B" from ever coexisting.[66] "Flip-flop switch" conveys the normal sleep/wake brain function but I think it is better represented by this more primitive graphic:

As abnormal sleep continues unabated for years on end the "sleep switches" lose the ability to properly coordinate. The patients tend to end up at one of two equally horrible end states; sleep inversion, sleeping during the day or not at all, or severe hypersomulence, which we've called narcolepsy. These are both severe disorders that take months to years to improve in my experience, even using everything described above.

The triad of narcolepsy, cataplexy and hypnogogic hallucinations is an excellent example of a severe malfunction that explains why we are designed not to be able to be awake and asleep at the same time. It is potentially fatal to become abruptly paralyzed while walking or driving. Cataplexy is abnormal activation of the nucleus reticularis pontis oralis caudalis during the wake state. Hypnogogic hallucinations are the coexistence of the REM dream state and the wake state.

In the last five years I have treated over 5000 patients with a regimen of B50 (50 mg or mcg of each B 400 mcg folate) or B100 plus vitamin D supplementation to keep blood level 60-80ng/ml with excellent results. The regimen successfully improved multiple sleep issues including insomnia, REM

behavioral disorder, narcolepsy, multiple unexplained awakenings, inverted sleep phase syndrome, and apnea (used as adjunct to oral devices or CPAP). I believe that the success of this regimen rests on the combined use of all treatment |modalities. All patients are unique and it is my belief that it is sleep, not vitamins, that promotes repair. The brain is designed to repair itself given the proper building blocks as well as the ability to enter and stay in deep sleep. I do not mean to make the overly simplistic statement that "vitamins fix sleep disorders". Instead, based on the positive results obtained by adding the above regimen to the existing treatment modalities, we should try to incorporate the little that we do understand about the brainstem control of sleep to our patient observations and our treatment protocols. **OH**

Oral health welcomes this original article.

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