Sleep without End

A long-forgotten epidemic teaches us about the science of slumber

Unity Kinkaid finds it harder and harder to stay awake. She now sleeps for almost 20 hours a day. She used to dream; to shift in her sleep, muttering and sighing, locked in half-remembered fantasies ... Now she lies unmoving, breath shallow and silent, lost to the world. Unity sleeps.


In the above-cited comic, a necromancer imprisons Morpheus, an immortal who is master of sleep and dreams. Consequently, people are unable to stay awake, sleeping the days, months and years away, until Morpheus escapes and restores the natural order. The chilling real-life inspiration for this compelling serialized comic was an epidemic that swept the world between 1916 and 1926. A hundred years after the first cases of “sleepy sickness” came to the attention of the medical community, we still do not know what agents were responsible for this disease.

It emerged from the cold, wet plains and trenches of northern France and Belgium, the battlefields of World War I, shorn apart and denuded of trees by the endless barrage of explosions from artillery, mines and machine-gun fire, a landscape crowded with millions of young men living under atrocious and unsanitary conditions at close quarters. Indeed, one of the most famous victims of the disease may have been Adolf Hitler, who was wounded at the Battle of the Somme.

Two physicians from opposing sides, Jean-René Cruchet in Paris and Baron Constantin von Economo in Vienna, identified the condition’s principal manifestation—its profound effect on sleep, that restorative period during which the body is at rest and the brain disconnects from the external environment. It was the clinical acumen of the aristocratic von Economo, a professor of psychiatry and neurology of Greek origin, whose masterful monographs on the subject gave us the best description of the disease and its underlying pathology of encephalitis, an inflammation of the brain.

Encephalitis lethargica (EL), epidemic encephalitis or von Economo disease

BY CHRISTOF KOCH

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starts with sore throat, nausea, headache, joint pain and fever—the general malaise associated with flu. From there the illness progresses to abnormal eye movements (which often cause double vision as the two eyes are no longer coordinated), drooping eyelids, an inability to open the eyes, and an irresistible need to sleep, day and night. This lethargy lasts for weeks, even in some cases for a year or more. Eleanore Carey, an eloquent young woman living in New York City, fell into a Sleeping Beauty–like trance in February 1923. Many years later she described these symptoms in a magazine article:

After two months of illness I was in little pain, in fact, I was very comfortable, provided they did not prod me nor stand me on my head, turn me over in bed nor dash cold water on my face to waken me. It was so heavenly just to be allowed to sleep, but these people around me seemed determined to prevent my being comfortable! When the idea finally crept through my sleeping brain that I must waken, it seemed to be a physical impossibility. I wanted to be obliging, but I just could not. It seemed to me to be just as difficult to come to consciousness as it would have been had I been buried in a pit as deep as the center of the earth, where the circular walls about me were of shiny, polished marble. There were no crevices for my fingers on its sides nor any places to put my feet, but I must climb out of that pit with my bare hands!… Perhaps it will give the reader a vague inkling of the dreadful lethargy which completely overpowers the victim of this disease and renders him impotent to make the effort to help himself.

These periods experienced by Carey and others came replete with vivid dreams, hallucinations and nightmares. When patients were woken up by calling their name or shaking them, they responded intelligently before quickly succumbing to somnolence again, often before they could fully provide answers to questions asked. The victims could not feed or clean themselves. In severe cases, they were stuporous or even comatose.

EL is a protean disease with some victims showing the opposite pattern, suffering from extreme insomnia or from inverted sleep—drowsy and lethargic during the day but delirious at night.

Mortality in this acute phase of the disease ran as high as 30 to 40 percent. Medical science was powerless to intervene and had to let the disease run its natural course. Hand in hand with EL’s impact on sleep were its variegated effects on motor behavior, with patients displaying a menagerie of tics, motor and linguistic compulsions, tremors, rigidities and unconscious activities known as automatisms.

From Europe the disease spread to the Americas by way of New York and other port cities on the Atlantic coast. Estimates for the number of people worldwide who contracted EL ranged from about 52,000 reported cases upward to one million. The uncertainty derives from not knowing how many infected people experienced mild and short-lasting symptoms of EL that went unreported.

The aristocratic Viennese physician Baron Constantin von Economo composed masterful monographs on a condition that began with a sore throat, progressed to abnormal eye movements, and ended with a lethargy that could last for a year or more.

AN ELOQUENT YOUNG WOMAN LIVING IN NEW YORK CITY IN 1923 DESCRIBED THE SYMPTOMS OF ENCEPHALITIS LETHARGICA AS AKIN TO A SLEEPING BEAUTY–LIKE TRANCE.
Why the epidemic strain of EL disappeared 10 years later as abruptly as it did remains unknown. Since then, only a handful of sporadic cases have been reported. Medical sleuthing has revealed previous instances of outbreaks of an EL-like disease, in particular in Tübingen, Germany, in 1712 (where it was dubbed die Schlafkrankheit) and in northern Italy in 1890 (la nona).

It is disconcerting that to this day, the culprit responsible for EL remains unknown and, presumably, at large. As epidemic encephalitis partially overlapped with the 1918–1920 epidemic of influenza—the H1N1 or “Spanish flu” that killed an estimated 50 million people—some consider the former a consequence of the latter. Yet no concrete causal evidence of any such link to influenza has surfaced. Nor did pathologists isolate from the brains of EL patients any bacteria or viruses that could be identified as the responsible agents.

A currently popular hypothesis suggests that the initial cold or flu virus triggered an inappropriate immune response. If true, EL would join an ever growing list of autoimmune afflictions. This hypothesis, however, fails to explain how the epidemic form of EL could burst onto the world stage, affect tens of thousands and then vanish. Most likely multiple factors were responsible, a set of antecedents that might in time converge again under the appropriate conditions to haunt humankind.

Unfortunately, worse was in store for some of the patients who survived the acute phase of EL. They subsequently developed Parkinson’s disease to a varying degree, including an extreme form of akinesia, in which they remained immobile for decades, frozen statues locked away in nursing homes or wards for the terminally demented. These long-forgotten postencephalitic parkinsonian patients were the ones that neurologist Oliver Sacks awakened with L-DOPA drug therapy in the late 1960s, as famously described in his 1973 master-
piece Awakenings. The book became an eponymous movie with Robin Williams playing a character based on Sacks and an amazing, heart-wrenching performance by Robert De Niro portraying the patient Leonard L.

**Sleep Is Actively Regulated**

Historically the clinic has always served as the most fecund source of insight about the brain and the mind. EL remains a case in point. Most of von Economo’s patients had eye-movement abnormalities and slept excessively. When awakened, they interacted relatively normally with their environment but soon returned to sleep. That is, EL has specific symptoms that reflect that the underlying disease does not destroy gray matter willy-nilly but selectively attacks particular sites for unclear reasons.

Postmortem examination of brains of patients invariably reveals discrete lesions in the midbrain, a structure that aptly describes its own whereabouts. It lies above thepons and just below the thalamus, the quail-egg-shaped structure that is the gateway to the neocortex, the rumpled outer layers responsible for perception, memory, thought and consciousness. The damage often includes the oculomotor nucleus in the midbrain, explaining the pronounced eye-movement dysfunctions characteristic of EL.

Damage also occurs in another deep-brain structure, the substantia nigra, part of the basal ganglia, an explanation for the patients’ behavioral and motor pathologies. Von Economo proposed the existence of a structure in the midbrain that keeps the overlying thalamus and the neocortex in an activated, awakened state. This ascending arousal system sends fibers upward to the forebrain.

A smaller number of von Economo’s EL patients showed the opposite reaction. They were able to sleep fitfully only for a few hours, beset by drowsiness most of the day but thwarted from sleep at night. These insomniacs had lesions in the gray matter of the anterior hypothalamus (literally, “below the thalamus”), extending into the basal ganglia. The physician inferred the existence of another center controlling the onset and depth of sleep. He argued that sleep is not just the passive response of a run-down body, tired after a day’s work, ready to replenish itself. Rather it is an active state initiated and controlled by the tightly synchronized activity of specific organs in the central nervous system that are responsible for the daily choreography of our sleep-wake cycle.

Refined animal and clinical research over the past 80 years since von Economo published his work has validated his ideas and deepened our understanding of sleep and waking. We now know that there are two quite distinct forms of sleep, rapid eye movement (REM) and non-REM (or deep sleep). We know that circadian rhythms present in every cell in our body drive this system and are synchronized by the waxing and waning of daylight. The notion of a monolithic activating system has given way to the realization that sleep and arousal are controlled by activity within three dozen or more highly heterogeneous nuclei with idiosyncratic cell structures housed within the brain stem (that is, the medulla, thepons and the midbrain), as well as the hypothalamus and the basal forebrain.

It is a complex system that uses a variety of neurotransmitters: acetylcholine, noradrenaline, GABA, histamine, serotonin and orexin. Collectively they implement something akin to a bistable flip-flop, a type of electronic circuit in which two intrinsically excitatory networks mutually inhibit each other—when one is “on,” the other one is “off,” and vice versa. The system can be in one of two states—awake or asleep—with relatively abrupt transitions between the two.

When we lose the ability to sleep, to mercifully slip into its oblivion and forget our daily toils and troubles, we realize how utterly dependent we are on Morpheus’ power. Indeed, forced sleep deprivation is rightfully considered a form of torture.

Let me end with Haruki Murakami, who perfectly captures the sensations of falling asleep in the final phrase of his 2013 novel Colorless Tsukuru Tazaki and His Years of Pilgrimage:

*The rear light of consciousness, like the last express train of the night, began to fade into the distance, gradually speeding up, growing smaller until it was, finally, sucked into the depth of the night, where it disappeared. All that remained was the sound of wind slipping through a stand of white birch trees.*

**Sleep well tonight.**