Nobel Prize in Medicine awarded for discoveries on the circadian rhythm

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Life on Earth has adapted itself to the rotation of the planet. Through the study of living organisms, including human physiology, scientists have understood that organisms have developed internal biologic clocks that allow them to anticipate and adapt to daily variations. What had not been known till recently is how this process worked.

On Monday, the Nobel Prize in Medicine was awarded to three scientists from the United States, Dr. Jeffrey C. Hall, Dr. Michael Rosbash and Dr. Michael W. Young, for their work on the molecular mechanisms that control the body's circadian rhythm. Their findings help explain how plants, animals, and humans can adapt their biological rhythm to synchronize it with the Earth's rotation.

Dr. Hall received his doctorate in 1971 from the University of Washington and is currently professor emeritus of biology at Brandeis University. Dr. Rosbash received his doctorate from MIT and continued on to the faculty at Brandeis University. Dr. Young received his doctorate from the University of Texas, Austin in 1975 and is a professor of genetics at Rockefeller University in New York.

Their work on fruit flies was able to locate a gene that encodes a protein that accumulates in the cell during the night only to be degraded during the day. When this gene was mutated (or "knocked out") the fruit flies lost their rhythm. This protein is linked to other cellular processes that produce the "self-sustaining clockwork inside the cell." These biological clocks function under the same principle in all multicellular organisms, allowing the precise adaptation of the physiology to the various phases of the day. These include our metabolism, behavior, hormonal levels, body temperature and sleep patterns. That is why our well-being is affected if our external environment is not in synch with our inner biological clocks.

Schematically, genes within our DNA are "turned on" by molecular signals. A template of the gene in the form of Messenger RNA (mRNA) is created. The mRNA moves out of the nucleus into the cell's cytoplasm where the protein for that gene is produced.

At night PER (period protein) accumulates in the nucleus blocking the period gene from synthesizing mRNA for the manufacturing of PER. During the daytime, PER is degraded allowing the process to start again. TIM (timeless protein) is another protein that couples with PER allowing it move into the nucleus where it can inhibit the period gene. DBT (double-time protein) delays the accumulation of the PER protein allowing for adjustments to more closely match a 24-hour cycle. Other proteins have been discovered that allow light to influence and synchronize the clock.

The mechanisms described above for the fruit fly have been further elucidated in mammals and found to be more complex and intricate although basically similar. The circadian rhythm established by the molecular components of the mammalian circadian clock at an organism level sees a high cortisol release in the early morning. From this follows a rapid rise in blood pressure and heightened alertness. By early afternoon best coordination and fastest reaction times are evident. Our body temperature reaches its maximum by sunset. Our blood pressure is highest in the early evening. Later, melatonin is secreted and need for sleep ensues. After midnight we are in a deep sleep, and our body temperature reaches its lowest point.

From these, our sleep patterns are regulated, our feeding behaviors are developed. The core molecular clock components are composed of a dizzying number of genes controlled by transcription/translation feedback loops that oscillate with 24-hour rhythmicity

that regulates these seemingly instinctive human activities.

But what happens when we throw a wrench into this elegant evolutionary achievement? In a review published in *Circulation Research* in 2010 titled "Circadian rhythms and metabolic syndrome," the authors note that the incidence of Metabolic Syndrome continues to increase in the industrialized world. Though genetic and environmental factors have been known to implicate this spectrum of disorders, evidence suggests that alterations in the circadian rhythm are linked to the pathogenesis of these disease processes as well as many others.

The Metabolic Syndrome is a clustering of medical condition—abdominal obesity, high blood pressure, high blood sugar, high cholesterol or triglycerides, and low high-density lipoprotein (HDL) levels—that increase a person's risk of developing cardiovascular disease and diabetes. The syndrome is a global epidemic affecting 25-40 percent of individuals in the prime of their life.

The Metabolic Syndrome has been connected to the lack of exercise and poor diet which then leads to obesity and the development of the syndrome. There is growing evidence that the introduction of artificial light and lack of sleep leads to behaviors associated with circadian disorders such as the increased sensation of hunger, suppression of our metabolism, and changes in the hormonal signals that tell us when we are full. Epidemiologic studies have implicated "short sleep" in contributing to the risk of acquiring diabetes. Workers with alternating shifts have an independent risk for an increase in their body-mass-index. Prolonged sleep restriction has been shown to impair insulin sensitivity.

A better understanding of the molecular aberrations that lead to metabolic disorders in states of disrupted sleep awaits further investigation and, given its broader implication to human illness, is necessary and urgent in light of the importance of a properly functioning physiology synchronized with its circadian rhythm. For instance, genetic variations in our circadian cellular mechanisms are associated with psychiatric diseases like depression, bipolar disorder, and schizophrenia. Research in this area could afford novel strategies for the understanding and treatment of these illnesses.

Myocardial infarction, sudden cardiac death, pulmonary embolisms and aortic aneurysm rupture occur most frequently in the morning. Shift work increases the risk of heart attacks by as much as three-fold in men and women between ages 45-55. The risk of a fatal heart attack increases by 45 percent for people who chronically sleep less than five hours each night. Even transitioning to daylight saving time in the spring carries an increased incidence of a heart attack for the first three days after.

Instead of focusing on the social implications of the disruption in circadian rhythms in human life, the *New York Times* reports on these Nobel Prize research as novel discoveries for explaining the lethargy and irritability termed "jet lag" from air travel—an area much more interesting to high-income editors and readers than the condition of the working class in America in 2017. More compelling would be in exposing the connection between health and epidemic reports of obesity, diabetes and heart disease with the organization of work and production.

The CDC has estimated that about 84 million (35 percent) US adults get an insufficient quantity of sleep. Approximately 23 percent get less than six hours, and 12 percent get less than five hours. Lack of sleep, like many health issues, has a significant class dimension, as a recent report in the *Huffington Post* found, disproportionately affecting the poor and underprivileged. Those unable to work reported the lowest rates of healthy sleep. The southeastern US and the Appalachian region were characterized by a lower duration of healthy sleep, and also have higher rates of obesity, serious health conditions, and death.

There has also been a rise in Americans working multiple jobs under pressure of the persistent economic decline in past decades, felt most sharply working people who live paycheck to paycheck. American families work on average 11 more hours per week than they did 30 years ago. Wages for lower-income families have decreased 29 percent and for middle-income families 13 percent in the same period. These economic forces contribute significantly to worsening health conditions.