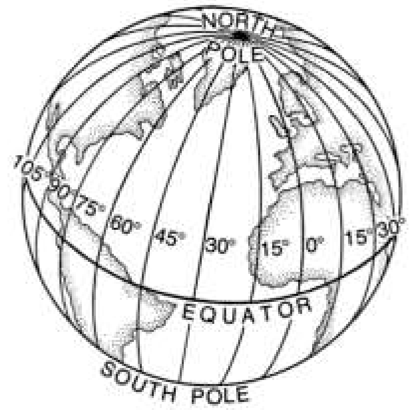
Melanopsin, Circadian Rhythms and Wellness in Humans

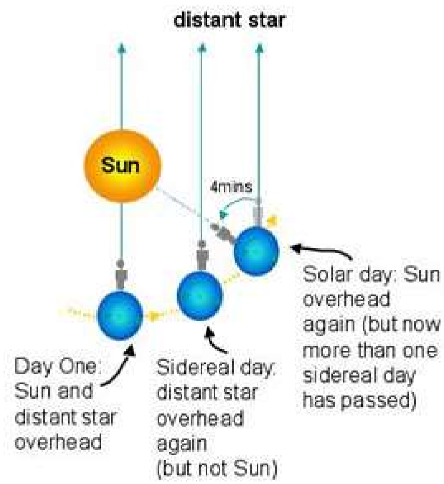


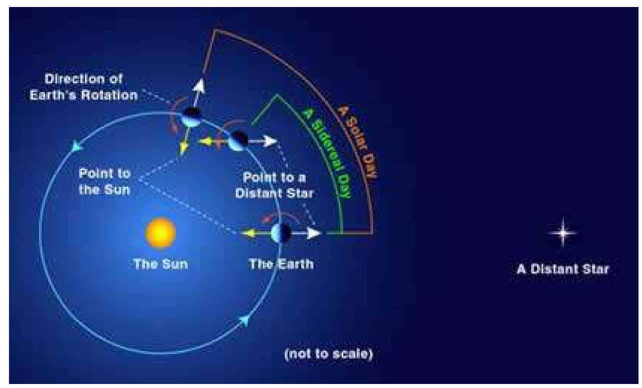
Living organisms from wild flowers to whales have **internal or endogenous biological clocks** that are normally synchronized with **the daily rotation of the earth upon its axis** that runs from the North Pole to the South Pole. The earth spins counter-clockwise as viewed from the North Pole. Consequently, no matter which latitude one resides and how long the photoperiod is, the sun appears to rise in the east and set in the west.

Photograph by George Rankin of the sun rise and set in the Arctic in January. Five exposures taken 1h apart.

Experience the rotation of the earth through **time-lapse photography** by Shane Black https://www.youtube.com/watch?v=9d8wWcJLnFI, Michael Shainblum https://www.youtube.com/watch?v=vLUNWYt3q1w, Andrew Arthur Breese https://www.youtube.com/watch?v=R5LRpH62mss, Anna Possberg https://www.youtube.com/watch?v=8GpDXV9BfLU, Harley Grady https://www.youtube.com/watch?v=nam90gorcPs, and Dimitry Pisank https://www.theguardian.com/science/video/2015/jun/23/earth-international-space-station-timelapse-video

The period of earth's rotation, which is known as the **solar day**, is the time it takes for the sun to appear directly overhead at two successive noons. The solar day is approximately 24 hours. Because the earth **orbits** around the sun as it **rotates**, the solar day is actually a little longer than the actual rotation period of the earth, which is known as the **sidereal day**. Because the speed of the earth as it orbits the sun is not constant but faster at **perihelion** ($r = r_{min}$) than that **aphelion** ($r = r_{max}$), the average speed of the earth around the average position of the sun is used to determine the solar day. The **sidereal day**, which is 23 hours and 56 minutes, is the time it takes for the distant stars to appear in the same position. The four minute difference between a solar day and **sidereal day** means that a viewer will see the same stars rise above the horizon four minutes earlier each **solar day**.

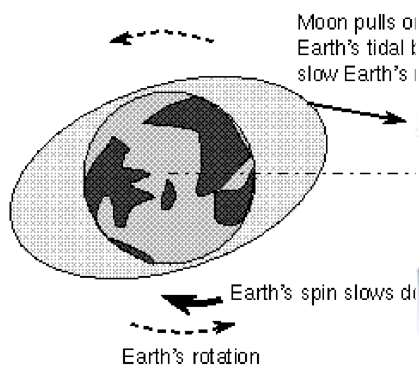


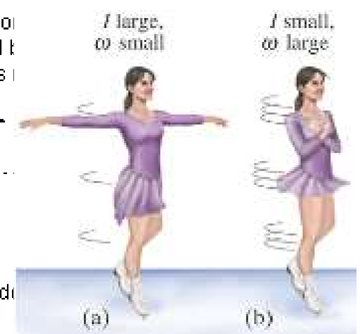


Before the widespread use of railroad trains in the 1840's, each community had its own **local time**, where twelve o'clock noon on each day was defined as the time when the sun was at its **zenith** or highest point in the sky. However, when it became crucial to coordinate train schedules to minimize train crashes on single train tracks, **standard time zones** were created that closely aligned to lines of longitude separated by 10° and **Greenwich England**, where the famous observatory was that provided maps for navigation, became the **prime meridian**.

In 1918, the Standard Time Act became law in the U. S. The Official U. S. time can be found at http://www.time.gov/.


Currencies, temperature, lengths, mass and even library books have been decimalized (Vera, 2009). Have you ever wondered why we never hear of **decimal time**? Decimal time was originally proposed by D'Alembert in 1754. On October 5, 1793, during the **French Revolution**, decimal time was introduced as part of its goal to decimalize everything that could be measured. Each day was divided into ten hours, each hour was divided into 100 minutes, and each minute was divided into 100 seconds. Decimal[1] time was never popular and was abandoned on April 7, 1795, the same day that the decimal system for length, volume and mass began. At this time, the meter was defined as one ten millionth of the distance between the North Pole and the Equator along the line of longitude passing through Paris, and the gram was defined as the mass of a cubic centimeter of water. See the current time in decimal time at http://minkukel.com/scripts/metric-clock/.

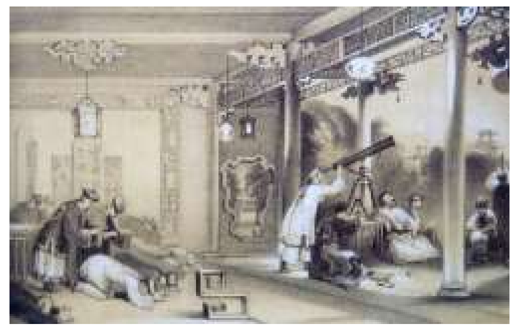




The **day length** on earth has ***not*** been constant over geological time because the daily period of rotation of the earth has not been constant. The length of the day has grown longer by **2 seconds per 100,000 years** as a consequence of the **tidal friction** between the earth and the moon. Overall, because **angular momentum is conserved**, the total angular momentum of the

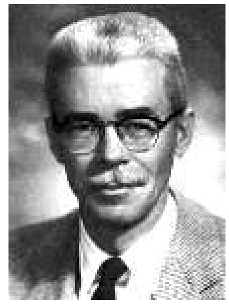
[1] The word decimation comes from the Roman times when one out of ten soldiers of an army were executed as a punishment for its cowardice.

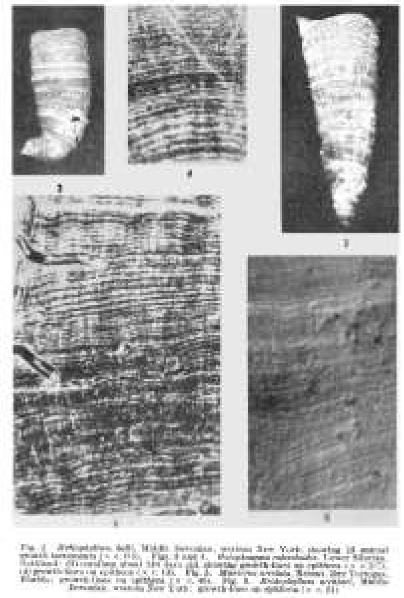
earth and moon stays constant, but the tidal friction results in a decrease in the angular momentum of the earth and an increase in the angular momentum of the moon. The decrease in the angular momentum of the earth, means that the earth rotates more slowly on its axis and the increase in the angular momentum of the moon means that the moon orbits the earth more slowly now than it did in the past and its distance from the earth continues to increase.



The increase in the length of the period of the earth's daily rotation is supported by diverse observations. For example, **historical records of solar eclipses over China**, from which the orbits of the sun and moon have been calculated, indicate that if the period of the earth's daily rotation were not increasing, then the reported shadows produced by the eclipsed sun would not be where they were recorded to be. Moreover, the moon's orbital radius as determined by the amount of time it takes laser light to travel from the earth to the **retro-reflector arrays placed on the moon** by Apollo 11, Apollo 14, Apollo 15 and Lunakhod 2, and back to earth again, has increased by 3.82 cm/year. This is consistent with the decrease in the daily period of rotation of the earth as a result of the transfer of angular momentum from the earth's rotation to the moon's orbital motion (Dickey et al. 1994). The increase in the moon's orbital radius also results in an increase in the period of the lunar month (Runcorn, 1966).

John Wells (1963), a geology professor at Cornell, used the relationship between light and life to discover the day length on earth hundreds of millions of years ago. Wells looked at **fossil corals** from the **Middle Devonian** (387 million years ago based on **radiometric dating**) and **Pennsylvanian** (307 million years ago based on **radiometric dating**) collected near Cornell University. The fossil corals show both **annual growth rings due to seasonal changes in temperature** and daily growth rings due to the **diurnal incorporation of calcium carbonate**.





The fossil corals from the Middle Devonian had more daily growth rings than the fossil corals from the Pennsylvanian that had more daily growth rings than the corals from the present. Wells (1963) concluded that there were about 400 days per year in the **Middle Devonian** about 387 days per year in the **Pennsylvanian** and about 365 days per year in the present.

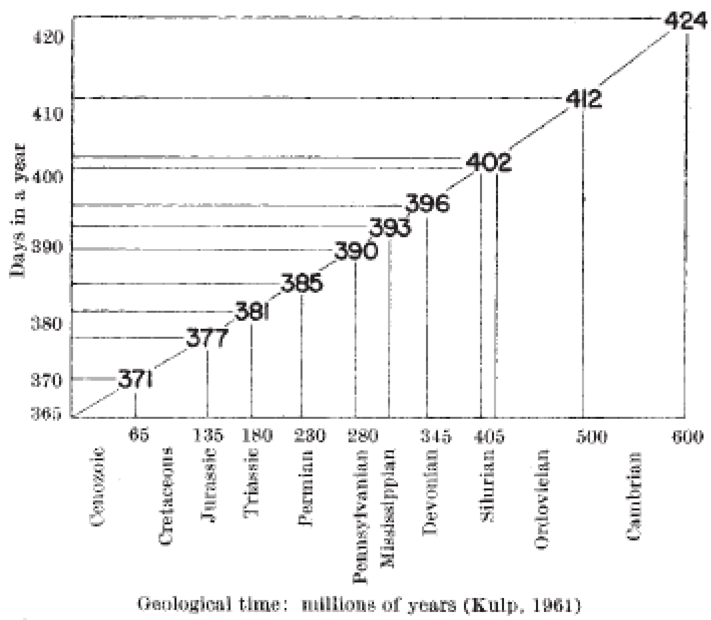


Fig. 1. Relation between days in each year and geological time (radioactive age data from Kulp, 1961)

By assuming that the period of the earth's orbit ($\frac{2\pi r\sqrt{r}}{\sqrt{GM_{sun}}}$) around the sun has been constant, Wells calculated the period of the daily rotation of the earth in various geological periods. He calculated that the daily rotation of the earth took about 21.9 hours in the **Middle Devonian**, 22.6 hours in the **Pennsylvanian**, and increased to its present value of about 24 hours.

In an article published in the *New York Times* on April 19, 1964, **John Burdon Sanderson Haldane** singled out John Wells as someone who could make great scientific strides with next to no money by using his visual system (eyes and mind) and a ten dollar hand lens to measure the number of fifty micrometer daily growth rings in an annular ring. Haldane wrote, "*Professor Wells of Cornell University also has this quality. He collects ancient and modern coral. Those which grow in seas where the temperature varies much with the seasons often show annual growth rings like trees. Wells found that some also show daily ridges of growth, which can be counted with a good hand lens costing perhaps $10. Modern corals show about 365 ridges a year….Silurian corals show about 400 rings a year. As the year has probably changed little, therefore the days have been getting longer. (They are getting longer, as we know, from records of ancient eclipses, among other evidence. This is thought to be due to the braking action of the tides, both in the sea and in the earth, which is not quite rigid.) Ask anyone who does not know the answer how much the apparatus cost which proved that the number of days in the year has increased by 35 in 350 million years and he will probably guess at $10 million or so.*"

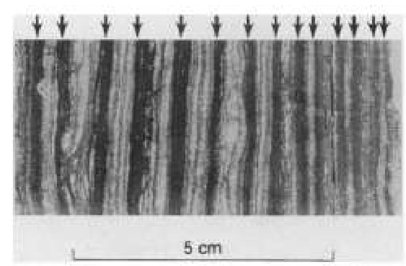
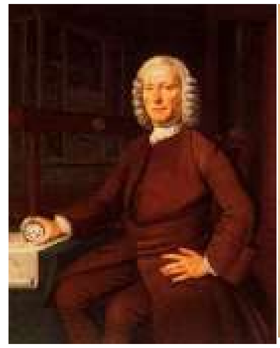


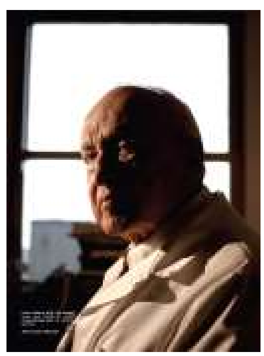
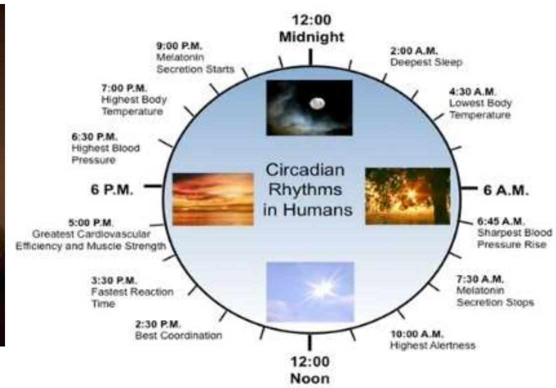
Fig. 1. Photograph of polished core of BCC tidalites. Laminae of coarse silt to fine-grained sand were transported only during the strongest spring tides. The thick dark bands (arrows) correspond to neap-tide deposition of fine-grained mud.

A more recent analysis of the laminated tidal sediments from the **Precambrian** indicates that **900 million years ago**, the length of a day on earth was approximately **18.2 hours** (Sonnett et al., 1996).

Now that we have a sense of the **astronomical** or environmental **clock**, independent of and **external** to our bodies, we will talk about the **endogenous biological clock** in humans and other mammals.



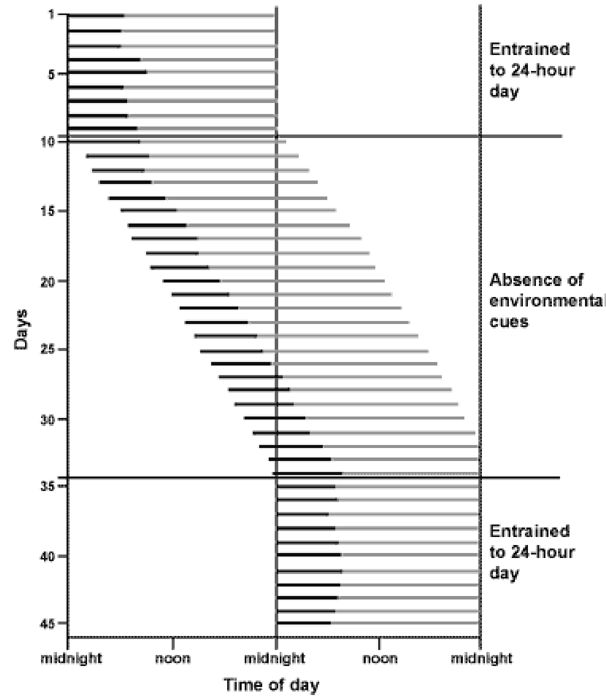

Like the accurate **chronometer** designed in the first half of the 18th century by **John Harrison** to determine **longitude**, biological clocks are relatively **temperature-insensitive**. The daily **entraining** or **synchronizing** event (time-giver or ***zeitgeber*** in German) is a result of the **daily light-dark transition** that takes place everywhere on the surface of the earth except at the poles at certain times of the year.

In the absence of environmental cues, the biological clock is no longer synchronized with the daily light-dark period, however, the **free running** biological clock still runs with a **circadian rhythm** that is about or "*circa*" in Latin a day or "*dies*" in Latin. The word, **circadian**, was coined by **Franz Halberg** in the 1950s.

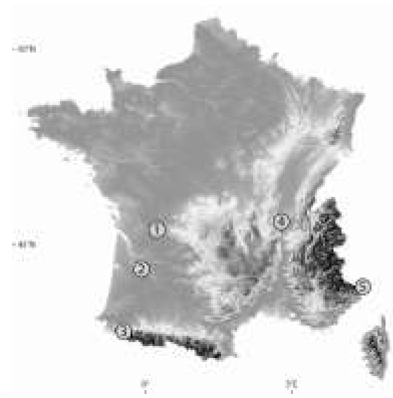
While we will only discuss circadian rhythms today, remember that living organisms also exhibit **monthly** (lunar) and **annual or seasonal** (solar) rhythms. In addition, animals that live in tidal zones have a tidal rhythm.

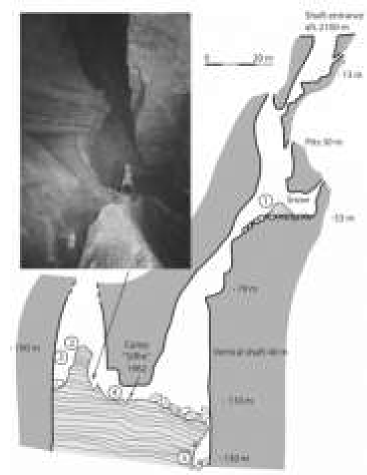
The figure on the right depicts the circadian **sleep-wake cycle** of one individual person. The black lines represent the periods in which the person slept and the gray lines represent the periods in which the person was awake. During regular time periods of light and darkness, the sleep-wake cycle was **entrained** to a period of 24 hours. However, on days 10 through 34, when the person was isolated from any environmental cues or ***zeitgeber***, the person went to sleep one hour later each day and after 24 days, the person was again going to bed at midnight. While the sleep-wake cycle continued to oscillate in the absence of environmental cues, indicating that the sleep-wake cycle rhythm is **endogenous**, the period of the endogenous rhythm was greater than 24 hours. On day 35, when the person was subjected again to the ***zeitgeber*** or **normal environmental cues**, the **sleep-wake** cycle became **entrained** and **synchronous with the daily rotation of the earth**.



Determining the natural free-running period of the biological clock in humans began following the **Cuban Missile Crisis** in October 1962, when it seemed like people might have to live in isolation in space capsules and nuclear submarines or in underground bunkers or deep subterranean caves for a period of time during and after a nuclear war. It was discovered that the **natural, free-running period of the biological clock** of humans in **underground bunkers** or **deep subterranean caves**, where they were ***not*** exposed to the ***zeitgeber* or**

environmental cues that cause an entrainment or synchronization of the endogenous biological clock with the daily rotation of the earth, is slightly ***greater than*** 24 h.



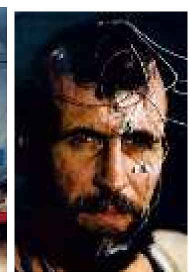


Michael Siffre loved geology, speleology, philosophy, and had a desire to investigate the mental and physical limits of human beings and our adaptive power by living for two months in **Scarasson Cavern**. In the cave, which was formed by water charged with carbonic acid (H_2CO_3) inside a subterranean glacier 375 feet underground, he was "*deprived of any points of reference in time and space."* Siffre (1964) wrote, "*Living underground for a protracted period would mean being shut off from the daily cycle: there would be no setting sun to tell me that night was approaching**. I wondered to what extent** the **cosmic phenomena of night and day controlled our periods of sleep and activity**. In short, I wanted to investigate time—the most inapprehensible and irreversible thing. I wanted to investigate that notion of time which has haunted humanity since its beginning. Perhaps time existed on three levels: that which is perceived, created by the brain, the result of conditioning to the twenty-four-hour cycle of night and day; biological time—a rhythm of activity-repose set up in the organism through the years; and objective time, measured by clocks*." Siffre found that his **biological clock** continued to work in the absence of environmental cues, but psychologically, he broke down and became depressed.

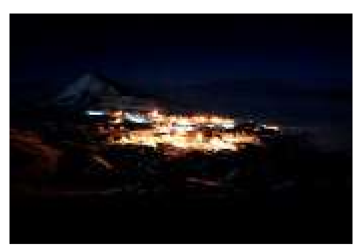
Michael Siffre ended his book, *Beyond Time* with the following advice: "*As to what I learned personally from my experience, I can only repeat that if I survived the difficult conditions in which I voluntarily placed myself, it was mainly due to my will power, my passionate resolve to see the thing through, and not* *disappoint my collaborators not lose my self-respect. I was not out to break a record; it was not a physical exploit that I intended to bring off; it was an experiment with scientific aims that I wanted and was determined to perform, come what may. Years ago an American classmate ironically repeated a folk saying that children two generations ago were made to copy in their exercise books: 'Where there's a will, there's a way.' I memorized it, for I sensed behind the words age-long experience. In my case, that simple truth was certainly proved more than once. And if other young fellows plan to embark upon an adventure such as mine, I can only advise them—at the risk of sounding like an old fogey—to school themselves daily in self control, which is a form of will power. Will power plays a part as important as, if not more important than, the careful choice of equipment and a rigorous course in physical training. I would tell young aspirants that, armed with this weapon, you can do a great deal; you can do anything*."

Below are pictures of an older **Michel Siffre** in a cave in Texas, repeating and extending to six months, the experiment he performed in his twenties. (http://www.cabinetmagazine.org/issues/30/foer.php).



Another place where human beings are ***not*** exposed to any ***zeitgeber*** or environmental cues that cause an entrainment or synchronization of the endogenous biological clock with the daily rotation of the earth is the **Antarctic** in winter. During the autumn when the sun rises and sets, the circadian rhythms of volunteers were entrained



with the daily rotation of the earth and had a period of 24 hours. However, during the 126 days of winter, from January 1987 to February 1988, the **natural, free-running periods** of the endogenous circadian clocks of four volunteers were 24 hours 29 minutes, 24 hours 45 minutes, 25 hours 7 minutes and 25 hours 14 minutes. The average **natural, free-running period** of the endogenous circadian clock was 24 hours 54 minutes, which is greater than the 24 hour daily rotation of the earth. I will discuss the discovery of fossils in Antarctica in the next lecture.

A Trident nuclear submarine such as the **USS Georgia** is another place where human beings are not exposed to the ***zeitgeber*** or environmental cues that cause an entrainment or synchronization of the endogenous circadian clock with the daily rotation of the earth. After submergence, synchronization of the endogenous clock, in terms of **salivary melatonin** levels, is lost. Here are data from two individuals, one with **a natural, free-running endogenous clock period** of 24.32 hours and one with **a natural, free-running endogenous clock period** of 24.75 hours. In both cases, there is a **phase shift** and the peak of salivary **melatonin** occurs later and later. Again, the natural, free-running **period** of the endogenous biological clock is greater than 24 hours.

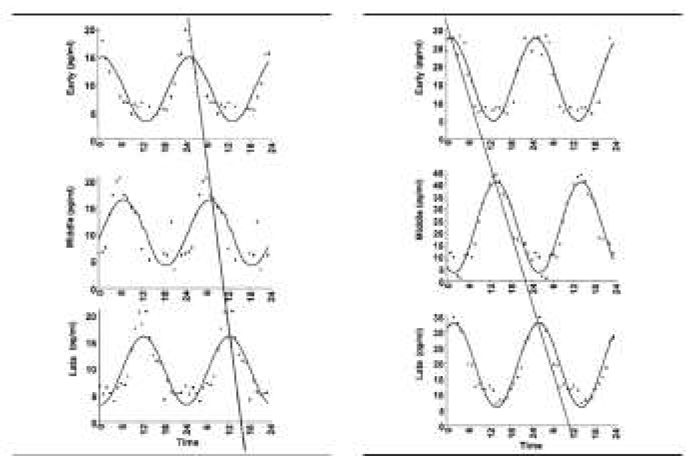


Figure 1. Double-plotted salivary melatonin data from a representative subject (105) working the 6/12 schedule. Top graph shows data collected at the start of the study, and the middle and lower graphs show data from about 3 weeks and 6 weeks later, respectively. The best-fitting cosinor is overlaid on each data set, and a line is drawn through the acrophases. Estimated tau = 24.32 h.

Figure 2. Double-plotted salivary melatonin data from a representative subject (108) working the 6/12 schedule. Top graph shows data collected at the start of the study, and the middle and lower graphs show data from about 3 weeks and 6 weeks later, respectively. The best-fitting cosinor is overlaid on each data set, and a line is drawn through the acrophases. Estimated tau = 24.75 h.

More recently, **Charles Czeisler** (left) et al. (1999) found that in humans living for one month in an environment free of any ***zeitgeber*** or environmental cues, the **natural, free-running period** of the endogenous circadian clock is typically **24 hours and 11 minutes**.

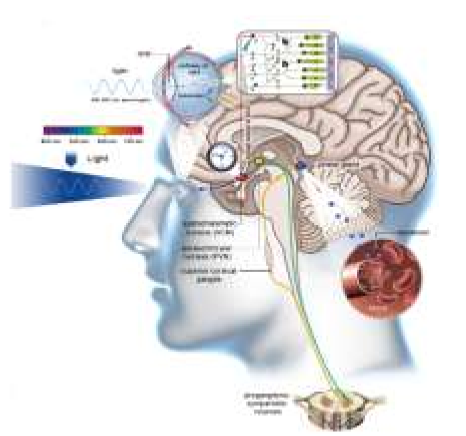
We have already seen that it was both **useful and simplistic** to consider eye color to be a dichotomous Mendelian trait that is controlled by one gene. Likewise, it is both **useful and simplistic** to consider the period of the endogenous biological clock to be identical among individuals.

Here is some actual data on the free-running period of the endogenous circadian clock determined from measurements of the rhythms of **core body temperature**, **melatonin levels in blood samples** and **cortisol levels in blood samples** of individuals.

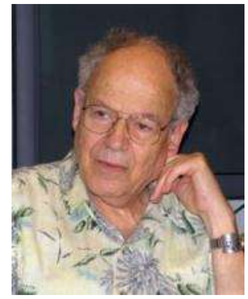
Table 1. Intrinsic periods of the temperature (τ_T), melatonin (τ_{mel}), and cortisol (τ_c) rhythms (expressed as hours:minutes) in young and older subjects in the 28-hour forced desynchrony protocol. For each subject, the estimated period of each of the three rhythms lies within the 95% confidence interval of the other two rhythms. τ_T, τ_{mel}, and τ_c were highly correlated [Pearson correlation: τ_T versus τ_{mel}, $r = 0.951$; τ_T versus τ_c, $r = 0.982$; τ_{mel} versus τ_c, $r = 0.984$ ($P < 0.0001$ in all cases)]. Our composite estimate of the intrinsic period for each subject (τ) was computed by averaging τ_T, τ_{mel}, and τ_c, if available. Constraints on the total blood collection volume and vascular access limited the number of older subjects for whom cortisol and melatonin data were available; also, in two young subjects (1145 and 1257), an inadequate number of blood samples were collected and analyzed for cortisol concentrations to obtain a reliable estimate of circadian period.

Subject	Age (years)	Sex	τ_T (±SD)	τ_{mel} (±SD)	τ_c (±SD)	τ
Young subjects						
1105	25	M	24:16 ± :02	24:14 ± :05	24:17 ± :10	24:16
1106	21	M	24:14 ± :01	24:14 ± :02	24:18 ± :07	24:16
1111	22	M	24:17 ± :01	24:17 ± :03	24:19 ± :05	24:18
1120	25	M	24:08 ± :01	24:09 ± :01	24:10 ± :07	24:09
1122	23	M	24:09 ± :01	24:07 ± :02	24:08 ± :09	24:08
1133	23	M	23:53 ± :01	23:51 ± :03	23:52 ± :10	23:52
1136	22	M	24:09 ± :01	24:10 ± :04	24:13 ± :07	24:11
1144	23	M	24:15 ± :01	24:17 ± :01	24:18 ± :06	24:16
1145	30	M	24:09 ± :01	24:11 ± :04	–	24:10
1209	21	M	24:06 ± :01	24:05 ± :00	24:08 ± :01	24:07
1257	26	M	24:19 ± :02	24:23 ± :01	–	24:21
Range	21–30		23:53–24:19	23:51–24:23	23:52–24:19	23:52–24:21
Mean	23.7		24:10	24:11	24:11	24:11
±SD	2.7		00:07	00:08	00:09	00:08
±SEM	0.8		00:02	00:03	00:03	00:02
Older subjects						
1213	74	F	24:02 ± :02	–	–	24:02
1215	64	M	24:07 ± :07	24:01 ± :02	24:07 ± :08	24:05
1304	64	M	24:03 ± :03	24:09 ± :07	–	24:06
1319	67	F	24:10 ± :02	24:10 ± :04	–	24:10
1355	69	M	24:25 ± :02	24:25 ± :03	–	24:25
1366	66	M	24:28 ± :05	24:30 ± :03	–	24:29
1375	66	M	24:19 ± :02	24:20 ± :05	–	24:20
1458	67	M	24:09 ± :02	24:13 ± :03	–	24:11
1475	72	F	24:00 ± :03	24:04 ± :07	–	24:02
1485	65	M	24:06 ± :01	24:09 ± :05	–	24:07
1490	71	F	24:13 ± :02	–	–	24:13
1466	65	M	24:04 ± :02	24:07 ± :02	–	24:05
1507	66	M	24:10 ± :03	–	–	24:10
Range	64–74		24:00–24:28	24:01–24:30		24:02–24:29
Mean	67.4		24:10	24:13		24:11
±SD	3.2		00:09	00:09		00:08
±SEM	0.2		00:02	00:03		00:02

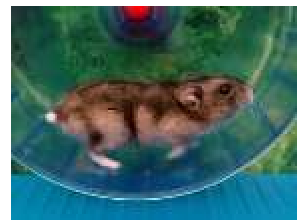
Where is the endogenous biological clock? In mammals, probably including humans, the primary endogenous circadian biological clock is in the **suprachiasmatic nucleus (SCN)** of the **hypothalamus**.



The suprachiasmatic nucleus (SCN) is a group of about 50,000 cells in the **hypothalamus** of the brain that is dedicated to the time-keeping function (**nucleus**) above (**supra**) the **optic chiasm** where the optic nerves that come from both eyes cross. There are two suprachiasmic nuclei, one connected to each eye.



The function of the suprachiasmic nucleus as the locus of the endogenous circadian clock has been demonstrated most conclusively with **ablation** (removal) and **transplantation** (replacement) experiments in **hamsters** performed by Martin Ralph and **Michael Menaker**.



Hamsters, like other rodents are **nocturnal**. They typically sleep during the day and are active at night. It is easy to measure the sleep-wake cycle of a hamster by connecting a monitor to an exercise wheel. Martin Ralph and Michael Menaker found that a typical hamster (A,B,C) has a sleep-wake cycle of 24.1 hours when it is exposed to a cycle of 14 hours of light and 10 hours of darkness. The active time on the wheel is during the dark period. They also found that when a typical hamster (A,B,C) is placed in continuous darkness, it more or less maintains its sleep-wake rhythm, with the active time on the wheel during the dark period. Then they found that abnormal hamsters (D,E,F) have a 22 hour sleep-wake cycle and ***cannot*** entrain or synchronize well with the light-dark cycle. They called the hamster with abnormal rhythm a *tau* (τ) mutant.

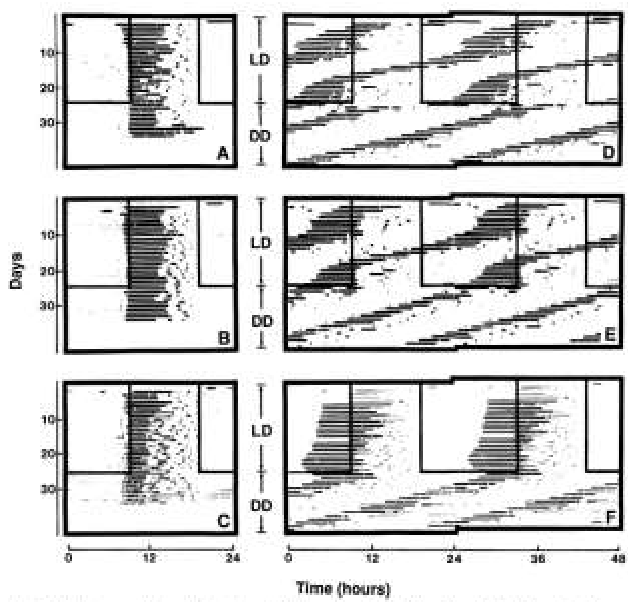


Fig. 1. Activity records (raw data) of six male F_1 littermates. Panels D to F are double plotted (as shown by the time axis). Boxes superimposed on each panel enclose the light portion (14 hours) of a light:dark cycle. LD, 14 hours of light in 100 lux; 10 hours of dark. DD, constant dark. Wheel running activity is indicated by the dark bands on each day.

Martin Ralph and Michael Menaker also found that when a typical hamster is mated with an abnormal hamster, the ratio of hamsters with a 24.03 hour or a 22.31 hour sleep-wake cycle was 1:1, consistent with a mating of a wild type with a heterozygote if there is only a **single gene** that is not on an X chromosome that codes for the duration of the sleep-dark cycle. They also found that when two heterozygotes with 22.31 hour sleep-wake cycle were mated, the offspring were of three types: 24 hour, 22 hour and 20 hour sleep-wake cycles, indicating that the abnormal hamsters with a 22 hour sleep-wake cycle have **one semi-dominant allele** at one locus and the abnormal hamsters with a 20 hour sleep-wake cycle have **two semi-dominant alleles** at that locus. Can you confirm Martin Ralph and Michael Menaker's conclusion using **Punnett squares**?

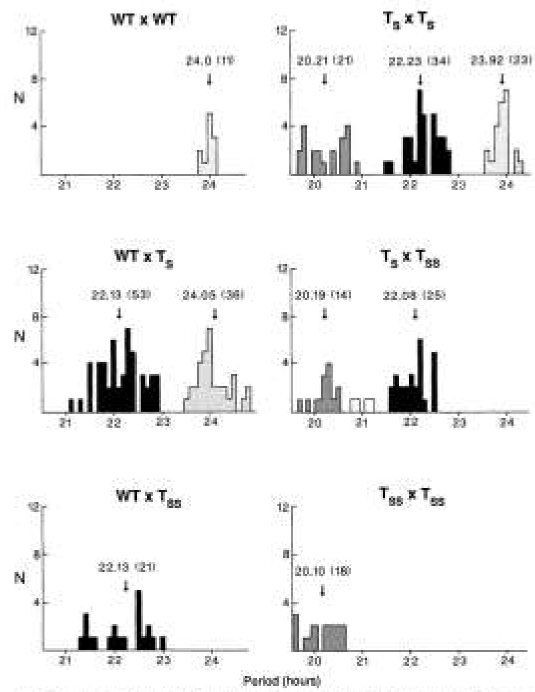
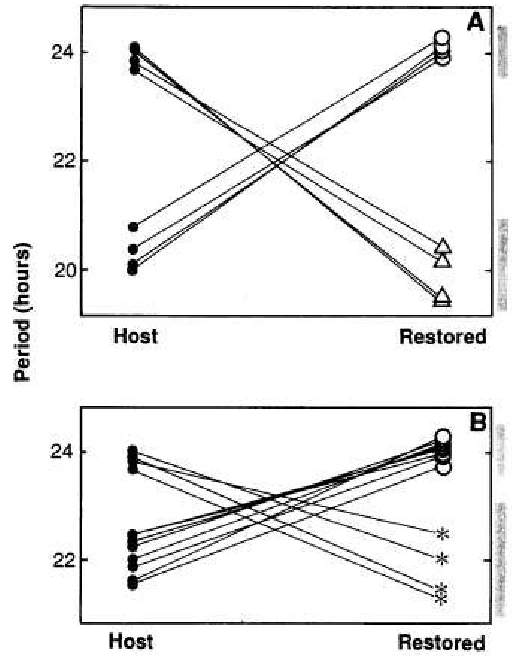


Fig. 2. Frequency distribution of τ from various crosses. After recording entrainment for 5 days, the animals were released into DD. Period was determined from the slope of a line fit by eye or regression analysis through the onsets of activity between day 4 and day 14 in DD. For statistical analysis, animals were assigned to particular groups on the basis of their phenotype: T_{ss} ($\tau \le 21.00$ hours); T_s ($21.00 < \tau \le 23.25$ hours); WT (23.25 hours $< \tau$). Our current data indicate that the ranges of the three groups do not overlap. Animals with τ values close to the extreme of the range for a group are routinely tested in backcrosses before genotype is inferred. Furthermore, many animals represented in this figure have been used in our breeding program, and in no case have the distributions of τ from their offspring indicated that we have been incorrect in assigning animals to a particular group. The four animals represented by the open histograms (in the $T_s \times T_{ss}$ panel) could not be assigned to a group based on phenotype alone and have not produced sufficient offspring to infer genotype; therefore, they have not been included in the statistical analysis. WT, wild type ($\tau \approx 24$ hours); T_s, putative heterozygote phenotype ($\tau \approx 22$ hours); and T_{ss}, putative homozygote mutant phenotype ($\tau \approx 20$ hours). Average τ for each group is indicated; number (n) of animals for each group is shown in parentheses; N is number of animals with a given free-running period.

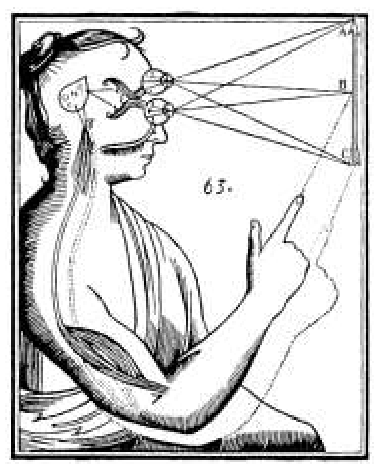
	W	W
W		
τ		

	W	τ
W		
τ		

The **suprachiasmatic nuclei** of a hamster can be ablated and replaced with the suprachiasmic nuclei of another hamster. **Reciprocal transplantion studies** between wild type hamsters with a sleep-wake cycle of 24 hours and homozygous tau hamsters (A) with a sleep-wake cycle of 20 hours, and reciprocal transplantation studies between wild type hamsters with a sleep-wake cycle of 24 hours and heterozygous tau hamsters (B) with a sleep-wake cycle of 22 hours show that the **sleep-wake cycle is controlled by the genetics of the cells of the suprachiasmatic nuclei**. This is good evidence that the suprachiasmic nuclei contains the circadian biological clock that regulates the sleep-wake cycle, but is the suprachiasmic nucleus the only biological clock in the hamster that regulates the sleep-wake cycle? Could there be other biological clocks in the hamster? Before we discuss other clocks, we will discuss how the endogenous biological clock in the suprachiasmic nuclei are entrained or synchronized by the daily **light-dark transition** with the 24 hour period of the daily rotation of the earth.

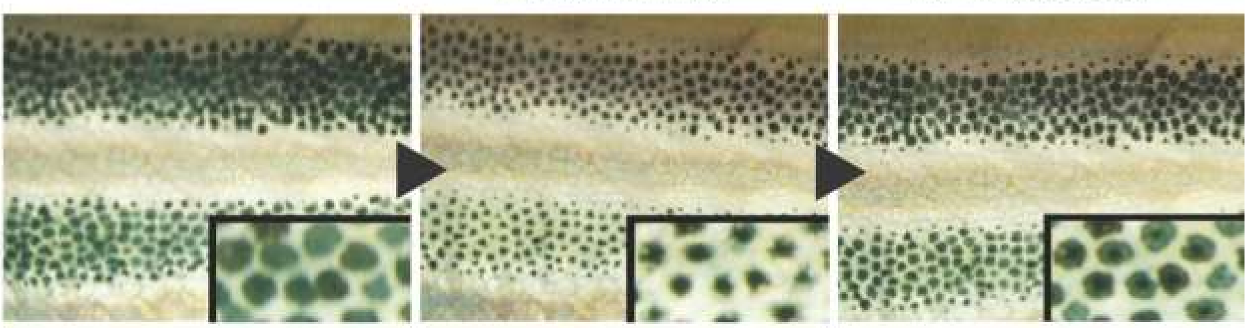


After more than two millenia of observations and research on vision and the eye, it was a surprise to learn in 1998 that **melanopsin**, a ***new*** photoreceptor pigment had been discovered in the retina. In order to follow the discovery of a new photoreceptor pigment, we have to take a detour and learn about the melanophores of cold-blooded animals. When we discussed eye color, we talked about the **melanocytes in the iris** that produced **melanin-containing melanosomes.** Melanin



producing cells are now called **melanocytes in warm-blooded animals** and **melanophores in cold-blooded animals**. The melanophores in cold-blooded animals, including fish, reptiles and amphibians allow the animals to **lighten or darken their skin tone** to **mimic** the **background** in order to **camouflage themselves**—a natural **optical illusion**.

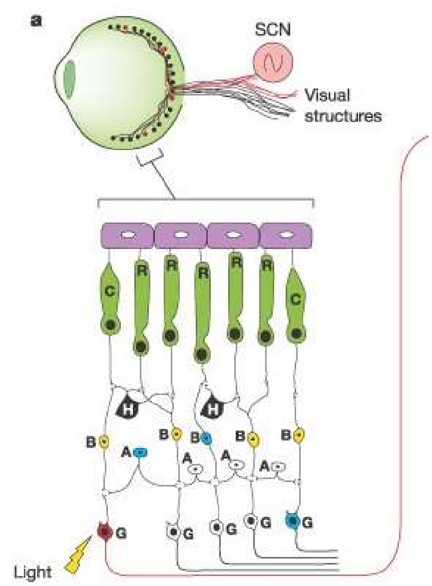
When the **melanosomes** in the **melanophores** in the skin of Zebrafish are **dispersed** throughout the cell, the melanophores in the **skin appear dark**. When the **melanosomes** in the **melanophores** in the skin of Zebrafish are aggregated in the cell, the melanophore in the **skin appears light** and the skin reflects the color of the cell beneath.



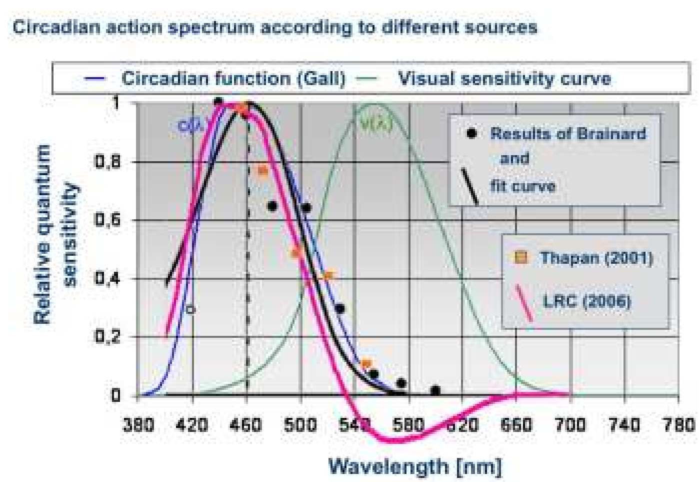
Ignacio Provencio discovered the gene for the **photoreceptor pigment** which he called **melanopsin** that controls the distribution of **melanin** in the **melanophores** of cold-blooded animals. Interestingly, a comparison of the amino acid sequence deduced from the nucleotide sequence of the melanopsin gene with the gene sequences of the visual opsins in rods (rhodopsin) and cones (photopsins) of vertebrates and the rhodopsins in invertebrates, including cephalopods and insects, shows that

melanopsin of vertebrates is more closely related (**homologous**) to **invertebrate** rhodopsin (39% identity) than to **vertebrate** opsins (30% identity). How can you explain this in terms of the evolution of the eye?

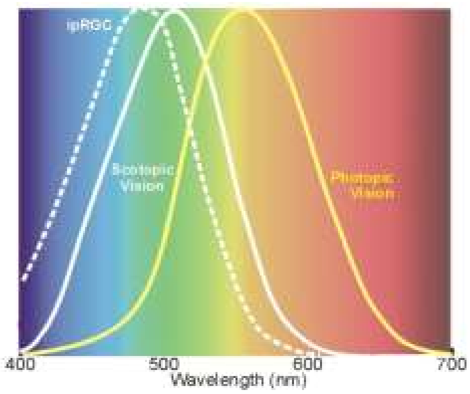
Unexpectedly, Provencio et al. (1998) found messenger RNA transcripts that coded for melanopsin, not only in the **melanophores in the skin of tadpoles**, but also in the **suprachiasmic nuclei**, the **iris**, the **retinal pigment epithelium** and in the **inner retina**. Two years later, Provencio et al. (2000) also discovered **melanopsin** in scattered cells in the **ganglion cell layer** of the **human retina**. The **intrinsically photosensitive retinal ganglion cells (ipRGC)**, which make up approximately 1-2% of the retinal ganglion cells, are connected directly through a bundle of neurons known as the **retinohypothalmic tract (RHT)** to the **suprachiasmatic nucleus (SCN)**. These clues suggest that light absorbed by **melanopsin** provides the ***zeitgeber*** to ensure the **endogenous biological clock** in the **suprachiasmic nuclei** is entrained by light, and thereby typically synchronized with the daily rhythm of the earth's rotation.



The **action spectrum** of the **synchronization signal** involved in synchronizing the endogenous biological clock with the daily rotation of the earth matches the **absorption spectrum of melanopsin** that has a peak around 460 nm and does ***not*** match the absorption spectrum of rhodopsin involved in rod-dominated



scotopic vision, which has a peak around 498 nm, or the photopsins involved in cone-dominated photopic vision, which has a peak around 555 nm.



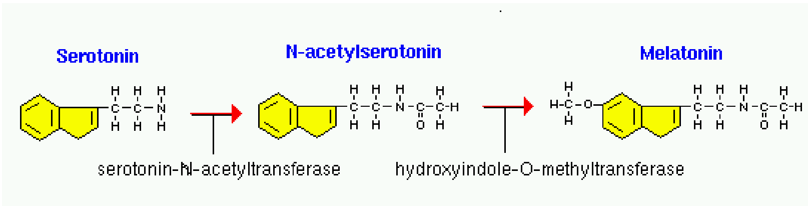
How does the endogenous biological clock in the suprachiasmic nuclei regulate the sleep-wake cycle? How does light absorbed by melanopsin in the **intrinsically photosensitive retinal ganglion cells (ipRGC)** affect the sleep-wake cycle?

The **intrinsically photosensitive retinal ganglion cells (ipRGC)** are connected directly by the neurons in the **retinohypothalmic tract (RHT)** to the **suprachiasmatic nucleus (SCN)**. Likewise, the **suprachiasmatic nucleus (SCN)** is connected by neurons to the **pineal gland**, which secretes a **soporific known as melatonin** into the blood stream. In order to understand how melatonin got its name, we have to make another detour to discuss the melanophores in cold-blooded animals.

Figs. 3 and 4. Photographs made by reflected light.
Fig. 3. Normal tadpoles—just prior to pineal feeding.
Fig. 4. Same tadpoles 30 minutes after feeding [illegible] extract of pineal gland. The darker portions of these tadpoles are due to denser viscera—heart, gills, intestinal contents, etc. The degree of translucency is identical in all parts of the skin.

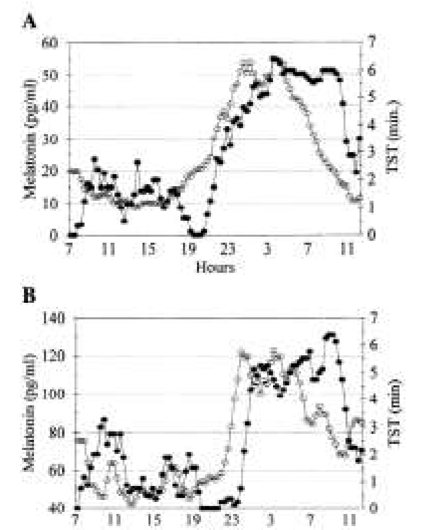
Melatonin got its name because it can cause the **melanosomes** in dermal **melanophores** of tadpoles to aggregate. Carey McCord and Floyd Allen (1917) fed **extracts of the pineal gland** of cows to tadpoles and found that thirty minutes later, the tadpoles became lighter in color. The extract had caused the aggregation of melanosomes in the dermal melanophores.

Noting that the **pineal extract** caused skin to lighten, **Aaron Lerner** (1958,1959,1960), a dematologist, and his colleagues repeated the work of McCord and Allen, isolated the chemical that lightened the frog’s skin by causing the aggregation of melanosomes, determined the structure of the **frog skin-lightening chemical**, and named it **melatonin**.



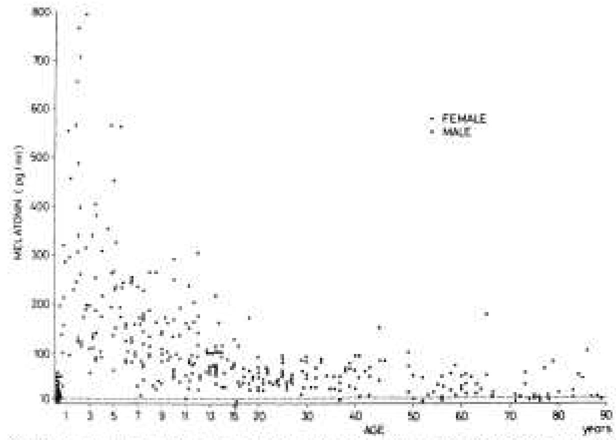
Unfortunately melatonin was not involved in causing skin-lightening conditions such as **vitiligo**. It does however seem to be involved in the **sleep-wake cycle** in humans, and melatonin had been given the nickname, the ***hormone of the darkness***. The levels of melatonin in the blood vary in a circadian fashion, **being low during daytime** and **high at night**. This rhythm persists for up to three weeks in individuals kept under very dim light conditions showing that **melatonin levels** in the blood are under the control of an **endogenous biological clock**.

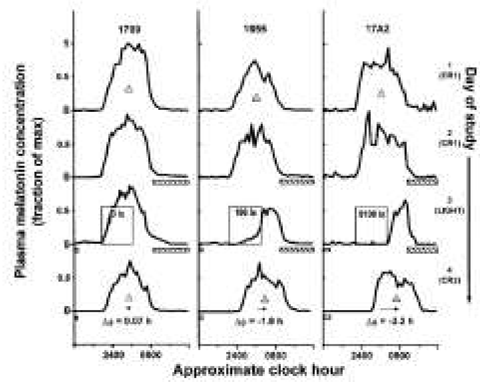
Shochat et al. (1997) showed that an ***increase* in melatonin** in the blood **precedes sleepiness** as measured by a propensity to sleep and a ***decrease* in melatonin in the blood precedes wakefulness** as measured by a propensity not to sleep.



1. Sleep propensity (TST; ●) and melatonin (○) curves of 2 cal subjects [*subjects 1* (*A*) and *4* (*B*)]. Nocturnal melatonin rise decline precede the rise and decline in nocturnal sleep propen- Curves were smoothed by a 4-point moving average window.

Waldhauser et al. (1988) found that the **magnitude of the melatonin peak declines with age** which is correlated with the difficulty in sleeping that comes with aging.





Zeitzer et al. (2000) found that an 6.5 hour **exposure to as little as 106 lux of white light** during early biological night **delays the secretion of melatonin into the blood**. Higher intensities (9100 lux) suppress the secretion of melatonin into the blood during the exposure and delay it when the light is turned off. Rüger et al. (2013) found that as little as 11.2 lux of 480 nm **blue light** was as effective as 10,000 lux white light, indicating that the photoreceptor pigment responsible for melanin suppression and delay is sensitive to blue light, as is true of melanopsin. Here are examples of illuminance in lux under various conditions.
11.2 lux is ***about*** the brightness of twilight.

Condition	Illumination	
	(ftcd)	*(lux)*
Sunlight	10,000	107,527
Full Daylight	1,000	10,752
Overcast Day	100	1,075
Very Dark Day	10	107
Twilight	1	10.8
Deep Twilight	.1	1.08
Full Moon	.01	.108
Quarter Moon	.001	.0108
Starlight	.0001	.0011
Overcast Night	.00001	.0001

Lux is a **photometric unit** that measures the **brightness** of a light as perceived by the human eye with photopic cone-dominated vision. One lux is equal to **one lumen per meter squared**. Free apps are available to turn smartphones into lux meters (https://play.google.com/store/apps/details?id=com.notquitethem.android.luxmeter and https://itunes.apple.com/us/app/luxmeter/id526675593?mt=8).

Demonstration: Use the Digital Lux Meter to measure the brightness of the light in the classroom and to get an idea of different brightnesses in terms of lux. Light meters that measure the brightness of light absorbed by melanopsin or **melanopic-lux** are being developed.

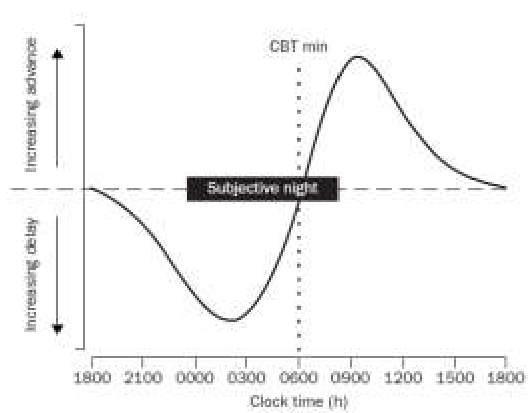
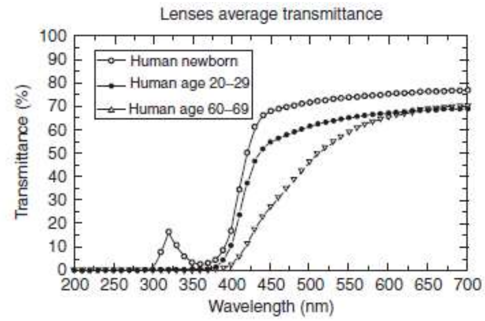


Figure 2: **Phase response curve (PRC) of a human being, in response to light**

The timing of the light pulse, in addition to its spectral composition, its intensity, and its duration, is important to know. A light pulse given near the beginning of the sleep period **delays the phase** (starting point) of the sleep-wake cycle making you less sleepy while a light pulse near the end of the sleep period **advances the phase** (starting point) of the sleep-wake cycle making you more awake. This can be visualized in a **phase-response curve**. Our response to light does ***not*** only depend on the physical quantities of light but also on when the light is given relative to the phase of our endogenous biological clock.

Brainard et al. (1997) found that **aging** is also correlated with a **yellowing of the crystalline lens** which blocks the transmission of the blue light that suppresses melatonin.



Sleep disturbances that are associated with desynchronization of the melatonin rhythms with the daily rotation of the earth can sometimes be ameliorated by **taking exogenous melatonin at the correct time**. The effectiveness of melatonin treatment seems to be variable—perhaps as a result of individual variability in the cycles and in part due to the lack of attention paid to timing—when in an individual's cycle one should take exogenous melatonin. An awareness and understanding of our **biological time** is especially important in our **24-hour society** (Rajaratnam and Arendt, 2001). Josephine Arendt (2000) wrote in *The New England Journal of Medicine*, "*the true potential of melatonin is becoming evident, and* ***the importance of the timing of treatment is becoming clear. Our 24-hour society, with its chaotic time cues and lack of natural light, may yet reap substantial benefits***."

Perhaps instead of taking **exogenous melatonin**, we can control the light around us to modulate the production of **endogenous melatonin** so we can sleep better. Amber bulbs and nightlights, blue-blocking filters for smartphones and tablets, and glasses that block blue light may be helpful at bedtime (https://www.lowbluelights.com/index.asp; https://www.lowbluelights.com/media/19552.mp3; Burkhardt and Phelps, 2009). It is also possible to get a free app that adjusts the **color temperature** of the displays of smartphones and tablets to the time of day—warm at night, like sunlight during the day (http://justgetflux.com/).

Eva Schernhammer and Abraham Haim have correlated **light at night** (LAN) that causes **circadian disruption** in the workplace and in the bedroom to increased risk of **breast cancer**.

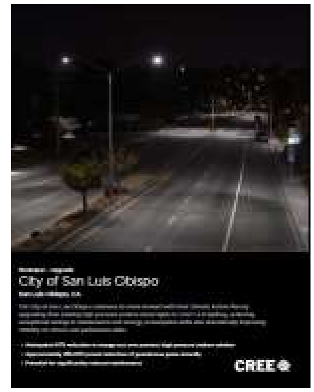
Perhaps it is a good time to remember that throughout most of human history, **sunlight** (supplemented at night with firelight) was the ***zeitgeber*** that entrained and synchronized the sleep-wake cycle with the daily rotation of the earth. The firelight evolved into light from an **oil lamp** about 4500 BC and then light from a **candle** about 3000 BC. Although the technology of artificial light improved, there was a cost to using it and so it was used frugally. In London in 1417, in Paris in 1524, and in Dublin in 1616, it became required by law to put a candle in the window of houses facing the street. Then came gas steet lighting.

Up until 1802, coal had only been used to power steam engines. In 1802, **William Murdoch** used the coal gas produced by heating coal to produce the first outdoor gaslight. The streets of London were lit by gaslight in 1807; the streets of Baltimore were lit by gaslight in 1816, the streets of Paris were lit by gaslight in 1829, and the streets of **Montreal** were lit in 1837.

Electric arc lamps replaced gaslights along the streets of Paris and London in 1878 and incandescent electric street lights were intoduced along streets in Newcastle-upon-Tyne and in Cleveland, Ohio in 1879. Georges Calude invented the **neon light** in 1910 and since that time it has been used to illuminate colorfully the streets in many cities, including **Times Square** in New York City and **Shibuya** in Tokyo Japan.

High Pressure Sodium vapor lamps that illuminate the streets monochromatically were introduced as street lights in 1964. The light spectrum of these lamps does not match the absorption spectrum of melanopsin and thus does not disrupt circadian rhythms.

Luminescent cold lights such as light emitting diode (LED) lamps are being introduced for street lights. They reduce the amount of energy needed to get a given amount of brightness, although the full spectrum LEDs are more disruptive to our circadian rhythms than the yellow high pressure sodium lights.



Satellite images from space show that some regions of the world are exposed to perpetual daylight—a form of **light pollution**.

Light pollution makes it seem like the sky has become emptied of stars. Light out of place or glare due to misdirected light makes it difficult to see astronomical objects such as the **Milky Way** even in rural areas such as Ithaca.

Intelligent street lighting, produced by Tvilight, uses motion sensors to brighten LED lamps only when they are needed. The use of intelligent street lighting saves energy and reduces light pollution.

And with our modern urbanized sleeping habitat, the perpetual daylight from artificial light came indoors:

And the light from smartphones and tablets at bedtime may reduce or delay the production of melatonin. Wood et al (2013) found that a two hour exposure to the blue light produced by an iPad reduces the salivary melatonin levels by 22%.

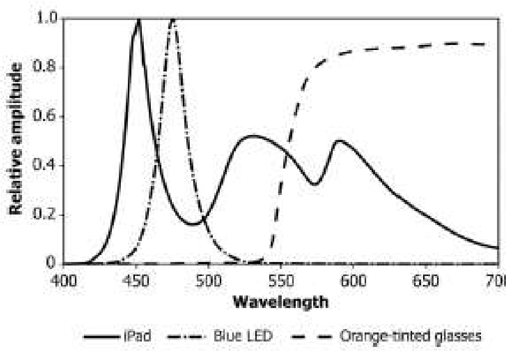


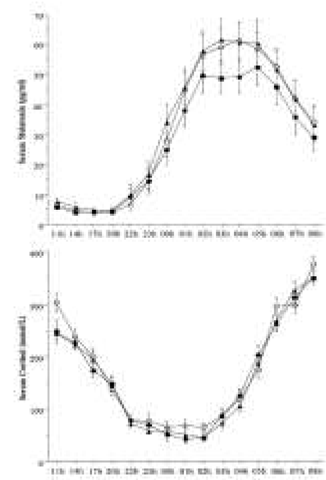
Fig. 1. Spectral transmittance of the orange-tinted glasses, the relative spectral power distribution (SPD) of a 470-nm (blue) LED, and the relative SPD of an iPad 1 (white screen, full brightness) used in the experiment.

Table 1
Lighting conditions (photopic illuminance in lux and CL_A measured with the Dimesimeter), predicted melatonin suppression (CS) and measured melatonin suppression after 1-h and 2-h exposures. Mean ± standard error of the mean (SEM) values are shown.

		Photopic illuminance (lux)	CL_A	CS[b]	Measured suppression (%)
1 h	Tablet + blue LEDs	59 ± 5.0	648 ± 4.9	0.46 ± 0.0013	48 ± 4
	Tablet + orange-tinted glasses[a]	9.8 ± 1.9	1.5 ± 0.31	0.0017 ± 0.0004	NA
	Tablet-only	18 ± 3.8	19 ± 4.6	0.03 ± 0.0066	7.0 ± 4
2 h	Tablet + blue LEDs	57 ± 3.8	645 ± 3.4	NA	66 ± 4
	Tablet + orange-tinted glasses[a]	9.9 ± 1.6	1.5 ± 0.29	NA	NA
	Tablet-only	16 ± 2.7	17 ± 3.51	NA	23 ± 6

NA: not applicable.
[a] The tablet with the orange-tinted glasses condition was used as the dark control.
[b] Based upon a 1-hr duration of light exposure and a 2.3 mm pupil diameter.

Melatonin is not the only hormone whose levels in the blood change in a circadian manner. **Cortisol** levels also change in a circadian manner (Selmaoui and Touitou, 2003). While the levels of melatonin are correlated with sleepiness, the levels of cortisol are correlated with **wakefulness**. Since cortisol is also a hormone produced in



stressful situations, **chronic stress** results in a constant production of cortisol and interferes with the ability to sleep.

Vitamin D, also known as the sunshine vitamin, is produced by the body in response to sunlight and is necessary for normal bone development. However, vitamin D is also a steroid **hormone** that can have significant effects on the body as a result of the variety of vitamin D receptors in the brain. As a result of spending less time in sunlight, more and more people are developing vitamin D deficiencies and the deficiencies are correlated with sleep disorders (Gominak and Stumpf, 2012). While studying people with headaches, Gominak serendipitously found that people who took vitamin D supplements were able to wake up rested. It seems that vitamin D reduces the level of melatonin in the body. The levels of vitamin D, like the levels of cortisol, are correlated with **wakefulness** and the **day-like physiological state**. Thus when vitamin D supplements are taken at night, they prevent sleepiness while the same supplements taken in the morning increase wakefulness.

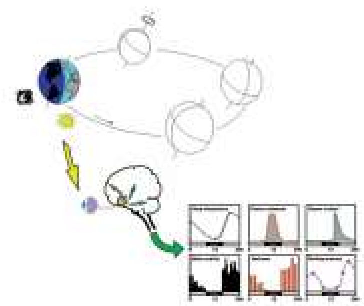
Anti-histamines often cause sleepiness, which led researchers to check if the hormone **histamine** changes in a circadian fashion (Brown et el. 2001). The levels of histamine, like the levels of cortisol, are correlated with **wakefulness** and the **day-like physiological state**.

Anti-diuretic hormone also varies in a circadian manner. It is highest at night so that our sleep in not interrupted by the urge to urinate.

The **Lighting Research Center at Rensselaer Polytechnic Institute** (http://www.lrc.rpi.edu/programs/lightHealth/index.asp) researches questions about light, health and circadian rhythms.

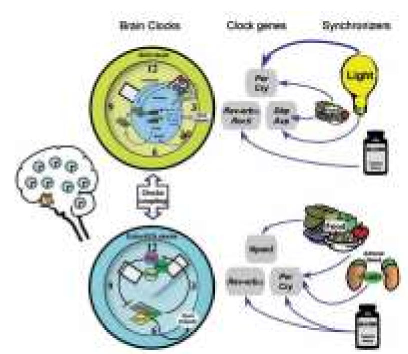
Just as there is more than one chemical that regulates sleep, there may be **more than one endogenous biological clock**. Tosini and Menaker (1996) have shown that retinas isolated from hamsters have a circadian rhythm of melatonin synthesis and the period of the rhythm depends on the genotype. Retinas from wild type hamsters have a 24 hour period while retinas from homozygous tau mutants have a 21 hour period.

In conclusion, we have an **endogenous biological clock** in our brain and perhaps elsewhere that regulates the **sleep-wake cycle** by rhythmically releasing hormones such as **melatonin** and **cortisol** into our blood stream that affect when we go to sleep and wake up. Our endogenous biological clock can be naturally reset by sunlight as a ***zeitgeber*** so that it is entrained or synchronized with the daily rotation of the earth.



Melatonin does not induce sleepiness in all organisms since in **nocturnal** organisms the levels of melatonin also rise during the dark period, which is the active period in nocturnal organisms. In general, **melatonin signals the dark period**, and when the melatonin level is high, diurnal organisms get sleepy and nocturnal organisms awaken.

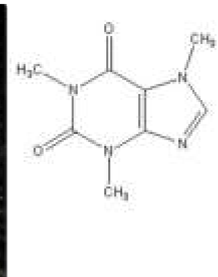
Exposure to bright light, particularly in the blue region of the spectrum, which is absorbed by **melanopsin** in the **intrinsically photoreceptive retinal ganglion cells (iPRGC)**, **resets the phase** of the endogenous clock, which regulates the timing of **melatonin** and **cortisol** release and the sleep-wake cycle so that they are no longer synchronized with the

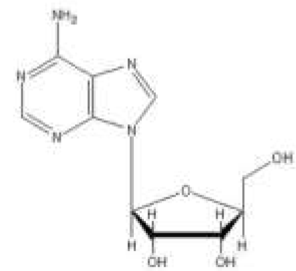


daily rotation of the earth. We can increase the amount of melatonin produced during the sleep period by avoiding bright blue light that acts as a ***zeitgeber*** before bedtime. On the other hand, bright blue light during the day increases our level of wakefulness.

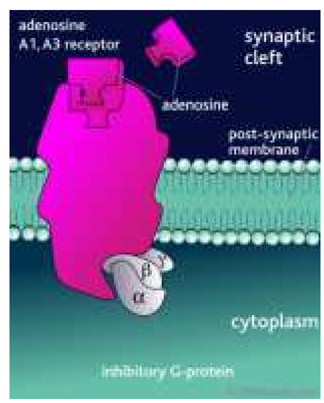
Cortisol levels are correlated with wakefulness and we can decrease the nighttime levels of cortisol by managing our **stress levels** and quality of stress. We want no stress at night and **eustress** not **distress** during the day.

Coffee and **tea**, which contain caffeine, help make us alert during the day and make it harder to sleep at night.

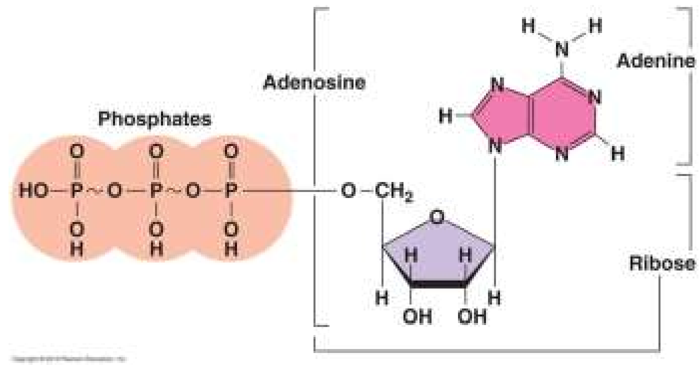

Caffeine


Adenosine

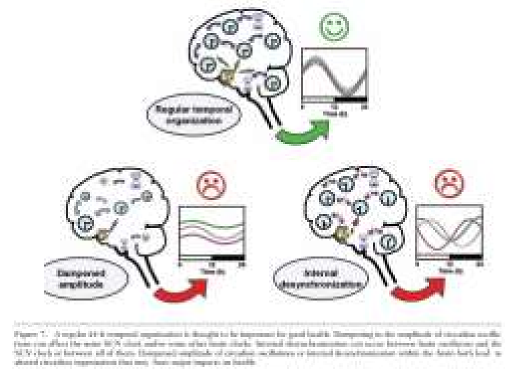
Caffeine increases our level of wakefulness not by interacting with the endogenous biological clock but by inhibiting the binding of **adenosine** to the **adenosine receptors** in the forebrain and hippocampus that when activated by adenosine, sedate the brain and cause sleepiness. When adenosine binds to the adenosine receptor, it sedates the brain by inhibiting the release of all neurotransmitters into the synapses.

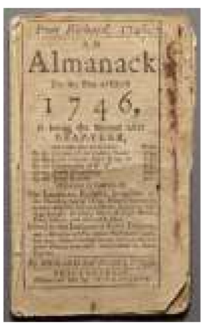


The buildup of adenosine comes from the breakdown of **adenosine triphosphate (ATP)** that occurs through **physical activity**. ATP is resynthesized from adenosine during sleep periods where the level of physical activity is low.



It is common sense and there is evidence from the National Sleep Foundation (http://sleepfoundation.org/) that the synchronization of the endogenous biological clock with the daily rotation of the earth results in a rested happy and healthy person. Indeed, **Benjamin Franklin** (1746), the son of a tallow chandler who would make money if people stayed up late, wrote, "*Early to bed and early to rise, makes a man healthy, wealthy, and wise.*"

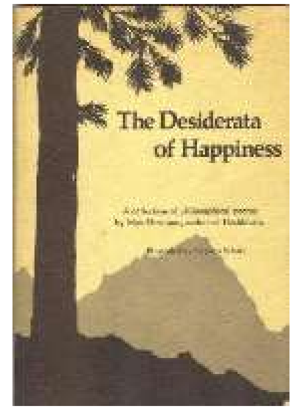




In this lecture, we have talked a lot about **time**. If time were an illusion, as the mathematical physicist's party line states, biological clocks would ***not*** be a fundamental scientific concept worthy of a lecture. Although I am in a minority of one, I think **time is real and absolute** and that biology with its **bio-logic** is more fundamental than current mathematical physics. See the following three videos for Brian Greene's, Michio Kaku's and Julian Barbour's view of time:

Brian Greene in *Fabric of the Cosmos: The Illusion of Time*
https://www.youtube.com/watch?v=9Qu9XaF2K10
Michio Kaku in *The True Nature of Time*
https://www.youtube.com/watch?v=2TiQidGPHA4
Julian Barbour on *Does Time Exist?*
https://www.youtube.com/watch?v=KkjXuS_Z1ds

I think that the **present** or **now** is fleeting, but as a part of the **universe**, you are also connected to its **past**. You are stardust in that the material that makes up your body was synthesized by stars that exploded billions of years ago. The stardust provided the material from which the earth and all its creatures were and will be formed. All the food you eat is fundamentally synthesized using the radiant energy produced by the nuclear fusion reactions in the core of the sun. Our endogenous clocks are timed with the rotation of the earth on its axis and synchronized by the sunrise. You are, as **Max Ehrmann** (1927) wrote in the poem *Desiderata*, which is Latin for *desired things*, "*…**a child of the universe** no less than the trees and the stars; you have a right to be here*."



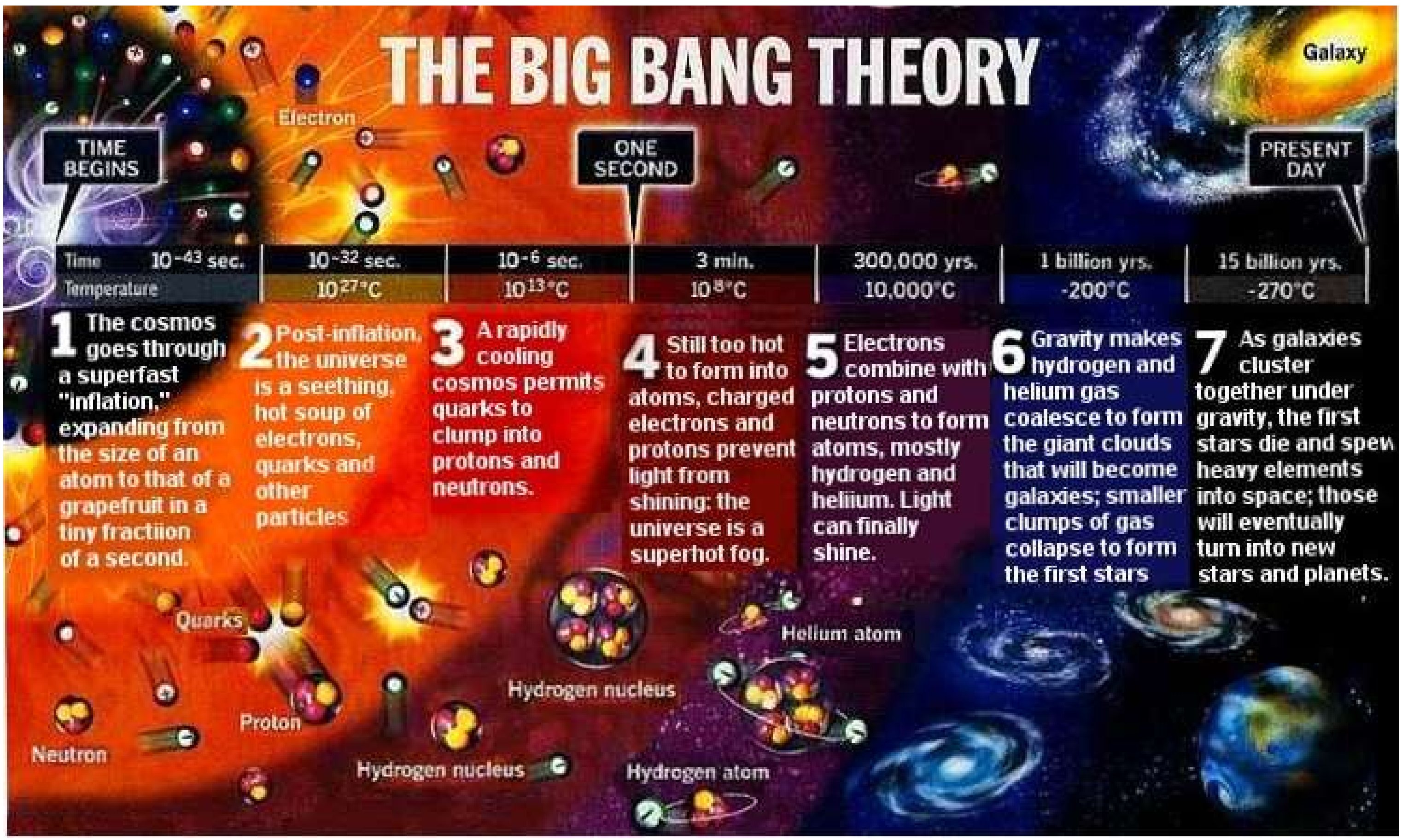
Desiderata: recited by Les Crane (1971), a radio and television personality, a civil rights activist mentioned in Phil Och's song *Love Me, I'm a Liberal*, and responsible for creating the Top 40: https://www.youtube.com/watch?v=398_oV5ovyw

Recited by Leonard Nimoy (Mister Spock):
https://www.youtube.com/watch?v=ZZJ1fJTezFE
Deteriorata (1972): a Parody by National Lampoon:
https://www.youtube.com/watch?v=Ey6ugTmCYMk

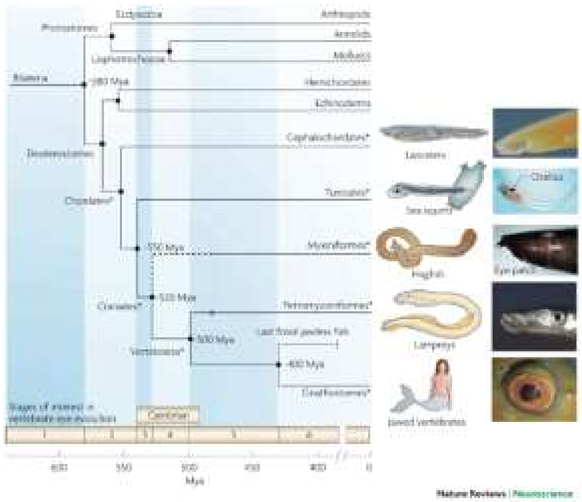
Over the semester we have considered time as an independent variable on which we could order various events. John F. Kennedy spoke about "our time" at the University of California at Berkeley on March 23, 1962:

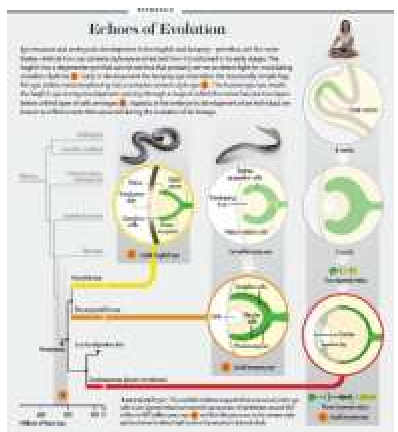
"*'Knowledge is the great sun of the firmament,' said Senator Daniel Webster. 'Life and power are scattered with all its beams.' In its light, we must think and act not* *only for the moment but for our time. I am reminded of the story of the great French Marshal Lyautey, who once asked his gardener to plant a tree. The gardener objected that the tree was slow-growing and would not reach maturity for a hundred years. The Marshal replied, 'In that case, there is no time to lose, plant it this afternoon.' Today a world of knowledge--a world of cooperation--a just and lasting peace--may be years away. But we have no time to lose. Let us plant our trees this afternoon.*"

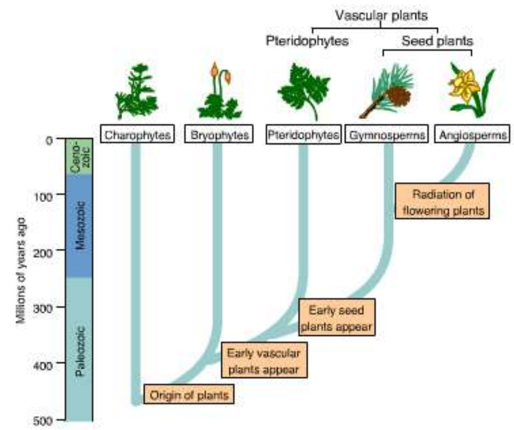
We have looked at the **big bang** in terms of astronomical time.



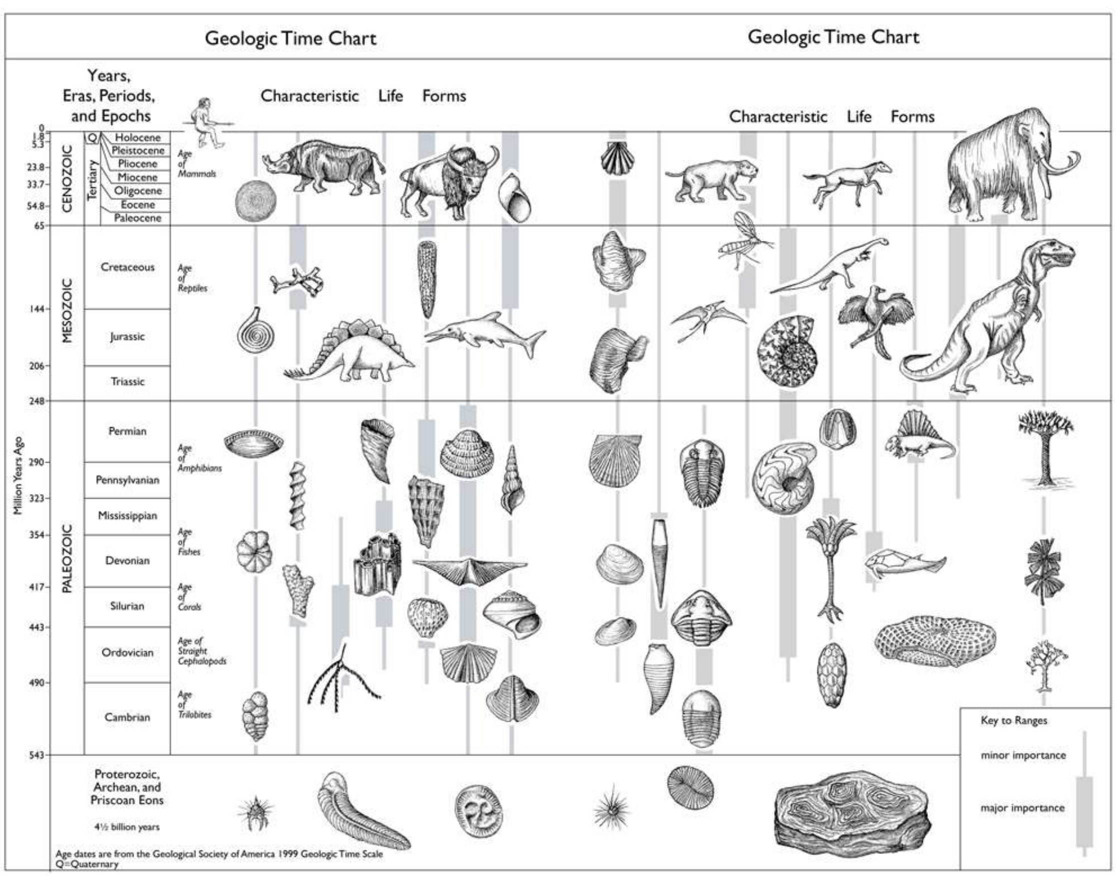
We have looked at the **biogenic origin of oxygen**, the **evolution of the eye** and the **plants found in coal balls** in terms of geological time.



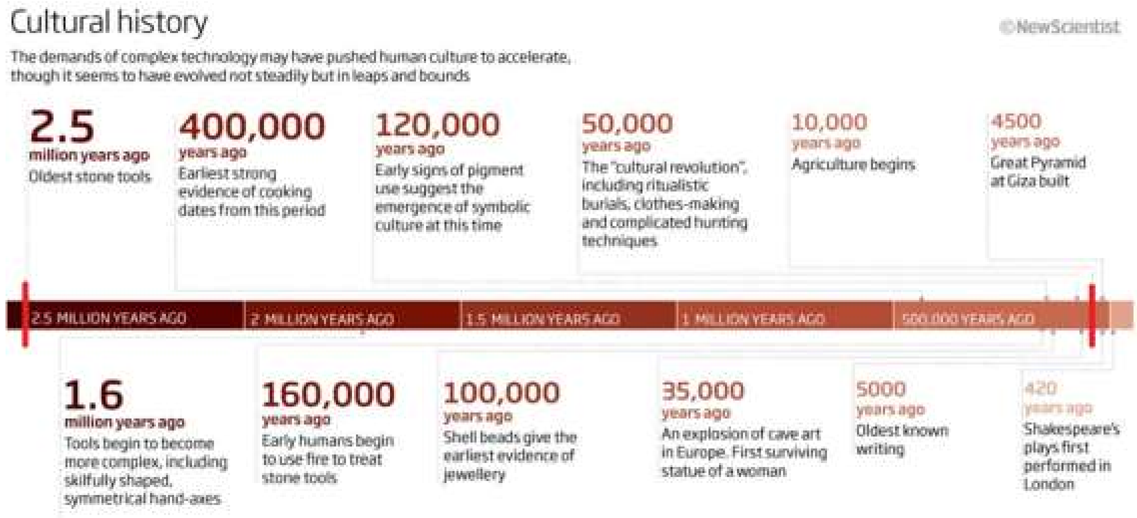




Below is a chart of geological time where the Carboniferous is split into the Mississippian and Pennsylvanian.



When we talked about the chemical history of a candle and charcoal, we considered our cultural history in terms of cave art produced 35,000 years ago:



A secular world, from the Latin word *saecularis* meaning "temporal" should be a world that believes that time is fundamental. After all, if time is an illusion, the whole secular world is an illusion. In so many ways, time is necessary for musicians. Without time, there is no music. There are many songs about time:

Solomon (Ecclesiastes 3), and later **Pete Seeger** and all who covered his song, *Turn! Turn! Turn! (to Everything There Is a Season)* considered the nature of time and realized that "*There is a time for everything, and a season for every activity under the heavens: a time to be born and a time to die, a time to plant and a time to uproot, a time to kill and a time to heal, a time to tear down and a time to build, a time to weep and a time to laugh, a time to mourn and a time to dance, a time to scatter stones and a time to gather them, a time to embrace and a time to refrain from embracing, a time to search and a time to give up, a time to keep and a time to throw away, a time to tear and a time to mend, a time to be silent and a time to speak, a time to love and a time to hate, a time for war and a time for peace*."

As Time Goes By sung by Dooley Wilson:
https://www.youtube.com/watch?v=zaAqze81y4Y
As Time Goes By sung by Binnie Hale (1932) with original lyrics about Einstein:
https://www.youtube.com/watch?v=iBGDg9w5AtI
Time is on my Side sung by the Rolling Stones:
https://www.youtube.com/watch?v=XzcWwmwChVE
Time after Time sung by Cyndi Lauper:
https://www.youtube.com/watch?v=h0NkCvFD5r4
Rock Around the Clock sung by Bill Haley and the Comets:
https://www.youtube.com/watch?v=F5fsqYctXgM
Time sung by Pink Floyd:
https://www.youtube.com/watch?v=JwYX52BP2Sk
Does Anyone Really Know What Time It Is? Sung by Chicago:
https://www.youtube.com/watch?v=7uy0ldI_1HA
Time in a Bottle sung by Jim Croce:
https://www.youtube.com/watch?v=dO1rMeYnOmM
Time Warp from Rocky Horror Picture Show:
https://www.youtube.com/watch?v=tkplPbd2f60
Feels Like the First Time sung by Foreigner:
https://www.youtube.com/watch?v=qHDy_b33cCQ
The Longest Time sung by Billy Joel:
https://www.youtube.com/watch?v=a_XgQhMPeEQ
Now's the Time sung by The Hollies:
https://www.youtube.com/watch?v=WBfFrNpjZmc
Now's the Time played by Charlie Parker:
https://www.youtube.com/watch?v=ryNtmkfeJk4
The Times They Are a Changin' sung by Bob Dylan:
https://www.youtube.com/watch?v=e7qQ6_RV4VQ
Summertime Blues by Eddie Cochran:
https://www.youtube.com/watch?v=HWbXCz9UZYo
Wintertime sung by the Steve Miller Band:
https://www.youtube.com/watch?v=S_rZ7to0rqQ
Summertime sung by Ella FitzGerald and Louis Armstrong:
https://www.youtube.com/watch?v=lnXLVTi_m_M
Springtime for Hitler from The Producers:
https://www.youtube.com/watch?v=BCIHUmjKD9U
Funny How Time Slips Away sung by Willie Nelson:
https://www.youtube.com/watch?v=iZaZqx9v3dU
Night Time is the Right Time sung by Ray Charles:
https://www.youtube.com/watch?v=PuNzqDUvods

Blues in Time performed by Gerry Mulligan and Paul Desmond:
https://www.youtube.com/watch?v=nhMUnYM2UPg
Hard Time Killing Floor Blues from O Brother, Where Art Thou?
https://www.youtube.com/watch?v=fhRmCMWdRqM
Evening: The Sunset-Twilight Time sung by the Moody Blues:
https://www.youtube.com/watch?v=Bbs_EBRnuBw
Long Time Gone sung by Crosby, Stills & Nash:
https://www.youtube.com/watch?v=2DUqplxIcNk
Clocks sung by Coldplay:
https://www.youtube.com/watch?v=d020hcWA_Wg

The Poets also write about time:

Acquainted with the Night by Robert Frost

I have been one acquainted with the night.
I have walked out in rain --and back in rain.
I have outwalked the furthest city light.

I have looked down the saddest city lane.
I have passed by the watchman on his beat
And dropped my eyes, unwilling to explain.

I have stood still and stopped the sound of feet
When far away an interrupted cry
Came over houses from another street,

But not to call me back or say good-bye;
And further still at an unearthly height
One luminary clock against the sky

Proclaimed the time was neither wrong nor right.
I have been one acquainted with the night.

The Paradox of Time by Henry Austin Dobson

Time goes, you say? Ah no!
Alas, Time stays, we go;
Or else, were this not so,
What need to chain the hours,

For Youth were always ours?
Time goes, you say?-ah no!

Ours is the eyes' deceit
Of men whose flying feet
Lead through some landscape low;
We pass, and think we see
The earth's fixed surface flee:-
Alas, Time stays,-we go!

Once in the days of old,
Your locks were curling gold,
And mine had shamed the crow.
Now, in the self-same stage,
We've reached the silver age;
Time goes, you say?-ah no!

Once, when my voice was strong,
I filled the woods with song
To praise your 'rose' and 'snow';
My bird, that sang, is dead;
Where are your roses fled?
Alas, Time stays,-we go!

See, in what traversed ways,
What backward Fate delays
The hopes we used to know;
Where are our old desires?-
Ah, where those vanished fires?
Time goes, you say?-ah no!

How far, how far, O Sweet,
The past behind our feet
Lies in the even-glow!
Now, on the forward way,
Let us fold hands, and pray;
Alas, Time stays,-we go!

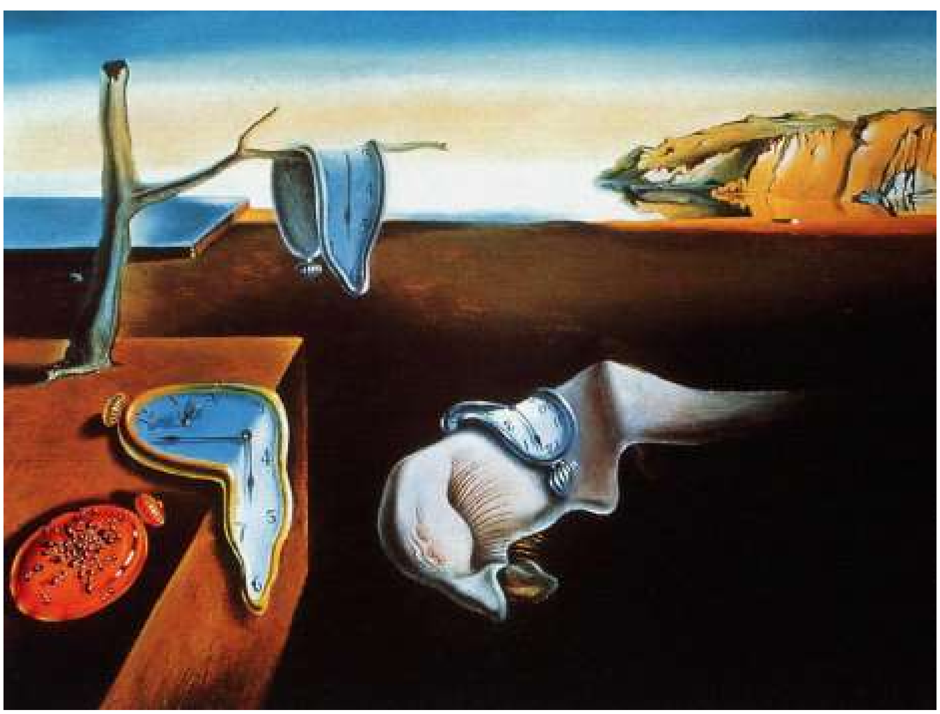
Various ideas of time have been expressed by artists.

Engraved by Phillips Galle after Pieter Bruegel's (1574) "*The Triumph of Time*"
https://www.youtube.com/watch?v=Nl0RXP0YioM

Agnolo Bronzino's (1545) *Venus, Cupid, Folly and Time*

Antonio de Pereda's (1632-1636) *Allegory of Vanity*

Salvador Dali's (1931) *The Persistence of Memory*



And Salvador Dali's (1954) *The Chromosome of a Highly-coloured Fish's Eye Starting the Harmonious Disintegration of the Persistence of Memory*

Alighiero y Boetti's (1968) *Gemelli*

Julie De Waroquier’s (2011) *The Weight of Time*

And movies: Harold Lloyd hanging from a clock in *Safety Last* (1923)

https://www.youtube.com/watch?v=VFBYJNAapyk

This picture was also used in Christian Marclay’s (2010) *The Clock*

https://www.youtube.com/watch?v=BXbQw0rE5UE

Tom Stoppard wrote about the irreversibility of time in his play *Arcadia* (Act II Scene 3).

Tom Stoppard's
ARCADIA
Directed by David Leveaux

ARCADIA opens at the Ethel Barrymore Theatre (243 W. 47th Street) on March 17, 2011.

Pictured (L-R): Bel Powley, Raúl Esparza, Lia Williams and Tom Riley

© Carol Rosegg, 2011

Hannah: What did she see?

Valentine: That you can't run the film backwards. Heat was the first thing which did not work that way. Not like Newton. A film of a pendulum, of a ball falling through the air—backwards, it looks the same.

Hannah: The ball would be going the wrong way.

Valentine: You'd have to know that. But with heat—friction—a ball breaking a window—

Hannah: Yes.

Valentine: It won't work backwards.

Hannah: Who thought it did?

Valentine: She saw why. You can put back the bits of glass but you can't collect up the heat of the smash. It's gone.

Septimus: So the Improved Newtonian Universe must cease and grow cold. Dear me.

Valentine: The heat goes into the mix.

Thomasina: Yes we must hurry if we are going to dance.

Valentine: And everything is mixing the same way, all the time, irreversibly—