

BIOLOGICAL RHYTHMS AND MEDICINE.

I. THE SUPRACHIASMATIC NUCLEUS.

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Knowledge of the circadian, seasonal and circannual rhythmicity of bodily functions has become increasingly important for the diagnosis and treatment of diseases.

Diurnal (or circadian) rhythms are the peaks and troughs of certain types of behaviour, endocrine events, cell division rates, and a large number of other biological functions over the 24 h period of a day. These rhythms are mostly dependent on the lengths of light and dark period. Well known are the diurnal rhythms of blood pressure and body temperature. Less well known is e.g. the diurnal rhythm of leucocytes. Their number per cubic millimeter of blood given in textbooks (5,000-10,000) is the morning value, as taking blood from patients or for research is usually done in the morning hours. However, the peak values in the evening can be dramatically different in a number of individuals, going as high as 15,000 per cubic millimeter under normal conditions. A patient coming to the hospital in the evening with vague pain around the umbilicus or more distinct pain around McBurney's point, subfebrile temperature, and a "leucocytosis" of 15,000 would be likely to undergo an immediate appendectomy. The result is not rarely the delivery of a healthy appendix.

Seasonal rhythms are additional peaks and troughs over a period of several days, weeks or months, such as the ovulatory cycle.

Circannual rhythms are peaks and troughs of functions over the period of one year, which are superimposed on diurnal and seasonal rhythms. They have been mostly studied in animals so far and include e.g. mating behaviour and migration. Some diseases may also follow circannual rhythms, reoccurring regularly at certain times of the year, e.g. ulcers, asthma, and winter depression.

In mammals, most diurnal and at least some circannual rhythms are triggered by two accumulations of small neurons in the hypothalamus, lying just above the optic chiasm on either side of the third ventricle, the **suprachiasmatic nuclei** (SCN). These neurons fire in synchrony, i.e. all at the same time (1). They are innervated by afferents from retinal ganglion cells (6), which are more active during light influence and less active during darkness. The optic synapses (4,5) transmit therefore a slow "drumbeat" to the neurons of the SCN during the 24 h period of a day. The duration of this drumbeat is dependent on the length of the light influence. It is exactly 12 h when one lives naturally and close to the equator. However, the further one lives away from the equator, the greater is the change of the lengths of light and darkness. This, of course, changes the duration of activity of the optic synapses and that of SCN neurons over the year. The retinal input to the SCN is therefore called the

“Zeitgeber” (German, which means “time giver” in English), which makes the up and down of neuronal activity in the SCN exactly diurnal, i.e. exactly 24 h.

When the optic nerves are experimentally or accidentally cut, amaurotic blindness follows, and the drumbeat to the SCN neurons stops. Nevertheless, SCN neurons continue to fire synchronously with their own rhythm of higher and lower activity. However, this rhythm shifts away from 24 h and becomes “free-running”. This means that now the high activity-low activity rhythm follows a period of e.g. 23 h or 25 h. The SCN is, therefore, considered to be a **“pacemaker”**, i.e. our internal biological clock (7). This clock also continues to tick, when persons or experimental animals live under constant environmental conditions in an artificial setting, e.g. in constant light or darkness. Here again the clock “free-runs”. As this rhythm is not exactly 24 h, it is called “circadian”, which means “about or close to 24 h”. Unfortunately, the terms “diurnal” and “circadian” are often mixed up in the literature, and “circadian” is used for both, “exactly 24 h” and “about 24 h” equally.

The SCN neurons send their axons to many regions in the central nervous system, especially the limbic system. Their activity also influences -- via several neuronal stations -- neurons in the brainstem, from there the sympathetic preganglionic neurons in the upper intermedio-lateral grey column of the spinal cord, which send their axons to the pineal gland. Here, finally, SCN activity influences the synthesis and release of the hormone **Melatonin**, which is high during darkness (night) and low during light influence (2). The pacemaker-induced rhythmic activity of limbic neurons, as well as high and low levels of melatonin in the brain and blood trigger rhythmic activity in other centres, until -- like in a chain reaction -- most bodily functions are affected accordingly.

The SCN is most probably on the top of a hierarchy of several biological clocks.

When the SCNs are experimentally destroyed, a large number of rhythmic functions are also abolished, such as melatonin synthesis and drinking behaviour in monkeys. Other rhythms continue (e.g. cortisol rhythm and core body temperature) now under the new pacemaker influence of secondary clocks, which are still not well defined (7).

During development, the mother synchronizes the fetal functions to her own diurnal rhythms via a still unknown mechanism (8). After birth, the maturing SCN shows a clear diurnal rhythm of neuronal activity at the end of the second week in rats. In humans, behavioural and other rhythms of the neonate are still irregular until about three months post partum.

It becomes now more clear that diagnostic tests can give different results when they are performed at different times of the day. The results may then be considered as abnormal (abnormally high or low, see above), although they are still in the range of a normal diurnal rhythm. On the other hand, a result may still appear within the normal range, although at another time of the day values are abnormal. Textbooks and laboratory handbooks should, therefore, include the diurnal variations of values for clinically important parameters as soon as possible. It also becomes clear that drugs have very different effects on their target tissues or systems when they are administered at different times of the day. It has been known for a long time that alcohol (which is considered by some to be medicine) is reasonably well tolerated in the evening, but has devastating results when it is ingested in the morning. Barbiturates are also not too toxic, when they are taken in large amounts by addicted persons in the late evening at bedtime, but have caused death when the same dose was ingested in the early morning hours.

Cytostatic drugs work best when given at the time of highest division rate of the tumor cells. This optimal time can be different for different types of tumors, but also slightly different for the same tumor type in different

individuals. Some hormones should be, if at all possible, administered only at the peak of their respective concentrations in the blood. If this topped-up peak is followed by a natural decline of hormone concentration the hypothalamic feedback system is not disturbed, and side effects are kept to a minimum. An example is cortisol, which ideally should be given only once, i.e. at about 6 to 7 AM, the time of its peak concentration in the blood. If however, the hormone is ingested three times per day, a natural trough cannot occur, the hypothalamic feedback system is disturbed, and dangerous side effects, such as stomach ulcers and Cushing, are more likely to develop.

The above mentioned results of the last two decades of research make it now understandable that sudden changes in lighting conditions disturb the pacemaker function of the SCN, and a large number of diurnal rhythms. This occurs in shift workers, such as doctors, nurses, pilots, flight attendants, airport personnel, police, fire fighters and many other professions. They also affect the traveller who jumps within a short time over several time-zones, and consequently suffers from "Jet Lag". Many shift workers with rotating shifts, especially when they are working under normal artificial lighting conditions at night, and sleep in a not completely darkened room under relatively high noise levels during day time, develop various kinds of disorders, e.g. excessive mood swings, digestive problems, disturbances of the menstrual cycle, skin problems, higher susceptibility to infections, a greater risk of cardiovascular disease and others. These problems can be greatly alleviated when care is taken that shift workers perform their duties at night under very bright light (7,000-12,000 Lux), and can sleep in total darkness under exclusion of noise during their free time (3). Under such conditions, the pacemaker can be "re-entrained" by the optic afferents in relatively short time

(about three days), although some rhythms may take somewhat longer to adapt to the new lighting situation. It is obvious that, ideally, working shifts should not change too quickly and too often.

The various rhythms of the respective bodily functions need to be in a correct relation to each other and should be diurnal for optimal health. If they become desynchronized we have the situation of an orchestra where some or all members play with different rhythms, which causes disharmony. Disharmony of bodily functions is not compatible with health.

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