Endogenous Rhythms as the Cause of Diseases and various Drug Tolerances

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„In the beginning was the rhythm“
Hans Guido, Count von Bülow
(1830-1894)

Introduction

Life is a process that proceeds with rhythmic vibrations, with the planetary motion determining the „music“ of our lives. If the rhythm of life comes to a halt, this means we are dead. Rhythm may reveal itself in many material things, but in itself it is movement, happening.

All of life’s processes are subject to a complicated temporal and spatial order, and this guarantees the collaboration of various vital functions. There are sequences in time, in which the processes take place in alternation. This presupposes a rhythmic structure, which may be encountered in all orders of magnitude, with a wide variety of periodic duration. A period of this kind may extend over several years, a year, a month, a week, a day, minutes, seconds or fractions thereof. Rhythmic stimuli make it possible to adapt the biological courses of events. They are referred to as „internal clocks“, and they design cyclical patterns for the individual processes of life. From the unicellular organism right up to the human being, the influence of these stimuli can be proven, and the analogies that can be observed are fascinating. Such impulses are vitally necessary for the preservation of each individual and the whole species.

Humankind alone is able to detach itself from the rhythmic environmental order, on account of progressive mechanisation, resulting in a high degree of time-related emancipation. In this way a strong degree of autonomy is achieved, whilst at the same time there is a weakening of the exogenous metronome effect in the long-wave area.

For a long time, it was thought that only the more highly evolved Eukaryotes - as opposed to the Prokaryotes - possessed an „internal clock“. However, in 1986, researchers studying the cyanobacterium Synechococcus discovered a circadianly independent behaviour! These organisms store more protein at certain times than at other times, and the cell division also takes place at rhythmic intervals. Further investigations showed that not only individual genes, but the entire genetic make-up of these cyanobacteria was under its own chronological control! The only living creatures, in which no biological clock has so far been found are the primeval archaebacteria. However, because cyanobacteria are some of the oldest organisms that exist, it can be stated with certainty that the first biological clocks are almost as old as life itself.

Three-and-a-half thousand million years ago, precursors of the cyanobacteria were already in existence, and they passed on this system of time-measurement to their descendants, from whom the variety of modern life-forms developed. According to Jakubowski, the longest cosmic period embraces more than 3.5 thousand millon years and is controlled from a cosmic centre that he has ranked highest in the hierarchy of the solar system. As to its situation, we can only guess. In the course of evolution, new clocks were added. For a short while, chronobiologists have known that „time measurement“ functions in more or less the same way in all organisms. Cells from higher organisms that are kept isolated in the laboratory follow rhythmic patterns, e.g. in their metabolic behaviour, although these may gradually get lost in the space of a week, depending on the time of day.

Some interesting research has been carried out on the green alga Acetabularia, which grows on tropical and subtropical sea shores. After removal or transplantation of the cell nucleus of this unicellular alga, which can grow to a height of up to 20 cm, the rhythmic vibrations of photosynthesis continued exactly according to their circadian rhythm. This was also the case, when parts of the alga without a nucleus were separated off, insofar as these segments survived. It was part of a hologram that continued to work. So long as life is present, there are rhythms; or should we maybe say: so long as there are rhythms, there is life?

Various Rhythms and what Stimulates Them

Rhythms may be differentiated according to their varying frequencies and pulses. So far as their wavelength is concerned, they can be divided into long-wave (years, months, weeks), medium-wave (minutes, seconds) and short-wave (fractions of a second). The long-wave stimuli are mostly hormones, whereas the shorter rhythms rather tend to be membranous processes with nerve stimuli.

Prevailing science categorises these impulses into:

1. Endorhythms: these occupy the living cells and individuals and are not susceptible to alteration by external changes.

2. Exorhythms: the stimuli are situated outside the living being and cause it to perform certain rhythmic activities and reactions (e.g. drop in temperature and hibernation).

3. Endo-exorhythms: inner (endogenous) rhythms are adapted (e.g. to times of day) by external stimuli.

Modern physicists concerned with Quantum Physics also classify endorhythms as cosmic stimuli, with which living beings come into resonance. Since these internal rhythms are clearly not controlled by the solar or lunar systems, but by heavenly bodies on a higher level, it is not possible for us to quantify nor classify them completely.

The „Internal Clock“

Endorhythms run their course in every cell and co-ordinate the various enzymatic processes. In more highly organised living beings there is a so-called „central clock“, whose principal function is to determine the processes within cells and organs according to the time of day. We are dealing here with the Nucleus suprachiasmaticus (SCN). This is situated above the optic nerve crossover and is a condensation of nerve cells measuring only a few mm^3. From this, nerve cells provide a direct link with the eyes. Based on the light impulses picked up by this sensory organ, the SCN controls the co-operation of different nuclear rhythms in humans and animals during daylight hours. That is important, because although the endogenous rhythms of body temperature and waking-sleeping behaviour require about 24 hours for a sequence, depending on the individual they have to be matched to the actual daily cycle by a superior „metronome“.

If humans and higher living beings are made to live in unlit spaces, bunkers and caves and have no contact with the external world, then the rhythms already mentioned „free-wheel“. For body temperature this means that - approximately every 24-25 hours - it starts a new daily cycle, whilst after 10-14 days the sleeping-waking behaviour adapts to an average daily cycle of 25-26 hours and more. These endogenous rhythms, encompassing about a day, are therefore called *circadian*. The change in body temperature over the course of the day stands for differing levels of energy consumption in the body, whereas the phases of sleeping and waking are an expression of the organism's varying need of rest, physical regeneration and growth on the one hand, and of activity, food consumption and communication on the other hand.

In experiments where the SCN of small rodents has been destroyed, the need for food and sleep as well as fluctuations in the behaviour of body temperature have certainly persisted, but the rhythms are no longer co-ordinated, the animals neglect themselves, stop seeking social contact, and quite soon they die from infections.

Extreme rhythmic chaos is found in Alzheimer's disease. This is an example of gradual destruction of the „internal clock“. The brain damage typical of this disease also attacks the SCN. In many residential homes the prevalent level of lighting is 50 lux. This means that these people spend the whole day in bed dozing in twilight, cut off from any light impulses. The patients' condition can frequently be improved considerably, if bright light is provided and they are also taken outside into daylight and fresh air and are mobilised!

Presentation of Individual Rhythms

In order to investigate the phenomenon of rhythm, precise time lines must be established and compared. Combining chronobiological measurement data of varying rhythms then aids our understanding of the way in which life processes work together. Many changes of rhythm are difficult to measure. Because of this, we shall confine our discussion here to cycles which encompass one day, with the aid of examples.

1. Body Temperature Rhythm

It was by measuring body temperature that researchers first came upon the idea that an internal „metronome“ must exist, causing the body temperature to rise at certain times of day, reaching a maximum level in the early afternoon, and then causing it to drop again to a minimum level, which is reached 12 hours later. In

a healthy human being the difference amounts to c. 1 degree, indicating the individual's various phases of activity. At the point when the body is at its warmest - c. 37.5 degrees - the person concerned is at his/her most active, is concerned with food and seeks social contact and communication; at the lowest point, with a temperature of 36.5 degrees, most bodily functions are just ticking over, the body cools down considerably on the periphery and maintains only the core temperature that is physiologically necessary. In order to translate this into action, at the start of the „cooling-down stage" the blood supply to the limbs is particularly good, so that the body temperature drops rapidly. (This is why we cannot go to sleep with cold feet.) Then the stage of deep sleep (NREM) begins, to be replaced after c. 90-120 minutes by a REM stage. The task of REM sleep, inter alia, is that of a thermostat, which ensures that the brain is briefly warmed up in the meantime. Then NREM sleep ensues again. In the course of the night REM stages increase in frequency and length, and it is from the last of these that the person awakes ready for the day's activity.

The daily temperature change in the body is an indicator of the sleep behaviour. When the body temperature drops, the sleepiness increases; when the temperature rises, the sleep becomes less deep, until waking occurs. This rhythm fits the circadian pattern, but even when „free-wheeling", it persists in a cycle of more or less 24 hours. Thus, it is precisely this rhythm that is responsible for the shift-workers' nocturnal low point in their activity, with consequent attention deficit and a certain sensitivity to the cold. Since the temperature rhythm is very persistent, chronobiologists are now recommending changes of shiftwork times every three days. During that time the temperature rhythm continues in a regular way and the time adjustment for phases of waking and sleeping has not yet come full circle. This means that workers should always be allocated first to thr early shift, then to the late, and finally to the night shift.

When we fly across time-zones, the body temperature phases are very slow to adapt. Generally it takes at least a fortnight for them to adjust to the new conditions. This is the reason for the deep-reaching problems of jetlag.

2. Sleeping-Waking Rhythm

This rhythm, which determines for every higher living being when activity and eating, or rest and recovery, are indicated, is particularly obvious. This is why it has always been suspected that its frequency was dictated exogenously by light. This was decisively refuted by the bunker experiments at Andechs and other investigations.

In principle, this circadian rhythm is determined endogenously, with the SCN having a particular influence; it is only on account of the exogenous metronome of light/daylight that an adaptation occurs to the actual 24-hour daily cycle of the Earth. The sleeping-waking rhythm only develops into the form with which we are familiar in the course of our life. Initially, the new-born child has a 50-minute cycle of two sleep phases (REM and NREM), which is embedded in a 4-hourly rhythm of hunger for food. The result of this is that food is demanded every four hours near or on the hour. The „adjustment" of the REM and NREM phases determines the waking and going back to sleep. At the beginning of the REM phase, waking is possible, and at the beginning of the NREM phase the „gateway" to sleep is open. This explains why, for instance, when babies are being fed, they fall asleep after 10-15 minutes, and then, 25 minutes later, they wake up and carry on drinking. While attending to the needs of such an infant, if the time for passing through the „gateway to sleep" has passed, then in spite of the most strenuous efforts it will take another 50 minutes before such an „over-wrought" infant can be put down for a sleep. The REM phase must be „stuck out", for at the onset of the NREM phase a healthy child will go off to sleep of its own accord. If people are aware of this problem, it becomes easier to adjust to it and, on the other hand, to pay close attention to infants' waking and sleeping phases. This is why rituals are of such importance in finding the „gateway" to sleep at the right moment and in the right mood.

During the first weeks of life (by about the tenth week), the four-hour period of demand for food is reduced by one phase at night, thus making an 8-hour continuous sleep possible, with its REM-NREM rhythm. During the first year of life, the sleeping-waking behaviour becomes established to the extent that, during the day, only one period of sleep occurs.

In adult life, the sleeping-waking rhythm is fully adapted to the times of day.

Both the individual's need for sleep and his times for waking and going to sleep vary from person to person and are endogenously controlled. Overall however, phases of rest and action are synchronised via the external „metronomes" of daylight and social milieu. Natural times of day and seasons are being wiped out by increasingly bright artificial light in the workplace and in people's private rooms. Night is being turned into day. In this way the signals of darkness, summoning us to sleep, are being elbowed out and the excretion of melatonin is reduced. However, melatonin is given off rhythmically in the body by the pineal gland as a nocturnal signal, with creatures reacting to it in differing ways. For diurnal beings it is a signal to go to sleep, and for nocturnal ones it is their „alarm clock". In modern shift-work, this knowledge is put to good use, by getting night-shift workers to work under particularly bright lights, so that they do not hit the natural nocturnal dip in performance - controlled by the body temperature - until the morning, when the night-shift has finished. On the way home in summer, of course, they should put on sunglasses and get to bed as soon as possible.

In this connection, it has been observed that the excretion of œstrogen increases in bright conditions. Appropriate investigations have not yet been concluded, but may establish a connection between night-shift work and breast cancer. An increased incidence of breast cancer has been found particularly in women who work at night. Besides this, a general tendency to overweight and infertility has been found in shift workers. Therefore, chronobiologists would be best pleased if shift work were abolished entirely, having recognised that it runs completely counter to natural processes.

Should desynchronisation occur between the rhythms of body temperature and sleeping-waking, then disturbed sleep is pre-programmed. One example is jetlag following flying across time zones, but there is also the „mini-jetlag" that occurs following the changing of the clocks from winter time to summer time. After 3-7 days, the sleeping-waking rhythm adapts to the daylight conditions, whereas the body temperature requires at least a fortnight or more to conform to the new rhythm. Thus, the two cycles drift apart, with the drop in body temperature constituting one impulse, and melatonin the other. Not until both phases are resonating harmoniously again do humans regain their full productive capacity. In jetlag, the synchronisation can be eased by doses of melatonin.

The changeover from winter time to summer time is particularly problematic, because the external time-setters remain the same. From England, we have reports that there are considerably more road traffic accidents during the first two days after the clocks change. As a consequence, 12% more people go to see a doctor, complaining of disturbed sleep and seeking appropriate medication.

People suffering from manic depression (bipolar disorder) constantly have disturbed sleep on account of this kind of internal desynchronisation of the two rhythms already referred to. On the basis of the bunker experiments at Andechs, such behaviour can be easily explained. Since the temperature cycle stubbornly persists in its 24-hour pattern and the sleeping-waking rhythm is free-wheeling and getting longer and longer, the lowest temperature points no longer fit the rest phase in the other cycle. The subjects in the Andechs experiments wanted to be active at a time when, because of the temperature, their bodies were polarised at rest and recovery. This made them listless, because their ability to achieve was weakened. At other times, when the cycles had arrived at a point of intersection, they were in good spirits and eager to be doing things. Thus, they were always fluctuating on a daily basis between „heavenly rejoicing and deathly depression", just like the patient with bipolar disorder. This kind of desynchronisation is referred to as cyclothymic. People who are constantly depressive suffer likewise from this kind of desynchronisation, where it is not known whether the illness is caused by a fault in the „internal clocks", or whether the illness is making the „internal clocks" sick. Moreover, depression is probably the most investigated common illness which is connected with dysfunctional „internal clocks".

It is well-known that one's mood follows the endogenous rhythms: even healthy people feel at their worst in the morning, but their spirits rise in the course of the day.

And many people feel worse in the winter than in the summer. To compensate, they like to eat during the winter, to sleep and be less active. The result: in winter they get fat. One out of ten people in Central and North Europe gets the „winter blues“. One in 50 reacts with particular sensitivity to the darkness of winter and sinks into winter depression, the so-called SAD (seasonal affective disorder). And yet, here too, it is not known where this comes from: in many people suffering from SAD the regulation of hormones and body temperature is slightly slowed down. Often too, these functions simply have a low profile, which possibly comes from the fact that they are out of tune with each other and therefore inhibit each other. It is possible that the melatonin which is created during the long nights does not get sufficiently broken down in the daytime. This again results in a slowing-down of the hormonal rhythm and a deficiency of the consequent hormone, serotonin. However, what is indisputable is that it is primarily the lack of daylight, since most SAD patients do not go into the daylight. This is why they get so much benefit from light therapy.

3. Sodium Chloride Circulation

Along with our food we ingest Sodium chloride, among other things, and this is absorbed via the mucosa of the digestive tract. For a good function of the stomach, it is essential that the parietal cells synthesise the pre-stages of hydrochloric acid from sodium chloride, water and carbonic acid, which is secreted in the gastric lumen in order to denature proteins. Furthermore, the parietal cells simultaneously discharge sodium bicarbonate into the bloodstream, as a by-product of hydrochloric acid synthesis. This acts as a physiological alkaline buffer and suffuses the connective tissue, inter alia, enabling the release of inorganic acid deposits in particular. As well as this, large quantities of this bicarbonate reach the liver, the pancreas and the Lieberkühn's glands in the gut. There they are blended with the secretions which alkalinise the acidic chyme from the stomach in the small intestine, so that the digestive enzymes can function properly. It is around 10.00 hrs in the evening that the organ produces the highest level of gastric acid. At that time, the alkaline level in the body begins to recede, and this continues until early in the morning. Not until then does the stomach get going, in the expectation that a meal will arrive, producing more hydrochloric acid and sodium bicarbonate, inter alia.

All around the globe, an endogenous rhythm has developed in human beings, making them hungry every four hours and causing them to take food. It is only at night, during sleep, that people are programmed to rest.

The 4-hourly rhythm of desire for food is present in all humans globally - with possible variations owing to national peculiarities - and accounts for the three or four meals a day that are consumed. In 2001, researchers (Cummings) discovered a steep increase in the ghrelin level (growth hormone release inducing), one to two hours before a mealtime, up to double the normal level. Thereafter, it drops again. New peaks occur over the course of the day every 4-5 hours, but these are absent during the night. It appears that the SCN is responsible for embedding them into the daily cycle. But they are also influenced by previous meals, insulin, glucagon and leptin. Insulin, for instance, rises in leaps and bounds after a meal and probably triggers the drop of ghrelin. As well as the peaks, the concentration of ghrelin rises quite gradually over the course of the day. This indicates that everything builds up towards the evening, when Hydrochloric acid production peaks in the stomach. So as to synchronise these processes, obviously a time pattern is dictated by the SCN, and this is supported by regular mealtimes. Diseases such as diabetes and obesity may well have their origins in a chronobiological muddle.

The high surge of gastric acid in the evening may be regarded as a protective function of the body, in order to support the liver in its activity. In this context, the stomach acts as a temporary proton store in patients with latent hyperacidity. People afflicted with this complain of heartburn and reflux. If the excessive amount of gastric acid is not neutralised by alkaline food, ulcerative changes may easily take place in the stomach and the duodenum which adjoins it. The symptoms are also present during the day; as they are very painful, they are treated by Orthodox medicine, for instance, with proton pump inhibitors. These medicines used to be prescribed throughout the day. As a result of chronobiological discoveries there has been a shift towards prescribing these medicines in the evening.

However, in doing this, it has turned out that both the circadian sodium chloride circulation and the evening hydrochloric acid production are very intransigent. After a certain time, the medicines that are used cease to be effective, because the body's need to discharge alkaline substances into the blood is so great that the stomach stubbornly insists on achieving its „acid high" in the evening.

The only sensible remedy is to consume vegetable foodstuffs rich in alkalis throughout the whole day. It is also important, particularly at night, to prescribe alkaline salt - a medicine-spoonful of ALKALA N in very warm water. This will cause a surge of alkalis, which helps the liver to carry out its heaviest work during the night. This also makes it easier for it to switch from its assimilatory phase to its secretory one at about 2.00 in the morning.

4. Liver Rhythm

In 1928, Forsgren was the first to undertake a scientific study of rhythmical processes in internal organs. He discovered - particularly with regard to the liver - a cyclical behaviour pattern, which in turn is significant for the regulation of the acid-alkaline balance, for renal activity and for gastric activity. The liver cycle runs in two phases, which can be differentiated according to the time of day: from 2.00 at night till about 14.00 is described as the secretory phase, followed by the assimilatory phase from 14.00 until 2.00 hrs.

During the secretory phase, there is increased detoxification of the connective tissues (Pischinger space) and the blood, and accumulations of bile salts, and disassimilation products such as urea and urobilinogen are moved from the periphery of the hepatic lobe towards the central vein. Glycogen is broken down and placed at the body's disposal in the form of glucose.

The assimilatory phase of the liver, which begins around 14.00 hrs is characterised by the conversion and synthesis of essential substances, in particular of the stored form of sugar, glycogen, and of proteins. From the central vein of the lobe these are deposited towards the periphery, with the bile salts being displaced from the cells of the lobe. The liver is dependent on alkaline buffering substances to carry out its tasks. Deposited salts can only be retrieved from the Pischinger space if the alkaline level is high, and are transported to the liver in the blood, in the form of neutral salts. These alkalis are available on the one hand via the diet, and on the other hand they are generated from the stomach's sodium chloride circulation.

Cholesterol is formed in the liver, especially at night, though also in the daytime, depending on mealtimes. This is why cholesterol-reducing drugs are particularly effective at night; statins should therefore be given - if at all - in the evening, so as to catch the peak production times and levels. Additionally, at that time the side-effects, e.g. damage to the muscle cells, are at their least. This can, of course, be due to the reduced activity of heart muscle and other muscles.

5. Heart and Circulatory Rhythm

In the course of a day, the physiological sequences in our blood supply are likewise subject to changes in rhythm. One thing that is particularly striking is the morning rise in blood pressure and in the heart and pulse rates. As well as this, in the mornings we find an elevated thrombocyte count and a tendency for the blood to coagulate while, at the same time, the arteriosclerotic plaques tend to rupture. This means that, in the morning, a human being is particularly at risk of coronary infarction, angina pectoris or stroke. The reason for this constellation of risk factors results from a gradual increase in the concentration of noradrenalin and adrenalin in the blood in the early hours of the morning. This leads to both the alpha receptors in the peripheral vessels and the beta receptors of the coronary vessels being particularly stimulated, resulting in a rise in blood pressure.

Getting up brings about an additional orthostatic stimulus, which is answered by increased exertion of the heart and a further rise in blood pressure. As a result of the nocturnal fluid losses the blood thickens, leading to a raised coagulatory tendency whilst, at the same time, the concentration of plasminogen is reduced. The rise in blood pressure and the risk factors just mentioned account for the sensations experienced early in the morning and in the forenoon.

Then there is another problematic peak in the afternoon, which is not so easy to explain. It is connected

to the siesta, which is controlled by the waking-sleeping rhythm.

Another phenomenon concerns the transmission of stimuli to the heart. It has been known for quite a long time that cardiac impulses are subject to a pronounced circadian rhythm. The morning mortality peak, which manifests in the shape of sudden heart attack, could be avoided by the timely administration of beta-adrenoreceptor blockers. Since the cause of sudden death from heart attack lies in myocardial ischæmia or infarction, there is a suspicion that sudden death from malignant cardiac dysrhythmias is only preventable by beta-blockers because ischæmia and infarction are preventable.

In patients with pacemakers, it was found that most ventricular tachycardias occurred between 6.00 and 12.00 noon, and were not susceptible to defibrillators. In a quarter of patients, there was even an acceleration of the heart rate during this time. From this, it can be clearly seen once more that the electro-physiological impulse transmission to the heart is subject to a steady circadian rhythm, which energetically withstands even a strong external stimulus.

Regarding anti-coagulants, it has been found that heparin has the best effect if it is injected subcutaneously in the evening. With acetylsalicylic acid the best action was attained if it was given in low doses in the morning over a long period of time.

Physiologically, blood pressure drops at night in healthy people - this is known as „dipping“. In patients with circulatory disorders - especially high blood pressure - there are two variants: either the blood pressure drops at night, these are the „dippers“; or the blood pressure is maintained at the same level as in the daytime; these are the „non-dippers“. With this in mind, blood-pressure lowering drugs should be given at different times as appropriate.

How problematic the dosage can be if this is not borne in mind was shown in the case of the ACE inhibitors. In „dippers“ it was observed that a dose in the morning led to the desired lowering of the blood pressure, with the circadian blood pressure rhythm remaining intact. If the dose was given in the evening, however, „super-dipping“ occurred: the nocturnal drop in pressure was particularly steep and the rise in the morning was slowed down. Of course, these „super-dippers“ are especially at risk, owing to the possibility of lacunar ischæmia. Non-dippers should take ACE inhibitors and Ca canal blockers in the evening, so that at first, a physiological lowering of the blood pressure takes place at night. In due course that may result in normalisation of the whole blood pressure rhythm. There are also investigations into diuretics in this respect, evaluation of which is not yet complete. Increasingly, there are indications that, with their help, a nocturnal lowering of blood pressure can be achieved in „non-dippers“.

To sum up, it may be stated that the heart and circulatory system shows evidence of a pronounced circadian rhythm. This concerns both the heart and vessels, and the individual cells of the system, right down to the sub-cellular level of signal transmission, enymatic activities, transcription and formation of m-RNA. The key to good health is in the fine tuning, for the rhythms may change when one is ill, may become displaced or may even invert. The early hours of the morning are the time of greatest cardiovascular risk.

Thus, experience has shown that MUCOKEHL should be given early in the morning, so as to improve the fluidity of the blood. If it is prescribed along with SANUVIS, the action can be optimised. From what I have said it should be clear how important it is to drink a lot of warm water in the mornings on an empty stomach, to provide the body with alkaline fluid.

In this connection, a brief mention should be made of the metabolic syndrome. Important metabolic processes can get totally out of hand. A dangerous mixture of risk factors and genuine disease can arise: blood pressure and sugar level are too high, those affected are overweight and acquire Type II diabetes at an early age. They have a tendency to heart disease and pathological snoring with apnœa. Treating the individual symptoms is generally not enough. Because of this, researchers are trying feverishly to find out what causes it. In the USA 47 million people are suffering from metabolic syndrome. It might be that a disorder of the temporal metabolic control is present in the diencephalon (interbrain), with a whole gamut of internal rhythms being involved, that have got out of

time. The body has problems in keeping phases of rest and energy storage apart from times of activity and food consumption. Thus, in diabetics and heart patients depressed melatonin levels have been measured. Appropriate experiments have shown that lowering of the blood pressure can be achieved by means of 2.5 mg-doses of melatonin one hour before going to sleep, and also above all a „dipping“ which is vitally necessary. As well as this, researchers have come to the conclusion that insulin functions - directly or indirectly - as a „metronome“ for the heart. This could explain why heart failure is the most common cause of death in diabetics.

6. Rhythm of the Lungs

Pulmonary function is subject to a circadian rhythm, which is closely linked to the sleeping-waking rhythm as regards the acid-alkaline balance and the supply of oxygen to the body. In this connection, we must take an especially close look at bronchial asthma. At the root of this disease-picture, as well as the general circadian pulmonary rhythm, we find various sensitivities of the mucosa to allergens and substances acting as broncho-constrictors in the course of the day. Clearly, it is a matter of very different circadian rhythms, which control hormonal, biochemical and cellular functions, resulting in marked bronchoconstriction right in the middle of the night. These are adrenergic and cholinergic stimuli, the NANC system (non-adrenergic-non-cholinergic mechanisms) and various peptides. The sensitivity of the lungs to histamine, acetylcholine and allergens such as house dust in particular is extremely high during the nocturnal rest period and is responsible for the nocturnal maximum of asthmatic attacks.

Both the kinetics and the effectiveness of anti-asthmatics such as theophyllin, â2-sympathicomimetics, anticholinergics and glucocorticoids are subject to fluctuations depending on the time of day. Implications for treatment: preferably give the medicine only once in the evening. This reduces the side-effects and economises on medicine. It was the German Asthma Liga who first recommended the single evening dose, in 1997. The action is also particularly good because the blood-supply to the gastro-intestinal tract and lungs - formed from the entoderm - is very pronounced at night. As well as this, it has been found, so far as theophyllin is concerned, that when it is given in the morning, a high concentration rapidly occurs in the plasma, whereas, when it is given in the evening, the concentration increases slowly. This also brings a slowing down of renal excretion. So, if we give theophyllin at 18.00 hrs, after a slow rise the maximum levels are reached between 2.00 and 6.00 hrs in the morning, which is precisely when they are needed. Taking it at 20.00 hrs prevents a peak and yields an even action throughout the night.

The same is true of retardants, e.g. â2-sympathicomimetics, (Bambuterol). Anticholinergics have a more powerful action by day than by night, because the body is in a sympathicotonic phase. Because of this, one must give a somewhat higher dose in the evening, so as to counteract the parasympathetic phase and protect the patient from attack. Great progress was achieved by the inhalant use of cortisol in asthma. When it is inhaled, the ciclesonide ester in the lungs is subject to an ester splitting. This converts it into active metabolites and the affinity for the corticoid receptor is enhanced by a factor of 100 (!) As well as that, it was possible to minimise the systemic action, so that the body's own production remains more or less uninfluenced.

From the point of view of Natural Medicine, preventive treatment avoids everything, which results in a particular accumulation of histamin in the body. This involves avoiding „ripened“ foods (cheese, smoked foods, alcoholically fermented drinks, sauerkraut), fish and so-called histamine liberators (strawberries, aubergines, paprika, tomatoes, etc.). The general intestinal situation regarding the flora and the immune system will be improved by an intestinal cleansing, following Dr. Werthmann's 4-stage plan, using isopathic remedies. This also promotes the formation of diamino oxidase (DAO) in the gut and mono-amino oxidase (MAO) in the liver. As already discussed regarding the liver, care should be taken to keep to an alkaline diet, and ALKALA N should be taken every evening, orally, as a foot-bath or whole-body bath, or as a full-body massage. After external use, the body must be rinsed with clear water. Supplying the body with alkaline substances is also necessary so that biogenous amines and particularly histamin remain bonded in Schiff alkalis.

Furthermore, the following should be employed: SANUVIS for deacidification (mixed potencies of dextrorotatory lactic acid), and CITROKEHL (mixed potencies of citric acid) to improve the cellular metabolism. Among isopathic remedies, NIGERSAN is the leading remedy for treatment of disordered pulmonary function.

7. Further Endogenous Rhythms

- Most metabolic functions follow a similar pattern to that of sleeping and waking; thus heart rate, respiration, blood pressure and renal function increase rapidly in the morning and rapidly reach their highest level for the day. Memory performance is subject to fluctuations according to the time of day, with short-term memory working best in the morning and long-term memory storing information better in the afternoon. Sensitivity to pain is lowest in the afternoon and highest at night. Just think of that dreadful toothache in the small hours! This is why, when going to the dentist, we need more anæsthetic in the morning than in the afternoon. On the one hand this is due to the higher sensitivity to pain in the morning and, on the other hand, to the more rapid breakdown of the medicine, and it does not matter whether a vasoconstrictor has been added or not. Hair and skin grow most rapidly at night; immune cells produce most defensive substances in the afternoon.

- The kidneys excrete most water in the mornings. It is unimportant for the discharge of the quantity of urine how the director of the investigation sets the length of the day and thus the point at which the day begins. For instance, without their knowledge, subjects in a trial in Spitzbergen at the time of the summer solstice had their wrist watches altered so that they had a day lasting 27 hours. Faithfully, according to their „time-clock" they still voided most urine in the mornings. However, independently of this, the salt content of the urine stubbornly followed the 24-hour rhythm. From this, we see that differing signals from the „internal clock" apply to water regulation in the body and the concentration of salts in the urine. As well as this, the pH level of the urine is important for the elimination of acid and alkaline products of the breakdown of metabolic and medicinal substances. The acidic salicylates, for instance, can barely be excreted at all in the mornings, because in the morning the physiological pH level of urine tends to be acidic. This is particularly the case, when the kidneys are required to excrete as many protons as possible in a latently over-acidic body. This reduced elimination is probably responsible for the fact that infarcts in the morning can be avoided by giving acetylsalicylic acid.

- Many hormones are excreted rhythmically. Precisely at the beginning of the night, when the whole body is programmed to rest, fluctuations in the hormonal balance can be fairly critical for the sick. Growth hormone is predominantly produced during deep sleep, particularly in the first 3-4 hours of sleep. That explains why children grow particularly fast at that time. Other hormones too follow a 24-hour rhythm with their daily maximum. Cortisol and testosterone, for instance, reach a peak in the morning, whilst melatonin is excreted in larger quantities at night. If we wish to carry out hormone substitution, we must match this to the cyclical changes of the body's own excretion. Therefore, cortisol should be given in the morning, since a systemic dose in the evening could rapidly result in the body discontinuing its own production. Particular attention must be paid to this problem when the dosage is long-term, as e.g. in bronchial asthma.

Conclusion

Studies have shown that the effects and side-effects of pharmaceuticals can vary considerably at different times of day, and that therefore the time at which a dose of a medicine or the galenic preparation is given is of particular importance, if the active principle is to be released at the correct time. Therefore, in future, more attention will need to be paid to ensuring that the right quantity of the right substance reaches the right target organ at the right time. If these criteria are observed, pharmaceuticals can be reduced to a minimum and, with them, the side-effects and the enormous cost of symptomatic treatments. Natural therapies aim to work with the body, so that its natural healing powers are activated and the rhythm restored.

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