CHRONOBIOLOGY: THE GROWTH AND DEVELOPMENT OF A SCIENCE

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by

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So do flux and reflux
The rhythm of change
Alternate and persist in everything under the sky.

Thomas Hardy

One characteristic that is common to all living creatures is the ability to be dynamic. Because movement cannot proceed forever in the same direction, sooner or later it must complete a circle, or stop and return in the opposite direction. In either case, a continuously repeated rhythm, cycle or periodicity ensues, often resulting in a balance of centrifugal or centripetal forces. This applies equally to biological as well as mechanical systems. Since biological systems are based essentially upon physiochemical processes, such as biochemical reaction systems or electrical nerve impulses, the situation could not be otherwise.

All living organisms are set into the solid framework of the physical world, the structure of which pulses with an abundance of "external rhythms": diurnal, tidal, seasonal, and solar. The capacity to follow them, to oscillate, would certainly enhance the survival potential of a species. The earliest humans probably utilized external rhythms when scheduling hunting, planting, or fishing activity.

The construction of our bodies, (randomly, genetically, and selectively determined) should therefore include components which are capable of rhythmic function. These rhythms do not necessarily have to be
formal for this purpose, but they must exist. Neither need they be absolutely conditioned by the environment. Once being present, for whatever reason, they might sometimes be expected to oscillate even if the external world is removed. \(^3\)

Unidirectional movement is against the principal of energy conservation. Such a system is sustained by the continuous conversion of one energy form into another with a concomitant heat production, a steady increase in entropy. The process can only proceed as long as fuel is constantly thrown in at one end and waste products constantly removed at the other end. It stops when it runs out of fuel. \(^4\) Humans would be constantly eating and excreting with little time for any other creative or constructive activity.

After observing the many systems involved in the workings of the body, one must consider the existence of some synchronizing, adaptive mechanism for maintaining order. In the study of biorhythms, this order is maintained by a biological clock. Biorhythms indicate a timed cycle of a biological clock.

The elementary observation of Jean de Mairan in 1729 marked the beginning of rhythm research. This French astronomer recorded the observation of periodic leaf movement in total darkness. \(^5\)

de Mairan's experiments were repeated several times in the eighteenth century. Rhythms of the body temperature in man were discovered by Jürgesen, fifteen years after the introduction of thermometry by Wunderlick. Forsgren, in 1927 discovered the periodic alternating storage of glycogen and bile, thereby opening up a wide field of the 24-hour periodic phenomena to investigation. Thus a new branch of science unfolded, biorhythm research, which slowly acquired manifold interconnections,
including medicine.\textsuperscript{6}

Not until the 1930's was it fully realized that diurnal rhythms represent surprisingly basic periodicities, which are only temporarily, if at all, disturbed by abnormal light: dark cycles, and most surprisingly that such rhythms are not lost even after organisms have been kept in constant darkness for many generations.\textsuperscript{7}

In 1937 seven scientists founded an international society for the study of biorhythms.\textsuperscript{8} A symposium on biological clocks was held in 1960 at Cold Spring Harbor that extensively contributed to the crystallization of chronobiology as a science. There have been numerous lectures and symposia held since 1937, but the science is still in its infancy.\textsuperscript{9} As one scientist aptly stated, "When chemistry was at the state of development that biorhythm research is now, it was called alchemy."

Previous to the founding of the chronobiological society, many people were conducting biorhythm research simultaneously with some degree of isolation. Each scientist was defining his own work in his own terms, causing confusion, fragmentation, and some duplication. Most terms at this time have one accepted meaning.

Rhythms are produced by oscillations. Parameters used to describe oscillations are: frequency, the number of cycles per unit of time; period, the amount of time needed by one cycle; amplitude, the extent of an oscillation; and phase, the fraction of a whole cycle.\textsuperscript{10}

These parameters can be appropriately applied to the reading on a heart monitor (oscilloscope), found in coronary care. The frequency of the cycle is the pulse rate, most often measured in a 60-second period. The period is the amount of time needed for the origination of the
impulse through the repolarization of the heart. The amplitude is the depression or exaggeration of certain waves, often used to determine myocardial damage in the heart's electrical system. One phase of the heart's oscillation would be the Q.R.S. complex, the contraction of the ventricles without considering any other part of the period.

Oscillators are divided into two main types, linear and non-linear. Linear oscillations exhibit resonance, an increase in amplitude when driven at their preferred frequency. A linear oscillator is a sine wave, or pure frequency, the oscillation of simple harmonic motion. A linear oscillation is produced when two energy stores transfer energy, alternating from one to the other at rates which depend linearly on the amount stored in each at every instant in time.

Non-linear oscillations have a saw-tooth wave form. The most common non-linear form is a relaxed oscillation. A steadily rising or falling variable crosses a threshold and then resets to a previous value. Instead of exhibiting resonance, non-linear oscillators entrain or synchronize with a periodic driving stimulus. Synchronization was observed by Huygens when two clocks ran at different rates until hung together on the same thin wooden board. Most biological rhythms generators are non-linear oscillators.

The capacity for oscillations may then be passive, the rhythm being entirely driven by some external driving agent, a synchronizer or "Zeitgeber." This oscillation produces an exogenous rhythm, one that is affected by external forces.

The capacity for oscillations may also be active, representing spontaneously oscillating systems with natural periods. Those with frequencies approximately equal to that of the external rhythm may have
been favored by evolitional selection, or a harmonic of the natural frequency may just happen to come close to the external one. In both cases, a complete synchronization is possible. If no synchronization takes place, the natural frequency takes over.\textsuperscript{20}

The observations of the limiting condition in biology (unidirectional movement cannot exist), gave rise to the concept of homeostasis, a precursor of modern cybernetics. When a function approaches a limit, the body counterregulates. Actually it tries to keep the level of activity constant, working like a servomechanism. Such systems are built upon the principles of feedback. They continuously search an equilibrium. If displaced, they return to it. If such disturbances occur at random, the function of the system in time may be described as an irregular chronobiological variation. If the disturbances describe a pattern, a passive regular chronobiological variation ensues.\textsuperscript{21}

The action of biological systems can be described in cybernetic terms where the interaction between parts is analyzed as a flow of information, and self-regulation is explained in terms of feedback.\textsuperscript{22}

Feedback, unfortunately, is as easy to understand in principle as it is difficult to handle mathematically (involving differential equations and non-linear functions).

If a process (information) runs from link to link in a mechanism, feedback exists if a later link acts back upon an earlier one, stimulating or depressing it, establishing a closed loop of action.\textsuperscript{23}

An endogenous rhythm persists if the rhythm originates internally. Endogenous rhythms persist under controlled conditions. Exogenous rhythms exist when oscillations can be controlled by manipulating
external factors. A circadian rhythm refers to the time period; this rhythm has a cycle of approximately 24 hours. A cycle can be both endogenous and circadian or be endogenous with a periodicity of longer than twenty-four hours.

There are some problems experienced in biorhythm research that are specific to this science. One should have these in mind before critically examining rhythm data. The time oriented nature of the research requires frequent sampling of the data. If the procedure for data collection involves disturbing the organism, isolation, as a constant condition, is broken and a possible stress factor or synchronizer is introduced.

Because of the ethics of research, it is difficult to use humans for research. One would not relish the idea of living under constant conditions, in isolation, for a long period of time. Stimulation deprivation would probably ensue with concomitant hallucinations. This fact makes sleep-wakefulness, human performance, and human activity studies nearly impossible.

Accuracy in the validity with which estimation can be made of the relationship between the stimulus and the produced rhythm is another problem. Since most biorhythms are non-linear and can be entrained, one must inspect very carefully for a Zeitgeber.

Unfortunately, authors have come to the wrong conclusions by ignoring the synchronizing effects of weak control lights and other factors. **Provisions for constant temperature and exact control of light and darkness are particularly important, since we know that in some cases fluctuation of less than one degree centigrade can significantly interfere with experiments.**

Light is a much more effective synchronizer
than temperature.

Only recently have laboratory conditions been available permitting a sufficiently accurate measurement of these physiological circadian oscillations or a satisfactory quantitative study of the influence of internal and external factors.  

Part of the excuse for ignorance of biorhythm changes in experimental biology and medicine, especially morphological research, seems to be based on three reasons. The first is in the conduct of morphological research itself; before having analyzed systematically the rhythmic variations in cells, tissues, and organs, many investigators devoted all their energies to the detection of the governing system by mathematical analysis of the oscillations.

The relative youth of histochemistry is certainly responsible, a discipline still in its beginning and mainly concerned, therefore, with the development of methods.

Finally, the most preponderant are probably empirical observations which do not concern themselves seriously with the influence of biological rhythms on histochemical results. An example of this is that very often there is no high or low glycogen amount found when a maximal or minimal content is to be expected at a particular time of day.

In morphological assays the detection of rhythms is complicated by the fact that there was not always a concordance between the biochemical values gained and the strength of histochemical reactions.

Technical factors play an important role in histochemical rhythmic studies, but when viewed from the angle of the rhythm itself, in spite of absolute standardization of the techniques, different results are gained regardless of the actual amount of the investigated substance at
a given time. The reason for these discrepancies is based on the fact that histochemistry utilizes the process of fixation in the majority of its methods. The fixatives are not capable of acting evenly in every physiological state, as the proteins which act in the fixation process either as a co-precipitant or preserving membrane, change rhythmically in the amount (Horvath, 1963) and probably in composition.32

In the cases where unfixed sections are used, the varying extractability during incubation with the histochemical reagents plays a definite role.33 These problems with morphological research plague those scientists interested in determining the level of certain chemicals within the tissue.

In H. von Mayersbach's first circadian investigation in 1960 strong differences of the nuclei were seen microscopically, both in size and the intensity of the Feulgen-reaction for histochemical demonstration of deoxyribonucleic acid (DNA);34 also a varying amount of histochemically demonstrable RNA in the cytoplasm was found.35

This lead to the investigation of the DNA and RNA content of the liver during circadian cycles which was performed in von Mayersbach's laboratory by Horvath in 1963 and continued by Cling. The analyses showed clearly that both substances vary considerably in amount throughout a twenty-four hour period. In biochemistry the DNA content in organs and tissues is regarded as constant and therefore used as a basic measure for comparative studies of other cell substances and quantity of cells (Glich, 1961).36

Barnum et. al. suggests that circadian DNA variations exist when he found that radio-active phosphorous is incorporated rhythmically.37

Karakoshian and Hastings succeeded in supressing the rhythm of
photosynthetic capacity in *Gonyaulax* with actinomycin D. Actinomycin is a substance which seems to affect cells by inhibiting DNA dependent RNA synthesis. This favors the hypothesis that clock function is dependent upon RNA synthesis. The more general question arises as to whether the inhibitory action is upon the clock mechanism or upon its expression.\(^{38}\)

Mitotic proliferation in the bone marrow of female rats and mice kept under constant standardized conditions with light from 6:00 a.m. to 6:00 p.m. exhibited a significant circadian periodicity with the greatest activity occurring from 6:00 a.m. to 12:00 noon. The reticulocyte levels in peripheral blood were highest at 8:00 a.m.\(^{39}\)

Halberg and Barcia-Sainz have found that cells from breast cancer do seem to show a circadian rhythm in regard to mitosis and proliferation.\(^{40}\)

In 1963 and 1964, Dr. Donald Pizzarello and his workers at the Bowman-Gray Medical School in Winston-Salem, North Carolina, had found that the dose of x-irradiation that made rodents sick during the day would kill them at night.\(^{41}\) Taken together, the results of DNA-RNA studies, mitotic proliferation studies, and x-irradiation research could help to maximize the existing treatment for carcinoma. If the cycle of proliferation of cancer cells could be charted for the human, therapy could be timed for maximum effect with the fewest number of side effects.

Although few biorhythm studies on humans, other than behavioral research, have been conducted, one such study was done on the spontaneous activity of uterine muscle. Variations in the contractile patterns of uterine muscle that occur without apparent external cause are a character of the spontaneous activity of the uterine muscle. Circadian variations in the average intrauterine pressure and in the average frequency of contraction were demonstrated in four non-pregnant Rhesus monkeys. Uterine
activity is lowest between 0400 and 0700 hour and highest between 1400 and 1700 hours. There is a statistically significant correlation between uterine activity and diurnal variation in core temperature.\textsuperscript{42}

This phenomena has been observed during the observation of excised myometrial strips in vitro during studies of non-pregnant humans, and sub-human primates utero in vivo. Numerous stimuli, both external and internal, may account for this activity. However, the occurrence in all phases of the menstrual cycle would suggest that they are not due to the alterations of the endocrine system.\textsuperscript{43}

Since the endocrine system and hormonal influences play such a major part in co-ordination of the body's systems, and in view of the ubiquity of physiological rhythms, it would be expected that hormonal secretion would commonly occur as a rhythmical phenomena.\textsuperscript{44} The most research is found on the adrenal glands and the pancreas. The reason for this might be the ease with which one can measure these hormonal influences. A diurnal rhythm in the excretion of adrenal cortex hormone exists, since older authors found evidence of a 24-hour rhythm in the excretion of 17-ketosteroid, which is characteristic of these hormones. On the basis of the investigations by Halberg and co-workers we may regard the ketosteroid excretion as a function controlled by the endogenous diurnal rhythm. Where the rhythm is located is not answered.\textsuperscript{45}

Halberg investigated thoroughly the influence of periodical activity changes in the adrenal gland. The number of eosinophils circulating in the blood reflects the course of this adrenal cycle. An extirpation or pathological loss of the adrenal gland function abolishes the eosinophil rhythm. An extirpation of the adrenal gland also abolishes the eosinophil rhythm in the liver.\textsuperscript{46} The periodicity in the
relative specific activity of phospholipid phosphorus is obliterated by adrenalectomy, and seems to depend largely upon the periodic secretion of adrenal hormones (Halberg, Halberg, Barnums, Bittner, 1957). It is remarkable that the C.N.S. is not required for the adrenal cycle. This cycle appears also in brainless animals.

Numerous reports on 24-hour physiological periodicities describe variables affected by, or dependent upon adrenal regulation, cortical as well as medullary. Adrenal periodicity, while responsive to changes in the external environment as well as in the internal physiology of the animal, persists in the absence of such changes. This view is not completely in agreement with the unqualified assumption that diurnal changes of adreno-cortical secretion constitutes responses to the stresses of daily life. Nevertheless, the peak of the mitotic rhythm in the adrenal cortical parenchyma and stroma of the mouse precedes the peak of corticosterone in the blood and also the major daily bursts of locomotory activity. This agrees with the suggestion that the adrenal cycle describes processes occurring, at least in part, in preparation for daily activities, rather than solely as intermediate reactions to them.

Circadian variation of corticosteroid concentrations in rat plasma is suppressed if corticosteroids are administered between the second and fourth days of neonatal life, but not if given from the twelfth day on. This indicates a critical period for the effect of corticosteroid administration on the central nervous system pathways regulating such periodicities. Circadian periodicity of corticosterone is not affected by neonatal administration of testosterone or reserpine.

Circadian variations in glucose tolerance tests have been established.
Annual variations in the incidence and severity of diabetics have long been known. The unstable diabetic displays with variations on the scale of hours to days in the amount of insulin required to maintain normoglycemia. In this study the periodicity indicated that social causes played no major role, but suggested a seasonal or weather-mediated effect might exist. The peaks (amplitude) existing when the data was spectrally analyzed appeared to be correlated to the lunar cycle.  

Doctors Walter Runge, Franklin Pass, and Franz Halberg found that the mouse pancreas exhibits a distinct chain of peak phases in the mitotic rhythms of certain cells. That is to say the peak mitoses in beta cells precedes the peak of alpha cells, which reach their peak eight hours ahead of the acinar cells. Thus, there is a circadian rhythm of mitosis that may not cause, but which does parallel, the usual levels of insulin in the blood. In the delicate balance of carbohydrate metabolism, levels of insulin must be timed to match and counterbalance the action of a hormone from the pituitary gland. This means that therapy aimed at approximating the normal phase relations of endocrine rhythms in the body may need to reproduce the correct phase of rising and falling insulin levels in the body instead of merely increasing deficient levels.  

Although the previous cycles of the body are important to function, the most interesting studies have probably been done in the area of behavior. The studies on mental efficiency have been inconclusive, but may have potential. Klietman did a waking day study to measure the mean efficiency for cerebral activity with a correlation of body temperature. The most definite statement Klietman could make was that an
individual's capacity for doing mental or physical work does not remain constant throughout a circadian cycle. Differences in the kind of work performed, differences in an individual's job attitude, and other extraneous variables such as the day of the week complicate this type of study.

Klietman seeks to demonstrate that temperature and performance variations are coincident during the day. In the case of tasks involving motor activity he implies that this parallelism is mediated by the underlying relationship between body temperature and muscular tonus. Where the task is predominately mental in character he suggests two possible interpretations of the co-variations of efficiency and temperatures. Assuming that the effect of body temperature indicates that one is dealing with a chemical phenomenon, then either mental processes represent chemical reactions in themselves or the speed of thinking depends upon the level of metabolic activity of the cells of the cerebral in the body temperature, one indirectly speeds up the thought process. Most of the curves of performance can be brought into line with the known 24-hour body temperature curves, allowing for individual skewing of the curves towards an earlier or later, rather than a mid-afternoon peak.

Klietman's results are partially refuted by Blake's studies, Blake found a measurable post lunch dip in efficiency, whether the work was mental or physical. There was no drop in temperature to correlate with the drop in efficiency.

Changing the phase of biorhythms was studied for human performance by Sollberger. By changing from day to night shift work, one seems to be 180° out of phase. Nervous disorders, such as gastric disorders and
insomnia are not infrequent unless adjustment occurs. Error-proneness varies throughout the 24-hour period, but peaks on the night shift. This may be because of sleep deficiency, poor work methods or a number of effects. The capacity to follow shift regimen varies strongly among individuals; it decreases with increasing age.

Periodicities were found in the pattern of epileptic seizures. Griffiths and Fox made a review of 39,920 seizures in 110 males at the Letchfield Colony in England. Some epileptic patients have a daily seizure at almost the same time every 24-hour period, but each patient may have a seizure at his own special time—which may be at any hour or the day or night. These authors state, however, that many of their patients tended to have seizure activity between 6 a.m. and 7 a.m., or between 10 p.m. and midnight. Langdon-Down and Brain reported similar diurnal variations in 66 institutionalized epileptics.

The original Pel-Ebstein syndrome (1887) was first formulated when a 19 year old male with Hodgkins’ Disease evidenced a 24 day clock. The periodicity manifested itself in periodic enlargement of the spleen and in remarkable changes in body temperature.

Professor Rex Hersey of the University of Pennsylvania conducted a study of the emotional fluctuation in male human beings. His conclusion was that although the emotional cycles of individual men vary with the individual from 16-63 days, the average length for most men is about five weeks. This is the typical length of time it takes for a normal man to move from one period of elation down the scale to a feeling of anxiety, the most destructive emotion according to Hersey, and back up again to the next period of elation. Each day for thirteen weeks the subjects were briefly interviewed four times and given
a "mood rating" for that day. In most cases, Hersey believed that the subjects own opinion of how he felt combined with the interviewer's observation resulted in a fairly objective rating. 63

To simplify and portray the fluctuating moods of his subjects, Professor Hersey constructed a scale of emotions to which he applied numerical values. Happiness and elation received the highest value, plus six; worry was assigned the lowest value, minus six. 64 Hersey and his group devoted an entire year to the observation of a group of normal (Hersey's classification) workers of various occupations, ages, personality types and ethnic backgrounds. Their behavior in countless areas, such as efficiency, productivity, cooperativeness, verbal outbursts, ideas, absenteeism, emotion and reverie was studied along with their blood pressure, weight, feeling of fatigue, and illnesses. 65

The major surprise to Hersey was that although different individuals had different cycle lengths, they were always fairly consistent for that individual. 66 In spite of domestic squabbles, trouble with the boss, great pleasures, promotions, job problems, unforseen good luck, and accidents this cycle did not vary by more than one week from the normal cycle for that person. 67

A 21-day cycle was demonstrated in an isolated patient with catatonic schizophrenia. A sharp transition separated the excitement and slightly depressed mood changes at intervals of 19-21 days. The clock was also revealed in records on his ability to concentrate and total nitrogen excretion. 68

Evidence for a six day behavior clock comes from observation on a number of patients, chiefly manic-depressive. Body weight, urine volume, and sodium excretion clearly revealed the presence of a six day clock. 69
Dr. J. H. Douglas Webster, whose chief contributions to the knowledge of rhythmic fluctuations are in the field of medicine, applied his efforts to exploring the possibility of cycles in creativity. His comprehensive research involved not only the assembling of data from the biographies and collected works of musicians and poets, but also a thorough review of earlier papers on the subject. The most prominent cycle he discovered in creativity averaged 7.6 months. Great artists, writers, musicians, and even scientists, have long felt that their best work was performed in spurts, followed by long gaps of unproductiveness. Unless they were in the mood, they were completely impotent artistically speaking.

Where there were daily records available through diaries and letters it was discovered that Christina Rossetti, Anne Bronte, Johann Wolfgang von Goethe, August Platen, and Franz Schubert had periods of creativity approximately every 7.6 months. Where there were monthly records available the same 7.6 month high in creativity was found in Rupert Brooke, John Keats, Percy Bysshe Shelly, Thomas Gray, Victor Hugo, Wolfgang Amadeus Mozart, Nikolai Rimski-Korsakov, Petre Tchaikovsky, and Jean Sibelius.

Psychological research on human's time sense has disclosed individual differences in the ability to measure time. These differences concern the accuracy, and variability of judgments, and the tendency to overestimate or underestimate. A clear but nominal difference was found between the sexes; women made more accurate judgments in acoustical tests, whereas men were more accurate in visual tests. In some people this clock works so well that they are able to estimate with a high degree of accuracy a period of time of several hours even if all
external time indicators are missing. These people are able to wake up with only the help of their physiological time-measurement just five minutes or less before the alarm goes off. This head clock works with greatest precision under hypnosis.

Pigeons have a knowledge of the course of the sun's arc at the location of their home, a day-to-day correction being made from memory as the elevation of the sun above the horizon changes according to the time of the year. If the bird finds itself in another place, it notes the change of the sun's arc in comparison with its home. A necessary presumption, therefore, in the navigation of birds is the existence of an accurate sense of time which functions for a time independently of the environment.

We now know that organisms can not only indicate the time of day with the help of their physiological clock, but also make use of this clock for actual time measurement. Sunrise does not initiate a "once only" process. Rather plants and animals "recognized" the benefit of measuring time by means of oscillations. The use of oscillations makes it possible to plan ahead for several days.

The study of photoperiodic responses has revealed some other very interesting examples of time measurement. It was first discovered in plants and later in animals that some developmental processes are controlled by the length of day. Dormancy of flowers can be regulated by this factor. In animals, day length can also control the annual cycle of reproduction or the beginning of rest periods. These photoperiodic reactions are actually caused by day length, not quantity of light.

The circadian tides that pervade our physiology have as a natural consequence daily rhythms in resistance or vulnerability to drugs, stress,
allergy, pain, and infection. The timing of an event may literally mean the difference between life and death. These rhythms have ramifications throughout medicine, from the administration of drugs and vaccines, to the toxicity studies of pharmacology.

The practical implications of such variations in daily susceptibility have not been overlooked by such agencies as the U.S. Department of Agriculture, where Dr. William Sullivan and other scientists have conducted time-series studies that may enable farmers to time the spraying of pesticides so as to reduce both pests and the amount of toxins spread on the earth. The domestic fly is most vulnerable to pyrethrum around 4:00 p.m., while other insects have their peak sensitivity to other poisons at different hours on their cycle.

There seems to be a time factor involving one's susceptibility to bacterial infection. For many years, seasonal differences have been noted in the incidence rate for certain communicable diseases. Dr. Ralph Feigin and his co-workers at Washington University, St. Louis, have challenged mice with the same doses of pneumococci at different hours of day and night. The mice survived best if injected at 4:00 a.m. at the peak of their activity cycle.

Dr. Feigin and his associates had previously tracked the circadian rhythm of certain amino acids in human beings, finding lowest levels around 4:00 a.m. and peaks around 8:00 p.m. They then found they could upset the amino acid rhythm with injections of a vaccine for a virus disease known as Venezuelan equine encephalomyelitis. Men immunized at 8:00 a.m. showed less disturbance of amino acid concentrations than did men who received the vaccine at 8:00 p.m.

As part of this thesis, a crude study was performed to test the
hypothesis that as the activity cycle increases in the human and the temperature rises, drugs have a quicker onset of action. The original study utilized rats under standardized conditions which were given varying amounts of amphetamine at timed intervals. The same dose that killed the animals at peak activity, did not kill the rats at a lower activity level. The activity-temperature cycle of man increases from early a.m. and peaks mid-afternoon.

This study was performed on pre-operative patients at Ball Memorial Hospital. Those patients given pre-op's between 7-9 a.m. and 12 noon-2 p.m. were studied. Most pre-operative medication, demerol, atropine, or morphine sulfate, has a 30 minute onset of action. Pulse rates were used as indicators of drug effect. If the onset of action occurred more quickly, the pulse rate would drop more quickly. A baseline pulse was taken at 7 a.m. on both groups and again twenty minutes after the drug was administered to determine the pulse drop.

In the 7-9 a.m. group the mean decrease was 4 pulse points. In the group of pulses taken between 12 noon-2 p.m. the mean decrease was 6 points. So that on the average each pulse in the afternoon group declined at least 2 pulse points lower than in the morning, indicating that there was a time oriented factor affecting the onset of action.

Twenty patients were studied; ten in the a.m. and ten in the p.m. Eleven were female and nine male. Ideally there would have been fifty percent of each sex, but at the time there seemed to be a lowered census of male surgical patients.

The mathematical average of age was 41.4 years. The range was from 18 to 79. The average age the male group was 60; the average age of the female patients was 31.
Several extraneous factors were not controlled, making conditions unstandardized, and placing limitations on the study. The level of anxiety of each patient was impossible to assess. The amount of information the patient had was not uniform. The patients were all in different rooms and units in the hospital meaning that none of them were reacting to the same personnel or floor conditions. Only a few of the medications were exactly the same.

The ideal study for testing this hypothesis would be conducted on an homogenous group of volunteers, who were of an approximately equal age, and weight, of the same sex, and receiving the same dosage of medication. They should be relaxed, free of pain, and have a full knowledge of what was to happen.

As is indicated by the many example of biorhythm data, there are many ways to utilize chronobiology. Because of the science's neonatal state, there is much room for new research. Much of the history of chronobiology is yet to be made.
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Periodicals

