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Reactive modifications of the autonomous time structure of biological functions in man

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Summary. - The spectrum of biological rhythms exhibits characteristic principles of biological time structure which also rule the functional behaviour. With increasing period lengths the rhythms become increasingly complex. In the long-wave section the rhythmic functions find their corresponding cycles in the environment, whereas the shorter waves represent only endogenous autonomous rhythms, which maintain an internal time order by means of frequency- and phase-coordination. Under resting conditions and in a state of complete adaptation only a few spontaneous rhythms dominate in the spectrum. However, under loading conditions as well as in pathological situations further periodicities come up. The spectrum of rhythms can be divided into certain blocks, with the period lenghts predominating in each of these whole number frequency ratios forming a harmonic system. Frequency- and phase-coordination establish a system of co-action which favours the functional economy of the organism. A tripartite organization of the autonomous rhythms involves different functional behaviours with regard to frequency, amplitude, and phase. Slower rhythms act upon the faster rhythms preferably by modulating their frequencies, while changes of the faster rhythms influence the slower ones by enhancing their amplitudes, multiplying their period lengths and shifting their phases. In principle the reactions of living systems are periodically structured. Reactive periodicity brings to appearance an endogenous time structure, which prefers whole number relationships with the spontaneous rhythms. The phase position of reactive periods depends on the stimulus. The amplitudes dampen down with increasing compensation. From the medical point of view so-called circaseptan (about 7 days) reactive periods are of predominant interest. This periodicity can be observed in numerous adaptive and compensating processes. It does not depend on the external week cycle and was already known to the antiquity.

Key words: chronobiology, biological rhythms, temporal order, modes of rhythm response, reactive periodicity, circaseptan periods.

Riassunto *(Modifiche reattive della struttura temporale autonoma delle funzioni biologiche nell'uomo)*. - Lo spettro dei ritmi biologici ci mostra principi peculiari che governano anche il comportamento funzionale. Con l'incremento della lunghezza del periodo i ritmi divengono sempre più complessi. Nelle più lunghe lunghezze d'onda le funzioni ritmiche ritrovano ritmi corrispondenti nell'ambiente, mentre nel dominio delle onde a più breve periodo esse rappresentano soltanto ritmi autonomi endogeni che mantengono un ordine temporale interno tramite la coordinazione della frequenza e della fase. In condizioni di riposo e di completo adattamento solo alcuni ritmi sono dominanti nello spettro. Peraltro, in condizioni di carico o in situazioni patologiche, altre periodicità si mostrano. Lo spettro dei ritmi può essere diviso in blocchi con lunghezze di periodi predominanti a formare un sistema di armoniche. La coordinazione in frequenza ed in fase costituisce un sistema di coazioni che favoriscono l'economia funzionale dell'organismo. Una organizzazione tripartita dei ritmi autonomi coinvolge comportamenti funzionali diversi riguardanti la frequenza, l'ampiezza e la fase. I ritmi più lenti agiscono prevalentemente su quelli più rapidi modulando le loro frequenze; le variazioni indotte nei ritmi più rapidi influenzano a loro volta i ritmi più lenti aumentando la loro ampiezza, moltiplicando la lunghezza del loro periodo e modulando la loro fase. Per principio le reazioni dei sistemi viventi sono periodicamente strutturate. La periodicità reattiva ha l'aspetto della struttura temporale endogena che intrattiene tutte le numerose relazioni con i ritmi spontanei. La posizione della fase dei periodi reattivi dipende dallo stimolo. Le ampiezze si riducono con crescente compensazione. Dal punto di vista medico, i ritmi reattivi circasettani (di circa sette giorni) suscitano il maggior interesse poiché essi si osservano in molti processi di adattamento e di compenso e non dipendono dal ciclo della settimana del calendario essendo già noti nella antichità.

Parole chiave: cronobiologia, modalità di risposta ritmica, ordine temporale, periodicità reattiva, periodi circasettani, ritmi biologici.

The time structure of human biological functions

The entire spectrum of biological rhythms in man exhibits characteristic principles of biological time structures, which also rule the functional behaviour of the rhythms in the different parts of the spectrum.

The rhythms are hierarchically ordered (Fig. 1). With increasing period duration they become likewise increasingly complex. The processes in question

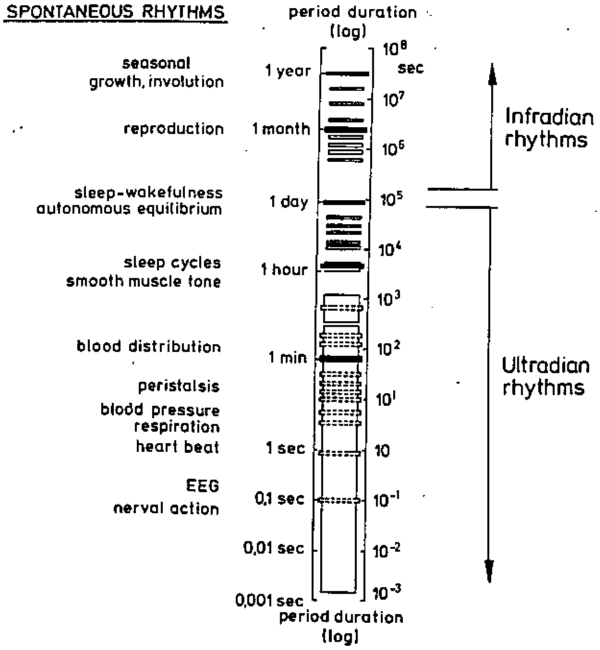

Fig. 1. - Spectrum of main types of spontaneous rhythmical functions in man. Logarithmic scale of period durations [1].

begin with cellular high frequency rhythms going on to organ and systemic rhythms up to the circadian rhythmic variations, which already involve the entire organism, finally to reproductive functions and rhythms of whole populations. More and more single functions are comprised by the rhythms in the long wave section of the spectrum. At the same time, rhythms are increasingly controlled by hormonal mechanisms whereas in the high frequency section nervous control is dominating.

The spectrum can be divided into two parts. In the long wave section, containing the circadian rhythm and the so-called infradian rhythms, the rhythmic functions are synchronized by external zeitgebers or find corresponding cycles in the environment. In the entire ultradian section, however, we find only endogenous autonomous rhythms, maintaining a more or less strong internal time order by means of frequency- and phase-cordination.

A compilation of all period lengths and relative frequencies of rhythmic functions as observed in the different parts of the spectrum is shown in Fig. 2. Under strict resting conditions and in a state of complete adaptation only a few spontaneous rhythms dominate in the spectrum and can easily be detected. However, particularly under loading conditions like strain and stress as well as in pathological situations quite a lot of further periodicities come up.

As demonstrated by the figure, the whole spectrum of rhythms can be divided into certain blocks, within each of them the period lengths (as a rule) exhibit predominantly simple whole number frequency ratios, forming a harmonic system. The most common ratio is 2:1 or 4:1, indicating frequency-multiplication or demultiplication to be an important mechanism of temporal order in the organism. However, ratios of 3:1 and others also occur in the blocks of the spectrum.

The connections between the various blocks seem to be different. In some cases there is no gap between the harmonic intervals, in other cases the transition is more complicated.

During the last decades several authors contributed to a better understanding of the harmonic structure of the rhythm spectrum in man. For instance, Hejl [2] presented a so-called "periodic system" of biological rhythms.

For some parts of the spectrum very clear indications already exist for the strict harmonic structure of the temporal order. Broughton [3] pointed out that the basic rest activity (REM-NONREM-) cycle of about 90 min period length is part of a harmonic row of submultiple periods of the 24 h rhythm.

By long-term observations Golenhofen & Von Loh [4] were able to show, that even small pieces of smooth muscle tissue from the gut of guinea pig exhibit a spontaneous activity of rhythmic contractions with period durations of 1, 2, 3 etc. up to 8 min (Fig. 3).

In the 1 min range, by computer analysis a harmonic spectrum of rhythms of various functions like heart rate, respiratory rate, peripheral blood flow, and reaction time was detected.

Finally, by our own research group [5], it was stated that heart beat, respiration, blood pressure rhythm and 1 min rhythm of peripheral blood flow under resting conditions form a complex harmonically ordered system (Fig. 4).

The mechanisms of this coordination is not yet understood in all cases. However, several findings exist [5-8] that internal phase coupling as a special case of synchronization is mainly involved. However, harmonic ratios between functional capacities and time constants respectively seem to play a role also.

Concerning the functional significance of the harmonic temporal order of biological systems, there is already an overwhelming amount of evidence that frequency- and phase-coordination establishes a system of economical co-action and hence, in general, can favour economy of the organism.

Responsive mechanisms of modulation in biological time structure

Looking again at the general overview of periods (Fig. 2), it is symbolized in the lower part, by the broader ranges of period lengths, that in the high frequency range of the spectrum the strength of the harmonic time order decreases, and this because of an increasing variability of the frequencies. For

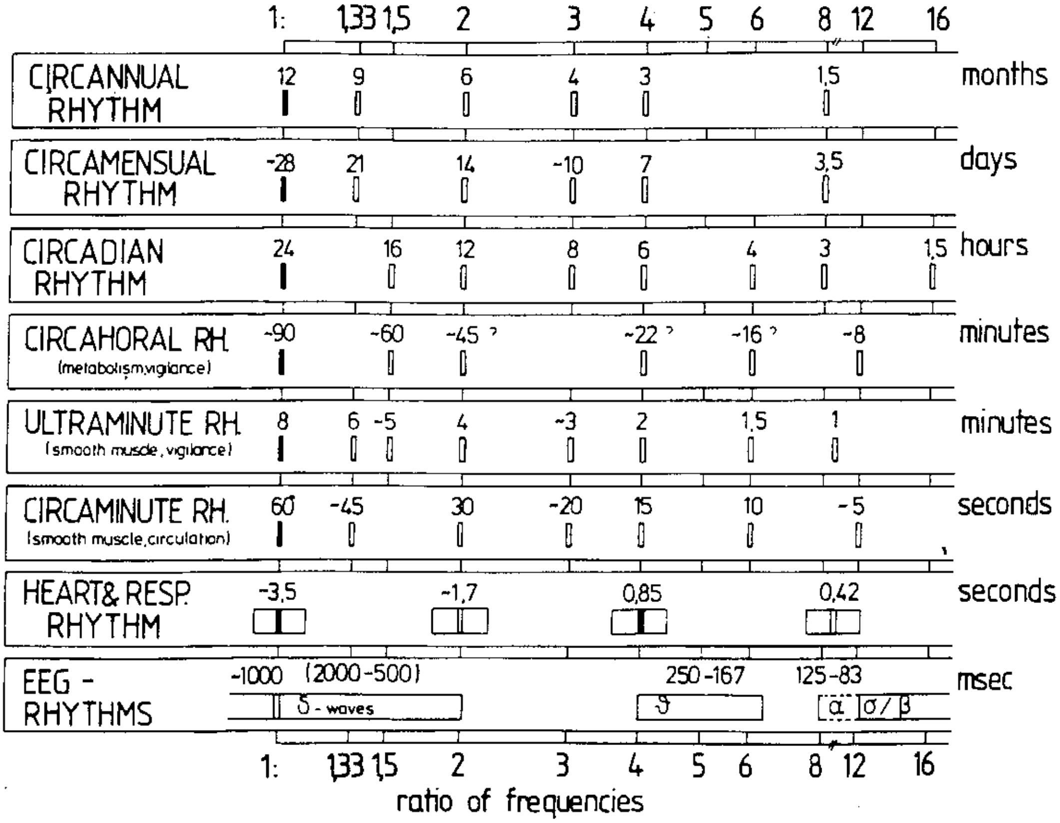

Fig. 2. - Ratios of frequencies within the different "blocks" of spontaneous rhythmical functions as indicated by the preferred period lengths.

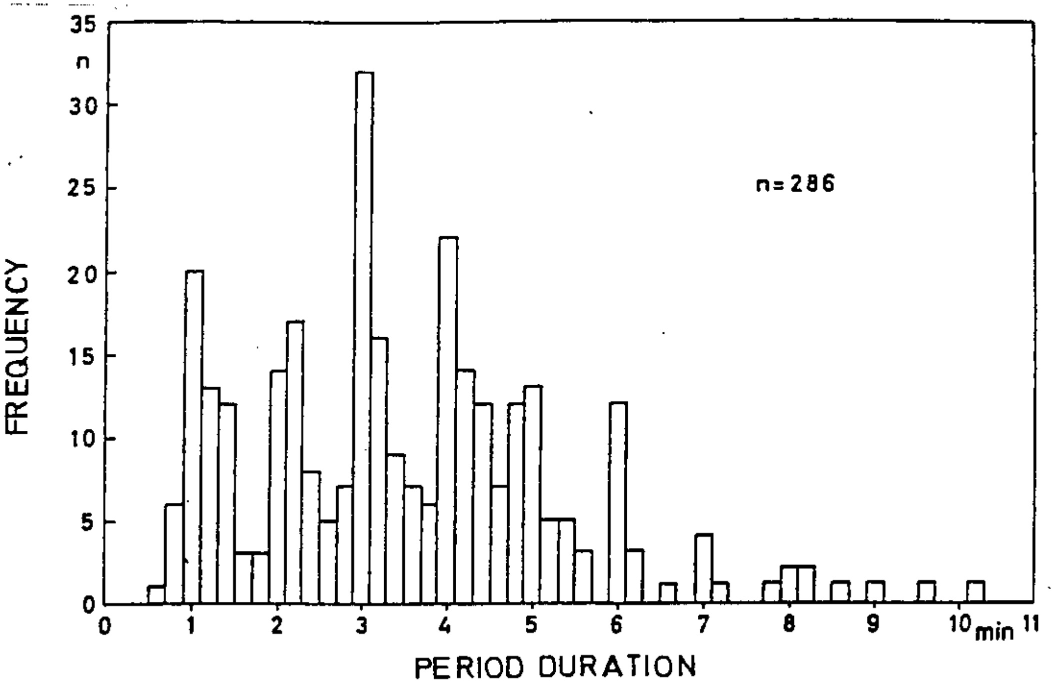

Fig. 3. - Histogram of period lengths of spontaneous smooth muscle contractions (*Taenia coli* of the guinea pig) [4].

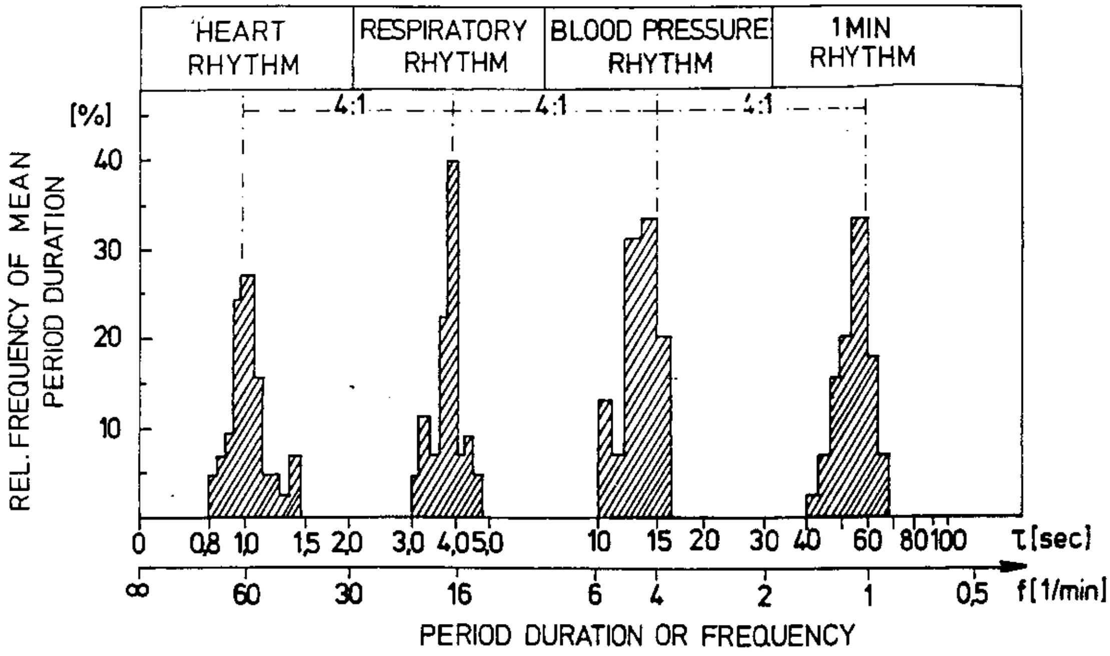

Fig. 4. - Frequency histogram of the mean heart rate, respiratory rate, blood pressure waves, and minute rhythms during night sleep, from 18 healthy subjects totalling 53 nights [5].

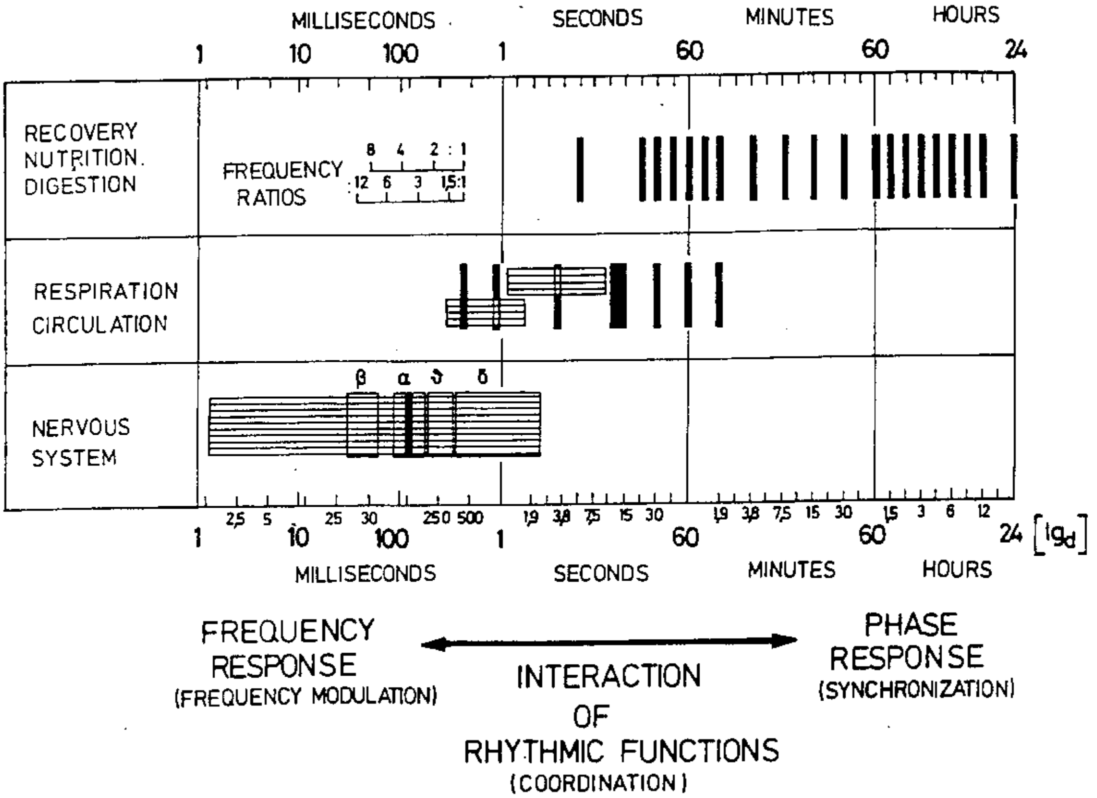

Fig. 5. - Frequency behaviour and modes of interaction of the endogenous rhythmic functions in different parts of the spectrum. Black vertical bars indicate the preferred frequency bands, horizontal hatching indicates the range of frequency modulation [9].

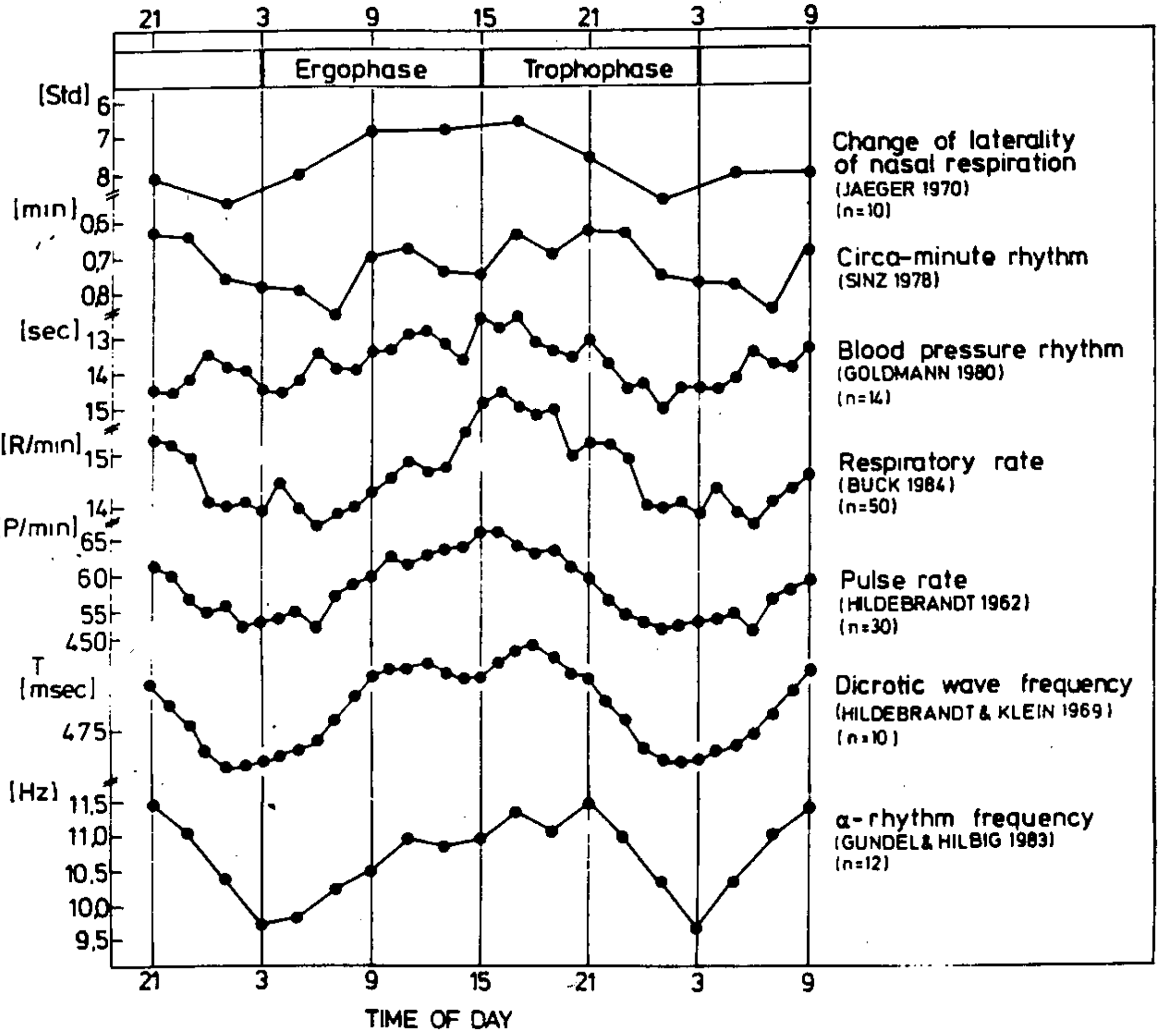

Fig. 6. - Daily courses of the mean frequencies of various ultradian rhythms. A compilation of data from the literature.

instance, in the EEG frequency spectrum even during night sleep we were not able to establish empirically a strict temporal order of the different types of waves. Even within the block of heart and respiratory rhythms the preference of integer frequency ratios, we demonstrated, only exists in the sense of an statistical preference during day time, when various disturbing influences can modulate the frequency of the rhythmic functions.

Frequency modulation as a response of rhythmic functions to stimulation or strain is, of course, the most disturbing effect on the harmonic temporal order of the biological rhythms. However, it is not the only mode of rhythm response. Checking again the whole spectrum of autonomous endogenous rhythms in man, another principle of functional organization becomes evident (Fig. 5).

Concerning the functional significance, in the longer wave section we find mainly rhythms of the metabolic system, e.g. nutritional, digestive, and recovery functions. In contrast, the short wave section contains the rhythmic actions of the nervous system, forming an information system. In the intermediate range we find a predominance of rhythms serving transport and distribution functions, mainly of the circulatory, respiratory, and intestinal type.

This tripartite organization of the autonomous spectrum includes also a different functional behaviour in respect to frequency, amplitude, and phase. As symbolized by the horizontal hatching, the rhythms of neural action exhibit the greatest variability of frequency. They are responsible for all the transmission and communication in the information system be portraying the momentary degree of excitation by means of frequency modulation. It is only during night sleep that the rhythmicity of the central nervous system becomes partially synchronized into certain frequency bands of the EEG. We can speak of a *frequency-responding system*.

In contrast, in the longer wave section the rhythms of the metabolic system prefer distinct frequency bands, which are ordered into integer ratios. In the figure, the black bars mark the preferred frequency bands or frequency norms, respectively. Some of them have been proved to dispose of stabilizing mechanisms, for instance in respect to temperature. The abscissa represents a logarithmic scale, hence the frequency ratios as indicated apply to all parts of the spectrum. In order to maintain this temporal order, the rhythmic functions tend to respond to interferences by changing their amplitude or phase, whereby changes in frequency only occur by "jumping" into other preferred bands of the harmonic system. Therefore, these rhythms of the metabolic system are characterized by *amplitude- and phase-responses*, leading to frequency multiplication, demultiplication, and/or synchronization.

In the middle wave length section, the rhythmical functions of the transport and distribution system exhibit both frequency modulation response to functional load, as well as, changes in amplitude and setting of frequency norms by coordinating the rhythmical actions to a larger harmonic time structure of integer frequency ratios, based on the preference of phase response.

Concerning the interactions of the different rhythmic functions, from the point of view of this structural principles, we must expect that slower rhythms are capable to act upon the faster rhythms preferably by modulating the frequencies; on the other hand, changes of the faster rhythms, as mostly evoked by external loads, may influence the slower ones preferably by enhancing their amplitude, multiplying their period length, and/or shifting their phase.

This can be verified, for example, by the frequency modulation of faster rhythms, as induced by the circadian rhythm under resting conditions. As shown in Fig. 6, circadian changes in frequency not only occur in pulse and respiratory rate, but also in α-frequency, arterial dicrotic wave length, blood pressure rhythm, circa-minute rhythm as well as in the rhythmic change of laterality of the nasal respiration. The circadian amplitude of frequency modulation is similar in all these functions, amounting to about 10-20%. However, the slower rhythms like circa-minute rhythm and laterality rhythm exhibit multimodal frequency distributions of their period lengths. Therefore it remains open whether or not the circadian changes of the mean frequency are produced by frequency modulation or by frequency jumps within the spectrum of preferred frequency bands.

On the other hand, the circadian rhythm originates characteristic changes in the strength of the harmonic time order, as measured by the rates of phase coupling between the different rhythmical functions. For example, daily courses of the coupling rate, leading to integer frequency ratios between various minute rhythms, i.e., blood pressure rhythm and respiration, blinking rhythm and respiration, heart beat and respiration, as well as, heart beat and dicrotic arterial oscillation are shown in Fig. 7. In all parameters, the coupling rates increase during the increasing trophotropic state of the autonomous system in the afternoon and night, whereas during the ergotropic phase of the circadian variation the coupling rates decline to a minimum.

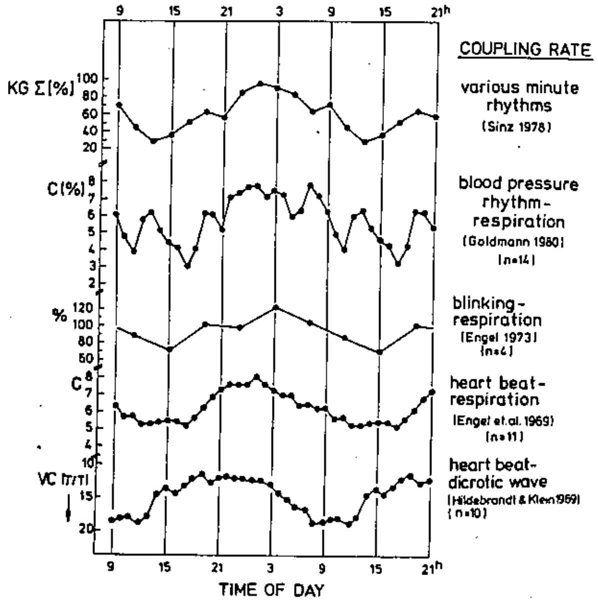

Fig. 7. - Mean daily courses of the coupling rates between various ultradian rhythmic functions in man. Compilation of results from the literature.

Biological meaning of frequency- and phase-coordination

It is important to point out that the increase of functional economy, which is brought about by strengthening of the harmonical time order, is an important precondition for the recuperation and regeneration during night sleep. Several findings could prove that functional economy is, in general, favoured by an enhancement of the harmonic time structure.

In contrast, the destructive effects of physiological and pathological strain or stress on the harmonic temporal order has been demonstrated in the different parts of the rhythm spectrum. Apart from the well known desynchronizing effects on the EEG, a compilation from Raschke & Hildebrandt [12], shows effects on the rate of phase coupling between heart and respiratory rhythm at different sleep stages and at different amounts of work load (Fig. 8). Whereas during sleep the coordination between the

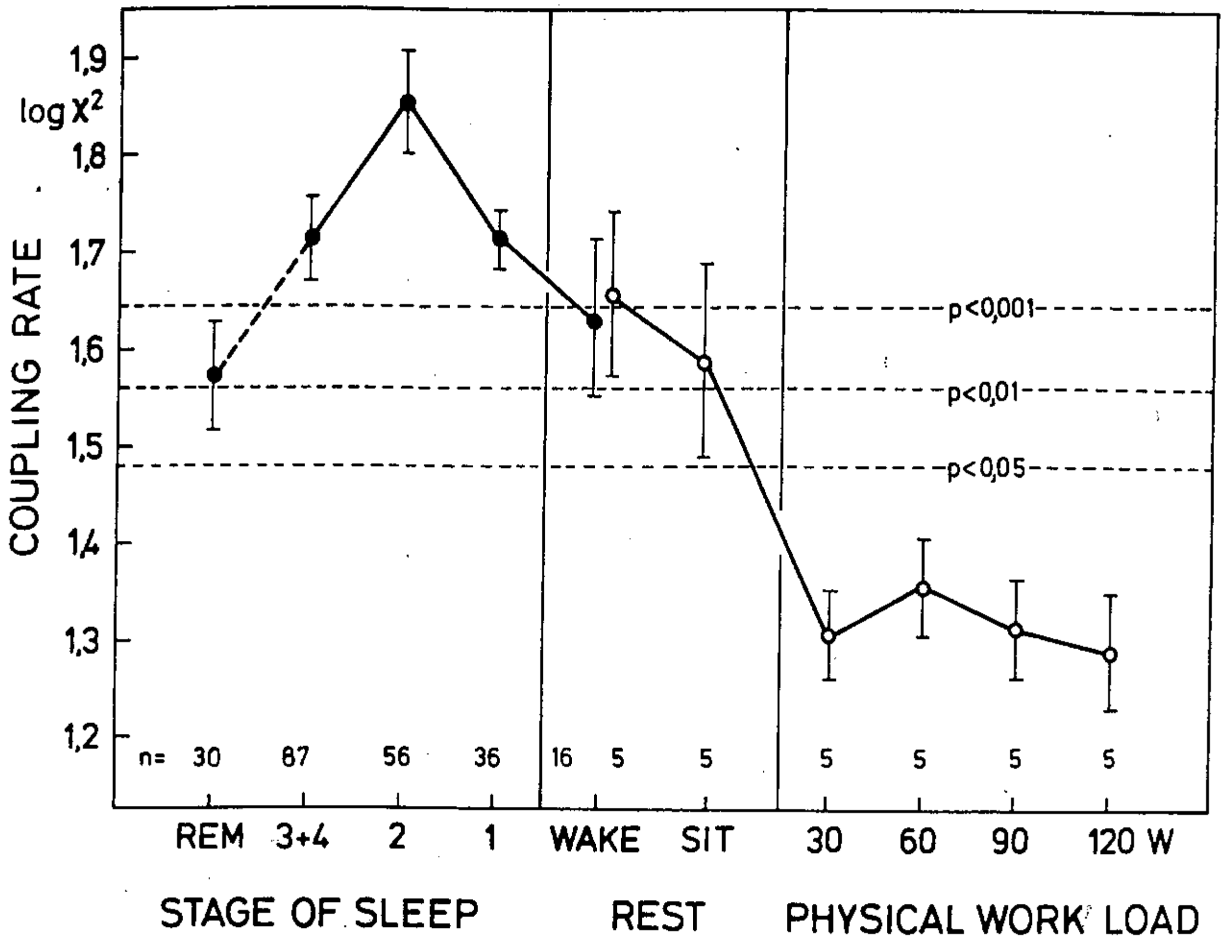

Fig. 8. - Mean coupling rates between onset of inspiration and heart beat in healthy subjects during different sleep stages, waking, and sitting, as compared to different amounts of physical work load [12].

both rhythmic functions is strengthened, even small amounts of work load are able to abolish completely the rhythmic interaction.

In healthy subjects under resting conditions the ratio 2:1 between heart period and arterial dicrotic wave length is markedly preferred (as shown in Fig. 9). Eckermann [14] has calculated that the economical effect of this coordination amounts to about 30%. In trained subjects with increased trophotropy of the autonomous system the preference of the integer ratio is much more pronounced, and (because of the bradycardia) the ratio of 3:1 is also preferred. In a group of patients, however, suffering from functional disorders of the circulatory system, we could observe a drastic deviation from the normal phase- or frequency-coordination [13].

A further example concerns the coordination between respiration and blood pressure rhythm in man (Fig. 10). In a lying position the phase coupling is very strict, but in the standing position the coupling rate is markedly decreased, demonstrating again that ergotropic frequency modulation tends to weaken the autonomous temporal order [15].

Most extensive studies on the effects of strain on the time structure of rhythmic functions have been performed in the range of circadian rhythms, and this preferably in respect to the response to the load of night and shift work. In principle, three different modes of response of the circadian system can be observed, as shown by the examples of three night nurses (Fig. 11), whose circadian courses of rectal temperature were measured under strict resting conditions after normal daily routine (recovery) and after a period of 3 weeks of permanent night work.

In the upper example, night work is responded to by a phase shift of the circadian rhythm of body temperature, corresponding to the shift of the daily routine. In the middle example, the load of the night work leads to a more or less complete flattening of the circadian amplitude. This mode of circadian response is also well known for pathological conditions. Menzel [17] was the first to point out, that in patients with increasing severeness of an illness the circadian amplitude is decreased. In the lower example, besides of an increase of the amplitude, after the night work period

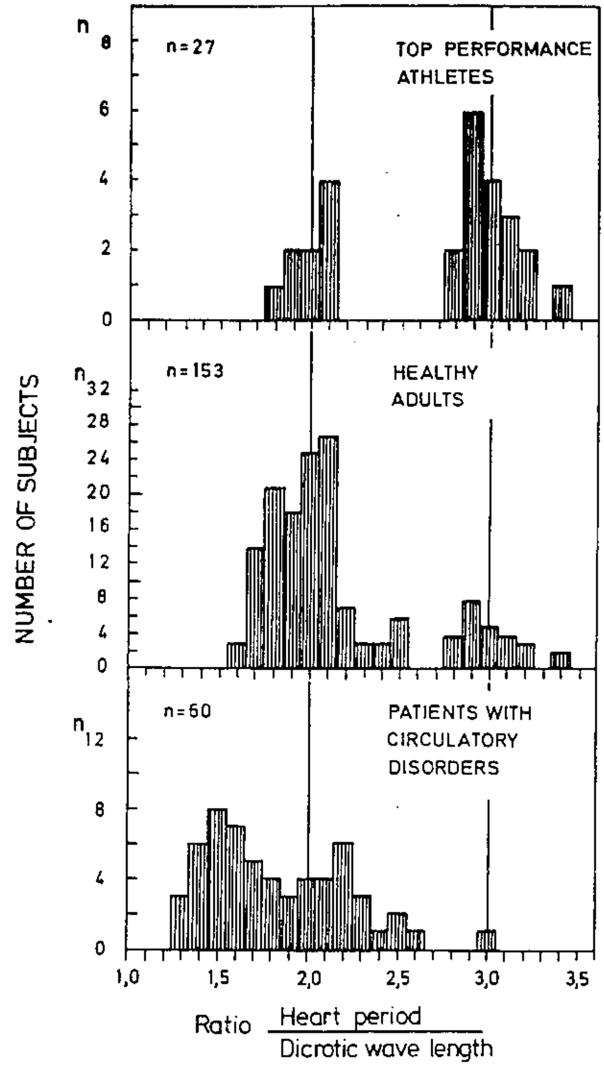

Fig. 9. - Histogram of the mean ratios between heart period and dicrotic wave length under resting conditions in top-performance athletes (top), healthy adults (center), and patients suffering from circulatory disorders (bottom) [13].

the subject exhibited a two-peaked 12 h periodicity instead of the 24 h rhythm. Such frequency multiplications mainly occur when the organism is loaded without having sufficient opportunity for recuperation. In studies on engine drivers we were able to show, that the amplitude of the 12 h period increases with increasing amount of tiredness [18].

Menzel [17] again was the first to point out that patients suffering from sleep disorders exhibit a prominent 12 h period of vegetative functions instead of the normal 24 h rhythm. Furthermore, he observed in patients that with increasing loss of functioning the daily courses were superimposed by submultiple periods of the circadian rhythm.

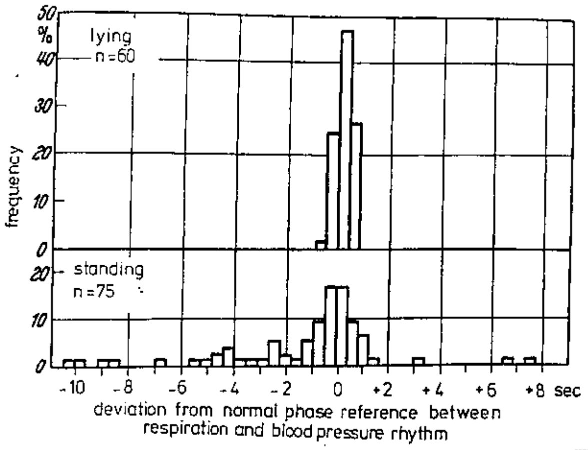

Fig. 10. - Frequency distributions of the deviations from the normal phase reference between respiration and blood pressure rhythm in a healthy adult in lying and standing position [15].

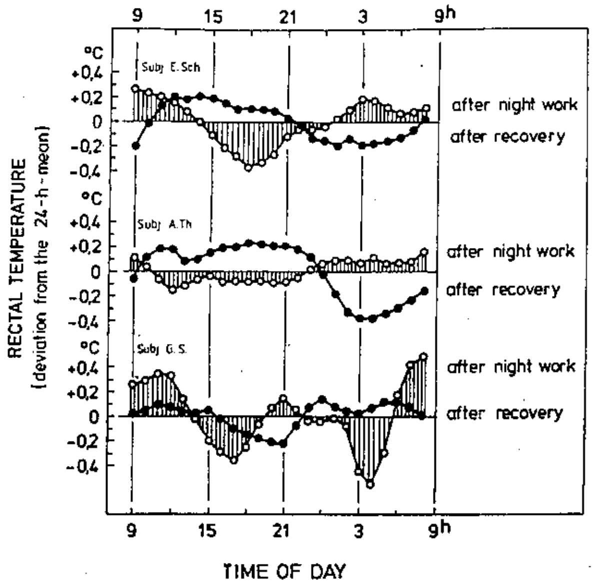

Fig. 11. - Three examples of the daily course of body temperature of night nurses after a period of night work and after a recovery period. Curves are plotted as deviations from the 24 h average. For further explanation see text [16].

Reactive periodicities of biological time structure

In principle, it has been known since long time that the reactions of living systems are periodically structured. However, up to now only few chronobiologists have tried to ascertain the particular properties of these reactive periodicities, and to examine their interactions to the spontaneous rhythmic functions. The main interest has been focussed on the spontaneous rhythms. These, however, become overt only under undisturbed and unmasked conditions, when the organism is in a regulatory equilibrium with both the outer and the inner environment, that means in a state of complete adaptation.

Of course, reactions never represent a direct continuation of the stimulus, neither with regard to quality nor to quantity, but can be evoked by the stimulus. Hence, a stimulus induced periodicity brings to appearance an endogenous time structure may it be already active or in a latent state.

According to our results, reactive periodicity can be evoked by single, repeated, or continuous stimulation. As an important characteristic, the phase position of reactive periods depends on the stimulus, the stressor acting as a synchronizer of the reacting functions.

The amplitudes of reactive periodicity dampen down with increasing compensation. Hence, reactive periods often appear to be transients during adaptive processes.

Concerning the time structure, the period lengths of reactive periodicities differ from those of the spontaneous rhythms, however, they prefer whole-number frequency relationships with the spontaneous ones. By this, they prove to be parts of the coordinated harmonic time structure of the organism. Under strain, rhythmic functions can transitorily undergo frequency-multiplications or demultiplications, returning to the spontaneous rhythmicity after compensation is completed, or - as sometimes - reactive periodicity dampens down completely, indicating that the responding oscillator returns to latency. These characteristic properties of reactive periodicity can be observed in all ranges of the spectrum.

An example of frequency-demodulation is given by the two curves of human muscle blood flow (Fig. 12), as observed by Golenhofen [19], representing an adaptive reaction of the blood vessels to the continuous infusion of adrenaline. In both cases the drug evokes a periodic response, the onset of which is strongly related to the begin of injection and the amplitudes dampen down under the continuous action of the drug. The period duration amounts to 2 min, thus doubling the spontaneous 1 min rhythm of muscle blood flow in man.

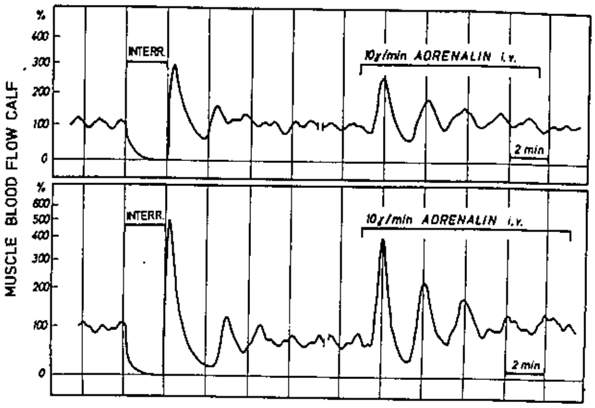

Fig. 12. - Two examples of reactive periodicity, evoked by a continuous infusion of adrenaline, in the course of muscle blood flow in man. Blood flow was measured by means of a heated thermocouple element. Interr. = interruption of the spontaneous blood flow by inflation of a cuff. Ordinates are calibrated in % of the average resting blood flow [19].

In the ultradian range of the spectrum, the more or less abrupt changes of the external milieu between day and night are responded to by periodic reactions (Fig. 13). There are several functions which respond to the morning onset of the day by a steep initial deviation continuing as a reactive periodicity, the amplitude of which is dampened down during the day. The period lengths mostly represent submultiples of the 24 h period.

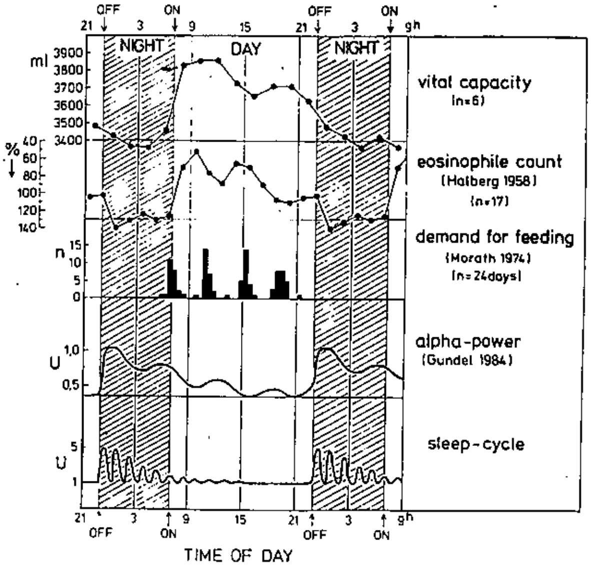

Fig. 13. - Examples of the ultradian periodic response to onset and offset of the day, respectively. For further explanation see text [10].

There are, however, other rhythmical functions, which respond to the offset of day or sleep begin by forming periodically structured reactions, the amplitudes of which dampening down during the night and the following day. There are, for instance, some indications [20] that the sleep cycle as a basic rest-activity cycle continues during the first half of the day. The period lengths of the off-responses also represent submultiples of the circadian period.

From the medical point of view, periodic reactions, which are structured by multiple frequencies of the circamensual cycle, are of predominant inter-

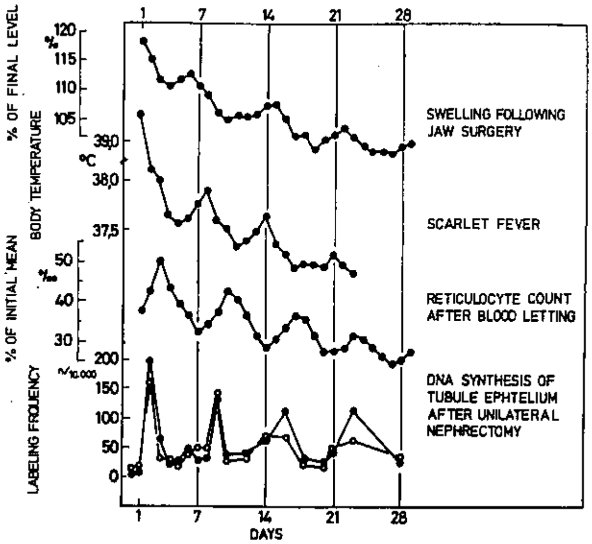

Fig. 14. - Examples of the circaseptan reactive periodicity in the courses of several functions during various adaptive processes [21].

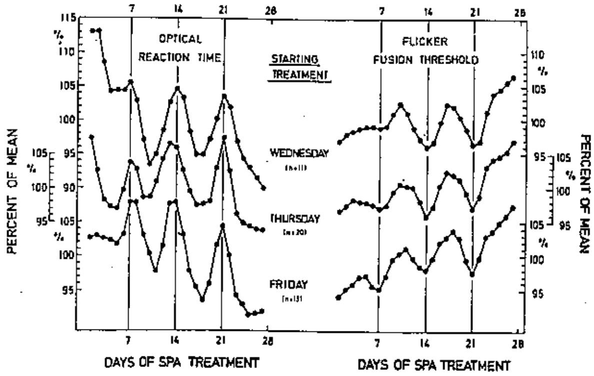

Fig. 15. - Mean courses of optical reaction time and flicker fusion threshold in 3 subgroups of patients starting spa treatment on different days of the week [22].

est. Here the preferred period length amounts to about 7 days.

This so-called circaseptan periodicity can be seen in numerous adaptive and compensating processes for instance in wound healing, in immunological adaptation like in infectious diseases or in rejection of organ transplants (Fig. 14). Furthermore, the circaseptan periodicity synchronizes the cycles of cell division of erythropoietic reactions to high altitude as well as of compensatory growth of organs.

Therapeutical induction of circaseptan periodicity during cure treatment could prove the decisive fact that this reactive periodicity is not a simple consequence of the social week cycle, but is evoked by

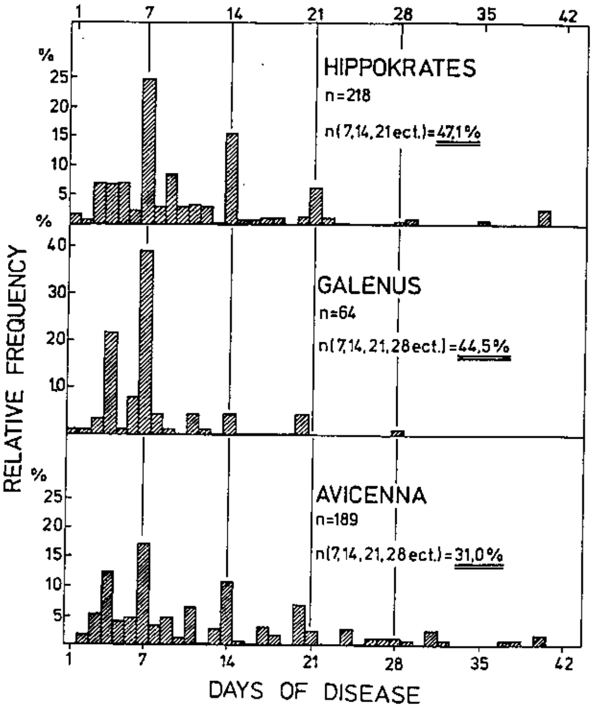

Fig. 16. - Temporal distributions of the critical and prognostically important days of diseases, as reported by the Corpus hippokraticum, galenus and avicenna [23].

the synchronizing onset of physical treatment. As shown in Fig. 15, the circaseptan periodicity of reaction time and flicker fusion threshold in groups of patients is strictly synchronized over the days of treatment and does not show any phase difference according to the day of the week, when treatment was started.

Obviously, these properties of the circaseptan-periodic time structure have been well known already to the physicians of the classical antiquity as shown by the three histograms of critical and prognostically important days of diseases (Fig. 16). Hippokrates, Galenus and Avicenna published special issues on the calculation of critical days in the course of diseases. There is a more or less clear cut predominance of the relative frequencies of nominations at day 7, 14, and 21 of the diseases, that means an evidence of an underlying circaseptan-periodic time structure.

Looking again at the spectrum of rhythmic functions (Fig. 17), the complexity of the periodic reactions increases also with increasing period length, gaining more and more adaptive significance. In any range, the period durations of the reactive periods are ranged between the respective spontaneous rhythms, which dominate the time structure of the organism under resting conditions and in complete adaptation.

From the standpoint of a faster spontaneous rhythm, the appearance of a slower reactive peri-

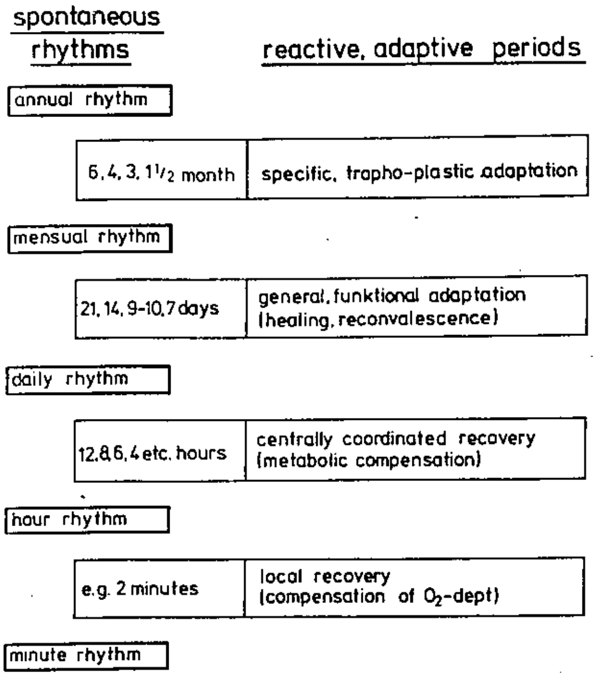

Fig. 17. - The positions of reactive periods between the spontaneous biological rhythms and their adaptive significance in the different parts of the rhythm spectrum. For further explanation see text [1].

odicity involves a period multiplication, which at the same time increases the autonomous amplitudes, leading to longer-lasting and more intensive recovery processes, thus preparing for increases in functional capacity.

From the standpoint of a slower spontaneous rhythm, however, the induction of a reactive periodicity of higher frequency represents a frequency multiplication, which is able to make use more economically of the actual capacity, according to the well-known principle of interval training.

Both mechanisms are decisive preconditions for proper compensation or adaptation.

Conclusive remarks

Considering all the findings, one can summarize, that there exist at least five different modes of rhythm response (Fig. 18), each of them leading to different consequences in respect to the temporal order in the organism:

1. Rhythmic functions can react by frequency modulation. This mainly occurs in the high frequency section of the spectrum, and must originate a more or less complete loss of the harmonic time structure.

2. Under strain, rhythmic functions can develop frequency jumps in the sense of frequency multiplication or demultiplication. The resulting reactive periods modify the harmonic time structure of the organism, using an emergency time order to improve compensatory or adaptive efficiency. This mode of rhythm response can be observed in all slower functions, which are not able to respond by frequency modulations.

3. The, so to speak, classical mode of rhythm response by phase shift mainly occurs in the longer wave section of the spectrum. It has to be differen-

MODE OF RHYTHM RESPONSE ——►	TEMPORAL DISORDER
1. Frequency Modulation	Loss of Time Structure
2. Frequency (De)-Multiplication Frequency "Jumps" Reactive Periodicity	Modification of the Harmonic Time Structure ("Emergency Order")
3. Phase Shifting through Zeitgeber Response	Internal Desynchronization (Preservation of External Order)
4. Phase Shifting through Transitory Uncoupling	External Desynchronization (Preservation of Internal Order)
5. Amplitude Response	No Change in Temporal Order

Fig. 18. - Modes of rhythm response leading to different types of temporal disorder. For further explanation see text [24].

tiated: there is phase shifting, which is induced by zeitgeber action. This may lead to internal desynchronization because of the different responsiveness of the compartments of the long wave system concerned.

4. Recent findings in night- and shift work, which showed that the speed of phase shift of the circadian system does not depend on the rotation speed of the shift schedule, lead to the assumption that delaying phase shifts can be caused by a transitory uncoupling from the environmental zeitgeber regimen. In this case, the internal time order can be preserved at the cost of an external desynchronization (c.f. Hildebrandt *et al.* [25]).

5. Finally, rhythmic functions can respond by mere changes in amplitude. This response will not change the temporal order of the organism, however, amplitude response implies high functional capacities. It is interesting to remind that well trained subjects prefer amplitude response, for instance in the stroke volume of the heart, and at the same time, they are able to strengthen the co-ordination of rhythmic functions, leading to higher economy.

Chronobiology up to now was mainly concerned with the spontaneous rhythmic functions and its harmonic temporal order. The reactive behaviour and modifications of this time structure have not been taken sufficiently into consideration.

Besides of the resulting theoretical deficit, from the practical point of view, it is important to discriminate between the spontaneous rhythmicity under completely adapted resting conditions and the various modes of reactive modifications of the time structure by rhythm response. This might contribute to a better understanding of the temporal order in the organism and help to avoid misjudgements of temporal disorders, as caused by physiological strain or pathological impacts, respectively.

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