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CIRCADIAN RHYTHMS IN AEROSPACE MEDICINE

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INTRODUCTION

Aeronautics and astronautics carry man into a medium which is not his usual medium of life. In addition, because of the properties of the speed and duration of flight, when he returns to his medium he is going to meet, in most cases, social, climatic and time conditions which will not coincide with those he left at the beginning of the flight, because of the time which has passed.

To this we must add that military pilots have working hours which are absolutely different from the monotonous cyclical activity of conventional work. This is important in view of the type of mission to be carried out, requiring maximum efficiency.

In aerospace medicine, the problem is even greater because the dissociation with the medium lasts much longer and is more complete.

In this paper we intend to review the cyclical nature of organic functions in general, and in particular the ones which are of most interest to aerospace medicine because of what has been said above.

GENERAL CONSIDERATIONS

Claude Bernard postulated the concept of the invariability of the internal medium, later modified by Cannon who attributed a certain degree of flexibility to it by introducing the term of homeostasis.

In reviewing the bibliography we find that in 1845 Davy [1] reported daily variations in body temperature. Between now and then the concept of invariability in the internal medium has become a concept of cyclical periodicity for almost all functions, so physiology is not constant throughout the day.

About 1910, the concept of daily rhythm appeared, and only

the day-night situation was left, the nyctoheremal rhythm, found in 1938 [2].

In 1957 Halberg [3], was the one who set up the rhythm of approximately 24 hours, calling it etymologically the Circadian Rhythm.

As we shall soon see, a daily cyclical periodicity exists in the majority of functions, if not all. The problem is finding out the cause of this periodicity.

Exogeneous circadian rhythm is defined as being produced by an external factor with a cause-effect relationship; for example, solar light-pigmentation, with the effect stopping when the cause stops. On the other hand endogeneous rhythms are defined as autonomous since the only thing environmental circumstances produce is a temporal adjustment of it, as isolating the individual from the environmental circumstances leads to the following:

a) continuation with a similar periodicity

b) acquisition of an autonomous periodicity of more or less 24 hours, but not precisely.

Another problem is to know whether the rhythm is autonomous or is conditioned by another pre-existing rhythm which, one might say, prompts it.

Having said this, I shall describe the functions subject to a circadian rhythm function.

BODY TEMPERATURE

In 1845 Davy [1] studied the variation in his body temperature, remaining in a dwelling with a constant temperature, and found a daily cyclical curve with minima at 0400 hours and maxima between 1800 and 1900 hours.

In 1966, Ogle described the fact that night workers have inverted the body temperature curve with their inverted life schedule.

It is worthwhile to keep in mind the fact that Benedict met a night watchman in 1904 with an unadjusted temperature rhythm, but this was because he had a job during the morning.

Pembrey maintained that the temperature rhythm was a reflection of the rhythmical nature of the activity of cellular

metabolism, but Bornstein [4] showed the independence of these two rhythms.

Nevertheless, there does exist a correlation between the vasomotor tone and temperature [5].

The temperature rhythm is parallel to the circadian rhythm of the diuresis and excretion of the 17 ketosteroids, thus inversely to the level of eosinophiles in the blood.

There is a controversy about the localization of the center regulating this rhythmical nature.

Kleitman [6] found subjects with cerebral tumors who had lost their rhythm. On the other hand, subjects with subtotal hemispherectomies maintained the rhythmical pattern.

According to Haldberg [7], there is no specific localization responsible, and this is undoubtedly a matter of an endogenous rhythm, since individuals isolated in bunkers, in total and continuous darkness, and without any knowledge of the time, adopted a cyclical rhythm slightly greater than 24 hours. The average was 25.3 hours [8].

In another experiment in which an individual spent six months alone in a cave, he showed a rhythm of 24 hours, 28 minutes for the first two months and 24 hours, 44 minutes for the other four.

ENDOCRINE RHYTHMS: ACTH

In healthy subjects Liddle [9] found a variation in the level of blood ACTH by means of two extractions, at 0600 hours and at 1800 hours, the first being 0.25 µ/100 ml and the second 0.11 µ/100 ml; in patients with Addison's disease he also found a rhythmical pattern with elimination much lower at 1800 hours than in the rate at 0600 hours.

Going into more detail, it has been proven that there is a periodic rhythm in the response to brake tests with dexamethasone or stimulation with B hydroxylase blocks, such as Metopirone (SU 4885) [10], which means that the negative feedback of cortisol on the hypophysis has a circadian cycle sensitivity.

In 1966 Demura confirmed the cyclical nature of ACTH secretion by a radioimmunu assay, showing a maximum secretion peak at around 0700 hours.

In 1966 Schally confirmed the existence of the CRF, Corticotrophin releasing factor, isolating and synthesizing it.

Clayton, in 1963 [11] showed a cyclical sensitivity of the anterior hypophysis to CRF, with greater sensitivity at 1700 and at 2400 hours than at 0800 hours; he did this by using periodic injection of CRF of the same quantity and with concomitant determination of ACTH.

In order to explain the rhythmical inequality between ACTH and the adrenal glands, Retienn postulated the existence of two autonomous hypothalmic centers receiving feedback from cortisol, one for rapid response and the other for cyclical activity.

GONADOTROPIN

In 1967, Faiman and Ryan [12] used radioimmuno assays techniques to show a cyclical secretion of FSH, with a maximum of 0.2 μ/ml at 0500 hours and a minimum of 0.14 μ/ml at 1430 hours.

No secretion rhythm has been described for the luteinizing hormone LH.

PROLACTIN

The rat has prolactin secretion rhythms [14] but it is difficult to demonstrate in human beings that the rhythm of this hormone is different from that of the growth hormone.

THE MELANOTROPIC HORMONE

Jores [15] described a MSH rhythm with a maximum at 0700 hours and a minimum at 1800 hours.

THE THYROTROPIC HORMONE

Some authors describe peaks at 0200 hours, while others deny this [16].

The explanation for this disagreement can be that ingestion extremely alters feedback, the source of rapid control of the secretion of this hormone.

THE GROWTH HORMONE

There is a description for this hormone which details a circadian rhythm with an increase in secretion during the night [17]

but it must be recalled that a peak is produced at the beginning of deep sleep, a maximal secretion which cannot be inhibited by glucose but which can be by free fatty acids.

My personal expalanation for this phenomenon is the following:

The secretion of STH is inversely proportional to glycemia and to the level of free fatty acids.

The STH-glycemia relation is completed by glycostasis which keeps the hypophysis checked until the glycemia drops. This glycostasis is located in the deep temporal zones. At the moment that sleep begins, the connection between these centers and the hypothalamus is broken, freeing the hypophysis. This is why it is not checked by glucose, but is by fatty acids.

THE ANTIDIURETIC HORMONE

Schindl [18] notes an increase in the amount of ADH in urine in the morning. Zsoter found higher concentrations of ADH in the blood at midnight.

CORTICOIDS

The rhythm of corticoid secretion was the first circadian rhythm described in 1943 by Pincus, who established a maximum around 0800 hours and a minimum between 2000 and 0400 hours.

The maximum secretion peak in night workers has been found at the normal hour of rising [20].

The rhythm becomes autonomous in individuals isolated in caves and takes on a variable periodicity of 12 to 16 hours [21].

In individuals making time shifts by long distance flights, such as from the United States to Korea, there is a time shift of nine and a half hours; they lose their rhythm and require two months to regain their normal amplitude.

Others flying from England to Chicago, with a six-hour shift, have lost the cycle for 11 days and require 25 days to become normalized.

A cyclical sensitivity has been proven for the suprarenal gland in regard to ACTH, with less sensitivity in the morning.

The cyclical secretion of ACTH is controlled by deep cerebral centers, since alterations in sleep and consciousness are closely

associated with a change in the rhythm of plasma corticoids [23].

ALDOSTERONE

A rhythm has been described for the secretion of aldosterone. It increases during the day and drops at night, with the maximum secretion peak at noon and a secondary peak at twilight.

The effect of posture of aldosterone secretion must be kept in mind. After three hours on food, the level of aldosterone in the blood increases, but not that of cortisol. This experiment peformed with an individual submerged in water did not produce any increase in secretion.

This effect is influenced by the plasma levels of Rennin [25].

CATECHOLAMINES

Euler described an increase in the secretion of adrenalin during the day.

Levi proved the existence of a rhythm independent of waking or sleeping, and Weil proved the independence of the rhythm with intellectual activity.

Noradrenalin has a rhythmical nature similar to that of adrenalin, but with a lower and more advanced cycle, about three hours ahead of adrenalin.

It has been suggested that the greater amplitude in the rhythm of adrenalin, especially in the morning, is due to the greater amount of adrenalin formed from noradrenalin because of the high state of cortisol at this time.

SEROTONIN

Haldberg [26] described a very low rhythm with peaks at 0400 and 1400 hours, and with maximum variations varying from 1.7 gr/100 ml to 19 gr/100 ml.

RENNIN

Brown observed an increase of 31 percent between 0400 and 1000 hours, without controlling posture, diet, or exercise. The explanation for this phenomenon is that a discharge of catecholamines produced by the increase in cortisol is brought about on rising, which conditions an arteriolar vasoconstriction with a

reduction in the blood flow through the juxtaglomerular apparatus with a discharge of rennin and a following increase in the production of aldosterone. A rhythm with a drop between 1200 and 1800 hours and an increase between 0200 hours and 0800 hours has been seen under conditions of isolation and rest [27].

THE THYROID GLAND

There is a great lack of harmony in the rhythmical pattern of the thyroid gland. Authors give maximum peaks between 0200 and 0800 hours [28], and between 0700 and 1700 hours. However, the most significant fact is that total iodine does not vary, but the PBI does, being low at 0800 hours, continuing so until 1600 hours, and then rising to a minimum [sic] at 2400 hours.

INSULIN

Periodic determinations of insulinemia by means of radioimmuno assays have shown higher figures at 0700 and 0800 hours than at 1500 and 1600 hours, with no variation in glycemia, which implies less insulin efficiency in the morning [29].

SEX HORMONES

Dray [30] found the lowest level of testosterone at 0800 and the highest between 0700 and 1300 hours. Some attribute this phenomenon to the drop in the production of the adrenal gland in the morning.

KIDNEYS

Hart and Verney found a spontaneous increase in the urinary fluid in the morning in subjects at rest, and being fed continuously. The relationship between this fact that ADH rhythm has not been established.

The following has been observed in connection with the secretion of electrolytes:

Increase in the elimination of Na and K around 0800 hours, coinciding with the lowest elimination of H ions [31].

For P Mino gives maximum elimination at 2000 hours and minimum at 0800 hours.

THE CARDIOVASCULAR SYSTEM

In 1897 Howell reported a nocturnal drop in arterial pressure. Later studies have confirmed this fact with the following curve: deep drop in the first hour of sleep, a gradual increase later, and a sudden rise at the moment of awakening.

The pulse parallels the body temperature curve.

A drop in the pulse rate was found in pilots when they should normally have been asleep.

HEMATOLOGY

The total number of leukocytes varies throughout the day, a fact known since 1900.

Sabin described maximum peaks in the afternoon. Tatai [32] reported the rhythm of eosinophiles with a maximum at 0500 hours and a minimum at 1400 hours.

Pincus reported the close relationship with the corticoid cycle, since the rhythm of corticoids in patients with Addison's disease disappears, along with the rhythm of the eosinophiles.

A curious fact is the one reported by Appel [33] and later confirmed that morning eosinopenia is lacking or delayed in blind people.

Radnot communicated that there is no drop in eosinophiles in the morning in people kept in the dark, and that if they are suddenly exposed to light they produce eosinopenia regardless of the time [34]. This demonstrated independence from the adrenal glands, since the light is the direct producer of the eosinopenia.

To summarize, at dawn an increase in the total number of leukocytes is produced, with a drop in eosinophiles, lymphocytes and neutrophiles.

RESPIRATION

The vital capacity gradually diminishes during the day, reaching a minimum around midnight and rising from then to a maximum on rising.

CEREBRAL FUNCTIONS: PSYCHIC FATIGUE

Psychic fatigue is of a rhythmic nature, with the disagreeable property of being cumulative.

Levi and Froberg reported that in a study made with 63 normal individuals, kept awake and active for three days, the subjective feeling of fatigue took on a cyclical form with increases at 2000 and 0800 hours and light remissions of approximately 20% between 0800 and 2000 hours.

In our environment it is worth keeping this in mind because of the danger it entails; since it is cumulative and partially remitted during the day, an individual believes himself capable of further nocturnal actions during which fatigue will reappear with increased intensity.

INTELLIGENCE

Through numerous tests Kleitman [35] gives some cyclical results with maximum effectivness between 1000 and 1200 hours, and with minimum effectiveness between 2300 and 0600 hours.

There are very many works on this subject [36], but the results are essentially similar to those of Kleitman in all of them.

Kleitman also noted the adjusted relationship between intellectual effectiveness and body temperature, to the point that many authors [37] have adopted it as an indirect measurement in their work. In work with individuals isolated in bunkers, Aschoff found a total dissociation between the two curves, and postulated that this is due to two different time-marking nuclei, joined when an external Zeitgeber (philosophical clock) exists [42].

ESTIMATION OF TIME

The subjective estimation of time is subject to a cyclical rhythm with a faster sensation around 1500 hours, one which seems longer in night workers [38].

Under different conditions it has been postulated that the parameter causing this periodicity in the subjective interpretation of time is the frequency of the pulse of the individual himself. [39-40].

BIRTH

Klaiser [41] made a statistical study of 601,222 births, and found and confirmed a greater incidence of birth between 0200 and 0600 hours, with the lowest percentage between 1400 and 1800 hours.

BEGINNING AND DEVELOPMENT OF THE CIRCADIAN RHYTHM

In studying the sleep-waking rhythm of children from the 11th to the 182nd day after birth, Kleitman found the following: there was a free rhythm up to three weeks of age, a 25.00 hour periodicity in waking and sleeping from the third to the 17-18th day, and then establishment of the normal 24-hour rhythm.

SYNCHRONIZATION AND MAINTENANCE OF CIRCADIAN RHYTHMS

Opinions on this subject are extremely varied, but almost all of them blend with the opinion of Aschoff [42], for whom ontologically the internal medium is rhythmic in some of its functions which condition the majority of them. This periodicity is endogenous, but is adjusted to the environment for some Zeitgeber or external cyclical marker. This Zeitgeber can be environmental, such as temperature, light, humidity, etc., or social.

In order to explain autonomous endogenous periodicity, Ehret and Trucco [43] postulated the concept of "cronon" taking as a base the cyclical nature of the mechanism regulating DNA-RNA transcription, where the cycle is:

$$\text{DNA} \rightarrow \text{RNA} \rightarrow \text{Protein} \rightarrow \text{Cronon}$$

Thus the rhythm is a fact. If we break the connection between an individual and his environment, he loses the normal circadian rhythm of 24 hours and adopts an autonomous rhythm of approximately 25 hours. This puts an end to all of the theories according to which the causes of rhythmical periodicity are cyclical changes in the biosphere, such as daily variations in environmental temperature, light, changes in the magnetosphere due to the movement in the rotation of the earth or fluctuations in the solar wind which feeds the Van Allen belts, thus producing a daily

cyclical variation in the charges in the high layers of the ionosphere, with an increase in protons in the morning, etc.

Rhythmicity is a tendency or innate factor in living beings. All that the environmental factors of their biosphere do is to produce a synchronization in all of the cycles, acting as a Zeitgeber or environmental clock.

The great unknown in all of the theories about it is to know where the rhythm originates and the way in which the biosphere synchronizes it.

CONCLUSIONS

As we have seen, the internal medium is not monotonous and invariable but is subject to a continuous change which maintains a cyclical rhythm in all of its functions. This means that we are different as a function of the time at which we look at ourselves. Our production and psychophysical aptitude is not identical throughout the day, and this should be kept in mind in situations which require 100% of our capacity.

When an individual is disconnected from rhythmical synchronnization, whether he is isolated from his medium, working at night or rapidly transported through several time zones, his circadian cycle comes into disagreement with the environmental rhythm, and his physiological functions suffer changes which cause deterioration in his production and aptitude, producing fatigue.

In studies carried out with pilots subject to time zone changes, K. E. Klein [44], has shown that the ones who suffer the least reduction in tests of psychophysical production when time is skipped were the ones who showed daily cyclical variations in their biological functions under normal conditions, i.e., those whose cyclical rhythms was least affected by environmental conditions.

Wegmann and K. Klein have shown that physiological changes which appear during a transmeridian flight are much greater west to east, than east to west.

Industrial medicine should take circadian rhythm into account when workers on night shifts are involved. In order to prevent

reduction in production, these workers should always be the same men, since the incidence of industrial accidents and least production from these individuals will be on Monday and Tuesday, because the rhythm will have become desynchronized during rest over the weekend.

In aeronautics, the subject should be broken down according to the type of mission in the unit to be studied. Thus we shall take:

- Military personnel
- Personnel of civil airlines
- Transcontinental flight passengers, and
- Astronauts.

Military Personnel

The problem in our environment is produced by breaking the rhythm, caused by night duty, alerts, and alarms. This is a problem because the efficiency of military personnel in these situations should be 100%, and as we have already seen, the biological potential of the individual is reduced at night. The ideal solution would be to have crews and auxiliary personnel with a night rhythm for flying. As this is not a solution, we should have recourse to seeing that the individuals who make night missions are in the optimal conditions for them. Hygienic measures should be accentuated the most; these include rest before a mission, and the elimination of toxicants such as alcohol, tobacco and even coffee, which acts as a stimulant producing a false increase in the state of alertness and potentiating the appearance of fatigue. Missions should be as far apart as possible, and there should be a definite attempt to prevent any other factor from causing fatigue.

In forces whose personnel make transmeridian journeys, changes which arise with the time shift must be added to what has been said before; we shall see this below.

Civil Airlines Personnel

In airline companies which make transcontinental flights, the crews are subjected to continuous changes in time zones, as well as to climatic, social, and culinary conditions, which completely

alter their nyctohemeral rhythms. The time for resynchronization varies from 8 to 20 days depending on the time shift produced and the feeling of displacement, since it is actually impossible to reacclimate this type of personnel. The consequences are extremely varied, but all of them can be included in the syndrome called "flight fatigue" which includes psychic symptoms like insomnia, somnolentia, headaches, dizziness, asthenia, anorexia, etc., and somatic symptoms which are of the most varied nature, such as palpitations, tachycardia, impotence, various allergies, constipation, diarrhea, various digestive problems, etc.

There should be two fronts in combatting all of this: the individual selected should be the most balanced and healthful possible, and the companies should separate flights as far as possible, and break up routes and intermediate points by relief crews, so that the time shifts will be lesser; in short, every kind of measure to care for this group of personnel whose social responsibility is extremely great.

Transcontinental Flight Passengers

In this type of individual the relative time shift between the point of departure and the point of destination must be considered. Normally, he will subjectively feel disturbance in sleep in the first 48 hours, and his eating rhythm will be disrupted; this is a very important matter in mental diseases and in connection with digestive pathology or diabetics. The recommendation to be made to such people is that they try to follow the rhythm of their clock with gradual apaptation to a new time system and nothing else, since in 8-10 days they will be completely adapted to the new time system. The problem is greater with diabetic patients, since the relationship between exogenous insulin and glycemia is greater in the morning because of the varied effectiveness of insulin.

Preparation for travel should be exhaustive with this type of patient, going as far as prohibiting labile diabetics unaccustomed to flight from making this type of flight, since the emotional stress caused by flying, added to the time shift, will exaggerate their illness.

In regard to patients under corticoid mediation, let us recall the fact described by Dr. Di Raimondo [45], that a single dose of

prednisone or of another corticoid, administered in a single dose between 0800 and 1000 hours, depresses the hypophysis less than dividing it into doses every six hours, while in the opposite case, when it is desired to check the hypophysis as in the adrenogenital syndrome, the most suppressant administration is the one given at 1400 hours.

Astronauts

Even though the opposite would be expected, the problem of circadian rhythmicity in astronauts is of minimal importance. This is due to the semiautomatic nature of manned flights, which allows a pre-established rhythm to be maintained during the flight. Thus, the Russians follow a time rhythm in their capsules similar to that which they had on earth [46, 47].

The crew of the "Voskhod", made up of three astronauts, was trained so that there would always be two awake and one asleep, advanced training for which is a simple matter.

The Americans Copper and Conrad in GT 5 slept at the same time, corresponding to night at Cape Kennedy [48].

During the "Apollo" flights to the moon, they suffered disturbances in their rhythm caused by the light-dark rhythm, with the advent of flight fatigue which the astronauts refer to as "the most disagreeable experience of the flight" [49].

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