Biological rhythms of functions of immune system and possibility of their regulation in patients with malignant tumours (The review of published and authors' own research data)

I.F.Labunets[1,2],Yu.A.Grinevich[2]

[1]Institute of Genetic and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine, Kiev

[2]National Institute of Cancer of the Health Ministry of Ukraine, Kiev

Classification of biorhythms, their regulation in normal and tumour organism

Rhythmicity of the organization of physiological processes in time – the important property of living organisms [4,17,29]. Biological rhythms with the periods which are close to certain geophysical constants (circarhythms), have internal nature, relative stability of the period and are capable to "capture" by external fluctuating factors [4,17,47]. Among such external factors as light exposure, temperature, a geomagnetic field and humidity the photoperiod has the most stable synchronouzing properties in the relation of circadian (daily) and circannual (seasonal) rhythms of functions of some organism's organs and systems. If circadian rhythms provide fast adaptation of organism functions to changing of day and night, circannual – control of potential possibilities of functions and processes of a differentiation [9,15].

The monitoring system of circarhythythms includes three key components: 1) the central "clock" – pacemaker, a generator of rhythms; 2) afferent way defining the last according to astrophysical time; 3) efferent way in which signals are transferred from central "clock" to peripheral organs where are peripheral oscillators; the expression of the last is coordinated with influences of external synchronouzing factors [4,48].

Function of the basic driver of biorhythms in an organism carry out suprachiasmatic nucleus (SCN) of hypothalamus, receiving the information about conditions of external illumination through retinohypothalamic tract according to which it is modulated their pacemaker activity and changes an expression of "clock" genes (Per1, Per2, Per3, Cry1, Cry2, Clock, Bmall|Mop3, Tim) [29,59]. From SCN of hypothalamus the transformed signals arrive in the centres of this organ in wich influence on the activity of lymbic structures, peripheral endocrine glands, first of all adrenal cortex.

In control of biorhythms functions of organism hypothalamic SCN cooperate with other structures of a brain among which the predominating place occupies epiphysis (pineal gland) [39,66]. Epiphysis regulates of biorhythms thanks to rhythmic synthesis and secretion of the basic indole hormone melatonin. These processes are diminishe on light and amplify in a dark phase of days. Melatonin production raises also with photoperiod shortening, thereby confirming its participation in mechanisms of seasonal reorganisations of some functions of an organism [2,72]. Melatonin joins in functioning SCN of hypothalamus on a feedback mechanism, influencing through the receptors, density and affinity which in these nucleuses change during days, raising in the dark [29,46]. It was shown link of melatonin with oscillators in peripheral tissues in which are “clock” genes [1].

At tumour growth the changes of interactions basic components circarhythms can be connected with their morphophynctional disturbances [2,18,41,42,51]. At tumours the disturbances of SCN hypothalamus and pinealocytes structure are combined with changes in levels accordingly the biogenic amines and melatonin [1,27]. Decreasing in melatonin level at tumoral process is caused by falling of its synthesis in pineal gland as a result of reduction of key enzymes activity, amount of pineal β-adrenoreseptors and/or their sensitivity to stimulation of noradrenaline, with a disbalance neuromediators in a brain and changes of metabolism of this hormone [18,71]. In turn, it is proved that suppression of melatoninsynthesing function of

pineal gland accelerates development of tumours whereas its increasing or introduction exogenous melatonin influencing the opposite manner [1,7,41,55]. Melatonin synchronouze the changed amplitude and a phase of rhythms of some functions in animals with tumours. Such changes are accompanied by increase of duration of their life, reduction of weight of a tumour, antimetastatic effect [63].

At development of tumours disturbances of control by expression melatonin of "clock genes" in peripheral tissues can promote its growth [1,34,69]. So, mice with a mutation of gene Per2 are more inclined to spontaneous cancerogenesis, and decreasing the expression of genes group Per connected with apoptosis, leads to uncontrollable proliferation of cells and DNA damages.

Thus, at tumoral process the results of disturbances of functioning the basic components of the monitoring system of biorhythms organs and systems can be desynchronozing the last. To one of the organism system which functional normal state is subordinated to rhythmic fluctuations, is immune system.

Biorhythms of functions of the central and peripheral links of immune system in healthy and oncological patients

Healthy people. It is known that for functioning of a peripheral link of immune system young healthy people are peculiar circadian and circannual rhythms [35,45,56,58,64]. So, in peripheral blood of young healthy people at night increase the amount of lymphocytes, their T- and B-populations, CD4+-lymphocytes, shift in balance of T-helper first and second types towards the first is observed, levels such cytokines as interleukin (IL)-1 β, IL-2, a tumour necrosis factor - α, granulocytes-macrophage coloniestimulating factor, interferon (IF) - γ grows. During day time the amount of granylocytes, natural cell-killers (NK), CD8 +-limphocytes, the basic classes of antibodies (Ig) and IL-6 raises. Within days values of indicators of metabolic activity of lymphocytes peripheral blood change. It is shown that in blood of young healthy people the amount of T-limphocytes and T-helpers grows in the

summer and autumn, T-supressors in the winter, B-limphocytes and IgG in the autumn-winter period of year.

In turn, dependence of functioning of immune system from the influence of hormones of its central organ thymus [3,16,36,37] is proved. In particular, it is shown that thymic serum factor (TSF) or thymulin which is a highly active hormone of this gland, influences all stages of differentiation T-limphocytes, activity of their regulatory subpopulations, activity of macrophages, NK etc. [13,16,57]. Changes of thymulin level in blood of animals and the person within days [61] are established. Moreover, are received the data that rhythmic changes of functions of immune system first of all reflect features of intersystem mutual relations [31,33].

Therefore we investigated in young healthy people communication circadian and circannual rhythms of TSF level, on the one hand, and indicators of peripheral immune system state, with another [14,20,21,23].

Level of TSF in blood of people (log2 titer) estimated on a method [40]. In peripheral blood defined the amount of T - and B-lymphocytes, T-lymphocytes with supressor and helper functions, content of Ig classes M, G, A, and also IF and IL-1 β [11,13,23]. Degree of a maturity circulating in blood T-lymphocytes judged on their sensitivity in vitro to thymic biologically active factor "thymostimulin".

It has been established that in young healthy people endocrine function of thymus is activated at night and weakens in day (fig. 1). Level of blood FTS fluctuates as well within a year, making accordingly in the spring, in the summer, in the autumn and in the winter 3,8±0,6, 4,7±0,3, 5,2±0,3 and 3,3±0,3; thus in the autumn the hormone content above, than in the winter and in the spring, and in the summer - than in the winter ($p < 0,05$) [21,23,52].

It appears that increasing of blood level TSF at night is combined with growth of amount T-lymphocytes, and in the autumn - with quantity increase T -, B-lymphocytes, concentration IgG and decrease in number T-supressors [14,23]. Thus at

all times year circulating in blood T-lymphocytes were "mature" and not sensitive in vitro to “thymostimulin”.

So, at young healthy people biorhythms of indicators cellular and humoral links of immune system are interfaced to features of rhythm in level blood thymic hormone.

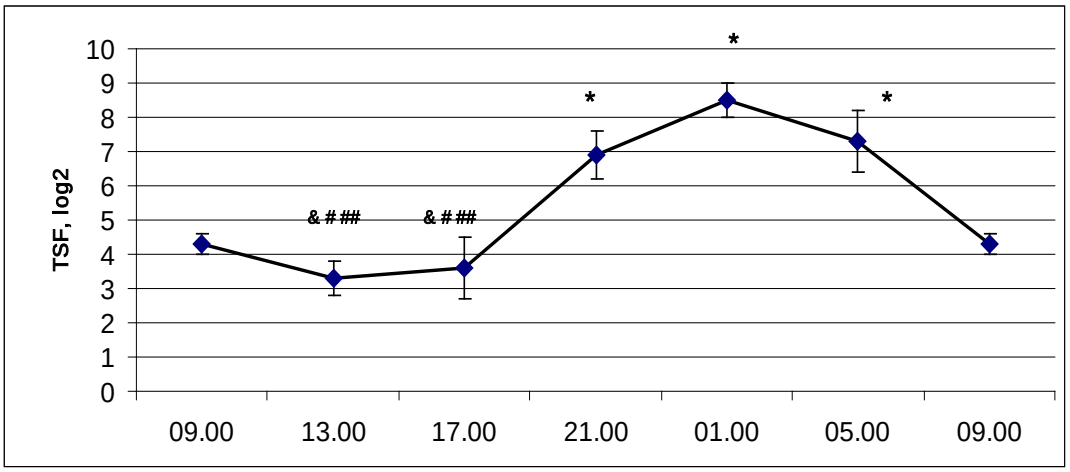

Fig. 1. Circadian rhythm of level thymic serum factor in blood of young healthy people (M ± m) [20,21].

* - P <0,05 in comparison with 9.00; # - P <0,05 in comparison with 21.00;

- P <0,05 in comparison with 1.00; and - P <0,05 in comparison with 5.00.

Oncological patients. From the literature data it is known that at tumour growth circadian rhythms of blood lymphocytes and their T-populations are broken, and seasonal variations in growth of tumours are substantially connected with degree of expressiveness of dysfunction of immune system [5,28,62]. As in oncological patients disturbances of a functional state immune system are formed at level of its central organ thymus [13,16], it is obviously important to reveal the link between desynchronouze of thymic endocrine function and functioning of peripheral immune system.

Circadian rhythms of indicators of immune system state are studied in patients with cancer of _esophagus and cardia (CEC) stages T2-4N0-3M0-1 of both sexes at

the age from 50 till 73 years [25]. Blood for researches took from patients with an interval 12 hour: at 9.00 and 21.00. The period for research - October-November.

Curcannual rhythms of indicators are studied in patients at the age from 20 till 40 years: in men and women with melanoma of a skin (MS) of stage T1-2N0M0, thymoma and cancer of stomach (CS) III-IV stages; in women with not metastatic form of chorioncarcinoma uterus (CCU); in the men with breast cancer (BC) of stage T3-4N0-1M0 [21,23,54].

Besides, patients with pretumoral diseases of the same age have been surveyed: men with hynecomastiya (HM) and women with chorionadenoma (CA) [23].

Blood for researches took from patients in the morning (9.00-10.00) at various times year (spring, summer, autumn, winter).

In oncological patients with CEC the associativity of features of disturbances of daily fluctuations thymic endocrine function, on the one hand, and the amount in blood of T-lymphocytes and IgG, with another [25] is established. Thus, in oncopatients with a monotonous rhythm of TSF titer the increasing at night of amount T-lymphocytes and decreasing in concentration IgG it was not observed.

Disturbances of circannual fluctuations TSF titer at oncopathology are characterised by monotony (MS, thymoma, BC) or displacement seasonal акрофазы (CCU) that is combined with decreasing in level of a hormone during separate seasons of year in relation to healthy people (fig. 2). The monotony combination of thymic endocrine function with its decreasing is characteristic also for patients CS and CA [23].

It appears that features circannual fluctuations of T-limphocytes amount in peripheral blood of oncopatients in many respects remind those of thymic hormone level. So, in patients with MS and CS, unlike healthy people, number T-lymphocytes decreases in the autumn, in patients with CCU the seasonal peak of values of an indicator is displaced for the spring, and at BC and thymoma fluctuations of the last

become monotonous [23]. Change of seasonal fluctuations of amount T-lymphocytes in blood is registered already at pretumoral diseases (CA) [23].

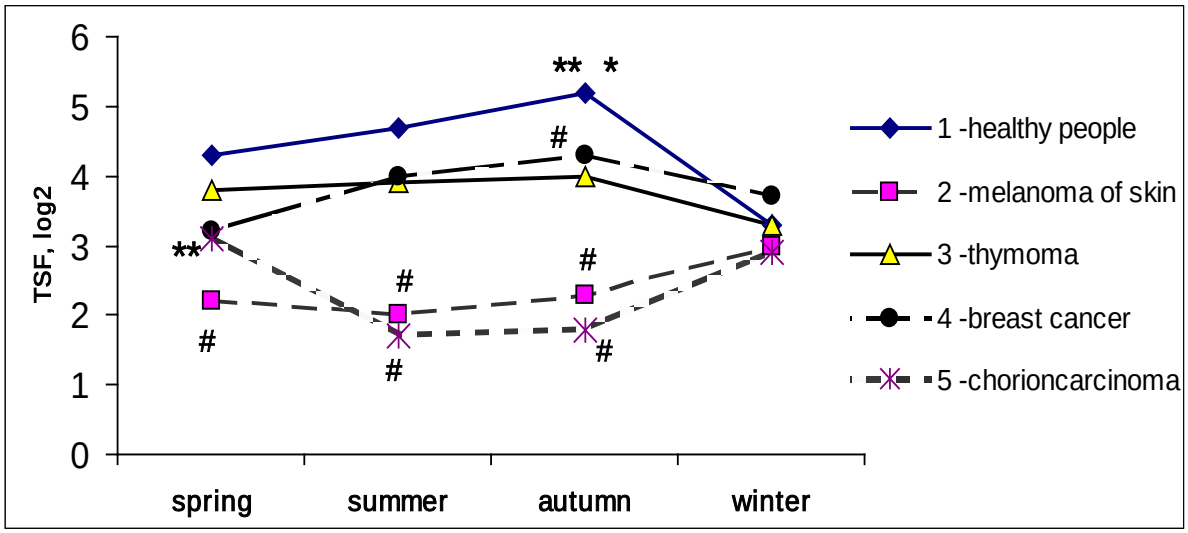

Fig 2. Circannual fluctuations TSF titer in blood of oncological patients and healthy people [21,23,54].

* - P <0,05 in comparison with winter; ** - P <0,05 in comparison with summer;

- P <0,05 in comparison with healthy people in the same season

Results of our chronobiological researches, and also the given literatures testifying to change of sensitivity T-lymphocytes to influences of thymic hormones at pathological conditions [32], were the precondition to studying of its seasonal features in oncological patients. Under our data, seasonal reaction T-lymphocytes of peripheral blood of oncopatients on action of thymic factors in vitro is perverted [23]. If in healthy people the amount of T-lymphocytes does not change after incubation in vitro with thymostimulin, in turn, in group of oncopatients with the same number of T-lymphocytes during separate seasons of its value after incubation with thymic factor decrease (BC- in the autumn) or raise (MS - in the winter, CS - in the summer). In sick CA T-lymphocytes on incubation with thymostimulin during the autumn period of year practically do not react, despite sharp decrease in their amount.

The amount of teophilynsensitive cells among which, as it is known, prevail T-supressors, does not change within a year in blood of patients CCU; in case of preservation at MS character of rhythm of this indicer increasing of its values in the winter against autumn was intensive, than in norma that was accompanied by increasing in a seasonal difference of amount T-supressors from 1,3 times to 1,9 times [11,23].

Against changes of amount B-lymphocytes in blood oncopatients we observed monotony of fluctuations of an indicer (MS, CCU, BC), displacement its seasonal acrophase (thymoma) or rhythm inversion (CS) [23]. In oncopatients, unlike healthy people, the steady tendency to decrease in concentration IgG in the winter and absence of changes of level IF and IL-1β during a year [23] is marked.

Results of the analysis combinations of disturbances circannual rhythms of investigated immunological indicers testify that in all groups oncological patients there are signs intersystem desynchronoses which take place, on the one hand, between indicers of a peripheral link of immune system, with another - the last and thymic hormone (tab. 1).

Table 1. A combination of disturbances of circannual rhythms immunological indicators in patients of oncological profile [23].

Combination of disturbances of a rhythms indicers	MS	Thymoma	CCU	BC	CS
TSF and T-cells	(+)	(+)	(+)	(+)	(+)
TSF and IF, IL-1β	N.a.	(+)	N.a.	N.a.	N.a.
TSF and T-supressors	(+)	N.a.	(+)	N.a.	N.a.
TSF and B-cells	(+)	(+)	(+)	(+).	N.a.
T-cells and their reaction to thymostimilin	(+)	(–)	(+)	(+)	(+)
B-cells and Ig G	(+)	(+)	(+)	N.a	(+)

(+) - is in certain seasons; (-) - is absent in separate seasons; N.a. - did not analyze

It was shown the influence of thymic hormones on those processes in cells of immune system (migration, proliferation, differentiation), circadian relations of which define the maintenance lymphocytes in lymphatic organs and in circulation [13,33]. Presence in oncopatients correlation between fluctuations TSF titer and amount T-lymphocytes including with regulatory functions, suggests that their rhythms at malignant tumours are interconnected. Moreover, in realisation of action of thymic hormones on T-lymphocytes are important not only time of their introduction, but also synchronisation of a rhythm of hormones production and sensitivity lymphocytes to their influence that can be connected with recurrence of an expression on T-lymphocytes corresponding receptors [32]. Disturbances of mutual relations of biorhythms of level in blood thymic hormone and seasonal sensitivity T-lymphocytes to its influence is characteristic for patients both with tumoral, and with pretumoral diseases.

In an organism thymic hormones supervise variety synthesis cytokines which represent itself as mediators of many immunological reactions and, in turn, are subject to rhythmic changes [64]. Antineoplastic properties of IF are well studied [8,16]. As changes of levels IF and TSF at some kinds of oncopathology positively correlate among themselves, and thymic factors are capable increasing interferonogenesis at tumoral process, we believe that thymic endocrine function desynchronouses and level of its mediators in oncopatients are interconnected [16,23].

From the literature it is known about influence of thymic hormones on differentiation T-lymphocytes in bone marrow and their interaction with other cells of immune system at realisation of the immune answer, and also about ability the thymic factors to restore the lowered level of antibodies in blood of people and animals with an immunodeficiency [6,16]. In our experiments it was shown the possibility of thymic factors to restore of broken circannual rhythms of antibodies formation that, apparently, is connected with adequate seasonal formation of T-supressors in such conditions [19]. Really, MS patients at desynchronouses of thymic

endocrine function we observed considerable strengthening of seasonal scope of fluctuations of amount T-supressors in blood oncopatients. As it is established, not only decrease, but also increase of amplitude of rhythms is interfaced with decreasing adaptable possibilities of an organism [17].

Thus, at patients with tumours of various genesis disturbances of biorhythms of FTS can be carried function of one of important pathogenetic mechanisms of changes of rhythms cellular and humoral links of immune system. Possible mechanisms of communication of dysfunction thymus and changes immunological indicers at tumoral process are in detail analysed in the review [13]. In turn, desynchronouse of thymic functional state at tumoral growth can be connected with disturbances of intersystem relations of this gland with functioning of other endocrine glands [16]. Unlike them, thymus carries out not only endocrine, but also cytocrine functions. A particular interest represent relations of rhythm thymiko-lymphatic system functional state with such components circadian systems as pineal gland and adrenal glands'cortex.

Role of pineal gland and adrenal gland cortex dysfunction in endocrine mechanisms intraimmune desynchronouse in patients with tumours.

Biorhythms of pineal gland and adrenal gland functions in oncological patients. By authors it is noticed that the night peak of concentration melatonin blood in healthy people decreases at a number of malignant tumours (BC, CS, cancer of thyroid gland, lungs and prostatae) [18,41]. Thus expressiveness of decreasing in level of hormone correlates as with the clinical current of disease substantially depending on its stage, biological properties of a tumour and its localisation, and with life expectancy oncological patients. At initial stages of tumoral process and the rather well differentiated tumours melatonin level in blood and urine can not deviate from normal indicers.

The pineal gland a considerable part of its influences in an organism realises through hypothalamus-hypohys-adrenal cortex system which hormones are extremely

important for development of adaptable reactions of an organism [10,44,49,66]. Development of hypercortisism at tumoral process it is combined with disease progressing, appearance of recidives and metastasises [11,16]. The individual given literatures testify to monotony circadian rhythm cortisol level in blood oncological patients whereas in young healthy people concentration of hormone raises in the morning, and reaction of the last to influence АКТГ changes within days [16,49].

We not only have established the facts disturbances of circadian and circannual rhythms pineal gland and adrenal glands cortex in oncological patients, but also have shown presence of their interrelation [21,23,25]. Melatonin level in blood of people defined radioimmunoassay, using kit “Melatonin-125” (firms Biosource, Belgium and DRG, USA). The content cortisol in blood investigated radioimmunoassay (kit “CORTCTK-125”, firms Cea-Ire-Sorin, France-Italy) and immunopherment (kits “IFACortisol”, "Biotehnol" of firm Hema, Russia) methods.

It is established that in young healthy people concentration of melatonin in blood starts to raise in the evening and essentially grows at night (fig. 2) whereas at healthy people more 50 years the difference between day and night values of this indicer decreases to 2 times (p <0,05) [20,21,26].

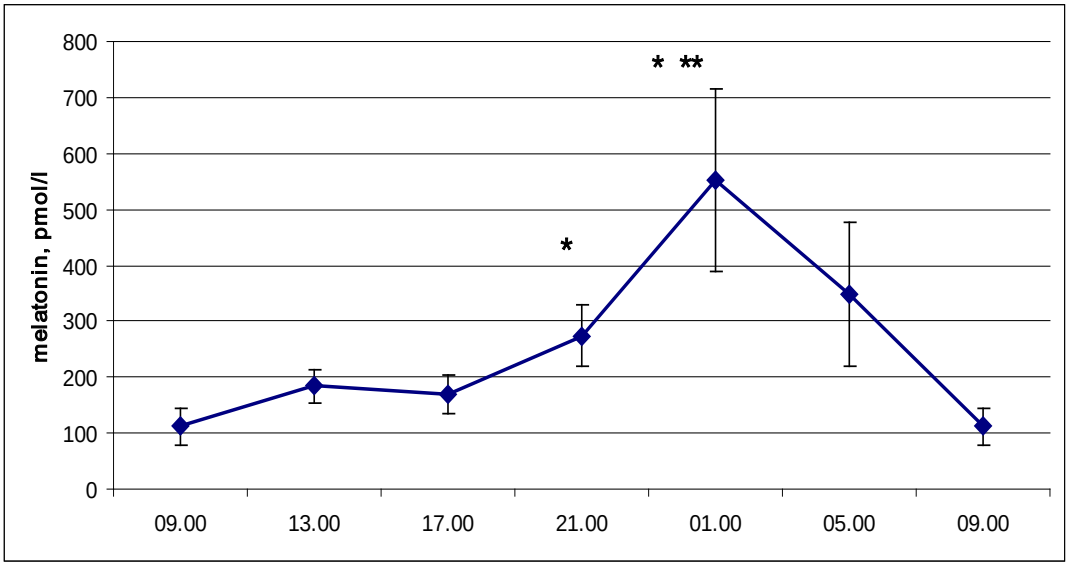

Fig. 3. Circadian rhythm of melatonin level in blood of young healthy people [20,21]: * - P <0,05 in comparison with 9.00; ** - P <0,05 in comparison with 17.00

In patients with tumours the changes of circadian rhythms melatonin blood level are shown differently (fig. 4) [21,25]. So, it is shown that at the majority of surveyed patients CEC hormone blood level does not raise at 21.00 in relation to 9.00, and in some cases was even more low in the evening, than in the morning (patients with the monotonous or inverted rhythms of a hormone). In a part of patients, despite increasing melatonin concentration at 21.00, its values were more low, than in age control. Thus activation pineal gland function in the evening we observed mainly in patients with II stage CEC, whereas its absence - in patients with III-IV stages of disease [25].

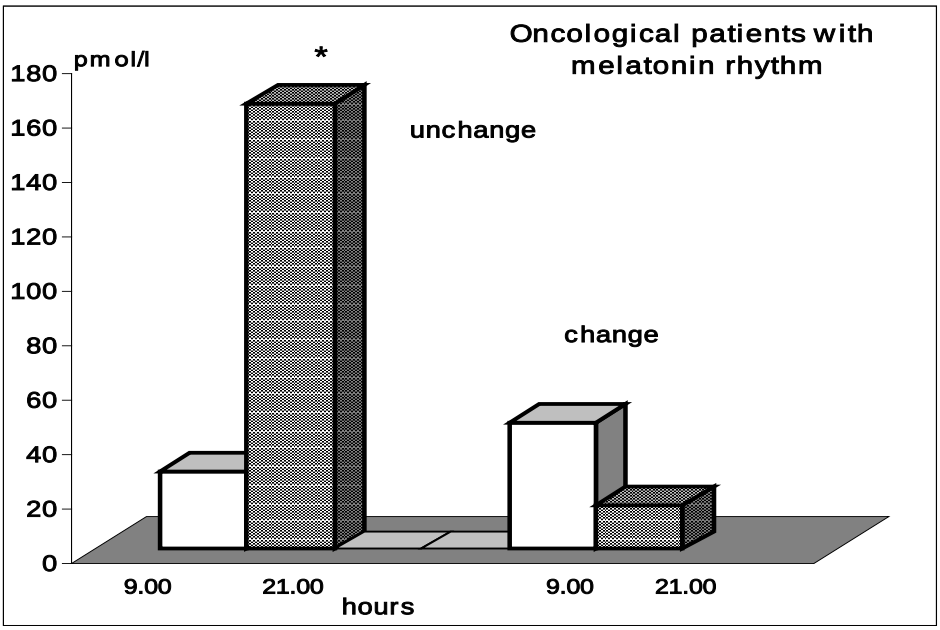

Fig. 4. Concentration of melatonin in blood of patients with CEC depending on time of days [25]:

*-p <0,05 in comparison with morning

The analysis dependence of features circadian rhythms of cortisol level in blood patients with CEC from character of dysfunction pineal gland has allowed to establish the following. In case of monotony or inversion circadian rhythm of pineal gland function scope of daily fluctuations of cortisol level was considerably above (18 times), than in patients with activation pineal gland function in the evening (8 times)

and in persons of group of age control (3 times). It can specify on formation in such patients a bark of adrenal glands cortex function, it is probable as a result to development of chronic stress [10,21,25]. Thus in oncopatiens increasing of a daily difference was observed basically as a result of growth of morning values of this indicer.

At research circannual rhythms pineal gland function it is established that the winter peak of concentration melatonin blood level peculiar for healthy people decreases in all surveyed groups oncopatients (tab. 2) therefore in the majority of patients seasonal fluctuations of level of a hormone become monotonous, and at patients CS its maximum values are displaced for the spring [23,50,53]. Earlier by us in patients MS monotony seasonal excretion with urine 6-oksisulfatmelatonin [12,54] is shown. In the men sick HM activation pineal gland function is absent in the winter, and melatonin blood level was more low, than in healthy people.

Table 2 Concentration of melatonin in blood of oncological patients and healthy people depending on a season of year (pmol/l) [23]

Group surveyed	The season of year			
	Spring	Summer	Autumn	Winter
BC	153,9±30,9 (8)	149,5±47,7 (4)	113,0±16,3 (4)	117,4±41,1*** (4)
CS	301,9±88,2**,*** (6)	131,5±36,3 (5)	99,7±18,9 (6)	147,5±46,0*** (4)
Thymoma	143,6±43,3 (7)	–	116,1±29,7 (7)	103,2±45,4*** (7)
CCU	–	–	128,7±12,0 (5)	90,7±35,2*** (4)
Healthy people	96,5±24,8* (14)	96,2±21,2*(15)	132,9±36,4* (11)	253,7±11,2 (9)

* - statistically differs from winter, p <0,05; ** - statistically differs from autumn, p <0,05; *** - statistically differs from healthy people in a similar season, p <0,05.

Immunnoendocrine interrelations in oncopatients. One of the mechanisms oncostatic effect of melatonin is connected with its immunomodulatory action substantially mediated by normalisation of zinc balance and thymulin level, activation hemapoesis [1,60]. Strengthening melathoninforming pineal gland's function in animals with the transplanted and chemically induced tumours brakes their development that is observed withh simultaneous activation endocrine function of thymus [38]. According to D. P. Cardinali and al. [43], thymus is a primary target organ for melatonin action.

At surveyed by us in oncopatients for formation of disturbances of biorhythms of functions thymus and a peripheral link of immune system has great value change not only rhythms melatoninforming pineal gland function and adrenal gland cortex function, but also character of their mutual relations; in process of distribution of tumoral process of display intersystem desynchronouzing amplify [21,23,25]. So, activation of thymic function in patients CEC in the evening (titer TSF at 9.00 and 21.00 has made accordingly 4,0±0,6 and 5,6±0,5, $p < 0,05$) is observed only in case of increasing at this time the concentration of melatonin blood. At monotony or inversion of a rhythm of pineal gland function rhythm of endocrine thymic function also was monotonous (TSF titer in the morning and in the evening was according to 5,3±0,8 and 4,8±0,5, $p > 0,05$).

It is shown that melatonin is capable to influence directly synthesis and secretion of hormones by thymus, in epithelial cells of which are found out highaffinity receptors to this hormone [43,67]. We in experiment registered increase of TSF level in supernatant cultivated in vitro thymic stroma after addition to it of physiological concentration of melatonin [22]. The mediated way of influence pineal gland on thymic endocrine function, through change of hypothalamus-hypophis-adrenal gland cortex system functioning [49,65,68] is possible also. So, glucocorticoids in high concentration make suppressing impact on endocrine function of thymus, operating through receptors in epithelial component of organ [16,68]. In condition of short-term

hypocortizism efficiency of using thymic preparations [11,16] raises. At the same time it patients CEC surveyed by us with inversion of daily rhythm of pineal gland function and the raised morning blood cortisol level TSF titer practically did not differ from age control. Absence of suppressing influence of surplus of glucocorticoids on thymic endocrine function can be caused either short duration hypercorticizm, or change of amount and/or sensitivity to them of receptors in cells of this gland which fluctuations of an expression, in turn, is controled by melatonin [67].

It is known that at aged people after 40 years frequency of a tumours increase each next 5 years [30]. In connection with this data attracts attention the fact received by us, testifying that in oncopatients at the age of 20-40 years the feature of immunoendocrine relations remind a picture in healthy people of advanced age [21,23]. So, in patients are younger 40 years seasonal peak of concentration of melatonin is observed in the spring, instead of in the winter as in age control, and thus exceeds values in healthy people of the same age. The rhythm of FTS titer, unlike age control, becomes monotonous, and amount T-lymphocytes - inverted with the highest values in the spring. This data suggests about possible acceleration in oncological patients age changes circannual rhythm of functions pineal gland, thymus, and also values immunological indicers. Results of researches in oncological patients younger than 40 years the changes of seasonal reaction T-lymphocytes of peripheral blood on regulatory influences by thymicfactors also confirm such possibility. We observed similar changes of intersystem interactions in experiment when in old animals reaction of thymocytes on fluctuations of TSF blood level [21] changed.

Prospects chronobiological researches of immunoendocrine interactions in oncology.

Taking into account the data of the literature and results of own works carrying out of similar researches important in following aspects.

First, the account of biorhythms of immune and endocrine systems' functions can appear useful at diagnostics, working out of criteria of the prognosis and

allocation risk factors development of malignant tumours or appearens of recidives and metastasises after carrying out of the basic treatment. It is connected by that at pathological conditions the earliest disturbances of an organism functions mention their chronobiological structure and are registered already before occurrence of clinical signs of disease [18,33]. As by us it is established, the rhythms of functioning pineal gland, thymus, amount of T-cells and the answer of the last to influences of thymic factors differs from healthy people already at pretumoral diseases, and formation of melatoninforming pineal gland dysfunction has advancing character [21,23].

It is not excluded that in some cases the absence in oncological patients the changes in immulogical and endocrinological indicers from norm it is possible to explain absence of accurate methodical approaches for their estimation. So, it is shown that at some kinds of a pathology of values of these indicators, received only in the morning, did not differ almost from norm [32,33]. At the same time in the evening values of indicers change in relation to healthy people that can testify about changes of amplitude of their daily rhythm. Therefore for objective estimations of functions immune and endocrine systems in oncopatients, allowing to reveal presence of disturbances, expedient research of their circadian rhythm (at least in the morning and in the evening), and not only the fixing of morning values of an indicers.

Secondly, the estimation of an orientation of influence immunomodulating agents on immune system functions of oncological patients should be spent taking into account a season of year. Thus it is necessary to take into consideration possibility of existence of perversity of seasonal reaction lymphocytes on their influence during separate seasons.

Thirdly, the account circadian and circannual rhythms of proliferative activity lymphoid and bone marrow cells [19,28] so also their sensitivity to damaging action chimio - and hormonetherapy, will allow to personalise modes of the last.

And, at last, as pharmacological agents, restored at tumoral process not only functions of immune system as preparations thymic origins [11,13,16], but also their changes rhythms, can be used the pineal factors. The last change a phase and/or amplitude of rhythms, regulate fluctuations of an expression of receptors to hormones on lymphocytes, realise the synchronising influence on immune system through its central organ thymus, cooperating thus with a cortex of adrenal glands [1,2,11,21,39,66,67]. With the similar mechanism of action are melatonin and pineal peptides (epithalamine, epithalone) which raise the melatonin content in an organism [1]. Therefore the preparation of pineal gland as synchronising agents can be applied independently or in a combination with basic methods of treatment of oncological patients which not only lead to the further decreasing endocrine thymic function and to disturbances of a peripheral link of immune system, but also promote appearence or strengthening desynchronouses immune and endocrine systems functions [13.24].

As, under our data, in oncological patients character of fluctuations the indicers of immune and endocrine systems state in many respects reminds that in healthy people more advanced age, schemes of introduction of pineal gland preparations should be based on age features of system sensitivity to their influence [21]. Efficiency using of similar approaches is already proved at treatment by melatonin and pineal gland peptides of desynchronouses immune and endocrine systems connected with disturbances of interrelations of functioning thymus, pineal gland and adrenal glands cortex, in patients with cardiovascular diseases [21].

The conclusion

Thus, in the literature review argument the importance of using in the plan of the basic treatment oncological patients the pineal gland preparations under the optimised schemes that will promote improvement intra- and intersystem interactions, and as the result, can essentially raise its efficiency is proved. As synchronousing agents preparations of pineal gland will be effective for preventive maintenance of recidives and metastasises in oncological patients after carrying out of basic treatment and also

at primary preventive maintenance of oncological diseases in groups of risk, people of elderly and senile age with signs desynchronouse functions immune and endocrine systems. Pineal gland preparations also can be useful in oncological practice at using in a combination with preparations of thymic origins in adjuvant regiment. For maximum efficiency this immunotherapy should be carry out in the evening, courses (twice during year), with estimate its influences dependently from season of year.

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