Light & Engineering
Vol. 27, No. 3, pp. 14–25, 2019
https://doi.org/10.33383/2018-120

LIGHT DESYNCHRONOSIS AND HEALTH

Vladimir N. ANISIMOV

N.N. Petrov National Medical Research Oncology Centre of the Ministry of Health of the Russian Federation, St. Petersburg, Russia
Email: aging@mail.ru

ABSTRACT

The review summarizes the modern knowledge of the impact of day-night, light-darkness rhythm disorders on the aging process and on the risk of development of the age-related conditions. Significant evidence has been obtained of that the constant artificial illumination and the daylight of the North has a stimulating effect on the occurrence and development of tumours in laboratory animals. It has been shown that long-term shift work, trans-meridian flights (jet-lag) and insomnia increase the risk of cardiovascular diseases, diabetes mellitus, and malignancies in humans. Particular attention is given to the studies where the relationship between light intensity, light wavelength and its ability to suppress the synthesis of melatonin produced at night in the pineal gland, are investigated. It has been established that melatonin synthesis is most effectively suppressed with blue light sources of a wavelength from 446 to 477 nm. The use of exogenous melatonin prevents premature aging of the reproductive system and the body as a whole prevents the development of immune-suppression, metabolic syndrome and tumours caused by light pollution. An urgent task is to develop recommendations for optimizing the illumination of workplaces and residential premises, of cities and towns as a prevention measure for premature aging and age-related pathology, which, ultimately, will contribute to the long-term maintaining of performance and improving the quality of life.

Keywords: night light, light pollution, circadian rhythm, melatonin, aging, cancer

1. INTRODUCTION

The most vital phenomenon of nature on the planet Earth is the alternation of day and night, light and darkness. The axial rotation of our planet, and at the same time, around the Sun, measures the days, seasons and years of our lives. We accumulate the knowledge increasingly regarding the role of the pineal gland as the main pacemaker of body functions. Light inhibits the synthesis and secretion of melatonin hormone in the pineal gland, and therefore the maximum blood level of this hormone in humans and animals of many species is observed at night, and the minimum level – during daytime hours. The convincing data regarding circadian rhythm gene expression violation during aging has emerged in recent years [1]. It is significant that with aging, the activity of the pineal gland is reduced, which is seen, first of all, by a rhythm disturbance and a decrease in melatonin secretion level [2]. If the epiphysis can be considered as a biological clock of the body, then the melatonin can be considered as a pendulum that runs these clocks; the decrease in the amplitude of the pendulum causes the clocks to stop. Perhaps it will be more accurate to compare the epiphysis with the sundial, in which melatonin plays the role of a shadow from the ancient astronomical instrument, i.e. the gnomon – a rod casting a shadow from the sun. In the afternoon the sun is high, and the shadow is short (the level of melatonin is minimal), and in the middle of the night, there is a peak of melatonin synthesis and its secretion into the blood from the pineal gland. At the same time, it is important that the melatonin is synthesized in a daily rhythm, i.e. its measuring unit is the chronological metronome, namely, the daily rotation of the Earth around its axis [3]. If the pineal gland is the body's sundial, then, obviously, any changes in the length of daylight should have a significant impact on its functions and, ultimately, on the aging rate. The circadian rhythm is essential not only for the temporal organization of the physiological functions but also for the human life expectancy. In a number of works, it has been shown that the violation of photoperiods can lead to a significant decrease in the life expectancy of animals [4, 5].

2. EFFECT OF LIGHT ON THE SYNTHESIS OF MELATONIN BY THE PINEAL GLAND IN HUMANS AND ANIMALS

Day and night (light and dark) is the main synchronizer (*Zeitgeber*) that regulates melatonin synthesis in the appendage of the brain – the pineal gland (epiphysis). The endogenous rhythm managing the synthesis and secretion of melatonin is adjusted to the duration of night-time in various mammalian species, regardless of whether they are of nocturnal or daytime habits [6–9]. In people who are active throughout the day, the high melatonin concentration and excretion in epiphysis are observed over the night. In addition to its effect as a circadian clock adjusting agent, the light acts as a masking factor when the body is exposed to light during the usual light phase of the day. The photoreception system involved in the regulation of clocks is different from the pattern recognition system. The daily change of light and darkness adjusts the endogenous circadian clock in the special brain structure – the hypothalamus – to the astronomical duration of the day (24 hours). The congenital period of the hypothalamic clock is slightly longer than 24 hours. Retinal receptors containing photo pigment constitute about 1 % of retinal ganglion cells and directly respond to light, acting as a synchronizer to the hypothalamic suprachiasmatic nucleus. The photo-pigment is melanopsin, an opsin/vitamin *A* complex with a blue spectrum sensitivity peak at 480 nm [10]. The radiation effect of different wavelength on melatonin synthesis in epiphysis was investigated, as it was found that melatonin synthesis is suppressed in a rather wide range of wavelengths, from 420 nm up to 600 nm, but most effectively in the interval from 446 nm to 477 nm. Suppression of the nocturnal peak of melatonin synthesis by illuminance exposure (200–500) lx for 1 hour is the same for men and women and is proportional to illumination. Low illuminance (90–180) lx, which is often present in living rooms, is enough to suppress melatonin synthesis. In apparently healthy subjects, the maximum sensitivity to light is within the range of very short wavelengths (420, 440 and 470 nm) [11–14].

Photosensitivity, assessed by suppressing melatonin levels, partly depends on the subject's previous exposure to light. It increases after exposure to the dark or to the dull lighting, which suggests an adaptation of photoreceptors or a response to the previous light exposure.

It was shown in [15], that at illuminance 800 lx the use of protective glasses blocking the most active short-wavelength part of the spectrum (lower than 530 nm), prevents light-induced suppression of nocturnal melatonin content in saliva. At the same time, individuals maintain night melatonin levels similar to those under dim lighting, and subjective drowsiness, anxiety and ability to act are not disturbed. Bright light at night causes a phase shift and a switching of the circadian phase. A phase shift can be observed even with much less illumination (for example, at 180 lx, normal lighting in a residential area). Moreover, it has been shown that very dim lighting (20 lx) can synchronize the circadian system in humans, normalizing sleep, awakening, and meal times. The circadian phase shift caused by short wavelengths radiation (with two peaks at 436 nm and 456 nm) during a 4-hour exposure (8 lx, 29 $\mu W/cm^2$) after a normal awakening led to a melatonin profile phase shift comparable to that of white light (12000 lx, 4300 $\mu W/cm^2$), despite the fact that white light contains many more photons than short wavelength radiation [15].

In addition to information on turning on and off the daily photoperiod, melatonin provides information about the length of the day. Melatonin synthesis and secretion duration in animals and humans varies depending on the duration of the dark hours. The longer dark period of the day takes in the laboratory or the longer the night takes in nature, the longer melatonin synthesis and secretion – regardless of whether this period is the time of activity of nocturnal rodents or the time of rest of animals with daytime activity, including humans [6, 14]. In ordinary laboratory animals, it is not possible to increase daytime melatonin levels when placed into a dark room, but there is strong evidence of a decrease in their melatonin night time levels after exposure to the short light flashes over the night. Most mammals use changes in the length of the day and night to determine seasonal changes, thus adjusting the seasonal and/or synchronizing the near-year behavioural rhythms. Seasonal differences in reproduction are directly controlled by the relative length of light and dark periods [6, 7].

In modern urban conditions of electrification, the daylight and night time duration seasonal changes and, accordingly, the duration of melatonin secretion in humans, are obviously masked. In a number of studies, it was acknowledged that at low and middle latitudes the seasonal changes in melatonin secretion are absent. In contrast, seasonal changes associated with longer melatonin secretion in winter were observed in sub polar and polar high latitudes, with significant changes in photoperiod and illumination level, and high daytime levels of melatonin [7].

Light is the most powerful circadian synchronizer in humans and can have a prominent influence on the phase and amplitude of a human circadian pacemaker. Relatively intense illumination over the night almost completely suppresses the night peak of melatonin synthesis and secretion. Table 1 summarizes data on the extent of the blood melatonin inhibition in humans exposed to light, produced by incandescent and fluorescent lamps with different intensity. Fluorescent lamps reduce the melatonin concentration more intensively. The illumination level in residential areas rarely exceeds 200 lx. The data regarding operating rules adopted in Russia of illumination level in different facilities are summarized in Table 2. It is easy to see that the light exposure of such intensity over the night can significantly suppress the blood melatonin level.

Studies of melatonin synthesis suppression with light made it possible to calculate a threshold illumination sufficient to decrease it by 15 %, which, on illumination with white light and 30-minute exposure, is about 30 lx at the cornea level. It is important to note that in residential areas, when additional light sources are turned on with a special purpose, for example, for reading, sewing on a sewing machine or washing, the illumination at the level of the cornea can reach as much as (150–200) lx.

In the literature reports the individual variability of sensitivity to light at night hours [2] was noted: deeper melatonin suppression with brighter light, the ability of light to shift the melatonin rhythm phase, with bright light in the morning moving it forward, while in the evening it causes night melatonin peak to delay. A valuable biomarker for circadian rhythm disorders may be a quantitative measurement of the time dependence of the melatonin renal excretion level [2].

In turn, melatonin, depending on the stage of the circadian rhythm, can synchronize it and shift it to an earlier or later time. Low doses of melatonin (0.3–10) mg being administered during "biological day" when endogenous melatonin level is low, can cause drowsiness or sleep and decrease the body temperature [6]. The daytime single administration of 5 mg of highly soluble melatonin can shift the internal clock forward by 1.5 hours. The timely administration of melatonin (0.5–5) mg at 24-hour intervals, preferably before bed, can completely fine-tune the free-running circadian rhythm in most blind patients. Acting as circadian synchronizer between the central and peripheral "clocks", melatonin optimizes phases in relation to the external time, thus providing the optimization of cellular and systemic processes and enhancing the action of defence systems, which significantly expands the ranges of its possible therapeutic use.

Noteworthy, the effect of light on melatonin synthesis may depend on the season and individual sensitivity to light. In winter, the light inhibits the level of human melatonin in saliva 2 times more intensely than in summer [17]. Interestingly, the Arctic seasonal workers who worked in December in the open air demonstrated the night melatonin secretion level 2 times higher than in April [18]. Authors suggest that that the diffuse light reflected by snow in April is enough to reduce melatonin levels.

3. GEOGRAPHIC LATITUDE AND HEALTH

It is known that health and life expectancy indicators in different geographic regions can vary significantly. I.A. Gundarov and N.L. Zilbert hypothesized that there is a connection between public health indicators and such an important parameter as the location of the region relative to the equator [19]. To establish this, a geographic latitude was used as an indicator. The statistical analysis between 1986–1987 showed that mortality rate in USSR constituent republics increased almost in a linear fashion progressively from the South to the North, with a correlation coefficient of 0.82 ($p<0,01$). Even more marginal association was between geographic latitude and incidence of malignancy. According to the WHO data, the total mortality rate in 72 countries in Europe and America in 1980–1985 increased progressively with the increased distance from the equator, with a correlation coefficient of 0.65 ($p <0.01$). The value of standardized mortality from malignancies between males of 45 countries in Europe and America in 1981–1985 differed 8.7 times: from 38.1 in Honduras to 330.0 in Hungary. The relationship with geographic latitude was shown with a correlation coefficient of 0.70 ($p <0.01$). Also, a positive correlation with geographic latitude was observed for hypertension, atherosclerosis, and the incidence of hypercholesterolemia [19].

Considering that there is a long night in polar region, Erren and Pekarsky [20] suggested that the indigenous population of the Arctic region should have a reduced incidence of malignancy as compared to the residents of temperate latitudes. Indeed, the incidence of malignancies is reduced in Saami, a nationality living in the North of Europe [21]. At the same time, the mortality from breast cancer (BC) among Alaska Natives (Eskimos, Indians, and Aleuts) has tripled since 1969 – according to the authors, for an unknown reason [22]. In 2008 *Circumpolar Inuit Cancer Review Working Group* published the results of cancer study in polar Innu (umbrella term which replaced the term "Eskimo"), living in Alaska territory, in Canada and Greenland, between 1989 and 2003 as compared to the period between 1969–1988, i.e., for the total of 35 years [23]. It was noted that there is a significant increase in the incidence of BC, uterine corpus cancer, lung cancer and colon cancer, which is related with lifestyle changes of the natives due to its so-called westernization. For the period of 1974–2003, the incidence of BC in female natives of Alaska has been increased by 105 %, whereas in Caucasian females of the USA – by 31 %. In the same years, the incidence of uterine corpus cancer has increased among Alaska native females by 500 %, while among white Americans it has decreased by 30 %. The analysis showed that a significant increase in the incidence of breast and endometrial cancer in the Alaska natives can be best explained by environmental changes. The authors noted that in women of Alaska the incidence of obesity and diabetes has significantly increased for 30 years, and this increase is associated with a change in dietary habits. However, along with the westernization of food, there is a significant increase in the level of light pollution due to the doubling of the population over the same time and the industrialization, which, in our opinion, can play a leading role in the observed phenomenon. According to IARC data for 1985 and 1992, the incidence of BC, uterine corpus cancer, ovarian cancer and colon cancer in females was higher in countries located closer to the poles (North and South), and less in equatorial countries [3, 24–26].

It should be considered that the differences found (or the absence thereof) are not necessarily related to the light regimen, and therefore, with geographic latitude. It is known that the above-mentioned malignancies have multiple etiological factors. As mentioned above, features of reproductive status, excess fat, and carbohydrates in the diet, etc. play their important role in the development of female reproductive system neoplasm. Therefore, despite the character of the light regimen, it is necessary to consider climatic conditions related to geographic latitude, the extent of industrialization and lifestyle features. In general, it is not possible to state certainly that the light regimen or geographic location are the key factors of malignancies development, but this statement should not be underestimated whatsoever [27, 28].

4. SHIFT WORK: TERMINOLOGY AND PREVALENCE

Shift work is referred to as a method of arranging the work process in a duty fashion where workers change each other at one workplace in a certain sequence, in accordance with approved schedule. In addition to these definitions, in scientific literature the term "Shift work" is commonly used, and normally includes any forms of workflow arrangement different from the standard daytime work (from 7–8 a.m. till 5–6 p.m.).

According to the International Agency for Research on Cancer (IARC) [29] data, there are several types of shift work:

- Constant work – employees regularly shift only for one period, for example, morning, day or night, or rotation takes place – employees change their job shifts more or less periodically;

• Continuous work – employees work all days of the week or carry out work intermittently on weekends or on Sundays;

• Night work – working hours include all or part of the night, and the number of working nights per week/month/year can vary significantly. The period of night work may differ across countries: from 8, 9 or 10 p.m. until 5, 6 or 7 a.m., or from 11 or 12 p.m. until 5–6 a.m.

Arrangement of shift work can also vary significantly [29], and this can variously affect the health of workers, leading to circadian rhythm disturbances and important physiological dysfunctions, including insomnia.

In modern industrial society, also called "24-hour", "round-the-clock" society, shift and night work is becoming more and more common. Shift work is required in many technological processes (for example, power plants, oil refineries, and metallurgical production), social services (hospitals, transport, police and security services, fire fighting services, hotels, telecommunications), some industries and services (for example, in manufacturing of textile, paper, food, chemicals). According to the International Labour Organization, more than 2.5 million people officially have shift work, 2/3 of them located in Asia. In European countries, more than 17 % of employees are shift workers.

5. SHIFT WORK AND HEALTH

A frequent sequel of internal circadian desynchronise with external environmental rhythms is the development of various diseases. As shown in numerous studies, shift workers often develop malignant neoplasm, diabetes mellitus, peptic ulcer disease, hypertension and cardiovascular diseases, psychogenic disorders and many other diseases [4, 5, 30–34].

In all mammals, the cardiovascular system is a highly organized system in terms of timing. It was well documented in epidemiological studies that many cardiovascular pathological processes, such as myocardial infarction, stroke, arrhythmia, most frequently occur in the early morning hours, and this is the time when fatal outcomes are also more common.

In a survey covering 17 studies where the relationship between shift work and cardiovascular diseases was investigated, it was estimated that shift-working people have a 40 % increased risk of cardiovascular diseases when compared with individuals with the daytime job [32]. The duration of the shift work is also important: the morbidity was higher in those who had it for more than 6 years.

Approximately 20 % of all workers cease working in shifts shortly after the start of such working due to serious health problems, 10 % do not have any problems associated with shift work during their entire work activity, whereas 70 % are faced with certain problems of varying severity, manifested as discomfort, everyday life troubles or diseases [29]. Some individual habits and features can modify the effects that shift work has on health. For example, it is believed that there are more smokers among shift workers, they more often consume caffeinated beverages or alcohol at night, eat more sweets and carbohydrates. They are more likely to have metabolic disorders, an increased risk of cardiovascular diseases and obesity [29].

During long-distance trans-meridian flights, circadian systems do not immediately adjust to the new local time. This requires several days, depending on the number of crossed time (hourly) zones, and the more zones are crossed, the more time is needed for normalization. It is believed that human circadian systems adjust to no more than (60–90) min per day [29].

Recovery is faster during the flights to the west (about 1-day recovery for 1-hour shift) than for flights to the east (about 1.5 hours for a shift of 1-hour time zone). Full recovery after 6-time zone travel takes 10 to 13 days, depending on the direction of the flight (to the west or east, respectively) [29]. In addition, aircraft crew members are affected by other additional factors such as cosmic radiation, electromagnetic fields, illumination, noise, acceleration, vibration, psychological stress, low mobility, high atmospheric pressure [36].

Seafarers often have a rotation (shift) working during the entire trip, and they also move through time zones, although not as quickly as aircraft crews do. Merchant seamen often use a 4-hour shift rotation, although the 6-hour shift is becoming increasingly popular. For oil workers, the rotation nature of working usually includes a 12-hour work shift for several weeks, followed by a rest at home. Similar problems are observed in truck drivers, the so-called "truckers", train locomotive drivers and conductors on long-distance passenger trains.

In Japan, there was a study of the incidence of diabetes mellitus in 2,860 "white-collar workers", "blue-collar workers" with a fixed daytime job, and "blue-collar workers" in shift work. The relative risk of diabetes in shift workers was 1.33–1.73 times higher than in "daytime blue collars" and 2.01 times higher than in white-collar workers [37]. In shift "blue collars" body mass indices and cholesterol level were significantly higher than in daytime workers [38].

In [39], it was shown that shift work contributes to an increase in the incidence of GI disorders in car factory workers. Sleep disturbances reported in shift workers play an important role in the higher incidence of peptic gastric and duodenal ulcers in this population [40]. There are findings indicating a significant increase in the risk of duodenal ulcer development in shift workers infected with *Helicobacter pilori* [41].

The exact mechanisms of cardiovascular diseases development in shift workers are not completely understood, although circadian rhythm disorders and concomitant factors like smoking, irregular diet, and social issues are considered to play a key role, causing usual stress in shift workers [29, 42].

Desynchronisation of circadian clocks that can be caused by shift work, leads to hypertension, dyslipidemia, insulin resistance and obesity [29]. The serum level of total cholesterol and low-density lipoproteins in shift workers was significantly higher as compared with the controls, i.e. those working in daytime, which allowed shift working to conclude in a risk factor for employees.

Glucose tolerance has fluctuations from day to day, and the observed variability is due to inconstant cortisol level during the day. Glucose tolerance decreases in normal individuals through the day-time, and eating at night is, therefore, a cause of increased obesity and weight gain, which are often seen in shift workers [29]. Abdominal obesity, hypertriglyceridemia (> 1.7 mmol / l), low level of high density liptoproteins (<1.03 mmol / l in men and <1.29 mmol/l in women) and impaired glucose tolerance were detected more often in night shift workers, more susceptible to the development of the metabolic syndrome [43].

6. ILLUMINATION OVERNIGHT AND CANCER

A number of papers have convincingly demonstrated an increased incidence of spontaneous and chemically induced malignancies in laboratory animals kept under the constant illumination conditions or those of the Arctic region [3–5, 26, 28, 44, 45].

Using satellites, the level of light pollution over night was investigated and evaluated in 147 Israel municipalities, after which, using the method of multiple regression analysis, the relationship between night illumination and the frequency of breast cancer and lung cancer in women were calculated. After allowance for corrections on the ethnic composition, number of births, population density and income level, a high degree of correlation was established between the intensity of night illumination and the frequency of breast cancer ($p < 0.05$), moreover, this association increased ($p < 0.01$), when statistically significant factors only were considered for the regression analysis. On the other hand, no association has been found between the night illumination intensity and the frequency of lung cancer [46]. It was noted that 73 % of the maximum breast cancer frequency estimates were in those public entities with maximum illumination at night.

Using the same approach, the relationship between night illumination and the frequency of the three most common malignant tumours (prostate, lung, colon cancer) in men in 164 countries was studied. A high positive association was found between the light exposure of the population at night and the incidence of prostate cancer, but not lung or colon cancer [47]. The authors explain the presence of the found association between prostate cancer and night time illumination by suppressing the level of melatonin and clock-genes dysfunction. The risk of prostate cancer in countries with the most intensive night illumination was 110 % higher than that in countries with the lowest light pollution.

Subsequently, the same authors compared the frequency of the five most common neoplasm in women in 164 countries with the level of night illumination and found a high positive correlation between illumination and the frequency of breast cancer [48]. No such correlation was found between night illumination and colon cancer, and malignancies of larynx, liver, and lungs. The breast cancer risk in countries with the highest night illumination was 30–50 % higher than in countries with the least illumination.

Several cohort studies have shown that women, who often turn on lights in the bedroom at night, have an increased risk of breast cancer [29, 49, 50].

An analysis of the effect of night-time bedroom illumination intensity performed in Israel found that this factor is very significant and increases the risk of breast cancer in women with a habit of sleeping with the lights on ($OR = 1.22$, $p < 0.001$) [48].

Comparing their own data with the results obtained in [49], the authors of [48] note that during the 15 years since this study (1992–95), the light pollution has been increased, and currently women are exposed to a more intensive illumination as energy-saving lamps emitting in the blue spectrum (at 460 nm) are increasingly used. It is emphasized that this is the first large-scale randomized study where a positive correlation between illumination in the bedroom (habit to sleep in the light), light overnight hours (light pollution) and breast cancer (BC) has been established, and where the evidence was provided that the relative risk of BC increases proportionally to the intensity of night-time illumination in the bedroom. Therefore, not only the shift work over night hours is a risk factor for BC, but also the habit of sleeping in the light [4, 5, 29].

According to the International Agency for Research on Cancer in 2000 BC accounted for the majority of cancer cases in developed countries. The most common malignancy among women – breast cancer – each year affects about 1 million women (22 % of all female malignancies with the number of deaths of 375,000). More than half of all new cases are reported in economically developed countries: around 335,000 in Europe and 195,000 in North America [51]. Breast cancer is still not the most common among women in developing countries, but even in those countries, there is a steady increase in incidence. Increasing risk of breast cancer is caused with high socio-economic status (annual income, education, housing, etc.), because it is related with such health indicators as the onset of menstrual activity and menopause, obesity, big height, alcohol consumption, late age of first birth, small number of births, hormone replacement therapy, dietary patterns, etc. Two more factors characteristic of developed countries that may be of importance: the increasing night illumination exposure [29] and low-frequency electromagnetic fields (50–60) Hz [52].

Much higher mortality rates from malignancies are reported in shift workers who worked in production for at least 10 years, compared with those employed only in day shifts. In Denmark, in a large controlled randomized study (about 7,000 subjects in each group), it was shown that evening work significantly increases the risk of breast cancer in women aged 30 to 54 years. Among those working at night, the most reliable results were found among waiters of restaurants working on night shifts (300 cases). Similar observations were made during a survey of flight attendants in a large breast cancer risk cohort study in Finland. In California flight attendants, breast cancer was found 30 % more often and malignant melanoma was detected 2 times more often than in the rest of the population of California [29].

An epidemiological randomized study conducted in the US in 813 breast cancer female patients investigated the lifestyle features of these patients over the past 10 years compared with healthy women. At the same time, the light exposure at night was considered, based on the following parameters: night insomnia, lighting level in a bedroom at night and working in night shifts (at least 3 nights per month). It was found that the risk of cancer increases with increasing night insomnia, increased lighting level in a bedroom and when working on night shifts. In the latter case, the risk also increased with work experience [49].

According to [53] data from health research among nurses, which included questions on their experience, shift work, day, night and evening shifts, among nurses with more than 30 years of experience and shift work, the relative BC risk was 1.36 when compared to those nurses not working in shifts. Nurses who work for a long time with night shifts had a reduced level of melatonin and an increased level of oestrogen in the blood. The meta-analysis based on 13 studies, including 7 studies in workers of airlines and 6 studies in workers of other professions with night shifts, shown that the overall risk assessment was 1.48. The flight crew of airlines and women working on night shifts had a significant risk of developing BC.

The study, which focused on the health data of almost 45,000 nurses in Norway, found that working at night for 30 years or more poses the additional risk of breast cancer of 2.21. An increased risk of BC and colon cancer was found in Seattle residents who worked for a long time at night shifts [29].

The risk of colon cancer and rectal cancer was reported to increase in women working on radio and telegraph. The authors of [53] examined the Harvard data on the health research of 79,000 nurses

Table 1. The Degree of Suppression of the Night Melatonin Level Under the Illumination with Incandescent Lamps (IL) or Fluorescent Lamps (FL) [16]

Illuminance, lx	Suppression of melatonin concentration after turning on the light,%					
	After 30 min		After 60 min		After 90 min	
	IL	FL	IL	FL	IL	FL
0.1	0	0	0	0	0	0
0.3	0	0	0	0	0	1
1	0	1	1	1	1	1
3	1	2	2	3	2	4
10	3	6	5	9	5	10
30	8	14	11	19	13	20
100	19	29	25	36	27	39
300	35	47	42	53	45	55
1000	54	62	59	65	60	66
3000	65	69	68	71	69	71

and found that nurses working at night shifts have a higher risk of breast cancer. The authors also found that colon and rectal cancer are more common among workers who have at least 3-night shifts per month for 15 years or more. The mechanisms underlying this increased risk of cancer among night workers and flight crews may be similar. Probably, the circadian rhythms disturbance and the forced light exposure at night both lead to a decreased production of melatonin, which is a known biological blocker of the development of malignant tumours.

7. THE EFFECT OF MELATONIN ON THE DEVELOPMENT OF TUMOURS IN ANIMALS AND HUMANS

In experiments using various carcinogens and experimental designs, it was found that the use of melatonin has a suppressive effect on the development of tumours in animals. The spectrum of the anti-carcinogenic effect of melatonin is quite wide – it inhibits the carcinogenesis in the skin, subcutaneous tissue, breast, cervix and vagina, endometrium, lung, liver, and colon [27, 28, 55, 56]. Experimental data are in compliance with the results of clinical observations. So, the work of Canadian researchers provided the results of a meta-analysis of 10 randomized controlled studies of the effectiveness of melatonin for the treatment of solid cancer patients [58]. In total, 643 patients received treatment. The use of melatonin reduced the relative risk of death within 1 year to 0.66, and no side effects of the drug were recorded.

Possible mechanisms of the inhibitory effect of melatonin on carcinogenesis have been intensively discussed recently [54]. Melatonin has been found to have effects on both systemic and tissue levels and on cellular and sub cellular levels. At the same time, the action of melatonin prevents processes leading to aging and cancer. In particular, at the system level, melatonin reduces the synthesis of hormones that contribute to these processes and stimulates the immune surveillance system. At the same time, the formation of oxygen free radicals is suppressed, and the antioxidant defence system is stimulated. Melatonin inhibits the proliferative activity of cells and increases the level of apoptosis, preventing the tumour onset and development. At the genetic level, it inhibits the effect of mutagens, and also suppresses the expression of oncogens [55, 57].

8. THE EFFECT OF MELATONIN ON LIFE EXPECTANCY

Numerous studies have shown the ability of melatonin to slow down the aging process and increase the lifespan of laboratory animals (fruit flies, flatworms, mice, rats) [26, 57]. Some optimism is raised by publications about the ability of melatonin to increase resistance to oxidative

Table 2. Some Russian Regulatory Values of Light Illumination in Public, Residential and Auxiliary Premises (SP52.13330.2016)

Type of room	Illuminance of working surfaces in general lighting, lx
Administrative buildings	
Computer rooms	200–400
Business and work facilities, offices	300
Conference rooms, meeting rooms	200
Recreations Coulouirs, lobbies	150
LABORATORIES	400
Institutions of general education, primary, secondary and higher	
Classrooms, schoolrooms, secondary school rooms	500
Sports halls	200
Classrooms, training rooms, laboratories of technical schools and universities	400
Classrooms and teachers' rooms	300
Recreations	200
Medical institutions	
Adult wards	100
Procedural, manipulation rooms	500
Operating rooms	500
Massage and physical therapy exercises rooms	200
Shops	
Supermarket retail spaces	500
Trading rooms of the shops without self-service	300

stress and reduce the manifestations of some age-related diseases, such as retinal macular dystrophy, Parkinson's disease, Alzheimer's disease, diabetes, etc. [55, 58]. Comprehensive clinical trials are needed for melatonin use in various diseases, which, as we believe, will significantly expand its use for the treatment and prevention of age-related desynchronosis.

9. CONCLUSION

Data provided in a new atlas of artificial night sky lighting, suggest that 80 % of the world and 99 % of American and European populations live under light pollution [59]. 23 % of the Earth's surface between 75° N. and 60° S, 88 % of Europe and almost half of the United States are subject to light pollution. The light exposure overnight has been increased and became an essential part of the modern lifestyle, being accompanied by many serious behavioural and health disorders, including premature aging, cardiovascular diseases, obesity, diabetes and cancer [14, 28, 29, 45, 60]. Obtained in animal experiments, strong evidence of carcinogenicity of light-induced desynchronosis, caused by constant lighting or daylight of the North, served as a basis for recognizing circadian rhythm disorders by the International Agency for Research on Cancer as a factor increasing the risk of cancer in humans [29, 33]. In experiments using various carcinogens and experimental designs, it was found that the use of melatonin has a suppressive effect on the development of tumours of different localizations. Convincing experimental evidence has also been obtained that the use of melatonin prevents premature aging of the reproductive system and the body as a whole prevents the development of immune-suppression, metabolic syndrome and different tumours caused by light pollution. The widespread introduction of LED light sources sets a problem of developing guidelines for optimizing the light mode of working and living areas, for lighting cities and other settlements, which will ensure long-term maintenance of working performance, high quality of life, and ultimately will contribute to the prevention of premature aging and the development of diseases, including malignant neoplasm.

REFERENCES

1. Panchenko, A.V., Gubareva, E.A., Anisimov, V.N. Circadian system and aging in rodent models. In: Circadian Rhythms and Their Impact on Aging. Health Ageing and Longevity 7. S.M. Jazwinski, V.P. Belancio, S.M. Hill, Eds. Springer International Publishing AG, 2017, pp. 103–128. DOI: 10.1007/978–3–319–64543–8_5.

2. Touitou, Y, Reinberg, A, Touitou, D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption. Life Sci.– 2017, 173, pp. 94–106. DOI: 10.1016/j.lfs.2017.02.008

3. Anisimov, V.N. Light pollution, reproductive function and cancer risk // Neuro Endocrinol. Lett.– 2006, Vol. 27, pp. 35–52.

4. Anisimov V.N., Vinogradova I.A., Bukalev A.V. et al. Light desynchronosis and risk of malignant neoplasms in humans: problem state // Problems. oncol. 2013, Vol 5, No. 3, pp. 302–313.

4. Anisimov V.N., Vinogradova I.A., Bukalev A.V. i dr. Svetovoi' desinkhronoz i risk zlokachestvenny'kh novoobrazovanii' u cheloveka: sostoianie problemy' // Vopr. onkol.2013, Vol 59., No. 3, pp. 302–313.

5. Anisimov V.N., Vinogradova I.A., Bukalev A.V. et al. Light desynchronosis and risk of malignant neoplasms in laboratory animals: problem state // Problems. oncol. 2014, Vol 60, No. 2, pp. 15–27.

5. Anisimov V.N., Vinogradova I.A., Bukalev A.V. i dr. Svetovoi' desinkhronoz i risk zlokachestvenny'kh novoobrazovanii' u laboratorny'kh zhivotny'kh: sostoianie problemy' // Vopr. onkol. 2014, Vol. 60, No. 2, pp. 15–27.

6. Arendt, J. Melatonin and the Mammalian Pineal Gland. London: Chapman & Hall. 1995, 331 p.

7. Arendt, J. Biological rhythms during residence in polar regions//Chronobiol. Internat, 2012, Vol.29, (4), pp. 319–394.

8. Brainard George C. and Provencio I, Photoreception for the Neurobehavioral Effects of Light in Humans// Light & Engineering Journal, 2008, V.16, #1, pp.5–18.

9. Komarov F.I., Rapoport S.I., Malinovskaya N.K., Anisimov V.N. Melatonin in norm and pathology. M .: ID Medpractica-M, 2004, 308p.

9. Komarov F.I., Rapoport S.I., Malinovskaia N.K., Anisimov V.N. Melatonin v norme i patologii. M.: ID Medpraktika-M, 2004, 308p.

10. Brainard G.K., Provencio I. The perception of light as a stimulus for non-visual reactions in humans // Svetotehnika. 2008, No. 1, pp. 6–13.

10. Brei'nard G.K., Provensio I. Vospriiatie sveta kak stimula nezritel'ny'kh reaktcii' cheloveka // Svetotekhnika. 2008, No. 1, pp. 6–13.

11. Revel, F.G., Herwig, A., Garidou, M.-L. et al. The circadian clock stops ticking during deep hibernation in the European hamster // Proc. Natl. Acad. Sci. USA, 2007, Vol. 104, pp. 13826–13820.

12. Brainard, George C. and Hanifin, John P. Exploring the Power of Light: From Photons to Human Health// Light & Engineering, 2014, Vol. 22, #4, pp.4–14.

13. Kyba, C.C.M., Kuester, T., Sanchez de, Miguel, A. et al. Artificially lit surface of Earth at night increasing in radiance and extent // Sci. Adv., 2017; 3: e17017258

14. Russart, K.L.G., Nelson, R.J. Light at night as an environmental endocrine disruptor// Physiol. Behav. 2018, Vol. 190, pp.82–89. DOI: 10.1016/j.physbeh.2017.08.029.

15. Gaston, K.J., Davies, T.W., Nedelec, S.L., Holt, L.A. Impact of artificial light at night on biological tim ings// Ann. Rev.Ecol.Eviol.Syst. 2017, Vol. 48, pp. 49–68.

16. Rea, M.S., Figueiro, M.G., Bullough, J.D., Bierman, A. A model of phototransduction by the human circadian system. // Brain Res. Rev. 2005, Vol. 50, pp. 213–228.

17. Higuchi, S., Motohashi, Y., Ishibashi, K., Maeda, T. Less exposure to daily ambient light in winter increases sensitivity of melatonin to light suppression // Chronobiol. Int. 2007, Vol. 24, pp. 31–43.

18. Leppaluoto, J., Sikkila, K., Meyer-Rochow, V.B., Hassi, J. Spring snow lowers human melatonin // Int. J. Circumpolar Health. 2004, Vol. 63. Suppl.2, pp. 161–163.

19. Gundarov I.A., Zilbert N.L. Study of regional differences in morbidity and mortality of the population in terms of geographical latitude syndrome // Annals of AMN USSR. 1991, Vol. 11, pp. 52–56.

19. Gundarov I.A., Zil'bert N.L. Izuchenie regional'ny'kh razlichii' v zabolevaemosti i smertnosti naseleniia s pozitcii' sindroma geograficheskoi' shiroty' // Vestneyk AMN SSSR. 1991, Vol. 11, pp. 52–56.

20. Erren, T.C., Piekarski, C. Does winter darkness in the Arctic protect against cancer? // Med. Hypothesis. 1999, Vol. 53, pp. 1–5.

21. Hassler, S., Soininen, L., Sjolander, P., Pukkala, E. Cancer among the Sami – A review on the Norwegian, Swedish and Finnish Sami populations // Int. J. Circumpolar Health. 2008, Vol. 67, pp. 421–432.

22. Kelly, J.J., Lanier, A.P., Alberts, S., Wiggins, C.L. Differences in cancer incidence among Indians in Alaska and New Mexico and U.S. Whites, 1993–2002 // Cancer Epidemiol. Biomarkers Prev. 2006, Vol.15, pp. 1515–1519.

23. Circumpolar Inuit Cancer Review Working Group. Cancer among the circumpolar Inuit, 1988–2003. II. Patterns and trends // Int. J. Circumpolar Health. 2008, Vol. 67, pp. 408–420.

24. Bartsch, C., Bartsch, H., Peschke, E. Light, melatonin and cancer: current results and future perspectives // Biol. Rhythm Res. 2009, Vol.40, pp. 17–35.

25. Borisenkov MF, Anisimov VN Cancer risk in women: possible association with geographic latitude and some economic and social factors // Vopr. onkol. 2011, Vol. 57, No. 3, pp. 343–354.

25. Borisenkov M.F., Anisimov V.N. Risk raka u zhenshchin: vozmozhnaia sviaz' s geograficheskoi' shirotoi' i nekotory'mi e'konomicheskimi i sotcial'ny'mi faktorami // Vopr. onkol. 2011. Vol. 57, No. 3, pp. 343–354.

26. Vinogradova, I.A., Anisimov, V.N. Light regime of the North and age pathology. Petrozavodsk: PetroPress, 2012, 128 p.

26. Vinogradova I.A., Anisimov V.N. Svetovoi' rezhim Severa i vozrastnaia patologiia. – Petrozavodsk: PetroPress, 2012, 128 p.

27. Anisimov, V.N., Popovich, I.G., Zabezhinski, M.A. et al. Melatonin as antioxidant, geroprotector and anticarcinogen // Biochim. Biophys. Acta. 2006, Vol. 1757, pp. 573–589.

28. Anisimov, V.N., Vinogradova, I.A., Panchenko, A.V. et al. Light-at-night-induced circadian disruption, cancer, and aging // Current Aging Science, 2012, Vol. 5, No.3, pp. 170–177.

29. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol.98. Painting, Firefighting, and Shiftwork. Lyon: IARC, 2010, 804 p.

30. Taylor, P.J., Pocock, S.J. Mortality of shift and day workers 1956–68 // Brit. J. Industr. Med.1972, Vol. 29, pp. 201–207.

31. Stevens, R.G., Wilson, B.W., Anderson, L.E. Melatonin Hypothesis. Breast Cancer and Use of Electric Power". Columbus: Battele Press. 1997, 760 p.

32. Knutsson, A. Health disorders of shift workers.// Occupat. Med. 2003, Vol. 53, pp. 103–108.

33. Straif, K., Baan, R., Grosse, Y. et al. Carcinogenicity of shift-work, painting, and fire-fighting // Lancet Oncol. 2007, Vol.8, pp. 1065–1066.

34. Gibson, E.M., Williams, W.P., Kriegsfeld, L.J. Aging in the circadian system: Considerations for health, disease prevention and longevity // Exp. Gerontol. 2009, Vol. 44, pp. 51–56.

35. Mosendane, T., Mosendane, T., Raal, F.J. Shift work and its effect on the cardiovascular system // Cradiovasc. J. Afr., 2008, Vol. 19, pp. 710–715.

36. Wegmann, H.M., Esser, P., Klein, K.E. Significance of circadian rhythms for aviation and space operations // J. UOEH. 1985, Vol. 7, Supplement, pp.131–140.

37. Morikawa, Y., Nakagawa, H., Miura, K. et al. Shift work and the risk of diabetes mellitus among Japanese mae factory workers // Scand. J. Work Environ. Health. 2005, Vol. 31, pp. 179–183.

38. Morikawa, Y., Nakagawa, H., Miura, K. et al. Effect of shift work on body mass index and metabolic parameters // Scand. J. Work Environ. Health. 2007, Vol. 33, pp. 45–50.

39. Caruso, C.C., Lusk, S.L., Gillespie, B.W. Relationship of work schedules to gastrointestinal diagnoses, symptoms, and medication use in auto factory workers // Am.J. Ind. Med. 2004. Vol. 46, pp. 586–598.

40. Segawa, K., Nakazawa, S., Tsukamoto, Y., Kurita, Y., Goto, H., Fuku, A., Takano, K. Peptide ulcer prevalent among shift workers // Dig. Dis. Sci. 1987, Vol. 32, pp. 449–453.

41. Pietroiusti, A., Forlini, A., Margini, A., Galante, A., Coppeta, L., Gemma, G., Romeo, E., Bergamaschi, A. Shift work increases the frequency of duodenal ulcer in H. pylori infected workers // Occup. Environ. Med. 2006, Vol. 63, pp. 773–775.

42. Knutsson, A., Boggild, H. Shiftwork, risk factors and cardiovascular disease: review of disease mechanisms.// Rev. Environ. Health. 2000. Vol. 15, pp. 359–372.

43. Sookoian, S., Gemma, C., Fernandez Gianotti T., Burgueno, A., Alvarez, A., Gonzalez, C.D., Pirola, C.J. Effects of rotating shift work on biomarkers of metabolic syndrome and inflammation // J. Intern. Med. 2007, Vol. 261, pp. 285–292.

44. Vinogradova, I.A., Anisimov, V.N., Bukalev, A.V. et al. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats // Aging (Albany, NY). 2009, Vol. 1, pp. 855–865.

45. Haim, A., Portnov, B.A. Light Pollution as a New Risk Factor for human Breast and Prostate Cancer., Dodrecht: Springer Sciences, 2013, 168 p.

46. Kloog, I., Haim, A., Stevens, R.G., Portnov, B.A. Light at night co-distributes with nident breast ut not lung cancer in the female population of Israel // Chronobiol. Int. 2008, Vol. 25, pp. 65–81.

47. Kloog, I., Haim, A., Stevens, R.G., Portnov, B.A. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men // Chronobiol. Int. 2009, Vol. 26, pp. 108–125.

48. Kloog, I., Stevens, R.G., Haim, A., Portnov, B.A. Nighttime light level co-distributes with breast cancer incidence worldwide // Cancer Cases Control. 2010, Vol. 21, pp. 2059–2968.

49. Davis, S., Kaune, W.T., Mirick, D.K. et al. Residental magnetic fields, light-at-night, and nocturnal urinary 6-sulfatoxymelatonin concentration in women // Am.J. Epidemiol. 2001, Vol. 154, pp. 591–600.

50. Kloog, I., Portnov, B.A., Rennert, H.S., Haim, A. Does the modern urbanized sleeping habitat rose a breast cancer risk? // Chonobiol. Int. 2011, Vol. 28, pp 76–80.

51. Parkin, D.M., Bray, F.I., Deseva, S.S. Cancer burden in the year 2000. The global picture. Eur. J. Cancer. 2001, Vol. 37, pp. S4–S66.

52. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol.80. Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields. -Lyon: IARC, 2002, 438 p.

53. Schernhammer E.S., Laden F., Speizer F.E. et al. Night-shifts work and risk of colorectal cancer in the nurses' health study // J. Natl. Cancer Inst. 2003, Vol. 95, pp. 825–828.

54. Wegrzyn, L.R, Tamimi, R.M, Rosner, B.A. et al. Rotating night-shift work and the risk of breast cancer in the nurses' health studies // Am.J. Epidemiol. 2017, Vol. 186 (5), pp. 532–540. DOI: 10.1093/aje/kwx140.

55. Reiter, RJ, Rosales-Corral, S, Tan, D.X, Jou, M.J, Galano, A., Xu, B. Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. Cell Mol Life Sci. 2017, Vol. 74, № 21, pp. 3863–3881. DOI: 10.1007/s00018–017–2609–7.

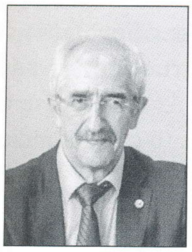
56. Guidice, A., Crispo, M., Polo, A., Grimaldi, M. et al. The effect of light exposure at night (LAN) on c carcinogenesis via decreased nocturnal melatonin synthesis.// Molecules, 2018, Vol. 23, 1308 p. DOI: 10.3390/molecules2306.1308.

57. Anisimov, V.N. Effect of melatonin on longevity // In: Modulating Aging and Longevity / Rattan S.I.S., Ed. London: Kluwer Acad. Publ., 2003, pp. 239–260.

58. Mills E, Wu P, Seely D, Guyatt G. Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. J Pineal Res. 2005, Vol. 39, № 4, pp. 360–6.

59. Falchi, F., Cinzano, P., Duriscoe, D. et al. The new world atlas of artificial night sky brightness // Sci. Adv. 2016, Vol 10, № 6, pp. e1600377, DOI: 10.1126/sciadv.1600377.

60. Davies, T.W., Smyth, T. Why artificial light at night should be a focus for global change research in the 21st century // Glob. Change Biol. 2018, Vol. 24, pp. 972–882. https://doi.org/10.1111/gcb.13927.



Vladimir N. Anisimov,
Prof., Dr. of Medical Sciences, Corresponding Member of the Russian Academy of Sciences, Head of the Scientific Department of Carcinogenesis and Oncoherontology of the National Medical Research Centre of Oncology named after N.N. Petrov, Ministry of Health of Russian Federation