Quo Vadis, Chronopsychology?

A. A. Putilov

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This is the first review in chronopsychology, a relatively new interdisciplinary area of research which has developed rapidly at the junction of chronobiology, somnology, and psychology. Chronopsychology studies the mechanisms of rhythmicity in behavior and the mind based on methods of chronobiology, somnology, and psychometry. In particular, chronobiology studies biological clocks, while somnology addresses their influences on regulatory processes directly controlling the sleep–waking cycle, impairments to which have adverse impact on mental activity. Psychometric and differential psychology methods are widely used, for example, in studies of the chronotype and its relationship with a great diversity of human characteristics – genetic, psychophysiological, behavioral, cognitive, personality, and psychopathological. Particular attention is paid to sleep, drowsiness, fatigue, work/study productivity, and healthy/unhealthy lifestyles in people of different sexes and ages. Applied research includes the development – taking account of the chronotype of each specific person – of recommendations supporting preservation of good quality sleep and health in specific temporal situations, optimizing work/rest patterns, efficient assimilation of new skills, and preventing accidents during vigorous activity at times of day unsuitable for these activities.

Introduction. The word "chronopsychology" is not hard to find in the vastness of the internet. It has been around for decades and since 1999 the Japanese hip-hop group M-Flo has performed a notorious song with this title. The paradox, however, is that it is much harder to answer the question of what constitutes the area of scientific research designated by the term "chronopsychology." The answer is not obtained by listening to the song or from more serious studies of all biological sources containing this word. Among these, in particular, there are no reviews of the history or current state of chronopsychology in either English or Russian. This is thus the first such review.

Being a relatively young area of interdisciplinary research, chronopsychology has developed rapidly in recent years at the junction of chronobiology, somnology, and psychology. It addresses the mechanisms and manifestations of rhythmicity in behavioral and psychological processes. Its theoretical bases lie in two biological disciplines – chronobiology and somnology. The area of experimental studies in the former of these disciplines includes biological clocks, while the latter addresses their influences on those regulatory process directly controlling the sleep–waking cycle. Serious impairments to this cycle – and almost everyone is familiar with this – have adverse impacts on mental activity, wellbeing, and mood. The theory and methodology of chronopsychology research are not linked solely with the biological sciences. Methods first developed in personality psychology (differential psychology) and which apply to the behavior of such psychological disciplines as psychometry and psychodiagnosis are widely used. An example of the wide use of these psychometric methods (an area of science linking psychology with mathematics and statistics) is provided by research into the chronotype (the type of daily rhythm) and its interaction with a great diversity of characteristics in humans – genetic, psychophysiological, cognitive, personality, psychopathological, etc. Specialists working in chronopsychology pay special attention to working/

Federal Research Center for Basic and Translational Medicine, Novosibirsk, Russia; e-mail: putilov@ngs.ru.

studying regimes, sleep, drowsiness, fatigue, and healthy/ unhealthy lifestyles in people of different sexes, ages, abilities, types of occupational activity, etc. The applied aspects of such studies include the development of recommendations – taking account of the chronotypes of individual people and their temporal environments – to preserve good quality sleep and health, to improve working ability, to ensure more efficient assimilation of new skills and study material, to decrease levels of drowsiness and the risk of "burnout" at work, to optimize work/rest patterns, and to prevent accidents and risks to life and health associated with vigorous activity at times of day unsuitable for such activities.

This review addresses the history and various aspects of contemporary chronopsychology – its theoretical, mathematical, and methodological bases, data acquisition methods, controversial questions, unresolved problems, and the potential for further development.

1. History of Chronobiology and the Origins of the Chronopsychological Approach. Chronobiology is one of the theoretical and methodological bases of chronopsychology. The title was unlucky because it would better be termed biorhythmology (a term rarely used in the Russian literature on biological rhythms). However, this direction of scientific research condensed into its own scientific discipline at the same time (the beginning of the 1960s), when the pseudoscientific concept there were three "biorhythms" was current. To ensure that serious scientists were not linked with this false idea, some preferred the term chronobiology, while others continued to term this scientific direction using three words: biological rhythm research (for more detail on the history of experimental research in chronobiology see [Putilov, 2016]).

The Symposium on Biological Clocks organized by Colin Pittendrigh (1918–1996) in June 1960 at Cold Spring Harbor, the location of the laboratory of that name, is taken as the moment at which chronobiology arose as specific segment of scientific knowledge. Tens of scientists gathered at this symposium, including the founders ("Roman Popes") of chronobiology Colin Pittendrigh, Jürgen Aschoff (1913–1998), and Franz Halberg (1919–2013). The main results of the symposium were published in 1961 in the collection *Biological Clocks* [Pittendrigh, 1961], which included the reports read at the symposium and discussions (the Russian edition, *Biological Clocks*, was published in 1964).

The idea of adding the prefix "circa" to the names of biological rhythms belongs to one of the founders of chronobiology – Franz Halbert. The prefix "circa" was first added to create the word now widely used in many languages, "circadian" (approximately one day) in an article in 1959 [Halberg and Stephens, 1959]. This emphasizes that the endogenous (internal or intrinsic) period of the body's rhythm is not necessarily exactly 24 h. Halberg proposed for this then very young area the already excessively broad term "chronobiology" [Halberg, 1969].

The main contribution of the third founder of chronobiology – Jürgen Aschoff – was that he initiated the first large-scale scientific experiments addressing human biological rhythms in conditions of isolation from external time cues [Aschoff et al., 1967]. Over the preceding 250 years, experimental studies in this area had been performed only on plants and animals. Hundreds of experiments lasting many days in bunkers led to the conclusion that like plants and animals already involved in this type of isolation experiment, people also have intrinsic biological clocks [Aschoff, 1965].

The outcome of the initial period of development of chronobiology – to its adult stage (20 years) – was presented in one of five volumes of a textbook on the neurobiology of behavior, entitled *Biological Rhythms* [Aschoff, 1981] (a Russian translation was published in 1984). Around 40 years have passed since Aschoff's book was published. During this time, chronobiology grew into a wide scientific discipline and branched off in many more or less powerful directions. As in many other disciplines, a number of hybrid areas developed at the junction of multiple disciplines, including chronopsychology.

For example, one potential direction arose at the meeting with the genetics of behavior and molecular genetics. In the framework of this direction, the mechanisms of biological clocks were studied at the cellular level. The first discovery was in an investigation in the laboratory of Seymour Benzer (1921–2007) by his student Ronald Konopka (1947–2015) [Konopka and Benzer, 1971]. A mutagen yielded fruit flies which hatched from eggs arrhythmically or reproduced with very short (20-h) or very long (28-h) periodicity. Furthermore, all these impairments were found to be located in a single previously undescribed gene. This was named PER ("period") and was the first of a whole family of so-called "clock" genes – the individual "gears" of this molecular-genetic mechanism [Konopka and Benzer, 1971]. However, the potential of the search for the molecular-genetic bases of biorhythms was not immediately realized by the scientific community. The situation finally changed only because of the 2017 Nobel prize for Physiology and Medicine being awarded "for the discovery of the molecular mechanism controlling circadian rhythms." This went to Jeffrey Hall, Michael Rosbash, and Michael Young, who in particular published the first result on the structure of the *PER* gene [Zehring et al., 1984; Bargiello et al., 1984] (for more detail on the history of this and preceding discoveries see [Putilov, 2018]).

The chronopsychology direction arose in the framework of chronopsychology in the 1970s. Halberg himself was close to its initiation. He used the term "educative chronobiology" for this young interdisciplinary scientific direction. In an article whose title contained this term, Halberg identified the need to consider the importance of the time of day at which students were taught and noted that this need was ignored by most experimental psychologists [Halberg, 1974]. This term was probably first used to designate the chronopsychological trend of chronobiological research by Simon Folkard. He used this term in the title of the abstracts

published in the journal *Chronobiologia*, which at that time was produced and edited by Halberg [Folkard, 1977]. Two years later, Carl Englund defended a dissertation with this term in its title, though this was never published [Englund, 1979]. A further three years after that, a collection of articles on the rhythmic aspects of behavior included a chapter written by Englund's colleague Paul Naitoh. With references to the publications of Halberg and Folkard, he defined the aim of this chapter as that of presenting the basic principles and main concepts of chronopsychology and to provide examples of their use in altering the lifestyle of individuals and groups such that their working and resting hours would be more acceptable for them [Naitoh, 1982].

Thus, these first chronopsychological investigations mainly sought to optimize human work capacity on the basis of chronobiological concepts and methods of studying the body's circadian rhythms [Folkard and Monk, 1983]. Thus, chronopsychology in this sense was mostly defined as "the chronopsychological approach to optimizing human performance" [Naitoh, 1982; Folkard and Monk, 1983].

2. The Methodology of Chronobiology. Aschoff [1981] took the view that the study of biological rhythms mainly addresses four "circa rhythms:" the circadian, the circatidal, the circalunar, and the circannual. These are those biological rhythms whose occurrence is linked with the operation of natural (biological) clocks in the living beings populating planet earth. These support adaptation to cosmic and geophysical oscillations in the surrounding world. Thus, the intrinsic biorhythms of such beings are characteristic periods approximately but not exactly corresponding to 1) the daily movement of the sun (the circadian rhythm), 2) the periodicity of the tides due to lunar gravitation (the circatidal rhythm), 3) the sidereal or synodic lunar cycle (the circalunar rhythm), and 4) the annual cycle (the circannual rhythm) [Aschoff, 1981].

Most studies address circadian rhythms and this area is termed circadian biology. Humans, like most other living beings, show only one biological clock, i.e., the circadian. This does not mean that people are unable to adapt to other – the three other – external (exogenous) periodicities. The circadian clock also allows annual oscillations in many periodic environmental factors, including seasonal changes in the photoperiod (day length), to be considered [Chang et al., 2011]. In addition, it does not mean that the human body is unable to generate rhythms with periodicities close to these. An example is provided by the menstrual cycle (studies of this periodicity have been reviewed in more detail in book form [Dubrov, 1990].

The biological (circadian) clock in mammals was first located in 1972 by two independent research groups – Robert Moore and Victor Eichler on the one hand and Friedrich Stephan and Irving Zucker on the other. The clock was seen in bilateral hypothalamic nuclei, which were termed the suprachiasmatic nuclei because of their location directly above the decussation of the optic nerves, i.e., the

chiasm [Moore and Eichler, 1972; Stephan and Zuckler, 1972]. Almost every cell, every organ, and every function of importance to the body has its own intrinsic more or less complex clock system. However, it is sufficient to lesion this microscopic piece of nervous tissue (about 100,000 neurons in humans) for all these billions of extremely diverse clocks to start to run out of synch. When the clock is lost, the overall circadian rhythm simply ceases to be seen because other oscillations with different phases and periods overlap each other [Moore and Eichler, 1972; Stephan and Zuckler, 1972].

This phenomenon was initially no more than a prediction by one of the founders of chronobiology, Colin Pittendrigh. In 1958–1960 he developed the hypothetical idea of a separate light-sensitive oscillator imposing a rhythm on the whole body (a pacemaker) [Pittendrigh, 1960–1961]. There is a reason why these nuclei are located close to the decussation of the optic nerves. They arose during mammalian evolution to show all the body's functions the time "displayed" by the external source of cyclic illumination. A biological clock with a period close but not exactly equal to day length is adjusted by the strictly 24-h illumination regime. Pittendrigh included the term "entrainment" in his dictionary of chronobiology as very important for understanding the functions of the biological clock. (For more detail of the contributions of the founders of chronobiology to studies of this phenomenon, see Daan's lectures [2000].) Unfortunately, this term does not have any widely accepted translation into Russian. Translations include the Russian word which normally means "inclusion" or "dragging," in the sense of "pulling/attracting to a sphere of influence."

Although entrainment is formally similar to synchronization, it is not synchronization in the usual sense. If there is some, however weak, physical interaction between two oscillations with different periods, for example pendulums, they will quite quickly become synchronized, i.e., their periods will become the same or multiples of each other [Blekhman, 1981]. Formally, the action of such an external oscillation as the daily dark-light rhythm on the internal (circadian) clock and the action of this clock on various other oscillations in the body leads to exactly the same result. The periods of circadian rhythms become equal or multiples of 24 h [Putilov, 1987]. However, the light regime has almost no direct physical action on the clock of the suprachiasmatic nuclei, and the clock in turn has virtually no action in the physical sense on the oscillations of all other parts of the brain or on the oscillations of the most diverse processes occurring in the rest of the body [Pittendrigh and Daan, 1976]. The illumination regime is used by the clock only as a source of information on the time of day – just like solar and other clocks invented by humans themselves. Harmony with the surrounding world is achieved because these diverse oscillations within the body are tuned to the clock rhythm which in turn is tuned to the rhythm of the earth's rotation around its axis [Roenneberg et al., 2003].

Development of contemporary methodology for experimental studies of entrainment started with work by Nathaniel Kleitman (1895–1999), an American immigrant from Russia who is regarded as the founder (the "Roman Pope") of somnology (sleep science). As early as 1939 he started experiments which over time led to the appearance of the "gold standard" in contemporaneous experimental studies of the effects of different light regimes on human biological clocks. (Another of Kleitman's notable contributions was his services to chronopsychology, as he made the first attempt to compare extreme chronotypes – morning and evening – in terms of body temperature rhythm with the aim of explaining differences between them in terms of differences in the time of reaching the peak of the rhythm [Kleitman, 1962]). Further development of the human biorhythm research using isolation conditions initiated by Kleitman were continued in studies reported by Elliot David Weitzman (1929–1983). He was the first in the USA to create a laboratory for studies in this area, and in 1978 the results of the first of the series of experiments in this laboratory were published in collaboration with Charles Czeisler and Martin Moore-Ede as abstracts [Weitzman and Moore-Ede, 1978]. A few years later, Czeisler headed studies based on the method named in the first – also an abstract – publication as the "forced desynchronization protocol" [Czeisler et al., 1985].

The basic idea of "forced desynchronization" studies consists of using the experimental participant's ability to live voluntarily in isolation from external time signals with constant dim illumination in accordance with an imposed sleep–waking regime. The duration of this imposed sleep–waking regime is either longer of shorter than the day by 3 h. Most of the rhythmic indicators in humans which are most stringently controlled by biological clocks are unable to adjust to such a regime, in contrast to the sleep–waking cycle. The more "strongly" the internal (endogenous) rhythm influences the indicator measured, the narrower its area of entrainment, i.e., the range of periods within which it can "compel" the rhythm to follow the sleep–waking cycle imposed on it. The best studied and in this regard the most reliable biological indicators of pacemaker operation are the body temperature rhythm and the melatonin secretion rhythm. If the period of the external (exogenous) cycle is beyond the limits of the entrainment area for these rhythms, they display an endogenous "free-running" rhythm, i.e., the rhythm of these indicators in these conditions "flows freely," usually with a period a little longer than a day. It turns out that the phase of a "free-running" rhythm (for example, the moment when the value of the circadian oscillations in body temperature in an experimental participant is minimal) occurs at different phases of the imposed 21- or 27-h sleep–waking cycle. This allows precise determination of the parameters of the endogenous circadian rhythm, for example, the amplitude, period, and phase of the circadian oscillation in body temperature. This requires the value linked with

the state of sleep (which induces reductions in temperature) or the value associated with the state of waking (which increases it) to be subtracted from the current value of the indicator [Czeisler et al., 1999].

The term "masking" was introduced to designate this non-pacemaker-associated influence [Aschoff and von Goetz, 1988]. This reflected the fact that it is impossible to assess the phase or other characteristics of the circadian pacemaker from simple measurements, made in normal conditions, of physiological or hormonal indicators over a day or longer. The masking influences on these indicators comes from multiple unaccountable factors, not only the state of sleep and waking and not only the phase or stage of sleep, but also the body position, level of activity, presence of food in the stomach, being in the light or dark at the moment of assessment, etc. Despite the opportunities presented to contemporary humans to lead a purely nocturnal lifestyle or to work different shifts, the daily 24-h alternation of light and dark does not become any less important an indicator of the time of day for biological clocks in such people. For example, the opportunity for the sleep–waking regime to entrain circadian rhythms in humans is limited by the fact that this regime is a weaker indicator of time of day than the light-dark regime [Danilenko et al., 2003].

It is important to emphasize that entrainment is not just a specific mechanism by which the light regime is used for daily correction of the periods of circadian rhythms in a very diverse range of living beings, including modern humans. It is a fundamental property of an oscillatory process which is seen in many different oscillators regardless of their physical nature [Comas et al., 2007]. As entrainment of a circadian rhythm is formally the same for all possible types of synchronized processes everywhere in living and nonliving nature, they can all be described by the same mathematical theory of oscillations [Magnus, 1976]. As a result, chronobiology, even at the very beginning of its compartmentalization as a separate field of science, could claim the status of an exact science. In other words, in this science, as in any other – such as physics – phenomena and processes could be described and predicted in the language of mathematics, i.e., using mathematical models. Mathematics gives scientists wings. For this reason, the history of chronobiology is rich in examples of mathematical modeling of the main properties of biological time-measuring systems. Mathematical modeling of the rhythmic nature of biological phenomena has never been reduced to solving differential equations and adapting them to achieve a more precise correspondence with the acquired empirical data (simple simulation). Modeling allows 1) critical analysis of existing sets of empirical data, 2) extraction of additional information on these datasets beyond the framework of what could be obtained by standard statistical analysis, 3) more effective use of research resources, 4) optimization of the development of experimental protocols, 5) accurate prediction of results from experimental conditions yet to be addressed,

6) identification of hypothetical structures and processes which might be observed in later studies, 7) discovery of the fundamental mechanisms and most important details of these mechanisms, 8) utilization of a common language by researchers working on different rhythmic phenomena using different species, organs, systems, processes, functions, etc. as examples [Putilov, 2017b].

An example of the special role of models based on mathematical oscillation theory in the discovery of the mechanism of the biological clock is provided by a model of cellular clocks. This was first proposed in an article by Paul Hardin in collaboration with the future Nobel laureates Rosbash and Hall [Hardin, Hall, and Rosbash, 1990]. Periodically arising excess quantities of PER protein, which is produced on the basis of information read by RNA from DNA at the site of the *PER* gene, switch off its own production. This results in a rhythm with a period close to 24 h, which is based on the universal principle of feedback with delay. The model explaining this mechanism was termed the transcriptional-translational negative feedback model [Hardin et al., 1990]. There was no need to write new equations to present the Hardin–Hall–Rosbash model in the lofty language of mathematics. Many chronobiologists and mathematicians at the dawn of chronobiology – long before experimental observation of the molecular clocks of cells – sought to explain the mathematical principles of the operation of these clocks. These included Brian Goodwill (1931–2009), who in 1965 proposed a model of a hypothetical biochemical oscillator operating on the principle of negative feedback with a delay [Goodwin, 1965]. In this model he included only three variables, which is the minimum number required for producing oscillations in a negative feedback loop with delay.

In relation to the Hardin–Hall–Rosbash transcription-translation negative feedback model [Hardin et al., 1990], these variables are usually interpreted as the concentrations of three molecules: RNA, its corresponding protein, and a transcription (RNA synthesis on a DNA template) inhibitor. The occurrence of a circadian cycle in this particular statement of the model can be described verbally as follows. Initially, the DNA for the gene, which is located within the cell nucleus, is used to read information on the structure of the protein into RNA. This information is used outside the nucleus to manufacture the protein of interest. The protein gradually accumulates outside the nucleus and, after some period of time, starts to enter the cell nucleus. Its appearance there leads to temporary cessation of the reading the information relating to the protein from the DNA. This cessation in turn leads to gradual depletion io the accumulated stock of the protein, with the result that the protein is unable to interfere with resumption of reading information about it from DNA. The result is that the entire cycle, with a period of about a day, starts again.

Publication of experimental results from molecular-genetic studies following this report [Hardin et al., 1990] revealed the details of the structure of the genetic basis of cellular clocks, including the fact of repeated duplication of some of the most important elements. A detailed understanding of the structure of clocks generating the circadian rhythm and indicating "what time it is" for at least half of all the other genes expressed in given cell [Takahashi, 2015; Crumbley et al., 2010] gradually developed. Throughout this period, to the current time, new discoveries consistently confirmed the transcription-translation model [Partch et al., 2014] (the model and its history are described in more detail in [Putilov, 2016, 2018]).

3. The Methodology of Somnology. Another model of the clock apparatus needs to be described in this review if only because it was the model that allowed chronobiology to be "married" to somnology. Its development and subsequent use clearly demonstrated that in the area of sleep studies, mathematical models and simulations based on them provide powerful tools for understanding the mechanisms underlying the daily alternation of the states of sleep and waking. As noted above, the founder of somnology also made a significant contribution to the establishment of both chronobiology and chronopsychology. However, despite the obvious fact that the sleep–waking cycle is a biological rhythm, chronobiology and somnology developed in relative isolation from each other for decades. In particular, few chronobiology researchers burdened experimental participants with polysomnography, a method which from the 1930s became the main source of objective information on sleep for somnologists (for more detail on the history of the relationship between these sciences see [Putilov, 2020]).

It was only at the beginning of the 1980s that the sleep researcher Alexander Borbély started to develop ideas that had recently been considered in discussions with chronobiologist Serge Daan (1940–2018), one of Aschoff's students. To model the sleep–waking cycle, Daan in turn attracted the young mathematician Domien Beersma, one of the few who had already "befriended" computers. Daan, Beersma, and Borbély published a mathematical version of the so-called two-process sleep regulation model [Daan et al., 1984]. With the passage of 45 years, this model has remained one of the most frequently cited in the literature of chronobiology and somnology theories. The somnology part in this model consists of process S (for Sleep). This regulatory process is recognized as maintaining the balance between the sleep and waking phases of a 24-h cycle. It increases/decreases sleep duration and intensity depending on the duration of the waking preceding sleep. This process is therefore often termed homeostatic or somnostatic. It is important that Borbély showed: having obtained polysomnographic sleep recordings, the somnostatic process could be measured quantitatively by assessing the power of the slow-wave (1–4 Hz) part of the electroencephalogram (EEG) spectrum in sleep [Borbély et al., 1981; Borbély, 1982]. Changes in power during normal sleep provide evidence that slow-wave activity decreases exponentially from one cycle of alternation of

the slow- and rapid-wave sleep phases to the next during the night [Aeschbach and Borbely, 1993]. If a person is awake for a period of time significantly longer than the usual, power in the first sleep cycle increases more strongly than usual, with the result that the subsequent exponential decrease occurs more steeply and sleep lasts longer than the usual amount of time [Dijk et al., 1990]. Conversely, if a person goes to sleep much earlier than the usual time, the power of slow-wave activity at the beginning of sleep is lower than usual and sleep is shorter [Dijk et al., 1987]. The chronobiological part of the model is process C (for circadian). The circadian pacemaker in this classical version of the model specifies upper and lower thresholds in the form of a circadian oscillation. The normal growth of process S between these thresholds runs from the morning to the beginning of the night and its normal decay takes place from the beginning of the night to the morning [Daan et al., 1984].

In the initial version of this model, one process interacts with the other only at the moments of substitution of the states of sleep and waking. A version of the model was proposed in which the pacemaker constantly modulates the parameters of the somnostatic process, such that the somnostatic process is converted into a rhythmostatic process [Putilov, 1995]. Parameters were selected for this model based on data from several previously published experiments, such that simple computation provided for assessment of "sleep debt" accumulating during particular periods of waking (otherwise known as its "pressure"), with subsequent checking of the correctness of the computations by measuring EEG spectral power during subsequent sleep [Putilov, 1995, 2014a]. In contrast to the classical two-process model, the rhythmostatic sleep–waking regulation model predicts that the power of slow-wave activity will be modulated by the circadian pacemaker. It was long believed that this activity reflects almost exclusively the homeostatic influence [Dijk and Czeisler, 1995]. However, very recent studies using forced desynchronization provided the first experimental demonstration of the circadian influence predicted by the rhythmostatic model, with a peak at the postprandial time of day [Lazar et al., 2015]. In particular, the model predicts that decreases in sleep "pressure" in the daytime cannot occur as effectively as during the night.

Another modification of the classical two-process regulatory model which, in fact, was not initially formulated mathematically, regards process C as an opponent of process S. This was first proposed in the 1990s by the founder of sleep medicine, William Dement, working with Dale Edgar and Charles Fuller to explain the results of experiments on sleep and waking and oscillations in body temperature in squirrel monkeys [Edgar et al., 1993]. The proportion of sleep after extirpation of the suprachiasmatic nuclei was found to increase, i.e., process S runs at above the normal level – sleep drive increases in the absence of these nuclei. The model explained this decrease in the level of sleep-opposing waking drive in terms of the absence of the influence of the circadian pacemaker which in this model operates as process C [Edgar et al., 1993]. Derk-Jan Dijk and Charles Czeisler used this idea of two opposing processes to explain the results of experiments using forced desynchronization of human biorhythms. Using the method described above, they discriminated circadian oscillations of physiological indicators into two components. One is linked with the circadian pacemaker and the other with the somnostat, i.e., processes C and S, respectively, [Dijk and Czeisler, 1995]. The model predicted that nocturnal sleep in humans must be uninterrupted as the period of the nocturnal decline in process S (the sleep phase of the sleep–waking cycle) coincides with the period of the decrease in process C in the second half of the day (this process reaches its minimum at night) [Dijk and Czeisler, 1995].

The model of two opposing processes is attractive for attempts to build new bridges between chronobiology and somnology. In particular, it provides a link between chronobiology and current neurobiological concepts of the regulation of sleep states and substates and waking [Koval'zon, 2013; Saper, 2013]. In particular, these views include the concept of an interaction between promoters and inhibitors of sleep and waking [Saper et al., 2001]. Groups of neurons opposing each other can control the process of substitution of sleep–waking states and the sequencing of slow- and rapid-wave sleep phases [Boutrel and Koob, 2004].

In addition, attempts were made to link results from analysis of the dynamics of EEG spectral characteristics recorded during sleep with the opposing interaction of the two processes. Thus, the inverse relationship between the power levels of slow-wave and β-activity (above 12 Hz) was explained in terms of an antagonistic interaction of the S process and the W process (for wake or wakefulness). An increase in the former – the homeostatic regulator of sleep – occurs during prolonged waking and an increase in the latter – the homeostatic regulator of waking – occurs during subsequent sleep [Perlis et al., 2001]. In particular, these ideas were propounded with the aim of explaining sleeplessness as an anomalous predominance of process W over process S [Perlis et al., 2001; Staner et al., 2003].

Not only spectral power in individual frequency ranges, but also the values of the two main components of the EEG spectrum show opposing interactions of the processes during sleep [Putilov, 2011]. These two components can be linked by processes promoting and inhibiting sleep/waking states and also specific sleep substates [Putilov, 2014a, b]. Various experiments using manipulation of the durations of sleep and waking [Putilov, 2011, 2014a, 2015] have linked the dynamics of values of the first component with sleep promoters and dynamics of values of the second with waking promoters [Putilov et al., 2014, 2019].

Both modeling of the sleep–waking cycle and modeling of daily oscillations in the level of drowsiness are of interest for chronopsychologists addressing the challenge of increasing work ability. The dynamics of the level of drows-

iness are very tightly linked with daily oscillations in work ability, such that the daily plots of drowsiness essentially repeats on a one-for-one basis the plot of road traffic and industrial accidents [Mitler et al., 1988; Samkoff and Jacques, 1992; Leger, 1994; Dinges, 1995; Van Dongen, 2006].

Although common sense suggests that oscillations in the level of wakefulness/drowsiness are a simple reflection of the sleep–waking cycle, they nonetheless demonstrate the properties of powerful circadian rhythms under the strict control of the circadian pacemaker (like the body temperature rhythm or the melatonin secretion rhythm). For example, Folkard et al. found that the wakefulness–drowsiness rhythm was characterized by a narrower range of entrainment than the temperature rhythm [Folkard et al., 1985]. It is therefore no surprise that during forced desynchronization, oscillations in wakefulness–drowsiness retain the rhythm characteristic of temperature and melatonin and do not follow the 21- or 27-h sleep–waking cycle [Johnson et al., 1992; Dijk, Duffy, and Czeisler, 1992; Wyatt et al., 1999]. A whole series of models of oscillations in drowsiness and work ability can be regarded as modifications of the classical two-process model [Achermann and Borbély, 1994; Åkerstedt and Folkard, 1997; Jewett and Kronauer, 1999; Fulcher et al., 2010; Putilov, 2014b, 2015; Putilov, Donskaya, and Verevkin, 2015, 2019]. Thus, a model was proposed explaining the daily dynamics of work ability by superimposing three processes: the homeostatic process S, the circadian process C, and an inertial process accounting for the smoothness of the transition from sleep to waking [Folkard and Åkerstedt, 1992]. The rhythmostatic model also required addition of a new process for the transfer from simulation of sleep and waking to simulation of wakefulness and drowsiness. It is suggested that this process depends on waking drive W and an opponent process linked with sleep drive S and that the parameters of both of these processes are modulated by circadian pacemaker C. This is only a minimal increase in the complexity of the initial rhythmostat model: after all, the same formula was used to describe and predict the dynamics of each of the two antagonistic processes whose superimposition produces more complex oscillations of wakefulness–drowsiness levels both in the normal 24-h cycle and in the process of prolonged – one-day or two-day – waking [Putilov, 2014b; Putilov et al., 2014, 2015, 2019]. Oscillations in wakefulness–drowsiness levels presented as resulting from two processes opposing each other were found possibly to be linked with their markers detected in the EEG spectrum, i.e., with the first and second components of this spectrum. The dynamics of the first component were found to control the sleep drive and the dynamics of the second controlled the counteracting waking drive, and additional curves for these components during sleep and waking were subject to the modulatory influences of circadian clocks [Putilov et al., 2015, 2019].

This model additionally provided for quite accurate reproduction and prediction of direct measurements of levels of wakefulness–drowsiness in different manipulations of the sleep–waking regime. It allowed the dynamics of drowsiness to be modeled not only using self-assessment data on changes in ongoing drowsiness levels, but also using objective data [Putilov et al., 2105; Putilov, 2014b, 2016]. EEG spectral characteristics are known to have stable individual properties (for example, Bazanova [2011], Lebedeva and Karimova [2020]). At the same time, many previous studies of transformations of the EEG spectrum during sleep deprivation in people of different sexes and ages demonstrated a relationship between such transformations and changes in ongoing levels of subjective drowsiness [Matousek and Petersen, 1983; Oken and Salinsky, 1992; Lorenzo et al., 1995; Finelli et al., 2000; Leproult et al., 2003; Strijkstra et al., 2003; Putilov and Donskaya, 2013, 2014]. A method was proposed allowing spectral EEG markers obtained by analysis of EEG traces recorded for just one minute (EEG drowsiness traces) to be used for objective evaluation of levels and dynamics of drowsiness. Correlation coefficients between two-day curves of subjective and objective drowsiness obtained in sleep deprivation experiments reached 0.98 [Putilov et al., 2019].

4. Methodology of Psychometry and Chronopsychometry. Parameters of oscillations in wakefulness–drowsiness and work ability levels vary from individual to individual. The difference between the peaks of two individuals is quite often more than half a day. People can be classified in terms of chronotype on the basis of questionnaire-based self-assessments of such oscillations in wakefulness–drowsiness levels or from self-assessments of daily dynamics of work ability [Horne and Ostberg, 1977; Kerkhof et al., 1985; Adan et al., 2013; Levandovski et al., 2013]. In addition, sensitivity to sleep loss and impairment vary individually. Differences between people in terms of the responses of their wakefulness–drowsiness and work ability rhythms to sleep loss were very significant (differing by an order of magnitude) and such differences remained constant over time [Van Dongen, 2006; Chua et al., 2014; Sletten et al., 2015; Dennis et al., 2017; Tkachenko and Dinges, 2018].

Studies also showed that the chronotype was among the individual characteristics of people associated with their tolerance to shift and/or night work [Breithaupt et al., 1978; Åkerstadt and Torsvall, 1981; Härmä et al., 1988; Costa et al., 1989; Moog and Hildebrandt, 1989; Saksvik et al., 2011; Bhatti et al., 2014; Leung et al., 2017]. One of the most important aims of chronopsychology research is to detect the neurophysiological basis of individual differences in wakefulness–drowsiness rhythms and sensitivity/resistance to sleep loss. The results of such studies can be used by applied scientists to develop personally oriented approaches to preventing accidents and risks to health associated with vigorous activities at unsuitable times of day [Arsen'ev et al., 2014; Dorokhov, 2013].

However, it is one thing to evaluate the parameters of circadian rhythms in experimental conditions in quite small

groups of experimental participants and quite another to study individual variability in these parameters. Such studies require notably larger numbers of experimental participants. Given that precise determination of the parameters of circadian rhythmicity such as its period, phase, and amplitude requires costly experiments, a significant number of studies are currently oriented not to experiments (for example, "forced desynchronization") but to questionnaires for self-assessment of chronotype. Questionnaire data can be obtained easily from large numbers of people without significant financial outlay, specially equipped facilities, purchase of expensive equipment, costs for consumables and analysis of hormone levels in biological samples, employment of large numbers of scientists in "day-round vigils," etc. Differential psychology (the psychology of personality) and psychometric methods developed in studies of individual psychological differences [Furr and Bacharach, 2017] provide yet another methodological basis for chronopsychology, especially those studies using questionnaires for self-assessment of chronotypes. The lack of accuracy of assessment of chronobiological characteristics is made up for by the ability to obtain quantitative data for quite large cohorts (details on the history and current state of the methodology of chronopsychological questionnaires can be found in reviews in English [Putilov, 2017a] and Russian [Putilov, 2018].

Special knowledge and experience is required for construction, adaptation, and validation of questionnaires; psychologists are familiar with these, though the chronobiologists and somnologists who initiated questionnaire chronopsychology studies in the 1970s had little experience with them. The first questionnaires were prepared, so to speak, "on the back of an envelope," without employing psychometric methods. Nonetheless, the first questionnaire is still the most widely used despite being rather unsuccessful and difficult to complete and process [Horne and Östberg, 1976]. This may be why the many drawbacks of questionnaires are compensated for by the ability to produce new data which can easily be compared with the enormous and diverse set of data already published over nearly 45 years. Questions in the Horne-Östberg questionnaire [Horne and Östberg, 1976] mainly address morning/evening preferences, for example, the most convenient times for work, going to bed, waking, physical exercise, etc. Numerical summation of questionnaire responses yielda total points scores on a morning–evening scale. Depending on the score, a person is assigned to a type: extreme evening or extreme morning, or intermediate (i.e., neither).

Publication of the text and key of the first questionnaire for assessment of morning/evening preference was followed by several attempts to either modify or shorten it and to construct questionnaires with largely similar content [Bohle et al., 2001; Smith et al., 2002; Torsvall and Åkerstedt, 1980]. All these questionnaires use one-dimensional scaling, i.e., the opportunity to rank the people completing the questionnaire along a single line from extreme "owls" to extreme "larks." Serious flaws were discovered when the procedure for psychometric analysis of questionnaire structure came to be used in chronopsychology. For example, factor analysis of interactions between responses to questions in such questionnaires showed that it was essentially impossible to link all questions with a single first factor, which is the idea behind a single scale [Wendt, 1977; Larsen 1985; Monk and Kupfer, 2007; Neubauer, 1992]. The structure of such questionnaires generally involves three groups of questions (factors): those associated with morning, those associated with evening/night, and those linked with selection between different times of day [Di Milla et al., 2013]. Thus, questionnaire questions are grouped into subscales, each of which reflects a separate individual characteristic.

Relatively recently, in 2003, the assortment of methods for such ranking of people along a single scale of phase differences in the daily rhythm was expanded by Till Roenneberg, Ana Wirz-Justice, and Martha Merrow. While other scales usually contain at least five questions to obtain overall assessments of morning/evening preference, the questions in this questionnaire sought to identify specific times on the time scale [Roenneberg et al., 2003]. A simple arithmetic operation was applied to the answers to the questions of the time at which sleep started and ended on work/study days and work/study-free days to determine the time corresponding to the middle of the period of nocturnal sleep on free days, sometimes taking account of the fact that people sleep longer on free days (like many laypersons, the questionnaire authors supposed that this was an attempt to compensate for "undersleep" accumulated on work days). The questionnaire authors also took the view that such questionnaire determinations of chronotypes yield information on the phase of the circadian rhythm entrained by biological clocks in its sphere of influence [Roenneberg et al., 2004]. The main difference between this scaling and the classical approach is that it evaluates the concrete result of adaptation of the human sleep–waking cycle to specific environmental times, while all previous questionnaires assessed the predisposition to sleep/wake and achieve maximum activity and work ability at particular times of day when given a free choice of daily regime. In psychology, one is opposed to the other as a state and an individual trait.

In psychology, it is also accepted that not only should state be distinguished from individual trait, but also that such a trait should be distinguished from ability. The questionnaire first proposed by in 1979 by Simon Folkard, Timothy Monk, and Mary Lobban addressed ability. Its authors postulated several measures of chronobiological differences between people and suggested that self-assessment could determine whether a person has an internal – biological – capacity for adaptation of the body to shift and/or night work [Folkard et al., 1979]. Thus, such capacities for adaptation of circadian rhythms in humans could be assessed quantitatively using various scales. Factor analysis of the structure of the questionnaire, which consisted of 20

questions, showed that apart from generally accepted individual characteristics such as morning/evening preference, there were more characteristics. Scales with questions addressing these characteristics were termed "rigidity/flexibility" (of sleeping habits) and "languidness/vigorousness" (or, in other words, "the ability to cope with drowsiness) [Folkard et al., 1979].

The literature in subsequent years barely mentions rigidity/flexibility and languid/vigorous types, this also applying to Folkard's own work. However, questionnaires with scales evaluating differences other than morningness/eveningness in the characteristics of daily rhythms were nonetheless published. These are generally attempts to assess the amplitude or stability of these rhythms [Di Milia et al., 2011; Ogińska et al., 2011; Randler et al., 2016]. Although questionnaires of this type, aiming to carry out chronotyping using multiple scales, were initially focused on applying psychometric methods to analysis of their structure and composition, attempts to create even one scale to assess a different, non-phasic, individual characteristic of the daily rhythm have not yet come to any consensus regarding content.

The development of Russian-language questionnaires to evaluate the adaptive capacities of the sleep–waking cycle included selection from a much longer list of initial statements (200) [Putilov, 1990]. The results of this development were used to create a model of the structure of individual variability in such capacities, which was three-dimensional and, from the formal point of view, analogous to the structure of personality traits [Putilov, 2007, 2010, 2016, 2018a]. In particular, identification of this structure made it possible to predict that the initial versions of the questionnaire would lack [Putilov, 1990; Putilov, 2000] a single scale which would be added to the final version of the questionnaire and then be validated experimentally in sleep deprivation studies [Putilov, 2007, 2010; Putilov et al., 2017; Verevkin et al., 2008].

An interesting questionnaire was developed under the direction of Olivier Mairesse. This contained 19 questions on drowsiness levels at 19 time points over the period of continuous waking from 08:00 to the middle of the following day [Marcoen et al., 2015]. Factor analysis of the structure of this questionnaire supported the predictions made by a structural model of individual variability in the adaptive capacities of the sleep–waking cycle [Putilov, 2016] in relation to the possibility of identifying, within the usual period of waking (from morning tonight), three relatively independent periods – morning, daytime, and evening. At each interval, the level in any person could change from low to high. Thus, there was a need to increase the number of classes of chronotypes to six in place of the usual division into morning and evening chronotypes. Some 95% of persons completing the questionnaire were found to be able to assign themselves to one of these six types, combined into three opponent pairs: "morning" and "evening" types (with decreases and increases in activity in the evening), "highly active" and "moder-

ately active" types (with stable high or stable low levels of activity), and "daytime" and "daytime sleepy" types (with peaks or drops in activity in the afternoon period). The frequency of each of these types in the population was found to be greater than 0.05 [Putilov et al., 2021].

Although the number of publications on chronopsychological variability has consistently increased in all subsequent years, we should expect an even faster rise in this number in forthcoming years, accompanied by an increase in quality. This comes from the appearance of new methodological approaches and progress in previously developed methods due to new technologies. Firstly, platforms such as Google make it easy to construct large-scale online questionnaires. Information on chronotypological characteristics can be extracted from data obtained from large numbers of people by simple traffic analysis in social networks such as Facebook. Secondly, it has become possible to obtain large quantities of data on individual chronopsychological characteristics by measuring objective parameters in everyday life. This is associated with the fact that devices capable of "at-home" polysomnography have come onto the market in enormous quantities, including watches (Smartwatch) which have sleep monitoring functions, actigraphs (for monitoring the activity-rest cycle), accelerometers (for monitoring humans' movements), and many other devices (for example, [Schoedel et al., 2020]). These have provided for objective – not based on people's words – assessments of daily rhythmicity (for example, Martinez-Nicolas et al., 2019]). This information can also be acquired from very large numbers of people, sometimes even unaware that they are taking part in scientific research.

5. Examples of Intriguing Themes in Chronopsychological Research. *5.1. Correlates of the chronotype.* Although this sounds paradoxical, the marked increase in the number of publications on chronopsychological variability in recent years has not been accompanied by such marked growth in the number of experimental studies of this variability. Most new publications contain results from so-called cross-sectional questionnaire studies and aim to find links between chronotypes and something else. These studies do not need two or more visits or multiple-day involvement of an individual person, and single visits do not require facilities specially equipped for sleep and biorhythms research and no not need measurement of objective parameters using expensive methods and apparatus. The only need is for hundreds of people (often the students or patients of the authors of these studies) to fill in two or more questionnaires, including one already-published questionnaire to identify morning and evening (early and late) types. The results are used to publish another report, or several, on sex-related or age-related differences in chronotype and/or its connection with something else, which is generally evaluated using other questionnaire(s).

It is not possible to place all the connections found in this way under the microscope in this review. For exam-

ple, both sex-related and age-related differences have been found between people of the morning (early) and evening (late) types, links have been found between the chronotype and various personality features, cognitive abilities, food-related behavior, overweight, health measures, sleep and drowsiness, seasonality of wellbeing and mood, depression and other psychopathologies, bad habits and addictions, sociosexuality, partner selection, number of offspring, etc., etc. The links found almost always suggest that the behavior of "owls" is yet again lacking such that they do not deserve the same praise as "larks."

As an example, we can cite a study awarded the 2014 Ig Nobel prize (which is awarded in various fields for achievements that "first make people laugh, and then make them think"). The Psychology prize was awarded to Peter Jonason, Amy Jones, and Minna Lyons for "amassing evidence that people who habitually stay up late are, on average, more self-admiring, more manipulative, and more psychopathic than people who habitually arise early in the morning." These characteristic features seen in "owls" more often than in "larks" are termed the "dark triad" in the psychology literature and include narcissism, psychopathy, and machiavellianism [Jonason et al., 2014].

It would not be an overstatement to note that this and most other similar "evidence" of connections between the chronotype and various other things are only correlations, not causal relationships. It is even more important to note that all these many studies are based on questionnaire assessments obtained using various existing scales to discriminate people into morning (early) and evening (late) types (a brief review of such results can be found in [Adan et al., 2013; Levandovski et al., 2013]). Due to a lack of any widely recognized questionnaire method for categorizing people along other dimensions of chronobiological variability, the relationships between these other dimensions and age, sex, and a multiplicity of very diverse individual human characteristics remain poorly studied. There are grounds for suggesting that if these relationships were studied as intensely as relationships with morning/evening (early/late) differences, the number of significant relationships worthy of publication would be no smaller. At the very least, this conclusion can be drawn from attempts to evaluate the extent of relationships between the three-dimensional structures of individual variability in the psychology of personality (the structure of personality features) and chronopsychology (the structure of the adaptive potentials of the sleep-waking cycle). It turns out that assessment of individual variations in one area predict up to 10% of the individual variation in another area [Putilov et al., 2013]. Finally, it is important to note that the results of questionnaire studies cannot be completely reproduced or can even contradict each other because different questionnaires evaluate somewhat different morning/evening features, abilities, or states. In particular, links between the chronotype and any other individual characteristic are found to be weak or nonexistent because

they are characteristic of only one, for example evening, component of morning/evening preference or, conversely, its other, morning component [Booker et al., 1991; Plusnin and Putilov, 1990; Dorokhov et al., 2018; Putilov, 2018b].

5.2. Evolutionary psychology and the genetics of chronotypological differences. Questions of the importance of the inherited (genetic) bases of individual chronobiological variability and its evolutionary origin need particular attention. The fact that this variability was initially inherent in people and appeared whenever conditions were suitable can be seen from the biographies of Julius Caesar and the first 11 Caesars compiled by Suetonius [Putilov, 1977]. As people have been hunter-gatherers for 99% of the evolutionary history of our species and they remained in Africa for most of this period, it is reasonable to ask questions on the selective advantages that "owls" might have over "larks" in thee conditions, i.e., not far from the equator, when, for example, the dark part of the day starts at 6 pm and ends at 6 am (bearing in mind that people become absolutely helpless in the dark). Several explanations proposing particular selective advantages of "owls" have been put forward [Kanazawa and Perina, 2009; Piffer, 2010; Randler et al., 2012; Jonason et al., 2013; Putilov, 2014b; Samson et al., 2017], though obtaining empirical support for these, as for other explanations developed in the framework of the evolutionary psychology approach to understanding psychological phenomena, is a difficult task.

Some of these explanations propose a relationship between evening preference and a hypothetical "temporal lekking," by analogy with the spatial lekking familiar to many in various bird species such as the black grouse [Piffer, 2010; Gunawardane et al., 2011; Putilov, 2014b]. In particular, the cause of "temporal lekking" can be linked with the sexual distribution of labor, which continues to exist in human societies (and can reach 100%). The result of dividing labor in space is that one sex has barely any opportunity to assess the advantages of members of the other sex ("good genes" in the terminology of evolutionary psychology). For example, females cannot observe males' hunting skills for large and not so large game. For "larks," this "professional" activity must have been easier, as they carried it out at the peak of their work capacity (in Africa, hunting and other types of the most vigorous activity in males in traditional societies is still mostly carried out in the morning hours and is completely finished by the start of the midday heat). There is only one interval during the day when all work is complete, as the sun has set, but air temperature is still near-maximal, so it is still too hot to fall asleep quickly. During this period of time, all adults, regardless of sex, usually gather together around the fire. Clearly, if such "temporal lekking" had not appeared during evolution in the ancestors of modern man, it is unlikely that humans would have developed various types of species-specific behavior in evolution, i.e., behavior characteristic only of our species and not seen in other mammals. Despite fatigue ac-

cumulated during the day, "owls" must have found it easier than "larks" to display species-specific behaviors such as dancing, playing musical instruments, singing, composing and reciting poetry, telling stories demonstrating the ability to joke, laugh, parody, etc. Sexual selection must have aided the appearance and development of these forms of behavior, such that they could signal "good genes" to the opposite sex, i.e., genes which by means of such species-specific behavior demonstrate the ability to develop good speech, cognitive, motor, sensory, imitation, and other skills important for survival and reproduction of any human society. Sexual selection would more favor those displaying such behavior at the peak of working ability, after sunset, i.e., "owls" but not "larks" [Putilov, 2014b]. However, "lekking" has not changed markedly in the modern world, as people largely continue to socialize during rest periods at the end of the working/studying day, i.e., mainly in the evening and early hours of the night.

It remains possible that after emergence from Africa, selection became even more favorable for "owls" during the subsequent dissemination of humans across the territories of Eurasia to regions with significant seasonal changes in day length (the photoperiod). In any case, the frequency of "owls" increases and the frequency of "larks" decreases from the equator to the poles in both the northern [Randler and Rahafar, 2017] and southern [Leocadio-Miguel et al., 2017] hemispheres. Questionnaire data indicate that "owls" are those inhabitants of the USA whose ancestors immigrated from Europe rather than those whose ancestors came from equatorial Africa [Eastman et al., 2016; Malone et al., 2017]. The period of the circadian rhythm in the former was longer than that in the latter in a variety of experimental conditions [Eastman et al., 2012; Eastman et al., 2016, 2017; Paech et al., 2017]. We analyzed the geographical variation in allele frequencies of 26 sets of genes (a total of 23,000 polymorphic variants). The genetic signatures of latitude-dependent adaptation were seen in those polymorphisms which had previously been found to be linked with the chronotype [Putilov et al., 2018; Putilov et al., 2019]. It is interesting that soon after the emergence from Africa, one such variant (allele C of the marker termed rs75804782, close to the *ASB1* gene) was borrowed from a relative of modern humans then living more in northerly areas – Neanderthals. Interbreeding between the two subspecies of *Homo sapiens* produced introgression of part of the genome belonging to a former root inhabitant of Eurasia [Dannemann and Kelso, 2017]. The location of the introgression close to one of the three *PER* genes suggests that some fragment of this region was probably involved in regulating the expression of this gene [Dannemann and Kelso, 2107; Putilov et al., 2019].

Studies in behavioral genetics provide evidence of a link between predisposition to nocturnal lifestyle and the genetic component of chronobiological differences [Hur et al., 1998; Hur, 2007; Koskenvuo et al., 2007; Watson et al., 2013].

However, all attempts to find chronotype marker polymorphisms led to the same result as analogous attempts to find genetic markers for other complex quantitative traits. Such traits depend on an enormous number of genetic variants. They are formed by polygenic selection and a key property of adaptation controlled by this type of selection is that very small changes in allele frequencies are distributed over an enormous number of genes and intergenic intervals [Pritchard and Di Rienzo, 2010]. Detection of such changes is therefore no easy task [Daub et al., 2013]. Virtually all genes expressed in cells can influence the functions of genes associated with the main trait. Thus, the greater part of inheritance can be explained by actions on genes outside the main pathways forming the genetic bases of this trait [Boyle et al., 2017].

Studies of the genetic basis of the chronotype are still markedly behind studies on the detection of genes responsible for various other complex quantitative traits, so they sequentially, step by step, repeat all the stages covered by more "advanced" molecular genetic research. First to appear were studies linking the chronotype with a rare mutation (for example, one of the "clock" genes [Toh et al., 2001]). The effect of this mutation was very strong, though as it is encountered extremely rarely, so this mutation alone cannot explain why so many of the other people around us who are either "owls" or "larks" do not carry this rare mutation or any other equally rare mutation in the "clock" or any other genes (It is, however, possible that there are many diverse but as yet unknown rare mutations scattered throughout the genome [Wainschtein et al., 2019].)

This was followed by the appearance of publications on one of the polymorphisms of one of the "clock" genes. For example, differences in chronotype were seen in the English population in patients with short and long tandem repeats of nucleotide sequences (VNTR) in one of the *PER* genes (the rs57875989 marker) [Archer et al., 2003]. When a large quantity of publications of confirmatory studies had accumulated over the next few years, it turned out that joy was premature. Although links were sometimes statistically significant, they could also contradict previously discovered links. In most cases, confirmatory studies did not find any links [Putilov et al., 2019]. Essentially the same results were obtained for all other well studied individual polymorphisms in different "clock" genes [Dorokhov et al., 2018]. Then, four articles were published over the period in 2016–2019 on genome-wide association studies (GWAS) seeking links between the chronotype (the latest report, based on the largest cohort size, was by Jones et al. [2019]). All used data from a biobank in the UK from the root population of the kingdom. A whole series of chronotype-associated genetic variants were named in two or more of these four reports. However, results from a recently published chronotype GWAS in the Finnish population [Maukonen et al., 2020] did not find any of the variants found in the last of the British studies (despite the fact that a total of 7741 previously associated genetic variants were confirmed).

For this reason, the good times, when a specific person could obtain his or her chronotype not by filling in a questionnaire but from summing genetic variants read in the genome, have not yet arrived.

5.3. Social desynchronosis and weekday naps. The daily light regime easily corrects the period of the circadian pacemaker and, following the pacemaker, all the body's other circadian rhythms within its sphere of influence are entrained by the 24-h dark–light regime. Illumination before sleep shifts the pacemaker phase to later times, but then, the next morning, the action of light at the end of sleep or after sleep compensates for this shift. As a result, in conditions of the natural succession of day and night, circadian rhythms in most people almost constantly run over 24 h and are not "free-running" [Roenneberg et al., 2003]. When a person spends a lot of time during the day in locations with illumination levels greater than 2500–100,000 Lx and then use weak illumination (about 100 Lx) in the evening prior to sleep, this has virtually no effect on the 24-h periodicity of physiological and hormonal functions. However, many spend the whole day in locations at illumination levels rarely exceeding 500 Lx. In the evening they still use low-intensity artificial illumination and sleep long in the morning in darkened places (less light passes through naturally if their eyes are closed). Chronobiology predicts that their biological clocks will show a different time from the clock of a person not isolated in that location all day. The essence is that their illumination regime is anomalous, and thus not infrequently induces a delayed shift in the pacemaker phase to the evening because of the weak contrast between the dim daytime and dim evening illumination, while full compensation for the advanced morning displacement does not occur because of the weak and delayed morning illumination. In the best case, as shown by questionnaires, the result of living with this unnatural illumination is a delay in the sleep phase, as seen in the inhabitants of large cities [Roenneberg et al., 2007]. The less the daytime illumination due to long periods of time in such a location, the greater the delay.

In the worst case, the phases and periods of circadian rhythms will demonstrate "free flow." As the intrinsic circadian clock in most people is somewhat longer than 24 h, the phase of these "dungeon children" and "denizens of the stone jungle" generally show a day-to-day drift towards delay. This type of phenomenon, in which the phases of some of the body's circadian rhythms are shifted relative to the phases of other rhythms, is termed "jet lag." Boris Sergeevich Alyakrinskii (1911–1990) suggested that this term should be translated into Russian as "desynchronosis" [Alyakrinskii, 1973, 1983]. The concept of jet lag appeared in the English-language literature at the dawn of jet aviation due to attempts to explain the unpleasant consequences of flights across multiple time zones. Although the pacemaker can immediately shift its phase and correctly show the time of the new time zone, many other body clocks are unable to keep up with such extreme shifts. As a result of the

fact that different periodic processes with different speeds are retuned to the new time (some quickly, others taking more than a month), clocks at the periphery tick out of time throughout this period. Thus, at least one week after flight, especially in the eastern direction, people experience problems with tuning the body's operation to local time [Baron and Reid, 2014]. This state was later defined as a disorder [Cingi et al., 2018] and recommendations were developed to ameliorate its symptoms and accelerate adjustment to the new light regime [Matyukhin et al., 1983; Bin et al., 2019].

In the case of flights to another time zone, desynchronosis is temporary, while shift work and, frequently, night work is associated with permanent and regularly exacerbated desynchronosis. After all, the external light regime and some social time markers (home life, noises in apartment buildings and on the street) remain unaltered and work time comes into temporary or permanent conflict with them throughout the working week [Saksvik et al., 2011; Boivin and Boudreau, 2014]. The practical task of preventing this type of chronic impairment to the body's circadian rhythms which, like classical desynchronosis, is regarded as a disorder [Drake et al., 2004], was one of the leitmotifs for the first studies and recommendations in optimizing work capacity as noted above. As the diagnosis has been defined, contemporary studies of desynchronosis can now be regarded as the chronomedicine area of chronobiology research.

Relatively recently, in 2006, Wittman et al. introduced the new term "social jet lag" into scientific terminology. This has been found in the literature in recent years far more frequently than jet lag in its original meaning. This term defines the conflict between social and biological clocks arising as a result of the common practice of shifting the start of the work or study day to the early morning hours [Wittman et al., 2006]. Stability in the phases of the pacemaker subordinate to the natural light regime is postulated to operate throughout the week, with a relative shift in sleep phases which – if measured in terms of the mid-point of the sleep period – is shifted back and forth on weekend/week days [Wittman et al., 2006; Roenneberg et al., 2007]. Starting from the moment of its appearance, the concept of social jet lag, in contrast to the classical concept of jet lag, remains a quite speculative idea. Even the originators of this concept were recently forced to recognize that it has serious drawbacks, though only partially and in the haziest of expressions [Roenneberg et al., 2019]. Furthermore, the authors of this report [Roenneberg et al., 2019] themselves cited several publications (in particular [Burgess and Eastman, 2006]) showing that the sleep phase remains synphasic during the weekday phase of the circadian pacemaker. These observations were not at all consistent with the concept proposed by the authors that the circadian phase through the week and the back-and-forth shifts in sleep phase on week/weekend days are stable. Furthermore, in the dissertation of one of the authors, a delay in the pacemaker phase on weekdays was seen in young people with late

sleep times, while in young people with early sleep phases the pacemaker remained unaltered [Zerbini, 2017], i.e., they showed "normal" rather than social jet lag. Finally, none of the symptoms of "normal" jet lag was seen in social jet lag [Tavares et al., 2020] and the adverse effects of social jet lag on the body remain insufficiently documented [Beauvalet et al., 2017; Vetter, 2018].

As an enormous number of publications contain data on the time of day at which study participants go to bed and get up on week and weekend days, data on hundreds of cohorts were simulated using the rhythmostat model described above. The simulation did not show any signs of either normal or social jet lag in the majority of cohorts [Putilov and Verevkin, 2018; Putilov et al., 2020b]. It turned out that what was termed social jet lag is actually no more than loss of sleep on weekdays which can be calculated using the model for each of these cohorts and in the longer term for each individual person [Putilov et al., 2020a; Putilov et al., 2020b]. Although the time of going to sleep on weekdays shifts to earlier times because of early waking on these days, the model predicts that because of the modulatory influence of the circadian pacemaker on the process of decreasing sleep "pressure," sleep on weekdays, if not interrupted the following day, spontaneously ends at the same time as on weekend days. Sleep loss on weekdays was found to be very large because of the expected greater duration than on weekend days. Furthermore, on these weekend days people do not catch up on sleep, but simply sleep the number of hours they are "ordered" to sleep at this time of day by their own rhythm drivers [Putilov et al., 2020b].

Simulations have shown that sleep loss is particularly large in older school students. They start classes at the same time as other school students and their sleep phase at this age is significantly displaced to later hours both in relation to the phase in younger school students and in relation to the phase in older people [Putilov and Verevkin, 2018]. For example, calculations from sleep data from school students living in the Russian North in the 2010s, published by Borisenko et al. [2016], showed that sleep loss amounts to up to a third of the duration that would be seen in conditions of spontaneous waking on weekdays [Putilov et al., 2020a]. Thus, it is sleep loss rather than jet lag that causes what American investigators of this chronopsychological problem termed an "epidemic of sleep deprivation in adolescents" (Carskadon, 2011; Crowley et al., 2014].

6. Conclusions: Unsolved and Controversial Problems. Although the number of studies in chronopsychology in recent decades has increased from year to year, many problems have remained unsolved for decades. There are also problems which only require clear formulation, i.e., most investigators working in this field remain unaware of them. For example, some problems, albeit formulated by someone at some time, are simply ignored by the majority. Some examples of unsolved and controversial problems are given below, without literature references, exclusively to

identify them and give some general views on their nature, acuity, and relevance.

Currently we can only hope that chronopsychology will at some time cross a threshold at which the prospects for achieving a consensus on methods of measuring individual chronopsychological differences open up. In particular, there is presently no generally accepted view in questionnaire studies as to which questionnaires provide better assessments of morning/evening (early/late) differences, or how many – one or several (for example, morning and evening) – scales should be used, etc. However, there are currently no great hopes of reaching a consensus as to how many measurements of chronobiological variability exist, how to interpret them, and which shales should be selected from those already proposed or how many new scales need to be constructed to obtain reliable questionnaire assessments for each measurement.

Virtually no-one can doubt that people's psychophysiological and genetic characteristics constitute the biological basis for questionnaire assessments of differences between them in adaptive capacities, behavior, and habits associated with the cyclicity of sleep and waking. Nonetheless, the main unsolved problem in chronopsychological testing remains the lack of generally accepted objective (psychophysiological and genetic) markers for chronopsychological variability. In other words, it has not been shown that differences identified by questionnaires can be linked directly with any differences in objective indicators measured at the molecular level or in chronobiological and somnological experiments. For example, the phases of physiological and hormonal rhythms, the phase of the objectively assessed propensity to fall asleep, polysomnographically assessed times of the beginning and end of sleep, etc. usually indicate a difference of just 2–3 hours between people of the morning and evening types, while the difference in their peak in work capacity or peaks in subjective assessment of the daily dynamics of drowsiness is no less than 9 h. Such significant differences between peaks in these two chronotypes do not therefore correspond to the relatively small, though significant, differences in peaks on the curves of the various objective indicators. Although the possibility of finding such a significant difference (9–12 h) was demonstrated using objective (EEG) indicators of variations in the ongoing level of drowsiness, such measures are not widely used in chronotypological research.

Almost no investigators are currently addressing the problem of explaining the mechanisms responsible for the sometimes very striking discrepancies between subjective and objective assessments of chronobiological and somnological differences. Even when such discrepancies are noted and explained at the hypothetical level, very diverse causes – often mutually exclusive – are suggested, from the purely psychological to the exclusively biological. In particular, there is as yet no generally accepted approach to explaining sex- and age-related differences in subjective and objective

assessments of sleep quality and drowsiness levels. There is no doubt regarding the fact that objective (polysomnographic) sleep characteristics which people of middle age evaluate as excellent correspond to those characteristics as seen in sleep disorders in youth. While the objective characteristics of sleep in women provide that their sleep is qualitatively better than that in men, their subjective assessment of their sleep indicates the opposite.

Technical innovations currently used in chronopsychology research have opened the possibility of running less expensive and laborious (so-called field) research on a large scale and involving large number of people. These guarantee qualitative acceleration in the development of chronopsychology in coming decades. They allow faster and larger-scale solution of practical tasks, such as developing and introducing theoretically grounded personalized approaches to preventing and correcting impairments to biorhythms and sleep and to making improvements in the daily regime and level of work capacity.

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