**(Slide 1) Lecture 20**

**Physiology of adaptation. Chronobiology and chronomedicine**

**(Slide 2)** Lecture plan:

1. Physiological Adaptation Definition.

2. Types of Adaptations.

3. Nature of Physiological Adaptations.

4. Functions of Physiological Adaptations.

5. Adaptive variation in regulation.

6. What is chronobiology?

7. What is the mechanism of circadian rhythms?

8. Circadian desynchrony.

9. What is chronomedicine?

**(Slide 3)** Out of all the different types of adaptations, physiological adaptations display a wealth of diversity, functions, and significance in almost all forms of life on this planet. So, when asked what is physiological adaptation, it can be defined as “a set of ongoing types of intracellular, biochemical and metabolic adjustments inside an organism’s body in order to maintain it in equilibrium under any kind of environmental condition”. This form of adaptation keeps evolving over time taking different forms as per the organismal requirement; hence it’s dynamic in nature. For sustenance and reproductive advantage, plant and animal adaptation to their environment is the primary driving force for species continuation, no matter how extreme the environmental, climatic, resource, or niche competition prevails.

**(Slide 4)** How do adaptations take place? Nature poses a plethora of challenges to each species from time to time. It could be a search for:

* Suitable place to live
* Availability of resources (food, water, sunlight, nutrients, etc.)
* Fight for a mate (to produce progeny and pass on genes)

**(Slide 5)** So, we understand that all these challenges come as varying stimuli to an organism or species. Challenges along with them bring in a lot of pressure and stress. In order to counter these stresses, species over millions of years develop a set of “adaptive responses”.

**(Slide 6)** Physiological adaptation (biology definition): a metabolic or physiologic adjustment within the cell, or tissues, of an organism in response to an environmental stimulus resulting in the improved ability of that organism to cope with its changing environment. It may also be the response of the organism to a specific external stimulus in order to maintain homeostasis.

**(Slide 7)** Examples of physiological adaptations: tanning of skin when exposed to the sun over long periods, the formation of calluses on hands in response to repeated contact or pressure, and the ability of certain organisms to absorb nutrients under low oxygen tensions.

**(Slide 8)** There are basically 3 types of adaptations namely structural adaptations, behavioral adaptations, and physiological adaptations.

**(Slide 9)** A. Structural adaptations

Role: Bring changes in the physical structure of a species over time to make it physically equipped.

Examples: Changes in body sizes, coloration, the shape of organs, and appendages.

Nature of adaptations: Usually inheritable and pertain to transgenerational adjustments.

In the plant kingdom, the heat-coping mechanism is such that desert plants develop thick stems and reduced leaves called spines. These changes in physical features help them to adapt well to extreme heat.

In the animal kingdom, camouflage is the perfect example. Chameleons are able to evade their predators as they change their physical appearance i.e. color and become undetectable to the eyes.

**(Slide 10)** B. Behavioural adaptations

Role: Responsible for the changes in behaviors and the way in which members of a species act.

Examples: Migratory skills, hibernation, insect trapping ability in insectivorous plants, and mating behaviors in birds and animals.

Nature of adaptation: Usually not inherited from one generation to another, rather they are learned by each organism of the species over its lifetime.

In the plant kingdom, various types of tropisms like phototropism, thigmotropism, gravitropism, etc. are behavioral adaptations. Plants grow their shoots towards the source of light to maximize their photosynthetic yields.

In the animal kingdom, the migratory behavior of birds is important to survive the hardships of one habitat they primarily live in. They move from one habitat to another in search of food, a place to live and reproduce.

**(Slide 11)** C. Physiological adaptations

These adaptations are the physiological responses of an organism to the changes in its micro– and macro-environment. They confer improved ability to an organism to adapt to the changing environmental conditions by acting at cellular, physiological, metabolic, and biochemical levels. In biology, the definition of physiological adaptation goes like “changes in the basic metabolome of an organism to maintain homeostasis under the worst of environmental circumstances and trends”. Here, it becomes important for us to understand two basic terms: metabolome and homeostasis.

**(Slide 12)** Metabolome is the collection of all the metabolites produced by all the cells of an organism’s body in the due course of metabolic activities that it carries out to sustain life and basic functioning. Metabolome thus gives us a clear measurement and readout of the physiological characteristics and status of an organism. In order to adapt to extreme conditions, the cells of the body have to behave differently, thus producing a whole new or modified spectrum of metabolites that can aid easy acclimatization to the new conditions.

**(Slide 13)** Homeostasis is the mechanism of the body to maintain a fairly stable equilibrium. Whether the body will remain in this natural physiological equilibrium or not, is determined by the balance between 2 primary factors: new environmental conditions and the organism’s ability to respond. Look at the figure below in order to understand the concept of homeostasis maintenance and what essential role is physiological adaptation playing in it.

Now as we know how to define physiological adaptation in a broader aspect, let’s move next to understand its nature.

**(Slide 14) Nature of Physiological Adaptations.** There are many conflicts of opinions on its nature if it’s inheritable or not. Any ability of an organism that is at a cellular level is meant to be guided by the genetic make-up of the organism. Now since physiological adaptation is a display of cellular and metabolic changes, it should be genetically defined and hence inheritable from one generation to another.

On the contrary, since an organism is highly capable to acquire internal changes within its lifetime in response to altered external conditions (like tanning), physiological adaptations don’t seem to be inheritable or genetically defined rather acquirable in one’s own lifetime.

**(Slide 15)** In biology, adaptation refers to the adjustment or changes in behavior, physiology, and structure of an organism to become more suited or fit to an environment. According to Charles Darwin’s theory of evolution by natural selection, the organisms adapt to their environment to become better fitted to survive and pass their genes on to the next generation. However, unlike evolutionary adaptation that involves transgenerational adjustment, physiological adaptation is generally narrow in scope and involves the response of an individual to a particular, usually narrow, range of stimuli.

**(Slide 16) Functions of Physiological Adaptations.** What is the role of physiological adaptations in organisms and in the environment? Some of them are as follows:

Physiological adaptations aid the survival of organisms in their ecological niches.

* Physiological adaptations aid normal growth and development.
* Physiological adaptations aid the regulation of body temperature, pressure, ionic balances, and metabolic rates.
* Physiological adaptationsaid in resource conservation (water/nutrients) or resource maximization (sunlight/ions)

For animals and humans to function effectively in any given environment, adaptation to their environment is a prerequisite. Few examples of adaptations in animals are:

**(Slide 17) Production of venom:** This is a physicochemical adaptation that helps the animals to ward off predators and capture their prey more easily. Examples: snakes, bees, spiders.

**(Slide 18) Concentration of urine:** Desert animals live in dry, arid, and extreme conditions and require an animal adaptation that can grant them suitability to survive even in acute scarcity of water. For this, there is a modified urine concentration mechanism in their kidneys. Examples- fennec fox, camels, etc.

**(Slide 19) Offensive odor production:** In order to keep away all potential predators or competitors, skunk produces a distinctive, disgusting chemical and sprays it.

**(Slide 20) Tanning (in humans):** This adaptation is the most important one for the human populations living in the temperature range of 23-46 ºC as this zone has varying levels and intensities of UVB depending on the season.

**(Slide 21) HIIT (in humans):** Many recent studies show that high-intensity interval training (HIIT) confers very high endurance to humans and helps in evading most of the chronic health issues associated with modern lifestyles. It acts at the cell’s physiological level and increases the mitochondrial biogenesis in human body cells, thereby empowering it.

**(Slide 22) Video\_Types of Adaptations**

**(Slide 23) Adaptive variation in regulation.** When tolerance cannot evolve because of costs or constraints, a species can regulate its internal state to persist in extreme environments. The benefit of physiological regulation depends on an organism’s tolerance of environmental conditions. A specialist, which performs well only within a narrow range of conditions, would benefit greatly from regulation. The cost of regulation depends on the time and energy required to maintain an internal state that deviates from the external one. From an optimality perspective, we should expect either a high benefit or a low cost to cause the evolution of effective regulation.

**(Slide 24)** Much evidence of adaptive regulation comes from studies of thermal and hydric states, which often depend on one another. In particular, mammals and birds provide outstanding examples of adaptive regulation in the face of varying costs. In cold environments, these animals rely on metabolic reactions to generate the thermal energy needed to maintain warm bodies (endothermy). In hot environments, excess thermal energy can be dissipated through the evaporation of water. For many species, these regulatory processes result in a nearly constant body temperature. Nevertheless, both mammals and birds adjust the intensity of thermoregulation when either energy or water becomes scarce. Experimental manipulations of feeding rate, ambient temperature, and thermal insulation have shown that mammals and birds let their bodies cool considerably when maintaining an elevated temperature becomes energetically costly. Furthermore, these animals let their bodies warm to unusually high temperatures when dehydrated. This tradeoff between balancing thermal and hydric states also occurs in organisms that rely primarily on solar radiation to thermoregulate (ectothermy).

**(Slide 25)** As with physiological tolerance, physiological regulation varies adaptively along abiotic gradients. Comparisons of populations within and among species of Drosophila have generated a comprehensive viewon the regulation of water loss, reinforced by studies of experimental evolution. In general, flies from temperate environments resist desiccation better than do flies from tropical environments. This resistance to desiccation comes from enhanced regulation of water loss rather than enhanced tolerance of dehydration. Allen Gibbs and his colleagues used experimental evolution to discover mechanisms underlying the adaptation of water regulation in Drosophila melanogaster. Populations exposed periodically to dry conditions evolved genotypes that develop relatively long chains of hydrocarbons in their cuticles, a biochemical strategy thought to reduce water loss. This example illustrates the complementary nature of comparative and experimental approaches to the study of physiological adaptation.

**(Slide 26)** Many body tissues have their own timetables, organized by cyclic oscillations in the expression of a network of numerous 'clock genes'. “,” says Derk-Jan Dijk, director of the Surrey Sleep Research Centre in Guildford, UK. “It's a house with clocks in every room and every corner, yet in one way or another they work in an organized way.” The timing of all these various 'peripheral oscillators' can profoundly affect metabolic activity, immune cell proliferation, and numerous other critical functions. But there is a central pacemaker that gives the body a sense of the time of day: the suprachiasmatic nucleus (SCN), a group of neurons in the hypothalamus.

When melanopsin photoreceptors in the eye detect light, the SCN is activated and responds by initiating a host of rhythm-establishing physiological responses, including suppressing production of the hormone melatonin by the pineal gland (see 'The light switch'). The peripheral oscillators can be shifted by physical activity or by altering meal times, but most research suggests that light exposure is by far the most important determinant of rhythms driven by the SCN. “If you look at the data for humans, every time they suggested that exercise or food may shift the clock, they also suggest that light may have been involved,” says Debra Skene, who studies chronobiology at the University of Surrey, UK.

**(Slide 27)** Light is the dominant influence on circadian rhythms, but other factors can come into play. A small subset of completely blind people who lack melanopsin photoreceptors, for example, can still achieve some circadian entrainment through external cues and lifestyle1. This timetable can be shattered by a trip across a few time zones, however, requiring long periods of readjustment without the assistance of light to signal the time of day. Many other totally blind individuals fail to entrain at all, with profound effects. “They sleep at night because that's when they're told to sleep, so they have very short sleep of poor quality, and at lunchtime their circadian system starts saying they should go to sleep,” says Skene. “So we see them extremely tired — they nap and they don't perform well.”

**(Slide 28)** Humans are diurnal animals and so tend to be active by day and rest at night. But personal preferences for when to sleep can differ considerably among individuals, and even at different stages in the same person's life — the difference between being early birds or night owls.

**(Slide 29)** Researchers are still grappling with the best approach to measure the innate timing of someone's internal clock. As an indicator of 'biological night', levels of melatonin in various body fluids can give researchers a way to monitor the SCN cycle directly in an individual. But this requires repeated body fluid sampling over extended periods, and is therefore impractical for population-scale studies. Instead, most sleep researchers rely on surveys in which people self-report their sleeping habits.

**(Slide 30)** One of the biggest surveys of sleeping habits, with more than 150,000 respondents from around the world, is the Munich Chronotype Questionnaire (MCTQ), run by Till Roenneberg at the Ludwig Maximilians University in Munich, Germany. His team devised an online survey that asks people to describe the timing of their sleep behaviour on a day-to-day basis, both on normal working or school days and at weekends or holidays. By characterizing individual sleep patterns — what Roenneberg calls a 'chronotype' — it is possible to quantify habits previously observed only at an anecdotal level, such as the tendencies of children to wake early and of teenagers to sleep late. “We were able to show how drastically the clock gets later from childhood through adolescence, reaching peak lateness in women at 19-and-a-half and in men at 21, and after those ages people get earlier again until they die,” says Roenneberg.

**(Slide 31) Alarm clock shock.** The Munich Chronotype Questionnaire data have also provided insights into how our biology is altered by living and working in the artificially illuminated, industrialized world. By assessing both rural and urban populations, Roenneberg and others have shown how modern life scatters people's sleep patterns even further around the clock. “If we were all farmers, working outside all day, chronotypes would vary only by three to four hours,” says Roenneberg. “But since most of us work predominantly indoors and use artificial light after sunset, our clocks don't receive strong synchronizing signals anymore, and chronotypes nowadays span up to 12 hours.”

**(Slide 32)** Circadian desynchrony is most acute in people whose work schedules make them live nocturnal lives. “They are exposed to a very complex light–dark cycle, where there is artificial light at night but still some natural light that you may see during the commute home or to work,” says Dijk. “In the majority of those types of shift workers, their central clock does not adapt.”

**(Slide 33) Video\_The Circadian Rhythm and Your Biological Clock in 3 Minutes**

**(Slide 34)** Roenneberg's team has found that circadian desynchrony may be far more pervasive, however. Many modern workers effectively live on two different timetables — one enforced by their weekday alarm clock, and the other aligned to their weekend socializing and 'sleeping in' — resulting in disruption that he has dubbed 'social jetlag'3. “In most people, it looks as if they were travelling from Europe to the United States on a Friday evening and back on a Monday morning, because their displacement is so large,” says Roenneberg. This disconnect begins at adolescence, when our body clocks reach their latest preferred wake time, and continues all the way to retirement age.

People who operate on schedules not aligned to their internal rhythms, either due to shift work or social jetlag, often exhibit signs of chronic sleep restriction or disruption that can impair both job performance and overall wellbeing. “During wakefulness, you will have problems maintaining sustained attention,” says Dijk. “You will be sleepier and experience disruption in working memory — you will see the effects across all cognitive domains.”

**(Slide 35)** In the long term, such desynchrony can exacerbate the risk of cardiovascular disease, obesity and other health problems3,4 (see 'Heavy sleepers', page S8). “In our animal models of 'clock gene' mutations, we're seeing diabetes and a propensity for obesity and metabolic disorders,” says Joseph Takahashi, who studies circadian rhythms at the University of Texas Southwestern Medical Center in Dallas. Several studies have found a similar connection in shift workers and other individuals operating on schedules not aligned to their internal rhythms3,4. These findings “don't necessarily mean that there are immediate health consequences”, says Dijk, “but we can see the impact of being asleep or being awake at the wrong phase of your circadian cycle immediately.”

**(Slide 36)** At night, artificial lighting continues to activate the SCN and disrupt the natural release of melatonin, which normally heralds the onset of biological night. But not all light stimulates the SCN equally. Skene and others have shown that specific wavelengths are especially important 'waking' signals. “We observed peak light sensitivity at a wavelength of around 460 to 480 nanometres — a nice, deep blue,” she says. Red light, by contrast, has only a weak impact on melanopsin receptors and is less prone to stimulate wakefulness. So adjusting the relative levels of blue and red light that people are exposed to throughout the day could preserve normal circadian timing even during prolonged exposure to artificial light.

**(Slide 37)** Klerman is collaborating with her colleague Steven Lockley at Brigham & Women's Hospital and with George Brainard of Thomas Jefferson University in Philadelphia, Pennsylvania, to test this approach in an extreme situation: the International Space Station. Long-term isolation in cramped quarters poses many problems for astronauts, and they also experience disorienting light–dark cycles resulting from the station's orbital time of 90 minutes. “This is too short for our circadian system to synchronize,” says Lockley. “The body clock starts to free run on its own time, just like for blind people.” This is further confounded by the need to interact with people operating on various Earth schedules, such as mission control in the United States or crews arriving from Russia.

**(Slide 38)** Lockley and colleagues previously showed that blue light could help to synchronize Earth-based crews with the Martian day as part of the Phoenix Mars Lander mission. The researchers are now exploring programmable LED (light-emitting diode) systems that dynamically shift from blue-enriched to red-enriched white light on a 24-hour cycle. “We're working on shifting people's rhythms more quickly and maintaining their alertness at a better level,” says Lockley.

This technology may be most valuable in extreme places such as spacecraft, submarines or Antarctic research facilities, but the broader potential is obvious. The electronics company Philips, based in Amsterdam, the Netherlands, is one of several developing controllable, dynamic lighting systems for homes, schools and offices that boost blue wavelengths early in the day and in the post-lunch slump, and shift to redder wavelengths later in the afternoon.

**(Slide 39)** It is not yet known whether these lighting systems will be effective in groups composed of people with widely varying chronotypes, but drugs that tinker with circadian rhythms could provide a more personalized approach. The hormone melatonin may not be sufficient by itself to send someone to sleep, but it nevertheless helps the body to prepare for sleep, and there is evidence it can affect the timing of sleep. “The general consensus is that melatonin can phase-shift circadian rhythms when properly applied,” says Klerman. Indeed, a growing body of work suggests that the combination of properly timed melatonin dosing and managed light exposure can counter the circadian problems associated with both jetlag and shift work6.

**(Slide 40)** Melatonin requires a prescription in Europe but is available over the counter at health-food stores in the United States. However, the US Food and Drug Administration has limited oversight over the quality and content of such 'natural supplements', so it is difficult for US consumers to achieve correct dosing. As a more reliable alternative, several drug companies are developing synthetic agents that mimic the effects of melatonin, such as tasimelteon, developed by Vanda Pharmaceuticals in Washington, DC. Klerman and colleagues have shown that tasimelteon can improve sleep quality in time-shifted human subjects7, and it is now in a phase III clinical trial for use in blind individuals who lack melanopsin receptors. Such people “have recurrent jetlag”, says Klerman, “so they are an ideal population that you would want to try to entrain with melatonin agonists.”

**(Slide 41)** Several other potential circadian modulators have been discovered in the past two years. Pharmacology researcher Thomas Burris and colleagues at the Scripps Research Institute in Jupiter, Florida, identified two compounds, for example, that alter circadian rhythms by acting on a key regulator of clock gene activity. These compounds, known as SR9009 and SR9011, also affect weight gain and metabolism in mice8. “Small molecules that can reset the clock might help in recovering from jetlag more rapidly,” says Takahashi, who collaborated with the Burris team and has launched a circadian drug-discovery company, Reset Therapeutics, based in Burlingame, California. He adds that circadian drugs could potentially treat metabolic problems associated with off-kilter body clocks, and counter the disturbed sleep that commonly afflicts elderly people.

It is less clear whether these drugs would be an appropriate solution for chronic, lifestyle-associated jetlag, however. “Medication should be used if people are sick,” says Roenneberg. “I'm not comfortable with using medication to align people to what society wants.” As an alternative, he recommends designing work schedules to suit individual employees and their particular chronotype, which can be determined by questionnaires such as the Munich Chronotype Questionnaire.

**(Slide 42)** Several industries are already using smarter schedules and training methodologies that maximize the health, performance and efficiency of their workers. Major corporations such as Procter & Gamble and Goldman Sachs are using 'sleep hygiene' programmes based on circadian research to keep their personnel sharp — for example, coaching staff to optimize their individual sleep schedules, and to switch off laptops and e-readers in advance of bedtime. The need for such efforts is especially keen in industries with round-the-clock operations — particularly those where working while tired could prove fatal, such as mining or manufacturing. In aviation, the US Federal Aviation Administration has recently put in place 'fatigue risk management systems' that aim to improve the safety of air travel by using carefully regulated work schedules and mandated rest time to minimize flight-crew fatigue.

However, Lockley questions the wisdom of retraining the public to adapt to schedules that are contrary to their biological needs. “Where we have to have 24/7 society — in health and safety services, for example — we should do it,” he says. “But we should critically review whether we need 24-hour supermarkets or TV.”

To help people make the most of their sleep while also leading happy and productive lives, we need a better sense of what natural human sleep patterns really are, and how our lifestyles reshape them. But this requires more data. Several research groups are now working with pre-industrial communities in the Amazon to get a better understanding of how the natural human clock runs in a non-electric world. Meanwhile, Roenneberg hopes to build on the success of the MCTQ with a much broader Human Sleep Project that will bring together leading sleep researchers to characterize circadian rhythms and sleep patterns at the population scale.

**(Slide 43)** Waking up early to start work at four o'clock in the morning may never be entirely natural for people such as Klerman's train conductor, but better insights into sleep management could make such schedules more comfortable and the transition from weekend to the working week less jarring. “We need huge databases where thousands to millions of people have contributed data from their daily life,” says Roenneberg. “Once we understand that, we can change our society and technology so that people can sleep in their proper, individual sleep windows.”

**(Slide 44) Video\_Chronomedicine**

**(Slide 45)**

Questions that we will analyze for a lesson on this topic:

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6. What is chronobiology?

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8. Circadian desynchrony.

9. What is chronomedicine?

Finish for today

The full lecture is at the indicated website.

**Thank you for attention**