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Assessment of the Characteristics of Hyperthermia in Human Health and Its Therapy

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Abstract: Hyperthermia is an increase in the body's core temperature caused by its inability to dissipate heat or reduce its production. The problem is serious and leads to the death of several people every year. One of its causes is exposure to excessive heat. On very hot days, for example, we must be careful to avoid the occurrence of the problem, drinking plenty of water and avoiding outdoor physical activities. This manuscript aims to evaluate the characteristics of hyperthermia in human health and its therapy. Data were collected using a quantitative and descriptive approach, through books and the following databases: SciVerse Scopus, Scientific Electronic Library Online (SciELO), and the Academic Search Tool (Scholar Google) Academia.edu., Researchgate, Library of Medicine and National Institute of Health – USA (PubMed) and Scientific, Latin American Literature in Health Sciences (LILACS). The search was developed using the subject descriptor, mosquito, diseases, filaria, hosts, transmission, diagnosis, and treatment referred to in journals, through a review of the literature on the subject. In the initial search, the titles and abstracts of the articles were considered for a broad selection of likely works of interest, with the abstracts being highlighted. The time frame was between 1999 and 2024, as we preferred to search for recent publications, and those that did not meet the established criteria were excluded. The search was conducted using the subject descriptors: "Cardiac system", "Nervous system", "Energy", "Hydration, metabolism", "Risk factors", "Temperature," "Thermoregulatory mechanism, "El Niño" and "Climate change".

Keywords: Climate change, Energy, Metabolism, Temperature, Thermoregulatory.

Review Paper

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1. INTRODUCTION

Hyperthermia is an increase in the body's core temperature caused by its inability to dissipate heat or reduce production. The problem is serious and leads to the death of several people every year. One of its causes is exposure to excessive heat. On very hot days, for example, we must be careful to avoid the occurrence of the problem, drinking plenty of water and avoiding outdoor physical activities (Figure 1) (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020; Rede D'Or, 2024; Santos, 2024).

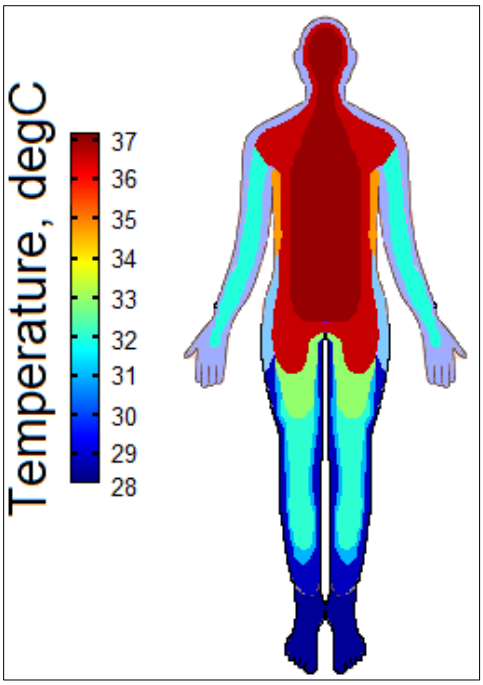

Figure 1: Fields of temperature and heat fluxes in the human body
Source: https://www.researchgate.net/figure/Fields-of-temperature-and-heat-fluxes-in-the-human-body_fig1_350296619

1.2. Objective: This manuscript aims to evaluate the characteristics of hyperthermia in human health and its therapy.

2.0. METHODS

Data were collected using a quantitative and descriptive approach, through books and the following databases: SciVerse Scopus, Scientific Electronic Library Online (SciELO), and the Academic Search Tool (Scholar Google) Academia.edu., Researchgate, Library of Medicine and National Institute of Health – USA (PubMed) and Scientific, Latin American Literature in Health Sciences (LILACS). The search was developed using the subject descriptor, mosquito, diseases, filaria, hosts, transmission, diagnosis, and treatment referred to in journals, through a review of the literature on the subject. In the initial search, the titles and abstracts of the articles were considered for a broad selection of likely works of interest, with the abstracts being highlighted. The time frame used was between 1999 and 2024, as we preferred to search for recent publications, and those that did not meet the established criteria were excluded. The search was conducted using the subject descriptors as: "Cardiac system", "Nervous system", "Energy", "Hydration, metabolism", "Risk factors", "Temperature," "Thermoregulatory mechanism, "El Niño" and "Climate change".

3.0. SELECTED STUDIES

Unlike a fever, in which the body fights to combat the increase in temperature according to the patient's normal body temperature indicators, this does not happen in hyperthermia. It is as if the body is unable to dissipate its heat naturally. In a fever, the body desires and longs for an increase in temperature to fight the microorganisms such as viruses and bacteria affecting the body. Maintaining our body's core temperature within a normal range is essential for proper functioning. Changes in this temperature, whether below or above normal values, can trigger dysfunctions in various organs, causing, for example, kidney and respiratory failure (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020; Rede D'Or, 2024; Santos, 2024).

3.1. Hyperthermia is usually divided in to Three Basic Forms: Classic, Exertion-Induced, and Malignant

Classic hyperthermia is triggered by prolonged exposure to excessive heat and mainly affects children and the elderly. If a person is exposed to the sun for a long time without adequately hydrating themselves, they will lose a lot of water through sweat and become dehydrated. Sweat will no longer be produced, and their body will not be cooled (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012).

In exertion-induced hyperthermia, there is an increase in internal temperature due to prolonged muscle activity, which produces heat, combined with factors such as high ambient temperature and humidity. The inability to dissipate heat adequately leads to an increase in body temperature (Figure 2) (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020; Rede D'Or, 2024; Santos, 2024).

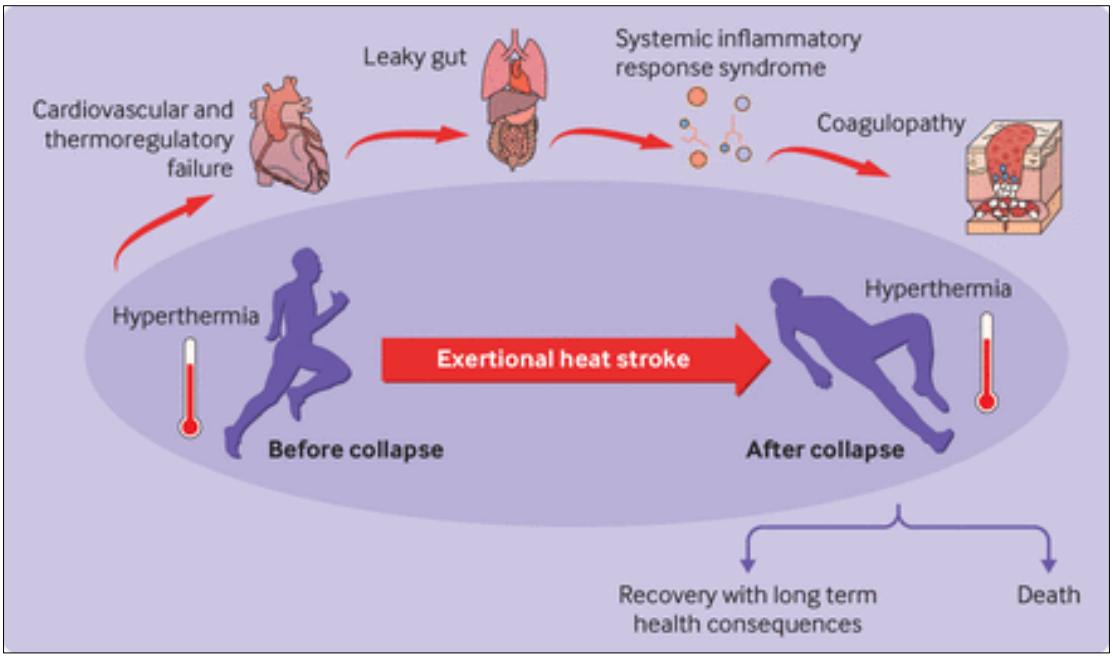

Figure 2: Shifts in blood flow lead to increased intestinal permeability, causing leakage of intestinal content into the systemic circulation, a response known as the leaky gut hypothesis. Intestinal content and hyperthermia lead to the systemic inflammatory response syndrome, which promotes disseminated intravascular coagulation characterizing the coagulopathy. Most of these responses remain after collapse or until the victim is adequately cooled and regains consciousness

Source: Based on the original graphical scheme prepared using Servier Medical Art (smart.servier.com)

Finally, there is malignant hyperthermia, considered a potentially lethal pharmacogenetic syndrome, which manifests in predisposed individuals when subjected to halogenated inhaled anesthetics and/or depolarizing neuromuscular blockers. The manifestation of malignant hyperthermia can occur, more rarely, after prolonged sun exposure and intense physical activities. Hyperthermia is usually divided into three basic forms: classic, exertion-induced, and malignant (Figure 3) (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020; Rede D'Or, 2024; Santos, 2024).

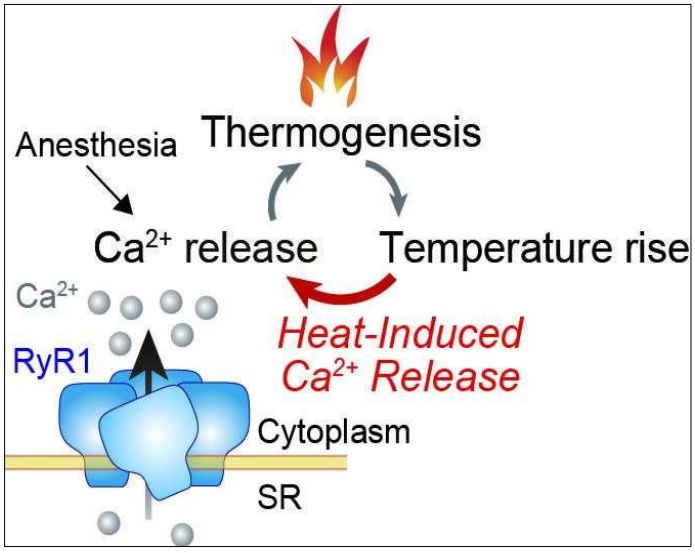

Figure 3: Malignant hyperthermia occurs when runaway thermogenesis is caused by a heat-sensitive Ca^{2+}-release channel (RyR1). Anesthesia is known to trigger Ca^{2+} release through mutant RyR1 variants, facilitating thermogenesis in muscle cells (gray arrows). In the present study, we found that applying heat causes Ca^{2+} release through RyR1 by a mechanism that we call "Heat-Induced Ca^{2+} Release (HICR)" (a red arrow). This creates a positive feedback loop that accelerates the progression of the disease

Source: Credit: Kotaro Oyama *et al.*, 2024

3.2. Temperature: Difference between Hyperthermia and Fever

However, the difference is the mechanism that leads to the development of temperature increases. In the case of hyperthermia, the increase occurs due to the failure of the heat dissipation mechanisms, while in fever, the temperature thermoregulation points change to higher levels. The hypothalamus contains the thermoregulatory center, which acts like a thermostat, keeping our temperature within normal ranges. When we have a fever, what happens is a kind of readjustment of this thermostat, with a change in the thermoregulation point, which is a pre-established point of heat regulation (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020).

"A person who has a high temperature for a long time suffers hemolysis, which is the destruction of red blood cells. The body begins to alter blood proteins; we must remember that everything is protein. Antibodies, cells, white blood cells, and blood plasma all begin to denature. The heart rate increases significantly, and the kidneys, liver, and brain begin to have difficulty functioning," (Figure 4) [Carlos Machado, general practitioner specializing in preventive medicine] (Salgado *et al.*, 2015; Azevedo, 2020; Rede D'Or, 2024; Santos, 2024).

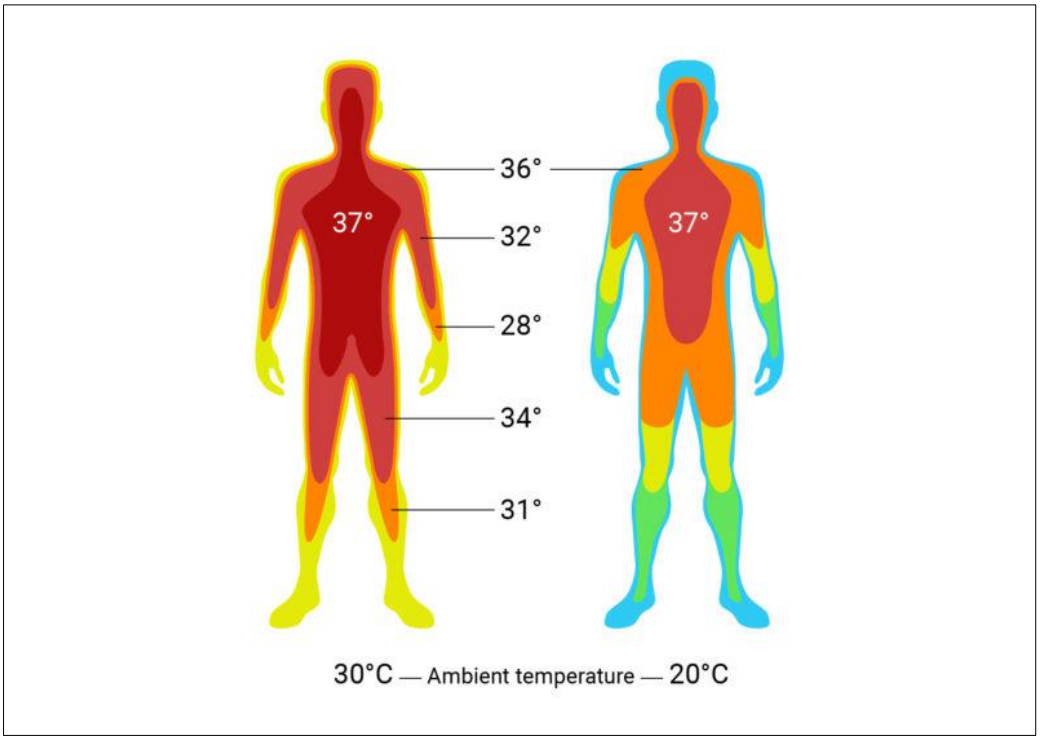

Figure 4: Temperature field of the human body. The body core remains largely constant in temperature, while the temperature of the body shell is subject to external and internal influences
Source: https://www.cosinuss.com/en/measured-data/vital-signs/body-temperature/

The heat waves that are hitting several parts of Brazil are making people hot-headed. The effects of all this heat can cause hyperthermia, a condition characterized by an uncontrolled increase in body temperature. If the temperature exceeds 40°C, there can be serious consequences for the person. The National Institute of Meteorology (INMET) issued a warning about the risk of death due to hyperthermia in some regions of the states of São Paulo, Minas Gerais, Goiás, Mato Grosso, Mato Grosso do Sul, Tocantins, and the Federal District. Rio de Janeiro was classified as a potential danger in the third heat wave classification on a scale of four (Figure 5) (Murahovschi, 2003; Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020; Garcia *et al.*, 2022; Rede D'Or, 2024; Santos, 2024).

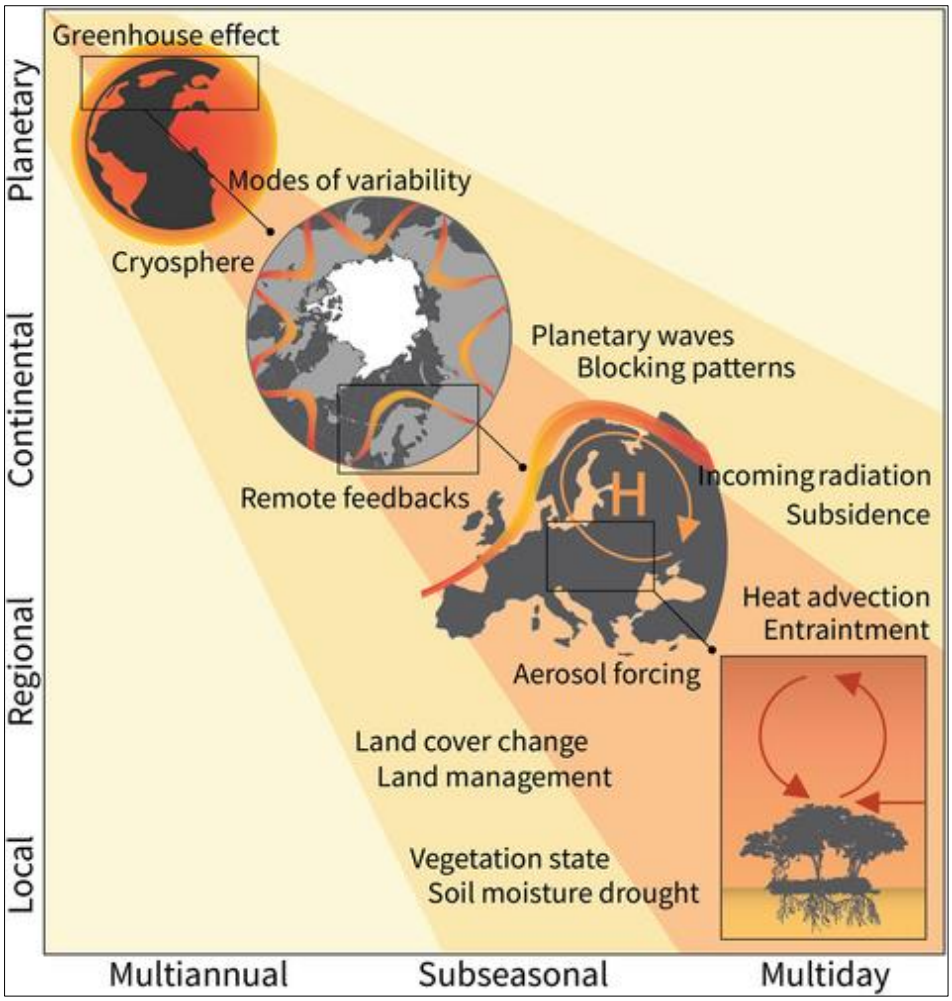

Figure 5: Spatial and temporal scales of characteristic heat wave (HW) drivers. Diagram identifying the characteristic HW drivers and their relevant scales, from planetary to local spatial scale, and from multiannual to multiday temporal scale. Based on synthesizing previous literature studies, different processes are identified and allocated to specific scales. Note that different drivers may interact with each other at multiple scales and that smaller-scale processes are conditioned on larger-scale states that may trigger changes in those smaller-scale processes
Source: BMJ Medicine 2022; 1: e000239

Direct exposure to the sun causes hyperthermia, and staying indoors in hot environments with little air circulation can also cause the condition. The main symptoms are the cessation of sweating due to a lack of fluid in the body after sweating excessively, accelerated heartbeat, excessive thirst, a feeling of low blood pressure, dizziness, and mental confusion, which can lead to fainting (Azevedo, 2020; Doctor's Area Rede D'Or, 2024; Santos, 2024).

3.3. Hydration

The best way to assess a person's hydration level is by analyzing the color of their urine. Ideally, it should be a light yellow color. If it is orange, it is very concentrated, which may indicate low hydration. How to protect yourself Drink water staying well hydrated is essential to deal with the heat. Ideally, you should drink at least 35 ml of water for every kilo of weight. To know how many liters you need to drink, simply multiply your weight by 35. Example: A person who weighs 70 kilos should drink 2.4 liters of water per day (70 x 35 = 2,450) Drink isotonic drinks isotonic drinks are great for replacing mineral salts lost through sweat. Coconut water is a great natural isotonic drink Advertisement Wear light clothing the body's thermostatic balance only occurs when sweat can be eliminated into the environment. Therefore, it is important to wear clothes that facilitate this change: choose thinner and lighter fabrics (Correia *et al.,* 2012; El-Radhi, 2012; Salgado *et al.,* 2015; Azevedo, 2020).

Avoid exposure to heat whenever possible and avoid being in the sun between 10 am and 4 pm. Also avoid stuffy environments, with lots of people and no air circulation. Don't exercise in hot environments if you exercise outdoors, always prefer the morning or late afternoon. Doing activities in places with a lot of sunlight and high temperatures increases the risk of hyperthermia. Avoid alcoholic and carbonated drinks. Despite being one of the favorite choices for "cooling off" on hot days, alcoholic drinks help the body to dehydrate. Therefore, instead of helping, they only make the situation worse.

The same goes for carbonated drinks, as they tend to be high in salt and sugar, which can lead to dehydration (Figure 6) (Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Azevedo, 2020; Santos, 2024).

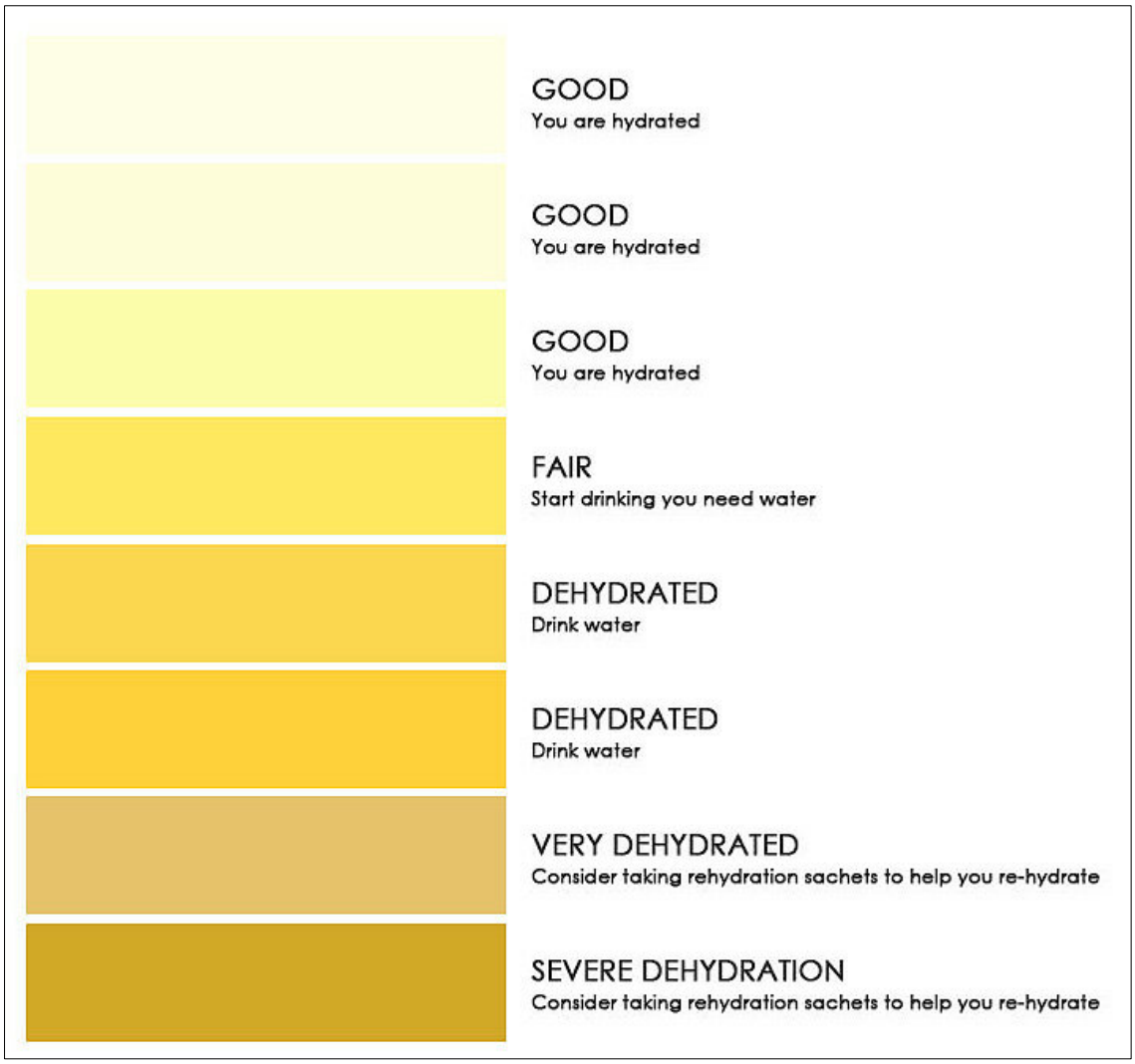

Figure 6: Color scale urine hydration chart
Source: https://www.researchgate.net/figure/color-scale-urine-hydration-chart_fig2_327291962

3.4. Metabolism

The body's energy is focused on reducing body temperature, which is why metabolism slows down. Avoid eating heavy meals, as it will take longer for the body to digest them, which can cause discomfort. Heatstroke hyperthermia is a condition of exhaustion of the body caused by excessive heat and sun exposure, in which the body temperature exceeds 40 degrees. It occurs when your body absorbs more heat than it releases. Sweat is your body's natural cooling mechanism, but sometimes perspiration is not enough to keep your body at a normal temperature. When this happens, your body temperature can rise and there is a risk of permanent after-effects and serious complications, such as damage to vital organs, including the kidneys and brain, as well as coma and death. Physical exertion in very hot and humid weather is the most common cause of hyperthermia (Figure 7) (Blank, 2012; Correia *et al.*, 2012; El-Radhi, 2012; Salgado *et al.*, 2015; Azevedo, 2020).

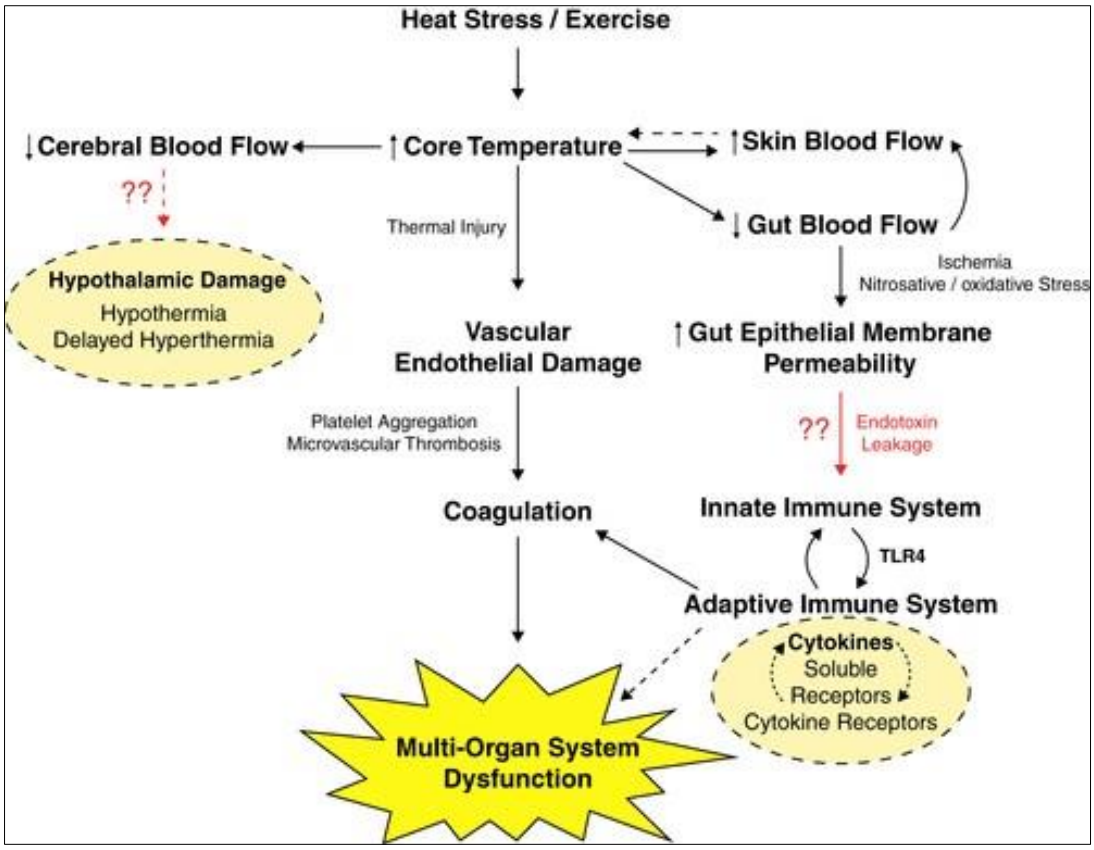

Figure 7: Progression of "normal" physiological responses to exercise-heat stress that can progress to pathophysiological responses that culminate in heat stroke with multiorgan system failure. Events highlighted in red denote two out of the eight areas of dispute that are addressed in this review. TLR4, Toll-like receptor-4
Source: Doi.org/10.3390/cancers15020346

Some endogenous factors can also challenge thermal stability, with muscular activity being the most important. Physical exercise increases metabolism, considerably increasing heat production. Depending on the intensity of physical effort and environmental conditions, core body temperature can rise to levels that are harmful to health. Heat storage and the consequent increase in core body temperature to critical levels lead to the incidence of heat-related illnesses, especially heat exhaustion and Exertional Heat Stroke (EHS), two forms of heat stroke that affect both athletes and workers exposed to heat stress situations (Cohen and Wood, 2002; Gambrell, 2002; Dul and Weerdmeester, 2004; Kroemer and Grandjean, 2005; Uyton and Hall, 2006; Widmaier *et al.*, 2006; Camargo and Furlan, 2011).

Hot environments and situations that cause a rapid increase in body temperature increase the risk of heat stroke. Such as: Being over 65 or under 4 years of age. Special attention is recommended for children and the elderly; Exposure to the sun for many hours at a time; Practicing strenuous physical activities (which cause physical exhaustion); Excessive clothing during hot weather; Not staying properly hydrated; Excessive intake of caffeine and alcoholic beverages in hot weather, promote dehydration; Use of medications for high blood pressure, diuretics, antidepressants and antipsychotics; Gastroenteritis; Having certain medical conditions, such as problems with the heart, lungs, kidneys, liver, thyroid or blood vessels; Being over or underweight (Cohen and Wood, 2002; Gambrell, 2002; Dul and Weerdmeester, 2004; Kroemer and Grandjean, 2005; Uyton and Hall, 2006; Widmaier *et al.*, 2006; Camargo and Furlan, 2011).

Heatstroke is a serious condition caused by excessive exposure to the sun and intense heat. It occurs when the body temperature exceeds 40ºC, causing the sweating mechanism to fail and the body to be unable to cool itself. Heatstroke deserves special attention because, with the rapid increase in body temperature, the person ends up losing a lot of water, salts, and nutrients that are important for maintaining the body's balance. It is important to remember that heatstroke is closely associated with hot and dry weather, but it can also occur in humid environments (Figure 8) (Gov.br., 2024; Zhang, 2024).

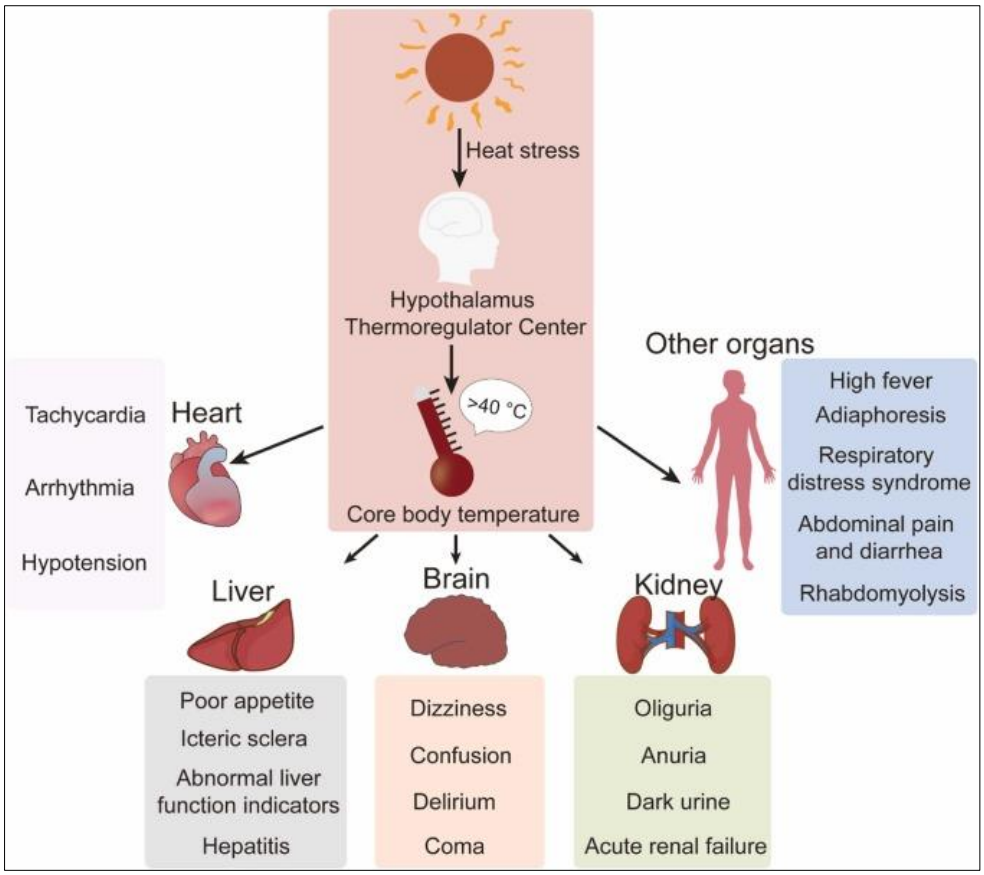

Figure 8: Heat stroke: Pathogenesis, diagnosis, and current treatment
Source: Doi: org/10.1016/j.arr.2024.10240

Heatstroke is caused by situations of prolonged exposure to the sun and heat. It usually occurs in very hot environments or in situations that cause a rapid increase in body temperature, such as: Spending a lot of time exposed to the sun without sunscreen on the beach, at the club, or in the pool. Engaging in strenuous activities, that is activities that cause exhaustion and physical weakness. Wearing excessive clothing, especially in hot weather. Going without hydration for a long time (Gov.Br., 2024).

Some factors, habits, postures, behaviors, and situations can increase the risk of heat stroke. Children, the elderly, people with chronic diseases such as cancer, diabetes, and hypertension, and people with low immunity, such as transplant recipients and people with HIV/AIDS, should be especially careful with heat stroke, as this condition can cause serious side effects that are more likely to occur in this group. Not drinking enough fluids. Drinking too much alcohol or caffeine. People who have gastroenteritis. People who use medications for high blood pressure, diuretics, antidepressants, or antipsychotics (Gov. Br., 2024).

3.5. Energy

Humans need energy to be able to perform their activities. Even when completely resting, the organism consumes energy to maintain its vital functions. This energy corresponds to basal metabolism. Additional energy is spent to perform work. Foods are composed of carbohydrates, lipids, and proteins. They can be degraded in cells, releasing large amounts of energy in this process (Gambrell, 2002; Dul *et al.*, 2005; Uyton & Hall, 2006; Widmaier *et al.*, 2006; Camargo and Furlan, 2011).

The chemical energy contained in these energy substrates is released slowly and is temporarily stored in the form of Adenosine Triphosphate (ATP) the main energy compound in cells. However, during metabolism, approximately 60% of the energy released from organic molecules appears immediately as heat, and the breakdown of ATP during work releases a large part of its energy as heat. In this sense, heat is considered a byproduct of the transformation of energy, in its various forms, during the synthesis and use of ATP (Figure 9) (Cohen and Wood, 2002; Dul and Weerdmeester, 2004; Uyton & Hall, 2006; Widmaier *et al.*, 2006).

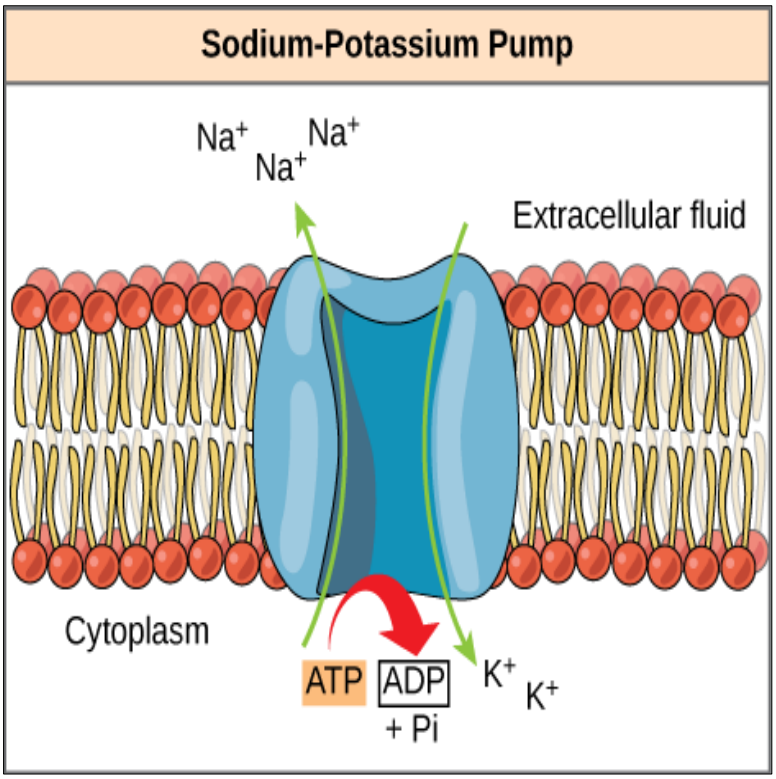

Figure 9: The sodium-potassium pump is an example of energy coupling. The energy derived from exergonic ATP hydrolysis is used to pump sodium and potassium ions across the cell membrane
Source: https://oercommons.org/courseware/lesson/14965/overview

Humans need energy to be able to perform their activities. Even when completely resting, the organism consumes energy to maintain its vital functions. This energy corresponds to basal metabolism. Additional energy is spent to perform work. Foods are composed of carbohydrates, lipids, and proteins. They can be degraded in cells, releasing large amounts of energy in this process. The chemical energy contained in these energy substrates is released slowly and is temporarily stored in the form of ATP adenosine triphosphate the main energy compound in cells (Kroemer and Grandjean, 2005; Uyton & Hall, 2006; Widmaier *et al.*, 2006; Camargo and Furlan, 2011).

However, during metabolism, approximately 60% of the energy released from organic molecules appears immediately as heat, and the breakdown of ATP during work releases a large part of its energy as heat. In this sense, heat is considered a byproduct of the transformation of energy, in its various forms, during the synthesis and use of ATP. Heat cramps, heat edema, and heat syncope are mild heat illnesses that occur without compromising thermoregulation and are not associated with hyperthermia. These illnesses are caused by physiological changes resulting from acclimatization and heat stress and improve with rest and hydration (Cohen and Wood, 2002; Gambrell, 2002; Dul and Weerdmeester, 2004; Kroemer and Grandjean, 2005; Uyton and Hall, 2006; Widmaier *et al.*, 2006; Camargo and Furlan, 2011).

3.6. Thermoregulatory Mechanism

When the nerve endings detect a drop in temperature, in addition to the subjective sensation of cold and goosebumps, vasoconstriction occurs, a decrease in the caliber of blood vessels, especially in the skin. This is why the skin feels cold. This is the body's initial response to reduce heat loss and maintain internal body temperature. When this vasoconstriction is ineffective in preventing a temperature drop, tremors occur. Tremors are involuntary contractions of skeletal muscles, a contraction that generates heat (Figure 10) (Schulz, 2009).

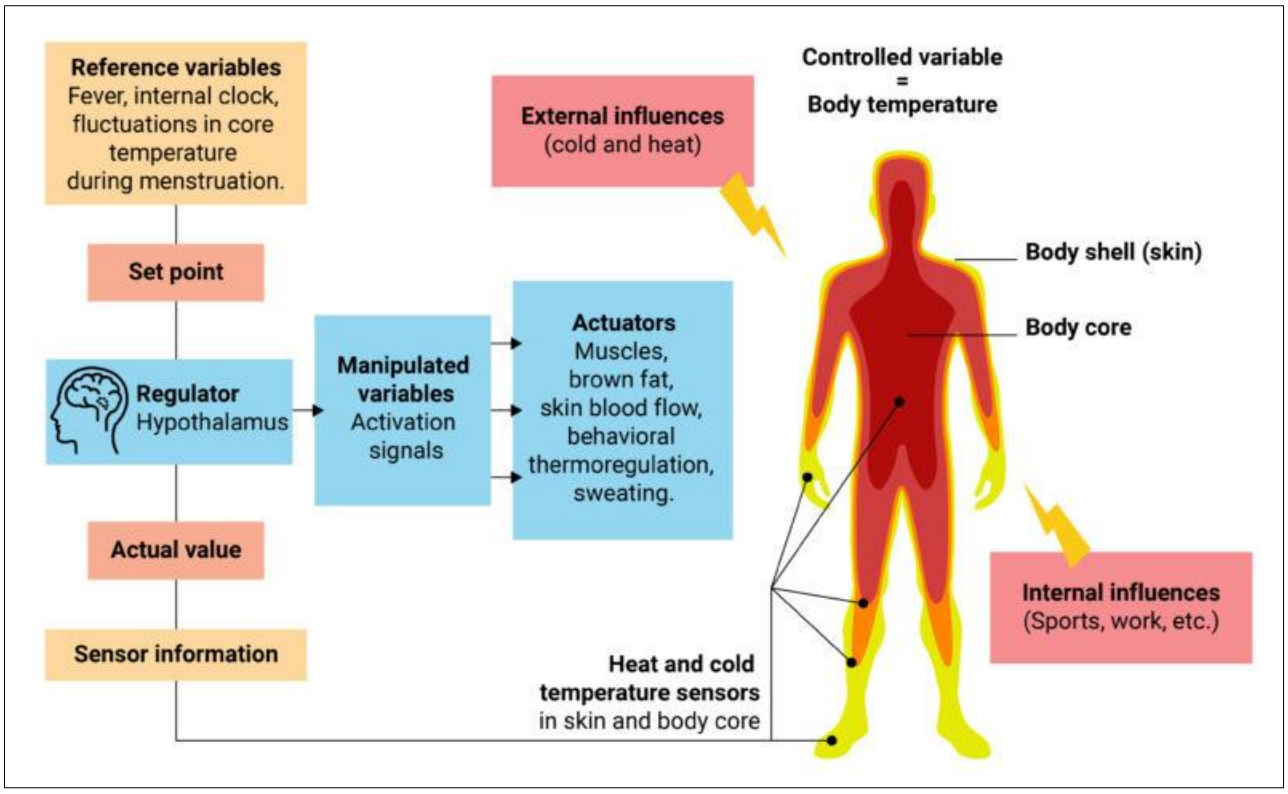

Figure 10: Control loop of thermoregulation. The actual value of the body temperature is changed by influences. These changes are registered by the hypothalamus. As a result, corresponding actuators are adjusted to bring the body temperature back to the setpoint

Source: Https://www.bbc.co.uk/bitesize/guides/zxgmfcw/revision/1

Exposure to environmental cold is prolonged, tremors decrease or cease, mental changes occur and motor performance decreases. Progressively, the thermoregulatory mechanism is collapsed, including vasodilation in the skin and consequent loss of heat to the outside. Thus, a vicious cycle is completed and the athlete's level of consciousness begins to decrease, he becomes prostrate, exhausted, and stuporous, and vital functions change, especially heart rate, respiratory rate, and blood pressure, until death. During these events, cold injuries may occur, mainly on the extremities (hands, feet, nose, ears, and lips, the most serious of which is frostbite (Schulz, 2009).

3.7. "El Niño"

One of the expected effects of the "El Niño" phenomenon is an increase in the incidence of infectious and communicable diseases It is known that the events corresponding to the years 1997-98 have been warmer for more than three decades and that many of the changes seem to be related to climatic variations in the world 2,4. These processes, through variations in the frequency and intensity of extreme climatic events (and consequently natural disasters), have repercussions on health 5,6, hence the growing interest in the influence of climatic factors on health. One of them, mainly on the Peruvian coast, is the rise in ambient temperature above average levels as well as the increase in relative humidity (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mannt *et al.,* 2000; Miranda *et al.,* 2003).

The association between high ambient temperatures and the development of heat-related diseases is documented8-12, with an increase in the fatality rate due to heat-related conditions reported during these periods Kalkstein states that even in people with a certain degree of acclimatization, temperature increases in the range of 2°C-4°C increase the risk of mortality fourfold (Figure 11) (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mannt *et al.,* 2000; Miranda *et al.,* 2003).

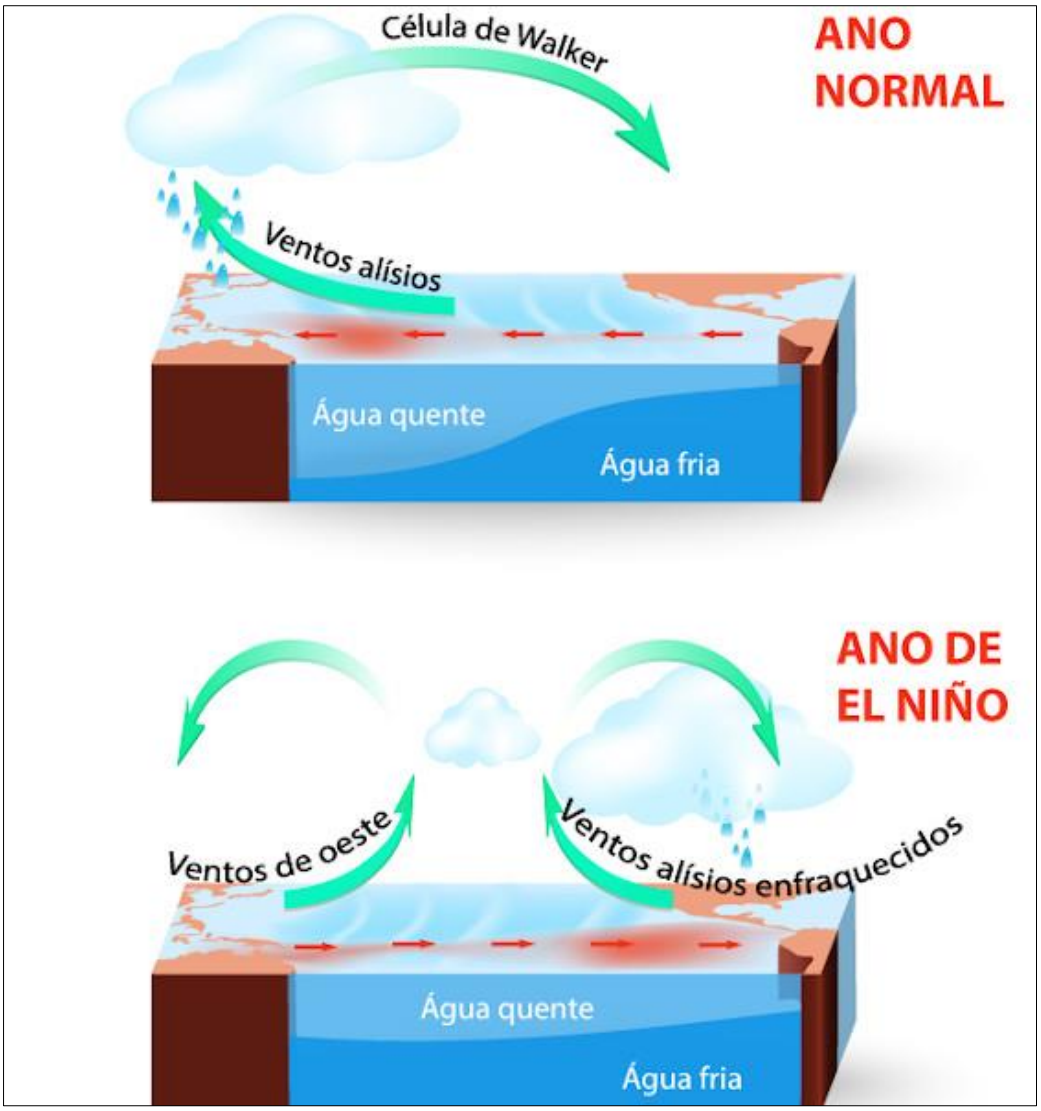

Figure 11: Simplified diagram of the behavior of two winds and their influence on the temperature of Pacific waters in normal years and in "El Niño years"
Source: https://brasilescola.uol.com.br/geografia/el-nino.htm

These processes, through variations in the frequency and intensity of extreme weather events and consequently natural disasters, have repercussions on health hence the growing interest in the influence of climate factors on health. One of them, especially on the Peruvian coast, is the rise in ambient temperature above average levels, as well as the increase in relative humidity. The association between high temperatures and environmental conditions and the development of heat-related diseases has been documented, reporting an increase in the heat-related fatality rate during these periods. States that even in people with a certain degree of acclimatization, temperature increases in the range of 2°C-4°C increase the risk of mortality fourfold (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mannt *et al.,* 2000; Miranda *et al.,* 2003).

During the onset of a fever, the body must initially save heat to reach the new equilibrium point established in the hypothalamus. This is achieved at the cost of redistribution of vascular flow toward the deep beds to minimize heat loss through the skin, activation of autonomic components decreased sweating), endocrine responses decreased vasopressin secretion reducing body volume when heated, and behavioral responses of shivering and seeking a warmer environment 25 that decrease peripheral temperature. These events are the opposite of what occurs during hyperthermia, where overheating is general; therefore, the axillary temperature is elevated to lose heat. If we assume, in our study group, an adjustment factor for axillary temperature to estimate rectal temperature as concomitant symptoms, patients showed diarrhea, cough, weight loss, irritability, nausea or vomiting, rhinorrhea, and convulsions (Figure 12) (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mann *et al.,* 2000; Miranda *et al.,* 2003).

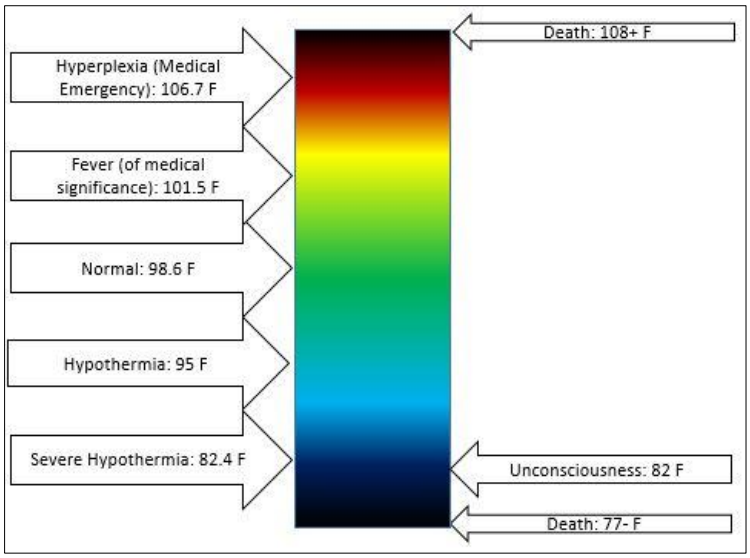

Figure 12: Difference between Hyperthermia and Fever
Source: https://iibec.org/osha-fine-hyperthermia-death/

3.8. Cardiac and Nervous System

The first two can be explained by vascular redistribution that decreases fluidization of secretions internally. Rhinorrhea is explainable by the same mechanism of vascular redistribution, showing vasodilation. They know the magnitude, but the effect must be considered in itself of heat at the tissue and cellular level, participating in the appearance of such symptoms, especially convulsions, simulating what would correspond to a febrile convulsion, a condition that occurs due to the increase in internal temperature. Irritability, hyporexia, nausea or vomiting, tachycardia, and tachypnea are other findings in our cases, which are also frequent in the entity called heat exhaustion, a term that we do not use because the time of illness that presented in our cases does not agree with what is described. Heat exhaustion generally corresponds to a state of hours or a few days, but 68% presented a time of illness greater than 15 days, characterized mainly due to high temperatures (Figure 13) (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mannt *et al.*, 2000; Miranda *et al.*, 2003; Docherty *et al.*, 2021).

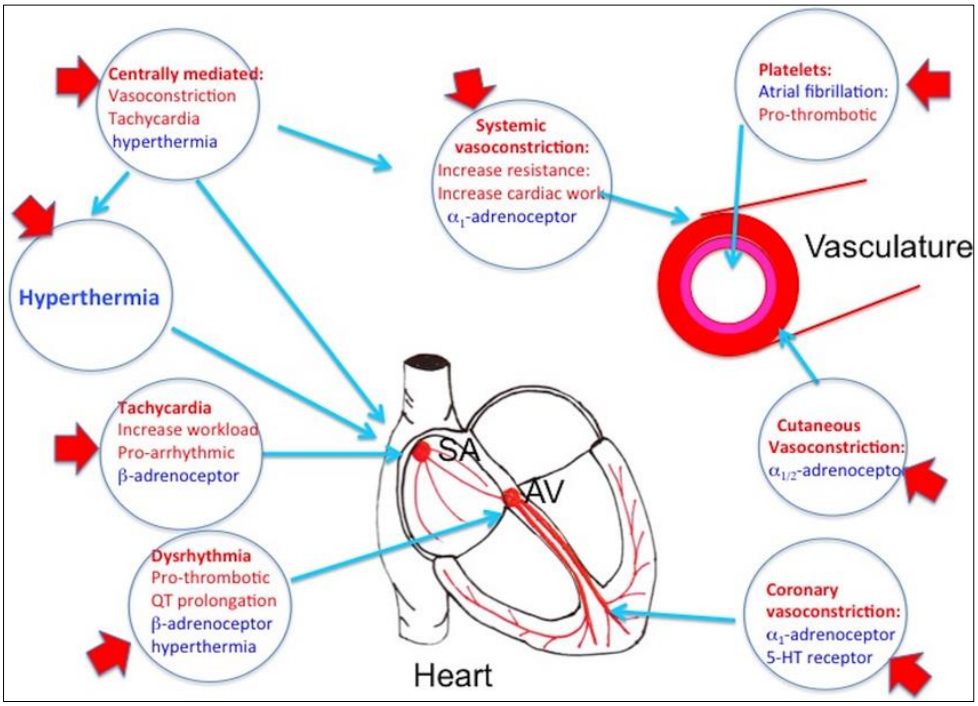

Figure 13: Cardiovascular actions of stimulants. Possible sites of action of stimulants, particularly cocaine and MDMA, in the cardiovascular indicate major mechanisms involved. Abbreviations: AV, atrioventricular node; SA, sino-atrial node
Source: DOI: 10.1111/bph

Even though the human body can withstand variations in external temperature, which affect it internally, its responses vary depending on pre-existing conditions and the length of exposure. "With a temperature above 40°C and direct exposure to the sun for more than an hour, you may already have some sign of hyperthermia. The first thing that happens is a loss of water, a dehydration of the body". At the same time, the body begins to sweat a lot and the individual feels weak [Sampaio] (Mannt *et al.*, 2000; Miranda *et al.*, 2003; Docherty *et al.*, 2021).

"It depends a lot on the temperature itself, the length of exposure, and the place where you are", emphasizes the cardiologist, that is, the risk is not in going to the supermarket and walking a few blocks, for example. However, excessive exposure to heat can cause dysfunction in some organs and seriously affect the individual. On the neurological side, it is possible to feel a very strong headache, dizziness, irritability, change in behavior, faintness, and, sometimes, even fainting. In adverse conditions, the person may enter a state of unconsciousness (stupor), and "the most that could happen from a neurological point of view, if the person were exposed for long periods, would be a coma" [Sampaio] (Figure 14) (Kalkstein, 1993; Simon, 1993; Saper and Breder, 1994; Martens, 1998; Mannt *et al.*, 2000; Miranda *et al.*, 2003; Docherty *et al.*, 2021).

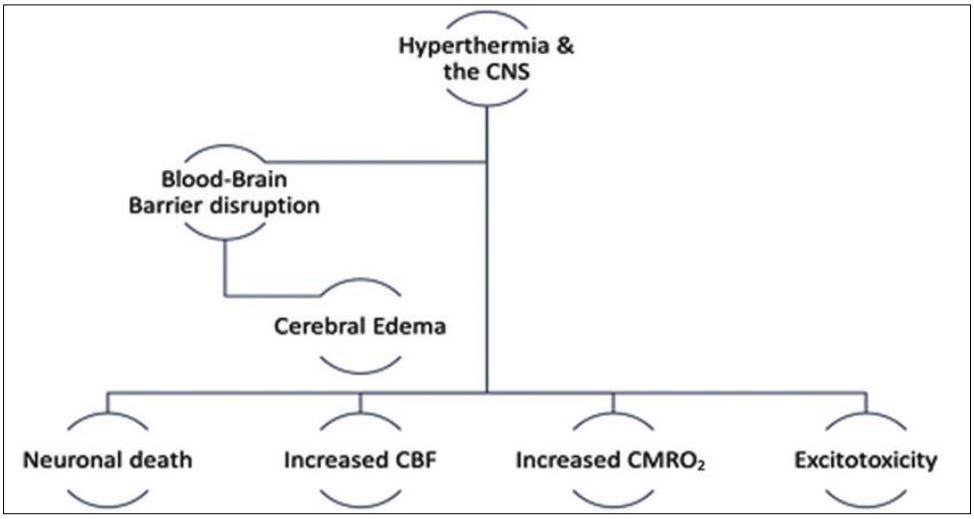

Figure 14: Effects of hyperthermia on central nervous system

Source: https://www.researchgate.net/figure/Effects-of-hyperthermia-on-central-nervous-system_fig1_337405360

3.9. Hyperthermic Syndromes

As for the cardiological part, there is a reduction in blood pressure. There is also an increase in heart rate and blood thickness thickening, which can trigger the formation of clots. In turn, these clots can clog the arteries, causing a heart attack or stroke, depending on where the blood flow is interrupted. Neuroleptic malignant syndrome is a neurological emergency that occurs in 0.02 to 3% of patients treated with neuroleptics. It generally occurs in the first month of therapy, especially in the first 2 weeks. NMS is a disorder of excessive heat production. The pathophysiology is still unknown, but it is believed to occur due to the blockade of dopaminergic receptors in the nigrostriatal tract, which culminates in the exacerbated contraction of skeletal muscles with parkinsonism-like symptoms, which ends up producing excessive heat (Figure 15) (Gurrera *et al.*, 2017; Nicolau, 2024).

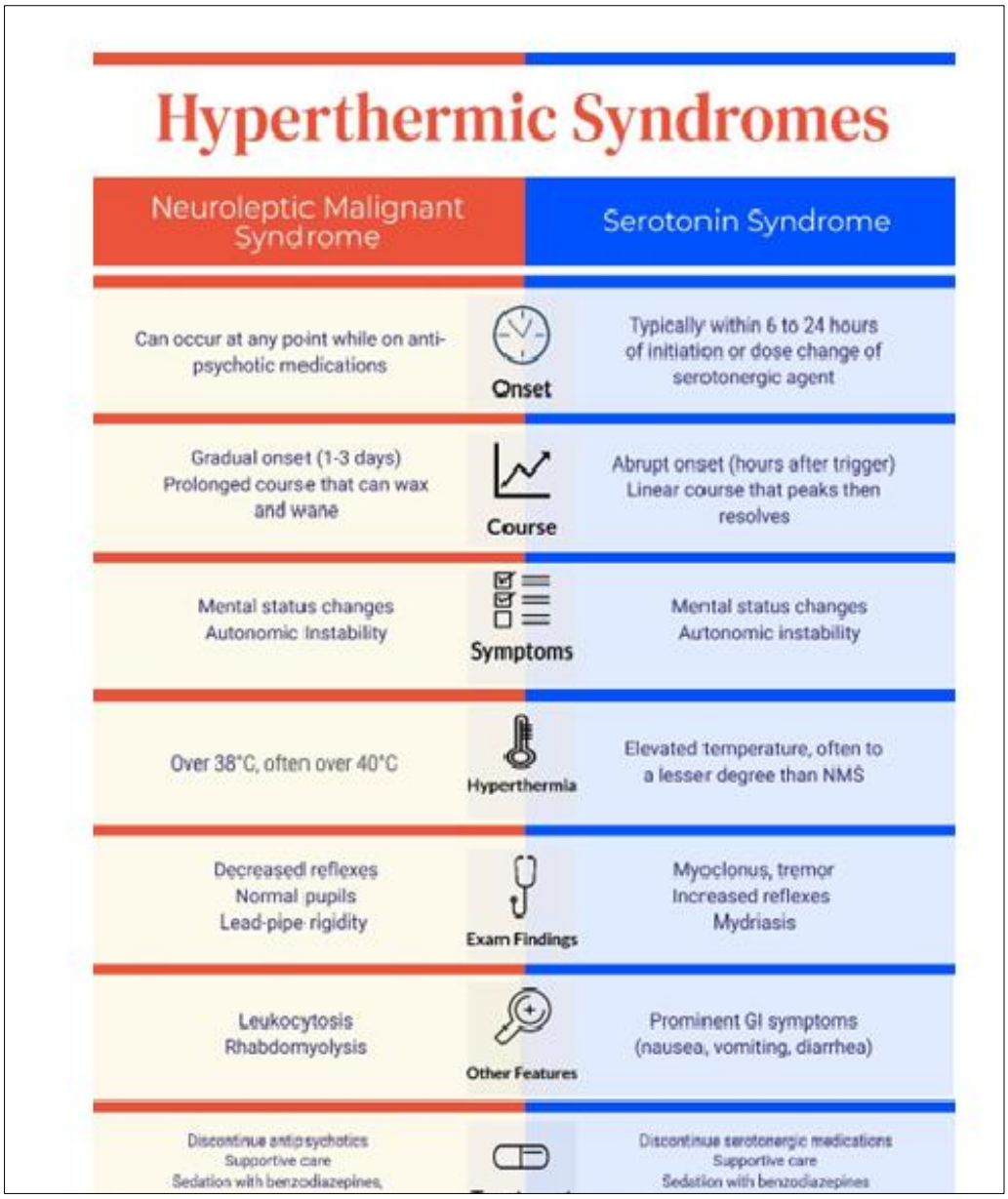

Figure 15: Hyperthermic Syndromes

Source: https://canadiem.org/hyperthermic-conditions-in-the-psychiatric-patient/

3.10. Main Associated Drugs

Main associated drugs: Antipsychotics Haloperidol; Chlorpromazine; Risperidone; Olanzapine; Antiemetics Metoclopramide; Promethazine; Domperidone; Withdrawal of dopaminergic medications for Parkinson's disease. Risk factors: High doses of medications: NMS is not a dose-dependent phenomenon, as previously stated, but higher doses of medications are a risk factor; Recent dose escalation; Antipsychotic change; Parenteral administration of antipsychotic depot formulations Clinical manifestations: Hyperthermia Extrapyramidal symptoms: Muscle rigidity; Tremor; Chorea; Bradykinesia; Dystonia refractory to anticholinergic therapy; Altered mental status: Initial: Agitation and mental confusion; Progression: Catatonia, Mutism and Coma (Gurrera *et al.*, 2017; Nicolau, 2024).

4.0. TREATMENT

4.1. Treatment 1

Infrared hyperthermia is an innovative therapy that uses the power of therapeutic heat to stimulate the body to reach a controlled high temperature. In this treatment, low-emission infrared rays are directed at the body, penetrating deep into the tissues and inducing an increase in internal temperature. This treatment helps promote vasodilation, increase blood circulation, improve metabolism, and provide a series of therapeutic benefits for the body and mind. Optimizes heart rate; Regulates blood pressure, cortisol levels, and cholesterol; Improves sleep; Relieves pain; Combats inflammation values (Figure 16) (Hergt *et al.*, 2004; Banquinho *et al.*, 2013; Lima *et al.*, 2014; Mendonça, 2015).

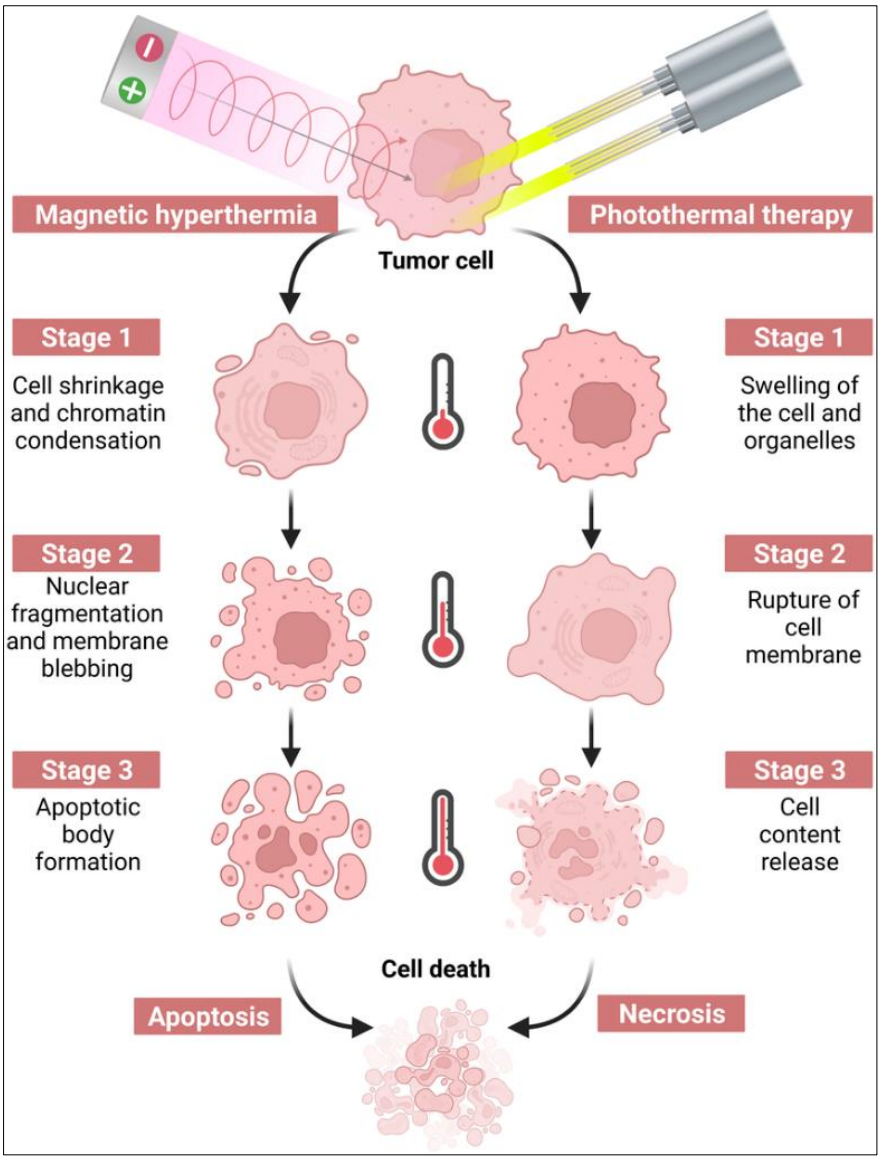

Figure 16: Hyperthermia therapy induced by a near-infrared laser or an alternating magnetic field causes tumor cell death via apoptosis or necrosis by increasing the temperature

Source: https://www.researchgate.net/figure/Hyperthermia-therapy-induced-by-a-near-infrared-laser-or-an-alternating-magnetic-field_fig2_374523805

4.2. Treatment 2

The scientific community is aware of the use of magnetic hyperthermia (MH) in the treatment of diseases, but to this day, it still presents several challenges for researchers. In the treatment of cancer, for example, MH can be combined with other types of treatments, such as radiotherapy and chemotherapy (Hergt *et al.*, 2004; Banquinho *et al.*, 2013).

4.3. Treatment 3

Magnetic hyperthermia treatments involve exposing diseased tissues to an increase in temperature, generally between 43°C and 46°C, for a certain time. The generation of magnetic nanoparticles (NPs) occurs through the application of an alternating AC magnetic field with frequencies between 100 and 500 Hz (Hergt *et al.*, 2004; Banquinho *et al.*, 2013).

3.4. Treatment 4

The application in biomedicine is limited by physiological factors that suggest that the power released should be limited by magnetic fields with amplitude H0 and frequency f with very specific values (Hergt *et al.*, 2004; Banquinho *et al.*, 2013).

4.5. Treatment 5

Infrared hyperthermia is an innovative therapy that uses the power of therapeutic heat to stimulate the body to reach a controlled high temperature. In this treatment, low-emission infrared rays are directed at the body, penetrating deep into the tissues and inducing an increase in internal temperature. This treatment helps promote vasodilation, increase blood circulation, improve metabolism, and provide a series of therapeutic benefits for the body and mind. It optimizes heart rate;

Regulates blood pressure, cortisol levels, and cholesterol; Improves sleep; Relieves pain; and Fights inflammation (Figure 17) (TV Pampa, 2024; Marcussi, 2024).

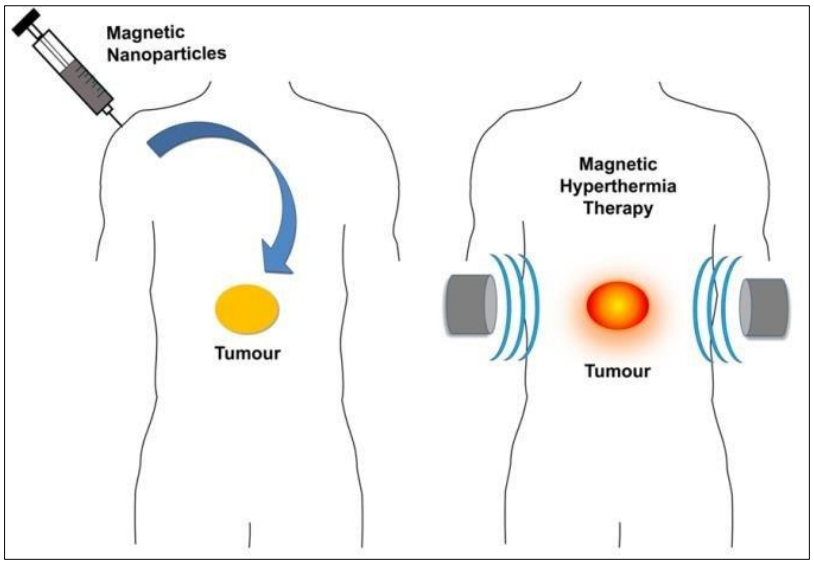

Figure 17: Hyperthermia treatment in a magnetic nanoparticle system. Reprinted from "Coating Nanomagnetic Particles for Biomedical Applications" In "Biomedical Engineering -Frontiers and Challenges by R. Fazel (Ed.), Intech Open Access.

Sources: p.165) by A. Andrade & R. Ferreira, 2011 and by R. Fazel (Ed.), Intech Open Access

The regulation aims to prevent, diagnose, treat, and provide appropriate guidance to patients susceptible to Malignant Hyperthermia and their families, to ensure that all hospitals, both public and private, have access to appropriate medications to combat the disease, especially Dantrolene Sodium, and to eradicate the number of deaths resulting from this syndrome in the State of Amazonas. Furthermore, a data collection system on those with the syndrome should be implemented to maintain a state registry with information on the incidence of the disease in the population and the registration of deaths, contributing to the improvement of scientific research on Malignant Hyperthermia in the state (Figure 18) (ALEAM, 2023).

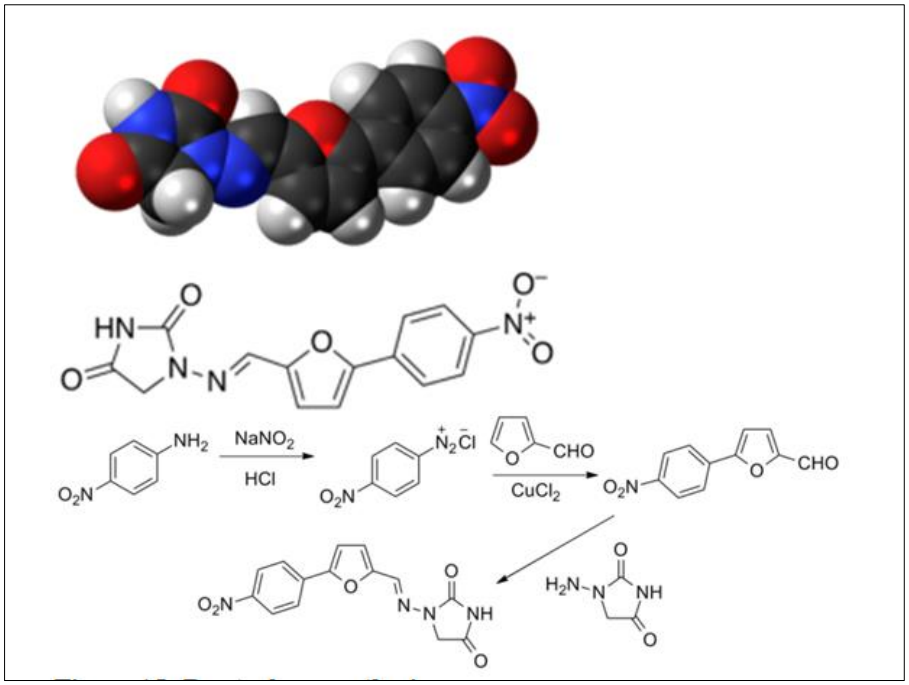

Figure 18: Dantrolene synthesis

Sources: Davis and Snyder; U.S. patent 3,415,821 (1968 to Norwich Pharma Co) and Doi:10.1021/jm00317a011

The groundbreaking research was the development of silica particles containing samarium and iron oxide for cancer treatment using brachytherapy and magnetic hyperthermia. The work addresses a synthetic, biodegradable material for cancer treatment using combined spinal therapy and magnetic hyperthermia. In addition, the novelty of the research is due to the use of the chemical element samarium as a source of radiation, the novelty of the research is due to the use of the chemical element samarium as a source of radiation (Figure 19) (Reverso, 2024).

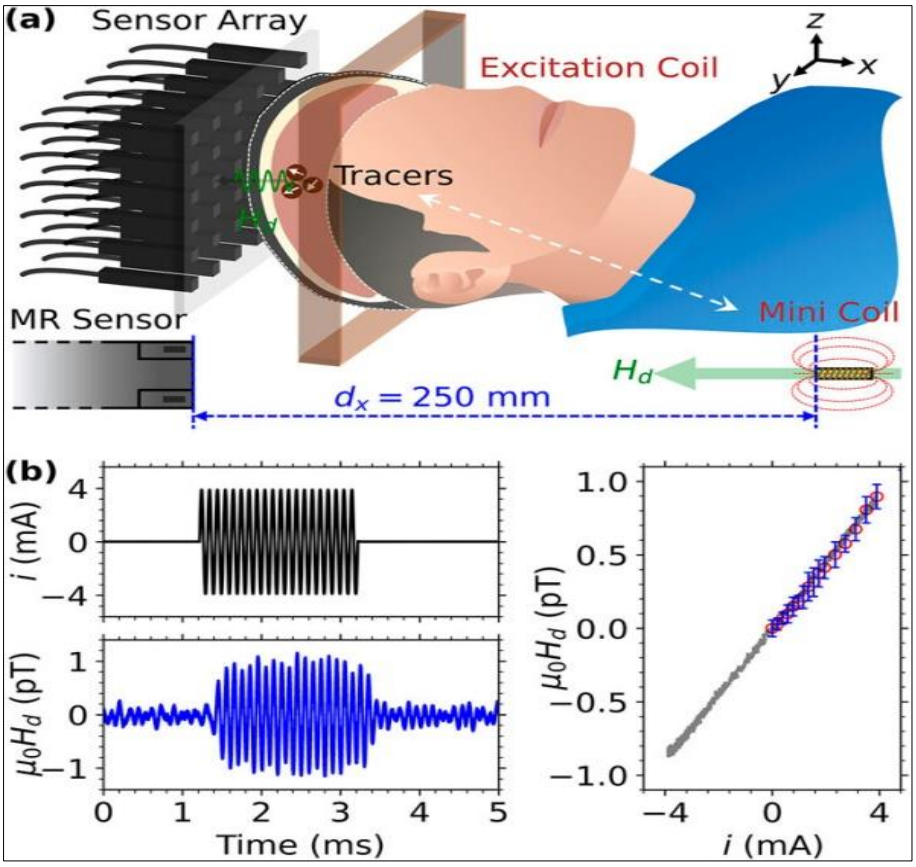

Figure 19: (a) Oscillatory magnetometric Magnetic nanoparticles were experimentally modeled by a mini coil placed system using MR sensor array and (b) output linearity of single MR sensor below 1 pT at 10 kHz. 250 mm away from the sensor

5.0. Projector

Bill No. 662/2023 is currently being processed in the Legislative Assembly of Amazonas (ALEAM), which provides for the State Policy for the Prevention, Diagnosis, and Treatment of Malignant Hyperthermia (MH) in the State of Amazonas. The proposal was authored by Congresswoman Dr. Mayara Pinheiro Reis. According to the Brazilian Society of Anesthesiology, Malignant Hyperthermia is a hereditary and latent condition, classically characterized by a hypermetabolic syndrome in response to exposure to volatile anesthetics and/or succinylcholine, widely used in surgeries or as muscle relaxants, but can be fatal for people with MH (ALEAM, 2023).

5.1. Projector

The Legislative Assembly of the State of Goiás (ALEG), under art. 23, § 7, of the State Constitution, decrees and sanction the following Law: The policy for the prevention, diagnosis, and Treatment of Malignant Hyperthermia (TMH) is hereby instituted in the State of Goiás, which will be developed under the terms of this law. The policy for prevention, diagnosis, and treatment of malignant hyperthermia (MH) has the following guidelines: to prevent, diagnose, treat, and adequately guide patients susceptible to malignant hyperthermia and their families (ALEG, 2023).

To ensure that all public and private hospitals, group medicine companies, medical work cooperatives, or others that act in the form of direct provision or intermediation of medical-hospital services and operate in the State of Goiás, have appropriate medications to combat the disease, especially Dantrolene Sodium, which serves as an antidote for Malignant Hyperthermia Syndrome; to eradicate the number of deaths resulting from this syndrome in the State; to produce promotional materials for health professionals in the State containing the main information about malignant hyperthermia and ways to avoid its fatal effects on patients; to hold informative lectures on malignant hyperthermia for doctors and paramedics in hospitals in the State of Goiás;

implement a data collection system on people with the syndrome (ALEG, 2004) aiming to:

a. Maintain a State Registry with information on the incidence of the disease in the population of Goiás and the number of deaths resulting from it.
b. Obtain information on the population affected by the disease.
c. Contribute to the improvement of scientific research on malignant hyperthermia. State public hospitals are required to inform the Agency responsible for updating the State Registry whenever there are victims of Malignant Hyperthermia Syndrome; Failure to comply with the provisions of this Law subjects offenders to the fines provided for in Law No. 13,569, of December 27, 1999 (Figure 20) (ALEG, 2004). Source: https://www.researchgate.net/figure/a-Osc

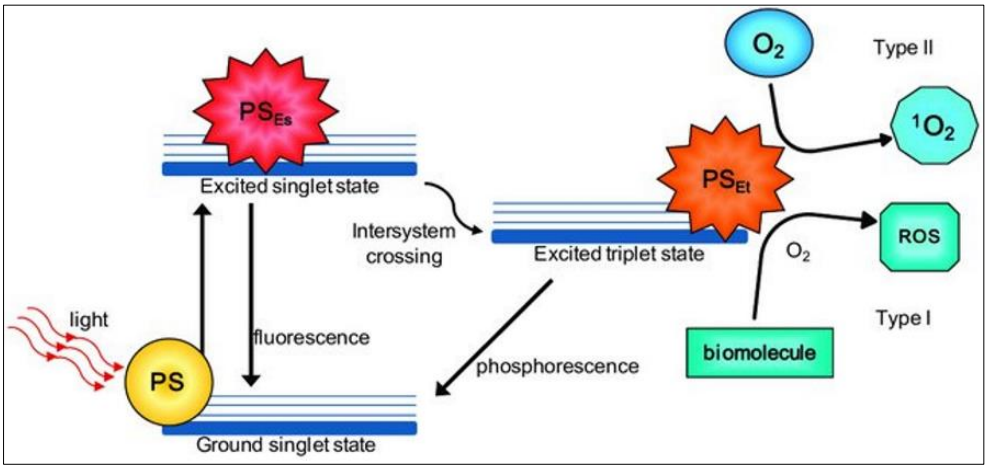

Figure 20: Photodynamic Reaction Mechanism. Photodynamic therapy in cancer treatment: properties and applications in nanoparticles
Source: Doi.org/10.1590/1519-6984.268892

The research combines cancer treatment methods already used in medicine, but the innovation lies in combining two treatments: brachytherapy and magnetic hyperthermia. Brachytherapy, known as internal radiotherapy, is a form of radiotherapy in which a radiation source is placed inside or next to the area that needs treatment. Magnetic hyperthermia, in turn, is an alternative treatment for curing cancer that is based on overheating the tumor region, facilitating the death of malignant cells [CEFET-MG researcher Gabriela Veloso] [CEFET-MG researcher Gabriela Veloso] (Figure 21) (POSMAT, 2022; Reverso, 2024; Younusa *et al.*, 2024).

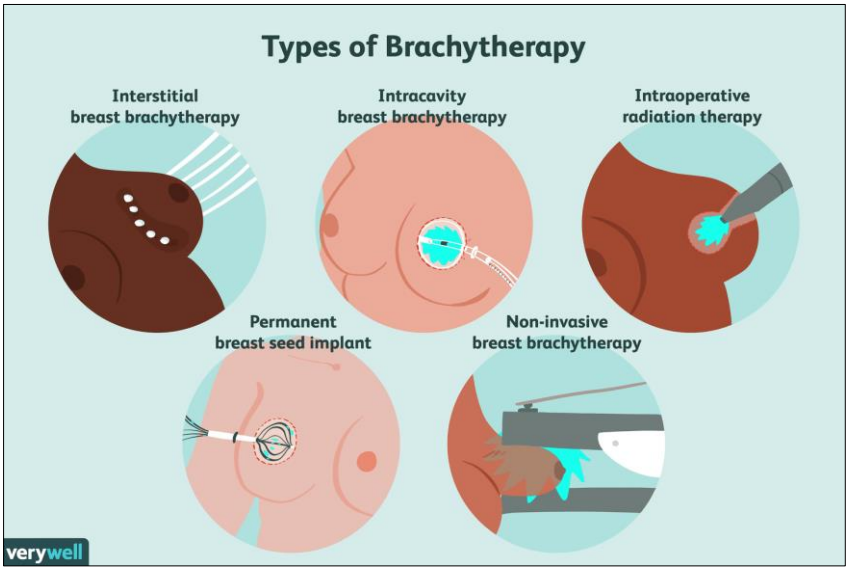

Figure 21: Brachytherapy for early-stage breast cancer
Sources: Jaime, R., & Herndon and Verywell / Emily Roberts

The chemical element samarium is a source of radiation and magnetic iron oxide nanoparticles from titanium mining. At room temperature, samarium is in a solid state and is used in carbon electrode lamps in medicine, and treatments for bone pain with samarium-based medications. Magnetic iron oxide nanoparticles have the appearance of a fine brown powder and are widely studied, including drug transport, medicine, and contrast media in magnetic resonance imaging. This is a material whose silica matrix contains magnetic nanoparticles and samarium. Magnetic nanoparticles are responsible for treating cancer via magnetic hyperthermia, and samarium, via brachytherapy. In other words, the same material treats cancer using two methods [CEFET-MG researcher Gabriela Veloso] [CEFET-MG researcher Gabriela Veloso] (POSMAT, 2022; Reverso, 2024; Younusa *et al.,* 2024).

The use of cold water immersion in the initial minutes after hyperthermia induced by physical exertion seems to be the best recommendation for controlling this health problem, as it allows for an efficient reduction in the time during which the core temperature remains elevated. In physical activities and environmental conditions in which individuals are more susceptible to severe hyperthermia, the maintenance of the infrastructure necessary for carrying out this procedure should be considered (Figure 22) (Viveiros *et al.,* 2009).

Figure 22: If you are alone in cold water: Pull your knees up toward your chin and cross your arms tightly over your chest. This position will help protect the parts of your body most prone to heat loss, such as your armpits and the backs of your knees. If you are alone in cold water: Pull your knees up toward your chin and cross your arms tightly over your chest. This position will help protect the parts of your body most prone to heat loss, such as your armpits and the backs of your knees

Source: https://www.boatsmartexam.com/knowledge-base/article/cold-water-immersion-and-hypothermia/

They point out that locoregional hyperthermia improves the complete response, that is, until the tumor goes into remission, of cancer treatments by up to 20%. And, as they point out, the combination of hyperthermia with radiotherapy and/or chemotherapy enhances its effects in advanced stages, achieving better results [Specialists from the Quirónsalud hospitals in Seville -- Quirónsalud Infanta Luisa, Sagrado Corazón and Materno-Infantil-- and the Comprehensive Oncology Department of the Quirónsalud Málaga, Quirónsalud Marbella and Quirónsalud Campo de Gibraltar hospitals] (Figure 23) (Okamura *et al.,* 2022; Quirónsalud, 2024).

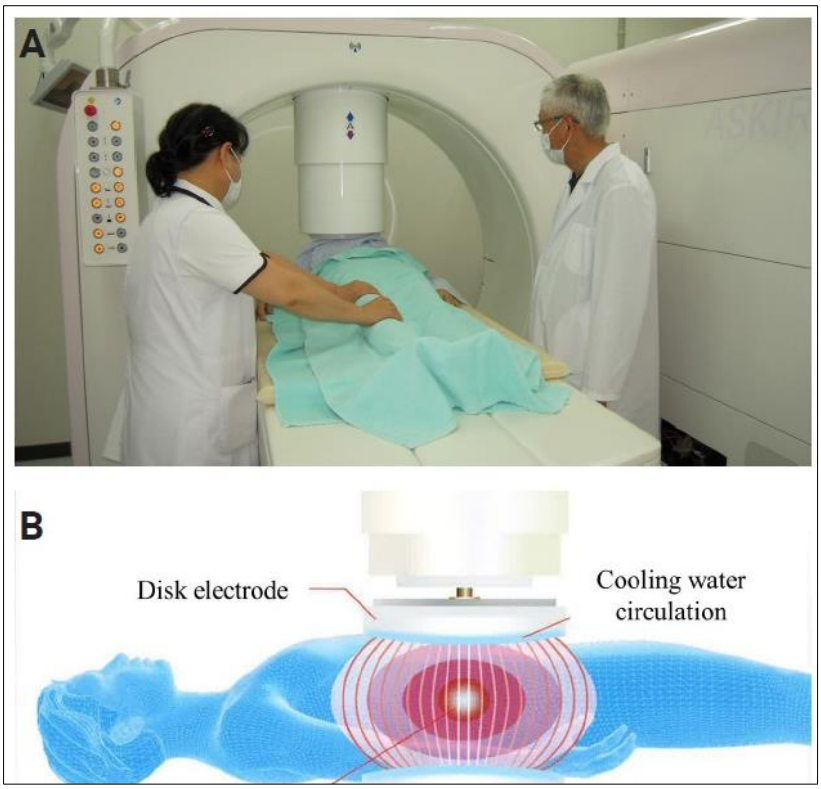

Figure 23: Low-aggressive long-term continuous hyperthermia in combination with extremely low-dose chemotherapy for prostate cancer patients at medoc health clinic in Japan

They emphasize that the objective of this technique is to "enhance the results of conventional oncological treatments for those patients where the expectations of success are not very high." "Hyperthermia is always associated with other conventional treatment modalities radiotherapy and/or chemotherapy and/or immunotherapy - and they are administered simultaneously," she said. This was pointed out by radiation oncologist [Julia Montañes Uceda of Quirónsalud Infanta Luisa Hospital, within the framework of the meeting 'Oncological Hyperthermia: present and future in cancer treatment', [organized by the Medical Oncology and Radiotherapy services of Quirónsalud Infanta Luisa and Sagrado Corazón] (Quirónsalud, 2024).

Treatment is usually twice a week, in cycles of approximately 10 or 12 sessions, as Dr. Montañes Uceda indicated, emphasizing that "they are usually patients who are receiving retreatment or have tumors in advanced stages." In these cases, "associating hyperthermia with radiotherapy and/or chemotherapy enhances the effect of these other treatments, thus achieving better results," she emphasizes (Quirónsalud, 2024).

6.0. CLIMATE CHANGE

Climate change also increases the risk of new pandemics and infectious diseases. “We can see this impact in the increase in the planet’s temperature, for example, which is responsible for hyperthermia (when the body experiences a sharp increase in temperature) and death. The greater volume of rainfall and disasters is also another condition that increases the risk of infectious diseases, such as leptospirosis, hepatitis, dengue, chikungunya, and zika,” [explains Ricardo Heinzelmann, physician and professor at the Department of Public Health at the Federal University of Santa Maria (UFSM)] (Kroll *et al.,* 2023).

In addition, extremes of temperature and humidity are among the main factors that can influence human health. Heat and cold waves can become more intense and affect various systems in our bodies. It is common to associate cold with the development of respiratory diseases; however, the circulatory system can also be damaged [explains Ricardo Heinzelmann, physician and professor at the Department of Public Health at the Federal University of Santa Maria (UFSM)] (Kroll *et al.,* 2023).

7. CONCLUSION

The groundbreaking research was the development of silica particles containing samarium and iron oxide for cancer treatment using brachytherapy and magnetic hyperthermia. The work addresses a synthetic, biodegradable material for cancer treatment using combined spinal therapy and magnetic hyperthermia. In addition, the novelty of the research is due to the use of the chemical element samarium as a source of radiation, the novelty of the research is due to the use of the chemical element samarium as a source of radiation.

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