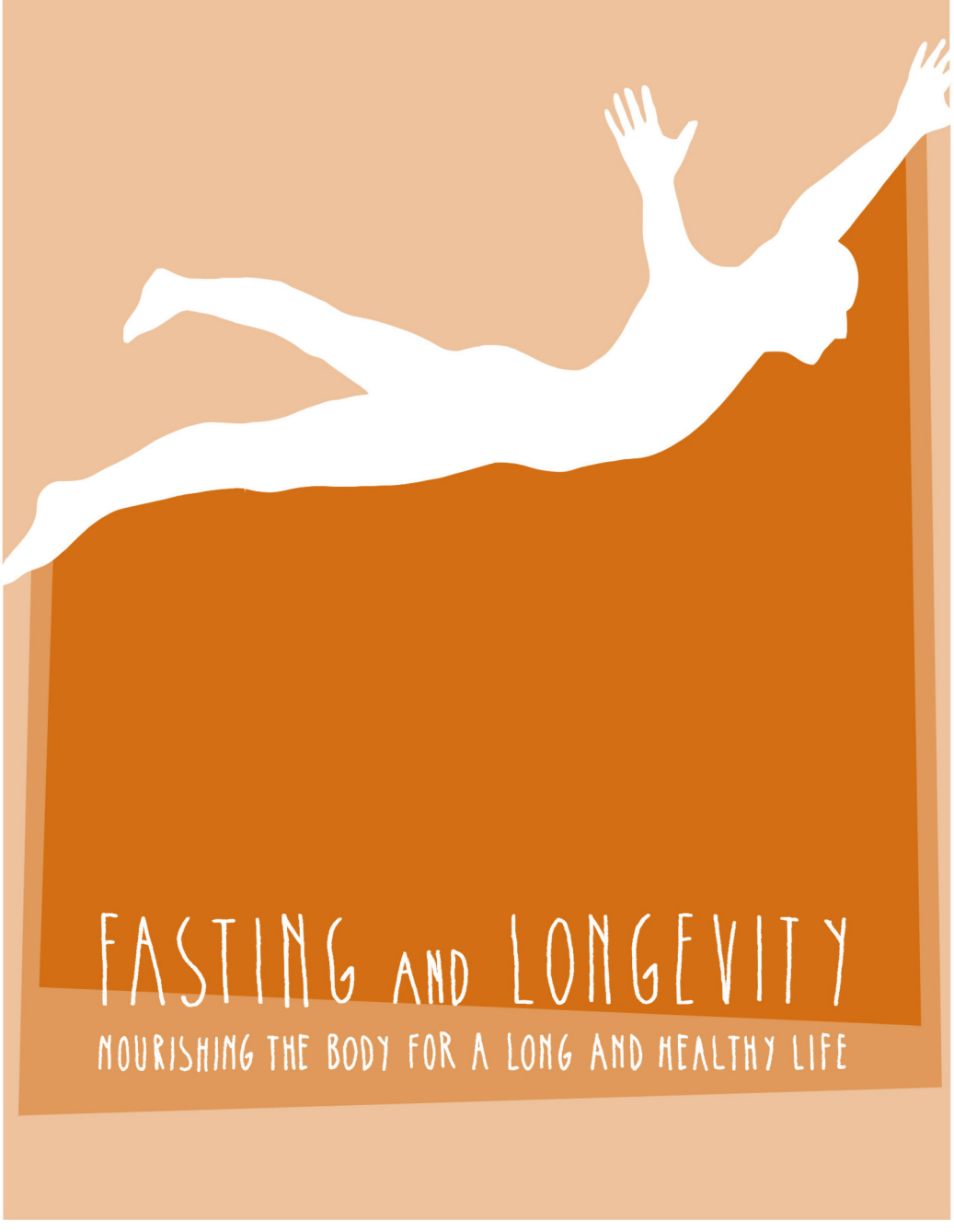

FASTING AND LONGEVITY

NOURISHING THE BODY FOR A LONG AND HEALTHY LIFE

NUTRITION, HEALTH and LONGEVITY

FONDAZIONE
VALTER LONGO

VALTER LONGO FOUNDATION

FASTING AND LONGEVITY

Nourishing the Body for a Long and Healthy Life

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Cover by Manuela Lupis

Our mission is to offer everyone
the opportunity for a long and healthy life

Valter Longo Foundation

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FOREWORD

The Valter Longo Foundation was founded in Italy in 2017 by Professor Valter Longo, Ph.D, Director of the Longevity Institute of the School of Gerontology at the University of Southern California (USC) in Los Angeles and Director of the Oncology and Longevity Program at the IFOM in Milan, Italy. Professor Longo was included by the American magazine "Time" in the list of the 50 most influential people of 2018 in the health sector and is known throughout the world for the creation of the "fasting-mimicking diet" and for his world-wide bestseller "The Longevity Diet". In 2021 the American scientific magazine "Science" described him as a pioneer in the field of nutrition and cancer.

The Valter Longo Foundation is a non-profit organization that aims to promote, implement, and optimize healthy and sustainable longevity for oneself, for others, and for the environment. This path towards longevity and health begins in childhood and continues throughout the entire life cycle, in order to create a correct lifestyle and be able to live in the best way possible so as to prevent various types of serious diseases, including tumors, diabetes, obesity, cardiovascular diseases, autoimmune diseases such as Crohn's disease, and neurodegenerative diseases such as Alzheimer's.

The mission of its founder and of the Foundation is to offer everyone without distinction the opportunity for a long and healthy life. To achieve its institutional goals, the Foundation dedicates its daily efforts from both a preventive and therapeutic point of view to:

- The promotion, financing and direct and immediate provision of health and social assistance and nutritional consultancy, based on certain scientific data. This aims to treat, prevent, or support people suffering from various pathologies and living in a particular emergency condition or experiencing psychological, physical, and economic distress. Additionally, it offers guidance to all those who wish to pursue healthy longevity.

- Raising awareness and educating the public of all ages on issues related to nutrition and a balanced and healthy lifestyle based on scientific data.

The book *"Fasting and Longevity. Nourishing the Body for A Long and Healthy Life"* was born from the desire to educate and raise awareness about aging, longevity, nutrition, prevention, and treatment of diseases. It provides valuable, useful, and practical information, along with concrete tools to empower individuals in making informed choices and living a long and healthy life.

This book pursues this goal, and the modest requested contribution will support the Valter Longo Foundation and its free programs. These programs benefit all of us, including patients facing critical health and financial conditions, schools, children, young people, families, teachers, centers for people with disabilities, and those in the third and fourth age. Additionally, the foundation extends its support to women embarking on a path to escape violence.

We thank you for your contribution and kindly ask for your continued support by following our activities and sharing them. Together, we strive to fulfill our mission of offering everyone the opportunity for a long and healthy life. "Help us help". Thank you!

Valter Longo Foundation

INTRODUCTION

Fasting represents an ancient practice that involves the voluntary renunciation of food intake for a specific period of time. This tradition has deep cultural, religious, and therapeutic roots in many areas of the world and can vary in terms of purposes, duration, and methods. Indeed, throughout history, fasting has been and continues to be adopted for a variety of reasons including spiritual reasons, improved health, weight control, exercise of self-discipline, and even for medical treatments in certain circumstances.

From a religious perspective, fasting is often associated with periods of purification, reflection, and devotion. Many religions including Islam, Christianity, Judaism, Buddhism, and Hinduism include fasting as an integral part of their ritual practices in different forms.

In addition to its religious significance, fasting has sparked interest for its potential health benefits.

Periodic fasting, for example, can contribute to:

- improving metabolism, that is, the set of biochemical reactions that produce the necessary energy and that allow our organism to function in such a way that the organism can grow and renew itself;
- promoting weight loss;
- increasing sensitivity to insulin, a hormone produced by the pancreas that lowers glucose (sugar) levels in the blood as it allows glucose to enter the cells where it is used to obtain energy;
- offering support in the prevention and treatment of chronic diseases such as, for example, diabetes, cancer, and cardiovascular diseases.

Currently, the significant interesting surrounding fasting is focused on its ability to slow aging in most species and to protect against various diseases, including neurodegenerative diseases,

metabolic disorders, and cancer.

However, experts' opinions on this topic sometimes vary. Therefore, the practice of fasting should be approached with caution, especially in cases of pre-existing health problems. It is, in fact, important to note that fasting is not suitable for everyone, and that people should take into consideration their individual situation, medical conditions and consult a health professional before undertaking any type of fasting.

The purpose of this book is precisely to offer a compendium and a point of reference for the general public. The objective is to define the various protocols about food restrictions and fasting, describing in detail the molecular, cellular, and metabolic mechanisms that come into play. Furthermore, on the basis of the most up-to-date scientific articles and through clinical experience with the patients of the Valter Longo Foundation, also thanks to the direct training of professionals by Professor Longo, the different nutritional approaches are described, as applied to the various pathologies related to aging, such as cancer, diabetes, cardiovascular, autoimmune, and neurodegenerative diseases.

In summary, fasting is a complex topic that encompasses cultural, religious, health, and self-discipline aspects. Its rich history and multiple facets make it a topic of interest and debate in many communities and fields. For this reason, the Valter Longo Foundation has dedicated this new book in the "Nutrition, Health and Longevity" series to this fascinating and interesting topic for our health.

FASTING IN NATURE

In recent years, fasting has attracted growing interest as a therapeutic approach in the field of nutrition, due to its role in the regulation of intracellular mechanisms related to aging, of the intestinal microbiota, i.e., the set of microorganisms that inhabit our intestine, and in processes related to daily cycles such as sleep and wakefulness (which are collectively known as circadian rhythms). Despite growing scientific interest in recent years, it is important to note that fasting is a practice that has existed forever, with examples occurring in nature.

In fact, there are several animals that have evolved and adapted to face extreme conditions, including the absence of food and water, for long periods of time due to their life cycles or the environment in which they live. Here are some examples below.

1. **Camels:** camels are known for their ability to survive without food and water in order to travel long distances in the desert. They can store water in their body and use it gradually during fasting periods.

2. **Emperor penguins:** during the breeding season, male emperor penguins gather in large colonies and incubate eggs while the females go offshore to feed. These males can fast for over two months, surviving on accumulated fat reserves.

3. **Swallows:** some swallow species migrate long distances between their nesting site and areas where they find food. During migrations, they can cross the ocean without food for days or even weeks.

4. **Sea turtles:** sea turtles may face periods of fasting when they migrate or during periods in which they are affected by unfavorable weather conditions. Their fat reserves provide them with energy during these times.

5. **Insects like the aphids:** aphids are known for their adapta-

tion to prolonged fasting. They can reduce their basal metabolic rate, i.e., the calories they consume at rest just to stay alive and survive without food for several days.

6. **Brown Bears:** brown bears prepare for winter by accumulating fat reserves during the summer and fall. During winter hibernation, they reduce their metabolism and live off fat reserves accumulated without eating.

7. **Artemia salina**: also known as the **sea monkey**, it is a small crustacean with a "water tank" that can resist long periods of dehydration thanks to its biochemical adaptations and the ability to enter a state of cryptoanabiosis, i.e., the ability to revive after a period of apparent death or latent life.

These examples illustrate how different animals have developed strategies to cope with fasting to survive in their specific environmental conditions or life cycles.

FASTING IN RELIGIONS

For humans, as well as for the primates who came before them, prolonged periodic fasting has been a common occurrence throughout history. This was caused by several factors, including lack of food due to climatic or seasonal conditions, difficulty in obtaining food resources, and competition with other individuals or species for food.

Later, fasting became a voluntary choice, often inspired by religious traditions that required abstinence from food as a means of purification for both the body and soul. The practice of fasting has historically been widespread among many religions. However, over time, certain fasting practices have been modified or abandoned, although their spiritual significance may persist in some specific religious forms or contexts.

For example, Muslims practice Ramadan. During this month they abstain from eating and drinking anything throughout the day, and then eat from sunset to sunrise, along with practicing various religious rituals and prayers.

In the past, Christians practiced over a month of severe calorie restriction, i.e., the period of Lent, which ended with a week of real fasting, consuming only water. This practice has also been abandoned or modified by followers over time.

In Judaism, as a further example, a solemn period of fasting of 25 hours is practiced during the annual Day of Atonement or Yom Kippur (from sundown when Yom Kippur begins until sundown of the following evening), accompanied by prayers and meditation, to express repentance towards any mistakes committed or demonstrate the seriousness of the commitment made towards God.[1]

For Buddhism, fasting is a form of internal discipline, which serves to free the mind and reach a higher level of spirituality, and it is practiced in periods of intensive meditation during spiritual retreats.

Within the various beliefs, philosophies, doctrines, and rites in the country of India, which had been defined in the past as Hinduism, fasting is a practice connected to purification to get closer to the divinity and is carried out on fixed days of the month or week. For example, worshipers of Shiva fast on Mondays. People also fast during festivals and holidays, for example, many practice fasting during the month of Śravaṇa (July/August or August/September, depending on the calendar).

In Taoism there is a type of fasting, called "bigu", which involves abstention from cereals as a method of purification and is based on the idea that this allows one to live a longer life and possibly become immortal.[2]

Further forms of fasting present in various capacities in many other religions concern, for example, the ancient Greeks, who practiced fasting before consulting the oracles,[3] or the African shamans, who still practice forms of fasting during rites to contact the spirits.[4]

These periods of purification are practices that have influenced our history and are not a novelty or a new trend. Evidently, they are effective practices that the Ancients already engage in to experience their beneficial effects, and they are presumed to be safe.

AGING, DISEASES AND THE ROLE OF FASTING

Before getting into the technical details of nutritional approaches related to fasting, it is essential to understand the role of nutrients in aging. Once there is a clear understanding of the molecular mechanisms that influence the aging process and how these can be modulated by nutrition and fasting, it becomes more intuitive to understand how to manage one's own diet, fasting methods and timing to optimize health and pursue healthy longevity.

Aging is a natural phenomenon that involves the set of changes that occur over time and is an inevitable process in the life of every individual.

In some cases, the experience gained over the years can lead to significant improvements, both physically and mentally. For example, experienced athletes can benefit from accumulating experience and training over the years, improving their performance in sport. Additionally, mental maturity and the acquisition of knowledge throughout life can lead to greater wisdom and problem-solving abilities.

However, it is true that the aging process is often associated with physical and functional changes that can negatively affect the well-being and normal functioning of the human organism. These changes may include decreased muscle strength, loss of bone density, decreased cognitive abilities, and the onset of age-related health conditions.

Over the centuries, scientists have proposed various theories to try to explain the aging process. Among these, **Darwin and Wallace's theory of evolution** stands out. It highlights the role of natural selection in preserving individuals capable of generating healthy offspring, while those who are no longer able to do so are eliminated. These two scientists were the first to suggest that aging and death were programmed processes, despite not being able to demonstrate it.

Furthermore, **Kirkwood's "disposable" soma theory** states that organisms invest their resources, i.e., energy and vitality, primarily in reproduction, viewing the body as a "disposable" genetic resource as long as it continues to produce offspring. As a result, individuals maintain health and vitality only as long as they can pass on their genes through procreation. When this reproductive contribution is reduced and disappears, the body becomes "disposable" and the resources decrease and are redirected elsewhere: no longer in reproduction, but for example in the maintenance of vital functions and the survival of the individual.

Other theories, such as that of **free radicals**, argue that oxidizing molecules, such as oxygen, damage cells, proteins, and DNA, thus contributing to aging.

The analysis of aging, upon which these theories were based, began with an understanding the mechanisms linked to this process and the consequences for the organism. Until now, theories had mainly focused on deterioration and aging that begins around the age of 40-50. However, recently, the perspective has changed. In order to understand how we age, it is also essential to study the previous phase, youth, to understand how to prolong this phase of life and live longer and in a healthier way.

THE STUDY OF YOUTH

To maintain a young and functional body, it is essential that it is programmed to last longer. To this end, protection, repair, and replacement processes are activated. Which ones are they? To carry out the scientific analysis of these processes, a new field of research has emerged, called **"Juventology"**.

Juventology, recently validated by the scientific community through a study published in the scientific journal "Aging Cell", introduces the concept of **"youthspan"**, a period of life in which the organism is young, healthy and functions efficiently. This field of research aims to explore the mechanisms that regulate this "youthspan", prolonging the period of healthy life and maintaining youth. How does it achieve this? Through what is defined as "programmed longevity".

PROGRAMMED LONGEVITY

"Juventology" can provide valuable information to identify strategies that slow down the aging process without compromising our well-being. In this context, the theory of **"programmed longevity"** emerges, as developed by Professor Valter Longo, who collected significant experimental evidence and published it in "Nature Review Genetics", drawing inspiration from the studies of Darwin and Wallace.[5]

According to this theory, it is possible to slow down aging, making the decline begin only after 60-70 years of age, instead of 40-50 years, as commonly observed. Programmed longevity represents an evolved biological strategy to improve health and extend life through protective and regenerative mechanisms. To understand how we can maintain a young and healthy condition, it is essential to acquire an in-depth understanding of the mechanisms that regulate longevity, especially by studying the genes that regulate aging and longevity.

While our genetic makeup is largely unalterable, there are viable strategies to promote protective, regenerative, and rejuvenating effects that can help ensure we live a long and healthy life. These strategies, as we will see in depth later, mainly focus on promoting **balanced dietary plans and physical exercise**, which can preserve our body's health for a longer time. We will first analyze the research related to aging and then focus on strategies to slow it down.

SCIENTIFIC RESEARCH ON AGING

Numerous scientists around the world have devoted and continue to devote their energies to investigating aging processes. Initially, much research was conducted on mice* (see Appendix: Disclaimer – To animal activists) and much experimentation was done on humans, but the complexity of such organisms made it difficult to quickly identify the genes responsible for aging and understand its mechanisms of action.

As a result, attention has shifted to single-celled organisms, such

as the baker's yeast known as *Saccharomyces cerevisiae*. This organism, composed of a single cell, offers the advantageous possibility of being easily found, studied, and subjected to genetic modifications. Thanks to research on the "chronological life of yeast", it was possible to identify key genes that influence aging.[6]

Valter Longo, based on the study of *Saccharomyces cerevisiae*, has made significant discoveries. He noticed that by "starving" the yeast, moving it from an environment rich in sugars and nutrients to an environment with only water, the life of the yeast doubled. Furthermore, he identified sugar as the main nutrient responsible for aging, as it activates the "pro-aging" genes Ras and PKA, while deactivating protective factors and enzymes against it. These factors are called antioxidants because they counteract oxidation, that is, the imbalance between the production of reactive free radicals and the body's ability to neutralize them.

Subsequently, how our body uses sugar was discovered (i.e., the 'metabolic pathway of sugar' was discovered) and how this is involved in the aging process.

This process also involves the growth hormone, which plays a fundamental role. The growth hormone (GH) plays several roles in the body such as: regulating development and growth during childhood, influencing metabolism and aging.

These discoveries subsequently stimulated research into more complex model animals, such as worms, leading to the identification of other genes that influence the aging process. These genes include Daf-2 and Tor-S6K.[7]

THE MOLECULAR STRATEGY TO EXTEND HEALTHY LIFE

Discoveries made in yeast and worms have led to the belief that living organisms share a similar molecular strategy for slowing down aging. This idea was later confirmed by studies conducted on mice in laboratories. In fact, it has emerged that the same genes and metabolic pathways that influence longevity in simple organisms, such as yeasts, also play a significant role in mammals, including mice, but also in humans, in protecting them

from diseases associated with aging.

In particular, at the basis of the mechanisms that lead to the appearance of age-related diseases, we have the growth hormone, a hormone that promotes greater and faster growth of cells and of the organism in general.

A significant example comes from a study conducted in Ecuador on individuals suffering from a rare syndrome that causes a shorter than average height, Laron syndrome, characterized by the lack of the growth hormone receptor.[8] These individuals have demonstrated an extraordinarily low incidence of diabetes and cancer, despite an unhealthy lifestyle and unregulated diet. The basis of these diseases is precisely the growth hormone: since it is defective in these individuals, they do not grow in height, but they also age more healthily.

This evidence confirmed that mutations in the growth hormone receptor protect individuals from the appearance of age-related diseases, both in simple organisms, such as yeasts, and in more complex organisms, such as humans.

INTERVENING DIRECTLY ON AGING

The characterization, i.e., the process of identification, description, and detailed analysis, of the metabolic pathways and genes that regulate growth and aging, obtained through decades of scientific research, has made it possible to identify aging itself as the main risk factor responsible for the onset of diseases that lead to death, such as cardiovascular diseases, tumors, and neurodegenerative diseases such as Alzheimer's. The main risk factor for the development of fatal diseases is therefore age. For this reason, one of the most effective strategies to improve health and prolong life is to intervene directly on this process.

The approach of preventing and treating specific diseases one at a time, known as "one disorder at a time," is a complex and often less effective process because it has limited power in prolonging all-round health. For example, it has been estimated that, considering an average life expectancy of 80 years for humans, the

complete cure of tumors or cardiovascular diseases could extend life by approximately 4-5 years. Adding diabetes treatment could extend life by about 14 years. Only by slowing down the aging process could we aspire to extend life by at least 30 years, bringing life expectancy to over 100 years, while maintaining good health.[9]

Scientists are therefore trying to discover the mechanisms involved in the aging process, since direct intervention on them they may be able to significantly extend human lifespan. We will see how in the following sections.

HOW NUTRIENTS AFFECT METABOLISM

Several scientific studies have demonstrated how sugars and amino acids (the building blocks that allow the construction of proteins) influence genes associated with aging, such as GH-IGF-1, Tor-S6K and Ras-PKA.[10]

Animal proteins increase growth factor IGF-1 levels, which is closely linked to uncontrolled cell proliferation and consequently aging and predisposition to the appearance of tumors. Additionally, proteins and amino acids, such as leucine, can activate Tor-S6K genes, which are also involved in aging. On the other hand, sugars, like simple carbohydrates, activate Ras-PKA genes, also contributing to the acceleration of aging. The combination of sugars and proteins in the daily diet, if taken in excess, can maximize the activation of molecules that contribute to the degeneration of the organism.

These scientific results are the product of the hard work of geneticists and molecular biologists from prestigious universities and research institutes, including UCLA (University of California Los Angeles - USA), USC (University of Southern California - USA), UCSF (University of California, San Francisco - USA), MIT (Massachusetts Institute of Technology - USA), Harvard University (Boston - USA), Brown University (Providence - USA) and UCL (University College London - UK).

It is therefore essential to continue scientific research to understand how nutrition can influence and regulate these genes, with

the aim of reprogramming and optimizing the human body's longevity.

WHAT TO EAT (AND WHAT NOT TO EAT) FOR A LONG AND HEALTHY LIFE

The concept that "we are what we eat" has been introduced in the past by philosophers such as Ludwig Feuerbach and by doctors such as Hippocrates, who argued that food can act as medicine. These thinkers recognized the crucial importance of nutrition for our health.

As a matter of fact, food acts as our vital fuel. The choice to adopt a careful and healthy approach in its selection can produce beneficial effects for our body. On the other hand, opting for junk food can put our overall well-being at risk. Being aware of this underlines the fundamental importance of adopting a healthy and balanced diet.

If we want to ensure a healthy and long-lasting life, there are a series of practices that can prove extremely useful. First of all, if our eating habits are disordered, it is essential to improve our diet by moving towards a healthy approach. In general, it is advisable to follow the instructions of medical experts and nutritionists who can guide us towards a well-considered, personalized food plan based on research and clinical studies.

In addition to maintaining adequate control of weight and body fat distribution with the daily practice of the Longevity Diet (see the "Conclusions" of this book and the book "The Longevity Diet" by V. Longo)[11], it may be beneficial to periodically follow fasting cycles, in particular daily 12-hour fasting and fasting-mimicking diet cycles, as we will see later on.

The association between fasting and aging is a topic of great scientific interest due to its effects on longevity, on the overall well-being of the processes and biochemical reactions that occur within the body, i.e., the so-called metabolic health, on resistance to disease and general well-being.

Fasting has been the subject of interest in scientific research as it appears to have several positive impacts on health and aging. One of the key processes related to fasting is cellular autophagy. Autophagy is a mechanism by which cells "eat" parts of themselves that are damaged, old, or no longer functional. This process is important because it helps keep cells in a healthy state and prevents the buildup of damaged material. When autophagy is activated, cells shed damaged cellular components and recycle them to produce new, vital molecules. This process has been associated with delaying aging and preventing diseases related to the accumulation of damaged material within cells.

Additionally, fasting can help reduce oxidative stress, caused by the excessive production of free radicals, which are highly reactive molecules that can damage cells and DNA. Fasting can reduce the production of free radicals and increase the body's ability to neutralize them through specific antioxidant systems (among these, just as an example, we can mention the superoxide dismutase enzyme and the glutathione enzyme in reduced form), thus contributing to maintaining cells in a state of lower oxidative stress.

Finally, fasting can improve insulin sensitivity. Insulin is a hormone produced by the pancreas that regulates blood sugar levels, allowing glucose to enter cells to be used as an energy source. Reduced sensitivity to insulin, known as insulin resistance, is associated with conditions such as type 2 diabetes. Intermittent fasting and prolonged fasting can help improve cells' response to insulin, which can help prevent diabetes and improve blood glucose level management.

It is important to note that the fasting practices described below are often implemented on a regular basis, following a defined plan, and are often integrated into a coherent weekly pattern.

Many rely on the fact that these methodologies can bring health benefits, including weight loss, improvement of insulin resistance, and other positive effects on metabolism. However, it is crucial to fast responsibly, ensuring that the body still receives the essential nutrients it needs to function properly.

It is important to emphasize once again that most fastings should be undertaken carefully and under the supervision of a healthcare professional. This is because these practices can have a significant impact on the body and overall health. Proper management and adaptation of these practices can help maximize potential benefits and reduce health risks.

CALORIE RESTRICTION AND FASTING

Fasting can be interpreted as an extreme form of calorie restriction, from which it does however differs, as we will see later on. It is therefore important to better define the terms that indicate different dietary interventions for the promotion of a long and healthy life, such as calorie restriction and fasting in all its variants.

Calorie restriction is recognized as one of the most effective non-pharmacological approaches to promoting metabolic health, that is the overall well-being of the metabolic processes and biochemical reactions that occur within the body.

As said, metabolic health is a term that refers to the overall well-being of an individual's metabolism. Metabolism is the set of chemical processes that occur within the body to convert food into energy and to carry out other vital functions. Metabolic health is therefore an indicator of the body's ability to regulate blood sugar levels, metabolize fats, manage energy, and perform other metabolic functions in a balanced way.

Metabolic health is influenced by many factors, including diet, physical activity, genetics, and lifestyle. A good state of metabolic health is often associated with stable blood sugar levels, normal blood pressure, a healthy lipid profile (for example, adequate blood cholesterol levels), and good body weight management. Conversely, poor metabolic health can lead to conditions such as diabetes, obesity, and cardiovascular disease.

Maintaining good metabolic health is important for overall health and well-being and for the prevention of chronic diseases, also known as "noncommunicable diseases." They are medical conditions characterized by a prolonged or permanent duration, that develop slowly over time and tend to persist for long periods, often for life.

Returning to the topic of calorie restriction, as the name sug-

gests, it indicates a dietary regime that involves reducing the daily calorie intake, without however causing malnutrition. It is in fact also known as a “low-calorie diet”.

The restriction can be defined 1) in relation to the quantity of calories consumed in the period preceding the adoption of the calorie restriction itself; or 2) in relation to an average calorie consumption of people with similar physical characteristics. For example, consider a calorie restriction of 20% of habitual calorie intake. This nutritional intervention is normally long-term, meaning it must be maintained over time to achieve its potential benefits.

It is important to note that calorie restriction is not limited to a simple decrease in calories but involves a conscious choice of foods to ensure that the body still receives all the essential nutrients necessary for its optimal functioning (carbohydrates, proteins, fats, and micronutrients in appropriate percentages).

The positive effects of calorie restriction go beyond simple weight loss and also concern the reduction of damage caused by oxidation or oxidative stress, i.e., the imbalance between the production of reactive free radicals and the body’s ability to neutralize them.

Free radicals are unstable molecules that can damage cells and contribute to several diseases, as noted above. Our body usually produces free radicals as part of metabolic processes. We talk about oxidative stress when the number of radicals grows excessively, and the body is unable to keep them under control. This imbalance can cause cellular damage and contribute to conditions such as premature aging and the development of chronic diseases. Furthermore, with increasing age, our body’s ability to neutralize these elements is reduced, inducing a physiological accumulation that leads to damage to cell membranes.

Studies, which we will review shortly, have suggested that calorie restriction may have beneficial effects on longevity and the prevention of age-related diseases, such as type 2 diabetes, heart disease, and some neurodegenerative conditions. It is

also believed that it can influence various biological processes, including metabolism, the reduction of inflammation, and the protection of DNA from damage such as oxidative stress, but also solar radiation, chemical agents, pollution, etc. It is important to remember that DNA damage can lead to various consequences, including genetic mutations, and can contribute to the development of diseases such as cancer.

SOME CLINICAL STUDIES ON CALORIE RESTRICTION

Conducting studies on calorie restriction on humans represents a complex challenge since, as previously mentioned, it requires long observation periods in order to accurately evaluate its effects. Two large studies have been carried out on the effects of calorie restriction: Biosphere II[12] and the CALERIE I and II project.[13,14]

The **Biosphere II** project aimed to explore the interaction between humans and the environment, within a closed ecosystem. In this experiment, participants were confined within a biosphere-like structure. Within this biosphere, the volunteers' task was to sustain their own survival by producing their own food. However, they encountered difficulties as some elements of the food production process were not carried out successfully, inevitably leading to a significant reduction in daily calorie intake over a two-year period. It should be noted that, despite the difficulties, the food that the participants consumed within the biosphere was highly nutritious and mainly composed of vegetables, fruits, nuts, cereals, and legumes. The amounts of dairy, eggs and meat were limited. The results of this experience are evident in the data related to various health indicators.

During their stay in the biosphere, the Body Mass Index (BMI, a system that assesses weight in relation to height and also allows the risk of diseases to be evaluated) decreased for all participants, reaching healthier levels. This was accompanied by a significant reduction in both diastolic blood pressure (the "minimum", which occurs when the heart relaxes between two beats and blood flows continuously through the arteries) and systolic blood pressure (the "maximum", which occurs when

the heart the heart contracts and pumps blood through the arteries). In addition, there was a significant improvement in glycemia levels, i.e., the concentration of glucose in the blood, and in insulin levels. This improvement is important in preventing diseases such as diabetes and cardiovascular diseases, contributing to sustaining the body in an optimal state of health.

In summary, the data analysis showed a significant impact on indicators associated with diseases such as cancer, heart disease, diabetes, and hypertension among participants during their time in the biosphere. However, it was observed that the levels of all these biomarkers, which are biological parameters indicating health status and the risk of developing a disease, reverted to their previous levels after the participants left the confined environment of the biosphere.

These findings indicate that, while calorie restriction can lead to temporary health benefits, these improvements tend to be transient and not long-lasting. This is confirmed by the participants' return to a more conventional living environment, where their parameters, such as weight, blood sugar, blood pressure, cholesterol, etc., reverted to their previous levels.

Another research project of relevance in this context is represented by the **CALERIE Project**, which focused on calorie restriction in a city in Louisiana, in the US. This study involved 48 healthy individuals, both men and women, of approximately 50-55 years of age, and a body mass index (BMI) of approximately 27, i.e., in the "overweight" category. The duration of the intervention was six months and involved lifestyle management that included advice on healthy diets and physical activity.

As part of this study, participants were assigned to one of the following groups: a control group (who therefore made no changes to their lifestyle); a group in which they had to follow a very low calorie diet (which in this setting we will not take into consideration, as it is not relevant to the explanation of the results); a group subjected to a 25% calorie restriction; a group engaged in physical activity exercises to achieve the same calorie deficit as the calorie restriction group (12.5% resulting from

calorie restriction and 12.5% from exercise).

The results highlight that both calorie restriction and exercise had a significant impact on the change in participants' body weight. On average, after six months, a body weight loss of approximately 10% was recorded. This percentage was confirmed by the project's continuation, known as CALERIE 2, which lasted for two years.

These results are impressive and demonstrate the ability to positively impact body weight management through calorie restriction.

The benefits of calorie restriction also extend to biomarkers associated with health. Analysis of the data revealed notable improvements in levels of cholesterol, triglycerides in the blood, insulin resistance (i.e., a resistance to insulin that prevents the proper transport of glucose from the bloodstream into cells), and average blood pressure in subjects subjected to prolonged calorie restriction. These findings suggest that calorie restriction may positively influence various aspects of human health, helping to reduce the risk of diseases associated with aging.

Despite the promising results, it is essential to consider that calorie restriction does not represent a universal solution applicable to everyone. Longevity effects found in mouse studies are inconclusive and vary depending on the strain and sex examined. Furthermore, calorie restriction is associated with a non-negligible difficulty in the human context. The challenge of maintaining long-term calorie restriction is clearly evident in the CALERIE projects, where participants failed to fully achieve caloric reduction goals. Initially, they maintained a restriction of 19% in the first 6 months and 9% for the remainder of the study, instead of the foreseen 25%.

In conclusion, although there is evidence of the health benefits of calorie restriction, it is clear that this practice can be difficult to maintain in the long-term and is not suitable for everyone. Research continues to investigate the effects of calorie restriction, and further studies are needed to fully understand the

benefits and limitations of this strategy for human health.

FASTING

Fasting is an extreme form of calorie restriction. Unlike the latter, however, it involves the deliberate and temporary abstention from the consumption of food and, in some cases, caloric drinks, for a certain period of time. While it is understood that during fasting you deprive yourself of your usual calorie intake, it can vary in duration and intensity. It can be practiced for short periods (a few hours or a whole day) or prolonged periods (several days or even weeks).

There are several health-related reasons that drive people to consider or adopt fasting as part of their routine. These reasons include:

Weight Management. Many people seek out fasting as a means to manage their body weight. Intermittent fasting, for example, can help reduce overall calorie intake and promote weight loss, if done properly. Intermittent fasting refers to abstaining from food for a predetermined number of hours during the 24 hours of the day, such as fasting for 12 hours during the night and eating during the remaining 12 hours. This topic will be further explored in one of the following chapters.

Metabolic Health Benefits. Intermittent fasting and other forms of fasting can have a positive impact on metabolic health. This may include improved insulin sensitivity, reduced risk of type 2 diabetes, and regulation of blood sugar levels.

Immune System Benefits. Some research suggests that intermittent fasting may have positive effects on the immune system. The process of self-digestion of damaged cells during fasting (autophagy) can support the cleansing and regeneration of the immune system.

Cleansing Needs. Some people practice fasting as part of a “cleanse” or “detox” of the body. This may involve avoiding processed foods and consuming water or soups for a certain period

in order to eliminate toxins accumulated in the body.[15]

MECHANISMS UNDERLYING CALORIE RESTRICTION AND FASTING

The reduction in nutrients encountered during approaches such as calorie restriction and fasting can induce stress in the body which in turn produces responses on different levels.

From a **physiological** point of view, calorie restriction activates mechanisms that help maintain normal levels of glucose, a simple carbohydrate used as a source of energy by the body. Glucose can be obtained through carbohydrate food sources (bread, cereals, pasta, and potatoes) and is mainly used as an energy source. Consequently, when we eat less food and therefore less glucose, the body begins to draw energy from the body's reserves, such as subcutaneous fat and muscles. This degradation process is known as "catabolism".

At a **cellular** level, however, the stress response mechanisms represented by the cyclical and controlled restriction of calories or specific macronutrients (in particular proteins and carbohydrates) decrease the availability of growth factors.

Growth factors are essential bioactive substances that play a fundamental role in regulating and controlling the process of growth, repair, and maintenance of cells and tissues in our body. Their presence and quantity must be maintained in an ideal balance, which can vary based on age and physiological needs. During growth and development phases, such as childhood, a greater supply of these factors is necessary, as they are essential for tissue growth, development, and repair. However, in adulthood, it is important to maintain the right balance, as an excess of these factors can pose health risks. In particular, a high presence of these factors can favor uncontrolled cell proliferation, increasing the risk of developing tumors, damaged or dysfunctional cells.

Essentially, growth factors are fundamental for the health and functioning of our body, but it is important to carefully regulate

their balance, especially in adulthood, to avoid potential negative consequences such as the risk of tumors or other disease related to uncontrolled cell growth.

During calorie restriction (and even more so during fasting), cells, which usually divide to continue growing and living thanks to growth factors, go into "energy saving" mode. Instead of growing, they must find an alternative way to survive by using what they already have inside the cell as an energy source. In accordance with the need for energy saving, the cells are able to recycle the damaged components within them first, implementing a sort of cellular "remediation" and cleaning.[16]

The stress caused by the lack of nutrients therefore causes cells to adapt to survive, to "clean up", but also to prepare for growth again once nutrients become available again.

This is a very important step, which differentiates a chronic approach such as calorie restriction, from a cyclical approach, such as a short period of fasting.

In fact, calorie restriction represents a chronic approach (which implies a continuous duration and this, in addition to involving significant challenges linked to adherence and weakening of the organism, with consequent increase in the possibility of incurring infections) does not offer a real advantage in cell regeneration compared to shorter but more targeted interventions, such as fasting.

In fasting, once nutrients become available again, cellular regeneration processes are activated. For this reason, the moment in which you return to eating normally appears to be as important as the fasting period itself. This suggests that some dietary interventions, although shorter, may be more effective than others in the process of cell regeneration.

WHAT OCCURS DURING FASTING

Over the course of evolution, many species, including humans, have adapted to an environment in which food resources were

not always abundant or easily accessible. This situation affected the survival and reproduction of individuals. The need to cope with periods of food deficiency has allowed the development and selection of mechanisms within cells that allow us to withstand fasting.

Essentially, evolution has favored the selection of cellular mechanisms that allow us to withstand periods of fasting, exploiting energy reserves and maintaining survival during phases of food deficiency, which were common in the natural environment in which life developed.

These mechanisms allow the body to exploit energy reserves stored in the form of fat in adipose tissue and glycogen, a glucose reserve, in muscles and the liver, when nutrient intake becomes insufficient.

In human beings, glycogen reserves, if not replaced with new nutrients, are generally exhausted in about 24 hours, after which the organism begins to produce glucose from the amino acids that make up proteins and which are found, for example, in the muscles through a process known as "gluconeogenesis", to try to keep blood glucose levels stable. In this way, the organism can survive even when access to food is limited.

When fasting is prolonged, and in particular 2-3 days after the start of abstinence from food, low levels of insulin are reached, that is the hormone produced by the cells of the pancreas which lowers blood glucose levels. Low insulin levels stimulate lipolysis, which is the breakdown of stored triglycerides into glycerol and fatty acids.

- Glycerol can be used as a substrate for gluconeogenesis, in other words, sugar is obtained from fats and is used for energy production.
- Fatty acids can be directly used to produce energy in various tissues, except in the brain, since they do not cross the blood-brain barrier, a thin but very resistant membrane that acts as a defense barrier for the brain.

As fasting continues and glucose begins to become unavailable in the body and brain cells risk being deprived of essential nutrients, our body is able to activate an alternative mechanism to produce energy. In this case, the body begins to use fats as an energy source.

Fats are broken down via a process called “beta-oxidation” to generate molecules called “fatty acids” which are then converted into a specific form of energy known as “ketone bodies.” Ketone bodies are able to overcome the “blood-brain” barrier and are therefore used as a source of energy for brain cells, ensuring the correct functioning of the brain even in the absence of glucose.

After 5 days of fasting, almost all of the energy needed by the body is therefore produced from free fatty acids and ketone bodies.

This process is carefully regulated by the hormonal system. During fasting, the absence of sugar intake, as mentioned earlier, leads to a decrease in the pancreas’ release of insulin, while the levels of other hormones such as the growth hormone, glucagon, and adrenaline increase. These are just some of the hormones involved in the process, as we will explain shortly.

Whilst fasting, the increase in the growth hormone plays an important role in preserving muscle and bone mass.

Glucagon, which comes into action during fasting, performs several crucial functions. First, it instructs the liver to release sugar into the blood from glycogen, thus helping to keep blood glucose levels stable. Furthermore, it prevents the body from producing new fats and, on the contrary, promotes the process of using and breaking down fats already present in the body. Finally, glucagon stimulates the adrenal glands to release hormones such as adrenaline, which is part of the catecholamine group, chemical compounds with a crucial role in regulating the functions of the nervous system, fundamental for the body’s response to stressful situations, for blood pressure regulation, and brain function and which are also known

as neurotransmitters.

In summary, during fasting, the growth hormone, glucagon, and catecholamines are involved in the body's adaptation to ensure adequate energy availability, promoting the mobilization of energy reserves and glucose production. These processes help ensure that the body can efficiently deal with periods of fasting and food deficiency.[17]

WHICH IS BETTER, CALORIE RESTRICTION OR FASTING?

As just highlighted, calorie restriction and fasting are two approaches that both involve reducing calorie intake, but essentially differ in terms of duration and overall quantity of calories consumed. Calorie restriction implies a chronic, i.e., continuous and long-term, intervention, while fasting is a shorter-term approach, characterized by periods of normal food consumption. As a result, the processes activated in these two cases can differ significantly.

Also, for this reason, it is always and continuously important to underline that both calorie restriction and fasting must be undertaken with caution and under the supervision of a health professional, especially in the case of people with particular caloric needs or pre-existing medical conditions. Although they may have health benefits, it is essential to ensure that the body still receives all the nutrients it requires to function properly.

Both approaches, especially if prolonged or extreme and without adequate medical supervision, can pose health risks, such as deficiency of essential nutrients and impaired electrolyte balance (the balance between all minerals, such as calcium, magnesium, sodium, potassium, etc. in the body that maintains an individual's state of health). Before undertaking any form of calorie restriction or fasting, it is advisable to consult a health professional to assess your individual conditions and ensure that the necessary precautions are taken, in order to optimize benefits.

FASTING AND HEALTH TODAY

As previously mentioned, in recent years the practice of fasting has come back into fashion, especially for health-related issues. Nowadays, less rigid and shorter fasting methods are sometimes used rather than the strict fasts previously described.

As we have seen, although the word "fasting" defines abstention from food, depending on its characteristics it can indicate very different interventions. Some differences concern the duration: from a few hours to weeks; the composition of the (albeit reduced) diet; the frequency with which it is carried out, just to name a few.

Recently, a very popular term in nutrition is **"intermittent fasting"**. This approach involves regular cycles of food consumption and periods of abstinence from food. The term "intermittent fasting" is a broad concept that encompasses several strategies, but commonly refers to overnight fasting. Overnight fasting is often practiced to take advantage of the body's rest period, allowing the digestive system to relax and the body to engage in cellular repair and cleansing processes. It is believed that overnight fasting can help regulate metabolism, improve appetite control, and help achieve personal health goals.

Below and in the following chapter, we will analyze the most common forms of fasting that we find today, from alternate day fasting to the fasting-mimicking diet.[18]

FASTING 5:2

Fasting known as 5:2, is a dietary approach that involves a cycle of 5 days of a normo-caloric diet followed by 2 days of more intense calorie restriction. During these two days, which may or may not be consecutive, calorie intake is limited to a maximum of 500 kcal for the entire day, and people have the flexibility to split these calories into one or more meals at their discretion.

This type of intermittent fasting can lead to several beneficial ef-

fects on health, such as potential weight loss and improved insulin sensitivity, resulting in optimized metabolism.

ALTERNATE DAY FASTING

Alternate day fasting is a dietary approach developed by Dr. Krista Varady of the University of Illinois in Chicago. This nutritional regime shares some similarities with 5:2 fasting but is distinguished by its particular structure. Alternate day fasting involves days in which calorie intake is significantly limited alternating with days in which you eat freely (*ad libitum*).[19]

80% of the approximately 500 kcal allowed on "fasting" days are consumed during the main meal, at lunch, while the remaining 20% can be shared between breakfast and dinner, depending on personal preferences.[20]

24-HOUR FAST

This practice consists of fasting on water only (or unsweetened drinks) for an entire day. This day of abstention from food is practiced by some people as a moment of "purification" and a break from normal eating and can be repeated as often as desired, for example once a week or once a month.

TIME-RESTRICTED EATING

Mealtime restriction, also known as TRE, is a dietary approach that is based on consuming food during a specific period of time within the day, followed by a period of fasting in which food is not consumed. TRE is a popular dietary strategy that punctuates main mealtimes based on diurnal circadian rhythms, allowing a free diet that does not include any calorie restriction, during a narrow time window of approximately 8-12 hours per day.

This approach aims to regulate the timing of meals, rather than focusing exclusively on what we eat, taking into strong consideration our body's circadian rhythms, i.e., the cyclical alternation between sleep and wakefulness over a 24-hour period.

The 24-hour circadian rhythm plays an important role at a molecular, physiological, and behavioral level.[21] In particular, its regulation works through the genes of the "core/master" clock, a set of neurons that exert their effects on several secondary clocks distributed throughout the body. This structure is known as the "suprachiasmatic nucleus" where, together with internal regulation, external inputs, such as light exposure and nutrient consumption, influence the circadian rhythm. These inputs activate and regulate the metabolism and the production of hormones. This allows the individual to carry out normal vital functions (for example digesting, sleeping, and waking up).

TRE connects metabolism to the set of genes regulated by the light and the dark which collectively constitute the so-called "circadian clock". Alternating between daytime and nighttime hours instructs the body to slowly transition from "anabolism", a metabolic process during which the body "builds" reserves starting from nutrients obtained from food (for example the production of proteins or cellular renewal), to "catabolism", a process in which the body uses these reserves, breaking down what it has stored.

The obvious question is: what is the positive effect of time-restricted eating on this process? This question finds its answer in some theories and potential benefits, including:

1. Insulin regulation. Restricting the period of food intake may enhance insulin sensitivity and aid in blood glucose management, reducing the risk of developing type 2 diabetes.

2. Circadian Rhythm. Some research suggests that aligning food consumption with the circadian rhythm can have positive effects on metabolic health and on sleep.

3. Weight control. By limiting the amount of time during which eating is allowed, total calorie intake throughout the day may be reduced, which may help to control weight.

4. Reduction of inflammation. Some preliminary studies indicate that restricting mealtimes could have beneficial effects on reducing inflammation in the body.

Furthermore, it has been observed that overnight fasting, since it is associated with lower nocturnal cortisol levels, improves sleep and increases alertness, optimizing wakefulness and productivity in the early hours of the day. Not coincidentally, cortisol, a hormone produced by the adrenal glands, is also defined as the "stress hormone". In case of stress, it is produced upon impulse of the nervous system and released into the blood following greater tension and energy demand on the body's part. The latter leads to an increase in the concentration of fats in the blood and in blood sugar levels.

Consequently, having balanced cortisol levels is important as it also serves to regulate blood pressure, blood glucose concentration, and the immune system. In this case, overnight fasting can contribute to this regulation.

16-HOUR INTERMITTENT FASTING

Many studies report positive effects with 16-hour fastings followed by 8 hours of food consumption, the so-called 16:8 dietary pattern. However, this increases the risk of developing gallstones compared to a 10-hour fast,[22,23] for two different reasons:

1. Reduced Bile Flow. During fasting, the liver's production of bile may decrease due to the lack of nutrients to digest. Bile is a liquid that contributes to the digestion of fats in the intestine and prevents the formation of gallstones. When bile production is reduced, there is an increased risk of stone formation due to the presence of undigested fats, particularly cholesterol crystals.

2. Gallbladder Contraction. During fasting, the gallbladder (the organ that stores bile) may contract less frequently. This can lead to a slowdown in bile flow, once again favoring the formation of gallstones.

The development of gallstones is often asymptomatic, but, in some cases, you can experience very painful biliary colic or cholecystitis which can compromise intestinal, liver, or pancreatic function.

Furthermore, those who decide to follow a 16-hour intermittent fasting every day are forced to choose whether to skip dinner (often the only moment of conviviality within the family) or breakfast, exposing themselves to many other risks that outweigh the benefits given by a16-hour fasting.

12-HOUR INTERMITTENT FASTING

Since numerous studies have observed a correlation between prolonged fasting and the formation of gallstones, to optimize the positive aspects and reduce the contraindications, it is recommended to:

1. reduce the night-time fasting window to a maximum of 12-14 hours;

2. try to have both breakfast and the evening meal, bringing the time window in which you eat closer together and avoid skipping main meals, especially breakfast;

3. combine physical activity to support muscle mass;

4. do not exceed 4 consecutive weeks if you want to carry out prolonged intermittent fasting (for example 16 hours of fasting and 8 hours of eating every day).[24]

The recommendation to maintain a time-restricted eating period of 10 to 12 hours seems to be the most sensible, since in this case it is very likely that the health effects seen with a longer fasting period will occur, whilst reducing the adverse events.

Eating dinner early (before it gets dark) and having breakfast as soon as you wake up, effectively allowing around 12 hours to go by, is a habit of many centenarians and long-lived populations. Overall, this suggests that it is a healthy practice with no adverse effects.

OTHER FORMS OF INTERMITTENT FASTING

There are many other existing variations on the timing of inter-

mittent fasting. For example, there are some people who follow a 20-hour daily fasting. However, there are currently not enough studies to be able to express a definitive opinion on these protocols, other than, as previously mentioned, advising against fastings longer than 15-16 hours each day.

Some forms of intermittent fasting could also be beneficial for cancer patients or for those who have had a history of cancer. In fact, overnight fasting seems to cause improvements in the regulation of blood glucose and sleep, two factors that potentially reduce the risk of relapses, or the recurrence of the tumor.

For example, research published in 2016 showed that a short overnight fasting (13 hours or less per night) was associated with a greater risk of breast cancer recurrence (36%), compared to a fasting of 13 or more hours per night, in a sample of women who participated in the prospective Women's Healthy Eating and Living study, conducted between 1995 and 2007. In the case of women with a family history of breast cancer or already affected by this type of tumor, perhaps it is worth extending the overnight fasting to 13-14 hours to potentially gain additional benefits without the risks linked to the production of gallstones over a longer period of time.[25]

Therefore, adopting a daily fasting period of 12-14 hours represents a simple and feasible approach to potentially reduce the recurrence of breast cancer. The phenomenon may be based in part on the ability to adopt daily fasting periods to lower blood glucose and insulin levels. Additionally, it is likely that these fasting periods contribute to the reduction of IGF-1 and other growth factors which, in turn, can also impede the growth and proliferation of cancerous cells.

In addition, the risk of getting type 2 diabetes and suffering from cardiovascular disorders could also be reduced.

THE RISKS ASSOCIATED WITH SKIPPING BREAKFAST

As we have seen, one of the problems of those who decide to practice intermittent fasting for more than 15-16 hours a day is sacri-

ficing breakfast. Beyond the desire to follow intermittent fasting, adults, teenagers, and children tend to skip breakfast for various reasons: being in a hurry, poor morning appetite, eating habits that are often consolidated among family members, etc.

In reality, breakfast is a very important meal and should correspond to approximately 15% of the daily requirements, balanced from both a caloric and nutritional standpoint, to start the day off correctly. This is especially important because, after overnight fasting, it is advisable to eat a balanced diet, with a meal that provides all the necessary nutrients for health, as well intellectual and physical performance. Another particularly worrying reason given by those who abstain from this meal lies in the belief that this can serve to "save" some calories and therefore promote weight loss.

Numerous studies show that those who regularly consume breakfast are less predisposed to overweight and obesity. Additionally, normal weight adolescents who often skip breakfast are more likely to experience an increase in their Body Mass Index in adulthood (i.e., a value derived from their weight and height, also referred to as BMI).[26] Conversely, only a few studies on adults state that eating breakfast would not help to lose weight.[27] Further observations and in-depth analyses, currently insufficient, will be needed to better understand the role of breakfast on weight gain.

The habit of eating breakfast, however, can impact not only on weight, but also on mental clarity. Skipping breakfast exposes individuals to alterations in intellectual functions, likely due to the stress of prolonged night-time fasting.[28] It is crucial to remember that the brain bases its functioning solely on the use of glucose as an energy source. Although our body can produce glucose starting from any nutrient, this process is slow and difficult. Moreover, a growing body of research associates the habit of regularly skipping breakfast with an increased risk of developing cardiovascular diseases.[29,30,31]

Over the years, the scientific community has in fact conducted a series of studies to understand the impact of breakfast on human health, including energy balance, metabolism, weight control, and the reduction of risk factors for mortality from all causes.

A very recent study published in July 2023 highlighted the acute effect of skipping breakfast compared to its consumption on cardio-metabolic risk markers, appetite, and perceived mood during rest and/or exercise in adolescent girls classified as regular breakfast consumers.

The results showed that peak glucose and insulin levels were significantly higher in the group of girls who skipped breakfast compared to those who consumed it. Additionally, researchers observed a significantly higher perception of hunger before lunch accompanied by increased tiredness, resulting in reduced perceived energy and concentration.[32]

In another study of nearly ten thousand individuals aged 20 and older, followed through surveys for up to 27 years, researchers saw that those who skipped breakfast had an elevated risk of cardiovascular mortality over time. Furthermore, in participants with other risk factors, mortality from cerebrovascular diseases, such as stroke, also increased.[33]

In summary, scientific evidence suggests that breakfast plays a crucial role in regulating energy, metabolism, weight control, and even mental health. It is important to highlight that choosing nutritious and balanced foods for breakfast can positively influence overall health and should be an integral part of a healthy lifestyle.

THERAPEUTIC FASTING

The concept of long-term therapeutic fasting refers to an approach in which people abstain from food for extended periods, often relying on a diet limited to substances such as water, low-calorie broths, or vegetable purees. These therapeutic fasting treatments usually take place in a clinical setting, where patients spend an extended period of abstinence from food, which can range from over a week to sometimes up to three weeks.

These therapeutic fasting regimens are offered in specialized facilities, such as the Charité University Hospital in Berlin, which offers a very low-calorie diet, or the True North Clinic in North-

ern California, which offers a water-only diet. In these environments, patients undergoing therapeutic fasting are closely monitored by medical professionals.

The goal of such long-term therapeutic fasting can vary, but often includes cleansing the body, reducing inflammation, improving metabolism, and helping manage specific medical conditions. These fasting regimens are complex and require rigorous medical supervision to ensure patient safety.

THE FASTING-MIMICKING DIET

FASTING-MIMICKING DIET

Having recognized the notable benefits induced by controlled periods of fasting, as well as the associated dangers, Professor Longo developed a clinical protocol that combines the benefits of water-only fasting while reducing the side effects, thus giving rise to the fasting-mimicking diet.

The fasting-mimicking diet represents a particular calorie restriction diet that simulates fasting, but still allows for a controlled intake of food. This dietary approach is the result of in-depth scientific research conducted by Professor Valter Longo and his team, which defined the optimal duration, quantity of food, and essential nutrients involved.

The fasting-mimicking diet consists of 5 days of calorie restriction, during which you mainly consume vegetables in the form of soup, dried fruit, tea, herbal teas, and water. In addition, multivitamin and omega-3 supplements are taken to ensure adequate intake of essential nutrients, vitamins, and minerals.

The fasting-mimicking diet consists of a highly low-calorie diet, in which the first day consists of 1100 kcal and the other 4 days of approximately 800 kcal, with low sugars and little protein. The fasting-mimicking diet has a very specific formulation that has been clinically tested.

Unlike water-only fasting, fasting-mimicking diets are more like a drug treatment, as they offer specific benefits and can be tailored to individual needs. The frequency, composition, and duration of these diets can be adjusted to suit personal needs.

Particular caution is required for individuals over the age of 65-70, especially if they have shown a tendency towards unwanted weight loss. For individuals suffering from disease, it is necessary to request the approval of the specialist doctor and have

closer supervision, also to evaluate any changes in medication.

It is therefore a diet to be followed under medical supervision, if pathological conditions exist, and/or by a specialized nutritional biologist in the case of healthy patients.

SCIENTIFIC BASIS OF THE FASTING-MIMICKING DIET

In the laboratory, scientists have shown that yeast cells transferred from an environment rich in sugars to one with only water live twice as long on average and are protected from various types of cellular damage. Similarly, it has been shown that mice, by switching from free feeding, referred to as "ad libitum", to fasting, are also protected from oxidative stress.[34]

The unknown element is whether this protective effect continues even after the end of the fasting itself, when a calorie-rich diet is resumed.

Another crucial point is to find a form of fasting that, whilst maintaining the health benefits, is acceptable and safe for people, which therefore is not excessively prolonged and does not present significant side effects.

Speaking of side effects, as a matter of fact, it has been observed that both monkeys and humans, subjected to chronic (rather than periodic) calorie restriction, for example, manifest deficits in the immune system and healing, as well as high levels of stress.[35]

The goal of periodic fasting is to avoid these effects, whilst at the same time making the cells enter a so-called "high protection mode", characterized by four fundamental aspects:

- Lowering levels of the growth factor IGF-1, which, if present in high levels, can support the uncontrolled growth of cancer cells and can lead to the premature aging of cells.
- Increased levels of the IGF-1 inhibitor, IGFBP-1 (Insulin-like growth factor binding protein 1), i.e., proteins that counteract the action of the growth factors.

- Lowering of glucose levels.
- Increased levels of by-products of fat metabolism, i.e., ketone bodies.

This particular fasting-mimicking diet was developed to achieve these objectives. It does not involve total fasting, in order to limit the side effects, but still reduces the daily caloric intake and the intake of proteins and sugars, instead increasing the intake of unsaturated fats. Achieving these goals allows the body to optimize health, prevent the appearance of many diseases, and delay the physiological aging process.

This has been demonstrated through numerous studies over the years, both at a preclinical and clinical level. The most relevant ones will be presented below.

THE FASTING-MIMICKING DIET: PRECLINICAL STUDIES

The scientific research behind the fasting-mimicking diet originates from studies conducted on mice (see Appendix: Disclaimer – To animal activists) subjected to periodic fasting with a diet low in sugar and protein, but rich in healthy fats. As regards animal studies, also referred to as preclinical studies, the fasting-mimicking diet was tested with a 4-day calorie restriction, repeated twice a month, in 16-month-old mice (equivalent to 45 years in humans).

The results of these studies demonstrated significant benefits: an increase in the life expectancy of mice from 8% to 11%; a reduction in body fat, particularly in the abdominal area, without loss of muscle mass; reduced loss of bone density linked to aging; and a significant reduction in tumor cases, which only appeared after 26 months (equivalent to 80 years in humans). Additionally, elderly mice showed improvements in motor coordination, memory, and learning, along with a strengthened immune system through stem cell regeneration.

The results reported in the studies are listed below:

- Extension of the average lifespan by 11-18%.

- Loss of abdominal fat, without loss of muscle mass.
- Reduced loss of bone mineral density linked to ageing.
- Reduction in the incidence of tumors by 50% and a later age of onset (at 26 months of life instead of 20 months, approximately equivalent to 80 years of age instead of 60 years in humans). Furthermore, a greater percentage of the tumors were benign and affected a maximum of two organs.
- Reduction of inflammatory skin disorders.
- Increased cell regeneration rate, seen particularly in liver, muscle, brain, and immune system cells along with an overall increase in stem cell population.
- Better motor coordination also in older mice, as well as better performance in learning and memorization in three cognitive tests, therefore improving brain function.[36]

Another study, also conducted on mice, highlighted that the fasting-mimicking diet induces the destruction of a large part of the cells of the immune system but, at the same time, activates the stem cells present in the blood and spinal cord. Therefore, it is the old, damaged, and dysfunctional cells that are destroyed, while the new stem cells, when the mouse returns to eating normally, trigger a massive regeneration of the immune system and the nervous system, giving life to younger, healthier, and more functional cell populations.[37]

THE FASTING-MIMICKING DIET: CLINICAL STUDIES

Moving on to human trials, it was deemed necessary that the fasting-mimicking diet, in addition to providing enough calories to avoid the side effects of total water-only fasting, while maintaining its effectiveness, also provided a variety of foods that were enjoyable for the majority of people.

The first randomized study conducted on 100 patients involved the use of a fasting-mimicking diet for 5 days a month, for three consecutive months, while for the remaining 25 days a month, participants could continue to eat as usual. The results obtained are listed below:

- Weight loss, on average -3.6 kg (7.9 lbs.), with fat loss local-

ized especially at an abdominal level.
- Increased percentage of relative muscle mass.
- Average decrease in blood sugar of -12 mg/dL in subjects who already had high fasting blood sugar.
- Reduction in blood pressure of -6 mmHg on average in subjects with hypertension or borderline values, but not in those with normal blood pressure values.
- Reduction in total cholesterol in the blood by -20 mg/dL.
- Decrease in blood triglycerides of -25 mg/dL.
- Reduction in IGF-1 levels (oncology risk factor) by -60 ng/mL in subjects at risk.
- Reduction of CRP (C-reactive protein, marker of inflammation and cardiovascular risk factor) by -1.5 mg/dL.
- Increase in stem cells circulating in the blood.

Three months after the end of the fasting-mimicking diet protocol, the tested subjects still benefited from these positive changes, with reductions in body fat, abdominal circumference, blood sugar, IGF-1, and blood pressure.[38] Therefore, although the fasting-mimicking diet has a limited duration of only five days, the effects do not appear to be just temporary.

It can be simplified by stating that these patients' organism was "deceived". Despite having eaten (even if in a small amount and in a controlled way), all the typical mechanisms of fasting were activated, inducing the cells to destroy damaged and/or unnecessary components and to renew themselves (this process, as indicated previously, is called ''autophagy''), also causing the death of aging cells. A "self-healing" program was thus activated, which the human body is actually already predisposed to carry out, thanks to millions of years of evolution.

THE BENEFICIAL EFFECTS OF THE FASTING-MIMICKING DIET

The fasting-mimicking diet consequently activates a process of renewal and self-healing in the human body which involves the regeneration of healthy cells and the elimination of damaged ones. This mechanism is based on the increase in stem cells and the strengthening of the immune system, making it strong-

er and more efficient.

During the simulation provided by fasting, cells enter a "stand-by" state, necessary to destroy and remove elements that are no longer needed, such as mitochondria (the cell's powerhouses) and damaged proteins, while deteriorated cells are eliminated.

This self-healing program promotes the repair and replacement of damaged cells, tissues, and organs, leading to macroscopic benefits, including weight loss, reduction of: blood sugar levels, the insulin-like growth factor IGF-1, blood pressure and inflammation, and risk factors for chronic diseases. Ultimately, the fasting-mimicking diet contributes to slowing down aging and optimizing health.

Further beneficial effects expected at the end of the fasting-mimicking diet, in addition to weight loss and reduction of abdominal fat and those previously indicated, are:

- brighter skin (several patients report their skin looking "younger");
- reduction of drowsiness and increased energy;
- greater mental clarity;
- less inclination to abuse substances such as sugar, caffeine, alcoholic beverages, therefore greater self-control while eating.

THE FASTING-MIMICKING DIET: POSSIBLE SIDE EFFECTS

Some side effects may occur during the fasting-mimicking diet, including:

- feeling of weakness, especially in the first 1-2 days of the fasting-mimicking diet;
- headache, which generally decreases from the second or third day (often due to the reduction in caffeine intake and the production of ketone bodies, molecules that derive from fats and are used for energy production);
- hunger, especially in the first 1 or 2 days;

- mild back pain.

HOW TO PREPARE FOR THE FASTING-MIMICKING DIET

The fasting-mimicking diet requires a preparation period, generally one week, as well as a short transition period at the end of the 5 days, in which it is recommended to eat according to the Longevity Diet and without binging. You will find more specific information below.

During the week before starting the fasting-mimicking diet it is recommended to limit protein to 0.8 g/kg (0.36 grams per pound of body weight) of body weight, favoring plant-based and fish protein; to eliminate refined sugars (sweets, snacks, sugary drinks, etc.) and to consume complex carbohydrates from whole grains and/or grains; to limit saturated fats. In short it involves faithfully following, as indicated, the Longevity Diet.

PHYSICAL EXERCISE DURING THE FASTING-MIMICKING DIET

For those who wish to combine physical exercise with the fasting-mimicking diet, we recommend following the exercises recommended in the videos on Fondazione Valter Longo's website (www.fondazionevalterlongo.org) in the section "Stay young and healthy", "Exercise & Longevity".

https://www.fondazionevalterlongo.org/en/exercise-and-longevity/

REFEEDING AFTER THE FASTING-MIMICKING DIET

On day 6 (referred to as transition day) it is recommended to eat vegetables, EVO oil (extra virgin olive oil), nuts such as almonds and walnuts, whilst reintroducing small quantities of whole grains and/or grains (barley, spelt, and rice), as well as fish and legumes.[39]

CONSIDERATIONS FOR THOSE INTERESTED IN THE FASTING-MIMICKING DIET

In addition to the categories just mentioned, the fasting-mimicking diet is not suitable for:

- pregnant women;
- underweight subjects;
- subjects suffering from an eating disorder;
- people taking drugs that lower blood pressure or blood sugar or already undergoing insulin therapy (in these cases it would be necessary to suspend the drugs or at least reduce the dosage, after careful medical evaluation);
- hypotensive individuals;
- individuals affected by genetic mutations that limit the body's ability to carry out gluconeogenesis;
- athletes in periods of intense physical effort (which would require glucose levels not available during the fasting-mimicking diet, with the risk of fainting).

FREQUENCY OF THE FASTING-MIMICKING DIET

Based on the specifics of the subject, it will be necessary to adapt the frequency of the fasting-mimicking diet:

- Once a month: overweight or obese subjects, with at least two risk factors for diabetes, cancer, as well as cardiovascular and neurodegenerative diseases;
- Once every 2 months: subjects of normal weight, but who still have at least two risk factors for the aforementioned diseases;
- Once every 3 months: normal weight people with only one risk factor for the same diseases;
- Once every 4 months: healthy, normal weight people who practice little physical activity;
- Once every 6 months: healthy, normal weight people with a particularly healthy diet and who regularly practice physical activity.

Since the fasting-mimicking diet is a nutritional protocol with therapeutic potential, numerous clinical studies are currently underway, some of which have already been completed and published. These studies aim to examine the role of this approach in combination with standard treatment for age-related diseases, such as neurodegenerative diseases, cancer, autoimmune diseases, and cardiometabolic conditions, including diabetes and cardiovascular diseases. In subsequent chapters, we will describe the state of the art of these studies for each group of diseases.

FASTING AND NEURODEGENERATIVE DISEASES

The study of the brain and neurodegenerative diseases has always attracted considerable interest in the context of aging and, consequently, represents one of the scientific community's greatest challenges.

Among the main neurodegenerative diseases, the most common are undoubtedly Alzheimer's and Parkinson's disease, each with specific clinical characteristics.

The precise causes of neurodegenerative disorders are not fully understood, but often involve a combination of genetic, environmental, and neurochemical factors.

Currently, there is no definitive cure for most neurodegenerative diseases. None the less, present-day treatments aim to slow the progression of the disease, relieve symptoms, and improve quality of life. Therapeutic approaches include medications to manage symptoms, physical and occupational therapies, adequate nutrition, psychological support, and active research to develop new drugs and therapies. Continued research is essential to better understand the causes and mechanisms of these diseases, as well as to develop new treatments that can modify the course of neurodegenerative diseases and improve the prognosis for those affected.

Nutrition plays a fundamental role in the prevention and management of these disease; therefore, carrying out research in this field is essential.

PRECLINICAL STUDIES

Fasting and fasting-mimicking diets are emerging as potential approaches to improve brain health and combat neurodegenerative diseases. Studies in mice (see Appendix: Disclaimer – To animal activists) have shown that these dietary regimens can lead to improvements in memory, learning, and even a reduction in brain

pathologies associated with diseases such as Alzheimer's and Parkinson's disease.

The results observed, as a matter of fact, show an increase in neurogenesis, i.e., the generation of new cells that make up the nervous system, known as neurons, and the promotion of better connections between them, known as synapses.

However, it is important to conduct further clinical research to confirm these results in patients and carefully evaluate the potential benefits and necessary precautions, especially in more elderly people.[40]

RECENT CLINICAL STUDIES

The increased incidence of Alzheimer's disease (AD) has been associated with excessive body weight resulting from a diet rich in carbohydrates and fats. Conversely, reducing calorie intake through a balanced diet could contribute to a longer healthy life and reduce the risk of Alzheimer's and related dementia.

Different types of diets have been proposed for this purpose, including the Mediterranean Diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and the MIND (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) diet. The evidence gathered from these studies indicates that 1) reducing the intake of trans fatty acids, saturated fats, and high-fat dairy products, and 2) increasing the consumption of vegetables, fruits, legumes (such as beans, peas, and lentils), and whole grains, can lower the risk of developing Alzheimer's disease.[41,42,43]

The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) represents the pioneering long-term study that demonstrates how a multidimensional (i.e., involving different aspects) lifestyle-based intervention can improve vascular and lifestyle-related risk factors. The interventions included lifestyle changes, dietary monitoring and modifications, regular physical activity, intellectual activities, and control of cardiovascular risk factors. This intervention not only preserves cognitive function but also reduces the onset of cognitive decline

among older individuals at risk of cognitive impairment. The study was launched in Finland and is an important international initiative aimed at evaluating the effects of lifestyle modifications and intervention strategies on people at risk of developing dementia and Alzheimer's.

Preliminary results of the study suggest that adopting a healthy lifestyle and engaging in physical and cognitive activities can have a positive impact on cognitive function and reduce the risk of cognitive decline.

To date, the FINGER Study is highlighting the importance of lifestyle interventions in preventing and slowing cognitive decline in at-risk older adults. These findings have significant implications for public health and the management of age-related conditions, including dementia.[44,45]

LIMITATIONS OF CLINICAL TRIALS

It must be considered that patients involved in studies concerning neurodegenerative diseases could be between the ages of 60 and 80. Therefore, it is crucial to ensure that any more aggressive approach does not result in weight loss due to calorie restriction. It is essential to carefully monitor the electrolyte balance (as previously indicated, the balance between all the minerals such as calcium, magnesium, sodium, potassium etc. in the body that maintains the individual's state of health) and ensure that no new changes occur in the levels of brain activity or energy.

Generally, the fasting-mimicking diet should be avoided by people over the age of 65-70 to limit muscle loss, but for patients who are over the age of 65 and who are in good health, the fasting-mimicking diet could represent a promising option, however, only after medical authorization.

FASTING AND AUTOIMMUNITY

Among the changes often related to aging, but which can occur at any age, there is damage to or malfunction of the cells of the immune system, which can lead to an inflammatory state which in turn can contribute to the onset of autoimmune diseases.

For example, under normal conditions some blood cells called white blood cells, including T lymphocytes, macrophages, and neutrophils, produce a series of proteins called 'cytokines', including TNF-alpha and IL-6. These cytokines play a crucial role in coordinating the different functions of the immune system. These functions include the attack and destruction of bacteria and viruses that can threaten the body, as well as the identification and elimination of damaged cells, including cancer cells. In essence, cytokines play a communication role between immune cells, allowing them to work together effectively to defend the body against external threats and abnormal cells within the body itself.

With the advancement of age and in association with numerous diseases, the production of these factors can become irregular, with immune cells releasing them even when they are not needed, causing chronic inflammatory states. This can lead to mild systemic inflammation, i.e., involving the entire body. Inflammation can contribute to autoimmune diseases such as multiple sclerosis or type 1 diabetes, in which immune cells attack parts of the body, or non-immunological diseases, such as cancer and cardiovascular disease.

One of the ways to evaluate whether this systemic inflammation is occurring is to measure the level of C-reactive protein (CRP) in the blood, a protein produced by the liver in response to inflammatory processes or infections.

Based on these measurements, approximately one-third of adults in the United States suffer from systemic inflammation. In other words, about a third of Americans, but also a large part of Ital-

ians, Europeans, and other populations who follow the so-called "Western diet", rich in foods containing excess fats and sugars, suffer from this dysfunction, due in part to aging and in part to unhealthy behaviors, such as obesity, the Western diet, and exposure to infectious agents.

In addition, although many Italians believe that the "Mediterranean Diet" protects them from these problems, this form of eating, even in its healthiest variant, has a limited impact on aging and disease. Even more alarming is the fact that only a minority of Italians (less than 10%) adopt this particularly protective form of the Mediterranean Diet.

As indicated, systemic inflammation is linked to the onset of autoimmune diseases. The most relevant immune disorders are autoimmune diseases such as type 1 diabetes, multiple sclerosis, Crohn's disease, psoriasis, lupus, and rheumatoid arthritis, to name the most common.

A recent global analysis found that approximately 8-9% of the world's population is affected by one of the top 29 autoimmune diseases. An alarming fact is that the incidence of these diseases, i.e., the number of new cases diagnosed, has been increasing for 30 years, but in the last 10 years it has seen a significant increase, with an increase of 19% every year.[46] This means that worldwide autoimmune diseases are doubling every five years. Certainly, part of this trend comes from the greater accuracy of diagnoses and attention to people's health, but it is very likely that a significant factor is the surrounding environment and our lifestyle.

Given that autoimmune diseases represent a class of disorders in which the body's immune system mistakenly attacks its own healthy tissues, causing inflammation and damage to various organs, in the search for new therapeutic strategies, attention has also turned to the use of fasting and its different forms as a possible complementary intervention.

In recent years of research, studies on animals and some preliminary evidence on humans have in fact suggested that fasting

could have positive effects on autoimmune diseases. In particular, fasting seems to cause a significant drop in the number of white blood cells in mice, which then return to normal levels when the mice start eating regularly again, thus allowing a sort of regeneration of the immune system cells.[47]

MULTIPLE SCLEROSIS: PRECLINICAL STUDIES

Multiple sclerosis (MS) is a neurodegenerative but also autoimmune disease of the central nervous system in which the immune system mistakenly attacks myelin, the substance that coats nerve fibers, causing inflammation and damage that can lead to stiffening of the body and muscles, loss of balance and of strength.

Management of multiple sclerosis primarily involves drug therapies aimed at slowing the progression of the disease and relieving symptoms. However, some patients and researchers have explored the use of nutritional interventions, including fasting, as part of an integrated approach to addressing the disease.

In a 2016 study, Professor Longo and his research team demonstrated that periodic 3-day cycles of a fasting-mimicking diet were effective in improving and reducing demyelination (a thinning or complete loss of the myelin sheath, that is, as indicated, the layer that covers nerve fibers of the central and peripheral nervous system and which is essential to guarantee their correct functioning) and symptoms in an experimental mouse model.

These fasting-mimicking diet cycles reduced the clinical intensity of the disease in all mice and were able to completely reverse symptoms in 20% of the animals (see Appendix: Disclaimer – To animal activists).

The results showed that each cycle of the fasting-mimicking diet was able to kill a portion of the autoimmune cells and 3 cycles could reverse the symptoms of the disease in all the mice. At the same time, the fasting-mimicking diet promoted the regeneration of damaged myelin in the spinal cord. [48]

In the same study, the results of a pilot study on 60 patients with

multiple sclerosis were reported, whose preliminary data is explained below.

MULTIPLE SCLEROSIS: CLINICAL STUDIES

In the same publication, the results of a randomized pilot study were reported to verify the safety and feasibility of the fasting-mimicking diet and the ketogenic diet, which we will analyze later, in 60 patients with relapsing-remitting multiple sclerosis (RRMS). This is a condition in which the disease presents itself with occasional clinical relapses (i.e., an occasional recurrence of symptoms), followed by remission (absence of symptoms) with partial or complete recovery.

The 60 patients were in fact divided into three groups: 1) 20 of them followed a control diet, i.e. without substantially changing anything compared to their usual diet; 2) 20 of them followed a ketogenic diet for 6 months; 3) the other 20 followed a single cycle of fasting-mimicking diet followed by a Mediterranean Diet (based mainly on whole grains, legumes, nuts, fruit, vegetables, and extra virgin olive oil), again for a total of 6 months.

Although there is currently no consensus on the most effective dietary therapies in the treatment of multiple sclerosis, the study aimed to explore, through the analysis of the fasting-mimicking diet, the ketogenic diet since some patients with multiple sclerosis have experienced benefits from this diet, although scientific evidence is still limited. What exactly is the ketogenic diet?

The ketogenic diet is a high-fat, low-carbohydrate, and moderate-protein diet that aims to induce a state of ketosis in the body, a state in which the body begins to use fats as its main source of energy rather than carbohydrates. The intake of fats through nuts, seeds, olives, avocados, dairy products, and proteins such as meat, fish, and eggs without consuming complex carbohydrates and simple sugars means that the body can mainly use fats as a source of energy. Therefore, important changes occur at a metabolic level that cause the body to enter a state of ketosis, which occurs when ketone bodies are found in the blood (ketonemia) and urine (ketonuria). As previously indicated, ketone

bodies, produced by the liver, are lipid derivatives and are used as an energy source.

Returning to our study, despite some side effects, the dietary therapies were well tolerated and were not accompanied by serious problems. Both patients who followed the fasting-mimicking diet and those who followed the ketogenic diet reported improvements in their levels of quality-of-life, i.e., a reduction in symptoms that caused daily discomfort. Reported positive effects include reduced inflammation, improved cognitive function, reduced feelings of hunger, and increased energy.

However, further research is needed to confirm these findings and determine their long-term impact on multiple sclerosis progression.[49]

Overall, the results indicate that both diets can be considered promising nutritional approaches, but further research is needed to fully evaluate their effectiveness.

An important difference between the fasting-mimicking diet protocol and the ketogenic diet concerns timing. In fact, while the ketogenic diet was followed continuously for six months, the fasting-mimicking diet lasted only seven days at the beginning of the six-month study. This alternation between fasting and refeeding appears to be the basis of the decrease in autoimmune lymphocytes, the immune system's cells responsible for triggering the symptoms of the disease.

Since, unlike the experiments conducted on mice, the fasting-mimicking diet was administered to patients only once, it will be important to test the effects of multiple cycles on multiple sclerosis patients in larger, randomized (with random treatment assignment), and supervised studies. A study of this type 1s currently underway at the San Martino Hospital in Genoa, Italy and should be published soon.

TYPE 1 DIABETES

Type 1 diabetes, also known as type 1 diabetes mellitus or in-

sulin-dependent diabetes, is a chronic autoimmune disease. In this condition, the body's immune system attacks and destroys beta cells in the pancreas, which are responsible for producing insulin. Insulin is an essential hormone for regulating blood sugar levels, allowing cells to absorb glucose and use it as an energy source.

The loss of beta cells and, consequently, the ability to produce insulin lead to high blood sugar levels, causing typical symptoms of diabetes, including excessive thirst, increased urination (urine production), fatigue, weight loss, and blurred vision. These symptoms can occur suddenly.

Type 1 diabetes, unlike type 2 diabetes, is usually diagnosed at a young age, often during childhood or adolescence, but can occur at any age. The exact cause of type 1 diabetes is not fully understood, but it is believed to be the result of a combination of genetic and environmental factors. Genetic predisposition appears to be an important element, and in some cases, the onset of the disease can be triggered by viral infections or other environmental factors.

The main treatment of type 1 diabetes is to take insulin daily through injections or an insulin pump. This is essential for maintaining blood glucose under control and preventing long-term complications such as damage to blood vessels, kidneys, eyes, nerves, and heart. Individuals with type 1 diabetes must also carefully monitor their diet and physical activity to keep blood sugar levels stable.

Management of type 1 diabetes requires good knowledge of the disease and active patient involvement to ensure long-term well-being. Research continues to find new treatments and therapies for type 1 diabetes and improve the quality of life of people affected by this condition.

TYPE 1 DIABETES AND FASTING: CURRENT STUDIES

In a study published in 2017, Professor Longo's research group demonstrated that the fasting-mimicking diet leads to a temporary

reduction in the number of beta cells in the pancreas, followed by their subsequent regeneration during the refeeding phase.[50] Specifically, six-eight cycles of the fasting-mimicking diet and refeeding eliminated non-active beta cells, replacing them with new functioning beta cells capable of producing and releasing insulin. The restoration of insulin, in turn, resulted in blood glucose levels returning to practically normal levels.

Through further experimental insights, the regeneration of pancreatic beta cells suggested to researchers that the fasting-mimicking diet is capable of modifying gene expression that normally suppresses beta cell generation in type 1 diabetes. In other words, it restores the production of cells responsible for insulin production in the pancreas.

These findings show how controlling what we eat can have an enormous impact on our body's cells and even influence how they function. This discovery could become an important way to help people with type 1 diabetes and other diseases in which the body attacks itself. In practice, it could mean using food specifically to help treat these conditions, opening up new avenues for medical treatments.

It is important to exercise caution when applying the fasting-mimicking diet in combination with hypoglycemic therapies aimed at lowering blood sugar levels such as insulin in patients with type 1 diabetes. This is because the combination of a restrictive diet such as the fasting-mimicking diet with hypoglycemic drugs (that reduce glycemia, that is the concentration of glucose in the blood) can pose significant health risks, including episodes of dangerous hypoglycemia (in which blood sugar levels are too low), which could put the patient's life at risk. Therefore, the use of this diet should be carefully monitored by medical professionals and administered in a controlled environment, such as a hospital, where any complications can be managed promptly.

Furthermore, it is important to underline that type 1 diabetes can manifest itself in childhood, but the fasting-mimicking diet has not yet been thoroughly tested in the pediatric population. Children with type 1 diabetes require specific care and treatments,

and any dietary intervention must be carefully evaluated to ensure it meets their unique nutritional needs and does not put their health at risk.

In summary, while there is interesting research on the potential impact of the fasting-mimicking diet in type 1 diabetes, it is essential to await the results of larger clinical trials conducted in patients and always consult a healthcare professional before making significant changes to diabetes management, especially in cases of type 1 diabetes in childhood.

Overall, the role of fasting in autoimmune diseases is an evolving field of research. Although preliminary studies suggest that fasting may have positive effects on the immune system and the severity of autoimmune diseases, further research is needed to fully understand the mechanisms involved and to establish clear guidelines for clinical use. Before considering any form of fasting as part of the treatment, it is essential to consult, as often repeated, a specialized medical professional who can take into account the specific needs and conditions of the patient.

FASTING AND CANCER

THE WARBURG EFFECT: WHAT DIFFERENTIATES TUMOR CELLS FROM HEALTHY ONES

Today we know with certainty that nutrition and its effect on metabolism play a fundamental role in the effectiveness of therapies that treat cancer. This understanding is not new, but dates back about a hundred years, when the famous scientist Otto Warburg made a revolutionary discovery.

Warburg observed that tumor cells had a different metabolic behavior compared to healthy cells. In particular, tumor cells were avid consumers of sugars (glucose) and produced large amounts of lactic acid during the metabolic process. Healthy ones, however, preferred to use other metabolic pathways involving mitochondria (organelles within cells considered 'energy power plants') through a pathway called the 'Krebs cycle'. This metabolic pathway, necessary for the production of energy, uses oxygen as a substrate in a long process that is much slower but allows for greater energy to be obtained.

Tumor cells, instead, unlike healthy cells, seem to prefer a metabolic pathway called glycolysis, which involves the production of energy from sugars, even in the presence of oxygen. In other words, instead of breathing fully in the presence of adequate oxygen, tumor cells ferment. This phenomenon is known as the "Warburg Effect", and it has been hypothesized that it is preferred by tumor cells to proliferate and divide quickly.

This discovery was pioneering and helped win Otto Warburg the Nobel Prize in 1931. His work laid the foundation for our understanding of the relationship between metabolism and cancer.

In later years, scientists discovered further details about how the metabolism of cancer cells differs from that of healthy cells. This understanding has led to the development of therapies that target specific metabolic processes in tumor cells, with the goal of slowing

their growth or destroying them.

In short, Otto Warburg's discovery paved the way for research into the relationship between metabolism and cancer, demonstrating that nutrition and the regulation of metabolism can influence the behavior of tumor cells. This field of study has become increasingly relevant in cancer research and is contributing to the development of new therapeutic strategies to combat the disease.

DIFFERENTIAL RESISTANCE TO STRESS

Tumors are extremely complex diseases influenced by various factors. The fasting-mimicking diet can be useful in their prevention as it can reduce certain risk factors associated with tumor development, including blood sugar levels and IGF-1.[51]

As regards therapies, there is an increasing number of studies, also in patients with cancer, concerning the fasting-mimicking diet. The extent and congruence of the effects of fasting and fasting-mimicking diet are very surprising.

In fact, if we think about cancer research, each treatment has its specificity. Immunotherapy, for example, is effective only against a small number of tumors and only on a percentage of patients affected by those tumors, while hormonal therapy works only on very particular types of tumor cells, those of breast and prostate tumors, which in the long term develop resistance to the therapy itself.

In contrast, fasting and fasting-mimicking diets may have a "wild card effect" that allows them to be combined with and enhance the performance of many types of cancer therapies, such as chemotherapy, immunotherapy, hormone therapy, and radiotherapy. This effect is based on what is called "differential resistance to stress" and "differential stress sensitization", i.e., on the creation of conditions that make tumor cells much more vulnerable to therapy and healthy cells and organs much more resistant.

In practice, unlike the vast majority of drugs which are by definition specific and therefore potentially able to work on one particular type of tumor and in a specific stage, fasting and fasting-mimick-

ing diet exploit characteristic properties of healthy cells and tumor cells. How?

Healthy cells know exactly what to do in conditions of food shortage, because for billions of years, if we look at their single-celled ancestors, they have been exposed to that condition. As we saw earlier in this book, evolution has allowed cells to face periods of lack of food, developing mechanisms such as autophagy (self-cannibalism of cells) precisely to be able to survive more or less prolonged periods of fasting.

Cancer cells, on the other hand, have evolved in the presence of excess nutrients and, when they find themselves in fasting conditions, desperately try to survive by continuing to eat what they find. If there is no food present, but only anti-tumor therapy, the cells will "eat" more chemotherapy (or other ongoing therapies). It is in this way that the therapy becomes more effective against tumor cells, while healthy cells are able to protect themselves from it and deal better with its side effects. Fasting can therefore be considered an important therapeutic "wild card".

NOT ONLY FASTING

As we have just seen, cancer cells acquire so many mutations and changes in their DNA that they are no longer able to properly manage the lack of food. This strongly influences one of their main characteristics, namely their rapid growth and proliferation. Their aim, in fact, is to multiply as much as possible and for this reason they require many nutrients to draw energy from, in particular sugars and amino acids, and growth factors to support their continuous division and multiplication. When these are missing, tumor cells are unable to grow and proliferate.

Among the various growth factors and signals, insulin could also support the growth of certain tumors, since it is a hormone with an "anabolic" effect, i.e., that promotes the construction and therefore the growth of tumor cells.

Managing to keep all these factors low (blood sugar levels, amino acids, growth factors, and insulin) can potentially contribute

to the “wild card” effect of fasting, in combination with standard therapies.

This information, however, also allows us to better understand how important the rest of the diet is, i.e., everyday nutrition, which, together with periodic fasting, can help keep these factors low, adequately nourishing the patient.

When talking about fasting, however, we cannot help but consider a topic that is rather debated by many healthcare professionals: that of preventing weight loss in cancer patients. This is correct and excessive malnutrition can also lead to the condition known as cachexia, in which there is an excessive loss of muscle, and in general lean, mass. This condition should absolutely be avoided, but it is also true that many cancer patients are overweight or even obese and losing weight in a healthy way can be useful for the treatment itself.

In addition, many individuals are afraid of not getting enough protein, when in reality their intake is excessive and could be associated with problems, as we will see below.

THE ROLE OF PROTEINS

There is a clear distinction between those who consume high quantities of protein, especially of animal origin, and those who have low levels of protein intake. Furthermore, it is possible to establish a link between protein intake and age groups, since each age group is associated with a certain protein intake to support the body’s normal functions.

A relevant epidemiological study conducted by Professor Longo’s research group in 2014 highlighted an interesting link between protein intake and the risk of developing age-related diseases, in particular cancer, in subjects under the age of 65. It was found that a protein intake above 20% is associated with an increased risk in this age group. However, the same amount of protein appeared to be associated with a lower risk for people over the age of 65.

This finding is partly related to IGF-1 (insulin-like growth factor)

levels. In adults, maintaining the level of IGF-1 is important to avoid loss of muscle mass, on the one hand, but it is also equally crucial to keep it within a moderate range to prevent excessive cell growth, including potential tumors.

In people over the age of 65, IGF-1 levels naturally tend to decrease, causing, for example, loss of muscle mass. As a result, people under the age of 65 need less protein, while those above this threshold benefit from a higher protein intake.[52]

The association between IGF-1 and protein intake is attributed to the fact that proteins, in particular the amino acids that constitute them, are an essential factor for the construction of IGF-1. When a person consumes protein, the body digests these proteins into amino acids, which are then used to make new proteins, including IGF-1.

The correlation between IGF-1 and the relative risk of cancer has been confirmed by other population studies, also referred to as "epidemiological". For example, in the case of breast cancer, an increased risk has been observed in the presence of high levels of IGF-1. Similarly, for prostate cancer, an association has been noted between increased IGF-1 levels and a higher risk of development.[53]

To demonstrate the influence of protein intake on the incidence and progression of tumors, a study was conducted on guinea pigs (*see Appendix- Disclaimer – To animal activists). The animals were fed two distinct diets: one with high protein content and the other with a low protein content. The group with lower protein intake had a lower number of registered cancer cases. This result is particularly significant since it also highlights a lower incidence of tumor progression.

In conclusion, protein intake is able to stimulate cell growth, through the production of both the growth hormone and other factors such as IGF-1, and to activate specific signaling pathways such as Tor and S6-kinase, which are pro-growth, pro-aging, and pro-disease signals for the cell. On the other hand, modulation of these pathways, by reducing either IGF-1 levels or protein intake itself, can have a significant impact on the development of age-re-

lated diseases.

To shed light on the complex association between IGF-1 levels and mortality in humans, Professor Longo, together with his research group, recently conducted a meta-analysis that collected the results of numerous studies. The analysis revealed that both high and low levels of IGF-1 increase the risk of mortality. This important study has enabled the identification of ideal levels associated with the lowest mortality, which appear to be 120-160 ng/ml.[54]

FASTING AND CANCER: PRECLINICAL STUDIES

Once again, it should be underlined that fasting-mimicking diets were conceived as a means to overcome nutritional deficiencies (especially of micronutrients such as vitamins and minerals) associated with traditional fasting, whilst still providing an adequate nutritional intake.

The fasting-mimicking diet is characterized by a low-calorie intake and a reduced quantity of sugars. These sugars come from complex carbohydrates and are associated with healthy fats such as those found in olives, seeds, nuts, and extra virgin olive oil. The nutritional composition thus formulated allows the body to be in a caloric deficit so as to obtain all the benefits of fasting on a metabolic level, without however suffering from malnutrition.

Initially, this diet was tested on middle-aged mice (*see the Appendix- Disclaimer - To animal activists), The mice were given four-day cycles of the fasting-mimicking diet every two weeks. Remarkably, this procedure completely reversed the age-related decline in red blood cell production. Furthermore, it has been discovered that the number of white blood cells, essential for the immune system, is correlated with the onset of tumors in relation to age.

This treatment rendered tumors responsive to chemotherapy without causing harm to normal cells, including those involved in blood cell production (red and white blood cells and platelets) and those of the immune system. Mice subjected to regular cycles of fasting-mimicking diet every two weeks showed an overall

reduction in tumor incidence and a significant delay in tumor development, especially lymphomas. Lymphomas are a type of cancer that develops in the lymphatic part of the body's immune system. They occur when lymphatic cells, known as lymphocytes, undergo abnormal and uncontrollable growth, forming tumors in lymphatic tissues.

The combined use of chemotherapy and a fasting-mimicking diet increased the number of lymphocytes in tumors, delaying the progression of breast cancer and melanoma, probably by improving the ability of T lymphocytes (which fight substances that are foreign to the body) to selectively kill tumor cells and stimulate the system responsible for the production of blood cells, thus helping to fight cancer.[55]

FASTING AND CANCER: CLINICAL STUDIES

As far as humans are concerned, on a physiological level, during the application of the fasting-mimicking diet protocol, as seen previously, there is a significant reduction in glucose levels, together with a notable decrease in systemic inflammation (i.e., inflammation that affects the whole body and is not localized in a single point), as evidenced by the CRP indicator (C-reactive protein), closely linked to cardiovascular diseases and general inflammation. Even more importantly, IGF-1 was significantly reduced in patients with the highest levels of this insulin-like growth factor.[56]

This combination of findings suggests that fasting-mimicking diets have the potential to significantly influence cancer prevention in humans by reducing risk factors such as IGF-1 and inflammatory status.

Returning to the combination of a fasting-mimicking diet and standard anti-tumor therapies, one of the first scientific articles that demonstrated how controlled fasting is able to reduce the growth of tumor cells and increase their sensitivity to chemotherapy dates back to 2012 and was published in the "New England Journal of Medicine".[57] The objective of this study was to understand whether the results obtained on mice and tumor cells could also be achieved in cancer patients.

This study was followed by others that shared the same purpose. In fact, in the last 10 years at least 13 new clinical studies have been published involving around 3000 people and there are at least 8 clinical studies (which provide results on over 2500 patients) underway around the world on this very topic.[58]

The information available at the moment indicates that fasting/fasting-mimicking diets can be combined with standard therapies, provided the oncologist following the patient agrees, in order to reduce side effects and potentially increase the effectiveness of the treatment. In practice, different standard therapies, such as immunotherapy or hormone therapy, are combined with nutritional therapies in which the availability of nutrients is radically changed both during and after therapy.

Based on clinical trials that have already been completed, which tested the use of fasting and fasting-mimicking diets in combination with standard medications, the findings indicate that the combination of these two elements is safe and potentially effective in protecting healthy cells from the toxic effects of chemotherapy and DNA damage in immune system cells, as well as in providing an improvement in several quality-of-life parameters and a reduction in the feeling of exhaustion.

For example, in a randomized crossover study (a study in which participants are randomly divided into two or more groups, receive treatment, and then switch groups), conducted on 34 patients with breast or ovarian cancer who had undertaken a fasting-mimicking diet regimen whilst undergoing chemotherapy, a notable improvement in their quality of life emerged. In fact, it was possible to observe an increase in levels of well-being from a social, emotional, and functional point of view. In particular, the combination with the fasting-mimicking diet allowed for the reduction of toxicities resulting from chemotherapy treatment.[59]

Studies show, therefore, that fasting can be utilized in patients with different conditions of tumor progression, including primary, recurrent, or metastatic (spread to various parts of the body), provided that certain safety and feasibility conditions exist. For example, it is advisable that the patient be of normal weight, with

a BMI of at least 20 kg/m2 and a phase angle, i.e., an indicator of muscle function, of at least 5°. The frequency of any fasting must not compromise the patient's state of health (if not positively). Therefore, it must not exceed five days a month. and any weight lost on behalf of the patient must be recovered in a healthy manner between fasting cycles.

It is absolutely necessary to await the results of clinical studies on long-term survival, as well as to define clear protocols in terms of nutrients, timing, and frequencies in different types of patients. However, the first clinical studies in which fasting/fasting-mimicking diet and chemotherapy are paired are quite promising.

For example, in a recent study conducted on 131 patients suffering from breast cancer, it appears that patients subjected to the fasting-mimicking diet did not experience an increase in side effects, despite the absence of a glucocorticoid drug (dexamethasone) that is normally administered to reduce therapy side effects. This provided the first evidence to support the fact that the fasting-mimicking diet could replace it in order to reduce side effects.

Furthermore, the number of patients in which chemotherapy was ineffective is almost 3 times lower in the fasting-mimicking diet group and over 5 times lower in patients who combined that diet with chemotherapies for at least half of the cycles (greater adherence).[60] This response was ascertained via radiographic (magnetic resonance imaging, ultrasounds) and pathological means. In fact, from the analysis of surgically removed tumor masses, it was observed that 45% of the masses removed from patients who had combined most of the chemotherapy cycles with the fasting-mimicking diet were 90 to 100% cancer-free, versus 20% in those who had continued to eat normally.

It should be noted that the more fasting-mimicking diet cycles were repeated, the better the patients' response was, in particular:

- high disease response (90-100% cancer-free) was observed in just 8% of patients who had not completed any cycle of the fasting-mimicking diet;

- 29% of those who had completed only one fasting-mimicking diet cycle;
- 33% of those who had completed half of the fasting-mimicking diet cycles;
- 53% of those who had combined all chemotherapy cycles with the fasting-mimicking diet.

This study also demonstrated that the fasting-mimicking diet induces changes such as increased ketone bodies (ketogenesis) and reduced levels of glucose, insulin, and the growth factor IGF-1. These changes are known for their ability to reduce the survival and growth of tumors, as confirmed in subsequent clinical studies.[61]

In early 2022, a clinical study involving 101 patients was conducted at the National Cancer Institute in Milan, Italy, and the results were published in the journal "Cancer Discovery". If confirmed that the combination of the fasting-mimicking diet with anti-tumor treatments can lead to changes in metabolism that are responsible for the anti-cancer effects of fasting (already seen in experiments on animals *see Appendix: Disclaimer – To animal activists), such as the constant reduction of sugars in the blood and growth factors. Additionally, this new research has revealed an important renewal of the immune system. This transformation has led to an improved immune system response to cancer, linked to better clinical outcomes for patients with this disease.[62]

Of the 101 patients enrolled in this clinical trial, researchers reported five cases with exceptional responses involving patients with very advanced tumors and therefore a poor prognosis: one with advanced small cell lung cancer; one with metastatic pancreatic adenocarcinoma; one with metastatic colon cancer; two with metastatic triple-negative breast cancer. These patients achieved complete and durable tumor responses (meaning the therapy worked well over time) when treated with a combination of fasting-mimicking diet cycles and their standard treatments. These results were characterized as "exceptional tumor responses", as reviewed in an article subsequently published in the scientific journal "European Journal of Cancer".[63]

Finally, a very recent clinical study conducted on 14 patients with advanced triple-negative breast cancer showed an almost double increase in overall survival when chemotherapy treatment was combined with a fasting-mimicking diet. Furthermore, 20% of these patients survived up to 40 months, unlike patients treated with chemotherapy alone. This is certainly a small study, but one with significant effects that will be worth investigating further.[64]

FASTING AND CANCER: CONCLUSION

Preclinical evidence has shown that nutrient deprivation enhances the antitumor activity of chemotherapy, immunotherapy, or targeted therapies in cancer models. This happens both because fasting has direct effects against tumor cells, affecting them so that they cannot grow, and because it leads to positive changes in the immune system cells present in the tumor. Several clinical studies have demonstrated that fasting and fasting-mimicking diets are feasible and well tolerated in combination with standard therapies for cancer patients, reducing chemotherapy-related toxicities and side effects.

Finally, despite the lack of randomized clinical trials, which are currently underway, demonstrating the anti-tumor activity of fasting and fasting-mimicking diets in cancer patients, preliminary clinical studies suggest that this experimental nutritional strategy could enhance the efficacy of chemotherapy in cancer patients.

Ongoing and future studies will allow us to characterize the role of fasting in improving the care of cancer patients.

FASTING AND DIABETES

Type 2 diabetes has become one of the most widespread diseases worldwide, with a significant increase over the last few decades. According to the World Health Organization, the number of diabetes diagnoses worldwide has increased dramatically, from 100 million cases in 1980 to 422 million in 2014. This worrying trend is becoming more and more common in many areas of the globe.

For example, in the United States, more than 27 million people have diabetes, with another 86 million experiencing prediabetes. In Italy, more than 3 million 200 thousand people are diabetic, 5.3% of the national population, and this figure is even higher among individuals over 65, with a rate of 16.5% (ISTAT 2020 data).

WHAT IS DIABETES?

Diabetes is a chronic disease characterized by the presence of high levels of glucose in the blood (hyperglycemia) and is caused by an altered quantity or function of insulin. The latter is the hormone produced by the pancreas that allows glucose to enter cells and be used as an energy source.[65] When this mechanism is altered, glucose accumulates in the bloodstream without being able to be used, causing a state of chronic hyperglycemia.

This disease is divided into two main forms: type 1 diabetes and type 2 diabetes. The basic difference is that hyperglycemia can be caused by an insufficient production of insulin by the pancreas (type 1) or by its inadequate action (type 2), i.e., although it is produced by the pancreas it is not able to get glucose into cells. The type 2, in particular, can progressively worsen over time and is established on the basis of a pre-existing condition of insulin resistance.[66]

It is important to underline that type 2 diabetes is often preceded by warning signs, such as overweight and obesity. Clinical

research has shown that the risk of developing diabetes increases as Body Mass Index (BMI) increases, which, as previously stated, is an estimate of the amount of body fat calculated by dividing weight, in kg, by height in squared meters. In women, the risk of developing diabetes is six times greater if the BMI is 25 (corresponding to overweight), while in men the risk increases with a BMI of 27.5. Furthermore, abdominal circumferences greater than 88 cm (~34.5 inches) in women and 102 cm (~40 inches) in men are indicators of diabetes risk.

Calorie restrictions, based on numerous animal and human studies, have demonstrated the potential to significantly reduce body weight below risk levels and decrease fasting blood sugar, thus preventing the onset of diabetes. However, it is important to note that daily calorie restriction may not have the same effect, or at least not as strongly, in obese people, compared to those who have a normal body weight. For this reason, it is important to understand which nutritional protocols can prevent and possibly treat excess weight in order to prevent the onset of type 2 diabetes.

DIETARY STRATEGIES FOR THE PREVENTION AND CONTROL OF TYPE 2 DIABETES

Scholars have identified some dietary strategies for the prevention and control of type 2 diabetes, which can be adopted by everyone:

- Following a vegan-pescetarian diet, combined with daily physical exercise.
- Eating within a 12-hour window during the day, respecting a “fast” in the other 12 hours (mealtime restrictions, as previously explained).
- Consuming lots of vegetables (about 200 grams / 7 oz. per meal), limiting carbohydrates that are too rich in starch such as pasta or rice (40 grams/ 1.5 oz. per portion), increasing the consumption of legumes (up to 400 grams / 0.8 lbs.), favoring healthy fats such as nuts (walnuts, almonds, and hazelnuts) and olive oil.
- Avoiding or minimizing foods such as those made with re-

fined flours, for instance white bread and sweets.
- Avoiding or minimizing saturated fats, especially those contained in cheeses and meat.
- Measuring protein intake, which must preferably be of plant-based origin (such as legumes) or from fish (maximum 2-3 times a week).
- Optimizing the distribution of meals according to weight, for example by having two main meals and a snack a day, if you are overweight or obese.

FASTING-MIMICKING DIET AND DIABETES: PRECLINICAL STUDIES

In the context of diabetes, the fasting-mimicking diet was effective in treating both type 1 diabetes (as we saw in the chapter on autoimmune diseases) and type 2 diabetes in mice.

In general, these studies demonstrate how fasting or fasting-mimicking diets can offer new perspectives in the treatment of diseases such as diabetes, through beneficial effects on health and longevity, allowing a reduction in body weight, improving control over the growth factor IGF-1, over blood sugar and over insulin.[67]

In any case, further studies and further years of research are needed to better understand how to apply fasting for therapeutic purposes in the treatment of this disease in a clinical setting. Below we will see the most relevant clinical studies that have been carried out to date.

FASTING-MIMICKING DIET AND DIABETES: CLINICAL STUDIES

In humans, clinical studies are underway to confirm the positive effects of the fasting-mimicking diet on type 1 and type 2 diabetes, but definitive results are not yet available.[68]

As far as already published studies are concerned, the fasting-mimicking diet was able to reduce hyperglycemia, body mass index (BMI or BMI), blood pressure, and IGF-1 levels,

which are risk factors associated with diabetes.[69,70]

Currently, a clinical study is underway at the Leiden University Medical Center to study the effects of a fasting-mimicking diet applied periodically in patients with type 2 diabetes. The study is called FIT, from "Fasting in Diabetes Treatment", and was designed to determine the effect of following the fasting-mimicking diet once a month for one year. The objective is to test metabolic parameters, such as blood glucose and glycated hemoglobin (long-term indicator of blood sugar levels), as well as the potential reduction in the use of drugs that lower blood sugar.

The study is being conducted on 100 patients with type 2 diabetes from medical practices in the Netherlands with a BMI above 27 kg/m2, therefore overweight. Everyone is given lifestyle advice, but one of the two groups is also given metformin, a hypoglycemic drug, which reduces blood sugar levels. The recruited patients are divided into two groups in such a way that each group is the same in its characteristics.

The primary outcomes are glycated hemoglobin (HbA1c, i.e., the parameter that reflects the trend in blood glucose levels over a period of 3 months) and the dosage of diabetes medications. Secondary outcomes include anthropometric data (weight and circumferences), blood pressure, plasma lipid profiles (cholesterol and triglycerides), quality of life, treatment satisfaction, blood tests, composition of the microbiota (set of microorganisms in the intestine), MRI, including heart function, fat distribution, and ectopic fat accumulation (fat cells located outside of adipose tissue, such as fat found in muscle and the liver).

The results of this study, once concluded, will establish whether monthly cycles of 5 days of fasting-mimicking diet over a year improve metabolic parameters and/or reduce the need for drugs in diabetes. Furthermore, additional health benefits will be measured and feasibility in clinical practice will be assessed, and a cost-effectiveness evaluation will also be conducted.[71]

For the moment, it is essential to consult a diabetologist and a

nutritionist before embarking on any diet, as drastic diets and changes in nutrition can be harmful to diabetic people, especially if they take drugs such as insulin. Maintaining a safe and monitored approach to managing diabetes appropriately is of paramount importance.

FASTING AND CARDIOVASCULAR DISEASES

Cardiovascular diseases represent a wide range of disorders that involve the cardiovascular system, i.e., the heart and blood vessels. These conditions can have a significant impact on people's health and quality of life, often leading to serious consequences, such as heart attacks, strokes, and heart failure.

Cardiovascular diseases can result from multiple factors, including unhealthy lifestyles (such as unhealthy diet, inactive and sedentary lifestyle, smoking, and excessive consumption of alcoholic beverages), genetic predisposition, hypertension, diabetes, obesity, and high cholesterol levels. The presence of one or more of these risk factors increases the likelihood of developing cardiovascular diseases. The most common conditions associated with cardiovascular disease include atherosclerosis (buildup of fatty plaques in the arteries), hypertension (high blood pressure), angina pectoris (chest pain), myocardial infarction (heart attack), heart failure, cardiac arrhythmias, and stroke.

Prevention and control of cardiovascular diseases are essential to promote cardiovascular health. These preventive measures include a balanced diet, regular exercise, weight control, abstention from smoking and excessive alcohol consumption, as well as monitoring and controlling risk factors such as blood pressure, cholesterol, and diabetes.

In the next paragraphs, the preclinical and clinical studies related to the association between nutrition, fasting and cardiovascular diseases will be analyzed.

THE PREVENTION OF CARDIOVASCULAR DISEASES IN ANIMAL MODELS: THE EXAMPLE OF MONKEYS

At a preclinical level, therefore with regards to animal studies, two pioneering studies conducted at the University of Wisconsin and the National Institute of Aging (NIA) in the United States are

very well known. Both of these studies analyzed the effects of a calorie restriction of approximately 30% on longevity and disease manifestation in an animal model consisting of Rhesus monkeys.

These animals live up to the age of about 40, they develop numerous diseases similar to ours, including diabetes, cancer, and cardiovascular diseases and have a genetic heritage that corresponds to that of humans for 93%. All these factors make them organisms very similar to us and allow them to be used as an experimental model to examine the response to different dietary strategies in controlled environments, allowing a study on their lifespan and the onset of diseases, including cardiovascular diseases.

The extensive study conducted at the University of Wisconsin for over 20 years showed that by reducing calorie intake by 30%, mortality was halved compared to the control group, which continued to follow a normal diet. In the control group, 42% developed prediabetes or diabetes, a condition that did not occur among the monkeys subjected to calorie restriction. Furthermore, in the latter group, cardiovascular diseases were reduced by 50%.[72]

Unlike the Wisconsin study, the NIA study found no significant differences in causes of death between the calorie restriction group and the control group. Both groups experienced cardiovascular disease, amyloidosis (a rare disease characterized by the accumulation and abnormal deposition of proteins, called amyloids, in the body's tissues and organs), tumors and a general worsening of health to a similar extent.[73]

The discrepancy between these two decades-long studies on monkey nutrition highlights the importance of diet composition associated with calorie restriction. In the case of the NIA study, the monkeys not subjected to calorie restriction received a healthy diet made up of plant-based proteins from wheat, corn, soy, and alfalfa (a plant rich in minerals, vitamins, enzymes, and proteins), supplemented with fish, and rich in balanced nutrients. Additionally, the animals in this study were only fed a targeted amount of food based on age and body weight twice a day.

In contrast, in the Wisconsin study, protein came primarily from

milk (lactalbumin) and the diet contained 10% fat, mostly corn oil, 5% cellulose, and 28.5% sucrose. In this study, Wisconsin monkeys not subjected to calorie restriction could consume food at will, representing a model of the typical Western diet.

In summary, the NIA monkeys followed an almost ideal diet, composed mainly of vegetables and fish proteins, with low sugar levels, while maintaining a healthy weight. On the other hand, the Wisconsin monkeys ate a diet high in animal protein and sugar, and they were allowed to gain weight.

It is therefore not surprising that the 30% calorie restriction in the Wisconsin study demonstrated greater effectiveness in protecting against aging and disease, considering that the restricted monkeys were compared with monkeys fed a clearly less healthy diet. In contrast, the standard diet of the NIA monkeys was already quite healthy, so the 30% calorie restriction did not result in a significant change in terms of aging and many of the diseases.

In conclusion, although these experiments are significant in the field of nutrition, they do not highlight a role for calorie restriction as a preventative measure for cardiovascular disease. Therefore, this approach could be considered not very useful in this context.

To better understand how nutritional interventions, such as fasting, can influence human health, it is necessary to thoroughly examine the results of published and ongoing clinical trials, which will be discussed below.

CLINICAL STUDIES ON CALORIE RESTRICTION AND RISK FACTORS FOR CARDIOVASCULAR DISEASES

As previously described, an example for the application of calorie restriction in humans is the Biosphere 2 project (see the paragraph “Some Clinical Studies on Calorie Restriction”). In this case, volunteers lived inside a Biosphere in the Arizona desert for a period of two years. While inside the biosphere, many of the volunteers experienced dramatic improvements in risk factors associated with cardiovascular disease. For example, their body mass index (BMI) decreased from 23 to 20, thus better falling

within the normal weight range, which is between 18.5 and 25. Furthermore, several blood values are returned to what we could define as “ideal” values and this concerned blood glucose levels, blood pressure, total cholesterol, and LDL cholesterol (low density cholesterol, also known as bad cholesterol).

As previously highlighted, analysis of the data demonstrated a significant impact in reducing risk factors for cancer, heart disease, diabetes, and hypertension among participants during the time they lived within the controlled environment of the biosphere. However, once the participants left this environment and returned to a more ordinary life, those same values returned to their previous levels.

In other words, although calorie restriction led to temporary health benefits while in the biosphere, these improvements were found to be short-lived. Additionally, they may be associated with a weakened immune system, making people on prolonged calorie restriction more likely to contract infections.

Once again, continuous calorie restriction is not shown to be effective in the prevention and treatment of factors related to cardiovascular diseases.

From this study, for example, it emerges that radical lifestyle changes such as prolonged calorie restriction are difficult to follow in the long term, limiting their usefulness and acceptability for large-scale diffusion. Chronic interventions also carry the risk of causing malnutrition and loss of lean body mass, which can have detrimental long-term health effects. Shorter dietary interventions, such as a few days of fasting, have instead proven to be very effective in the prevention of cardiovascular diseases, as analyzed in the following paragraph.

THE FASTING-MIMICKING DIET AND CARDIOVASCULAR DISEASES: PRECLINICAL STUDIES

If we focus on the fasting-mimicking diet, in a series of experiments conducted on mice (see Appendix: Disclaimer – To animal activists) fed a high-fat diet to induce negative conditions for the

health of the heart and cardiovascular system, the fasting-mimicking diet offers significant improvement. These improvements include better heart function, increased blood vessel density in the heart, and a reduction in the size of the left ventricle, which would otherwise tend to increase with a high-fat diet.

An enlarged left ventricle may indicate that the heart is working harder than necessary to pump blood through the body. This can be caused by a number of conditions, including hypertension and other cardiovascular diseases. When the size of the left ventricle decreases, it is often a sign of a healthier heart and of less pump pressure needed to circulate blood. Therefore, a reduction in the size of the left ventricle is considered a sign of improved heart function and may be indicative of better cardiovascular health.[74] Thus, fasting-mimicking diet cycles appear to have a positive impact on cardiovascular health in mice.

Furthermore, in mice consuming a high-fat diet, there is an increase in leptin levels. Leptin is a hormone that plays an important role in regulating appetite and food consumption. Increased leptin levels are often associated with obesity, as it can lead to increased feelings of hunger and increased food intake.

However, when mice are subjected to fasting-mimicking diet cycles, the increase in leptin levels caused by the high-fat diet does not occur. This means that mice tend to maintain more normal levels of leptin, which can help reduce feelings of hunger and excessive food consumption.

Furthermore, by analyzing visceral adipose tissue (the fat located around internal organs), it was discovered that mice following fasting-mimicking diet cycles show an increase in metabolism. This indicates that visceral adipose tissue is functioning more efficiently in burning energy, which may contribute to body fat loss.[75]

In summary, fasting-mimicking diet cycles appear to positively influence leptin levels, helping to control appetite, and improve visceral adipose tissue function, promoting greater metabolic efficiency.

Very interestingly, this nutritional protocol could restore the reduced life expectancy caused by a diet too rich in unhealthy fats. These results, if confirmed in published clinical studies, will allow the fasting-mimicking diet to be evaluated as an alternative to continuous dietary restrictions or pharmacological therapies.

THE FASTING-MIMICKING DIET AND CARDIOVASCULAR DISEASES: CLINICAL TRIALS, PREVENTION AND THERAPY

In the clinical study conducted by Professor Longo's research group on 100 patients, which we have talked about several times,[76] the fasting-mimicking diet cycles affected many of the main risk factors and risk markers that contribute to or are associated with cardiovascular diseases, especially in those at risk:

1. Reduction of fat and abdominal circumference.

2. Significant reduction of the inflammatory risk factor CRP (C-reactive protein).

3. Significant reduction in total and LDL cholesterol.

4. Decrease in triglycerides.

5. Decrease in systolic and diastolic blood pressure.

6. Significant reduction in fasting blood sugar.

In light of what has been discussed, we can conclude this section by underlining the crucial importance of specific fasting regimes in the context of the prevention and treatment of cardiovascular diseases.

Obesity and overweight, constantly increasing at a global level, represent a serious risk factor for these diseases, as well as other medical conditions. However, through targeted fasting, obesity and its related risk factors can be addressed, promoting better cardiometabolic health and helping to extend the length of time you live in good health.

These fasting regimes, characterized by low impact, long-term adherence, and proven safety, emerge as valuable tools in the fight against obesity and related diseases, offering the prospect of a longer and healthier life.

CONCLUSIONS: PRACTICAL ADVICE

Aging-associated diseases represent a crucial aspect of advancing age, influenced by several factors intrinsic to the aging process, including DNA damage, inflammation, and reduced immune system efficiency.

The prevention of these diseases requires not only targeted strategies, but also the opportunity to slow down the aging process and activate anti-aging approaches. In this context, the prevention and treatment of diseases associated with aging through nutrition focuses on a diet similar to the Longevity Diet, which also includes periods of fasting.

Often cited in this book, it now requires an in-depth analysis, that is useful for the reader. We intend to provide practical advice for daily life at the end of our joint exploration into fasting, calorie restriction, nutrition, and diseases.

THE PILLARS OF LONGEVITY

The Longevity Diet is based on the "5 Pillars of Longevity", which incorporate a wide range of knowledge from different areas of science and medicine. This approach ensures that dietary recommendations are deeply rooted in scientific basis and have a high likelihood of contributing to sustained, healthy longevity.

1. **Basic Science and Juventology/Biogerontology (First Pillar).** Basic research on simple organisms helps us understand how diet and nutrients can influence human health and longevity.

2. **Epidemiological Studies (Second Pillar).** This discipline studies the causes of diseases in populations, allowing the theories formulated by basic research to be validated, particularly regarding the effects of diet on metabolism.

3. **Clinical Trials (Third Pillar).** Controlled clinical studies are essential to prove the positive impacts of a healthy diet and its relationship with health, confirming the theories emerging from basic and epidemiological research. These studies involve the presence of a control group, which represents the general population and plays a crucial role in comparing the results obtained through a specific intervention applied to a treatment group.

4. **Study of Centenarians (Fourth Pillar).** The analysis of populations with a high number of centenarians is another important pillar as it provides concrete data on the effectiveness of dietary habits sustained throughout life.

5. **Study of Complex Systems (Fifth Pillar).** This approach analyzes the human body as a complex system, applying engineering models to simplify understanding.

The dietary recommendations for a long and healthy life are based on solid evidence from scientific and clinical research. These recommendations have been confirmed by positive results emerging from basic research studies, clinical studies, genetic and epidemiological studies, as well as from the direct observation of thousands of patients. Furthermore, many of these dietary recommendations align with the nutritional habits of populations characterized by good health and a long life, in which diet plays a central role.

Therefore, we transition from adopting perspectives limited to single studies or research fields, such as those of epidemiological studies, to formulating recommendations that take into account all pillars of longevity. These recommendations are likely to undergo significant evolutions in the coming decades.

Below, we summarize the main guidelines of the Longevity Diet, developed by Professor Longo on the basis of these 5 pillars.

CONSUME PROTEINS IN MODERATE QUANTITY

Studies have revealed that a diet with a low yet adequate, protein intake can have beneficial effects on longevity, reducing the risk

of diseases associated with aging. These diseases include neurodegenerative, autoimmune, and cardiovascular diseases, cancer, and diabetes.

For adults, protein intake should be limited to approximately 0.8 grams per kilogram (0.36 grams per pound of body weight) of ideal body weight. This applies to both overweight and obese people. It is important to adjust these quantities based on various factors, including age, physical activity, and nutritional status.

Research has shown that people who eat a low-protein diet (less than 10% of daily calories) have a significantly lower risk of developing cancer than those who consume a high-protein diet (more than 20% of daily calories). This beneficial effect is more evident in people under 65 years of age. However, older individuals should still consider moderate protein intake, incorporating a variety of protein sources, such as legumes, seeds, nuts, fish, eggs, and dairy products.

KEEP BLOOD SUGAR LEVELS MODERATE

It is important not to demonize sugars and carbohydrates in general. Instead, the focus should be on limiting excessive consumption of refined, high-starch carbohydrates, such as pasta, rice, bread, and potatoes. They can trigger high insulin levels and promote fat storage and insulin resistance. These foods can cause a rapid rise in blood sugar levels, contributing to weight gain and accelerated aging, both directly and through insulin activity.

FATS

The Longevity Diet provides a high content of unsaturated fats (the “good” ones for health) such as Omega 3 fatty acids, found, for example, in oily fish, which you are advised to consume 3-4 times a week, preferring small sized ones, to avoid the accumulation of heavy metals which can be toxic to the nervous system.

NUMBER OF MEALS

For people who are unable to maintain a healthy weight, it may be

helpful to eat only two meals and one snack a day, until they are back to an acceptable weight.

MEALTIME RESTRICTION

Food consumption is limited to a 10-to-12-hour window each day.

When overweight people limit themselves to consuming food for only 10 or 11 hours a day, there is a significant reduction in body weight. People also report greater mental clarity and better quality of sleep.

FASTING-MIMICKING DIET CYCLES

This diet is effective for reducing risk factors of diseases associated with aging, especially in combination with regular cycles of fasting-mimicking diet.

The frequency should span from once every 6 months for people in excellent health and without risk factors, to once a month for those with multiple risk factors, including a critical family medical history.

FASTING AND THE VALTER LONGO FOUNDATION

As stated several times in this book, fasting is an effective and useful tool for our health that has “always” been a part of our world. A practice already used in the animal kingdom and with a thousand-year history behind it, it can be a powerful ally on the journey towards a long and healthy life and, if you suffer from illnesses and diseases, a valid support to standard therapies (for example chemotherapy).

It is important to always remember that, during the fasting period, seeking for support and being accompanied by “healthcare professionals”, including doctors, nutritionists, and fasting experts is necessary to prevent any problems that might arise during “do-it-yourself” practices. Such practices are always potentially dangerous under any circumstances.

We hope that this book of ours has helped clarify your thoughts on this practice, which is growing even more popular in today's world, and has offered some minimal points of reference regarding a topic that is both ancient and modern at the same time.

In case you have doubts or want to undertake fasting, our Foundation is always at your disposal and you can write to our scientific team, always ready to meet your needs and requirements at: nutrizionisti@fondazionevalterlongo.org.

We wish to remind you that, for those of you who find themselves in a critical health and financial situation, it is always possible to check our website and ask for free or reduced-rate consultations (www.fondazionevalterlongo.org).

We would also like to remind you that the proceeds generated by this book and by the nutritional consultancies are intended to support research and non-profit projects promoted by the Foundation itself. These projects aim to promote nutritional education in schools and through "The Nutrition & Longevity Festival", and to provide nutritional assistance to people in particularly critical financial and health situations.

At the end of this journey together, we thank you for the support you have provided us by purchasing this book and "helping us help" those in need. At the same time, we hope, on our part, to have been useful and to have provided you with ideas, information and practical advice for your health and everyday life and, with yours, for that of your loved ones.

We look forward to seeing you at the Foundation with our nutritionists, at our "Nutrition & Longevity Festival", at our webinars for students, teachers, and families, as well as those for doctors and healthcare professionals. We are at your disposal to help you pursue a long and healthy life.

See you soon.

Valter Longo Foundation

APPENDIX

DISCLAIMER – TO ANIMAL RIGHTS ACTIVISTS

This text is taken from Professor Longo's book "Fasting Cancer":

"As I have already explained in my previous books, I am often contacted by animal rights activists who wonder why, in the name of research, mice must be subjected to suffering and death. Here's my answer:

1. We try to work as much as possible with cells and microorganisms, but it is still important and essential, before undertaking any human experiment, to test it on mice, to improve our research and help patients all over the world.

2. Forced fasting is not a cruel procedure, because:
   a) mice, like people, can survive for a few days without food;
   b) fasting brings them benefits, because it can prevent diseases and the mice can thus live longer and healthier.

I realize that subjecting mice to chemotherapy causes them to suffer. This doesn't leave me in any way indifferent, but I don't see any alternative if we wish to save human lives. For this reason, we limit studies on animals to the minimum necessary and, in general, to those that target advanced pathologies that are fatal or devastating for patients.

A few years ago, I responded to an activist's letter by asking: "If your son or sister or father were dying, and the only treatment that could save his life had to be tested on mice, would you allow the testing or would you choose to let him die? » While I know that many activists will continue to disagree, I ask them to respond truthfully and consider the consequences of their actions.

If you decide not to allow animal testing under any circumstances, including those necessary for research on deadly diseases, you should not use any drugs, including aspirin and antibiotics, and ask your family members to do the same. I

believe that animal testing should only be carried out if it is preliminary to clinical trials on people, with a view to the treatment of serious and advanced-stage diseases. In the absence of alternatives, they are unfortunately a necessary evil."

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Finally, a special thank you to Professor Longo and his desire to offer everyone the tools to live healthily and to his Foundation's team, who carries out this mission every day; the CEO Antonluca Matarazzo, the Executive Assistant Valeria Medori and the very valuable nutritionists, the heart and soul of all activities, led by Doctor Cervigni.

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The Valter Longo Foundation is a non-profit organization created to **optimize healthy and sustainable longevity**, which begins as early as childhood and continues throughout the entire life cycle. Our goal is to **promote a healthy lifestyle and balanced eating habits** to slow down and help counteract the onset of age-related and non-communicable diseases such as cancer, diabetes, obesity, cardiovascular, autoimmune, and neurodegenerative diseases. The Foundation’s mission is to offer **everyone the opportunity for a long and healthy life**, with a particular focus on providing support to those suffering from illnesses and in a critical financial situation (www.fondazionevalterlongo.org).

Proceeds are donated to research and non-profit projects of the Valter Longo Foundation

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