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Premature or pathological aging: longevity

Envelhecimento prematuro ou patológico: longevidade

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Abstract

The main objective of this literature review was to summarize and characterize the main factors and events that may negatively influence quality of life and human longevity. The factors that act on premature aging processes are essentially the same as those of natural or healthy aging, but in a more intense and uncontrolled manner. Such factors are: 1) genetic (genome); 2) metabolic (metabolome); 3) environmental (life conditions and style, including diet). Factors 1 and 2 are more difficult to control by individuals; once depending on socioeconomic, cultural and educational conditions. Differently of environmental factors that may be totally controlled by individuals. Unfamiliarity with these factors leads to chronic and/or degenerative diseases that compromise quality of life and longevity.

Keywords: *Human longevity; Metabolic changes; Aging; Life quality; Diet.*

Resumo

O principal objetivo desta revisão da literatura foi resumir e caracterizar os principais fatores e eventos que podem influenciar negativamente a qualidade de vida e a longevidade humana. Os fatores que atuam nos processos de envelhecimento prematuro são essencialmente os mesmos que aqueles relacionados ao envelhecimento saudável ou natural, mas em uma maior intensidade ou maneira descontrolada. Tais fatores são: 1) genéticos (genoma); 2) metabólicos (metaboloma); 3) ambientais (condições e estilos de vida, incluindo a alimentação). Os fatores dos itens 1 e 2 são mais difíceis de ser controlados, pois dependem das condições socioeconômicas, culturais e educacionais. Diferentemente dos fatores ambientais que podem ser controlados pelo indivíduo. A falta de familiaridade com esses fatores leva a doenças crônicas e/ou degenerativas que comprometem a qualidade de vida e a longevidade.

Palavras-chave: *Longevidade; Alterações metabólicas; Envelhecimento; Qualidade de vida; Alimentação.*

1 Introduction

The process of chronological and biological aging results in a buildup of molecular damage that occurs throughout life, resulting in a gradual increase in the number of defective cells and metabolic changes. Over the years, the increasing levels of these defects interfere with the performance and amount of functional tissues in different organs, resulting in weakness, functional disability and disease (KIRKWOOD, 2005). Such changes were classified and adopted by Arking (2008) as: cumulative, progressive, intrinsic, and deleterious, represented by the acronym CUPID.

The hypothesis of adaptive plasticity related to aging and longevity is still valid, i.e., an adaptive capacity to change the course of life history in response to adverse circumstances, as has been confirmed by the discovery that the fetal nutritional environment can change the risk of disease development in adults (BARKER et al., 2002; GLUCKMAN; HANSON, 2004). Whether these effects are indeed mediated by adaptive plasticity, affecting the allocation of metabolic resources for somatic maintenance remains to be discovered and understood. What is clear, however, is that in terms of the

fundamentals that drive aging, there is continuity between events happening in early age and those manifested in old age, as suggested by the pendulum model presented by Mathers (2002) in Figure 1.

2 Mechanisms of cell damage

Recent evidence suggests that a major link between many different types of cell and tissue damage is the action of reactive oxygen species (ROS), which are generated as byproducts of the essential use of oxygen by the body to produce cell energy (MARTIN et al., 1996; VON ZGLINICKI et al., 2001). Particularly significant are the contributions to cellular DNA damage induced by ROS through: 1) damage to chromosomal DNA in the cell nucleus, resulting in alteration of the normal function of genes or mutations; 2) damage to telomeres, protective structures of DNA that appear as a cover at the end of chromosomes; 3) DNA damage within organelles of energy-generating cells (mitochondria), disrupting the production of energy. In addition to these interferences, it has become apparent that, with age, progressive changes of an epigenetic nature occur in the genome, especially changes in DNA methylation, which may have profound effects on gene expression and cell function.

Several different mechanisms may contribute to cell aging and disease. For each one of them there is evidence to support the hypothesis that it is actually a senescence agent. However, their individual contribution to senescence seems invariably too small for their mechanism alone to account for biological age-related degeneration. The obvious response to this shortcoming is to admit that cellular aging is multifactorial and that several mechanisms act synergistically towards the final result. Methodological innovations based on computer modeling of interactions and synergism between different aging mechanisms have contributed to building a better and more integrated view of how cells degrade with age (KIKWOOD et al., 2003). Holliday (1995) mentions in Table 1 a number of structures or processes which go beyond the capacity of cells and tissues to maintain balance, resulting in certain pathologies that emerge in old age.

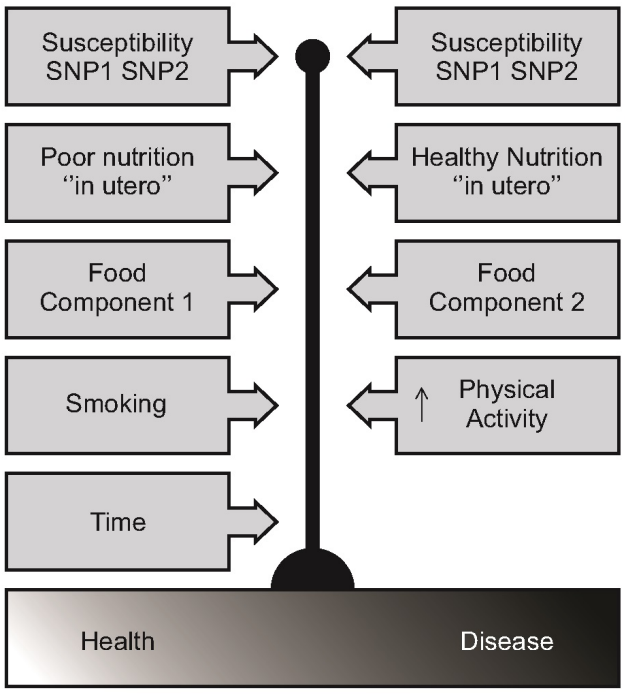


Figure 1. The health pendulum: adapted from Mathers (2002): conceptual model of the main factors that influence cell function during the course of life, with modifications that modulate the aging trajectory. SNP1 and SNP2: polymorphism involving single nucleotides.

The two main causes of death (cardiovascular diseases and cancer) are, for example, respectively attributed to failure in preventing damage to and preserving the coating of blood vessels, and to signal transduction mechanisms that regulate cell division. These two processes are at the forefront of modern biological research due to the social and political forces that release research funds for the study of diseases that are more pronounced with advancing age, despite not being, in most cases, a direct consequence of age.

According to several authors, the number of publications on environmental genetic interactions reflects the great interest in producing the required knowledge on metabolism, in the area of genetic factors, related to cardiovascular diseases. The current approach has not met the needs in this field. Most studies, especially those focused on gene-diet interactions, were carried out with less than ideal samples. Further studies focusing on interactions between genes and environmental factors should follow recent steps in studies on simple genotype-phenotype association and carry out "a priori" meta-analysis. Standardizing the environment, however, is much more complex than standardizing clinical trials

Table 1. Relation between cell or tissue dysfunction and certain age-related diseases.

Non-maintained structures/ processes	Main resulting pathologies
Retina, lens	Blindness
Neuron	Dementias
Insulin metabolism	Type II diabetes
Bone structure	Osteoporosis
Immune system	Autoimmune disorders
Epigenetic controls	Cancer
Joints	Arthritis
Glomeruli	Renal insufficiency
Blood vessels	Cardiovascular or cerebrovasculares diseases

or genetic factors, and more emphasis should be placed on new standardizing methods to collect environmental information. While this is happening, new statistical methods should be developed to address current limitations. However, according to the same authors, there is a great risk that current efforts to protect the confidentiality and privacy of individual genetic information might prevent or significantly hinder such research.

Table 2 features a limited number of genetic factors that may suppress or stimulate the emergence of several noncommunicable diseases (information obtained from various sources). Due to the complexity and to the significant trouble that some chronic diseases (obesity, cardiovascular diseases, diabetes, cancer and neurological disorders) cause to the individual, family and society in general, this study features information that is integrated and as updated as possible on key aspects of the abovementioned pathologies. Such diseases are based on inflammatory processes and energy and oxidative-antioxidative imbalance that lead to the body imbalance as a whole, generating what is now known as metabolic syndrome.

All aerobic cells produce free radicals through the action of various insoluble enzymes attached to biological membranes or soluble enzymes. The ability to produce free radicals varies according to the type of cell and specific metabolic pathways (KEHRER, 1993). Figure 2A illustrates the major natural oxidizing agents and the different cell sites on the membrane and within the cell where the production of free radicals occurs.

Protection of cell membrane and intracellular organelles can occur by both natural cell components and nutrients and non-nutrients supplied by food. The specific action sites of the various cell protection antioxidants are shown in Figure 2B (BENCH et al., 1990). Due to the great sensitivity of cells to oxidative stress, various organs and systems are affected by the action of free radicals, as shown in Table 3.

For cells and tissues to maintain their normal functions, the oxidation-reduction balance must be constantly maintained in all physiological ages and states. Otherwise, oxidative stress will cause metabolic imbalance and noncommunicable diseases. The major endogenous antioxidant protective agents can be classified into three groups: 1) free radical sequestrant enzymes (superoxide dismutase "SOD", catalase, glutathione peroxidase); 2) other metabolic antioxidants (NADH and NADPH, glutathione and thiols, ubiquinol "COE-Q", uric acid, bilirubin, metalloenzymes); 3) metal-binding proteins such as (Cu): ceruloplasmin,

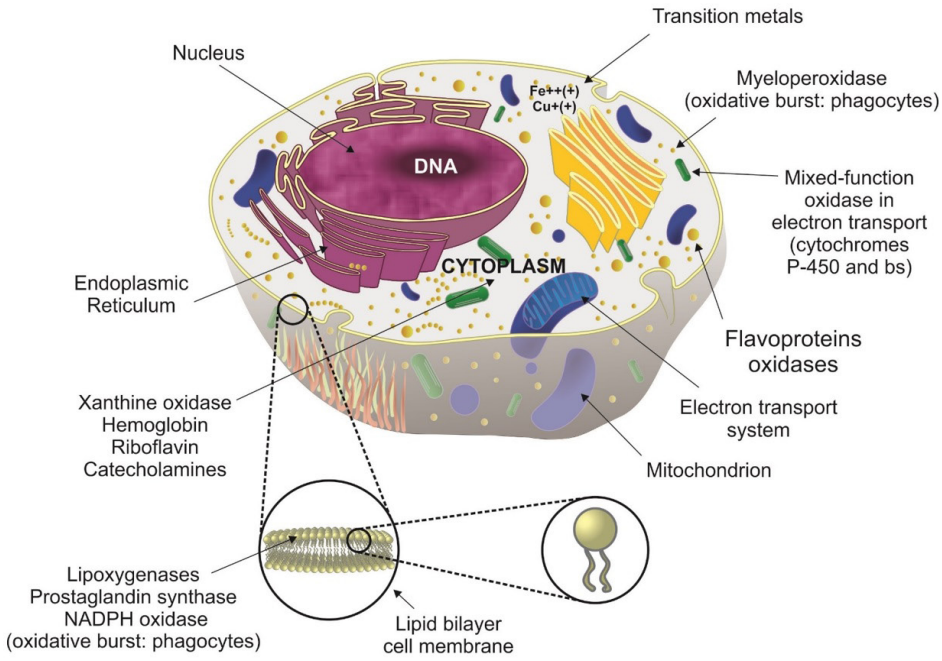
Table 2. Examples of genetic regulation by dietary factors.

Dietary Factor	Genetic Impact	Risk of Disease
Caloric restriction	↑ Expression of insulin	↓ Diabetes
	↓ Expression of oncogeneses	↓ Cancer
Unsaturated fatty acids	↑ Bind to transcription factors	↑Obesity
		↑ Cancer
ω-6 (omega 6)	↑ Lox /LT-A_1	↑ Asthma
	↑ Cox-2/PG G_1	↑ Arthritis and Cancer
Broccoli	↑ Apoptosis gene expression	↓ Cancer
Chocolate powder (12%)	↓ AG gene expression	↓ Fat loss (liver/ adipose tissue)
Fiber/SCFA (Butyric)	↑ DNA histone acetylation	↑ Apoptosis of cancer cells
Folic acid	↑ DNA methylation	↓ Cancer
Flavonoids	↑ Genes (enzymes/anticancer)	↓ Cancer
Zn/Se	↑ Expression of metallothionen m-RNA and other products	↓ Cancer
Zn	↓ Expression of Cox-2 m-RNA	↓ Inflammatory processes
Vitamin D	↑ m-RNA stability	↓ Kidney diseases
Flavones	↑ m-RNA synthesis	↓ Cancer
Theaflavins	↑ m-RNA synthesis	↓ Arthritis

Varied sources: ↑ higher gene expression and/or disease incidence; ↓ lower gene expression and/or disease incidence or seriousness.

Table 3. Tissue injury or diseases in which free radicals are important agents.

Organ/System	Disease (Causative agents)
Lungs	Emphysema (cigarette smoke: SO_2, NOx, O_3)
Heart and Cardiovascular system	Atherosclerosis (chemical products: ethanol, doxorubicin)
	Keshan disease (selenium deficiency)
Eyes	Macular degeneration, cataract (oxygen radicals)
Skin	Thermal injury (radiation: solar or ionizing, chemical products; photosynthesizers)
Muscle	Muscle lesions



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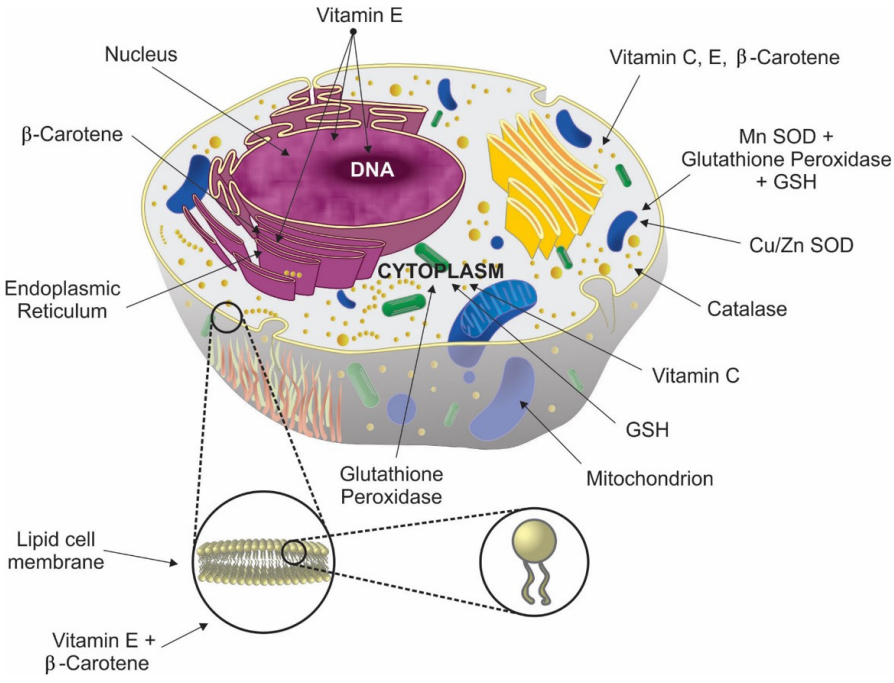

B

Figure 2. (A) Production sites of free radicals in the cell; (B) Antioxidant with protective action on cell membrane and organelles within the cell.

metallothionein, albumins; (Fe): transferrin, ferritin, myoglobin. Lipid peroxides are destroyed by glutathione peroxidase. All these cell defenses appear to be inducible, i.e., the amount of protective substances increases in response to use. There is considerable literature indicating that cells respond even to low levels of radiation, an oxidizing mutagen that can help protect against mutations caused by high radiation levels.

A critical factor in mutagenesis is cell division. When cells divide, irreparable DNA damage can result in a mutation. Therefore, an important factor in mutagenesis and carcinogenesis is the intensity of cell division in tumor

precursor cells. Stem cells are important as precursor cells in cancer because they are on the route to be discarded. Increased cell division rate increases the probability of mutations. Oxidizing agents are an important class of products that stimulate cell division. This may be related to the stimulation of cell division that occurs during the inflammatory process related to wound healing. Accordingly, antioxidants may reduce mutagenesis and carcinogenesis in two ways: by reducing oxidative damage to DNA and slowing down cell division. In this context it is of great interest to understand the mechanisms by which tocopherols and carotenoids can prevent cell division.

3 Most prevalent pathologies among older adults

Due to the increase in human longevity over the previous century, still observed in the early decades of the current century, degenerative chronic diseases have increased in this segment of the population, particularly in relation to cardiovascular diseases, type 2 diabetes, cancer and neurological diseases, especially dementias: Alzheimer's disease and Parkinson's disease.

3.1 Gut microbioma and health

The term "microflora" or "microbiota" refers to the community of living microorganisms assembled in a particular ecological niche of a host individual. The human gut is the natural habitat for a large, diverse and dynamic population of microorganisms which over millennia have adapted to live on the mucosal surfaces or in the lumen (GUARNER; MALAGELADA, 2003). The number of resident bacteria increases along the small bowel, from approximately 10^4 in the jejunum to 10^7 colony-forming units per gram of luminal content in distal ileum. The large intestine is the most heavily populated region of intestine, where several hundred grams of bacteria are harboured at densities around 10^{12} colony forming units per gram of luminal content.

As of August 2010, the Pub Med database included approximately 9,000 articles on probiotics or prebiotics. Various levels of host-microbe interaction can be distinguished, including microbe-gut epithelium interaction, microbe-immune system interaction, and microbe-microbe interaction.

Bifidobacteria have been shown to modulate the immune system, produce digestive enzymes, and restore activities of the gut microbiota following antibiotic therapy (McCRACKEN; GASKING, 1999). The gut microbiota is reported to contribute to human protein homeostasis, providing evidence that the intestinal microbiota is considered an important defence barrier. Probiotics can compete for some of the same attachment sites as pathogens use the same nutrients, and produce antimicrobial compounds that inhibit the growth of pathogen (LIÉVIN et al., 2000).

As we know now, the mucosal microbial communities may differ in composition and abundance from those present in the colon. This leads to the notion that intestinal microbes can be considered a personalized human organ with a metabolic activity second only to that of the liver (O'HARA; SHANAHAN, 2006). What was known as microflora has now been renamed as "microbiota" on the basis of the diversity of micro-organisms revealed mainly by ecologists. The collective genomes within the microbiome have been found to contain more than 3 million unique genes (QIN et al., 2010).

In recent years an association with varying degrees of support have been established between human intestinal microbiota and an increasing number of over 25 diseases, syndromes, or functional aberrations. The support for these associations can vary from anedoctal indications, to much firmer evidence obtained from large cohorts. In this review we will focus on just a few of them as specified below: 1. Obesity alterations of specific bacterial ratios as for "Bacteroidetes/Firmicutes" (MUSSO et al., 2011); 2. Type-2 diabetes-signature differences (KOOTTE et al., 2012); 3. Colorectal cancer-variation in Bacteroides species and fusobacteria (MARCHESI et al., 2011; WANG et al., 2012); 4. Bowel inflammatory diseases crohn's disease-diversity decrease and reduced "Faecalibacterium prausnitzii" (WILLING et al., 2010); 5. Ulcerative colitis-diversity decrease reduced "Akkermansia muciniphila" (LEPAGE et al., 2011); 6. Atherosclerosis - analysis of plaques in humans (KOREN et al., 2011); 7. Cardiovascular - diseased mice and microbial metabolism (WANG et al., 2011); 8. Nonalcoholic fatty liver disease-effect of choline depletion in human (SPENCER et al., 2011). 9. Alzheimer's disease - microbiota in a mouse model of Alzheimer's disease (KARRI et al., 2010). Parkinson's disease - role of enteric nervous system and review of Parkinson's disease development (BRAAK et al., 2003).

Considering the gastrointestinal (GIS) as a system interlinked with the whole body system, and more, considering the GIS as the main barrier between the external environment including the great variety of nutritional and non nutritional substances, it is not surprising that the GIS and its microbioma work as a very important body component influencing human health all along the lifespan.

In the limited space available in this review we will try to concentrate efforts to update some of the main public health problems which affect peoples well being and in most case taking their lives prematurely. These pathologies are multifactorial in which more than one factor are interlinked acting as principal or contributing factor in different diseases. Intrinsic and environmental factors are acting sequentially or simultaneously, making the diagnosis and treatment difficult and expensive.

The intricated link between GIS microbiota and several systemic functions or dysfunctions of the human body

were recognized by nutritional and medical scientists as "Metabolic Syndrome"; defined as a metabolic dysfunction associated with visceral obesity and insulin resistance in which the alterations in host-microbiota interactions play an important role. Besides diet and physical activity, new strategies are necessary to control metabolic syndrome, and as a consequence improving quality of life. It is expected that the above informations will: 1. Provide a conceptual basis for how the human intestinal microbiome affects diseases; 2. Contribute to the development of techniques for monitoring disease development; 3. Provide a basis for personalized treatment; 4. Indicate future therapeutic avenues; 5. Last but not least there is the metabolomic approach, which is a powerful tool that has been used in a great variety of studies addressing the impact of the intestinal microbiota on human health (HOLMES et al., 2011).

Notably, urine and blood metabolomics provide new insight into microbiota function, leading to the recent discovery of the involvement of intestinal microbes in promoting suitable diets for patients with atherosclerosis (WANG et al., 2011). One of the limitations of the present-day metabolomics, however, lies in identifying the observed metabolites and, in some cases, reliably determining their concentrations.

While these functional metagenomics tools will be instrumental in analysing the relation between microbiota function and health, they have not yet been applied in large-scale studies comparing healthy and diseased subjects. In many cases, the evidence for associations is rather premature and relies on single case reports.

3.2 Cardiovascular diseases (CVD)

Despite continued advances, cardiovascular function disorders remain the leading cause of death worldwide. This study will essentially use recent data published by Mitchell et al. (2012). According to the British Heart Foundation (BHF), cardiovascular diseases (CVD) caused more than 50,000 premature deaths in the United Kingdom in 2008 (BHF, 2010). Cardiovascular diseases are also responsible for a reduction in the quality of human life in later years. However, according to BHF and the World Health Organization (WHO, 2008), 80% of cases of cardiovascular diseases could be prevented or delayed by improved diet, greater physical activity and elimination of smoking. In the work reported by Mitchell et al. (2012), the following topics were discussed as risk predictors for cardiovascular diseases: biomarkers, components of the lipid fraction of diets (quantity and quality), food and/or bioactive substances in diets.

3.2.1 Biomarkers

Serum cholesterol has been used as a laboratory biomarker for cardiovascular diseases. However, in the so-called "Framingham Study," Genest Junior and Cohn (1995) showed that serum cholesterol behaved as a poor determinant of cardiovascular disease risk in different countries, with serum cholesterol concentration levels that did not represent any predictive power. Biomarkers based on health and disease definitions use a range of reference values, but people with subclinical risk are neither classified as healthy nor as patients, which leads to the question of how to define "normal people." Increased postprandial hyperlipidemia is the decreased ability of the body to remove fat and an important risk factor for coronary heart disease (GRIFFIN; FIELDING, 2001).

The number and quality of circulating low-density lipoprotein (LDL) is a more important atherogenicity factor than cholesterol itself. Increased levels of small LDL particles have shown to be a predictor of cardiovascular and cerebrovascular events in individuals with metabolic syndrome (RIZZO et al., 2009). This same work demonstrated the anti-atherogenic effect of high-density lipoprotein (HDL) with protective action against the effect of oxidized LDL in arterial walls, prompting cholesterol efflux. Low HDL is a powerful marker of atherosclerosis risk. However, what is really needed is a marker or markers of HDL function relating its cardioprotective functions, more specifically, anti-atherosclerotic, anti-oxidant, anti-inflammatory, anticoagulant (platelets), vascular dysfunction, aging and senescence.

The biomarker for endothelial dysfunction is brachial flow-mediated dilation, which can predict cardiovascular events in population studies (YEBOAH et al., 2009). Overweight, obesity and central adiposity may be defined according to body mass index (BMI) and waist circumference. Increased intra-hepatocellular fat measured by magnetic resonance spectroscopy (MRS) is a common finding in individuals with metabolic syndrome and also a determinant of cardiometabolic risk (KOTRONEN; YKI-JÄRVINEN, 2008). The liver can also predict the lipidemic response of plasma to dietary sugar (AHMAD et al., 2011).

3.2.2 Dietary lipids

Regarding dietary lipids as a risk factor for cardiovascular disorders, emphasis has been given to the importance of controlling the amount of calories as lipid at 25-30% maximum of total calories, not exceeding 10% as saturated fat. Other important features are maintaining an appropriate ratio of fatty acids of the omega-6 family (ω-6) to the omega-3 (ω-3) family; around 3 to 5:1; avoiding as much as possible food with a high level of trans fatty acids, particularly margarines produced by the catalytic hydrogenation process (Ni) from polyunsaturated vegetable oils (PUFA); consuming generous amounts of extra virgin olive oil, whose main lipid component is oleic acid (C18:1), which has proven anti-cholesteromic action and contains polyphenols that protect, especially the endothelial tissue, delaying and/or preventing atherosclerosis. Further, details on lipids that benefit the health of the cardiovascular

system, and especially those that should be avoided for their harmful action should be better understood002E

Mitchell et al. (2012) also discuss the importance of certain bioactive substances and some functional foods in protecting the cardiovascular system (CVS), among which are polyphenols, whole grains, and apple varieties, whose prominent bioactivities are summarized in Table 4. According to Mitchell et al. (2012), most premature deaths and disorders associated with cardiovascular diseases could be prevented by a conscious effort to maintain appropriate body weight associated with a diet and lifestyle considered as healthy, including: consuming at least two servings of fish per week, one of them rich in oil; consuming at least five portions of different fruit and vegetables per day; consuming 48 grams of whole grains per day; substantially reducing saturated fats and salt. These recommendations are very close to the so-called Mediterranean diet, which is the closest to a functional diet and is considered the main factor for a low rate of cardiovascular diseases among the population of that region.

3.2.3 Dietary profiles and lifestyle

The dietary profile best known now-a-days to prevent or retard CVD and other non-transmittable chronic diseases is the so called "Mediterranean Diet (MD)". The term was first used in the 1950's by the epidemiologist Ancel Keys who recognized various benefits to health of such dietary system. Since then the MD has been adapted to various changes, and in our days became known as "Traditional MD" to indicate the style of diet found in the rural communities in the beginning of the sixties specially in the south of Italy and Greece (particularly in the island of Creta). Since then new food technologies and healthy culinary habits have been developed and improved.

The main characteristic of the traditional MD can be found in the book written by Richard Hoffman and Mariette Gerber (HOFFMAN; GERBER, 2012), which summarizes its composition in terms of: 1. Consumption of a variety of fruits, vegetables, legume seeds, products integral grain herbs and seasonings, diverse types of nuts; 2. Consumption of fruits and vegetables is higher in the european countries of the mediterranean basin; 3. Green leef vegetable include not only several *Cruciferae* for salads, largely consumed in the north of Europe but also onion and garlic in great quantities; fresh fruits are consumed seasonally citric fruits constitute important source of vitamin C, figs and other dry fruits are an important source of fiber and certain fruits are particularly rich in nutrients and bioactive phytochemicals.

The MD became known for its allegations of healthy functional properties such as: 1. Protection against cardiovascular disease (CVD); 2. Protection against some types of cancer; 3. Protections against type 2 diabetes (T_2D); 4. Protect and promote bone tissue growth; 5. Modulate inflammatory processes obesity and fatty acids metabolism; 6. Retard cognitive functions decline ageing and increase longevity; 7. Helps in the control of metabolic syndrome and retard ageing.

The Mediterranean lifestyle was also investigated in healthy individuals. The "Siesta" at mid-day time revealed inversely associated to death rate by coronary disease, particularly among workers after control of interfering factors such as comorbidity, diet, and physical inactivity. Other lifestyle characteristics of the Mediterranean populations such as sociability and healthy food and other health habits contribute to improve their general health.

3.2.4 Visceral obesity

Visceral obesity is characterized by excess fat storage in and around the abdomen; it is the main cause of metabolic abnormalities, characterized as a chronic low grade inflammation in which the adipose tissue develops

Table 4. Bioactivity of some dietary components positively associated with preventing cardiovascular disorders.

Component	Bioactivity	Reference
Flavonoids	↓ Mortality from heart disease	Mink et al. (2007)
Red wine (procyanidins)	↑ FMD response and coronary microcirculation	Hozumi et al. (2006)
Cacao flavonols (procyanidins)	↑ FMD response	Balzer et al. (2008)
	↑ Endothelial function, patients with coronary disease	Heiss et al. (2010)
Apple (Epicatechin)	↑ Increases vasodilation	Castilla et al. (2006)
	↓ Decreases plasma lipid	
Fermented milk (peptides; VPP, IPP)	↓ Lowers blood pressure	Pripp (2008)
		Xu et al. (2008)
Whole grains	↓ Reduces CVD risk mechanisms: reduces inflammatory conditions, improves insulin response, improves vascular function and blood pressure, modifies lipid profile, facilitates weight control, pre-biotic e antioxidant function in the GIT	Seal and Brownlee (2010)
Aqueous tomato concentrate (Fruitflow™)	↓ Reduces platelet aggregation (prevents blood clots)	O'Kennedy et al. (2006)

FDM = brachial flow-mediated dilation; CVD = Cardiovascular disease; GIT = gastrointestinal tract; VPP = tripeptide (Valine-Proline-Proline); IPP = tripeptide (Isoleucine-Proline-Proline). Source: Mitchell et al. (2012).

a main regulatory roll and therefore an important target in the treatment of metabolic syndrome (Mets) (MATSUZAWA, 2006). The development of obesity is a complex process involving genetic and environmental factors. Several genes are related in the determination of body weight, affecting appetite, energy, and metabolic functions (CECIL et al., 2008).

Obesity is a chronic disease characterized by excessive accumulation of fat (CARVALHO et al., 2009). Its etymology is complex and multi factorial resulting from interactions of genes, environment, lifestyle and emotional factors. Besides representing a risk factor for many chronic diseases, obesity is associated with dyslipidemia, diabetes, hypertension and vascular hypertrophy (left), which are a coronary risk factor. Metabolic Syndrome (Mets), also known as syndrome X, is a condition characterized by elevated waist circumference, elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and elevated glycaemia profiles. This syndrome is typically associated with being overweight or obese and also relates to conditions leading to type 2 diabetes (T2D) and cardiovascular diseases (DUVNJAK; DUVNJAK, 2009). The prevalence of obesity has increased dramatically worldwide, mainly in the past three decades, becoming a pandemic. Not only more and more adults become obese, but also children and adolescents (KALLIOMAKI et al., 2008).

There has been little long-term success in treating established obesity through changes in lifestyle. Perhaps due to large permanent changes in diet and physical activities required to keep body weight. An alternative strategy to address the obesity epidemic involves not only weight loss but promoting small changes to prevent the beginning of weight gain (HILL, 2009).

Several diseases, however, are so important that they are worth including in this review, e.g., nonalcoholic fatty liver disease, which affects 30% of the USA population (SPENCER et al., 2011). The nonalcoholic fatty liver represents an association between composition of human gastrointestinal microbiome and the development of fatty liver, with choline deficiency as an additional risk for developing atherosclerosis and CVD. These cases require deep analysis of the microbiota as well as advanced phenotyping and genotyping of the human subjects.

Cardiometabolic diseases represent one of the biggest health challenges facing the world today. The largest economic efforts to retard these illnesses focuses on therapy, while relatively little is done in terms of prevention.

Changes in lifestyle, including increased physical activity, body weight control and healthy eating habits, may help to reduce the risk of developing cardiometabolic problems.

Dietary habits are one of the most important modifiable factors that contribute to maintaining the so called healthy ageing phenotype (MATHERS, 2013). In this context, certain dietary patterns (e.g.; Mediterranean diet) have attracted the attention of researchers and police maker in various countries, since they may reduce the risk of developing cardiovascular complications and other nontransmisible illnesses.

The task of adapting eating habits and other lifestyles from one region or country to another is not only difficult, but in most cases almost impossible, taking into account that factors such as geographical, cultural, educational, and even religion maybe involved.

A new and interesting approach is being followed by researchers at the “Food for Health Science Centre”, Lund University, Medicon Village, 22381 Lund, Sweden (TOVAR et al., 2012, 2016a,b; NILSSON et al., 2013).

The above mentioned researchers performed their studies aiming at comparing a control type diet based on the - “Nordic Nutrition Recommendation (NORDEN, 2004), for a balanced nutrition”. This traditional diet (used as control) was compared to what the authors named as a multifunctional diet (MFD). The overall nutritional composition of the two diets (in terms of traditional nutrients) were comparable. The study was designed as a randomized, controlled parallel trial of the effect of the multifunctional diet (MFD) on markers related to cardiometabolic risk.

The MFD was characterized by a combination of low-glycemic-index meals, soybean and soy protein containing products, almonds, whole barley kernel products, plant stanols, oily marine fish as source of long-chan omega-3 fatty acids, foods and ingredients rich in natural antioxidants, and soluble viscous dietary fiber (mainly from oats and whole grain barley). The nutritional profiles of control diet (CD) and MFD were very similar in overall composition (no statistical difference). The assessment and compliance for the two dietary group are specified in Table 5.

Table 5. Assessment of dietary compliance (%).

➢ **Vitamin C reduces the risk of cancer by:**
• Antioxidant action
• Reinforcing immune system functions
• Blocking the formation of hepatic toxins (via cytochrome P-450)
• Blocking the formation of fecal mutagens
➢ **Vitamin E reinforces enhanced immune response by:**
• Humoral antibody protection
• Reinforcing cell-mediated immunity
• Increasing resistance to bacterial infections
• Stimulating lymphocyte responses
• Stimulating the production of tumor necrosis factor (TNF)
• Stimulating the activity of natural killer cells, blocking the formation of fecal mutagens

The results of the above mentioned series of studies conformed the ability of MFD to effectively modulate various cardio-metabolic disease - related parameters.

Besides their mild hypercholesterolemic status, the cohort of adult overweight/ obese subjects, could be typified as healthy with relatively increased risk of developing cardio-metabolic complications. Hence, the beneficial changes recorded in some circulatory and anthropometric biomarkers, may be taken as indication of disease – preventive character of MFD.

Particularly noteworthy was the large reduction observed in the primary outcome of the study, i. e.; LDL cholesterol was decreased 32% and resembles that reported in the 4-week study (TOVAR et al., 2012). Also interesting is the slightly larger effect observed after 8-week period (35%), which is a clear indication of sustained cholesterol – lowering action of MFD. The remarkable magnitude of this effect is only comparable to those reported in hypercholesterolemic patients treated with potent pharmacologic agents (statins) or on strict vegetarian regime.

Important beneficial changes were also registered in circulating total cholesterol (-26%) and tryglicerides (-16%) as well as in LDL/HDL (-27%) and ApoB/ApoA$_1$ (-10%) ratios. It can thus be concluded that the weight reduction had no influence on the metabolic action of MFD, which is noteworthy, since relatively minor weight reduction (3% or more) has been reported to produce significant metabolic improvement.

The overall blood lipid profile – normalizing effect of MFD was thus confirmed. Its high effectiveness is likely due to the synergistic action of a combination of active ingredients capable of reducing blood lipid levels, i. e.; long – chain omega-3 fatty acids, natural prebiotic sources (whole grain, barley and oat fiber), soybean protein, plant stanols and antioxidant-rich products (TOVAR et al., 2012).

A breath hydrogen test practiced under fasting conditions revealed a marked difference between MFD and CD, with the former promoting a sustained 1.7 to 2.2-fold increase in the expired gas after 4 and 8 weeks, respectively. It can thus be proposed that the metabolic benefit of MFD is linked to increased gut fermentative activity (TOVAR et al., 2014), as a consequence of its elevated indigestible fermentable carbohydrate content, particularly soluble dietary fiber and resistant starch (TOVAR et al., 2012).

Results from this 8-week intervention in healthy overweigh/ obese subjects not only reiterate earlier observations made in shorter experimental trial but also reveal that the metabolic action of MFD does not depend on body weight reduction; MFD – inspired regimes are suggested as part of innovative strategies for the dietary prevention of cardio-metabolic diseases.

4 Human cancer, a multifactorial chronic disease: risk and prevention factors

Cancer diseases can be developed by influence of intrinsic and environmental factors. Among the most important intrinsic factors are genetic traces including genes transformation (degradation, silencing or activation, replication and epigenetic changes), and metabolic interactions.

As we know today the most important extrinsic (environmental) factors are dietary pattern and lifestyle, such as, sedentarism, smoking, excessive alcohol intake and, undernutrition or malnutrition.

At the beginning of this new millennium, cancer remains the second leading cause of death and disability in developed and developing countries, for the most productive age group (i, e., 45 to 64 years of age). Cancer cells are the result of multiple genetic defects resulting from exposure to environmental, dietary, inadequate lifestyle and other pressing factors.

Multistep and multistage carcinogenesis may take 20 years or more to develop, a time that provides research and clinical opportunities to suppress or slow the progress of the disease in its early and premalignant stages, before symptomatic invasive conditions. After all these years of research on genes sequencing and functional studies, further research opportunities arise in persuing studies on the mechanisms of the acquired capabilities of cancer cells, including their limitless replicable potential, sustained angiogenesis and invasion and avoidance of apoptosis. It is now estimated that nutrition and lifestyle factors may be able to prevent or control up to 80% of large bowel, breast and prostate cancer cases, and of one third of all other cancer incidences (GO et al., 2001).

Figure 3, adapted from Lepeslescu (2001), features an entire set of intrinsic and extrinsic factors which may be involved in all stages of carcinogenesis, such as initiation, promotion, conversion (primary tumour formation) and progression, potentially originating metastatic cells (metastasis).

Oxidative stress and oxidation byproducts in normal metabolism cause extensive damage to DNA, in proteins and lipids. Such damage, similar to that caused by radiation, contributes significantly to early aging and age-related degenerative diseases, such as cancer, cardiovascular disease, cataract, immune system decline and brain dysfunction. Antioxidant defenses against this damage include ascorbate (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids and polyphenols, the main dietary components associated with the intake of fruits and vegetables. Low dietary intake of fruits and vegetables doubles the risk of most types of cancer compared to high intake of those food components. Possible protection mechanisms against cancer by vitamins C and E are shown in Table 5. Oxidative burst of phagocytic cells

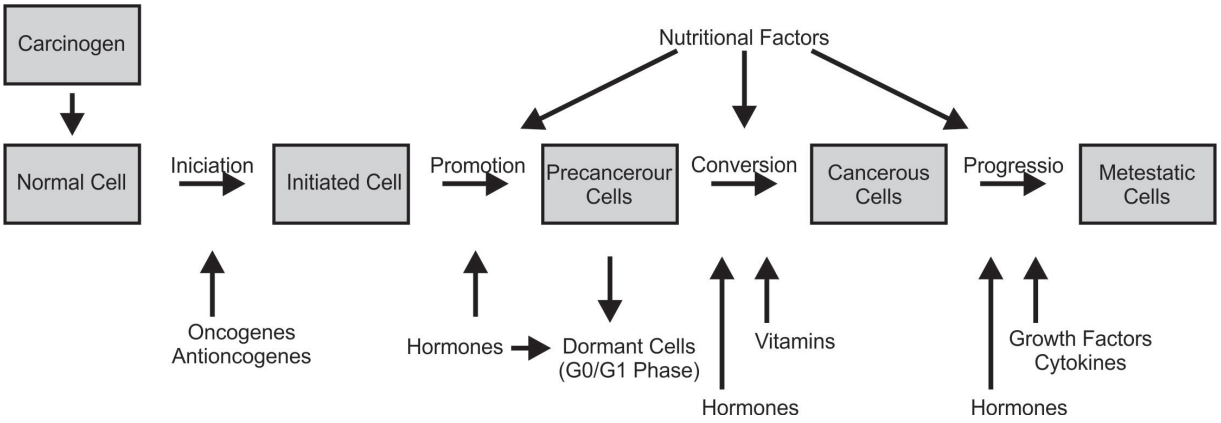

Figure 3. Factors involved in carcinogenesis.

protects against death from bacterial and viral infections, yet contributes to DNA damage, mutations and cancer.

Four endogenous sources are mainly responsible for the production of oxidants by the cell: 1) as a result of normal aerobic respiration, the mitochondrion consumes molecular oxygen, reducing it in sequential steps for the production of H_2O molecules. Byproducts of this process are inevitable, such as: oxygen superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($HO^{\cdot}$). Approximately 10^{12} O_2 molecules are processed daily by a mouse cell, and leakage of partially reduced O_2 molecules is approximately 2%, generating $2x10^{10}$ molecules of hydrogen peroxide (H_2O_2) per cell/day; 2) phagocytic cells destroy bacteria or viruses through oxidative burst, generating nitric oxide (·NO), $O_2^{\cdot-}$, H_2O_2, and hypochlorite oxide ($^{\cdot}OCl$). Infections caused by viruses, bacteria and parasites result in continuous phagocytic activity with consequent chronic inflammation, which is the greatest risk factor for cancer; 3) peroxisomes are organelles responsible for the degradation of fatty acids and other molecules, producing H_2O_2 as a byproduct, which is normally degraded by the enzyme catalase. Evidence suggests that under certain conditions, a considerable amount of H_2O_2 is not degraded, resulting in its migration to other parts of the cell and an increase in oxidative damage to DNA; 4) enzymes of the cytochrome P-450 group comprise one of the earliest defense systems against poisonous substances from plants, the major source of dietary toxins. Induction of these enzymes prevents acute toxic effects by extraneous chemicals, but may also result in oxidant byproducts which damage DNA.

Three exogenous sources can significantly increase the endogenous oxidant load, namely: 1) iron and copper salts, which trigger the generation of oxidant radicals from peroxide (Fenton reaction). People who absorb in their diet an amount of iron above normal levels (hemochromatosis) have high risk for both cancer and heart disease. Excess iron and copper, especially heme iron (found in red meat), is a risk factor in humans for cancer and heart disease; 2) nitrogen oxides (NO_x) present in cigarettes (about 1000 ppm) cause macromolecule oxidation and decrease antioxidant levels. Smoking is a major risk factor for heart disease as well as for a variety of cancers, in addition to lung cancer; 3) the normal diet contains foods of plant origin with high concentrations of phenolic compounds, such as chlorogenic and caffeic acids, besides numerous other polyphenols that can generate compound oxidants through the reduction-oxidation cycle (redox).

Oxidative burst of phagocytic cells protects against death by bacterial and viral infection, yet contributes to DNA damage, mutation and cancer. Processes such as infection and inflammation are causes of cancer. As mentioned earlier, phagocytic cells and leukocytes combat parasitic bacteria and viruses in infected cells by destroying them through the formation of H_2O_2 and radicals (·NO, $O^{\cdot-}$ and ^{-}OCl), a powerful oxidant mixture. These oxidants protect people from imminent death from infection, but cause oxidative damage to DNA and mutations, thus contributing to the process of carcinogenesis. Chronic infections contribute to about one third of cancer cases worldwide. Hepatitis B and C infect about 500 million people, mainly in Asia and Africa, being the main causes of hetapocellular carcinoma. Another important chronic infection is schistosomiasis, caused by a parasitic worm widespread in China and Egypt. The Chinese worm lays its eggs in the colon, producing inflammation that often causes colon cancer. The Egyptian worm lays its eggs in the bladder, causing bladder cancer. *Opisthorchis viverrini* (fluke), a worm that proliferates in the liver, infects millions of people in Thailand and Malaysia. The fluke lodges in carcinoma-specific bile ducts. *Helicobacter pylori* is a bacterium that infects the stomach of about one third of the world's population, which causes gastritis, gastric ulcers and stomach cancer. In rich countries these diseases do not occur or are partly asymptomatic, indicating that the effects of inflammation are at least partly suppressed, possibly by the ingestion of appropriate levels of antioxidants.

Antioxidant defenses against this damage include ascorbate (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids and polyphenols, the main dietary components associated with the intake of fruit and vegetables. Low dietary intake of fruit and vegetables doubles the risk of most types of cancer compared to high intake of those food components. Possible protection mechanisms against cancer by vitamins C and E are shown in Table 6. Oxidative burst of phagocytic cells protects against death from bacterial and viral infections, yet contributes to DNA damage, mutations and cancer.

Antioxidants can act against the development of many diseases that affect older people. Several defense mechanisms that limit the damage caused by natural oxidizing agents or those ingested with food have developed in the body. Among those defenders are enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (G-Px). Glutathione S-transferases inactivate mutagenic electrophilic substances, including aldehydes resulting from lipid peroxidation. There are also many structural defenses such as enzymes that sequester H_2O_2 in peroxisomes and chelators of free Fe^{+2} or Cu^{+2}, by proteins such as transferrin and ferritin or ceruloplasmin, respectively. Oxidized DNA is usually repaired by non-specific splicing enzymes and a variety of glycosidases that are specific for particular oxidized bases. In the absence of cell division, oxidative lesions are ineffective and mutations are kept to a minimum. Oxidized proteins are degraded by proteases.

4.1 Nutrigenomic or nutritional genomics

Nutrigenomics is considered a borderline discipline, a branch of eco genomics which studies the role of individual genetic polymorphisms and the influence of diet as risk factors for the occurrence of chronic diseases. Nutrigenomics is a powerful tool that guides investigators to a more global and molecular consideration of the various factors influencing the human biological response to diet.

Considering as a whole, diet encompasses the most diverse and complex assortments of compounds to which humans are exposed. The interaction between dietary constituents and genetic differences in the regulation of their absorption, transport, metabolism, and effects on target tissues and organs, has a potent impact on human health and diseases. Some of these are bioactive compounds with a variety of properties which may play a role in prevention or retardation of chronic diseases. In contrast several classes of foodborne chemicals are carcinogenic or toxic and associated with increased risk of cancer and other chronic diseases.

The genetic factors that modulate individual susceptibility to multifactorial diseases (i. g., cancer diabetes and cardiovascular diseases) represent common, but functionally different forms of genetic polymorphisms. These genes generally have a modest effect at individual level, but, because of their high frequency at population level, they can be associated with high attributable risks.

Environmental factors can facilitate the phenotypic expression of such susceptible genes. As outlined previously, most of the susceptible genes for common diseases do not have a primary etiologic role in predisposition to diseases, but they may act as response modifiers to environmental factors, such as diet. Our understanding of the extent to which subtle differences influence optimal nutrition, nutrient requirements, and susceptibility to diseases is still rudimentary.

However, in the case of multifactorial diseases, the interactions are complex, involving multiple genes and a variety of exposures. In some cases, for still poorly understood pathways, genetic and genetic variants have helped elucidate which compounds are key players in the complex pathways. In other cases, animal models, including transgenics, have improved the research understanding of gene-diet interactions (CASTLE; RIES, 2009; PATRAŞ; TUDOSE, 2013).

4.2 Nutrigenomics and stress study

Stress can be defined as a state in which the body receives some mental or physical load. In general our body can keep homeostase against external stress. However, if the stress continues for a long time and/or it is too strong, organisms are unable to maintain homeostasis. This response is known as stress disease, and the etiology of stress disease is called a stressor. Various mental and/or physical stressors exist, and major stress diseases include psychossomatic disorder, depression, and neurosis. Metabolic Syndrome is a stress disease in broad sense, particularly when regarding nutritional deflection as a stressor. However, because the developmental process of stress disease involves the accumulation of minute changes and because the causes are very complicated, the stress research field remains enigmatic.

Table 6. Genetic factors that predispose to Alzheimer's disease.

Cromossome	Gene disorder	Aging stage	Aβ phenotype
21	APP mutations	50s	↑ Total production of Aβ peptides or Aβ1-42/43 peptides
14	Presenilin-1 mutations	40s e 50s	↑ In the production of Aβ1-42/43 peptides
1	Presenilin-2 mutations	Anos 50	↑ Production of Aβ1-42/43 peptides
19	ApoE4 polimorfism	60s or above	↑ In the level of Aβ plaques and vascular deposits

↑ indicates increase of specific phenotype. Source: Adapted from Selkoe (1997).

4.3 Dietary components histone changes and carcinogenesis

In 2002, nutrigenomics was launched as a comprehensive method to investigate the effect of nutrients on the body. In Japan, this methodology has been applied mostly to functional food science. Functional Food Genomics was founded in the Graduate School of Agricultural and Life Sciences at the University of Tokyo, in 2003. The purpose of that chair was to obtain scientific evidence on the effects of functional foods by analyzing the gene expressions evoked by the body, when 32 representative food companies participated in the first stage (2003-2008). In collaboration with university staff, these companies have been employing transcriptomics to evaluate the physiological functionalities of food components, including polyphenols, carotenoids, tocopherol, lignan, amino acids, dietary fibers, some fermentation products and essential minerals. The target tissue include liver, intestine, adipose tissues, muscle, animal immune system, and human cell cultures.

The functional food genomics is still in progress in Japan, and elsewhere, and its activities are aimed at scientific and social benefits to the whole population (NAKAI et al., 2011). Scientifically, the efforts seek to: 1) find key molecules that may act as triggers for physiological functionalities; 2) elucidate their modes of interaction with the food components of interest; 3) define the strength and continuity of functional food components in the body, as well as the mechanisms evoked in target tissues; 4) construct useful assay systems for evaluating the total effect of each multifunctional food component; and 5) explore the area of genomics-based food safety assessment, with special emphasis on identifying risk factors for deficient or excessive food intake.

Studies provide evidence that dietary components may affect the carcinogenesis process in various ways. Isothiocyanates present in the family Cruciferae (cauliflower, cabbage and broccoli), diallyl sulfide (an organosulfur compound present in garlic), isoflavones, phytosterols, folate, selenium, vitamin E, flavonoids and dietary fiber may reduce the risk of cancer. Emerging evidence suggests that protective effects against cancer may be mediated through epigenetic mechanisms. Epigenetic modifications are heritable changes in gene expression that do not require changes in the DNA sequence (HERMAN; BAYLIN, 2003).

The major epigenetic control mechanisms in mammals are DNA methylation, histone modifications and interference with RNA (RNA silencing) (TOLLEFSBOL, 2008). The key epigenetic modification in mammals is the addition of a methyl group at position-5' of cytosine carbon in the dinucleotide sequence, cytosine-phosphate-guanidine (CpG). CpG dinucleotides are frequently grouped into DNA regions rich in CpG, known as CpG islands, which are frequently associated with transcription initiation sites (SZIF, 2005). The covalent addition of methyl groups is catalyzed by DNA methyltransferases (DNMTs), a family of enzymes that use S-adenosyl methionine (SAM) as a universal methyl donor (Figure 4).

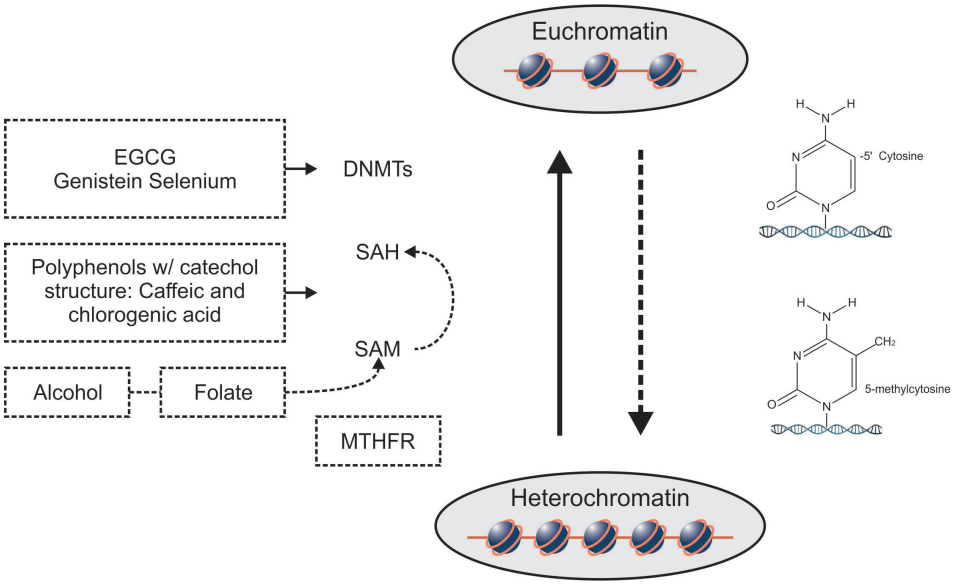

Figure 4. Cytosine DNA methylation located at position 5' in relation to guanidine of CpG islands in promoter genes leads to transcriptional silencing of tumor and malignant conversion suppressor genes. This reaction is catalyzed by DNA methyltransferase (DNMT), with S-adenosyl methionine (SAM) as a universal donor of methyl groups. Dietary compounds such as polyphenols, epigallocatechin-3-gallate (EGCG) from green tea, soy genistein and isothiocyanates of various vegetables are bioactive compounds with anticancer properties. Cancer inhibition promoted by dietary polyphenols is associated with gene reactivation through demethylation of tumor suppressor genes. The effects of polyphenols in the diet, such as of EGCG on DNMT, appear to occur through interaction with the catalytic site of the DNMT1 molecule, while polyphenols with catechol in their structure such as caffeic and chlorogenic acids affect the bioavailability of SAM (SUPIC et al., 2013).

While DNA-methyltransferase 1 (DNMT1) is primarily involved in DNA methylation following replication, DNMT3A and DNMT3B interact with the transcription mechanism by mediating de novo methylation. Several studies have shown an overexpression of DNMT enzymes (especially DNMT1 and DNMT3B) in multiple cancers (SZIF, 2005). A growing body of evidence suggests that organic compounds derived from plants and present in the diet have an impact on histone modifications. Histone acetylation is done by acetyltransferases (HAT) that neutralize the positive charge of lysine released at the histone tail of the negatively charged DNA, and thus chromatin becomes uncompressed and accessible to transcription factors. Histone deacetylases (HDAC) release acetyl radicals of lysine residues from histone tails, and thus the nucleosomes become compressed. On the other hand, methylation does not change loads in histones tails, but influences the chemical characteristics of histones and their affinity for transcription factors or other regulatory proteins. Histone methylation is catalyzed by histone methyltransferases (HMT) and histone demethylation by histone demethylases (HMD).

The potential ability of dietary components to epigenetically activate anticancer genes silenced in cancer cells has acquired importance in cancer prevention and therapy. The following describes the specific action of various bioactive components in carcinogenesis.

- Folate

Folate can influence histone methylation in hepatic cancer. A poor diet in methyl donors leads to changes in histone H4 (H4-K20) trimethylation and histone H3 (H3-K9) acetylation, as observed in hepatic carcinogenesis (POGRIBNY et al., 2007), favoring tumor development. Higher folate levels promote carcinogenesis inhibition.

- Epigallocatechin gallate (EGCG)

This induces change in several histones in human melanoma A431 cells treated with 20 μM for 6 days. Treatment with EGCG decreased histone deacetylase activity and increased lysine (K) acetylation at positions 5, 12 and 16 of H4 histone and lysine 9 and 14 of H3 histone also increased methylation levels in lysine 9 (H3K9), according to Nandakumar et al. (2011). So EGCG may influence cancer risk via two lines of action: DNA demethylation and histone changes, which, in turn, may induce transcriptional activation of tumor suppressor genes.

- Genistein

In addition to its effect on DNA methylation, its action has been associated with histone changes. Long-term treatment of MCF-7 breast cancer cells reduces H3 acetylation and alters growth response by mitogens, besides histone deacetylase inhibitors (JAWAID et al., 2010). Reactivation of PTEN and CYLD tumor suppressor genes was observed in LNCap and PC-3 prostate cancer cells (treated with 25 and 50 μM of genistein for 72 h), by modulation of histone methylation (H3K9) and deacetylation of those genes. Moreover, genistein increased histone H3K9 acetylation in p53 and FOX03a genes, through (-) regulation of endogenous deacetylation mediated by SIRT1 protein, regardless of DNA methylation promoter (KIKUNO et al., 2008). On the other hand, in the prostate cancer cell lines LNCap, DUPRO and RWPE, treatment with 10 to 25 μM/L of genistein increased H3K4 acetylation in p21 and p16 transcription initiation sites and expression of HAT (MAJID et al., 2008). In MDA-MB-231 and BT-20 breast cancer cells, four-day treatments with 15 and 30 μM of genistein, respectively, showed an induction in H1 phosphorylation, transcriptional activation and cell production blocking in the transformation of G2/M phases (CAPPELLETTI et al., 2000).

- Resveratrol

This antagonizes histone modifications induced by dioxin in the BRCA1 gene, suppression of BRCA1 encoded protein expression and reduces DNA fragmentation induced by dioxin in MCF-7 cells in breast cancer (PAPOUTSIS et al., 2010). Pre-treatment with resveratrol increased H4 and H3K9 acetylation, reduced H3K9 methylation and modulated the recruitment of MBD2 to BRCA1 gene promoter in MCF-7 breast cancer treated with tetrachlorobenzene dioxin (PAPOUTSIS et al., 2010). These findings indicate that epigenetic silencing of BRCA1 gene could be prevented with resveratrol, revealing the molecular basis for the development of therapeutic strategies for cancer control.

- Curcumin

Treatment of brain cancer cells with curcumin induced hypoacetylation of H3 and H4 histones (SHANKAR; SRIVASTAVA, 2007). The opposite was observed in cells in which curcumin induced H3 and H4 acetylation, and apoptosis by engagement of the Bcl-2 and p53 gene family. This discrepancy may have originated from the difference in the type of tumor, but could also be due to exposure time, cell type and dependence on the curcumin dose effect. All these problems require further investigation.

- Quercetin

Quercetin induced a significant delay in tumor growth induced by 7.2-dimethylbenzanthracene in oral carcinoma in hamsters. This effect was attributed to the induction of cell cycle blocking and apoptosis correlated with inhibition of histone deacetylase-1, HDAC-1 (PRIYADARSINI et al., 2011).

- Butyrate

This is an HDAC inhibitor and promotes histone acetylation, promoting the expression of genes involved in cell differentiation and apoptosis in several types of cancer (MYZAK; DASHWOOD, 2006). In addition, butyrate increases kinase ERK phosphorylation in HT29 colon cancer cells (SCHARLAU et al., 2009). In a colorectal cancer model in rats induced by dimethylhydrazine (DMH), sodium butyrate, single or in synergy with folic acid, significantly reduced the incidence of cancer and negatively regulated H3acetylation and p21 gene expression (LU et al., 2008).

- Sulforaphane

An isothiocyanate found in the Cruciferae plant family, particularly broccoli, which inhibits HDAC activity in human colon, prostate and breast cancer cells (NIAN et al., 2009). In prostate cancer cells (BPH-1, LNCap, PC3) *in vitro*, sulforaphane inhibited the activity of histone deacetylase (HDAC) 48 hours after treatment was started with 15 μM of sulforaphane. This action was accompanied by increased levels of proteins encoded by p21 and Bax genes, cell cycle blockage and apoptosis activation (MYZAK et al., 2006). Sulforaphane inhibited proliferation of MCF-7 and MDA-MB-231 cells breast cancer in a dose-dependent and time-dependent way (MEERAN et al., 2010). Cell growth was completely inhibited six days after treatment was started with 15 μM and 20 μM of sulforaphane, by DNA methyltransferase (DNMTs) inhibition, hTERT promoter demethylation, and increase of active chromatin markers (acetyl-H3, acetyl- H3K9 and acetyl-H4), with simultaneous decrease of inactive chromatin markers (trimethyl-H3K9 and trimethyl-H3K27), according Meeran et al. (2010). In the *in vivo* model, HDAC activity was significantly inhibited in colon and prostate mucosa and in peripheral blood mononuclear cells of "Apc-minus" mice after a single oral dose of 10μM of sulforaphane (MYZAK et al., 2006). The protective effect of broccoli was observed in smokers and nonsmokers undergoing a controlled diet containing broccoli, which was associated with a significant decrease of DNA strand breaks (RISO et al, 2009; HO et al., 2009). In healthy humans, a single intake of 68 g of broccoli (1 cup) inhibited HDAC activity in peripheral blood mononuclear cells 3 to 6 hours after consumption. However, HDAC activity returned to normal after 24 h; histone hyperacetylation was noted for at least 48 hours (MYZAK et al., 2007). This was the first study to demonstrate that broccoli dietary components have a substantial effect on the inhibition of histone deacetylase (HDAC) activity in humans.

- S-allyl mercaptocysteine

This organosulfur compound found in garlic acts as a HDAC inhibitor and induces rapid and persistent hypermethylation of H3 and H4 histones in human cancer cells (NIAN et al., 2009). Allyl mercaptan, an organosulfur compound derived from garlic, in doses of 2, 20 and 200 μM, revealed dose-dependent histone deacetylase inhibition and enhanced Sp3 binding on p21WAF1 promoter, followed by subsequent p53 recruitment (NIAN et al., 2009).

- Diallyl disulfide

This is a natural HDAC inhibitor present in garlic and other species of the same genus. Treatment with 200 μM of diallyl disulfide for 6h showed inhibited proliferation of HT-29 and Caco-2 colon cancer cells (DRUESNE et al., 2004). Diallyl disulfide exerts this effect through HDAC inhibition, histone hypermethylation, and stimulus to p21 gene expression. It is interesting that a single administration of diallyl disulfide has a transient effect on H3K14 acetylation, while repetitive treatment with the compound allyl disulfide results in prolonged H3 histone hyperacetylation.

The development of relevant models of cell culture and in animals for research on environmental and dietary impact on epigenetic changes will be essential to study their interrelations and full potential. Differences between species must be considered in interpreting results in cancer cell cultures, animal models and human cells. An important area for future research is the development of analytical methods to better clarify the complex interplay between DNA methylation, histone modifications and microRNAs. In addition, the influence of genetic and environmental factors on protective epigenetic changes induced by bioactive dietary components has yet to be established.

5 Multiple approach in cancer research

For various decades researchers have demonstrated increased interest in identifying an inverse association between adherence to an appropriate dietary profile and incidence of certain types of cancer, in different tissues and organs of the human body. A number of research in food science, nutrition and medical areas have persued this objective concentrating their efforts on the investigation of several aspects of the mediterranean diet (MD), which have been accepted as a dietary model best attending the requirements of a multifunctional diet, providing health benefits and longevity to the population of that region.

La Vecchia (2004) studied the association between different aspects of the MD and various types of common epithelium cancers, including the digestive tract and other non-digestive systems. For the majority of epithelium the increased consumption of fruits and vegetables, with a relative risk (RR) between 0.3 and 0.7 for the highest accuracy, compared with the lowest. For digestive tract cancer, the risk attributed to the population with low fruits and vegetables intake varied in the range between 15 and 40%. A protecting effect was also observed for mammary glands, women genital tract, urinary tract, and some other epithelium neoplasms. Various antioxidants

and micronutrients showed an inverse relation with cancer risk, however, the main components responsible for the favorable effects of a diet rich in fruits and vegetables, have not yet been completely defined. Fishes appeared as another favorable components. In contrast, participants reporting frequent consumption of red meat showed RR 1.0 for various types of cancer particularly for cancer of the superior digestive tract (sDT). This finding can be explained by the favorable effect of soluble and insoluble fibers, however, this topic still deserves further discussion and investigation. On the other side, ingestion of refined grains, consequently, elevated glycemic index, were positively associated with various types of cancer including mammary glands and colorectal (LA VECCHIA, 2004). From this investigation it was concluded that a low risk of cancer for consumer following the MD results from a continued high consumption of fruits and vegetables, as well as avoiding frequent high consumption of red meat and refined carbohydrate, low consumption of saturated fat, high consumption of extra-virgin olive oil, and a continued moderate consumption of polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

Many studies have been published on the antineoplastic and anti-inflammatory properties of EPA and DHA in the prevention of colon cancer, which is relevant considering that inflammation plays a critical role in the development and progression of colon cancer (HULL, 2011). It is known that long chain omega-3 fatty acids (EPA, DHA) may act through specific molecular mechanisms in the prevention of colon cancer. A key mechanisms of PUFAs ω-3 is it anti-inflammatory activity inhibiting the enzyme COX-2, which blocks the synthesis of prostaglandins (PGs), (COCKBAIN et al., 2012). The enzyme COX-2 has a fundamental role in colorectal carcinogenesis by converting arachidonic acid in prostaglandins, mainly of the serie PGE_2, which are pro-tumorigenics (WANG; DUBOIS, 2010). Acting as an alternative substrate for COX-2, the EPA promotes a reduction of PGE_2 favoring formation of series PGE_3, which exhibit ant-tumorigenic activity. It was demonstrated that a preparation of pure EPA (as free fatty acid) promoted a dramatic suppression in the number of polyps in $Apc^{min/+}$ mice model. It is important to emphasize that animals fed a preparation of pure EPA reveled a significant reduction of COX-2, a depression in the expression of nuclear β-catenine, and a significative decrease in lipid peroxidation (FINI et al., 2010).

It is important to notice that epidemiologic and experimental data, show an inverse relation between olive oil consumption and cancers incidence, mainly mammals, skin, and colon cancer (OWEN et al., 2000). The ant-tumorigenic activity of olive oil is attributed, mainly to the antioxidant activity of their phenolic compounds. The molecular activity of hydroxityrosol (HT), one of the most representative olive oil polyphenol compound has been extensively investigated and, in vitro studies, have revealed anti-proliferative, anti- apoptotic, and regulatory effects in several lines of colorectal cancer cells. On SW620 cancer colorectal cells, acted inhibiting the expression of the enzyme fatty acid synthase (FAS), inhibiting its activity and, inducing the inhibition of cells proliferation (NOTARNICOLA et al., 2011), while in HT29 cells, oleic acid inhibited phosphorylation of kinases (ERK) ½ regulated by signalization, and, consequently reducing the expression of cyclin D1 which, finally, culminated with the blockage of phase G_2/M of the cellular cycle (CORONA et al., 2009).

Among the fruits, apple is the most frequently consumed in a typical Mediterranean diet and it is very rich in polyphenols, with antioxidant and anticancer activities. The consumption of apples is inversely associated with colon cancer risk in a dose-dependent manner (JEDRYCHOWSKI et al., 2010). Modified apple polysaccharide showed potential chemo-preventive, apoptose induction, suppression of migration of induced lipopolysaccharide (LPS) and inhibition of the invasive capacity of cancer colorectal cells (CCR), through inhibition of nuclear factor KB (NFKB) in HT29 and SW620 colorectal cancer cells, showing that modified apple polysaccharides could prevent metastasis (ZHANG et al., 2013).

There are at least three molecular routs conducting to colorectal cancer and, although multiple phytochemicals may present redundant bioactivities, there is no isolated molecule capable of effectively acting in all of them. On the other side, the authors Fazio and Ricciardiello (2014) believe that the combination of multiple active compounds can accomplish more affective effects. Therefore, the study of combinations of different bioactivities, could be a promising field of research against chemoprevention of various types of cancer.

Taking into account the large number of bioactive compounds in human diets, and the variety of cancer modalities afflicting the human population worldwide, it seems that the best research approach to help in cancer control at population levels would be to simultaneously explore individual bioactivities in different items and, at the same time exploring various dietary approaches aiming at better adequating a dietary profile to prevent or control the disease in specific regions of different countries.

6 Diseases related to the Central Nervous System (CNS)

Some types of pathology that afflict older people cause suffering not only for patients, but also their families. Such diseases include dementias, Parkinson's disease and depression, among others.

6.1 Dementias

Dementia is characterized by an insidious and progressive loss of memory with altered intellectual functions and cognitive abilities. Dementia is defined as

a syndrome consisting of progressive loss of memory and at least one other cognitive impairment (including aphasia, apraxia, agnosia or executive function disorder) in the absence of any other explicable brain disorder (CUMMINGS, 2004). Different types of dementia are currently discernible, including Alzheimer's disease (AD), vascular dementia and dementia with Lewy bodies. Alzheimer's disease is the most common cause of dementia. Alzheimer's disease and vascular dementia have distinct pathological features, but both conditions coexist, and the combination is associated with greater cognitive impairment. This loss is a quantitative disorder and its distribution in the population shows continuous severity with dementia in the tail of the distribution. The fact that cognitive impairment is common in the population does not mean that it is intrinsic to aging. The distribution of cognitive impairment correlates with increasing age in such a way that mean scores decrease and prevalence of cognitive loss increases. While the etiology of Alzheimer's disease is unknown, some experts have speculated that the accumulation of β-amyloid peptides in the brain is the primary cause of the pathogenesis of Alzheimer's disease (CUMMINGS, 2004). Mutations in Aβ peptide precursor proteins lead to presenile dementia and overexpression of β-amyloid proteins in Down syndrome. Research with "Knock-out" mice has provided support for this hypothesis. Alternatives hypotheses for the etiology of Alzheimer's disease have placed particular emphasis on the role of vascular factors and neuronal cell death. Dementia with Lewy bodies is characterized by Parkinsonism, visual hallucinations and fluctuating confusion.

Neurons contain very thin filaments, known as neurofilaments. These filaments are intimately involved with the internal transport of neurotransmitter molecules from their synthesis site to their usage site, the synapse. Some older people show changes in these filaments, which become black fibrils, thicker, curled and much more prominent within the cell, called neurofibrillary tangles. In intellectually normal older individuals, groupings of these affected neurons may be found in specific locations (such as the anterior temporal lobe), although they are very rare in other brain regions (e.g., the neocortex). People suffering from senile dementia may show a greater number of such tangles than normal individuals. This phenomenon has been extensively studied in cases of Alzheimer's disease. Alzheimer's disease (AD), also known as senile dementia of the Alzheimer type, is a degenerative CNS disorder that results in progressive loss of memory and other intellectual functions of sufficient severity to significantly interfere with normal daily activities, as well as social relations. Alzheimer's disease is distinguished from age-related episodes of benign forgetfulness by progressive and irreversible loss of various functions controlled by the brain, such as: memory, space-time orientation, performance routine activities, language and communication skills, abstract thinking, learning ability, personality change and decision-making capacity (EVANS, 1996).

Genetic heritage, culture and socioeconomic status are known risk factors for Alzheimer's disease. This disease is a major health problem, and overall incidence is about 600 cases for a population of 100 thousand, or from 5 to 10% of people over 65 years of age (EVANS, 1996). Prevalence of Alzheimer's disease increases with age; however, the affected percentage doubles every decade for people over 65. A study in East Boston (USA) determined a prevalence of 0.6% for people aged 65-69, 1% for people aged 70-74, 2% for people aged 75-79, 3.3% for people aged 80-84, and 8.4% for people over 85 (EVANS, 1996). Estimates suggest that more than 100,000 Americans die of Alzheimer's disease each year. The natural history of Alzheimer's disease indicates that the average patient exhibits early symptoms around the age of 72, dying around the age of 91. The disease seems to progress more rapidly in men (84 months) than in women (108 months); however, this difference between men and women is not observed in all studies (JOST; GROSSBERG, 1995).

Autopsies have shown that the brains of people who die from Alzheimer's disease are abnormal (GEARING et al., 1995). Roughly speaking, there is atrophy in the neocortex and often in the hippocampus and amygdala, all of them key sites involved in thinking and memory. Neuritic – or senile – plaques are found in both intellectually normal subjects and people affected by the various dementias. Two main types of these plaques are documented: neuritic and diffuse. Neuritic plaques, strongly associated with Alzheimer's disease, are spherical structures approximately 80 μm in diameter, with thick neural filaments (or neurites) surrounding a fibril core of an abnormal protein called amyloid. Moreover, these neuritic plaques contain dense bodies supposed to be debris of lysosomes, mitochondria and paired helical filaments. Diffuse plaques, in turn, do not show abnormal neurites, appear to be more amorphous, and contain few, if any, amyloid fibrils, in diffused form. Diffuse plaques are often found in the brain of individuals with Alzheimer's disease. They may represent an early stage in the development of neuritic plaques. Selkoe (1997) suggested that they represent very early lesions, which may or may not progress to a mature lesion with visible symptoms, depending on various factors, including the individual's longevity.

In individuals suffering from Alzheimer's disease, the number of neurofibrillary tangles (NFT) in the affected brain areas is about six times greater than in an intellectually normal but severely affected person. NFTs are found mainly in the hippocampus and cerebral cortex; they have not been found in the cerebellum and spine. The tangle itself is intracellular and mostly composed of paired helical filaments (PHF) which, as the name suggests, are helically twisted pairs of protein filaments. These proteins

are abnormally phosphorylated forms of tau protein (often associated with microtubules) and form complexes with another protein, ubiquitin, which is normally used by the cell to mark proteins destined for degradation (MORI et al., 1987). Although NFTs are invariably found in patients with Alzheimer's disease, they can be found at lower levels in cognitively normal individuals, as well as in the brains of patients suffering from other neurological disorders. These plaques and tangles can be seen, but not the synapse loss and neuron death. The third neurological feature of Alzheimer's disease is amyloid angiopathy, or deposition of amyloid protein in the blood vessel walls of the meninges and cortex. Severity of deposition varies widely, and the same characteristic is sometimes found in the brains of normal older individuals.

Alzheimer's disease has a hereditary form and a non-hereditary form. Families with a very high incidence have been identified, affecting members over four or five generations (WURTMAN, 1985). The inheritance pattern is consistent with the idea that defective aging is transmitted as an autosomal dominant. Therefore, individuals develop full Alzheimer's disease when they inherit only one copy of the aberrant gene. Estimates are that between 40-75% of patients with Alzheimer's suffer from some form of the disease that is genetically transmitted. The remainder of affected individuals has a milder, non-hereditary form, which tends to become more apparent in advanced age; its etiology is still unclear. Currently, there are four known genetic alterations responsible for hereditary Alzheimer's disease, listed in Table 6. It is noted that the four mutations result in increased production of amyloid protein or its variants (SELKOE, 1997).

Amyloid is a generic term that describes proteins with a structure of beta-pleated sheets. The amyloid proteins related to Alzheimer's disease are derived mainly from the APP (Amyloid Precursor Protein), located on chromosome 21. The APP gene contains approximately 400 kilobases of DNA, which is cut and pasted at several points to produce various transcripts that encode a family of amyloid proteins (Aβ) which vary from 695 to 779 amino acid residues (SANDBRINK et al., 1996). The APP protein gene is expressed ubiquitously in mammals, by both neural and non-neural cells. It is highly preserved in vertebrates and homologous proteins have been identified in the fruit fly (*Drosophila melalnogaster*) and roundworm (*Caerhabditis elegans*). In all those cases, the protein encoded by APP is a transmembrane protein apparently involved in cell-cell signaling processes. Significant amounts of newly synthesized APP protein appear on the cell surface; some of these molecules may be cleaved at specific positions by unknown proteases. Apparently, it is not the actual APP-encoded protein that causes Alzheimer's disease, but the derived fragments. Cleavage usually produces a peptide with 40 amino acid residues (Aβ-40); this fragment seems not to play any role in the pathogenesis of Alzheimer's disease. However, when cleavage produces peptides of 42 or 43 residues (Aβ1-42/43), these fragments appear to form nuclei in amyloid fibrils and apparently lead to the structural abnormalities described above.

All four known genetic mutations (Table 6) involved in genetic Alzheimer's disease cause increased production of Aβ1-42/43 peptides and/or increased level of Aβ plaques. Work carried out in transgenic mice containing a mutant APP gene leads to the same conclusion (HSIAO et al., 1996). Together, these results strongly indicate that the accumulation of Aβ1-42/43 in the brain is an early and invariant event in the development of Alzheimer's disease (SELKOE, 1997), although the long periods of time prior to the appearance of symptoms suggest that these pathogenic peptides accumulate very slowly. The APP gene is located in chromosome 21, the same chromosome involved in Down syndrome (TANZI et al., 1987). All individuals affected by Down syndrome develop symptoms that are indistinguishable from those of Alzheimer's disease up to the age of 50, also presenting diffuse plaques as early as 12 years old. These observations were among the first evidence suggesting an important role played by the APP gene in the etiology of Alzheimer's disease.

Presenilin genes are located in chromosomes 1 and 14. They encode two homologous transmembrane proteins that are also involved in cell-cell signaling. Dewji and Singer (1996) suggested that PS1 and PS2 (presenilins 1 and 2) typically interact directly with the APP protein in an evolutionarily preserved intercellular signaling mechanism. Mutations in PS1 and PS2 genes apparently affect the way cells deal with the APP protein, and it is believed that these mutations are responsible for increased production of Aβ1-42/43 pathogenic fragments, through normal protein processing cell mechanisms.

The ApoE4 gene plays a role in homozygous individuals for apolipoprotein E, ApoE4, who are more likely to develop Alzheimer's disease compared to individuals with ApoE3 or ApoE2 alleles. This may happen because the ApoE4 allele is not capable of binding to the microtubule tau protein, thus allowing free tau proteins to be hyperphosphorylated in an abnormal way, resulting in neurofibrillary tangles (NFT) characteristic of Alzheimer's disease. However, ApoE3 and ApoE2 alleles are capable of binding to the tau protein, therefore NFT formation is delayed or suppressed with ApoE3 and ApoE2 alleles (KAMBOH, 1995; SCHACTER et al., 1994). In addition, the ApoE4 allele has lower levels of antioxidant, and such a decrease of the protective effect may also play a role in the pathogenesis of Alzheimer's disease (MIYATA; SMITH, 1996).

These various genetic processes enable a local accumulation of self-aggregating Aβ1-42/43 peptides. Inasmuch as it accumulates in its insoluble form (plaque),

this protein damages adjacent neurons directly, via neurotoxicity, or indirectly, via inflammatory reactions in microglial cells. The mechanisms that produce such damage are becoming clearer. It is already known that Aβ1-42/43 peptides may induce oxidative damage by specific binding with a particular protein receptor with limited expression in the adult CNS (YAN et al., 1996). This protein receptor normally binds to molecules that regulate neuritic growth, but may also bind to Aβ1-42/43 peptides. Aβ1-42/43 peptides can generate intermediates that react with oxygen and cause oxidative damage. However, when bound to the receiver they generate an additional and sustained production of oxidants, resulting in oxidative stress and neurotoxicity (YAN et al., 1996). The combination of receptor and Aβ1-42/43 peptides also activates microglial cells that react by secreting cytotoxic cytokines, initiating other aspects of an inflammatory response. In both cases, the resulting oxidative stress severely damages neurons and decreases their ability to withstand subsequent stresses. This reduction of oxidative resistance is probably exacerbated by low levels of mitochondrial activity, therefore low energy levels characteristic of patients with Alzheimer's disease (DAVIS et al., 1997). The low energy levels may be derived from mitochondrial damage induced by oxidative stress. Other metabolic changes probably include altered phosphorylation of tau protein and the formation of paired helical filaments (PHF) in neuritic plaques and neurofibrillary tangles (NFT).

The important clinical consequence of this series of events is inevitable synaptic loss and/or defect in neurotransmitters, both resulting in abnormal neural circuits and functions (SELKOE, 1997). However, there is no strict relationship between level of damage and the extent of observed behavior changes. Education, culture and socioeconomic status enable a significant modulation of the result. In the so-called "Nun Study," Snowdon (1997) combines a deep longitudinal and long-term study of the behavior and cognitive skills of a large number of nuns with detailed post-death autopsy data. This study produced the very interesting finding that high levels of education, verbal ability and/or continuous mental activity showed, at least for some individuals, normal behavior and cognitive levels, despite the great brain damage caused by Alzheimer's disease. If mental activity stimulates complex neural circuits, resulting redundancies may enable multiple additional routes through which information can enter and exit, and may mean that using the mind can prevent its loss.

Recent research in Brazil and abroad seeks new alternatives and suggests new paths to attain, if not the cure, at least the most effective control of the development of Alzheimer's disease. According to Tunes (2002), FM-USP researchers identified phospholipase A2 enzyme in the blood, which they hope might be an effective biomarker for early detection of Alzheimer's disease or even the key to its cure. Wagner Farid Gattaz, one of the team leaders, examined the blood of healthy older individuals and compared it with samples of patients with Alzheimer's and mild cognitive impairment (MCI), a disorder characterized merely by memory decline. Both investigated groups (AD and MCI) showed decreased levels of phospholipase A2 (PLA2), an enzyme that acts on the metabolism of phospholipids, cell membrane components. The more impaired the brain functions, the lower the levels of phospholipase A2. It was found that, besides being produced by the pancreas as a digestive enzyme, this enzyme is present in all cells, including neuron cells.

The membrane of neurons is formed by a double layer of phospholipids. This layer, the cell's boundary with the external environment, houses the neuroreceptors, responsible for transmitting information between neurons. It was noted that phospholipase A2 was reduced in the brain, and that this decrease related to the intensity of brain injury; the lower the level of enzyme, the greater the occurrence of senile plaques. A link was discovered between reduced PLA2 in the brain and in the blood. The presence of PLA2 in the blood allows extrapolations to activity in the brain. A potential biomarker for Alzheimer's disease had been found. Cássio Bottino, another researcher on the team, tested a potential genetic marker, the E4 allele of apolipoprotein E, located in chromosome 19 (Table 3). E4 is one of the three forms of the gene that encodes apolipoprotein E (ApoE4); the other two genes encode the E2 and E3 alleles. ApoE is a plasma protein related to transporting cholesterol to the liver, brain and other tissues. In blood testing for E4 allele, 20 control patients (healthy older individuals), 41 patients with Alzheimer's and 21 with mild cognitive impairment (MCI) were analyzed. In this study, Bottino et al. (2002) discovered rates that indicate that older people with E4 allele have 2.4 times more risk of developing Alzheimer's disease.

In addition to the genetic and enzymatic strategy, researchers from the University of São Paulo (USP), São Paulo State University (UNESP) and Rio de Janeiro Federal University (UFRJ) are currently seeking also to discover chemical compounds that act to prevent the formation of and/or destroy amyloid plaques. In recent studies at UFRJ, biochemist Sérgio Ferreira (ZORZETTO, 2004) identified nine substances, some of them produced by the body itself (such as melatonin and taurine) that, in laboratory tests, delayed or even blocked the neuron elimination process. At the UNESP campus in Araraquara, the team of pharmacist Vanderlan da Silva Bolzani extracted from *Senna spectabilis*, a tree up to 6m tall with green leaves and yellow-gold flowers, known as whitebark senna, a substance called spectaline, whose derivatives act against Alzheimer's. Three compounds derived from spectaline prevent the destruction of a substance responsible for communication between neurons and the neurotransmitter

acetylcholine, associated with the formation of memory, thus increasing the amount of acetylcholine in the nervous system by inactivating acetylcholinesterase. The advantage is that these compounds are not toxic like tacrine and rivastigmine, two of the drugs still used to fight damage caused by Alzheimer's. As they act on the acetylcholinesterase enzyme that degrades acetylcholine, spectaline and its derivatives may also aid in treating other neurological diseases, such as Parkinson's disease.

Taurine, essential for the absorption of fat by the intestine, acts in the nervous system like an antidote against the effects of the beta-amyloid peptide, which in very low amounts apparently stimulates the growth of neurons, but in Alzheimer's disease is produced uncontrollably, causing damage to thousands of nerve cells. Generated by the normal degradation of an important protein for the functioning of neurons, amyloid precursor protein (APP), beta-amyloid peptide binds to other molecules equal to it, outside the cells. Near spherical aggregates, called oligomers, are initially formed, followed by long strands known as amyloid fibers. In contact with the outer surface of nerve cells, beta-amyloid fibers bind with various proteins, one of them in particular, the glutamate receptor, associated with learning and memory formation. This binding causes the opening of small channels in the walls of the neurons and allows the entrance in these cells of Ca^{+2} ions (of positive electric charge). This large amount of positive particles alters for an extended period the electric charge inside the neurons, causing their death. In new experiments, UFRJ researchers performed a series of laboratory tests with retina neurons from chicks, grown in small glass dishes (ZORZETTO, 2004). In neurons treated with small doses of taurine, the toxic effects of beta-amyloid eliminated only 15% of nerve cells, while 65% of neurons that did not receive the taurine amino acid died. Such protective action was also observed when replacing taurine with a drug used to combat epilepsy, phenobarbital, which has the disadvantage of causing dependence and undesirable effects, such as drowsiness and mental confusion. The UFRJ team showed that taurine is not the only alternative to offset the imbalance of electric charges generated by beta-amyloid. The hormone melatonin, responsible for the induction of sleep, released mainly at night by the pineal gland, also prevents the death of neurons by acting in a manner similar to taurine. The team from UFRJ also demonstrated that two organic compounds, 2,4-dinitrophenol (DNP) and 3-nitrophenol, prevent neuron death by blocking the formation of beta-amyloid fibers or even by undoing them after they are formed. Rio de Janeiro Federal University (UFRJ) licensed in the Unites States the patent to use the product 2,4-dinitrophenol, whose license was given to the Brazilian pharmaceutical laboratory Eurofarma to test the compound's toxicity in animals.

In a project within the Biota-FAPESP Program, researchers from UFRJ, Rio de Janeiro, and UNESP, São Paulo, have already isolated more than 150 plant substances, among them spectaline and its derivatives, which showed very specific action in laboratory experiments and tests with rats. In the nervous system, two spectaline derivatives prevent the elimination of acetylcholine by inactivating acetylcholinesterase, consequently improving the ability to retain information without interacting with other substances of the central nervous system, a mechanism similar to that of another natural compound, galantamine, isolated from *Galanthus nivalis*, a plant up to 1m tall with white flowers, nowadays used in the treatment of Alzheimer's. In the rest of the body, the molecules of *Senna spectabilis* (spectaline) act as a potent analgesic. Most interestingly, in addition to improving the memory, spectaline derivatives are not toxic like tacrine, the drug most commonly used in the treatment of Alzheimer's. Recently, the Unesp team obtained the provisional patent registration of all spectaline derivatives in Brazil. The teams are now working on the development of a drug based on spectaline derivatives that can be tested in humans. The aforementioned information was extracted from the report by Zorzetto (2004).

Wolfe (2005) describes as a first step in the formation of β-amyloid the action of protease β-secretase, a protease that cleaves and releases most of the APP protein close to the outer cell membrane. The APP protein crosses the cell membrane, with most of it remaining outside the cell, while the rest is internal. According to Wolfe (2005), in 1999, five different groups of researchers discovered the enzyme β-secretase, which is particularly abundant in brain neurons. Although β-secretase is tightly bound to the membrane, it closely resembles a set of proteases found in aqueous environments inside and outside cells. Members of this set of proteases use aspartic acid to catalyze the lytic reaction of proteins. Enzymes from the aspartic protease family that employ a pair of aspartic acid to activate the water molecule in the hydrolysis reaction. Because β-secretase fits into this family, researchers were able to figure out how to inactivate it. Its previously known three-dimensional structure was used as a guide for the computerized design of potentially inhibitory drugs. Genetic studies suggest that blocking enzyme activity will not cause harmful side effects; turning off the β-secretase encoding gene allowed the elimination of β-amyloid formation in the brain of rodents without any apparent negative consequence. Until 2006, these inhibitors were not ready for clinical trials. The biggest challenge is to develop potent compounds small enough to penetrate the brain. Unlike blood vessels in other parts of the human body, brain capillaries are lined with very long endothelial cells. As there is little space between cells, protease inhibitors must be able to pass through the cell membrane to reach the posterior brain tissues, and most large molecules cannot overcome this blood-brain barrier.

The enzyme known as gamma-secretase (γ-secretase) executes the next step in the formation of β-amyloid. This second protease performs the rare feat of using water to hydrolyze the protein within the normally hydrophobic environment of the cell membrane. Still according to Wolfe (2005), in 1998, Dart De Strooper, from the Catholic University of Louvain, found that deleting the gene that encodes presenilin in mice largely reduces the hydrolysis of APP by γ-secretase, demonstrating that presenilin is essential to the hydrolytic function of γ-secretase. Then, in his own laboratory, Wolfe discovered that compounds of the same chemical category as classic inhibitors of aspartyl proteases could block APP cleavage by γ-secretase in cells. This result suggested that the γ-secretase contains an essential aspartic acid pair to catalyze protein hydrolysis. Specifically, γ-secretase cleaves a cell surface protein called Notch which, released from the membrane into the cell, sends a signal to the nucleus that controls the cell's fate. High doses of γ-secretase inhibitors cause severe toxic effects in mice because of the interruption of the Notch signal, which has raised fears concerning the application of this potential treatment. However, a drug candidate developed by pharmaceutical company Eli Lilly has passed safety tests on volunteers. The compound is about to enter the next level of testing in patients with early Alzheimer's.

In addition, researchers have identified molecules that adjust γ-secretase so that β-amyloid production is blocked without affecting Notch protein cleavage. Such molecules do not interact with aspartic acid; rather, they bind to another point of the enzyme and change its shape. One of these drugs, Flurizan, identified by a team from the University of California at San Diego and Mayo Clinic (USA), has proven to be very promising in patients in the early stages of Alzheimer's and is already entering the stage of more advanced clinical trials in the United States, which will include more than 1,000 people.

Another strategy to fight the disease is to rid the brain of the toxic clusters of β-amyloid after the peptide is produced. One approach is active immunization, which involves recruiting the patient's own immune system to attack the protein. In 1999, Dale Schenk and his colleagues at Elan Corporation made a pioneering discovery: the injection of β-amyloid in mice genetically engineered to develop amyloid plaques stimulated an immune response that prevented plaque formation in the brains of young animals, and cleared existing plaques in older ones. The rodents produced antibodies that recognized β-amyloid and apparently stimulated the immune cells of the brain, microglia, to attack the peptide clusters. In mice there was improvement in learning and memory, which led to initial human trials. Unfortunately, although the β-amyloid (Aβ) injection passed the initial safety tests, several patients developed encephalitis, inflammation in the brain, which led to early termination of the study in 2002. Follow-up research indicated that treatment may have caused inflammation by stimulating the T cells of the immune system, which are excessively aggressive to amyloid deposits.

However, the research confirmed that many patients produced antibodies against Aβ, and those who did so showed subtle signs of improved memory and cognition. Safety concerns with active immunization led some researchers to attempt passive immunization, which aims to eliminate the Aβ peptide by injecting patients with antibodies. Produced in guinea-pig cells and genetically engineered to prevent rejection in humans, these antibodies would hardly cause encephalitis, as they would not trigger a damaging T-cell response in the brain. A passive immunization treatment developed by Elan Corporation has already made progress with clinical trials in humans. How active or passive immunization removes Aβ from the brain is somewhat of a mystery, because it is unclear how these antibodies can cross the blood-brain barrier.

Some evidence suggests that brain entry might not even be necessary: perhaps the absorption of Aβ in the rest of the body causes an exodus of the brain peptide, since molecules tend to move from high to low concentrations. Although passive immunization appears to be more promising at the moment, active immunization has not yet been ruled out. Preliminary studies by Cynthia Lemere at Harvard have shown that immunization with selected parts of Aβ, rather than using the entire peptide, may stimulate antibody production by B cells of the immune system, without activating the T cells responsible for encephalitis.

Other researchers are testing non-immunological strategies to prevent Aβ agglutination. Some compounds interact directly with the protein to keep it dissolved in the fluid outside the brain neurons, preventing the formation of noxious clusters. The company Neurochem in Quebec, Canada, is developing the compound Alzhemed, a small molecule that apparently mimics heparin, an anticoagulant that prevents platelets from forming clots, but when bound to Aβ makes the peptide more prone to form deposits. As Alzhemed binds to these same Aβ points, it blocks the activity of heparin, thus reducing agglutination. The Alzhemed compound showed little or no toxicity even at high dosages, and treatment led to some cognitive improvement in patients with moderate Alzheimer's. Phase 3 clinical trials for this drug are well under way.

Still According to Wolfe (2005), Aβ is only half of the Alzheimer's equation. The other half, filaments of tau, a protein that causes neural tangles, is considered a promising target to prevent degeneration of brain neurons. Researchers are focusing on finding inhibitors capable of blocking kinases that fix an excessive amount of phosphates in the tau protein, which is an essential step for the activity of the secretases responsible for the formation of tangles.

An exciting recent breakthrough involves cell therapy. Mark Tuszynski and colleagues at the University of California in San Diego conducted skin biopsies of patients with mild Alzheimer's and inserted in the skin the encoding gene for neural growth factor (NGF). The genetically engineered cells were then surgically introduced into the brains of those patients. The idea was for them to produce and secrete NGF, which would compensate for the loss of acetylcholine-producing neurons and improve memory. Cell-based therapy was a clever strategy to distribute NGF, a high-molecular-weight protein, which would not otherwise be able to penetrate the brain. The results were good enough to warrant additional clinical trials. While some of these potential therapies have not paid off, scientists hope to find at least one agent that can effectively slow down or interrupt the gradual loss of neurons in the brain, a breakthrough that would save millions of people from the inexorable decline caused by Alzheimer's disease and pave the way for drugs to regenerate lost mental functions.

In a recent report, Guimarães (2008) describes the speed with which common proteins in the brain take on an anomalous structure and become entangled, forming complexes that are highly detrimental to neurons. The speed surprised American researchers, who used a special microscope (multiphoton) capable of monitoring in real time the deposition of amyloid plaques in live mice. These Aβ images play a central role in Alzheimer's, but there is controversy. There are people who die with Alzheimer's disease symptoms and do not have plaques in the brain, and many have plaques in the brain but do not develop the disease. According to Sérgio Ferreira, a biochemist at UFRJ, "In the vicinity of the plaques are other Aβ aggregates not visible with the use of most analysis techniques." He believes they are the villains; in fact, plaques indicate an excess of protein in the intricacies of the brain. Up to now, medicine has limited itself to delaying the loss of cognition without, however, delaying or eliminating the formation of the different Aβ aggregates.

American biologist Mark Mattson, one of the world's leading researchers in aging-related dementia, believes that the nuclear factor kappa-β protein (NF-kβ) protects the brain against the loss of neurons occurring in old age. At normal levels, the protein induces the brain to recruit protective substances. However, in the imbalance caused by excess β-amyloid, NF-kβ ends up activating genes linked to cell death. Intrigued by these biological responses, researchers from USP-SP, UFRJ-Rio and PUC-RS began to study possible mechanisms that could explain this behavior. To communicate with the interior of cells, Aβ surrounding neurons sends signals through N-methyl-D-aspartic (NMDA) receptors. The receptors activate NF-kβ, which migrates to the cell nucleus and therein influences genetic activity. This finding was essential for suggesting a way to block the signaling pathway triggered by Aβ that leads to cell death, i.e., block the receptors. Sérgio Ferreira and Fernanda De Felice (UFRJ) followed the lead of how to interfere with the signaling. One of the possibilities is the amino acid taurine, which exists in high levels in the young brain. Such levels fall with aging and Alzheimer's. Ferreira showed that taurine, present in energy drinks, protects neurons against the toxicity of Aβ. According to Ferreira, taurine acts as an antidote to N-methyl-D-aspartic activation. The brain's defense mechanisms against Aβ are not restricted to the production of NF-kβ. Researchers have detected gene activity in the brain that produces higher than expected brain-derived neurotrophic factor (BDNF) compared to other parts of the brain. Pharmacologist Iván Izquierdo, from the Catholic University of Rio Grande do Sul (PUC-RS), had already shown that this protein (BDNF) is essential for memory retention. The research team at USP-SP now reinforce its relationship with Alzheimer's. In brain regions sensitive to Alzheimer's disease, such as the hippocampus and prefrontal cortex, NF-kβ inhibits production of the neurotrophic factor. The exact opposite happens in the cerebellum, suggesting that the cerebellum is able to produce this protein (NF-kβ) by other means.

The findings favor the idea that protein loss is linked to the onset of Alzheimer's. The brain areas in which NF-kβ is most effective in inhibiting the production of the protective substance, the prefrontal cortex and the hippocampus, are responsible, respectively, for processing complex behaviors and for memory storage, capacities that are gradually lost by patients with AD. Izquierdo (2011) proved that injecting the brain-derived neurotrophic factor (BDNF) in the hippocampus is sufficient to restore to rats memory they had lost due to a deficiency in protein production. In addition, this factor promotes the growth of communication points between neurons (synapses). At high doses it can give rise to tumors. There are substances in the brain that protect cells and others that attack them. Researchers understand that as much as they discover the biochemical pathways, disrupting them can have adverse and serious effects. NF-kβ, for example, can promote or prevent cell death, depending on its levels and the region in which it is found.

Researchers from different areas seem to agree on one point: in order to balance the biochemical pathways, the safest answer seems not to be in drugs that alter proteins levels, but in diet. Calorie restriction, the only procedure that science has ever proven to prolong the life of laboratory animals, seems to shut down genes which trigger inflammatory processes. It also increases the levels of neurotrophic factor and WNT protein activity. WNT is yet another substance of variable action: in small doses it prevents the formation of Aβ plaques and can give rise to cancer when more abundant. When testing the effects of calorie restriction in rats aged 4 and 24 months, during one month, alternating periods of 24h

fasting and 24h *ad libitum,* the following was observed: in the younger mice, corresponding to adult humans aged about 30 years, calorie restriction reduced experimentally-induced inflammation in the hippocampus and increased the concentration of brain-derived neurotrophic factor (BDNF), a protein that protects neurons and promotes memory formation. Calorie restriction in older rats that did not diet when young causes oxidative stress, which along with inflammatory processes ends up causing brain cell death. Perhaps restriction should be constant throughout life, or a calorie restriction level suitable for advanced ages must be found. Strict diets impose physiological stress that may be excessive in old age. In young people, in turn, stress can strengthen the body. For example, it seems to be useless to begin a diet to avoid brain degeneration in middle age. In an increasing aging population, it is essential to take care of health from the origin of life.

Recently, a team of researchers from São Paulo (FM-USP) and Germany identified the brain region where the first lesions of the most common neurodegenerative disease among older adults appear (PIVETTA, 2008). According to the researchers, Alzheimer's begins in the brainstem, more specifically in an area called the dorsal raphe nucleus (Figure 5), and not in the cortex, which is the center of information processing and memory storage, as medicine traditionally postulates. This idea is defended by Brazilian scientists in partnership with colleagues from three German universities. The study's conclusion is based on the brain autopsy of 118 people, whose average age was 75 at the time of death. The researchers identified lesions in the dorsal raphe nucleus in eight older individuals who had no tangles in any other part of the brain. While all 80 individuals already had at least one tangle in the entorhinal cortex a region traditionally considered the first to be affected by Alzheimer's. Responsible for connecting the cortex to the spinal cord, the stem is not strictly part of the brain, but of the encephalon, which comprises brain, cerebellum and stem. Clinically, prior to autopsy it is impossible to be 100% sure that an older person suffers from Alzheimer's, especially at the beginning of the process of cognition loss. Not everyone who forgets things, whether older or not, necessarily has Alzheimer's disease or some other type of dementia.

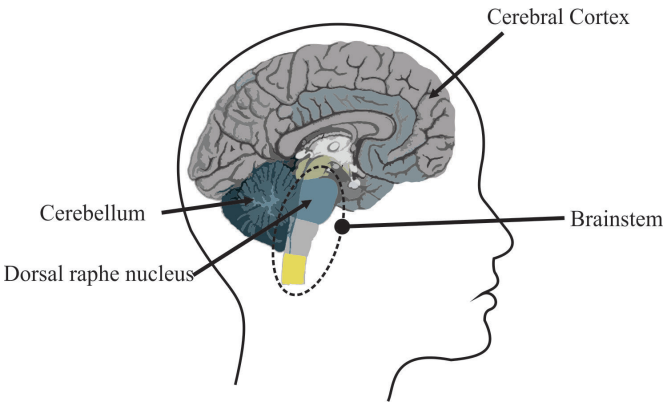

Figure 5. Illustration of cerebral cortex, cerebellum, and brainstem with dorsal raphe nucleus.

Seeking the cure for Alzheimer's disease is an extremely noble ambition for medical research. However, in the short term it may be more realistic to think of ways to slow down the progress of brain injuries leading to Alzheimer's and prevent as much as possible the appearance of cognitive problems that gradually reduce the quality of life of patients. Details of the latest research on Alzheimer's mentioned above can be found in recent publications (MARTINS et al., 2005; MORI et al., 2008; ANDRADE-MORAES et al., 2013; LOURENÇO et al., 2013; BALTHAZAR et al., 2014).

Another multifunctional substance under study is bradykinin, a natural peptide with vasodilation action, thus an adjuvant in antihypertensive action. Bradykinin is found in the blood and other body tissues and released in higher levels in inflammation. Discovered around the mid-20th century by Brazilian researchers, it now draws renewed attention for effects heretofore unimagined. Studies carried out in recent years have shown that bradykinin induces stem cells to transform into neurons and protects them from death in brain lesions. In adipose tissue, another line of work suggests that it regulates the release of the hormone leptin, which induces satiety and reduces fat accumulation. The hypothesis that bradykinin could have effects beyond lowering blood pressure and controlling localized inflammation, the body's natural response to injury, arose in the mid-1990s with research by the biochemist Alexander Henning Ulrich at the University of Hamburg, Germany. Ulrich investigated the mechanisms of proliferation of neural tissue tumors and observed that bradykinin triggered certain signaling mechanisms in these cells. From 2002, as professor at the Institute of Chemistry of USP-SP, he resumed study on this role of bradykinin. He found that when binding to the B2 receptor on the surface of the stem cell, bradykinin triggers a chain of chemical reactions that modify the intracellular environment. Small pockets release calcium ions into the cytoplasm, causing oscillations in Ca^{2+} levels, which can increase from 10 to 100 times. These ions function as a code that activates certain groups of genes in the nucleus and defines the fate of the stem cell: to continue multiplying and preserve its potential to originate different cell types, or to specialize in a certain function. The researchers observed that in the natural process of differentiation, the number of bradykinin receptors increases gradually. In addition, cells release to the external environment part of the bradykinin they manufacture, influencing the functioning of their neighbors. This results in the emergence of neurons sensitive to the neurotransmitter acetylcholine,

a chemical messenger that carries information from one brain cell to another, as detailed by Martins et al. (2005). According to the researchers, bradykinin does not initiate cell differentiation, but defines the pathways that cells will follow. In the presence of bradykinin, up to 30% more neurons than normal are formed, and a much smaller number of glial cells (astrocytes, oligodendrocytes). Neuron production was even greater when a compound called captopril was added to the stem cells in differentiation. This is the first antihypertensive drug to indirectly act in the preservation of bradykinin, keeping it active longer, through the inhibition of the enzyme that converts angiotensin I into angiotensin II (ACE), by captopril.

A greater production of neurons may be interesting in some situations. In addition to helping understand the brain's specific ability to recover from injury, there is the chance that by controlling the formation of neurons from stem cells, it may be possible to replace dead cells in cases of neurodegenerative diseases such as Parkinson's and Alzheimer's. Experiments with animals have shown that neuronal replacement was not the only beneficial effect of bradykinin on the central nervous system. Recent tests indicate that bradykinin can prevent the death of neurons in ischemia, an interruption of oxygen and nutrient flow caused by clogged blood vessels. Rats were treated with N-methyl-D-aspartic in the brain region that reproduces damage by ischemia. This compound, better known as NMDA, causes a torrent of calcium to enter the cells at 1,000 times the normal rate, killing them. Mediation of neuronal activity showed that 80% of hippocampal cells died after NMDA administration, while the cell death rate dropped to 20% when, in addition to NMDA, the hippocampus also received bradykinin.

By different mechanisms it was verified that bradykinin influences the body's energy consumption. Direct action of bradykinin on energy metabolism was identified when a type of transgenic mouse fattened less than common mice. The difference between the two groups of rodents is that the transgenic animals did not have in their cells the B1 receptor, to which a byproduct of bradykinin binds and triggers phenomena typical of inflammation. Animals without the B1 receptor were more sensitive to the hormone leptin, according to Mori et al. (2008). This hormone induces satiety and increases the body's energy consumption. Elimination of B1 receptor apparently induces cells to produce more B2 receptor, to which bradykinin binds, suggesting that it regulates sensitivity to leptin. Although the synthetic form of bradykinin has existed for almost half a century, it has not been approved for use in humans for having caused, in some studies, serious undesirable effects such as significant cerebral edema and low blood pressure. The hope of the researchers is to obtain an analogous molecule of bradykinin that causes fewer side effects and is also neuroprotective.

A few atypical cases have been reported in recent years. People over the age of 80 with a load of amyloid plaques characteristic of people with Alzheimer's disease and who did not present, in the last few years of life, the characteristic loss of memory, cognition and lucidity of Alzheimer's patients (ZOLNERKEVIC, 2014). Samples of those brains donated to the USP-SP encephalon bank were analyzed under a microscope and revealed plaque clusters and protein tangles, hallmarks of the advanced stages of Alzheimer's disease. The researchers could not understand at the time why those people did not develop dementia. In dementia there is a drastic reduction of neurons in the hippocampus and cortex, the brain regions responsible for memory consolidation and reasoning. On average, one in 10 people over the age of 65 has the clinical signs of Alzheimer's. The disease first manifests itself with small slips of memory, which over time become more frequent, followed by failure in moral judgment, in perception of space and time, and increased difficulty in communicating. Average survival time is eight years, during which the symptoms worsen until total incapacitation.

It has been known for quite some time that dementia is caused by the destruction of synapses, the trillions of connections between the 86 billion neurons, the brain cells that store and transmit information from which memories and thoughts emerge. A healthy neuron receives up to 10,000 synapses from other neurons, exchanging electrical signals and substances that keep it alive. In Alzheimer's, neurons prevented from maintaining synapses atrophy and die. As a consequence, hippocampal volume and cortex thickness decrease, which can be seen in magnetic resonance imaging (MRI). According to Márcio Balthazar, a neurologist who treats people with Alzheimer's at the Unicamp hospital, neuroimaging can help diagnose the disease, but cannot yet replace laboratory, clinical and psychological tests. In partnership with neurologist Fernando Cendes, also from Unicamp, researchers have been perfecting a new way of early identification of Alzheimer's disease: the use of neuroimaging to evaluate brain activity, and not just anatomy. The technique is to observe brain activity in functional magnetic resonance imaging (fMRI), when patients are relaxed, not thinking of anything. Even when people are resting, some areas of the brain are activated simultaneously, pulsating at the same frequency, which suggests that groups of neurons are communicating. This network is less active in a person with Alzheimer's (BALTHAZAR et al., 2014). The Unicamp group was able to distinguish with about 70% accuracy the images of brain activity in resting people with moderate symptoms of dementia, typical of healthy older people. The researchers also observed a relationship between network connection failures and degree of memory loss. According to Balthazar et al. (2014), the earlier the diagnosis is more effective the interventions that relieve symptoms; use of acetylcholinesterase inhibitors and practice of

occupational therapy, psychological rehabilitation and physical activity, as well as family planning for the future.

Autopsy of brain tissue reveals an excess of so-called neuritic plaques, anchored in ramifications of neurons and neurofibrillary tangles within the atrophied neurons. These signs are especially found in the hippocampus and in the cerebral cortex. Until a few years ago, most researchers believed that neuritic plaques were responsible for synaptic dysfunctions. However, recent studies by the team of neuroscientist Fernanda De Felice and biochemist Sérgio Ferreira (UFRJ) have shown that the plaques, although toxic, are not the main cause of the elimination of synapses and neuron death. In fact, the plaques are formed by the accumulation of small β-amyloid molecules. Usually produced by the brain, this protein is deformed in Alzheimer's disease. Many researchers today believe that clusters of molecules much smaller than β-amyloid (the oligomers), capable of diffusing into and out of neurons, are actually responsible for interfering with synapses. Further research suggests that these oligomers also form the neurofibrillary tangles which prevent the transport of substances within neurons and contribute to their death. According to this line of reasoning, plaque formation would be an attempt by the organism to remove the oligomers from the cells and away from the synapses.

The discovery of asymptomatic Alzheimer's disease patients reinforced this hypothesis. The first descriptions of such cases came from studies in the United States that monitored hundreds of older people. Comparison of the clinical exams to which they were periodically submitted together with analysis of their brains after death revealed that 25% to 40% of the cases diagnosed as Alzheimer's had not developed dementia. Asymptomatic individuals must possess some unknown physiological mechanism that protects their neuron networks from the effects of oligomers, something that removes the oligomers from the synapses by rapidly aggregating them into plaques. One factor to explain this mechanism is the more efficient performance of insulin in the brain of asymptomatic patients. Unlike what occurs in other organs, the role of insulin in the brain seems not to be control of glucose metabolism, but memory consolidation and formation of new synapses.

In vitro and animal experiments by Fernanda De Felice and Sérgio Ferreira have shown that insulin protects neurons from the action of oligomers (LOURENÇO et al., 2013). In this work the authors presented new neuronal mechanisms that cause loss of synapses in mice and monkeys similar to Alzheimer's. The study also showed that a drug used to treat type 2 diabetes (liraglutide) blocked neuronal damage in Alzheimer's animal models. Currently, a team from Imperial College London is testing liraglutide in 200 people with Alzheimer's. Another hypothesis is that asymptomatic patients have a greater cognitive reserve, perhaps resulting from a more complex synapsis network compared to individuals who develop dementia. This reserve would be more resistant to the effects of oligomers. This idea comes from the observation that asymptomatic patients are usually people with a higher level of education or who learned to speak and write early in childhood. At Unicamp, Balthazar is attempting to confirm the protective effect of the cognitive reserve by comparing the connectivity of neural networks in older patients with different levels of education, reading habits and social life.

Recent research (POLO-HERNANDEZ et al., 2014; ASTARITA et al., 2011; HAMILTON et al., 2015) has focused on the importance of oleic acid in the modulation mechanism of neural stem cell (NSC) transformation in neurons, neuron migration and synapse formation.

Polo-Hernandez et al. (2014) suggest that oleic acid functions as a neurotrophic factor that regulates the final stage of neuronal differentiation, but also promotes the migration of neurons, presumably to help them reach their definitive sites in brain structures. In addition to this function, oleic acid promotes the formation of synapses by stimulating the expression of pre- and post-synaptic proteins and their approximation. That confirms the role of oleic acid in postnatal brain development as an important factor in bidirectional astrocyte-neuron communication, enabling the formation of the final network that makes up the nervous tissue. It is interesting that the effect of oleic acid on neuron growth has been used experimentally in bone marrow repair, as described by the Taylor group (AVILA-MARTIN et al., 2011), who reported the early recovery of voluntary motor function in rats with spinal cord injury following treatment with albumin-oleic acid. Some lines of evidence have shown the occurrence of increased expression of the enzyme stearoyl-CoA-desaturase (SCD) in AD (ASTARITA et al., 2011).

Hamilton et al. (2015) identified a focus of lipid metabolism deregulation as a blocking mechanism in the reproduction of neural stem cells (NSC), resulting from Alzheimer's disease (AD). The authors demonstrated that interference in the signaling or synthesis of oleic acid blocked the proliferation of neural stem cells (NSC) in mouse models for AD. In the brain (postmortem) of patients with AD and triple transgenic mouse models for AD (3xTg-AD) they found an accumulation of neutral lipids in ependymal cells, the main support cells in the frontal brain for brain stem cells. Mass spectrometry and micro-array analyses identified triglyceride deposits enriched with metabolized oleic acid at this specific focus, unrelated to a defect in peripheral metabolism. In wild-type mice they observed that a localized increase of oleic acid was sufficient to reproduce the accumulation of triglyceride on ependymal cells and to inhibit the proliferation of NSCs. The study supports a pathogenic mechanism by which the disorder of the localized lipid metabolism, due to AD, inhibits homeostasis and normal neural stem cell (NSC) function.

Animal models have been used to study pathogenesis in degenerative diseases, but no particular model has been able to reveal all pathological changes in patients with AD. Therefore, extensive validation of therapeutic targets in different models will be indispensable before clinical research can advance. In recent research, Huang et al. (2015) determined that the absence of G-protein coupled receptor 3 (GPR3), a protein expressed in the brain, relieved cognitive deficits and reduced amyloid pathology in four different models for the study of AD, in mice. In addition, high levels of GPR3 were found in postmortem brain tissues in AD patients. The study revealed that deletion of GPR3 resulted in a significant reduction of amyloid plaques in APP/PS1 and $APP^{NL-F/NL-F}$ transgenic mice. This study showed that GPR3 protein is a potential therapeutic target for AD and provides the necessary validation for the future development of GPR3 modulators.

A potential alternative for AD control is presented by Leinenga and Götz (2015), using a mouse model for AD treated with repeated ultrasound scanning (USS). They observed an opening of the blood-brain barrier (BBB) involving extensive βA internalization in lysosomes of activated neuroglia in animals submitted to USS treatment, with a parallel increase in the number of microglia and a significant decrease of βA plaques in 75% of the treated animals. These same animals also showed improved performance in memory tests. The authors suggest that this type of study should be repeated in other animal models, since it represents a noninvasive form with therapeutic potential for AD.

While the aforementioned studies follow genetic, chemical, biochemical, immunological and pharmacological approaches in an attempt to delay and/or block the progress of Alzheimer's disease, scientists and researchers in the area of food and nutrition seek to find bioactive substances that, as part of the normal diet, are able to act on human metabolism, slowing the aging process and the manifestation of chronic diseases, particularly those affecting the central nervous system, causing dementias such as Alzheimer's and other neuropathologies. Zhang (2007) briefly describes the multifunctional properties of some naturally occurring phenolic compounds in foods, potentially capable of reducing the risk of Alzheimer's disease, such as: green tea, which contains epigallocatechin gallate (EGCG), able to inhibit the clustering of β-amyloid (Aβ), inhibit β-secretase and monoamine oxidase, activate α-secretase, able to chelate metabolic ions and sequester oxygen free radicals (ROS); red wine (resveratrol), which inhibits cyclooxygenase-1 and monoamine oxidase A enzymes, reduces cyclooxygenase-2, mitigates the formation of βA and sequesters reactive O_2 species (ROS); virgin olive oil, which contains (-) oleocanthal that inhibits cyclooxygenase-1 and cyclooxygenase-2 and sequesters ROS; oleuropein, which binds to β-amyloid and sequesters ROS; saffron (curcumin), which inhibits βA clustering, stimulates metal ion chelation and sequesters ROS. The structures of the multipotent anti-DA agents are diverse, yet they are all polyphenols. The multifunctionality of polyphenols is probably due to the following facts: 1) phenolic hydroxyls can act as hydrogen acceptors and H donors simultaneously, which helps their binding to target proteins; 2) phenolic hydroxyls are the most potent structures in radical sequestration through the donation of the H atom; 3) phenolic hydroxyls are good transition metal ion chelators; 4) the aromaticity of phenol rings helps to inhibit the formation of βA fibrils (ZHANG, 2006).

Data from the literature accumulated to date show that several anti-AD agents have been identified from foods, with most showing pharmacological effects. However, it should be borne in mind that the anti-Alzheimer potential identified *in vitro* is not necessarily reproduced *in vivo*, because factors such as bioavailability and interactivity may influence the behavior of these agents. It has been shown that the polyphenols herein studied are bioavailable and can penetrate the blood-brain barrier (BBB), at least in animal research models (BREUER et al., 2006; LIN et al., 2007). Sakamoto et al. (2007) describe the effects of supplementing the diet of adult gerbils with DHA and uridine monophosphate (UMP), which increased the density of spinal dendrites in the hippocampus of these animals and of phosphatides in neuronal membranes. DHA, polyunsaturated omega-3 fatty acid, is an essential component for the formation of phosphatides in membranes and has been recognized as essential in cognitive functions. Low levels of DHA in the blood or brain have been associated with various neurocognitive disorders, including Alzheimer's disease, in animal models. Animal models for the study of AD exhibit superior cognitive ability when receiving a diet enriched with DHA. In addition to the behavioral effect, cell membrane fluidity and apoptosis inhibition increase. In the abovementioned work, the authors demonstrated that DHA supplementation substantially increased the number of spinal dendrites in the hippocampus of adult gerbils, particularly when the animals were also supplemented with a source of uridine monophosphate (UMP), which caused an increase in brain levels of CTP, cytosine triphosphate, which modulates the synthesis of phosphatide in the brain. It has been concluded that orally administered DHA stimulates membrane synthesis and increases the number of synapses, especially when administered together with UMP (uridine monophosphate).

Research published by several authors confirm previous findings that uridine can positively affect phosphatide synthesis in neuron membranes (CANSEV et al., 2005; CANSEV, 2006). Uridine, a pyrimidine nucleoside, crosses the blood-brain barrier (BBB) easily, being a precursor of UTP and CTP (CANSEV et al., 2005; CANSEV, 2006). CTP, cytosine triphosphate, is the immediate and limiting

precursor in the synthesis of phosphatides (PC, PE, PS, and PI), which constitute neuron membranes. In brain cells, CTP reacts with phosphocholine and phosphoethanolamine to form CDP-choline and CDP-ethanolamine. These two products react with diacylglycerol (DAG) to form phosphatidylcholine (PC) and phosphatidylethanolamine (PE), respectively; CTP can also react directly with DAG to form CDP-DAG (cytidine phosphate-diacylglycerol) which then reacts with inositol to form phosphatidyl inositol (PI); phosphatidylserine is synthesized primarily through a base exchange mechanism in which the free serine replaces the nitrogenous base in the phosphatide. These metabolic processes may be limited by the availability of CTP or the percentage of DAG, represented by a particular species.

The effect on phosphatide synthesis in the formation of DAG, containing DHA, is maximized under conditions where there is also uridine administration, which further elevates CTP levels. The work of Sakamoto et al. (2007) demonstrates that the effect of oral administration on membrane synthesis and formation is substantially enhanced by UMP supplementation (as a source of uridine). Several psychiatric and neurological disorders such as schizophrenia, mental retardation syndromes and Alzheimer's disease (AD) are accompanied by subnormal numbers of brain synapses or dendritic spines (BLANPIED; EHLERS, 2004). Oral administration of DHA and uridine can be used to offset the loss of synapses in these disorders. Studies in animal models of Alzheimer's have demonstrated that the administration of DHA can improve their cognitive performance (HASHIMOTO et al., 2006). Holguin et al. (2008) published results of a research along the same lines as that of Sakamoto et al. (2007). They used gerbils as experimental animal and the following supplementation: UMP, 0.5%, choline, 0.1% via diet, and DHA, 300mg/kg/day by gavage for 4 weeks, continuing with the same treatment during training and trails.

As previously demonstrated, when the three compounds were administered there was a significant increase ($\rho<0.001$) in the brain content of total phospholipids and in the major phosphatide, phosphatidylcholine (PC). In the administration of single DHA or UMP, a lower phosphatide increase was observed. Uridine probably acts on the generation of both CTP and UTP, which activate P_2Y receptors coupled with neurite outgrowth and protein synthesis. These findings showed that treatments that increase the content of synaptic membranes may enhance cognitive functions in animal trials.

In January 2008, Patent no. US2008/0009Y67A1 was published, submitted by Henderson (2008), relating to therapeutic agents for treatment of Alzheimer's disease, mild cognitive disorder, and other diseases associated with reduction of neuronal metabolism, including Parkinson's disease, Huntington's disease and epilepsy, the basic information of which is as follows: Alzheimer's disease (AD) is a neurodegenerative disorder which mainly affects older adults. There are two forms of AD, early incidence and late incidence. The early incidence form is rare, affecting susceptible individuals around the age of 30, and is often associated with mutations of a small group of genes. Late or spontaneous incidence AD is common, affecting people aged 70-80, and is a multifactorial disease with many genetic risk factors. It is estimated that 7-10% of the American population over 65 and 40% aged 80 or over is affected by AD (MCKHANN et al., 1984; EVANS et al., 1989). At the onset of the disease patients suffer from loss of memory and orientation. As the disease progresses, additional cognitive functions become impaired, until complete incapacitation.

At the time this patent was published the cause of AD was unknown; however, a great amount of research has made it evident that AD is associated with a decrease in neuronal metabolism. In 1984, Blass and Zemcov proposed that AD resulted from a decrease in the metabolic intensity of subpopulations of cholinergic neurons. However, it has become clear that AD is not restricted to the cholinergic system, involving many types of transmitter systems and several discrete regions of the brain. Positron emission tomography has revealed low glucose utilization in the brains of patients with AD, and this metabolic disorder can be detected long before the clinical signs of dementia appear (REIMAN et al., 1996; MESSIER; GAGNON, 1996).

In addition, certain cell populations, such as somatostatin producing cells in the cortex of AD brains, are smaller and have reduced Golgi apparatus, both changes indicating decreased metabolic activity (SWAAB et al., 1998). Measurements of brain metabolic activity in healthy subjects, compared to AD patients, demonstrated a 20-40% reduction in glucose metabolism (HOYER, 1992). This decrease leads to a reduction of ATP to critically low levels in Alzheimer's patients. Severe decrease of glucose metabolism correlates with density of senile plaques (MEIER-RUGE et al., 1994). However, aging may aggravate the decrease in energy metabolism in AD. Insulin stimulation in glucose uptake is impaired in older adults, resulting in decreased insulin action and increased insulin resistance. For example, following a glycemic load, the mean increase in plasma glucose ranges from 10-30% in older adults over 65, compared to young people (FINCH; COHEN, 1997).

The human brain develops very high metabolic activity. For example, 20% of total O_2 consumed by the human body is used by the brain in the resting state. A large amount of ATP produced by neurons is used for brain functions, maintenance of electrical potential, synthesis of neurotransmitters, and synaptic remodeling. Brain neurons do not oxidize fatty acids efficiently; therefore, they depend on other organs and cells such as the liver and astrocytes to supply them with medium-chain fatty acids via ketone bodies originating from partial oxidation.

Ketone bodies are produced by the incomplete oxidation of fatty acids and are used to distribute energy throughout the body when glucose levels are low.

Current models propose that the brain only uses ketone bodies (KB) as fuel during special physiological states, such as neonatal development and periods of starvation. Partial oxidation of fatty acids generates D-beta-hydroxybutyrate (D-3-hydroxybutyrate) and acetoacetate, which together with acetone are collectively called ketone bodies (KB). Newborn mammals are dependent on milk for development, with the main source of carbon in milk being fat. Milk fatty acids are partially oxidized to supply ketone bodies that diffuse via the blood throughout the body as a source of energy for neonatal development. Numerous studies have shown that the preferred substrate for brain respiration in newborns is ketone bodies.

Henderson's (2008) invention, which originated the aforementioned Patent, basically consists in the development of some mixtures containing all nutrients required by older adults, some therapeutic agents such as naturally bioactive substances, like: anti-Alzheimer agents, antidiabetes agents, agents capable of increasing the use of lipids as medium-chain triacylglycerols (MCT) and/or medium-chain fatty acids (MCFA), as well as anti-sclerosis, antihypertensive, anti-inflammatory and anti-obesity agents. According to the author of the invention, such compounds would be adjusted in their proportions to act synergistically and preventively in the control of diseases with reduced neuronal metabolism, such as Alzheimer's and mild cognitive disorder. Such mechanisms include, but are not limited to, mitochondrial dysfunction, free radical attack, defective glucose transport and metabolism, imbalance of ionic potential in membranes, calcium influx and efflux dysfunction, and others. Medium-chain triglycerides (MCT) are composed of medium-chain fatty acids of between 5-12 carbons. The diet rich in MCT and/or MCT precursors promotes high levels of ketone bodies in the blood, which provide the energy required for brain cells with compromised glucose metabolism through rapid oxidation of medium-chain fatty acids (MCFA) in ketone bodies, which replace glucose as a source of metabolic energy.

There is much evidence showing that ketone bodies are used in a concentration-dependent manner, even in older adults. Ketone bodies (KB) offer several advantages over glucose as a memory facilitator in older adults: 1) KB can be artificially increased by the administration of large amounts of medium-chain triglycerides (MCT) or other substances capable of raising ketone body levels without altering glucose levels; 2) hyperketonemia can be induced and maintained for several hours; 3) ketone bodies easily cross the blood-brain barrier; 4) ketone bodies are readily metabolized by brain neurons and can be used to generate ATP and acetylcholine. In all proposed mixtures in the invention, L-carnitine or acetyl-L-carnitine is also used in different proportions.

Fernando et al. (2015) describe in an excellent review article the dietary potential of coconut in the prevention and treatment of AD. It presents recent literature suggesting that coconut oil (particularly extra virgin), coconut water and coconut cream have significant positive effects in lowering plasma cholesterol, blood pressure, and blood glucose control, all factors associated with AD. Coconut oil is very rich in medium-chain fatty acids (approximately 70%), being 48.5% lauric acid (C12) and 18% myristic acid (C14), excellent sources of ketone bodies, essential as a source of metabolic energy in AD. In addition to MCFA, coconut oil (extra virgin) contains phenolic compounds (antioxidants) and hormones (cytokinins) that act to prevent the clustering of βA- peptides, which are important in AD pathogenesis.

Recently, an international randomized controlled trial was described by Scheltens et al. (2010). A total of 225 patients with Alzheimer's who had not taken anti-Alzheimer's drugs participated in the trial. The initial trial lasted 12 weeks. The hypothesis to be tested was that combinations of certain nutrients could result in relevant benefits to patients with Alzheimer's disease. A medicinal food[1] called "Souvenaid" was then developed, which is a beverage containing multinutrients intended to act synergistically to enhance the formation and function of membranes in AD patients All components contained in this medicinal food have a history of safe use in other foods. The aforementioned paper presents results from the first clinical trial evaluating the efficacy, tolerability and safety of a medicinal food designed to restore synapses in the brains of patients with mild Alzheimer's disease. The authors developed a proof-of-concept clinical trial to investigate whether supplementation with the Souvenaid product could affect cognitive functions in Alzheimer's disease (AD). The researchers chose a 12-week study period, based on the very rapid response observed in animal studies (WURTMAN et al., 2006; SAKAMOTO et al., 2007), and chose to study patients with fairly moderate disease, a stage in which such intervention is likely to have the best effect.

The first results were for the "delayed verbal recall" test of the Wechsler Memory Scale-revised (WMS-r), according to Wechsler (1987), which seems to be a sensitive measure for memory episodes (PETERSEN, 1995; HODGES; PATTERSON, 1995) impaired in an early stage; and the 13-item modified Alzheimer's disease cognitive-scale test (ADAS-cog) (MOHS et al., 1997), often viewed as a "gold standard" evaluation tool in intervention studies in Alzheimer's disease. The two formulations tested (Souvenaid and control) are shown in Table 7, which highlights the

[1] Medicinal food (USA): food formulated to be enterally consumed under supervision.

ingredients and respective amounts used as reinforcement (Fortasyn Connect) in the Souvenaid medicinal product, developed by the authors of the international consortium, whose results were reported by Scheltens et al. (2010). In general, the group receiving the active formula (Souvenaid) showed significantly higher absorption of DHA and EPA in the erythrocyte membrane ($\rho<0.001$) compared to the control group, and the plasma vitamin E level increased significantly, 19% in the active formula, compared to control (-1%), ($\rho<0.001$). Concomitantly, the plasma homocysteine level was 23% lower in the Souvenaid group ($\rho<0.001$). The levels of DHA and EPA in the erythrocyte membrane, vitamin E and homocysteine of the control group did not change during the study. The authors concluded that the supplementation showed, after 12 weeks, that Souvenaid in beverage form was well tolerated and resulted in an improvement in the memory of patients with mild Alzheimer's. This trial shows that Souvenaid can be used as therapy in patients with mild to moderate Alzheimer's disease, in patients receiving anti-AD medication, or patients who do not receive pharmacological drugs in order to confirm and extend the results of the study herein presented.

Table 7. Composition of "Souvenaid" medicinal food (125 mL) and control formulation (124 mL).

Component	Souvenaid	Control
Macronutrient		
Energy, Kcal	125	125
Protein, g	3.8	3.8
Carbohydrate, g	16.5	16.5
Fat g	4.9	4.9
"Fortasyn Connect"		
EPA, mg	300	0
DHA, mg	1200	0
Phospholipids, mg	106	0
Colina, mg	400	0
UMP (Uridine monophosphate), mg	625	0
Vitamin E (α-TE), mg	40	0
Vitamin C, mg	80	0
Selenium, mcg	60	0
Vitamin B12, mcg	3	0
Vitamin B6 mg	1	0
Folic Acid, mcg	400	0
Minerals		
Sodium, mg	125	125
Potassium, mg	187.5	187.5
Chloride, mg	156.3	156.3
Calcium, mg	100	100
Phosphorus, mg	87.5	87.5
Magnesium, mg	25	25
Other trace elements		
Iron, mg	2	2
Zinc, mg	1.5	1.5
Iodine, mcg	16.3	16.3
Manganese, mg	0.41	0.41
Copper, mcg	225	225
Molybdenum, mcg	12.5	12.5
Chrome, mcg	8.4	8.4
Other vitamins		
Vitamin A, mcg	200	200
Thiamine (B1), mg	0.19	0.19
Riboflavin (B2), mg	0.20	0.20
Niacin (B3), mgNE	2.25	2.25
Pantothenic acid (B5), mg	0.66	0.66
Vitamin D, mcg	0.88	0.88
Biotin, mcg	5.0	5.0
Vitamin K, mcg	6.6	6.6

EPA = eicosapentaenoic acid; DHA = Docosahexaenoic acid; TE = tocopherol equivalents; NE = niacin equivalents. Adapted from Scheltens et al. (2010).

A study by Lee et al. (2010) cites some environmental factors related to lifestyle in increased or decreased risk of developing Alzheimer's disease. Among the modifiable risk factors, evidence suggests that certain behaviors such as smoking, physical activity, alcohol intake, diet and body weight significantly influence cognitive function and dementia in advanced age (ANSTEY et al., 2007; GOROSPE; DAVE, 2007; BEYDOUN et al., 2008; PETERS et al., 2008). These are known risk factors that strongly influence health. They are also conceptually linked with reduced vascular risk and cognitive reserve, metabolic pathways through which healthy behavior may be effective against cognitive decline and clinical manifestations of dementia (QIU et al., 2007).

Recreational physical activity, even at a moderate level, showed protective effects against dementia, while smoking increased the risk of Alzheimer's disease. Moderate alcohol consumption evidenced a protective tendency against cognitive decline and dementia, but teetotalers and frequent consumers showed risk of dementia and cognitive decline. Obesity in middle age represents an adverse effect on cognitive function in older adults. Frequent consumption of vegetables and fish has a beneficial effect, while high intake of saturated fat represents an increased risk of dementia.

Concerning physical activity, Chorna et al. (2013) demonstrate that voluntary exercise induced the expression of fatty acid synthase (FAS) and accumulation of saturated fatty acids, palmitate (PA) and stearate (SA) in the hippocampus, but not in the cerebellum or cortex, of 20 male mice aged 20 weeks. These results also suggest that such biochemical changes are associated with enhancement of hippocampus-dependent spatial learning and memory, as well as stimulation of cell proliferation in the Dentate Gyrus (DG) in response to physical exercise. Inhibition of FAS by its specific inhibitor (C75) may alter mechanisms potentially relevant to the processes stimulated by exercise, such as neurogenesis, synapse plasticity in the hippocampus, learning and memory. The authors

conclude that FAS is an essential factor in the mediation of exercise-induced cognitive enhancement and neurogenesis in the hippocampus, potentially via the specific action of palmitic and stearic fatty acids.

6.2 Parkinson's disease

Parkinson's disease is characterized by tremor, stiffness and akinesia (lack or absence of movement), and the diagnosis is based on clinical criteria. The clinical symptoms were described by James Parkinson in 1817 and still apply today. Symptoms include tremor in the hands and arms, in addition to other parts of the body, stiffness and trouble moving, impaired body balance and coordination (LANG; LOZANO, 1998).

The combination of asymmetry in symptoms and signs, presence of resting tremor, and good response to the drug levodopa helps to distinguish idiopathic Parkinson's disease from atypical Parkinsonism due to other causes (e.g., dementia with Lewy bodies, progressive supranuclear palsy, which presents a much more adverse prognosis). Prevalence of idiopathic Parkinson's disease increases exponentially with age, affecting about 3% of the population aged 65 and over. The etiology of Parkinson's disease is unknown, but neuropathological features involve the progressive death of the dopaminergic neurons of the "substantia nigra" in the region of the basal ganglia of the brain, which controls movement and coordination. The death of these neurons is closely associated with the accumulation of protein clusters in the brainstem, called Lewy bodies.

As in Alzheimer's disease, there is considerable debate whether the deposition of these proteins is the cause or a consequence of the disease. Lewy bodies are not specific to Parkinson's disease and may represent neurons that have sequestered toxic proteins and served as defense against the neurodegenerative process. An alternative view is that the formation of Lewy bodies from neurofilaments alters the critical function of neurons. Dementia is increasingly recognized as an important feature of Parkinson's disease in older adults and is more common in individuals with Parkinson's than older people of the same or higher age who served as controls. Most cases of Parkinson's disease end up having dementia. Oxidative stress promotes aggregation of the α-synuclein protein, and this is considered an important event in the pathogenesis of Parkinson's disease (PD).

In a meta-analysis, intake of vitamin E, almond and other nuts (antioxidants) was inversely associated with the risk of PD (ETMINAN et al., 2005). Vitamin C and β-carotene did not show any protection. Vitamin C activity may have been masked because it is water soluble and requires active transport for entry into the central nervous system (CNS). Folate can protect neurons by preventing the increase of homocysteine, which has been shown to be neurotoxic (LIPTON et al., 1997). Several mechanisms have been proposed for the protective effects of coffee in PD. Coffee is rich in antioxidants; in addition, it has been suggested that caffeine protects dopaminergic neurons against excitotoxic factors by blocking A_{2A} adenosine receptors (SÄÄKSJÄRVI et al., 2008). However, the data are still insufficient to prove that hypothesis. Estrogen may modify the effects of caffeine in women and that could explain the lack of protection against PD observed in some studies with women who use hormones in menopause.

Data obtained in the PREDIMED study showed, through multiple correlation analysis, an interrelation between alcohol consumption, particularly wine, and urinary excretion of hydroxytyrosol (CHISHTI et al., 2003). The authors of this study suggested that the alcohol generated hydroxytyrosol, which is a potent antioxidant, and could be a mechanism to explain the potential inverse association between alcohol consumption and decreased risk of PD.

Kuwana et al. (1999) showed that low doses of caffeine mainly antagonize A_{2A} adenosine receptors, which are located along with D_2 dopamine receptors in the striatum, i.e., the brain region involved in locomotion movements, where dopaminergic neurotransmission is dramatically impaired in patients with Parkinson's disease. Blockage of adenosine A_{2A} in the striatum increases motor activity through stimulation of D_2 receptors. In fact, A_{2A} adenosine receptor antagonists, such as caffeine, improve motor functions in animal models for Parkinson's disease (KUWANA et al., 1999).

Dopaminergic cells that degenerate in the "substantia nigra" in patients with PD are highly susceptible to oxidative stress. Stress defense mechanisms are limited in dopaminergic cells, and oxidative stress on dopamine is significant. Coffee may prevent oxidative stress through its antioxidant constituents and may also stimulate the production of antioxidants such as glutathione and induce the expression of enzymes involved in the detoxification of free O_2 radicals (ROS), such as catalase, glutathione peroxidase, superoxide dismutase, glutathione S-transferase and other anti-stress enzymes. Other antioxidants that may act against PD are caffeic acid and phenethyl ester (NOELKER et al., 2005; MA et al., 2006) and Ma et al. (2006). These compounds may exert a neuroprotective effect on nigral neurons and protect the "substantia nigra" in PD. Thus, the protective effects of both antioxidants may be of therapeutic benefit in Parkinson's disease. However, to date there is a lack of studies on the potential neuroprotective effects of caffeic acid and phenethyl ester (*in vivo*) which could allow the use of these compounds in the treatment of Parkinson's disease.

Table 8 summarizes the results of some meta-analyses and prospective studies on the association of coffee consumption and its relation to the risk of Parkinson's disease.

Table 8. Meta-analyses and prospective studies on the association between coffee consumption and Parkinson's disease.

Author	Type of study	Study Population	Results	Details
Hernán et al. (2002)	Meta-analysis	8 cases – control studies; 5 cohort studies	Positive	31% lower risk for coffee consumers compared to non-consumers.
Ross et al. (2000)	Cohort	8,004 men (USA)	Positive	Coffee consumption inversely associated with incidence of PD (p<0.001)
Ascherio et al. (2001)	Cohort	51,529 men (USA)	Positive	Significant inverse association with PD risk
	Cohort	121,700 women (USA)	Positive	Significant inverse association for women who consumed coffee; lower risk among those who consumed (1-3 cups /d)
Ascherio et al. (2003)	Cohort	77,713 women (USA)	Positive: (did not take hormones)	Caffeine associated with: - lower risk in women who never used estrogen (postmenopausal) - increased risk for women who always used postmenopausal estrogen
Ascherio et al. (2004)	Cohort	301,164 men (USA)	Positive: women without hormones, men	Coffee consumption: inverse association with beverage consumption No association with beverage consumption
Sääksjärvi et al. (2008)	Cohort	6,710 men and women (Finland)	Positive	Coffee consumers (≥ 10 cups/d) showed decreased PD risk
Hu et al. (2007)	Cohort	4,293 men (Finland) 15,042 women	Positive	Coffee consumption, inverse associativo with PD (both women and men)

6.3 Depression

The term depression covers a vast spectrum of moods or feelings, ranging from a normal feeling of happiness to an abnormal condition that is severe and disabling. Many factors may contribute to depression, including: social factors (loneliness, lack of social connection, etc.), a family history of depression, and lifestyle factors (drug use, lack of exercise, and difficulty following a healthy diet), in the following circumstances: the number of suicides identified as caused by depression is lower in countries of the Mediterranean region than in countries in northern Europe (CHISHTI et al., 2003), which aroused the interest in studying whether this phenomenon is more closely linked to diet or lifestyle in the Mediterranean region or both. Depression is commonly described as a unipolar depressive disorder with various subtypes according to the severity of symptoms (mild, moderate and severe) and the presence of other psychiatric symptoms. Depression symptoms can also be observed in bipolar affective disorder, a condition alternately characterized by manias and depression. Both types of depression show a prevalent feeling of sadness, emotional and social loss, which can be reflected in disrupted sleep, appetite and energy, as well as other physical symptoms. Depression is associated with disturbances in biogenic amines (noradrenaline and serotonin), but the etiology is not yet understood. Deep depression is commonly associated with heart disease, stroke and cancer. Recent research has focused on the role of vascular and nutritional components as risk factors for depression.

Low serum cobalamin (an indicator of nutritional status in vitamin B_{12}) and high levels of homocysteine and methylmalonic acid (metabolites that are high in vitamin B_{12} deficiency) have been associated with the risk of depression in older adults and inversely correlated with a variety of well-being indicators. There have been many publications associating folate deficiency with depression. Response to drugs for treating depression has been poor in patients with low serum folate levels, and improved response to treatment has been observed in clinical trials combining drugs with increased folate levels (COPPEN; BAILEY, 2000).

There is no clear evidence in randomized trials that dietary supplementation with ω3 fatty acids provides protection against depression. Results from recent trials investigating the effects of ω-3 supplementation on cognition and mood are more promising. A cross-sectional analysis of the association between intake of vitamin B complex and ω3 fatty acids and prevalence of depression was investigated in the study known as SUN (SÁNCHEZ-VILLEGAS et al., 2006). Folate intake was inversely associated with depression among men, especially smokers, and B_{12} intake was inversely associated with depression among women.

There was no significant association with ingestion of ω3 fatty acids. In the same cohort (10,094 subjects) analyzed longitudinally over 4.4 years, 480 new cases of depression were diagnosed. Full adherence to the Mediterranean diet pattern showed inverse association with depression ($p<0.001$), with inverse dose-response relation regarding fruit and nut intake, AGMI/AGS ratio, and vegetables (SÁNCHEZ-VILLEGAS et al., 2006).

In the Greek cohort of the EPIC study, the role of dietary lipids was assessed using the Geriatric Depression Scale (GDS) of depression increase (SÁNCHEZ-VILLEGAS et al., 2009). The GDS score showed a negative association with the intake of MUFAs and their main source, olive oil. GDS was positively associated with the ingestion of seed oils (rich in ω3 fatty acids), and as observed in the first SUN publication (SÁNCHEZ-VILLEGAS et al., 2006), there was no significant association with fish and seafood (rich in ω3 fatty acids). In contrast, in the MEDIS study (Mediterranean Islands) there was inverse correlation between GDS score and fish consumption (BOUNTZIOUKA et al., 2009). The aforementioned authors concluded that more epidemiological studies will be needed to better understand the component(s) responsible for opposing depression in the Mediterranean-style diet. Some mechanisms have been suggested to explain how the constituents in the Mediterranean diet (MD) that protect against depression overlap with mechanisms associated with the protection of other disorders. A good example is the protective relationship of cerebral vasculature.

Many constituents of the MD, such as those with an anti-inflammatory action and those that improve the vascular function of endothelial cells should be effective in combating depression. Endothelial cells in the brain synthesize and secrete brain-derived neurotrophic factor (BDNF), a neuroprotector factor that improves synaptic plasticity and has been recognized as deficient in individuals with depression. Therefore, a possible course of action of the MD against depression is maintenance of cerebral endothelium health, thus improving the production of BDNF. Exercise is also viewed as a cause for increased production of BDNF. B complex vitamins prevent excessive accumulation of homocysteine, and therefore reduce vascular damage and help maintain BDNF production. Olive oil also plays an important role in neurotransmitter function, since it stimulates the binding of serotonin to its receptors. Other possible action mechanisms for olive oil are through stimulating biosynthesis of sleep-inducing substances, oleamides, and antioxidant properties of phenolic substances present in the oil (LOGAN, 2005).

7 Future trends and projections

In his book "Biology of Aging", Robert Arking (2008) mentions that *Science* magazine asked 60 prominent scientists what they expected for the future of science.

According to the same author, this long-term trend should have important implications for society as a whole. In recent years, several popular magazines (in the US) have published long articles discussing the possible social and economic effects of the aging of future generations. Predictions in the economic field have been pessimistic given the high cost of constant medical care for older adults, who are likely to live on for several years. However, improving the health of the current older population suggests that the future may not lead to the economic depletion that some writers and the media have anticipated. What, then, should our social goals be?

The best way to define them is not by organizing a conference, but by looking at the data to determine what we are doing now. We must look at the figures. An interesting set of data consists of dependency figures, in which people under 15 or over 65 are considered to be dependent on the financial and social efforts of the age group between 16 and 64. However, this simple relation ignores the different contributions and needs of younger and older people without affording a clear idea of the problem.

The data in Table 9 show that historically a large majority of the population (20 to 40%) has already been dependent on labor efforts. In modern times, the dependency ratio peaked in 1960, reached its trough in 2010, and is expected to return to historical levels during the second half of the 21st century. Today the dependency ratio is approximately the same as in 1940, referred to as the "good old days." So it is not the dependency ratio itself that is so disturbing. According to the aforementioned author, the fact that 38% of people support about 62% of the population is as true today as it was more than half a century ago. Many members of the group that requires support are still young people. What differs is that the ratio of people requiring support shifted from five young

Table 9. Young people, older adults and total support ratios: age groups requiring support over the period 1900-2050.

Year	Older adults	Young people	Total
1900	7.4	76.3	83.7
1920	8.0	67.7	75.7
1940	10.9	51.9	62.8
1960	16.8	65.1	82.0
1980	18.6	45.8	64.4
1990	20.6	41.9	62.5
2000	21.1	40.7	61.8
2010	21.9	36.2	58.1
2020	28.7	36.9	65.6
2030	37.0	37.8	74.8
2040	37.9	36.7	74.6
2050	38.0	36.6	74.6

people to one older adult in 1940 to two young people to one older adult today, and it is predicted to be 1:1 by 2030.

What makes current and future situations qualitatively different from the past is the fact that life expectancy has dramatically increased, so individuals may need more expensive support for a longer period. In this debate, nothing is said about the ever-increasing time and costs that the education of young people now represents. Nothing is said either of the excessive costs of health care that other potentially high-risk groups can bring to society. Obese people, for example, have higher levels of morbidity and account for about 7% of all health care expenditure (SEIDELL, 1995; GORSKY et al., 1996; WOLFE; COLDITZ, 1996). However, no one proposes to withdraw or reduce public support for the care of those people. Older adults are often separated from young people and then abandoned. There may be political reasons for doing so, but are there logical reasons for such?

In his book, Arkin frustratingly affirms: "The net result of this overly pessimistic outlook is that we view the results of the incomparable success of biomedical research efforts of the second half of the last century as a problem, and not as a social achievement of which we are proud." What we are facing is a new challenge resulting from such success. No society has ever known what to do with people who are dependent and experienced at the same time. No other society has ever been lucky enough to face this problem, so there is no precedent. But we cannot let political preachers and media commentators define the unprecedented successes of our society as a calamitous problem, since none of them can predict the future.

There is a need to seek a more practical and forward-looking outlook for 21st century society, and also for the centuries to come.

In 2006, the United Kingdom started recruiting volunteers for a very large cohort study involving 500,000 middle-aged people who will be followed over several decades. Participants will be asked for information on medical history, lifestyle and diet, and blood samples for DNA testing and other biomarkers. The study aims to evaluate the combined effects of genotypes and nutrition on the risk of brain diseases in older adults, including heart attack, Parkinson's disease and dementia in its due course.

For Mathers (2009), the following aspects should be investigated in depth in the study of aging and the main noncommunicable diseases that affect the quality of life in senescence: 1) heart attack, dementia, Parkinson's disease and depression are diseases that affect the brain and account for the majority of disability cases in this age group. The incidence of these diseases increases exponentially with age; 2) because the brain is dependent on a constant supply of oxygen and nutrients for its optimal functioning, it is not surprising that these diseases have been linked to poor nutrition and deficient blood supply to the brain; 3) observational studies have suggested that vascular atherosclerotic disease and nutritional factors should be relevant in the etiology of cognitive disorder, dementia, Parkinson's disease and depression; 4) clarification of the role of lifestyle and nutrition in the control of these diseases is hindered by the difficulty to distinguish causal relationships associated with diet or other lifestyle aspects resulting from the actual diseases; 5) randomized trials of vascular risk factor change or vitamin supplementation will be required to evaluate whether such treatments can control these diseases. In such trials, therapy should be initiated prior to the establishment of the disease and include a sufficient numbers of participants in order to safely evaluate the effects of treatment; 6) randomized evidence of the effects of vitamin B complex on cognitive function should be available in about 20,000 of the 50,000 participants in 12 large, ongoing trials aimed at lowering homocysteine to prevent cardiovascular events; 7) randomized trials aimed at evaluating the effects of (n-3) fatty acids on heart attack, cognitive function and depression should be available in the coming years. The results should confirm observational studies; 8) physical inactivity is a risk factor for cardiovascular disease. Cohort studies have also shown a positive association between physical activity and cognitive function and lower cognitive decline with age; however, there are few data available from randomized trials.

Mathers (2009) also makes the following recommendations for future research: 1) large-scale epidemiological evidence in prospective studies is needed to evaluate the effects of specific dietary patterns, lipid profiles and fatty acids in the bloodstream and risk of brain diseases such as heart attack, dementia, depression and Parkinson's disease; 2) there is a need for research to discover processes of brief diagnosis that allow evaluate of cognitive function, depression and Parkinson's for use of these parameters in large-scale studies; 3) large-scale trials (and meta-analysis of such trials) should be carried out to clarify the role of long-chain fatty acids (n-3) and linolenic acid in the control of cardiovascular disease and mild cognitive impairment (MCI); 4) large-scale trials (and meta-analysis of such trials) of vitamin B complex will be required in people with prior cardiovascular disease in order to evaluate whether lowering homocysteine levels reduces the risk of cardiovascular disease and cognitive impairment. There is a need for further vitamin B_{12} supplementation trials in older people.

It is evident that studies of such duration and complexity will require effort from the scientific community, development agencies, and food producing companies, the development of research and innovation networks, political will of central and state governments, as well as substantial resources and great effort in coordination and cooperation.

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