

Nutrition – Ageing and Longevity

DANONE CHAIR MONOGRAPHS

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Nutrition Ageing and Longevity

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and University Hospitals,
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Avant-propos

The DANONE INSTITUTE is an association of scientists, who are specialists in the field of nutrition.

Its objectives are as follows:

- to encourage research in the field of nutrition,
- and to inform professionals in the areas of health and education about all matters related to foodstuffs.

The DANONE CHAIR contributes to this second objective, as it aims to highlight recent developments in the area of human nutrition. The chair was created in 1994 and every year it is awarded to both a Dutch-language university and a French-language university in Belgium. Under their patronage, they organise instruction by Belgian or non-Belgian scholars. This course of instruction, which is aimed at nutrition specialists from a multidisciplinary background, comprises an introductory lecture followed by fifteen hours of course work. All conferences are contained in an integrated publication in a series of monographs, which are edited by the DANONE INSTITUTE.

XI

Professor Jean-Pierre MICHEL of the Geneva Medical School and University Hospitals (Switzerland) was the holder of the Danone Chair awarded to the University of Antwerp for the academic year 2005-2006. At the time of the Chair, he was Head of the Department of Geriatrics and Rehabilitation at the University of Geneva. Inspired by his teaching, the work “Nutrition, Ageing and Longevity” complements the Danone Chair’s collection of monographs.

The DANONE INSTITUTE wishes to express its sincere gratitude to Professor Jean-Pierre MICHEL. The quality of the series of conferences was confirmed by the attendance of an attentive and enthusiastic audience. The monograph which was produced as a result of this will certainly answer many readers’ questions. The INSTITUTE would also like to express its gratitude to Ms Ann GILAD for her valuable contribution to the compilation of this publication. Lastly, the DANONE INSTITUTE expresses its deep gratitude to the staff of the University of Antwerp, and especially to Professor Dr. M. VANDEWOUDE.

Prof. Dr. Nicolas PAQUOT
President of the
Scientific Council

Dr. Daniel BRASSEUR
President of the
Board of Directors

Foreword

Professor Jean-Pierre Michel was elected as the chair holder of the Danone Chair organised by the Danone Institute in 2006. The Medical School at the University of Antwerp had the honour and the pleasure to welcome Professor Michel for the organisation of this exciting event. As one of the leading geriatricians in Europe he is the ideal candidate for addressing the complex topic of “Nutrition in older people” in all its aspects. Actually Jean-Pierre Michel is head of the Department of Geriatrics and Rehabilitation at the University of Geneva, Switzerland, where he co-founded the Interfaculty Gerontology Center and was the driving force in the establishment of the European Academy for the Medicine of Aging (EAMA). He is honorary professor in Limoges, France, at Beijing University Hospital, China, and adjunct professor at Mac Gill University, Montreal, Canada. He has been elected as president of the Academic Board of the European Union Geriatric Medicine Society (EUGMS). He is member of the Royal British College of Physicians (UK) and was awarded the Ignatius Nascher Prize of the town of Vienna for Geriatrics. He has authored 165 peer reviewed publications and he is editor of numerous books. He is actively involved in the organisation of different symposia and congresses such as the Geneva/Springfield Symposia and the meetings of the EUGMS.

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During the lectures of the Danone Chair an extensive overview of the interaction of nutrition with ageing was given in a way that was very much appreciated by the audience. The basic aspects of nutrition such as the nutritional requirements and the assessment of nutritional status in older people were addressed. Subsequently the lectures focused on very actual topics such as osteoporosis and the complex concept of frailty, introducing an integrated view of the dynamic changes that describe the evolution from robustness to functional disability. All these themes were brought with great enthusiasm in clear and interactive presentations so characteristic for Jean-Pierre Michel. These high quality lectures make him a very popular presentator who is continuously invited worldwide by universities and scientific organizations.

For those who have the privilege of knowing him on a more personal basis, it is clear that Jean-Pierre Michel is not only a leading scientist but also a warm-hearted and charismatic person, who enjoys life and especially good food as can be expected from a geriatrician with an interest in the effects of good nutrition on human health.

I have very much enjoyed the opportunity to play host to Jean-Pierre Michel as the Danone Lecturer at the University of Antwerp. The lecture series was very stimulating and contributed to a better understanding of the important role that nutrition has for the human life span.

Prof Dr M.Vandewoude
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XIV

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Summary

By 2050, world population is expected to reach 9.1 billion, with great heterogeneity in growth rates in the developed and the least-developed countries. It is estimated there will be more than 4.5 million hip fractures annually and more than 36 million patients with dementia, which are 2 profoundly disabling conditions explaining the concerns of an imminent pandemic of frailty, co-morbidity, and disability. This alarming forecast is often seen as if old age was a separate phase of life, initiating its own ailments. However, advanced knowledge of the long-term implications on subsequent clinical outcomes of physical and social exposure during gestation, childhood, young and mid-adulthood emphasizes how health has to be considered in a life-course perspective, from conception to extreme old age.

It is in this precise context that I have written the monograph as holder of the 2006 Danone Chair awarded to the University of Antwerp. The main focus of the book is to stress the essential role of an adequate nutritional intake so as to favour healthy ageing and to prevent the age-related ailing conditions such as atherosclerosis, dementia, osteoporosis, sarcopenia and falls whose dramatic consequences contribute to frailty, disability, shorter survival and a poor quality of life. This core development is integrated in a wider classical nutritional approach such as changes in appetite and weight, nutrition requirements and nutritional assessment, the impact of oral health on nutrients intake, and food/drugs interactions. The intricate problem linked to nutrition and hydration in older patients with life-limiting illnesses closes this geriatric overview of the fundamental role of nutrition in the entire life process.

I do hope that this monograph will mirror my enthusiasm and the pleasure I have had in giving the lectures and in sharing ideas while I was in Antwerp.. My deep recognition goes to Professor Dr Maurits Vandewoude who welcomed me so warmly during my stay in Belgium.

1 – Nutrition and longevity

« Issues in GERIATRIC NUTRITION are inextricably linked to broader issues facing the growing aging population »

MILLER DK & al [1]

This monograph will attempt to encapsulate Danone Chair lectures given at the University of Antwerp in 2006 on 'Nutrition and Longevity'. The aging population is on the rise on a worldwide scale. Concurrently, we have noticed some major changes in our nutritional habits over the past centuries. This raises the question on whether there is a relationship between nutrition and longevity.

1-1 Lengthening of life span

1

Ageing is a lifelong process which begins its course as soon as birth. Several recent epidemiological studies have demonstrated that early-life health and socio-economic environment, during pregnancy, childhood and/or teenage periods may have unexpected significant repercussions on the health status at midlife and older ages [2].

1-1-1 Life expectancy increase

Improvement in public health and superior hygienic environments, such as the widespread availability of drinking water or a mother and child's hygiene and care, are amongst the multiple factors that have increased life expectancy. In Sweden, birth mortality decreased from 240/1,000 in 1872 to 5.6/1,000 in 1998 [3]. A more comprehensive understanding on the different aspects of health and disease has also resulted in an increase of the population's mean age. The probability of dying at age 70 decreased in Sweden from 10% in 1872 to 2% in 1998 [3]. Moreover, the probability of dying decreased in Swedish octogenarians and nonagenarians, from 17.5% in 1950 to 9.5% in 1995. These advancements have allowed for some rapid developments in geriatric medicine. Women's life expectancy increased linearly from 1840 to 2000, rising from 45 to 85 years

old [4]. Due to the unknown limitations of the increase of life expectancy, it is impossible to predict the mean age reached by the end of the 21st century [5]. One can only wonder if Mrs. Jeanne Louise CALMENT (F), born in 1875 and died in 1997 at the venerable age of 122, reached her final limit. [6]

The major human life expectancy extension over the last century of Western society is currently occurring in developing countries at an accelerated rate. For instance, Brazil's life expectancy at birth was 40 years in 1950 and has already exceeded 60 years in 2000; it can be expected that this trend will continue over the next decades [7].

As a consequence of all these demographic changes, the world population of 390 million aged 65+ in 1997, will likely shift to be at least 800 million by 2025 [8].

1-1-2 Healthy active life expectancy

2

In the next few years, medicine and nutrition communities will have to face the ever-so present challenge of upholding optimal physical and psychological health. The healthy active life expectancy corresponds to the average number of years an individual is expected to live without any limitation for basic and/or instrumental activities of daily living (bADL and/or iADL) [9]. Since the 1970s, calculations of disability-free life expectancy (DFLE), based on the WHO classifications of disability, have been performed and regularly repeated for a growing number of countries [10]. In Western European countries (Austria, Belgium, France, Germany and Switzerland), less than 80% of men's and women's life is spent without disability [11] such that 20% of life is lived in a disabled state, which implies help from a caretaker in order to cope with the daily living activities. A survey conducted in the U.S. showed that for a non-disabled, 65 year old man, the probability of surviving to age 80 without disability is only 26% [12].

1-1-3 Preventing disability

One of the key issues associated with these calculations is determining the main causes of disability:

- A 32-year longitudinal study of 1,741 U.S. alumni (1998), was essentially based on three modifiable risk factors (weight, sedentary lifestyle,

and smoking), distinguished a low-risk group (normal weight, regular exercise and non-smoker) and a high-risk group (exactly the opposite). Disability was postponed by 10 years in the low-risk group compared to the high-risk group, formally demonstrating that lifestyle and health behaviour are crucial contributors to ageing without disability [13]. However, these findings remain questionable, considering that all the subjects of this study were only white, wealthy and well-educated individuals[14].

- A 12-year longitudinal study of 618 people over the age of 65 (at the start of the study in 2002) was based on the impact of the same three risk factors (weight, sedentary life style and smoking) and confirmed the results of the previous study. The high-risk group (overweight, sedentary and smoking) had a progressive functional decline over the 12 years of follow-up, with a long period of ADL limitations during their last period of life. Inversely, the low-risk group displayed no functional decline during the study period, but did show a sudden functional decline at the end of life, therefore confirming that lifestyle may be a key factor in disability prevention and morbidity compression [15].
- A Canadian longitudinal study of 603 mentally healthy community residents aged over 65, indicated that diseases are the main cause of disability in the 65-74 age group [16] . According to C. Mathers' diseases classification, the main disabling pathologies are those without death risk, but with a long-term functional decline. Dementia, locomotor trauma and disorders, as well as sensory impairments, represent the "geriatric diseases" and are characterized by a high-risk of functional decline, disability and handicap. Cardiovascular diseases and diabetes can now be included in this first category, because therapeutic advancements have allowed them to progress from fatal diseases to long-term disabling diseases [17]. The specific role of nutrition in all of these pathological processes will be discussed later in this monograph.
- The above-mentioned Canadian longitudinal study [16] demonstrated that disability is twice more frequent in the 75-84 age group compared with the 65-74 age group. In the older age range, ADL limitations may essentially be linked to increasing age itself.

The critical inference that can be drawn concerning healthy active life expectancy is simple and direct: the disablement process is linked to lifestyle, geriatric diseases and age. Therefore, the prevention of disability is a lifelong challenge.

1-1-4 The dynamics of healthy active life expectancy

The repeated calculation of active life or disability-free life expectancy provides a better understanding of the impact of prevention and/or health policy for one country or one specific area within a country. Three scenarios are possible:

- The increase in healthy active life expectancy is slower than the increase in total life expectancy, therefore resulting in an increase of the life expectancy with disability; this is the “pessimistic” scenario called “pandemic of morbidity and disability” or “expansion of morbidity” [18].
- The ratio of healthy active life expectancy to total life expectancy remains more or less stable; this corresponds to the “dynamic equilibrium” scenario [19].
- The increase in healthy active life expectancy is faster than the increase of total life expectancy, corresponding to a relative or an absolute decrease of the life expectancy lived with disability; this is named the scenario of “compression of morbidity” [20].
- These three scenarios may co-exist at the same time in different parts of the world, as demonstrated by countries having repeated calculations. These results suggest the probable existence of a cycle of “morbidity” going from pandemic to equilibrium and then compression. This last phase results in the increase in the length of life, which in turn leads to a rise in the eldest of the senior population. Consequently, this may open a new pandemic phase with an increase in the number of sick, frail and disabled persons [21].

1-2 Survival and nutrition

Within this context, it seems important to determine the exact role of nutrition on survival and more precisely, on healthy survival.

1-2-1 Survival impact of lifestyle in old age

A 10-year longitudinal SENECA study conducted in 7 different European countries examined three risk factors (smoking, physical activity and diet

quality) on 1,281 adults (m=631, w=650). In general, smokers did not perform regular physical exercise and followed poor quality diets. The study found that this group had a mortality risk 3 to 4 times greater than those who had the opposite health behaviour.

When only 2 out of the 3 mentioned risk factors were present, the mortality risk still remained 1.2 to 2 times higher [22,23].

1-2-2 Survival and obesity

In medical terms, obesity corresponds to an excess of adipose tissue for a given weight. In the U.S., the National Health and Nutrition Examination Survey III (NHANES III) showed an increase in the prevalence of obesity (BMI $\geq 30\text{kg/m}^2$) from 22.9% in 1988-94 to 30.5% in 1999-2000 [24]. The prevalence of obesity varies from 25 to 30 % in males over 55 years old and is quite similar for whites and blacks, while in the same age group, the prevalence of obesity is higher for females, between 30 to 35 % in whites and around 60 % in blacks [25]. Severe obesity is a major risk factor of early mortality in young adults; this relationship is less clear for mild obesity and for older people. Moreover, obesity remains a lifelong risk factor for disability.

5

Obesity at old age is very often associated with poor diet and frailty, which may lead to functional decline and disability; consequently, the quality of life can significantly be altered[26]. In the case of severe obesity, serious medical complications are frequent such as, type 2 diabetes, hypercholesterolemia, hypertriglyceridemia, gout, arterial hypertension and coronary diseases. Furthermore, the prevalence of cancer may be increased in obese women (breast, endometrial, gallbladder, cervix, and ovaries) as well as in obese men (colon and prostate) [27]. Other complications of obesity are deep venous embolism, pulmonary embolism, sleep apnea, Pickwickian syndrome and gallbladder disease, and more frequently, intertrigo, bed sores and poor wound healing. As previously mentioned, all these comorbidities influence functional decline and physical dependence in daily life.

The reduced longevity of young people with extreme obesity (BMI $\geq 45\text{kg/m}^2$) has been perfectly demonstrated by the data accumulated by the National Health and Nutrition Examination Surveys (I and II – 1971-72 and III 1988-94). Life expectancy lost due to extreme obesity varies from 13 to 20 years for white and black men and from 3 to 8 for white and black women. However, there is no difference in the decrease in life expectancy between moderate and severe obese individuals over the age of 60 [28].

1-2-3 Survival and undernutrition

Undernutrition is very common amongst the elderly. Risk factors for protein-energy malnutrition include i) socio-economic factors, such as poverty and social isolation, ii) psychological and mental factors, such as depression and dementia, and iii) physical factors, such as impaired mobility, severe visual deficit, poor dentition, chewing difficulties and somatic diseases (in particular hyperthyroidism and hyperparathyroidism). In addition, undernutrition in old age can also be linked to disability (limitations in basic and instrumental activities of daily life – such as the need for help for shopping and meal preparation, or feeding assistance) [1]. It can therefore be concluded that it is possible that undernutrition in old age results from interactions between ageing, social factors, psychological and medical difficulties and environment [23].

The prevalence of undernutrition in old age varies with the nutrition assessment tool used, the place of residence (individual or nursing home) and the comorbidities and functional abilities of the studied population. The prevalence of undernutrition varies from 5 to 10 % in independent healthy old people living at home, reaches 30 to 60% in hospitalized patients and culminates to 40 to 90% in long-term care institutions [29,30].

6

The consequences of undernutrition are multiple and often severe: decubitus ulcers, immune dysfunction which leads to infections, sarcopenia and osteopenia/osteoporosis, which in turn lead to falls and fractures, cognitive impairment, decreased breathing capacity, decreased glomerular filtration rate and indeed disturbed drug metabolism [27].

The impact of undernutrition on survival is evident. Among 83 acutely ill patients (83 ± 7 years) admitted in an acute geriatric ward, it was shown that the undernourished (evaluated using either the subjective global assessment or the mini nutritional assessment) had significantly higher risks of dying within a 1-year and 3-year interval than the well-nourished (respectively 40% compared to 20% ($p = 0.03$) and 80% compared to 50% ($p < 0.05$) [23].

1-2-4 Survival and caloric restriction

Can caloric restriction increase longevity? The idea of OBSORNE of limiting nutrient intake to increase rodents longevity dates back from 1917, however, the experimental confirmation of this hypothesis was established in

1935 by Mc CAY J. [31]. In contrast with undernutrition, which is associated with several deficits in essential nutrients, caloric restriction is a well-balanced reduction in food quantity, keeping the right balance of all essential nutrients, minerals and vitamins [32].

Numerous biological mechanisms are proposed to explain the role of caloric restriction on survival:

- a) Retardation of growth – the above-mentioned effects of caloric restriction in *Drosophila* are also valid in mice.
- b) Decrease in body fat – important role of the Sirtuin proteins to decrease fat deposition and to increase fat mobilization [33].
- c) Decrease of the metabolic rate – no real evidence [31].
- d) Decrease of oxidative damage – caloric restriction decreases the rate of production of Reactive Oxygen Species (ROS) which leads to an increase of both the efficiency of protective processes and repair activities [31].
- e) Alteration of glucose metabolism and insulin synthesis – caloric restriction increases glucose effectiveness and/or decreases insulin responsiveness which corresponds to a lower level of plasma insulin and a lower insulin signalling [31].
- f) Deregulation of the growth hormone, IgF1 axis – increased longevity observed in dwarf mice or experimentally produced in mice by disruption of the growth hormone receptor/binding protein is linked to a IgF1 reduction [34,35].
- g) Hormesis, which corresponds to the beneficial action of a low intensity stress [31] – caloric restriction increases longevity by boosting the resistance to stress and by counteracting the causes of ageing [36]. Theoretically, less energy for somatic maintenance might allow indefinite survival.

• Caloric restriction in *Drosophila melanogaster*

Recent experimental studies of impact of dietary restriction on longevity in *Drosophila melanogaster* help to better understand the impact of nutrition:

- a) Fully nourished *Drosophila* have a shorter life span than dietary restricted ones;
- b) Fully fed *Drosophila*, which get a dietary restriction at day 14 or day 22 after birth, increase significantly their survival;
- c) Caloric restricted *Drosophila* which get an ad libitum diet at day 14 or day 22 after birth, reduce significantly their survival [37].

At this moment, the impact of dietary restriction on increasing longevity is also confirmed in *Saccharomyces cerevisiae* and *Caenorhabditis elegans*.

- **Caloric restriction in rodents**

The ad libitum fed rats had survived 102 days, while the caloric restricted rats reached 203 days [38]. Caloric restriction plays a triple role in increasing life span and healthy ageing by:

- a) Delaying the start of the ageing process by preventing the accumulation of molecular damage throughout life and enhancing hepatic proteolytic capacities;
- b) Reducing the age related changes by limiting immune disorders and cancer incidence;
- c) Diminishing plasma cholesterol and improving cardio-vascular health [38] [39][40].

The precise impact of caloric restriction on each organ is not yet well understood, but knowledge on the matter increases rapidly. For example, with ageing, gene expressions of liver are less and less modulated by controls of over- and under-expressed genes. A four-week caloric restriction in adult rodents allows a reduction by 65% of over-expressed genes responsible for inflammatory responses, stress proteins chaperones and apoptosis negative regulations. Within the same delay, caloric restriction increases by 77% of under-expressed genes, whose roles are cell cycle regulation /DNA replication and xenobiotic metabolism [40].

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- **Caloric restriction in monkeys**

The first results are very encouraging with survival records (44 years) obtained in food restricted monkeys for 17 years [41]. However, until now, nothing was scientifically demonstrated in humans.

1-3 Summary

Ageing has to be considered in a lifelong perspective. Explanations as to why life expectancy has increased have changed a lot during the last decades:

- In the sixties, life span was only correlated to “clock genes” assumed to determine the maximum years of life for species and individuals.
- In the eighties, the concept of life span was modified by introducing the notion of “self-cell defences”.

- In the late nineties, the discovery of mutation genes and longevity genes completed the scene.
- Today, genes, diet and environment are integrated in the main theories of ageing, with a larger role for hormesis, which corresponds to a beneficial action resulting from the response of an organism exposed to a low intensity stress.

In effect, not much has really changed since Roger Bacon (1214-1294) who once said that to age well you need to get proper rest, exercise, lead a moderate lifestyle, and keep good hygiene, while inhaling the breath of a young virgin and enjoying “a control diet”.

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2 – Changes in appetite and weight regulatory systems with ageing

In each individual human being, the balance in energy is usually very precise; daily intake of food is highly variable and correlates poorly with energy expenditure, whereas over a longer period, body weight is stable in most adults [1]. With ageing, nutritional physiological changes appear, such as, increased feelings of satiety, increased leptin levels, decreased feeding drive and decreased volitional intake [2].

In order to better understand the modifications of appetite and weight regulatory systems with ageing, it is important to analyse the function of the central and peripheral regulatory systems and to study their interactions with the environment and the individual's behaviour.

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2-1 Central regulatory system of appetite and weight

Located in the hypothalamus, the arcuate nucleus plays a key role in the central regulatory system and is in constant interaction with the tractus solitarius and the other hypothalamic nuclei [3].

From the arcuate nucleus emerge two types of neurons with opposite actions:

- Facilitating neurones producing neuropeptides, neuropeptide Y (NPY) and Agouti-related peptide (AgRP), which increase appetite, body weight and fat deposition while decreasing metabolic rate.
- Inhibiting neurones producing Proopiomelanocortin (POMC) and Cocaine / Amphetamine Regulate Transcript (CART), which decrease appetite by secreting the α -melanocyte-stimulating hormone (α -MSH).

Afferent signals act on the arcuate nucleus stimulating or inhibiting the “awarding circuit” which produces opioids, endocannabinoid, serotonin and dopamine. The activation of this circuit limits food intake.

The non-activation of the “award circuit” leads to the inhibition of production of POMC, CART, α -melanocyte-stimulating hormone, which in turn does not block appetite. This mechanism can be partly responsible for numerous types of obesity.

2-2 The peripheral regulatory systems of appetite and weight

Food intake and energy expenditures interact on the arcuate nucleus to modulate the activities of two peripheral regulatory systems: a) short term or day to day regulation and b) long term or months to year regulation [3].

2-2-1 The short term peripheral regulatory system

Several hormones take part in this complex regulation:

- Ghrelin is an «appetite stimulating hormone» produced in the stomach. Its high level in the fasted state produces the feeling of hunger and facilitates meal initiation. After eating, the level of ghrelin usually decreases. However in obese individuals, food fails to suppress ghrelin levels [4].
- Peptide YY is an «appetite suppressant» produced by L cells of the gastrointestinal tract in proportion to the calories ingested during meals. Peptide YY facilitates the production of satiety factors and induces the terminal phase of the meal [4].
- Cholecystokinin is a «satiety hormone» rapidly produced by the intestine after eating a meal, which stimulates gall bladder contraction and gut mobility. Cholecystokinin also facilitates the production of satiety factors and induces meal termination [4].
- Glucagon-like peptide 1, oxyntomodulin and pancreatic polypeptide are other meal termination and satiety factors [4].

2-2-2 The long term peripheral regulatory system

It includes three main hormones:

- Amylin produced by the pancreas;
- Insulin or «hypoglycaemic hormone» also produced by the pancreas and;
- Leptin or «anti-obesity hormone» mainly produced by adipocytes.

These three hormones share similar characteristics, they are synthesised and secreted in direct proportion to body fat, they have access to appropriate areas of the central nervous system (CNS), and they influence food intake and body weight in predictable ways [3,5].

Moreover, insulin can cross the blood-brain barrier and act on insulin brain receptors as an anorexigenic signal (4). By knocking out brain insulin receptors in rats, a study was able to demonstrate an important increase of weight, body fat and plasma leptin [6].

Leptin, a hormone (16-kD protein) discovered in 1994 by Friedman, does not cross the brain barrier, as was demonstrated in obese and leptin deficient ob/ob mice [7-10]. Though the majority of leptin is produced by adipocytes (and in a lower proportion by gastric and liver cells), there is a hypothalamic production of leptin in the hippocampus, piriform cortex, neocortex and cerebellum [11-13].

Under life-threatening conditions, plasma level of leptin decreases and causes an inhibition of both somatotropic, gonadotropic, thyroidal and adrenal axes [13]. These inhibitions lead to a metabolic adaptation with the inactivation of the acetyl-CoA carboxylase (muscles) and stearyl-CoA desaturase-1 (liver), thereby provoking a decrease of fat deposit in muscles and liver [14]. In fact, the main role of leptin appears to be protective against weight loss in time of deprivation [3]. Therefore, leptin, also known as the “anti-obesity” hormone, can also be called the “stress-related” hormone [3] [13]. However, leptin is not the sole factor of the weight regulatory system. Other mechanisms are much more complex due to the multiple and subtle interactions exist with other hormonal regulations.

2-3 Eating behaviour and ageing

2-3-1 Body weight changes in old adults

It is well known that eating behaviour and weight regulation change considerably as humans age, as proved in a 90-day study where 7 young and 9 older adults underwent over- or under-feeding during 22 days, followed by an ad libitum diet (15). Their weight regulation was carefully monitored:

- During the over-feeding period of 22 days, weight gain was faster and greater in the younger than in the older individuals. At day 77, the younger adults had lost weight (returning to a “normal” weight) while the older adults continued to stay overweight.
- After the under-feeding period, weight loss was greater in the older subjects than in the younger ones. After 42 days, the younger ones continued to gain weight while the older ones continued to have a negative weight balance.

This study attests that the weight regulation in old adults is slow and not well adapted to environmental stimuli.

2-3-2 Eating behaviour and ageing

Eating behaviour is the result of multiple and interplaying components:

- Sensory properties of food and its hedonic evaluation are balanced by cultural habits and norms responding to “beauty criteria” at any age. However, latent brain modifications, such as a decreased blood supply and/or vitamin B12, B6 and folate deficiencies, can change old adults’ food appreciation.
- Changes in dietary habits are closely linked to social conditions (loneliness, widowhood) and financial situation (poor income). Nutritional changes also depend on education (preference of nutrients), and whether eating schedules are chosen or imposed. Moreover, the alterations of olfactory, gustative and visual systems with age often lead to an increased consumption of glucose and a lower protein intake [16]

2-3-3 Eating behaviour and common diseases in the elderly

Numerous conditions can suppress appetite and alter olfactory function:

- Nutritional deficiencies in zinc, niacin, vitamin B12 and folate (see above).
- Endocrine disturbances: diabetes, hypothyroidism and panhypopituitarism (...).
- Infections, such as sinusitis and upper respiratory tract infections (...).
- Head & neck diseases, such as dental problems, glossitis, rhinitis, nasal polyps, radiation therapy and Sjögren syndrome (...)
- Central nervous system diseases, such as Alzheimer's disease, Parkinson's, Multiple sclerosis and Korsakoff (...).

2-3-4 Eating behaviour as a consequence of drugs suppressing appetite and altering olfactory function

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Among numerous drugs used by the elderly, it is worth mentioning the deleterious effect of antidepressants, antihistamines, anti-inflammatories, antihypertensives, antimicrobials, antineoplastics, asthma medications, bronchodilators, cardiac medications, muscle relaxants, Parkinson's disease drugs and vasodilators (...). These drugs have side effects that may disturb appetite and olfactory function.

2-4 Summary

Appetite and weight regulatory systems are based on extremely complex mechanisms with multiple and subtle neuro-hormonal regulations. Until now, our basic knowledge is limited. Healthy older people have a slow and bad adaptation to dietary changes. Moreover, appetite and weight regulatory systems in the elderly are particularly influenced by extrinsic factors such as cultural habits, social-economic factors, environmental conditions, co-morbidity and drugs' side effects.

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3 – Oral health and nutrition

Nutrition is linked to a good oral health. This means having a stable oral cavity in a relatively disease-free condition and functioning comfortably and adequately to eat and speak [1]. Many changes in oral hygiene and dental status can occur with ageing and their impact on nutrition may be important.

3-1 The normal eating process

Eating is a complex, coordinated process whereby food is ingested, moistened, chewed, tasted and is then swallowed from the oral cavity down the pharynx and into the stomach [1]. The oral structures primarily functioning in the eating process include the salivary glands, teeth, gingiva (*gums*) / alveolar bones (*jaw*), temporomandibular joints, orofacial musculature, lips, tongue, palate, cheeks and mucous membranes. The following describes all the various phases of eating.

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3-1-1 Moistening

Saliva (which contains mucins and some enzymes) softens and binds the food material. Major salivary glands (parotid, submaxillary and sublingual) produce 95% of the total daily salivary flow, while minor salivary glands (mucous membranes of lips, tongue, palate and cheeks) produce the complement.

Moistening also involves the teeth for chewing, the tongue which consolidates the bolus and the posterior part of the oral cavity which allows swallowing [1].

3-1-2 Mastication or chewing

Numerous oral structures are involved in mastication:

- Teeth (the anterior cut and the posterior grind)
- The tongue elevates the food bolus against the hard palate.

- Oral tissues produce saliva and anchor teeth in the jaws.
- The temporo-mandibular joint (TMJ) swings (hinge-like) and slides in many different axes.
- The oro-facial musculature moves the mandible and the food bolus against the teeth and into the pharynx [1].

3-1-3 Tasting

The sense of tasting is a function attributed to the taste buds (sensory receptors in the oral cavity). Tasting requires saliva to dissolve flavours and bring them into contact with the taste buds, which are located on the tongue surface (papillae circumvallatae), epithelium of the palate, tonsillar pillars and around the nasopharynx. Food enjoyment depends essentially on the release of tasteants into the mouth during chewing [1].

3-1-4 Swallowing

Swallowing includes three successive phases:

- The oral stage is voluntary, corresponding to the transfer of food material from the oral cavity to the pharynx.
- The pharyngeal stage is an involuntary phase, constituted by a muscular contraction allowing food passage through the pharynx to the oesophagus.
- The oesophageal stage which is also involuntary, promotes the food passage from the pharynx into the stomach [1].

3-2 Impact of the ageing process on oral health

Successful ageing of the oral cavity is a combination of outcome variables:

- Maintenance of teeth.
- Proper periodontal condition.
- Positive perceived oral health.

– Satisfaction with the access to dental services [2].

A better condition of the oral cavity is more common since elderly people benefit from dental care earlier in their youth. However, most have alterations in their oral anatomic structures or physiologic functions which affect oral health and interfere with eating habits, food choice and, as a result, compromise nutritional status [1].

3-2-1 Compromised moistening

Xerostomia, more commonly known as dry mouth, occurs when saliva production is inadequate (fluid volume <0,1 ml/min UWS or <0,7 ml/min SWS), provoking sticking of food to teeth, burning sensation, oral soreness, glossodynia, atrophic glossitis, taste impairment and denture irritation [1]. The main risk factors for xerostomia are diabetes, Sjogren's syndrome, but also undesirable side effects of drugs such as antihypertensive drugs and tricyclic antidepressants. Radiation and/or surgery can cause permanent destruction of salivary glands and irreversible xerostomia.

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3-2-2 Compromised chewing

Chewing ability depends on the presence of teeth, the force exerted when biting and the length of chewing a bolus of food. Physiologic alterations of oral structures can lead to altered masticating. For example, muscle flaccidity can be the cause of swallowing disturbances; increased muscle tone can provoke chewing problems, while muscle coordination can lead to eating difficulties.

Older adults with a decreased chewing efficiency will more likely opt for softer foods that are easier to chew (which results in high sugar, fat and calorie intake and deficiencies in fibre, proteins, iron, calcium and vitamins) [1].

3-2-3 Impaired tasting

Oral sepsis, poor dental hygiene and/or medication side effects can impair taste sensitivity as well as alter flavour and palatability of foods/beverages (from dysgueusia to hypogueusia and agueusia). These changes in taste explain the preference of old people for salty and sweet foods.

3-2-4 Abnormal swallowing

Oropharyngeal dysphagia is a consequence of problems related to the initial steps in the act of swallowing. It increases the risk of aspiration of saliva and food (aspiration pneumonia).

Otodynophagia or pain during swallowing is linked to neurological, neuromuscular and structural or oral health problems (neoplasia, mucosal pathology).

3-3 Different dental status in the elderly

Two thirds of older adults have retained their natural dentition, but only 0.3% have a normal denture [3].

3-3-1 Dental status in community-dwelling elderly

While the edentulism rate is decreasing, the number of conserved natural teeth is increasing. However, these conserved teeth are accompanied by numerous and significant oral diseases, especially as older adults become functionally more dependent, cognitively impaired and/or medically compromised [4]. These oral diseases are often linked to the absence of regular medical dentistry consultation. In the Berlin Ageing Study (BASE), more than 10% of the 70-74 year age group and 33 % of the 95+ year age group lacked dental care utilisation for at least 60 months [5].

The most common oral diseases of the community-dwelling elderly are:

- **Periodontal diseases:** Closely linked to the frequency and the quality of personal oral care. Periodontal infections can be a source of bacteraemia, septicaemia, infective endocarditis and brain abscess [3].
- **Root tooth decays:** More common in independent older adults, while coronal decays occur frequently in dependent elders [6]. Between one fourth and two thirds of older people living at home suffer from root tooth decays [7]. Risk factors for developing root tooth decay are very old age, large root exposure, less than 20 risky teeth and male gender. Moreover, bad oral hygiene, dry mouth and a sweet diet accelerate the root decay onset. Functional status also

significantly contributes to an increased risk of developing tooth decay [6].

- **Leucoplakia** (white lesion without deposition): Less common in the very old than at mid life [8]. However, lichen plan (reticular & linear stripes, without deposition) should not be misdiagnosed because the malignancy risk is high in the short-term.

More medically compromised old patients living at home (increased life expectancy) retain their natural teeth (better oral hygiene). This will increase the need for ambulatory dental practice in the near future in order to reduce bad oral health on general medical conditions and vice versa [9].

3-3-2 Dental status in institutionalised elderly

The poorest oral health conditions are most prominent in the dependent, institutionalised patients. However, the onset of severe oral diseases appears to occur prior to institutionalisation, which stresses again the importance of community dental care [4].

In fact, the functional abilities of the oldest old constitute one key problem with oral health.

Oral impairment (no or few teeth) and oral functional limitations (chewing problems) were significantly related to general functional limitations (mobility problems and frequency of dental visits) in institutionalised 75+ elders prospectively followed for 5 years [10].

For these institutionalised patients, the access to dental care is limited. Mail questionnaires sent to different nursing home staff, perfectly demonstrate the dilemma:

- Managers of nursing homes (n = 47) agreed, in 85% of the cases, to organize transportation for the residents asking to go to a dental office. They ensure the follow-up of dental care in 79 % of the cases. However, they request a dental intervention in case of oral emergencies in only 68 % of the cases.
- Caregivers (n = 169) said that they did not receive education in oral hygiene care, and that they are not responsible for oral hygiene of the institutionalized patients. For them, the dentist is the only person responsible for the oral health care.
- Medical doctors (n = 30), responsible for the care of the residents in nursing homes, systematically examine the oral cavity in only one of three new residents. Moreover, only 20 % of medical doctors regard oral cavity as “an integrated part of the body” [11].

These results are truly alarming. They show the urgent necessity to provide more education and training to the primary health care professionals. Without this knowledge and an improved sense of responsibility, it is impossible to recognise and treat, for example, the under-prosthesis ulceration, a very frequent oral lesion, which alters both eating ability and quality of life.

3-4 Oral health and nutrition

3-4-1 Impact of oral health on quantity and quality of nutrient intake

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A cross-sectional survey of 3,429 adults (1,433 men and 1,996 women) randomly selected in Spanish primary care clinics and institutions (mean age 73.2 +/- 6.4) compared nutritional status of edentulous (31% of the studied population) and dentate subjects (69% of the studied population who had an average of 15 teeth). Malnutrition was noticed in 5% of the edentulous and 4% of the dentate subjects, while risk of malnutrition was noticed in 43% of the edentulous, and 39% of the dentate subjects [12].

Another study conducted on 77 Japanese subjects over 75 correlated the number of teeth with the 3-day intake using a precise weighing method. When comparing to older adults with ≥ 20 teeth, those with ≤ 19 teeth had a significantly inferior intake of vegetable, fish, shellfish and total protein, vitamins D, B₁, B₆, niacin and panthotenic acid [13].

The NHANES III survey, including 5,958 U.S. participants over 50, demonstrated the importance of posterior occluding pairs of teeth. When their number was below 5, the diversity of food decreases, as well as the intake of fruits, carotene and vitamin C. In parallel, these subjects showed a higher BMI, an elevated plasma cholesterol level and higher sodium intake [14].

These three selected studies show that the number of retained teeth (more or less than 19) and their location in the mouth (posterior occluding pairs) influence food intake (both in quality and in quantity).

3-4-2 Bad oral health can alter global health

As above mentioned, bad oral health or periodontal disease can lead to general infections such as bacteraemia, septicaemia, infective endocarditis and brain abscess. [3]. The NHANES III survey showed that dental caries and periodontal diseases represent a burden of unmet oral treatment need in older adults (bad oral health status leads to periodontal infection) and can provoke aspiration pneumonia and lead to diabetes disequilibrium [15].

It has also been proven that:

- Pharyngeal mucosa can be colonized by respiratory pathogens which is often a transient phenomenon;
- Dental plaques are a stable reservoir for respiratory pathogens and therefore a major route for nosocomial pneumonia (aspiration of pharyngeal bacteria) [16].

3-4-3 Geriatric diseases interacting with oral health

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Several diseases interact negatively with oral health in the elderly:

- **Specific geriatric diseases** : nutritional deficiencies which are particularly common in the elderly (vitamin B₁, B₂, B₆, B₁₂, folic acid, vitamin K and iron deficiency), as well as temporal arthritis, tuberculosis, hyperparathyroidism and Paget's disease .
- **Common diseases in the elderly:** diabetes, rheumatoid arthritis and Sjögren's syndrome, chronic renal failure, leukaemia and neutropenia.
- **Skin diseases frequently observed in the oldest population:** pemphigus, pemphigoid, herpes-zoster and herpetic stomatitis (I or II).
- **Other diseases:** Acquired Immuno Deficiency Syndrome (AIDS) and trigeminal neuralgia [3].

Major Depressive Disorder (MDD) is a specific disease that deserves special attention. Major Depressive Disorder may be associated with extensive dental disease due to a disinterest in performing appropriate oral hygiene, a cariogenic diet, a diminished salivary flow, rampant dental caries, advanced periodontal disease and oral dysesthesias. Moreover, many MDD medications increase the patient's xerostomia and alter gustatory function [17].

All these diseases intervene directly or indirectly with patients' quantity and quality of nutrient intake.

3-4-4 Major effects of drugs on the oral mucosa and diet of old patients

Oral ulceration can be caused by Aspirin, NSAID's, pancreatic extracts and potassium chloride [3]. Xerostomia can be due to anticholinergics, anti-convulsants, antidepressants, antihistamines, diuretics, hypnotics, sympathomimetics and tranquilizers. Confronted with fixed drug eruption, lichenoid eruptions, multiform erythema and/or salivary gland enlargement, clinicians should first check the patient's medications list to eliminate the side effects of drugs [3].

3-5 Summary

The mouth is a critical part of the body. Oral health should be a priority in geriatric patients. The discovery of good oral health (stable oral cavity, relatively disease-free, comfortable and adequate functioning to eat and speak) is an exception in geriatric practice. Clinicians should evaluate the number and the distribution of remaining natural teeth, as well as the quantity and quality of saliva present, as an integral part of medical and dental examinations. There is a strong relationship between oral health and nutritional status and infections (aspiration pneumonia, bacteraemia, infective endocarditis). Moreover, numerous geriatric diseases, particularly depression, and their specific treatment, interact negatively with oral health. From the association made between oral health and diseases emerges the need for better oral care in order to ensure an improved nutritional status in the ageing and aged populations.

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4 – Nutrition requirements in older people

Current recommended daily allowances (RDA) exist for all persons over 51; however, it seems they tend to overlook the heterogeneity of this group. In fact, the scope of nutrition is broader in older individuals than in their younger counterparts who do not experience the same degree of pathologic, physiologic, psychological, functional or financial limitations. [1]. Nutrition affects the ageing process throughout the different stages of life, however, it has a stronger influence during childhood and ageing. These two extreme life stages differ from one individual to another. Ageing is a unique individual process and differentiating between physiologic age-induced changes and nutritional deficiencies may be difficult. As a person ages, there is a higher risk of developing serious nutritional deficiencies due to the presence of an age-associated decrease in total food intake, very often combined with debilitating diseases [2]. All these age-related processes explain why nutritional recommendations need to be adapted to the elderly to a) maintain health and prevent diseases as part of the treatment of chronic diseases and b) facilitate health recovery after an acute medical episode [3].

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4-1 Energy needs in older adults

Basal energy requirements correspond to the total amount of energy needed for all the metabolic processes involved in the maintenance of cell function [3].

With ageing there is a significant decrease in energy needs (- 30%) in relation with several interacting elements [2]:

- Inefficient appetite control and weight balance.
- Diminished resting energy expenditure.
- Decreased physical activity often in relation with bone / joints disorders, heart, lung or neurological diseases and pain.

The decreased energy requirements are associated with a reduced “active” metabolic mass (reduced lean body mass); as a consequence, the total daily energy requirements are only 35 to 40 kcal/kg/d in seniors[2]. However, as previously mentioned, requirements vary from individual to individual, such as taking into account one’s level of activity (e.g. a physically active man of 75 years old has a higher energy requirement than a sedentary man of the same age).

4-2 Protein requirements

Protein requirements in the elderly may be slightly higher than in the younger adults. With ageing, there is no relation between the protein intake and the reduction of lean body mass. A lower energy requirement is related to a lower energy intake, and less retention of dietary nitrogen. Moreover, a decreased bone mass as well as an increased immobility (very often linked to disability) may be responsible for a negative nitrogen balance. As we age, an increased need of dietary protein is required to achieve this balance [3]. A recommendation of 0.8 g/kg/d of protein is considered insufficient for the following conditions: stress, trauma, infection, surgery, fractures, and unusual losses. For all these reasons, the protein requirements in the older subjects are estimated to be 1 to 1.2 g/kg/d [3].

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Causes of protein energy malnutrition (PEM) are well identified by J MORLEY and can be simply remembered by using the acronym “Meals on Wheels”, which includes factors such as medications, emotions (*depression*), alcoholism, late-life paranoia, swallowing problems, oral problems, poverty and to the end wandering (*dementia*), hyperthyroidism (*para-*), entry problems (*malabsorption*), eating problems, a low-salt, low-cholesterol diet and shopping problems [4].

The main consequences of PEM are decubitus ulcers, immune dysfunction, infections, falls, sarcopenia, osteopenia / osteoporosis, cognitive impairment, reduced breathing capacity, diminished glomerular filtration rate and altered drug metabolism [4]. Among all these severe consequences, immune dysfunction and nosocomial infections have the highest impact.

– PEM worsens the age-related changes of immune functions. There is a decrease in the number of T-cell, T-helper and T-suppressor cells, but also a reduced blastic response to mitogen and a state of anergy. Moreover, in PEM, β -cell function and auto-antibody production are normal but natural killers are diminished [2].

- Aged, hospitalised patients suffering from PEM develop significantly more nosocomial infections than their counterparts without PEM, independently of patients' age, length of hospital stay and presence of an urinary catheter [5].

Before concluding this section on protein requirements, it is important to specify the main animal protein sources: lean beef, fish, pork, poultry, eggs, tuna, reduced-fat cheeses, cottage cheese, no-fat powdered dry milk (added to soups and casseroles), pudding...etc. Vegetables, beans and cereals also contain proteins, but the quality is generally lower. Research on the possible negative effects of an extremely high protein intake (up to 25 % of energy) did not show any interference with renal function in the absence of known renal diseases (6).

4-3 Fat requirements in older people

Fat is an essential nutrient, which provides a) energy (dietary fat provides 9 kcal/g), b) essential fatty acids and c) fat-soluble vitamins (also available in other dietary sources). To cover all the above mentioned needs, saturated and unsaturated dietary fat should amount to 30 to 40% of total energy intake [7].

4-4 Carbohydrate needs in older adults

The diet must include both simple and complex carbohydrates. The latter are very important because they contain dietary fibres which increase glucose tolerance, reduce constipation and the formation of colonic diverticuli and decrease serum lipids. Carbohydrates must cover 55 to 60% of the total caloric intake.

4-5 Water requirements

Six or more servings of fluid equivalents (water and juices) are recommended per day.

4-6 Vitamin requirements

Vitamin requirements in older adults are extrapolated from data derived from younger adults (Recommended Dietary Allowances). Sub-clinical vitamin deficiencies may exist in people with no balanced dietary intake, with excessive metabolic demands and those using polypharmacy. However, overuse of a single vitamin or polyvitamins preparation is not uncommon.

There are two major classes of vitamins a) water soluble and b) fat soluble vitamins. For each category, only vitamins whose deficit/excess may cause serious complications in older people will be considered.

4-6-1 Water soluble vitamins

- **Vitamin B₆ (pyridoxine)**

Deficiency in Vitamin B₆ or pyridoxine is common in older people (10 to 45%). Vitamin B₆ deficiency is often associated with protein energy malnutrition and contributes to anaemia. It is responsible for decreased cell-mediated immunity, reduced lymphocyte proliferation and diminished Inter Leukine 2 production. In geriatrics, it also causes peri-orificial dermatitis around orifices.

The main sources of vitamin B₆ are bananas, whole wheat bread, chicken, eggs, oatmeal, peanut butter, tuna and potatoes [8].

Recommended daily allowances (RDA) for young and old adults are 2 mg/day for men and 1.6 mg/day for women. However, these RDA are likely to be insufficient for older people; between 25 to 50 mg/day is recommended for the geriatric population. Moreover, correction of vitamin B₆ deficiency requires repeated periods of repletion [9].

- **Vitamin B₁₂ (cyanocobalamin)**

Clinical deficiencies in vitamin B₁₂ or cyanocobalamin are rarely diagnosed in older subjects, due to its late manifestation (2 to 6 years after the inadequate intake). There are large intra hepatic stocks and there is a good entero-hepatic recycling ability of vitamin B₁₂.

Vitamin B₁₂ deficiency can cause anaemia, neuropathy and even dementia; symptoms are paresthesia in the feet or hands which lead to ataxia and weakness in the extremities. Clinical signs, which precede the diagnosis by several months, are loss of position sense in the index toes, loss of vibration sense, reduced pain and touch sensation, peripheral neuropathy and neuropsychiatric disorders (dementia) [10].

Biochemical indicators of vitamin B₁₂ deficiency are serum radio-assays of cobalamine alone or in combination with vitamin B₁₂ analogues, methylmalonic acid (MMA) and homocystein.

Causes of vitamin B₁₂ deficiency are atrophic gastritis, hypochlorhydia, chronic anti-acid use (Histamin2 blockers and PPI), gastric and ileal surgery, small intestine and terminal ileum diseases (Crohn, sprue, malabsorption), *Helicobacter pylori* infection, pancreatic insufficiency, parasitic infections (fish tapeworm), bacterial overgrowth syndromes, strict vegetarianism, AIDS, pernicious anaemia and possibly, metformin in as a long-term treatment.

The main sources of vitamin B₁₂ are meat, fish, shellfish, eggs, plants products like soybeans, yeast and some sea plants [8].

RDA, for young and old adults, are identical for both men and women: 2 µg/day. However, these RDA are probably too low for older people, and the geriatric recommendations are 3 to 5 µg/day [10].

A single injection (intra muscular or sub cutaneous) of 1000 µg achieves a complete remission of vitamin B₁₂ deficiency. Therefore, patients with continuing absorption problems will receive the same dose of 1000 µg every month during their whole life. Ten days after the first injection, the number of reticulocytes increases and there is a reduction in both leucocytes hypersegmentation and homocystein levels.

- **Folic acid (or vitamin B₉)**

Folate which is required for many methylation and nucleotide biosynthetic reactions is, like vitamin B₁₂, recycled into the entero-hepatic cycle. Folic acid deficiency leads to anaemia and contributes to atherosclerosis, dementia and cancer.

Causes of folic acid deficiency are decreased small bowel mucosal transport, diminished folate re-absorption, inflammatory bowel diseases, sepsis, uraemia, mucosal oedema during heart failure and alcohol abuse. Moreover, folate supplements are necessary for particular diseases, such as hereditary spherocytosis, chronic hemolytic anaemia, multiple myeloma and other malignancies.

The biomarkers of folic acid deficiency are a decreased erythrocytes count, macrocytosis, hyper-segmentation of neutrophils and hyper-homocysteinemia.

Folic acid is present in high concentration in vegetables (especially spinach), liver and kidney.

The official RDA (for all adults 51+) are 200 µg/day for men and 180 µg/day for women. However, in geriatrics the recommendation is 400 µg/day.

The treatment of folic acid deficiency includes a “balanced” diet and oral supplementation (5mg/d) of folic acid associated with other vitamins (B₆ and B₁₂). Although large doses of folic acid are generally safe, they can mask vitamins B₆ or B₁₂ deficiency [10].

- **Vitamin C**

Vitamin C, the most potent antioxidant in the body, is protective against stress-related disorders and degenerative diseases (protection against coronary heart disease and cataract).

There is a 10% prevalence of vitamin C deficiency in the geriatric population. Its clinical manifestation includes scurvy, capillary fragility and cataract. In geriatric medicine, infections due to a deficiency in vitamin C are not rare. The main cause of the deficiency is a long-term diet without fresh fruits and vegetables.

The official RDA for older adults of 60 to 140 mg/day seem valid. Treating vitamin C deficiency is easy and rapid, however if supplements include doses over 1g/d, kidney stone formation and chronic diarrhoea may occur [10].

4-6-2 Fat soluble vitamins

- **Vitamin A (retinol and β-carotene)**

Vitamin A has anti-oxidative properties (like vitamin C, vitamin E and pro-vitamin A). Its main functions are the maintenance of the integrity of epithelial tissues and proper immunologic function. Vitamin A deficiency is very rare in older people and essentially causes night vision impairment. The main reason for vitamin A deficiency is insufficient intake of animal products, plants and fruits.

The official RDA are 1000 µg / day in men and 800 µg/day in women of all ages. In geriatrics, RDA is reduced to 700 µg/day to fit with the age specific

threshold for toxic levels. Hypervitaminosis A provokes headaches, drowsiness, irritability, dizziness, nausea, vomiting and diarrhoea.

However, the therapeutical use of vitamin A is very useful: topical retinoids are effective in reversing skin pre-malignant or malignant lesions and β -carotene itself can reduce both stroke and cardiovascular disease as shown in the Physician's Health Survey [10].

- **Vitamin D (calciferol)**

Vitamin D is vital in protecting against osteomalacia and osteoporosis. However, half of the older population consume less than two thirds of the RDA and/or have a lack of sun exposure; vitamin D deficiency concerns 9% to 43% of the free living elderly and 35% to 90% of the institutionalized [10].

Factors contributing to vitamin D deficiency in seniors are inadequate dietary vitamin D intake, insufficient sun exposure, reduced cutaneous production of vitamin D, diminished intestinal absorption of vitamin D, deficit of renal production of $1.25(\text{OH})_2\text{D}$ and drugs reducing liver hydroxylation of vitamin D [11].

The official RDA established for young and old adults are 100 to 200 International Units per day (IU/d). However, the geriatric recommendations are higher, reaching 400 IU/d between the age of 50 to 70 and 600 IU/d after the age of 70.

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The recommended daily vitamin D supplementation in old adults living in nursing homes is 400 IU of vitamin D combined with 1.2 grams of calcium. When this treatment is followed for a period of 18 months, the incidence of non-vertebral fractures and of hip fractures decrease by 30% and 41% respectively [12].

However, toxic levels should be avoided; chronic vitamin D supplementation of over 25,000 or 50,000 IU/d causes hypercalcemia, whose clinical manifestations are anorexia, weakness, constipation, soft tissue calcifications (vessels, cardiac valves, and lung) and renal insufficiency. A constant monitoring of vitamin D supplementation is necessary particularly in patients with hyperparathyroidism and chronic renal insufficiency [10].

4-7 Minerals

4-7-1 Calcium

The peak age for calcium consumption is 9 years old, after which there is a progressive decrease in calcium daily intake. Inadequate intake (below the RDA) is observed in most adults and older people. Calcium deficiency in the older adults facilitates the development of osteopenia, osteoporosis and fractures.

Calcium is mainly present in dairy products such as milk and milk-products, meat, fish, shellfish, almonds and beans. In addition to the inadequate calcium intake, factors contributing to calcium deficiency in older persons are diminished intestinal absorption of calcium, oestrogen deficiency, prolonged immobilization, endocrine disorders, low physical activity and drugs [11].

The official RDA (for young and old adults) recommend a daily intake of 800 mg of calcium. Geriatric recommendations are 1.2 g/d [12]. The National Health and Nutrition Examination Surveys III (NHANES III) - 1988-9, proved that calcium supplements are inadequately taken in 75% of men and 87% of women (16). This study confirmed that prescription of calcium supplements requires careful monitoring of patients' supplements compliance.

4-7-2 Zinc

Zinc is an integral part of 60 or more vital enzymes involved in activities ranging from digestion to cellular replication. Zinc intake is directly related to caloric consumption; this corresponds to 8.2 to 12.6 mg/day for 55 to 64-year-old women and men. This intake decreases by more than 10% for the next decade of life.

The main characteristics of zinc deficiency are dermatitis, anorexia and gastrointestinal problems.

4-8 Summary

Although the official published RDA are theoretically valuable for all persons aged 51 years and over, numerous RDA-values should be adjusted to correspond with the increased daily needs of very old adults [9].

The actual macro- and micro-nutrients daily recommendations in the old adults are:

- | | |
|---------------------------|-----------------------------------|
| – Caloric requirements | 35-40 kcal/kg/d |
| – Protein requirements | 1.0-1.2 g/kg/d |
| – Vitamin B ₆ | 25-50 mg/d |
| – Vitamin B ₁₂ | 3-5 µg/d |
| – Folate | 400 µg/d |
| – Vitamin D | 400 IU/d between the age 50 to 70 |
| – Age 50-70 | 400 IU/d |
| – Age > 70 | 600 IU/d |
| – Calcium | 1200 mg/d |

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Fulfilling these daily recommendations is possible by following the daily intake suggestions presented in the modified food pyramid for seniors:

- 6 or more servings of fluid equivalents (water and juices);
- 6 or more servings of bread, fortified cereals, pastas or rice;
- 3 or more servings of vegetables;
- 3 or more servings of milk, yogurt, cheese or nuts;
- 2 or more servings of fruits;
- Sparingly consumption of fats or oil and sweets;
- Supplements if needed in calcium, vitamins D and B₁₂.

This daily diet will help avoid a number of intake deficiencies, which are an important cause of multiple and severe geriatric diseases and disease complications.

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5 – Nutritional assessment: updates

Nutritional assessment is an integral part of the overall care of the elderly [1]. The goal of nutritional assessment is to identify the presence, nature and extent of impaired nutritional status of any type: obesity or, perhaps more often among old people, undernutrition [1]. Nutritional assessment thoroughly evaluates different data related to dietary intake and/or body composition in order to develop a plan of care that will help improve the nutritional status.

Existing recommended daily allowances (RDA) concern all persons over the age of 51 years, ignoring the large heterogeneity of the elderly [1]. It is clear that this group is very heterogeneous at the physiological, functional, psychological and socio-economic levels.

For these reasons numerous indicators are proposed to determine nutritional status. The most difficult task for the clinician is to identify the most appropriate method and parameters for his/her daily practice:

- Percentage of weight loss during the previous 6 months;
- Body Mass Index (BMI);
- Waist circumference;
- Anthropometric measures :
 - Mid-arm circumference
 - Triceps skinfold thickness
- Bioelectrical impedance;
- Body composition studies :
 - Computerized tomography (essential to evaluate lean body mass)
 - Dual X-ray absorptiometry (bone mineral density)
- Laboratory measures :
 - Albumin
 - Prealbumin
 - Insulin growth factor (IGF-1) (...)

Before analysing the value, practicability and reliability of these measurement tools, it is necessary to integrate them in a valuable clinical and nutritional history.

5-1 Medical history and clinical examination as part of the nutritional assessment

Numerous general discomforts can affect nutrient intake: impaired vision, loss of appetite, disturbed smell, abnormal taste, dental problem, dry mouth, early satiety and even shortness of breath when eating [2].

Moreover dietary habits can be influenced by psycho-social conditions: alcohol abuse, isolation, loneliness, depression and cognitive impairment. Physical disability can limit shopping ability; economic restraints can limit food choice [2]. Cultural habits, cohort effects, negative family conditions, side effects of drugs are also possible causes of impaired nutrient intake [2].

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Clinical inspection to detect malnutrition in older people should focus on [1]:

- Thin, sparse, and straight hair with an easy pluckability;
- Diffuse depigmentation of the face with a nasolabial seborrhea;
- Pale conjunctivae, conjunctival and corneal xerosis, or keratomalacia;
- Angular stomatitis, angular scars of the lips or cheilosis;
- Oedema of the tongue, atrophic filiform papillae or glossitis;
- Xerosis of the skin, follicular hyperkeratosis, petechiae, ecchymoses, pellagrous dermatitis, scrotal and vulval dermatosis;
- Koilonychia nails ;
- Oedema of the subcutaneous tissues, low amount of subcutaneous fat;
- Muscle wasting, musculoskeletal haemorrhages, outward curving of the knees, local skeletal deformities [1].

Very often these symptoms are not present simultaneously; however, even the detection of one of them is very useful in screening procedures.

5-2 Dietary Intake

Three techniques can be applied to evaluate the diet intake [3]:

- Food diary, which is a written self-recording of current food intake for 3 to 7 days.
- Food recall of the consumption during the previous 24 hours. This technique has to be avoided in old people with cognitive disturbances.
- Food frequency questionnaires describe food consumption patterns for a 12-month period including seasonal variations.

Unfortunately, every method underestimates food intake [4]. A comparative quantitative energy and macronutrients intake evaluation between a 7-day food record and a food history in 175 men and 173 women aged 30-60 years selected at random from a wide Danish population, showed that both methods underestimated food intake, independently of age and BMI [5]. These errors arose from the use of food tables and the wrong assessment of the frequency of food consumption, portion size and daily variation. There was a failure to report usual diet or changes in habits. Moreover, the degree of patients misreporting or underreporting the choice or amount of food increases with repeated dietary assessments [6][7]. We can conclude that there is not yet an accurate method for the determination of dietary intake. The preferred method of investigation is a prospective approach, particularly in patients with memory problems [6]. This requires a great awareness from the dietitians or nursing staff (need of training and time) [7].

5-3 Anthropometric measures

5-3-1 Height

For both genders, height decreases by 1 cm per decade after the age of 20, due to vertebral bone loss, increased laxity of vertebral supportive ligaments, diminished disc space and posture alterations [8]. The problem becomes more complicated in older adults with postural abnormalities or when they are bedridden [9]. The only measurement that remains constant with ageing is knee-heel distance (KHd), which provides the most accurate

height a person should have. This measurement is based on Chumlae's formula:

- In men, height (cm) = KHd (cm) x 2.03) – (0.004 x Age) + 64.19
- In women, height (cm) = KHd (cm) x 1.83) – (0.024 x Age) + 84.88

5-3-2 Weight

Weight is one of the most important measurements for appreciating body composition. With ageing, there is overall increase in body weight, with a peak in the 40's in men and 50's in women, followed by a decrease after the age of 70 [8].

After the age of 30, there is usually a decrease of the lean body mass estimated at 6% per decade, which approximately corresponds to a loss of lean body mass reaching 5 kg in women and 12 kg in men at the age of 70 [8].

In parallel, fat distribution changes with age with more truncal and abdominal fat storage and less fat storage in the limbs. Changes in men and women are quite different and therefore the most valuable measurement of skin folds are at the sub scapular and supra-iliac levels in men and at the triceps and thigh in women [8]. However, in practice, skin fold measurements are less commonly used in the very old because their weak reliability (very thin skin, sarcopenia, dehydration or hyper-hydration).

It is important to indicate that significant malnutrition can exist in overweight or even obese elderly subjects. Therefore, it is always necessary to interpret changes in body weight within the medical history (chronic obesity, acute water retention due to heart, renal or liver failure).

5-3-3 Numerous weight specific measures exist [10]

- The Body Mass Index (BMI) corresponds to the ratio between body weight (kg) and the square of height (m²).
- The percentage of usual body weight (UBW) corresponds to the ratio between the current weight divided by the usual weight multiplied by 100.
- The ideal body weight (IBW) in pounds is calculated with the following formula

- Man: $[106 + 6 \times (\text{Height (inch)} - 60)] / 2.2$.
- Woman: $[106 + 5 \times (\text{Height (inch)} - 60)] / 2.2$.

A complete cross-sectional analysis of the anthropometric changes of a randomly selected sample of 3,356 Italian subjects showed that the mean BMI was significantly higher in men (27.6 ± 5.7) than in women (26.4 ± 3.7) ($p < .0001$) and decreased significantly with ageing in both genders ($p < .001$) [9].

5-3-4 Biochemical and haematological parameters

- Albumin, which corresponds to the visceral protein store, is a good marker because its half life is of one week.
- Prealbumin has a short half life of 48 hours. Its dosage corresponds only to the last two days of nutrient intake.
- Transferrin varies inversely with tissue iron stores, and the interpretation of its dosage is very complex.
- Total lymphocyte count does not change with ageing, but is remarkably reduced in states of malnourishment. Values below $1,500 \text{ per mm}^3$ may indicate marked immunosuppression [11].
- Numerous other specific serum levels can be useful per requested by the clinical state: folate, vitamin B₁₂ levels, calcium, phosphorus, zinc (...) [1].

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Biochemical and haematological changes in ageing and protein energy malnutrition (PEM) are quite subtle. With ageing, β -cell count decreases, which is normally observed in PEM. Furthermore, no auto-antibodies are found contrarily to PEM. Inversely, natural killer cells are high in ageing and low in PEM [8]. In malnutrition, the Insulin Growth Factor [IGF1] level is low and worsens with the alteration of nutritional status, the progression of disease and an increase of metabolic stress (hypothyroidism, hypo-insulinemia and low cortisol levels) [11]. In normal healthy volunteers, a 5-day fast decreased the [IGF1] level by 60 to 70% and was completely restored to initial levels by a refeeding period of eight days [11].

5-3-5 Body composition

The evaluation of the body composition in the elders is very complex. Different techniques are available. However, most of them are too invasive,

too expensive or not sensitive enough to use in older individuals in daily practice. It is clear that, with aging, body composition undergoes major changes.

- **Ageing changes in body composition**

Lean body mass (LBM) decreases with age from 45% of the total body weight in young adults (20 to 25 years) to 30% in older adults (60 to 65 years). The LBM decreases at the rate of 6 % per decade after the age of 30; by age 70, this represents a LBM loss of 5 kg in women and 12 kg in men[8,11]. The LBM decrease can be divided into two categories:

- A decrease in muscle mass (40%), liver mass (18%), kidney mass (9%) and lung mass (9%) [8,11].
- A change in total body water, more specifically a decrease in extra-cellular water. In normal healthy adults, 70% of the LBM is water while in older adults, it is only 60% [11].

In parallel, the “relative” fat body mass increases from 15% in young men to 25% of the total body weight in older men. In women, we can observe an increase of 25 to 35%. In addition, the total fat body mass (FBM) decreases with ageing, but at a lower rate (2% per decade) than the LBM (6% per decade) [11].

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The above-mentioned information was obtained and confirmed using high technological methods in nutritional laboratories. However, there question remains: what tools are accessible to the clinical practitioner to measure body composition?

- **Evaluation of the body composition in clinical practice**

Magnetic resonance imaging (MRI) gives excellent images showing the decrease of muscle mass, at the thigh level for example, but also the fat infiltration of the muscles that occurs with aging. However, this technique is very expensive, invasive and is not routinely used in practice for assessing nutritional status.

Bio-electrical impedance analysis (BIA) is a simple, non-invasive method for determining the relative proportion of fat, lean tissue and total body water and its sub compartments (extra-cellular, intracellular and third space water). The measurement is done with four electrodes, placed on the hands and feet, conducting a 50-kHz current at 800 μ A. Lean body, which contains water has a low resistance, while fat, which acts as an insulator has a high resistance. This allows for the calculation of fat and fat-free body mass with regression

equations. However, this technique is always difficult to apply and to interpret in frail old adults, with multiple diseases and changes in body water distribution (dehydration/oedema) [11]. In Geneva, BIA was used to compare 995 consecutive 55+ year old patients, admitted in the emergency room for an acute or sub-acute medical event, with 995 healthy, age- and height- matched volunteer adults [12]. Impedance analysis showed that fat-free mass was lower and fat mass was higher in acutely ill and chronically ill patients than the control group. The results of this study showed that weight and BMI incorrectly estimated these changes in body compartments. They were deemed as unreliable indicators, since it is unknown whether the weight changes were due to a decrease in fat free mass or an increase in fat mass [12].

5-4 Clinical tools for assessing the nutritional status

More than 40 nutritional assessment tools arise from the Medline and CINAHL search from 1975 to 2000 using the following key words: “nutritional-screening”, “nutritional-assessment methods”, and “reliability, validity and nutrition” [13]. Among this large inventory, only a few tools are currently used in clinical practice and will be analysed below:

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5-4-1 The “DETERMINE” checklist

It is a self-administered screening tool whereby each letter of its name corresponds to a mnemonics scored device [14]:

- **“D”** stands for Disease: “I have an illness or condition that made me change my food intake”.
- **“E”** for Eating problems: “I eat fewer than 2 meals per day; I eat few fruits or vegetables, little milk products and I have 3 or more drinks of beer, liquor or wine every day”.
- **“T”** for Tooth and mouth pain.
- **“E”** for Economical situation: I don’t always have enough money to buy the food I need.
- **“R”** stands for Reduced social contact: “I eat alone most of the time”.

- “M” for Multiple medicines: “I take 3 or more different prescribed or over-the-counter drugs/day”.
- “I” for Involuntary weight loss/gain of at least 10 pounds in the last 6 months.
- “N” for Needs of assistance for care: “I am not always physically able to shop, cook and/or feed myself”.
- “E” for Elderly, age is 80 years old and over.

This self-administered nutritional tool is not commonly used, however, it is a very simple, understandable instrument that may identify malnourished seniors or those at risk of malnutrition [14].

5-4-2 A simple nutritional assessment tool, called “LAW”

- “LAW” is a mnemonic device corresponding to the three items constituting this tool:
- “L” stands for Lymphocytes count, above or below 1,500 per millimetre.
- “A” signifies Albumin rate, above or below 35 grams per litre.
- “W” corresponds to Weight gain or loss.

5-4-3 The Malnutrition Universal Screening Tool (or MUST) from the British Association of Parenteral and Enteral Nutrition (BAPEN)

It is a five step screening tool, recommended by the European Society of Parenteral and Enteral Nutrition (ESPEN), used to identify adults who are malnourished or at risk of malnutrition. This tool was primarily developed to be used within communities where serious confounders of the effect of malnutrition are relatively rare [15].

5-4-4 The NRS-2002 (Nutritional Risk Screening)

The purpose of the NRS-2002 system is to detect the presence of malnutrition and the risk of developing malnutrition in hospitalized patients.

It contains nutritional components of the MUST as well as a grading of disease severity as a reflection of increased nutrient requirements [15].

5-4-5 The Subjective Global Assessment (SGA)

The SGA is not based on laboratory data, rather on:

- Medical history (weight change, dietary intake change, gastrointestinal symptoms, disease and its relation to nutritional requirements).
- Physical signs (loss of subcutaneous fat, muscle wasting, ankle oedema, sacral oedema, ascites).
- Functional signs (functional capacity).

The SGA allows a superficial evaluation of nutrition, which is observer-dependent due to its lack of specificity and reliability and a great difficulty of reassessment [16].

5-4-6 The Mini Nutritional Assessment (MNA)

Its purpose is the detection of malnourished patients or patients at risk of undernutrition in home care programs, hospitals or nursing homes. It is a combination of a screening and assessment tool which was validated against 3 diet markers:

- Anthropometric markers: height, weight, body mass index and skin fold thickness.
- Dietary intake: 3-day food record.
- Biological markers: albumin, pre-albumin, transferrin, retinol-binding protein, C-reactive protein, α 1-acid glycoprotein, ceruloplasmin, cholesterol, triglycerides, vitamins (A, D, E, B1, B2, B6, B12, and folate), copper, zinc, hematocrit, haemoglobin, and blood cell count.

The MNA scoring range is between 0 and 30; a score below 17 signifies true malnutrition, whereas a score between 17 and 24 attests a high risk of malnutrition and a score above 24 corresponds to a good nutritional status.

A 12-day inter-observer reliability study, including 67 newly admitted old residents of 2 Spanish nursing homes, revealed that the mean scores of the two assessments were 20.8 ± 5.4 vs. 21.3 ± 4.6 , which corresponded to an

intra-class consistency of 0.83 and 0.74. The test-retest variability (according to intra-class consistency) reached 0.89 for the total MNA score and for its continuing items [17]. This study proved that MNA has a good level of reliability, but that some nominal items of the classical MNA are slightly inconsistent. For this reason, a new form of MNA is now proposed with a few items (MNA-SF) [18]. In general, the MNA is the recommended method for the geriatric population.

5-4-7 Comparison of the different assessments tools

- **Comparison between SGA and MNA**

In 148 women and 113 men over the age of 65, the two methods were used at admission in a nursing home. The SGA identified 53% patients suffering from under-nutrition (sensitivity = 0.93 and specificity = 0.61), while the MNA detected 73% of undernourished or at risk of under-nutrition patients (sensitivity = 0.96 and specificity = 0.26) [19].

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- **Comparison between SGA, NRI, MUST and NRS-2002**

At hospital admission, 995 patients were assessed with 4 different nutritional tools: SGA (Subjective Global Assessment, used as referent tool), NRI (Nutritional Risk Index), MUST (Malnutrition Universal Screening Tool) and NSR-2002 (Nutritional Screening tool - 2002). Sensibility and specificity were 62% and 93% for NRI, 61% and 76% for MUST and, 49% and 89% for NSR-2002 [20].

- **Comparison between a large battery of tests including SGA, NRI, MUST, NRS-2002 and MNA**

This review suggests that MNA is the best clinical tool to evaluate the nutritional status of geriatric patients living at home, in a nursing home or who are hospitalized. They found a sensitivity of 96% and a specificity of 98% [21].

- **Comparison of 40 different nutrition assessment scales**

The evaluation criteria applied to each tool included a) its application, b) its development (content & format, derivation) and c) its reliability and

validity. The conclusion of the author is quite severe: “Not one tool is judged to have been published with sufficient care given to important aspects of its application, development and evaluation” [13].

5-5 Summary

Human nutrition is complex and eating is more than a question of nutrient intake; it is also a social event with psychological importance.

Nutritional assessment is an integral part of the overall care of the elderly [1]. Medical and diet history, as well as clinical symptoms/signs of the patients are important to consider. However, nutritional assessment is more detailed and precise. Numerous tools were developed to cope with the important risk of under-nutrition of seniors living either at home or in institution. Each tool has its own advantages, but also its disadvantages. However, it is important to use a tool which is easy to perform, valid, and reliable in detecting malnutrition risk in order to start an appropriate diet program to prevent disease, to facilitate recovery and to diminish the length of hospital stay. Moreover, adequate nutrition will enhance daily functioning and postpone the frailty/disablement process.

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6 – Role of nutrition in the frailty process and its consequences

Frailty is a state that is so strongly associated with ageing that it seems almost inevitable that most people will become frail as they age [1]. However, the term “frailty” is not interchangeable with comorbidity and disability [2]. In the 2006 meeting of the “Canadian Initiative on Frailty” in Montreal, the question, “Is frailty an accelerating ageing process?”, provoked very controversial answers from six internationally well-known experts in the field. In clinical practice, many geriatricians identify “frail older adults” as the subset of older persons with increased external vulnerability to stress.

The following will attempt to define frailty and the role of proper nutrition, as well as discuss the possibility of preventing or postponing it.

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6-1 Frailty is a life-long process

Frailty, a major problem in the elderly, corresponds to a decrease in function together with an increased vulnerability that ultimately leads to death [3]. There are several clinical presentations of frailty, depending on interacting variables such as age, gender, lifestyle, socio-economic status, co-morbidities, affective, cognitive and sensory impairments (...). However, frailty is a transitional state in the dynamic process, from robustness to functional decline. Along with this process there is a decrease of the “total” physiological reserve. A growing part of it is used to repair and maintain the function of the ageing body, which leads to the decrease of the remaining “available” reserves. Nevertheless, 30 % of the “normal” function still allows for adequate organ function [4].

6-1-1 The pre-frail process

The “pre-frail state” is a latent, clinically silent, but dynamic stage allowing the organism to respond adequately to any acute disease, injury or stress, with a chance of complete recovery.

6-1-2 The frailty state

The frailty state, clinically patent, is characterized by a slow and/or incomplete recovery after a new acute disease, injury or stress. It shows that the available functional reserves are insufficient to allow complete recovery. Thus, frailty appears as a stage of age-related physiologic vulnerability resulting from impaired homeostatic reserve and reduced capacity of the organism to withstand stress [5].

6-1-3 The frailty complications

The frailty state can lead to multiple interconnected complications such as recurrent falls, multiple and various trauma, functional decline, medication overuse, disability, hospitalization, nosocomial infection, institutionalization and death [6]. Moreover, personal suffering and caregiver burden should be added to this long list.

However, the recognition of frail elderly remains a key dilemma, because an operational or consensual definition of frailty is not yet defined. Frailty is a combination of impairments present before the functional decline, which ultimately leads to disability.

6-2 Physiopathology of the frailty process

The frailty process is more and more recognized as “an aggregate chronic and progressive process with a latent phase” [2]. The main goal is to

achieve a more comprehensive understanding on the underlying physiopathological mechanisms of this crucial, but latent “pre-frail” phase.

The “frailty cycle” usually begins in combination with ageing as well as the effects of a lack of physical activity, inadequate nutrition, unhealthy environment, injury, and disease and drugs side effects. These interconnected factors lead to chronic undernutrition, consolidated by age-related changes and a sedentary way of life, which causes loss of bone and skeletal muscle mass. Sarcopenia, with its decreased muscle strength/power, slows down walking speed and reduces respiratory function ($VO_2\text{Max}$), thereby emphasising the restriction of physical activity. These physiological changes result in an even greater decrease of resting metabolism and an important reduction of total energy expenditure, which eventually leads to chronic undernourishment. These events complete and help self-maintain the frailty cycle [2].

As mentioned above, sarcopenia plays a crucial role in the frailty process.

- Malnutrition is linked to sarcopenia; its biochemical markers are low plasma albumin, low vitamins C and E levels and increased reactive oxygen species (ROS) concentration.
- Inflammation with high levels of reactive protein (CRP), Inter Leukine (IL6), total white blood cells count including increased monocytes and leucocytes numbers are also part of the involved mechanisms.
- Hormonal deficiencies (Insulin Growth Factor - IGF1), dehydroandosterone sulphate (DHEAs) and testosterone play a role.
- Clotting factors (increased fibrinogen, factor VIII and D-dimers) interact with the previously mentioned abnormalities.
- These interconnected factors also depend on the central nervous system (CNS) which directs neural functioning (autonomic nervous system) and hormonal secretion (hypothalamic-pituitary axis) (2).

In general, the passage from the pre-frail phase (latent) to the frail state (clinically sounding above described phenotypes) is determined by any triggered event (injury, acute disease, psychological stress) of variable strength/importance. This suggests that the frailty process is linked to an inadequate adaptability of all of these interconnected systems, leading to a continuum from the latent phase over the frailty state, to complications, disability and death.

In this context, it is really important to integrate the multiple clinical consequences of this vicious frailty cycle. A 3-year survey has identified common outcomes associated with frailty: incident fall (OR = 1.18, 95% CI [0.63-2.19]), severe IADL disability (OR = 10.44, 95% CI [3.51-31.00]), severe ADL disability (OR = 15.79, 95% CI [5.83-42.78]) and death (OR = 6.03, 95% CI [3.00-12.08]) [7].

6-3 The clinical and biological phenotypes of frailty

6-3-1 The formally recognized clinical phenotypes of frailty

As no consensual definition of frailty exists, a need for agreement appears essential, even if this operational definition is probably transitory. The “Frailty task force” of the American Geriatric Society agreed to promote the definition of L. FRIED [5] as the best 2006 working definition:

- The frailty symptoms are unintentional weight loss (4 to 5 kg in one year), weakness (grip strength, bottom 20% dominant hand), fatigue, anorexia and physical inactivity.
- The frailty signs are undernutrition, sarcopenia, osteopenia, slow gait speed (bottom 20% for walking 15 feet), balance abnormalities and deconditioning.
- Moreover, the identified frailty risks are decreased resiliency and decreased ability to respond to stressors.

Two of the above mentioned symptoms/signs define the “pre-frail” state, while three of them correspond to the “frailty” state. Applying these criteria, the prevalence of frailty reached 6.9% in the population studied by Fried with a 4 year incidence of 7.2% [5].

6-3-2 Other important clinical domains of frailty

This functional definition of frailty is very useful, however it is only based on physical symptoms and signs, neglecting other potential important

components of the frailty syndrome such as mood, cognition, sensory disturbances and even socio-economic aspects of life. Is it possible to define frailty in only one unique physical domain? Are there several domains of frailty not yet explored and recognized as part of the frailty state [8]? Numerous new studies attempt to expand the frailty definition to other clinical domains.

• **The Beaver Dam Eye study**

This 4½ year-follow-up study, which introduces the frailty markers within the 1998-2000 data collection from the Beaver Dam Eye Study cohort (N = 2,962), demonstrates the following:

- “Robust” elderly (i.e. those who kept the best physiological reserves) have the best visual acuity and contrast sensibility when compared with the frailest elderly, who are defined in this study as being unable to stand from sitting in one try, having the slowest quartile gait time and the lowest quartile peak expiratory flow and hand grip strength [9].
- Gait time abnormality is an early sign of frailty. The inability to stand from sitting in one try, altered peak expiratory flow and grip strength is associated with severe frailty and the poorest survival, independently of age, gender and disease (diabetes, cardio-vascular diseases and arterial hypertension). However, the latter interfere directly with the severity of frailty and survival [10].

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Within the currently recognized definition of frailty, sensory impairment is not mentioned. Moreover, other signs are incorporated in this study’s definition of frailty, such as the ability to stand in one try from a sitting position or peak expiratory flow.

• **Depressive findings from the Cardiovascular Health Study**

This longitudinal study of daily functioning (ADL/IADL) and depression (10-item CES-D) in 5,888 old individuals, showed very interesting results in the understanding of frailty. Thus, the 4-year risk of functional decline corresponded to:

- O.R. = 1.00, in 378 non-depressed individuals or low intensity dysthymic patients (*matched on baseline ADL/IADL scores, gender and age*).
- O.R. = 2.39, 95% CI [1.55-3.69] in 259 temporarily depressed individuals.
- O.R. = 5.27, 95% CI [3.03-9.16] in 119 persistently depressed individuals [11].

In the previous definition of frailty, only fatigue or exhaustion is related to mood disturbances, which appear to be really important factors in frailty.

- **Cognitive speed and functional decline**

Numerous studies prove the strong impact of cognition on functional decline (12). One of the most demonstrative is the NUN's study, which is a cross sectional study including comprehensive cognitive and physical assessments, performed in 1992 (N = 678) and in 1994 (N = 575). Subjects with a low but normal cognitive function, in the first assessment, had a risk twice higher of being totally ADL dependent in the second assessment, than subjects with a higher cognitive function [13].

Once again, the previously discussed definition of frailty lacks the inclusion of cognitive speed and performances, which are considered rather important domains to mention.

6-3-3 Biological markers of frailty

- **Inflammatory bio mediators and frailty**

In 299 frail and 2,298 non-frail elderly individuals, CRP, fibrinogen, factor VIII and D-dimers were significantly higher in frail than in the non-frail group ($p < 0.001$) [14]. Moreover, the Duke Established Populations for Epidemiologic Studies of the Elderly, a 5-year follow-up of 1,723 subjects (aged >71 years), showed that the combination of the highest quartiles of serum levels of IL6 and D-dimers double the relative risk of death over a 5 year period [3].

- **Endocrine bio mediators and frailty**

Endocrine markers were also compared in the same population. Fasting glucose and insulin, as well as two-hour post-prandial glucose and insulin, were significantly higher in the frail compared to the non-frail subjects ($p < 0.001$) [3].

Moreover, serum levels of IGF1 and DHEAs are significantly lower in frail than in non-frail individuals [15].

6-4 The importance of early detection of frailty to avoid its consequences

The report of a few longitudinal studies will improve the understanding of why and when it is necessary to detect the frailty process:

6-4-1 Chin's study

The authors of this 3-year follow-up of functional decline and mortality in 450 persons, aged 69-89 years, found that the most significant symptoms associated with inactivity was neither low energy intake nor lean body mass, but rather unintentional weight loss. Physical inactivity, combined with unintentional weight loss, predicted both a significant 3-year disability risk (OR: 5.2, 95% CI [1.04-25.8]) and mortality risk (OR: 4.1, 95% CI [1.8-9.4]) in the studied population [16].

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6-4-2 L. FRIED's study

Being one of the best known studies on frailty, it consists of a secondary analysis of the Heart Longitudinal Study, which was a 3-year follow-up on 5,317 men and women, aged 65 years and older. The clinical syndrome of frailty included three of the five following symptoms: unintentional weight loss, self-reported exhaustion, slow walking speed, low physical activity or weakness (measured by the grip strength). The outcomes between frail and non-frail elderly were quite eye-opening after the 3-year follow-up period:

- 59 % of the frail had been hospitalised compared to 33 % of the non-frail.
- 28 % of the frail had a fall compared to 15 % of the non-frail.
- 39 % of the frail had worsening ADL compared to 8 % of the non-frail [5].

6-4-3 Ch LALIVE d'EPINAY's study

The SWILSO-O (Swiss Interdisciplinary Longitudinal Study on the Oldest Old) was a 4-year follow-up study of a randomized sample of 340 Swiss octogenarians living in a community environment and in institutions. The

syndrome of frailty included questions about 5 different domains: mobility, physical symptoms, sensory abilities, memory and energy. A frail octogenarian is defined as meeting at least 2 of the 5 criteria. At the end of the study period, the outcomes of the group defined as frail were significantly different from the non-frail group [17]:

- Fall (RR = 1.82, 95% IC [1.01-3.27])
- Diseases (RR = 2.73, 95% IC [1.58-4.71])
- Dependence (RR = 4.42, 95% IC [1.44-13.62])
- Death (RR = 2.02, 95% IC [1.25-3.27])

6-5 Frailty prevention

As noted above, the frailty process is at first latent and silent and not linked with overt disease. Its detection is only possible if a comprehensive geriatric assessment is conducted, allowing the start of a preventive program. The clinical recognition of frailty must lead to a rehabilitative program to postpone or reduce the drastic consequences leading to functional decline and death.

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The following consists of six possible preventive actions [18]:

- Adequate diet with sufficient proteins, vitamins and minerals intakes.
- Regular physical exercise practiced alone, at home or in groups, maintaining muscle strength and cardio-pulmonary reserves. A variety of different types of physical activity such as stretching, walking, dancing, dynamic balance exercises and lifting weights; all these represent efficient prevention actions.
- Regular monitoring of individual basic abilities: walking, equilibrium, exercise, cognition, weight.
- Prevention of acute diseases: flu, pneumococcal and herpes zoster vaccines.
- Better anticipation of stressful events (programmed surgery) with nutritional and respiratory interventions.
- Rapid retraining after stressful events: rapid re-nutrition, individualised physiotherapy.

Frailty prevention is effective, which has a significant reversibility potential, unlike ageing; therefore, it is important to differentiate between the

latter and frailty. Several recent studies confirm the reversible characteristics of frailty:

- The first study is a randomized controlled trial of 152 sedentary men and women (83 +/- 4 years) with mild to moderate physical frailty, as defined by the presence of two of the following three criteria: a) modified physical performance test (modified PPT) score, b) peak oxygen uptake and c) self-report of difficulty with one Basic or two instrumental activities of daily living (B- and I-ADL) (SFQ). The studied population was divided in two similar groups:
 - The control group benefited from a 9-month period flexibility exercise.
 - The exercising group benefited from a 9-month program including the flexibility exercise with light resistance, balance exercise as well as endurance training.
 - The results were impressive. At the end of the study, a) the modified PPT score was at 1 in the control group and 5.2 in the exercising group, b) the VO₂ peak was 0.9 ml/kg/mn in the control group and 3.6 ml/kg/mn in the exercising group, and c) the SFQ reached 1.6 and 4.9 respectively in the control and exercising group [19].
- The second study is also a randomized controlled trial involving 188 sedentary men and women (aged 75 and over), living at home with mild to moderate physical frailty. Each participant received a disability score scaled between 1 (light disability) to 16 (severe disability). Two comparable groups were formed :
 - The control group (disability score = 2.8 at the start of the study) benefited from a 12-month educational program.
 - The exercising group (disability score = 2.3 at the start of the study) benefited during the same period from the same educational program together with muscle strength and balance exercises, physiotherapy, ability to transfer and mobility training.
- The between-group comparison of the disability score is notable:
 - The mean disability score of the control group worsened from 2.8 at the start of the study, to 3.6 after 7 months and 4.2 at the end of the study.
 - The exercising group stabilized from 2.3 at the start, to 2.0 at 7 months and 2.7 at 12 months [20].

Both studies demonstrate that frailty is preventable and that the progression of frailty/disability can be slowed down and delayed.

VANITALLIE TB had mentioned that “One characteristic of the frailty syndrome, that distinguishes it from the effects of aging per se, is the potential reversibility of many of its features” [21].

6-6 Summary

One of the most imperative questions is how to differentiate the frailty concept from normal ageing and from accelerated ageing. Although this differentiation is not exact, there has been significant progress surrounding this issue:

- Frailty is the brutal revelation of a silent underlying process by a stressor. This is identified by biological changes and altered nutritional markers (albumin), increased inflammatory responses (IL6 and CRP), modification of the clotting process (Factor VIII, D-Dimers), and alteration of endocrine regulations (glucose intolerance, IGF1, androgen, DHEAs and cortisol). This pre-frail process does not necessarily happen in a co-morbid context.
- The present definition of frailty includes physical symptoms such as weakness, slowed performance, unintentional weight loss, fatigue and low activity. However, in the near future, this definition will probably be expanded by including additional domains (depression and cognition).
- The detection and the recognition of frailty are important to prevent or postpone multiple drastic consequences: repeated falls, fractures, increased medication use, hospitalisation, nosocomial infections, institutionalisation and death. Proposed interventions should not neglect the personal suffering of the frail elderly and their families.

Advanced knowledge of genetics and molecular mechanisms of the frailty process will transform this concept in a real syndrome or perhaps a disease, resulting in the concept that frailty is different from ageing because the former is reversible whereas the latter is not.

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7 - Sarcopenia: a consequence of protein energy malnutrition

Protein energy malnutrition (PEM) has many consequences. It primarily starts out as a latent and progressive immunological dysfunction, which is often represented by recurrent or nosocomial infections. A further consequence of PEM is skin atrophy which leads to decubitus ulcers in bedridden old patients.

Between these two stages of PEM, sarcopenia, osteoporosis with falls and fractures are common. These PEM consequences can lead to an important functional decline and disability. It is important to better understand the mechanisms of sarcopenia in order to improve prevention methods against its clinical irreversibility (e.g. bone loss, which is addressed in Chapter 8).

7-1 Definition of sarcopenia

Sarcopenia is an involuntary loss of skeletal muscle mass, combined with decrease of strength and function, leading to poor mobility and disability, and the incapacity to meet the extra demand of protein synthesis associated with disease and injury [1, 3]. This definition explains why sarcopenia is considered as “more than a vital sign” [4].

In spite of a high individual variation [5], muscle mass peaks at young adulthood (at around the age of 30) and eventually decreases by approximately 3-8 % per decade. The rate of the decline is even higher after the age of 60 [6]. The loss of skeletal muscle reaches 50 % by age 90 [7].

Sarcopenia is part of the frailty syndrome (see Chapter 6 for more on this topic).

7-2 Diagnosis of sarcopenia

The clinical evaluation of muscle mass loss is confirmed by medical imaging. The most valuable techniques are regional MRI and computed tomography (CT), which clearly illustrate any decrease of muscle volume and the important fat infiltration within the muscle and its surrounding. However, these techniques are not used often in clinical practice. Dual X-ray absorptiometry (DEXA) can also be used to determine the severity of sarcopenia, but the most commonly used technique is bioelectrical impedance (BIA) measurement [7,8].

Using BIA measurements of skeletal muscle index (SMI = skeletal muscle mass / BMI x 100) in 4,504 adults over 60 and participating in the third National Health and Nutrition Examination Survey (NHANES III), two categories of sarcopenia have been defined, in comparison to a « referent » SMI established in a group of young adults (18-39 years):

- Class I sarcopenia: less than 2 standard deviations from the « referent » SMI.
- Class II sarcopenia: more than 2 standard deviations from the « referent » SMI [9].

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This classification is very important in epidemiological studies, as will be shown later. The inconvenience with the BIA technique is that it only offers an indirect method of muscle mass estimation, which reflects the importance of standardization and the use of correct regression equations.

7-3 Epidemiology of sarcopenia

The prevalence of clinical sarcopenia in 337 healthy volunteers reaches 23 % in women and 27 % in men [10]. Between the ages of 70-80 years, it increases to about 20% to 50%, respectively. However, sarcopenia is more common in women than in men at the age of 70, and vice-versa at the age of 80 [7]. Moreover, sarcopenia is not only present in lean people but can also be seen in overweight persons, which highly complicates its clinical recognition. Among overweight 70+ and 80+ individuals, 10% and 5%, respectively, suffer from sarcopenia [11].

The use of BIA in the third National Health and Nutrition Examination Survey (NHANES III) confirms the existence of sarcopenia class I in 59 % after the sixth decade and sarcopenia class II in 10% in the same age group (see above paragraph). Moreover, sarcopenia class II was found to be significantly more prevalent in men than in women ($p < 0.001$) [9].

7-4 Mechanisms of sarcopenia

Sarcopenia is an integral part of ageing, and occurs even in the most elite of athletes, although it is clearly accelerated by physical inactivity [12]. Many of the changes that accompany physical inactivity coincide with those that occur during ageing [13].

Disuse or « lack of use » or « inappropriately modulated stimulation » is linked to three different clinical conditions:

- Insufficient exercise or physical inactivity.
- Bed rest, superimposed on ageing changes and/or disease(s), decrease physiologic reserves and accelerate functional decline.
- Lack of gravity or weightlessness in space causes the same changes than ageing and disuse [13].

The relationship between disuse due to insufficient exercise, bed rest or lack of gravity and ageing has some definite practical implications: a further decrease of physiologic reserves and an increased prevalence of pathology and disability [14].

To explain these changes on the muscular level, several mechanisms are evoked:

Mechanism 1: Specific age-related alterations at the cellular level of muscles

These changes are numerous and significant:

- Skeletal muscle mass decreases through the loss of individual myofibrils [15];
- Sarcomere spacing becomes disorganized;
- Muscle nuclei become centralized along the fibres;
- Plasma membrane is less excitable;
- Significant increase in fat within and around the muscle cells;
- The number of motoneurons decreases;
- Neuron regeneration is reduced;

- Fast-twitch type II fibers are less abundant;
- Sarcoplasmic reticulum volume decreases;
- Calcium pumping capacity diminishes [16].

Mechanism 2: Specific age-related alterations at the biochemical and metabolic levels of skeletal muscles

Mitochondrial DNA deletion mutations correspond to a reduction of glycolytic and oxidative enzymes, as well as a decrease of creatine phosphate and ATP stores. This is linked to a) oxidative damage and b) reduced mitochondrial protein synthesis, resulting in a decrease by 30 % in the ability to use O₂ during exercise [16].

These age-related muscle changes are associated with a deterioration of the VO₂ max, at a median rate of 0.5 % per year in normal subjects [17]. The VO₂ max acts as a « central biomarker »; muscle power deteriorates at a median rate of 0.75 % per year in competitive cyclists [18] and of 1 % per year in a bedridden individual [19].

Mechanism 3: Reduction in the basal muscle protein synthesis

Chemical and physical alterations in skeletal muscle proteins decrease the rate of contractile mitochondrial and enzyme protein synthesis. The clinical expression of this lower basal muscle protein synthesis is a reduction of a) the maximum voluntary muscle strength, b) the muscle strength per unit of muscle mass and c) the muscle power [20]. However, this theory is actually challenged because a cohort of healthy aged men does not show any difference in basal muscle protein turnover compared to young controls [21].

Mechanism 4: Muscle catabolism through chronic inflammation

Chronic inflammation, infections and malignant tumours are characterized by an increased secretion of cytokines (IL-1, IL-6 and TNF-alpha) that has a direct catabolic effect. Cytokines induce an increase insulin resistance (lipolysis) and a reduction of dietary energy intake (anorexia) and of GH and IGF₁ concentrations (protein degradation and slow albumin synthesis). The biological markers of these alterations are an elevated CRP and decreased plasma albumin; this triggers a loss of muscle cells (apoptosis), which occurs even in the absence of overt inflammatory disease [22, 24].

Mechanism 5: Endocrine changes within the muscles

Several important hormonal changes occur with ageing:

- Testosterone plasma level is below the normal values (young men) in 60 % of men over 65 (andropause).
- In women, estradiol has a marginal role in sarcopenia.
- Growth hormone and IGF-I : A cross-sectional analysis of IGF-I levels in 617 healthy community-dwelling women aged 70-79 years demonstrates that low IGF-1 levels are associated with a) slow walking speed ($P < 0.001$), b) poor knee extensor muscle strength ($P = 0.004$) and c) self-reported difficulty with mobility tasks [25].
- Dehydroepiandrosterone (DHEA) decreases fivefold in very old men compared with their younger counterparts, but its role in sarcopenia development is not affirmed.
- Insulin: With ageing, there is a change in body composition with the appearance of glucose intolerance and insulin resistance. This insulin resistance exists per unit of body mass but not per unit of lean body mass. Insulin resistance may be an important contributor to sarcopenia [26].

There is no unique mechanism able to explain entirely the development of sarcopenia with ageing. Multiple interacting mechanisms are most likely involved in the loss of skeletal muscle cells/mass.

7-5 Consequences of sarcopenia

The main consequences of sarcopenia are an increased risk of falling, a greater vulnerability to injury, functional decline, disability and increased death rate [27, 28]. Body composition changes appear, such as increased fat mass, decreased bone density, joint stiffness and stature modification (kyphosis). Moreover, these consequences linked to sarcopenia are even more severe in patients with diabetes type II, heart failure, obesity and osteoporosis [16].

The relationship between sarcopenia (measured by bio-impedance analysis) and disability (self-report) is well demonstrated by an 8-year follow-up study of 5,036 non- institutionalized participants in the Cardio-vascular

Health Survey [29]. The cross-sectional analysis of the likelihood of developing disability is only significantly positive with sarcopenia type II ($p < 0.001$). In class II sarcopenic patients, functional impairment and disability are two times greater in men and three times greater in women compared with persons with « referent » values of SMI [29].

A major clinical challenge is to identify sarcopenia in its early stages in order to prevent the disability outcome. Several studies have been able to offer interesting suggestions on the matter:

- *Walking/climbing ability and speed as predictor of disability* (The Women's Health and Aging study II). At baseline, among 436 community-dwelling not cognitively impaired women (70-80 years), 69.3 % have no difficulty with mobility. After 18 months, 16 % reported difficulty in walking half a mile. [Self-reported task modification [OR = 3.67] and walking speed (0.5 m/s difference) [OR = 2.16] and climbing up 10 stairs (11.7%), self-reported task modification [OR = 3.84] and stair climb speed (1/3 step/s difference) [OR= 2.08] [30].
- *Maximal grip strength as predictor of disability* (the Honolulu Heart Program). The maximal hand grip strength was measured from 1965 through 1970. The 3,218 survivors participated in the disability assessment from 1991 through 1993. The risk of functional limitations and disability is higher when baseline hand grip strength was lower. The risk of self-care disability (in activities of daily living) has doubled in the lowest grip strength group [31].
- *Interleukin 6 (IL6) as marker of disability*. IL6 is measured in 620 women (> 65 years) with moderate to severe disability. A serum level of IL6 > 3.1 pg/ml is associated with ADL disability, OR 1.4 (1.0-2.0) and severe walking limitations, OR 1.6 (1.0-2.4) [32].

Sarcopenia, a cause of disability, can potentially be reversed. Therefore, sarcopenia has to be recognized at its early stage to intervene as soon as possible with disability prevention programs.

7-6 Sarcopenia prevention

7-6-1 Physical exercises

The development of sarcopenia can be slowed down or reversed with high-intensity resistance [33]. Resistance exercise acutely and dramatically

increase the rate of muscle protein synthesis, muscle hypertrophy and improve muscle strength [34].

Prevention of an epidemic of sarcopenia-induced frailty will have to include public health interventions to prevent disability in aging adults [35].

7-6-2 Nutrition

Protein intake not associated with physical exercise has no significant positive action on sarcopenia. In association with physical activity, protein intake facilitates sarcopenia reversibility.

Ageing is associated with reductions in muscle mass and strength, but nutritional and exercise interventions can delay this progression and enhance the quality of life.

7-6-3 Medications

• Testosterone

It is proved that testosterone supplementation significantly increases muscle synthesis and fat free mass in:

- HIV-infected men with low testosterone levels;
- Older men with low testosterone concentrations.

The mechanisms by which testosterone increases muscle mass are unknown, but possibly involve modifications in the expression of multiple muscle growth regulators [38].

However, in healthy old men, with a “normal” age-related testosterone level, it is not demonstrated that injectable testosterone supplementation can:

- Enhance both physical function and health-related quality of life and;
- Prevent risk of falling and disability.

New data concerning oral testosterone supplementation (oxymetholone 50 and 100mg/d during 12 weeks) in 31 men between 65 and 80 years old seem very encouraging, without deleterious side effects [36]. Yet, these results still need to be confirmed.

- **Non steroid anti-inflammatory drugs (NSAI)**

As previously mentioned, chronic inflammation increases sarcopenia. To inhibit the inflammatory effect of tIL6, it is proposed to prescribe NSAI [32]. However it is not yet proved that NSAI may be useful for this indication.

- **Growth hormone secretagogue**

Very promising approach, but until now, no positive result exists.

7-7 Summary

Ageing is associated with reductions in both muscle mass and strength. Sarcopenia, which is part of the normal ageing process, is a key symptom of the frailty syndrome, which appears as a transitional state between robustness and functional decline. This is why an early detection of sarcopenia is crucial in order to prevent its irreversibility to disability and death. A better understanding of the multiple and interacting physiopathological pathways (cellular, biochemical, metabolic, inflammatory and hormonal changes), which cause sarcopenia, will considerably help to prevent a future sarcopenia pandemic. Unfortunately, at this moment, only high resistance exercise, possibly associated with a protein energetic diet, prove their effectiveness in reversing sarcopenia and avoiding its drastic consequences.

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8 – Nutrition and bone metabolism

The 2001 Behavioural Risk Factor Surveillance System demonstrated that 59 % of 65 year-olds and over suffer from chronic conditions associated with musculoskeletal ageing [1]. Osteoarthritis, sarcopenia, osteopenia and osteoporosis are responsible for serious functional and economic burden [2]. These pathologies are related to macronutrient excess as well as deficiencies:

- Macronutrients excess: obesity increases the risk for arterial hypertension, hyperlipidemia, coronary heart diseases, insulin resistance, non-insulin-dependent diabetes, and also osteoarthritis and functional decline.
- Macronutrients deficit: protein-energy-malnutrition (PEM) is frequently associated with deficiencies in micronutrients (such as vitamins D, B₁₂ and folates) and minerals (such as calcium) which lead to weight loss, sarcopenia, osteopenia and osteoporosis. These deficiencies increase the risk of infections, falls, fractures and functional decline.

This chapter will essentially focus on nutrient deficits, especially in relation to osteopenia and osteoporosis. (Sarcopenia is covered in Chapter 7).

8-1 The problem of bone mass loss and its consequences

The worldwide number of osteoporotic hip fractures was 1.66 million in 1990 and is expected to rise to 6.26 million in 2050. This considerable increase will mainly occur in Europe and the United States but may also appear in the older population in Asia and South America [3]. Besides hip fractures, osteopenia and osteoporosis also affect other fractures sites. A woman in her fifth decade, who presents with either a forearm or proximal humerus fracture, has an expected decrease in lifespan by 21 and 13 % respectively [4]. If, during her remaining lifetime, there is neither nutritional intervention nor bone loss treatment, the risk of a new fracture is extremely high, which will precipitate her functional decline.

8-2 Osteoporosis

8-2-1 Definition of osteoporosis

Osteoporosis is a disease characterized by a bone mass decrease and an alteration of the bone micro-architecture which leads to an increased risk of fractures [5]. Bone is made up of living tissue which modifies its shape with ageing. As the external long bone circumference and the internal bone marrow hole increases in size, the cortical bone becomes thinner and more prone to fracture. After the age of 50, the risk of fracture reaches 50% for women and 20% for men.

In Geneva, a 5-year follow-up analysis (1993-97) of all (> 95 %) hip-fractured patients proved that 92 % of them were linked to a low impact trauma (fall from standing height) [6]. After the age of 70, more than 90 % of hip fractures are linked to either osteopenia or osteoporosis [7]. Moreover, it has recently been demonstrated that there is a positive association between bone mineral density (BMD) and dietary protein intake (DPI). This means that undernutrition, or more precisely low protein intake, is a highly significant risk factor osteoporotic fracture [8].

8-2-2 Osteoporosis process

During the normal bone regulatory system (resorption–formation), there is a comparable amount of bone mass at the start and the end of the cycle. In osteoporosis, there is an increased resorption which is not adequately compensated by bone formation, thereby resulting in a loss of bone mass at the end of the cycle. The same sequence occurs when an oestrogen deficit exists and/or when there is a reduced protein intake [9].

8-2-3 Osteoporosis, sexual hormone deprivation and protein undernutrition

Experiments in rats confirm the important interaction between sexual hormone deprivation, low intake in protein and a loss of bone mass. At day 1, female rats fed by an isocaloric diet including 15 % of casein, underwent an ovariectomy or a sham procedure. After an autopsy performed at week 15, the

lumbar spine bone mass density (BMD) was evaluated by using a special crush press. Compared to the sham rats, the ovariectomized rats lost 5 to 10% of their BMD (g/cm^2) during the study period [9]. A similar experiment, in rats fed an isocaloric diet now including only 2.5% of casein, showed that BMD (g/cm^2) decreased during the study period by 10 to 15% in sham rats and by 15 to 20% in ovariectomized rats [9]. This study affirmed that sexual hormone deprivation as well as protein undernutrition may lead to the development of osteoporosis; the effects are additive. This means that 50 to 60 % of the variation in bone strength can be predicted (sexual hormonal deprivation and low protein intake) [10].

8-2-4 Role of protein undernutrition in the osteoporosis process

Protein undernutrition decreases IGF1 secretion, which in turn decreases both bone mass density and skeletal muscle mass, ultimately leading to falls. The combination of all these phenomena increases the fracture risk and the potential drastic complications of fractures. However, if the proper corrective measures are taken in regards to protein undernutrition, this inverses the process, leading to an increase in IGF1 secretion and in bone and muscle masses, thereby decreasing fracture risk [11].

These observations were supported by animal experiments. Female ovariectomized rats fed a low protein diet had a significant decrease of their lumbar spine BMD at week 10. The addition in the rats' diet of 5 essential amino acids completely restored the loss in BMD within the next ten weeks [12].

In conclusion, it is possible that low protein diets favour osteoporosis and that an adequate protein intake may facilitate the restoration of a normal bone mass density in rats. However, the results in humans are still unclear.

8-3 Falls

8-3-1 Fall incidence and prevalence

Studies performed in 921 community dwelling 65+ subjects (1995-1996) and in 2,400 patients hospitalized in the Geneva geriatric hospital (1996-1997) revealed that fall incidences varied from 28 to 30 % [13]. Moreover, the incidence, which was low (10 to 15%) in the 50-year-old individuals, reached

40 % in men and 50 % in women over 85 [13]. In 2002, in the Geneva geriatric hospital, 32 % of the 3,688 admitted patients fell during their hospital stay. Among those, 2.3 % experienced a fracture and 8.8 % suffered residual pain after the injury.

8-3-2 Fall mechanisms

Generally, falling is a multifactorial occurrence that can be classified in three main categories.

- Environmental factors: place of living, lighting, stairs, and carpets.
- Behavioural factors: physical activity, climbing up on a chair to change a lamp or coming back from the toilets.
- Intrinsic factors: individual health, sarcopenia, arterial hypotension, sensory disturbances.
- Medication effects: benzodiazepine

8-3-3 Fall consequences

As previously mentioned, fractures (particularly hip fractures) are linked to the most dramatic consequences.

8-3-4 Fall assessment

Unlike a unique fall which does not need specific investigation, repeated falls, or the occurrence of a previous fall in the last year, demand a global comprehensive assessment. This should not only include mobility tests, but also a detailed nutritional assessment to accurately determine an appropriate intervention program [14].

8-4 Post-fracture physical and nutritional programs

Every post-fracture rehabilitation program has two major goals:

- To restore independence and reduce disability.
- To prevent new fractures.

8-4-1 Restoration of independence

- **Physical training**

Power training and high resistance training associated with complex exercises increase one's coordination, equilibrium and ability in function. This program can be achieved by leading a normal lifestyle (home maintenance, stairs, urban life, public transportation and gardening).

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- **Nutritional program**

Protein supplements given in post surgery for hip fracture are very efficient in facilitating the patient's rehabilitation and recovery. It allows for a reduced hospitalization period as demonstrated by the Geneva study comparing the outcomes of hip fracture among two groups of patients: one receiving physiotherapy (control group) and the other receiving physiotherapy plus 20 grams per day of protein supplement (intervention group). The mean hospitalization period in surgery and rehabilitation was 53 ± 4.6 days for the control group and 42.2 ± 6.6 days for the intervention group [15]. Moreover, it was shown that the length of hospital stay post-hip fracture surgery is inversely correlated to IGF1 levels, bicep strength and the intake of protein supplements [15].

The results of this clinical study show the significant benefit of protein supplements in hip fracture patients and confirm previous findings in animal experiments.

8-4-2 - Prevention of subsequent fractures

Osteoporosis appears with or without fractures. In the latter case, the first fracture is either unidentified or neglected, which is very common in spine fractures. Vertebral compression fractures are often discovered on pulmonary X-rays, but only 47 % of the women with such fractures knew that they were suffering from osteoporosis before this examination. Moreover, only 69 % who knew the diagnosis were treated for osteoporosis [16].

The significance of a first fracture after a low-impact trauma confirms the existence of a potent osteoporotic disease. The occurrence of subsequent fractures is likely without any diet adaptation or physical/physiotherapy program or medications. Therefore, in order to prevent these repeated fractures, a multidisciplinary osteoporotic treatment program should be followed for all cases of surgery of a low impact trauma fracture.

The first step is collecting information on dietary habits and osteoporosis/fall risk factors. The second step involves confirming the osteoporotic aetiology of the fracture performing a bone densitometry examination (completed by dosages of nutritional parameters and biomarkers of bone metabolism). Finally, the third step, in collaboration with the patient's general practitioner (GP), consists in offering dietary advice, an educational program and osteoporosis treatment. The follow-up is administered by the patient's GP [17]. The initial results of such program are really encouraging. The patients and their family members usually participate with enthusiasm when solicited.

8-5 Long-term prevention of osteoporosis

Two complementary strategies are possible:

- Population-based strategies
- Identification of subjects at risk

8-5-1 Population-based strategies

The peak bone mass is built during childhood and teenage years, thus it is essential to accrue bone mineral mass during the first two decades of life.

Calcium intake and physical exercise in childhood and adolescence will determine, in great part, the peak bone mass in adulthood and subsequently, the osteoporotic fracture risk in old age.

Numerous studies show the positive preventive effects of an optimal diet (see Chapter 4 for more on nutrient requirements) [18]:

- Calcium: the daily recommended allowance (RDA) for older adults is 1200 mg/day. Its positive effect is demonstrated by randomized controlled and observational studies.
- Proteins: the RDA for the elderly is 1 to 1.2 g/kg/day. The positive effect of protein intake is proved by experiments in animal models and by cohort studies in humans. It is important to note that a high protein diet does not cause kidney problems in the absence of pre-existing renal disease [19].
- Vitamin D: the RDA for adults between the ages of 50 to 70 are 400 IU/d and after the age of 70, 600 to 800 IU/d. Numerous case-control studies attest the real positive effects of this daily consumption.
- Lastly, it is extremely important to highlight the positive results from the association of vitamin D (400 IU/d) and calcium (1200 mg/d) in old adults living in nursing homes; the non-vertebral fractures decreases by 30 % and the hip fractures by 41 % [20].

8-5-2 Osteoporosis prevention in subjects at risk

The following factors are key in identifying subjects at risk for osteoporosis:

- Previous fractures (vertebral or fragility fractures after the age of 40);
- Risk factor(s) (sedentary life, ovariectomy and institutionalization)
- Chronic diseases (renal diseases) and;
- Glucocorticoids treatment (≥ 5 mg/d, > 3 months)

Bone mineral density measurement is an essential parameter to guide clinical decisions [21]. When the T score is:

- < - 1.5: apply general measures (appropriate diet and physical exercise) and schedule a new bone densitometer examination after 12 to 24 months.
- < - 2: determine bone marker levels and offer advice for general measures (see above) associated with/without regimen treatment for bone loss.
- \leq - 2.5: determine bone markers, apply general measures (see above) and bone loss treatments.

In any case, a new bone densitometer exam must be scheduled in 18 to 24 months to evaluate the treatment's effectiveness.

8-6 Summary

The actual epidemic of falls and fractures, essentially linked to an ageing demographic, needs to be controlled as soon as possible. Osteoporosis is a condition that develops over many years without obvious symptoms; nutrient intake and physical exercise in childhood and adolescence are very important to attain a high peak bone mass which will protect against fracture at older age.

Among the osteoporosis mechanisms, the role of sexual hormonal deficiency and inadequate protein intake are clearly demonstrated both in animal models and in humans. Their synergistic actions increase the speed and severity of the osteoporotic process.

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A simple treatment such as sufficient dietary consumption of calcium, proteins and vitamins D coupled with physical activity, has shown to be effective at the population level. Moreover, a more accurate identification of risk factors for osteoporosis and individuals at risk allows for an early diagnosis; in turn, this ensures that the above-mentioned general measures will be taken in addition to an appropriate treatment for bone loss. The efficiency of such preventive and therapeutical strategies has been clearly established in randomized controlled trials, resulting in a significant decrease of fracture incidence as the primary end-point.

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9 – Nutrition and the process of atherosclerosis: preventive challenges

Atherosclerosis, which corresponds to the deposits of fatty plaques (*atheromas*) containing cholesterol, lipid material and lipophages within the intima and the inner media of large to medium-sized arteries, is the most common cause of chronic arterial narrowing [1]. Atherosclerosis is a multifactorial disease in which complex interactions between genetics and environmental factors appear to play an important role [2].

In fact, the relationship between diet and atherosclerosis was first reported in 1913 by ANICHKOV and CHALATOV who experimentally induced atherosclerotic lesions in rabbits on a high cholesterol diet. In the fifties, high plasma levels of cholesterol in humans were shown to be related to the intake of saturated fatty acids. Since then, multiple epidemiological studies have demonstrated that diet high in saturated fat as well as hypercholesterolemia are the primary causes of atherosclerosis and cardiovascular diseases in humans [3].

Several alarming pathological findings prove that atherosclerosis must be considered as a lifelong process:

- Autopsies of young soldiers who were killed in the Korean and Vietnam wars showed the presence of atherosclerosis [4-5].
- Identical findings were observed in autopsies of children and adolescents who died from accidents, homicides or suicides [6-7].
- Studies of babies born at the beginning of the 20th century, showed that intra-uterine and childhood development contribute to later cardiovascular risks [8].

Such data stress that exposure to high levels of cholesterol in early life may negatively affect future health [9]. Moreover, it is proved that a high LDL cholesterol level, an increased body mass index and other cardiovascular risk

factors during childhood significantly predict the increase of the carotid intima-media thickness in adulthood [9]. Conversely, a reduced exposure to cardiovascular risk factors in early life is associated with a lower coronary mortality rate in later years [10].

9-1 Impact of atherosclerosis on cardio- and neurovascular diseases

Non-communicable diseases are the leading causes of bad health conditions and death in developed countries (75 to 80 %) and are also becoming more prevalent (35 to 40 %) in developing countries [12]. These neuro- and cardiovascular pathologies represent 39 and 47 % (in both men and women respectively) of the 2004 reported causes of death within the European Union [11].

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In different countries of the European Union, the evolutionary trend may vary according to socio-economic changes [11]. For men aged 35-74 years old living in Austria, Denmark, France and UK, the prevalence of cardiovascular diseases decreased between 1968 and 2004. Opposite findings were observed in countries like Romania and Ukraine. Nonetheless, a cardio-vascular disease paradox exists: the decrease in midlife cardiovascular mortality, which corresponds to real global medical progress, results in a larger number of survivors who will develop heart failure at an older age.

Stroke is also a leading cause of death and disability [12]. As for cardiovascular diseases, there was a differential decrease of stroke incidence which was more dominant in Western rather than Eastern European countries. Age is also an important determinant [13].

Arterial hypertension represents another key problem closely linked with atherosclerosis. Epidemiological studies now emphasize important risk factors such as systolic blood pressure and pulse pressure [14]. Among hypertensive men, 39 % will present at least one atherosclerotic coronary event while 68 % of hypertensive women will do so [14]. The need for a multisystemic assessment is imperative in hypertensive patients as well as an adequate treatment and a good patient compliance. A recent Spanish study showed that although 85.1 % of the 60+ hypertensive patients who were being treated for their hypertension, only 16 % of them presented good blood pressure control [15].

9-2 The atherosclerosis process

As previously mentioned, atherosclerosis is a multifactor disease with complex interactions between genetic and environmental components, explaining the high variation in individual susceptibility [2]. The following is an analysis of the various stages of the atherosclerosis:

9-2-1 The genetic predisposition to different types of diet

Individuals homo- or heterozygote for Apolipoprotein E4 (Apo E4) have a higher plasma cholesterol level, a higher sensibility to the detrimental health impacts of high fat/high cholesterol diets and an increased incidence of coronary heart diseases (CHD). However, Apo E2 heterozygote individuals have, in general, lower plasma cholesterol levels and less CHD compared to the general population [16-17].

Apolipoprotein A4 (Apo A4) subjects have attenuated hyperlipidemia and hypercholesterolemia even in the case of low fat diet [18]. Homozygotes Apo B27 have a higher mean plasma cholesterol level in response to the same fat/cholesterol diet compared with homozygotes B24 [19], while Apo B26 carriers have an impaired regulation of cholesterol biosynthesis and in consequence, develop severe atherosclerosis when under a high cholesterol diet [19]. This inter-individual genetic variability explains the large discrepancy in diet-induced metabolic disturbances in response to saturated fatty acids or a high cholesterol diet [2]. Advanced knowledge and additional research of genetic factors will identify important pathways involved in the atherosclerosis process and allow the development of more precise biomarkers, which will likely result in the development of more specific drugs [2].

9-2-2 The endothelial dysfunction

The arterial walls are constantly under stress from numerous aggressors such as high plasma levels of glucose, cholesterol and triglycerides but also from increased systolic/pulse blood pressure. Moreover, these aggressors are also linked to the production of free radicals, thereby leading to a decrease of tetrahydrobiopterin and a reduced availability of nitric oxide (NO). These

multiple and life-long aggressors of the arterial walls gradually modify the endothelium function and increase the thickness of the intima and media of the arteries. Changes in arterial wall clotting ability and local inflammatory processes are a consequence of this chain of events [20-21].

9-2-3 The arterial wall inflammatory cascade

The endothelium dysfunction is both worsened and self-maintained by multiple interactions between the pro- and anti-inflammatory cytokines within the arterial wall and circulating blood [1]. Countless inflammatory modifications can be detected such as elevated circulating cytokines, increased adhesion molecules, tissue molecules and selectins, increased plasma level of Von Willebrand factor, CRP and fibrinogen [22-23]. In parallel, decreased erythrocyte deformability and increased erythrocytes aggregation both contribute to a higher blood viscosity which ultimately result slows the blood flow [24-25].

The global results of this inflammatory cascade are smooth muscle cell proliferation, facilitated leucocyte adhesion, an impaired blood flow and an increased risk of thrombosis [1].

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Atherosclerosis can be considered as an “inflammatory disease”, but until now, it seems impossible to confirm that the inflammatory process plays an initial role in both the endothelium dysfunction and the atherosclerosis plaque formation. Indeed, nutrition also intervenes in this process by modulating serum lipids and by interfering with the immune and inflammatory processes within the endothelium itself [1].

9-3 Diet and the atherosclerotic process

As previously stated, atherosclerosis represents the most common cause of chronic arterial narrowing, which leads to coronary heart diseases and stroke.

9-3-1 Reduction of saturated fatty acids

– *Trans-fatty acids* - usually found in stick margarine, vegetable shortenings, commercial bakery and deep fried foods - decrease serum HDL cholesterol

levels and increase LDL cholesterol and triglycerides. At the same time, trans-fatty acids alter the endothelial function, reduce the flow-mediated dilation and increase insulin resistance [26-27].

- *Saturated fatty acids* increase LDL cholesterol, while polyunsaturated fatty acids decrease them [3].

However, the largest and most detailed analysis, involving 4 repeated measures of diet over 14 years among 80,082 women (the Nurses' Health Study cohort), demonstrated that the opposite effects of different types of fat intake do not allow us to predict cardiovascular risks [28].

9-3-2 High polyunsaturated fat intake

Two major studies discussed the high intake of polyunsaturated fatty acids in atherosclerosis prevention (with or without a reduction of total fat intake):

- The Finnish study [29] followed 676 men without CHD history over a 6-year period. In comparison to the diet of the control group, the intervention group benefited from a) a total reduction of fat intake, b) a higher proportion of polyunsaturated fat (+13 %) and c) a lower amount of saturated fat intake (- 9 %). At the end of the study, the serum cholesterol level had decreased by 15 % and the CHD incidence was 44 % lower in the intervention than in the control group [29].
- The Minnesota study [30], published 10 years later, was a one-year follow-up study including a large population in primary prevention (4,393 men and 4,664 women). Major differences with the Finnish study were that a) the total fat intake was not reduced, b) the polyunsaturated fat proportion was increased (+ 15 %) c) while the saturated fat intake was lower (- 9 %, as in the previous study). At the end of the study, the results differed significantly, most probably due to the short length of the study. Although the decrease in the serum cholesterol level was quite comparable (-14%), but the rate of CHD events was identical in both the control and intervention groups [30].

9-3-3 High Omega-3 fatty acid intake

The intake of omega-3 fatty acids results in a decrease of serum triglycerides, cardiac arrhythmia, thrombolytic tendency; this leads to a

decrease in coronary heart disease risk associated with improved endothelial functioning.

A Dutch study with a 20-year follow-up demonstrated a significant inverse correlation between the quantity of fish intake and coronary mortality [31]. Fifteen subsequent studies not only confirm this initial finding, but also state that this inverse correlation is stronger for fatal than non-fatal CHD amongst populations with the highest cardiovascular risk factors.

- A two-year follow-up of 1,015 men in secondary prevention showed that patients consuming fish twice a week had a 16 % CHD and a 29 % cardiovascular mortality reduction compared to the control group [32].
- A randomized, double-blind, placebo controlled trial of 242 men with a recent myocardial history and who regularly consumed fish or mustard oil (N = 122) had a 30 % decrease in CHD after one year compared to only 19% for the placebo group (N = 118) [33].

Moreover, it is now commonly known that women eating fish twice a week reduce their risk of a CHD by 30 % [3]. Regularly eating vinegar oil salad dressing (which contains a major source of α -linoleic acid) has the same beneficial effect [28].

These primary and secondary prevention trials strongly support the protective effects of omega-3 fatty acids and fish oil as well as α -linoleic acid.

9-3-4 The whole-diet approach

Blood pressure may be influenced by dietary changes.

A meta-analysis of 11 randomized controlled trials evaluating the impact of sodium intake on blood pressure confirms a direct and significant relationship between the level of sodium intake and systolic blood pressure [34].

Since the Southern U.S. states has a high prevalence of hypertension, appearing to be the U.S. region with the highest stroke mortality, the National Health and Nutrition Examination Surveys (NHANES III) focused on the difference in dietary habits between the Western and Southern parts of the country (N = 17,752 participants) [35]. Contrasting to the Western inhabitants, those residing in the Southern part of the USA consume a) significantly more monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol and salt and b) significantly less fiber, potassium, calcium, iron, phosphorus, magnesium, copper, riboflavin and vitamins A, C and B₆ [35].

Another classical and interesting study compared eating habits between the Eastern and Southern regions of Europe. Atherosclerotic diseases prevailed in the Eastern part, which could be explained by the fact that a) the Eastern European diet contains more saturated fat, sugars and salt than the Mediterranean diet and on the other hand, b) the Mediterranean diet is rich in oils (oleic acids), fibres and fruits (antioxidants) [21].

Mindful that a whole-diet approach can prevent atherosclerosis and its drastic complications, should the Mediterranean diet be recommended? A double 4-week study observed Finnish subjects on a usual/classical diet for a period of 4 weeks, followed by a 4-week diet intervention consisting of a Mediterranean-inspired diet, which included twice more fiber, three times more omega-3 fatty acids and polyunsaturated fat, and four to nine times more antioxidants [36]. After at the end of the study, all the measured parameters improved (decrease in LDL cholesterol, triglycerides and Apo-B); however, HDL cholesterol and fibrinolytic capacity did not change, as well as indices of oxidative stress, endothelial functions in resistant vessels and arterial distensibility [36]. The same partially positive results were obtained in other surveys targeting healthy elderly of both genders or CHD patients (with or without hypercholesterolemia or diabetes). The length of time it takes for the diet to attain a positive endothelial effect must be defined for people who do not follow a daily Mediterranean diet. Four weeks are insufficient, but it seems that after 6 weeks on the diet regimen, endothelial functions are improved [37-38].

9-3-5 The role of specific food ingredients

To reduce atherosclerosis, CHD and stroke incidence, it is recommended to replace red meat by chicken or fish and to substitute single sugars by complex carbohydrates (spaghetti, oatmeal, viscose soluble fibre, rye, barley, oats...) [3]. These dietary changes are beneficial for diabetic patients.

The consumption of foods containing high folate levels is advised, because a) a lower serum folate level is related to a high CHD prevalence [39], b) a supplementation in folate and vitamin B₆ for 2 years decreases the CHD prevalence [40] and c) folate supplements taken for 6 months after a coronary angioplasty significantly reduce the re-stenosis prevalence [41].

An excellent meta-analysis concerning the impact of nuts, fruits and vegetables as well as whole grain intake [28] promotes these nutrients to prevent atherosclerosis and its serious complications.

9-3-6 Combined effects of diet and lifestyle

In conclusion to this chapter about dietary interventions to reduce atherosclerosis development, it is important to stress the relationship that exists between protein-energy intake and serum lipids. The lipid profile is worse in protein energy malnourished compared with well-nourished controls [42]. It is also important to mention the combination of a “healthy” diet (see above) with physical exercise.

9-4 Summary

Atherosclerosis is a multifactorial disease in which complex interactions between genetics and environmental factors appear to play an important role. As documented in several studies, the atherosclerosis process is a lifelong process, in which each life stage is important, from the in-utero period to the development in adolescence and adulthood. Diet and physical activity are key elements in this development. This concept leads to four stages of the atherosclerosis process:

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- Pre-clinic stage: The role of integrating genes, family history, environment and lifestyle are important to understand the clinical stage, with well-known diseases such as diabetes, obesity, arterial hypertension and hypercholesterolemia.
- Acute disease stage: Sudden onset of neuro- or cardiovascular events such as myocardial infarction, stroke or peripheral arterial disease.
- Chronic disease stage: Heart failure, post-stroke handicap, vascular dementias and disability are part of this last category.

At each of these stages of disease progression, nutrition plays a major role. Indeed, the essential element is primary prevention, but as stated in this chapter, diet interventions are also efficacious in secondary prevention.

However, more research is necessary to better understand the atherosclerosis process and to discover the most adequate treatment of atherosclerosis, which includes (19) :

- Maintaining or restoring endothelial functioning.
- Improving and controlling :
 - Erythrocytes deformability

- Erythrocytes (*and platelets*) aggregation
 - Blood flow
- Facilitating oxygen perfusion particularly in atherosclerosis-induced muscle ischemia.

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10 – Nutrition and cognition: preventive challenges

Cognitive impairments, dementias and affective disorders constitute one of the most important geriatric care challenges of the 21st century. These long-term mental dysfunctions do not only interfere with survival but also with daily functioning, independency, caregiver burden and institutionalization. They increase directly, indirectly and intangibly total illness costs. Worldwide surveys, starting in the 1980s, based on the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) classifications, confirm that the prevalence of dementias in the 65 year old and over population varies slightly between 5 to 6 % [1-4], and is consistently rising with age (for example, 30 % of men aged over 90 living in the Geneva community suffer from dementia [5]). It is estimated that the worldwide number of demented patients will increase to 29 million in 2020 and 37 million in 2050 [6-7]. These epidemiological forecasts, which include all types of dementia (Alzheimer, Lewy body and Fronto-temporal dementias, as well as vascular and mixed forms of dementia), are alarming because, until now, no promising cure for these pathologies exists.

The progression of Alzheimer's disease (AD) is now better understood. It is a lifelong process whereby the first neuropathological lesions occur at midlife, while the first classical clinical symptoms arise two to three decades later. It is important to note that between the beginning of the pathological changes and the first phase of the disease, no precise clinical manifestations have yet been identified; this period is still qualified as "asymptomatic". A few Mood personality changes as well as unintentional weight loss could be the first indicative symptoms of the disease [8-10]. As the disease progresses but long before spatio-temporal disorientation, the slipping of words and benign forgetting appear. In fact, the clinical onset of the disease is too often completely neglected for a long period. Clinical history, neuropsychological assessment and static or dynamic neuroimaging allow us to identify the diagnosis at an earlier stage and with greater certainty.

One of the major individual as well as public health goals is to determine any intervention that could delay the onset of dementia, and particularly of its most common type, Alzheimer's disease [11].

As already published in the late 1980s, postponing the dementia onset by just 5 years would decrease the prevalence of the disease by 50% in the most senior population [12].

Among different intervention strategies, the role of nutrition in particular needs to be seriously considered for multiple reasons:

- A 20-year follow-up of older community-dwelling men (N=134) and women (N=165,) who were cognitively alert at the start of the study, showed that 50 % of participants who developed dementia had unintentionally lost approximately 5 kg since their baseline evaluation. This decrease in body weight was less pronounced in those who had stayed cognitively alert during the entire study period, which indicates that unintentional weight loss might be considered as one of the earliest symptoms of dementia [8]
- Moreover, it is now well known that weight loss occurring during the dementia process presents a highly significant risk of severe cognitive impairment, disability onset and mortality [13].

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Numerous other longitudinal studies of large cohorts of old community-dwelling population confirmed the role of commonly known dementia risk factors, but also identified new ones, among several which concern lifelong nutritional issues. This chapter will place a special accent on these issues as well as the possible nutritional protective factors.

10-1 The classical and the “new” risk factors of dementia

Dementia is a lifelong pathological process involving genetic components. This is perfectly illustrated in the case of pre-senile dementia with a high risk factor for Apo E4 homozygotes, possible familial aggregation, and a higher susceptibility based on gender and low education. Age itself is an essential risk factor [14] frequently associated with other facilitating disorders, such as elevated systolic blood pressure, atrial fibrillation, dysthyreosis, late onset of depression and recent head trauma [15]. This list of risk factors should now be updated with newly published suspected triggers, closely linked with nutrition.

The impact of **diabetes** on the dementia onset is still under debate. A recent and extremely well documented review by M KIVIPELTO [16] has shown that while a few studies did not find any link between the two diseases [17-19], others have found a highly significant association between diabetes and dementia [20-24]. For example, the Honolulu-Asia Aging Study [22] demonstrated that type 2 diabetes patients had a relative risk of 1.8 (95 % CI [1.1-2.9]) for developing Alzheimer's disease and of 2.3 (95 % CI [1.1-5.0]) for developing vascular dementia, when compared with non-diabetic controls. This relative risk increased to 5.5 (95 % CI [2.2-13.7]) when the diabetic patients were also ApoE4 homozygotes. These data strongly support a positive association between type 2 diabetes and Alzheimer's as well as vascular dementias.

Does **overweightness** or obesity increase the dementia risk? A positive association was proved by several longitudinal studies [25-29], while a different conclusion emerged from two other recent papers [30,31]. KIVIPELTO stressed that the midlife weight plays a major role [29]. The crude odds ratio of developing late onset dementia reached 3.5 (95 % CI [1.8 -7.0]) when the midlife body mass index was over 30 kg/m². Adjusting these findings for age, gender, education level, systolic and diastolic blood pressure, smoking habits and plasma cholesterol level, decreased the odds ratios to successively 2.4 (95 % CI [1.1 -4.9]) for model one (adjusted for age, sex, education, and follow-up time) and 2.0 (95 % CI [0.98 -4.4]) for model two (additionally adjusted for midlife systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol and smoking) [29]. These data suggest that midlife overweightness or obesity has to be considered as a risk factor for late onset dementia.

Another nutrition issue refers to the impact of **saturated or unsaturated fatty acid intake** on dementia onset. Saturated fat intake seems to be significantly linked with dementia risk factors [32-36], except in one study [36]. The Rotterdam longitudinal study [32], which includes the follow-up of 5,386 community-dwelling adults aged over 55, is particularly impressive. The relative risk of developing late onset dementia reached 2.4 when considering the total fat intake and dropped to 1.7 when only the cholesterol intake is included. However, any precipitated conclusion should be avoided, since recent studies are sparse, not large enough and have a short follow-up.

The impact of **cholesterol** in the development of dementia is another key issue; brain tissue contains 30 grams of cholesterol, while the blood plasma pool and the liver only contain 5 grams. Brain cholesterol is characterized by the presence of the 2.4 hydroxylase. This enzyme, only present in the brain, maintains an active and constant regulation of the brain cholesterol metabolism [37]. The existence of this precise brain cholesterol

regulation is important to consider as it is now known that the plasma cholesterol level reaches a peak at midlife and then progressively decreases with age (without considering any malnutrition or thyroid abnormalities). Within this context, the midlife plasma level of cholesterol, rather than that in late life, has to be considered as a possible risk factor of dementia. The dementia assessment of the 444 survivors, of the Finnish cohort of “the seven countries studies”, aged between 70 and 89 years, proved that midlife hypercholesterolemia (> 6.5 mmol/l; measured 20 to 30 years earlier) is a significant predictor for Alzheimer’s disease (O.R.= 3.1 [1.2 - 8.5]) after controlling for apoE4 genotype [38]. The role of cholesterol in the pathophysiology of Alzheimer’s disease must be further investigated.

Another dementia risk factor is **arterial hypertension**. A 15-year follow-up of 382 non-demented community-dwelling elderly aged over 70 demonstrated that participants who developed dementia between 79 and 85 years of age had, at the start of the study, a significantly higher systolic and/or diastolic blood pressures than those who did not (mean systolic blood pressure = 178 vs. 164 mm Hg, $p = 0.034$, and mean diastolic blood pressure = 101 vs. 92 mm Hg, $p = 0.004$) [39]. These results should be linked with the occurrence of silent strokes, responsible for micro-lacunae, too frequently undetected or discovered later via brain imaging when clinical signs are already present [40].

The link between nutrition, vascular risk factors and dementia is obvious, but needs to be further underlined due to the cumulative effects of these factors, as proved by several clinical studies. A reassessment of 1,449 participants (65-79 years), prospectively followed for 21 years, shows that having both a high plasma cholesterol (> 6.5 mmol/l) and an elevated systolic blood pressure (> 160 mmHg) at midlife increase the risk of developing late onset dementia by 3.5 (95 % CI [1.6 -7.9]) [41]. In total, the midlife combination of obesity (BMI > 30 kg/m²), hypercholesterolemia (> 6.5 mmol/l) and a slightly high systolic blood pressure (> 140 mmHg) increases the risk of developing late-onset dementia by 6.2 [41].

10-2 Possible nutritional interventions for modifiable risk factors

Potential risk factors of dementia (diabetes, hypercholesterolemia, arterial hypertension...) are in some way modifiable, others, such as gender,

are not, while other factors are rather protective (Apo E2 homozygote, high education level). Appropriate lifestyle changes are likely to be most important and practical advice to offer, however, they may be difficult to follow in daily practice. Public health interventions often mentioned remain essential. In general, there are four rules that apply.

Firstly, it is now well demonstrated by a meta-analysis of 11 excellent studies that a direct and significant relationship exists between daily salt consumption and an increase in systolic blood pressure [42]. Considering the importance of blood pressure control in the prevention of dementia onset, recommending a low dietary sodium intake is evident.

Secondly, it is now proved that regular consumption of a small amount of alcohol may prevent atherosclerosis and results in a lower rate of cognitive decline. The Nurses' health study, which included a 15-year follow-up of 11,000 US nurses, showed that drinking between 1 to 14.9 g of alcohol per day (one glass or less per day) reduced the risk of cognitive decline (RR = 0.85 [0.74-0.98]) [43]. Is this not a "pseudo" political correctness argument rather than a scientific one? Not only about the study's methodology – repeated cross sectional studies, exclusive-inclusion of women, special settings and culture surroundings, phone interview, poor cognitive assessment [44] – but also concerning the difficulty to communicate this kind of message to the public. Moderate and controlled alcohol consumption is better for cognition than no consumption at all, but alcohol abuse is worse than anything else.

A third factor is smoking. In vitro studies show the stimulating effects tobacco has on neuron activities. However in vivo, smoking is, among others, a very high neurocardiac risk factor [45].

Finally, the fourth factor represents the possible relationship between physical activity and the prevention of cognitive decline. While several studies affirm that physical exercise has no effect on cognition [46,47,48], others demonstrate the opposite. The most striking report demonstrated that midlife leisure and physical activity play a role in the preventing all dementia types, especially Alzheimer's disease (O.R. = 0.35 [0.16-0.80]) [49-55]; this was confirmed after adjusting for age, gender, ApoE4 genotype, education level, smoking, alcohol consumption, systolic and diastolic blood pressures and neuro-cardiovascular medical history [56].

Respecting these four lifestyle aspects may be very effective in delaying dementia onset. However, other possible interventions also appear positive, as demonstrated below.

A 1992-1993 population-based cross-sectional study of 1,651 Italian subjects (560 men and 1091 women) led to the conclusion that respecting the

WHO guidelines for preventing chronic diseases such as following a “healthy diet”, decreases the risk of developing Alzheimer’s disease (OR = 0.85 [95% CI 0.77-0.93]), after adjusting for age, sex, education, total energy intake, cigarette smoking, alcohol consumption and physical activity [57]. However, no significant relationship was found between self-reported antioxidant intake (fruit, supplements in vitamins C, E, zinc and selenium) and cognitive functioning, after adjustment for age, gender and education (47). However, the Honolulu-Asia Aging study, a 5-year follow-up of 3,385 men regularly taking vitamin C and E supplements, proved that these supplements could be protective against vascular dementia [58].

The brain autopsy of 30 elderly Catholic sisters participating in the “Nun study”, who lived in the same Convent, ate the same food from the same kitchen and led the same lifestyle, demonstrated that a low serum folate is significantly associated with atrophy of the cerebral cortex [59]. Nevertheless, a systematic dosage of plasma homocystein in a randomized sample of 702 community-dwelling respondents over the age of 55 did not show any correlation between homocystein level and cognitive performance [60]. The long term follow-up of participants of the Scottish QI study born in 1932 and 1946, showed that the infant homocystein levels contribute to only 7 to 8 % in the variance of the old age cognitive performance of the survivors [61]. These inconsistent data are congruent with the fact that the administration of high doses of vitamin B₁₂ and minerals for one year in non-vitamin-deficient adults does not improve their cognitive functioning [62]. However, within a year, decreases in vitamin B₁₂ and/or folate intake associated with an increase in plasma homocystein levels were linked with a deterioration of the spatial coping skills [63].

These yet to be promising results still do not allow formulating recommendations for the prescription of vitamins, folates and/or antioxidant, to prevent cognitive decline.

The Rotterdam study generated much more interesting and important results by confirming that regular fish consumption reduces the relative risk of developing dementia to 0.4 [32]. This positive protective effect from fish is now confirmed by the results of the Chicago Health and Aging Project (a 6-year prospective follow-up), which involved a regular diet history and three complete in-home cognitive assessments of a community-dwelling cohort of 65+ adults. Cognitive scores (summing score of 4 standardized tests) declined on average at the rate of 0.04 “standardized units per year” (SU/y). The cognitive decline was more prominent in subjects consuming fish less than once per week than those who eat fish more often [64]. The results of these

two studies suggest that regular fish consumption may slow age-related cognitive decline.

Based on results from both animal models and large epidemiological surveys in humans, a recent review analysed the impact of inappropriate diet on primary and secondary prevention of cognitive decline. The possible mechanism of omega-3 fatty acids (particularly EPA and DHA), in decreasing the rate of cognitive decline, is by stimulating the antioxidative activities of vitamins C and E. These vitamins may not only prevent oxidative stress and inflammatory processes, but also strengthen the cell protective effects of omega-3 fatty acids. The synergistic actions of folates, omega-3s and vitamins B, C and E would prevent oxidative and inflammatory neuron damage and, in consequence, decelerate cognitive decline with ageing.

This interesting review did not include the promising positive force of a vitamin E (2,000 IU/d) and Selegiline combination [65]. It seems that adding this combination to the present classical treatment of Alzheimer's disease of choline esterase inhibitors may increase the effects of these drugs [66].

Before ending these series of possible nutritional interventions to prevent/delay dementia onset, it is of interest to mention two herbal supplements that are sold worldwide for their potentially beneficial capacities.

A randomized, double blind, placebo controlled trial of chronic oral treatment with Ginkgo Biloba (240 mg/d) for 3 months showed only slight improvement of cognitive performances [67]. No effect on Alzheimer's course was noticed after the study period. Due to these unconvincing findings, it appears necessary to wait for the long follow-up, multicentric on-going European Community sponsored study.

Four placebo-controlled trials with Ginseng in healthy volunteers only showed amelioration in arithmetic performance and complex problem-solving. It is believed that Ginseng is even more powerful when combined with Ginkgo Biloba [68]. The effect of this blend needs to be proved with sufficient and reliable evidence [69]

10-3 Possible drug interventions for modifiable risk factors

To keep in line with the nutritional aspect of the intervention, hormone replacement therapy as well as non-steroid anti-inflammatory drugs will not be discussed in this book. The discussion will be restricted to the antihypertensive preventive treatment of cognitive decline and lipid-lowering treatments.

A sub-trial of the Syst-Eur study followed 2,418 hypertensive patients over the age of 65 for 2 years and demonstrated that adequate blood pressure control (by nitrendipine and/or enalapril) decreased the risk of developing dementia by 50% during the study period, compared to untreated hypertensive subjects [70]. Initially, these results appear more than encouraging. However, translating the results to the number of patients to treat moderates the first enthusiasm. The 5-year blood pressure control of 1,000 hypertensive patients allows preventing the onset of 19 AD cases. A better control of midlife blood pressure would likely be one of the best methods to delay dementia onset.

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Another popular topic concerns the use of lipid-lowering drugs, and more precisely the use of statins in the prevention of cognitive decline/dementia. The first published study was very encouraging [71], however further surveys were less positive; it is necessary to wait for larger, randomized controlled trials with a longer follow-up before recommending the systematic use of this type of drugs for preventing dementia. The main questions regarding statin activity are two-fold [72]: a) Is their potential effect only linked to their lipid-lowering or anti-inflammatory activity? and b) Is their ability to cross the blood-brain barrier important? In other words, are lipophilic statins more active than hydrophilic ones?

10-4 Summary

Delaying or postponing the onset of cognitive decline and dementias is one of the main health public priorities in the early 21st century, which is by far a greying century.

Apart from uncontrollable risk factors (genetics, gender, advancing age...), several modifiable neurovascular risk factors exist such as

atherosclerosis, arterial hypertension, diabetes, hypercholesterolemia, saturated fat intake and obesity. They can be taken into account in an effective prevention program mainly through nutritional interventions, and certain lifestyle changes (decreasing salt and fat intakes, consuming less alcohol, stopping tobacco smoking and being regularly physically active). In addition to following a healthy diet enriched in vitamins and folates, a few drugs could be helpful to slow down the cognitive decline with ageing. An important statistic to remember is: “Postponing by 5 years the onset of dementia will decrease the disease prevalence by 50%”.

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11 – Food/Drugs interactions

The population aged over 65 takes at least 40 % of all prescriptions [1], excluding over-the-counter and under-the-counter additional drugs (20 to 25 % of all consumed drugs). Drug action may be altered in the elderly with modified body composition, changes in organ function, altered homeostatic regulation and multiple co-morbidities. In addition, compliance in this particular patient group is generally lower [2]. There is a significant relationship between the number of drugs taken daily and the frequency of side effects. For example, for 3 different prescribed drugs per day, the frequency of the observed side effects reaches to 40 % and for more than 8 different drugs taken per day, this doubles to 80 to 100 % [3]. As a consequence, adverse drug reactions in the elderly are the 4th leading cause of death in hospitalised patients [4].

Nutritional habits can also interfere with drug metabolism. Drug-nutrient interactions affect kinetics or dynamics between a drug and a nutritional element, and may result in poor nutritional status [5]. The simultaneous intake of food and drugs can slow down, accelerate or modify drug absorption. Other factors include the galenic form of the drug as well as its administration route and timing (before, during or after the meals). Moreover, there is a direct relationship between the prevalence of drug-food interactions and dosage, drug regimen and drug compliance [6]. The complexity of the underlying mechanisms differs for all drugs and foods; at this moment, detailed information becomes available for a few drugs interfering, in particular, with the liver P450 cytochrome. In general, two opposite manifestations of these food-drug interactions can be identified:

- Quick and severe reactions occurring immediately after the introduction or the change of a drug or a nutrient. In this case, the recognition of the interaction is simple and treatment is rapidly effective.
- Chronic interferences with the nutritional status provoked by a long-term drug intake. This proves to be more challenging to pinpoint. Nutritional deficiencies induced by drugs may take months or years to develop in previously well-nourished patients [1].

11-1 Pharmacokinetics and possible food-drug interactions

The following describes the four types of pharmacological food-drug interactions[7]:

- The ex-vivo bio-inactivation corresponds to biochemical or physical reactions between the various agents (hydrolysis, oxidation, precipitation...).
- The interactions modifying drug absorption are linked to an alteration of the function of an enzyme or an active transport mechanism (inhibition of biotransformation or transport).
- After absorption, the existence of systemic, physiologic or cellular competitive interferences can modify the action of drugs or other co-factors functions (such as clotting or hormonal activity).
- Elimination or clearance of drugs / nutrients can be altered by modulation, antagonism or impairment of the usual elimination pathway.

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Knowledge of these interactions is very important to i) optimize the effect of drug therapy and ii) prevent nutritional deficiencies in the long-term.

11-1-1 Drug absorption in the elderly and possible food-drug interactions

The most important age-related changes in the process of daily absorption of nutrients or drugs are the decrease of gastric acidity (elevation of the gastric PH), the loss of absorptive surface (many drugs are absorbed by intestine transporters) and the reduction of splanchnic blood flow; these are all associated with diminished gastro-intestinal tract mobility.

These classical age-related changes in absorption are sometimes worsened by associated pathological problems such as achlorhydria, diarrhoea, malabsorption, pancreatitis or gastrectomy. They can also be linked to therapies such as the use of anti-acids and anticholinergic treatments [6].

The consequences of the changes in absorption can differ [6]. Drugs stay longer in the stomach, and later reach their site of action. For example,

taking salicylic acid while fasting, initiates immediate drug activity, whereas taking it on a full stomach will delay the drug activity by 2 hours.

- Food increases the gastric PH of seniors from 1-2 to 4-5, thereby changing drug ionisation/stability and absorptive rate. However, fruit juices and cola beverages decrease gastric PH.
- Fatty foods or incompletely chewed nutrients slow down the gastric emptying.
- Fatty foods allow for a better dissolution/absorption of liposoluble drugs such as pro-drugs of cefalosporine, erythromycine and chloroquine.
- On the other hand, high water consumption increases absorption of water-soluble drugs.

Numerous drugs interfere directly with the overall absorption process by [6]:

- Decreasing absorption ability: amoxicillin, ampicillin, atenolol, cefaclor, cimetidine, diclofenac, digoxin, doxycycline, hydrocortisone, ibuprofen, isoniazid, ketoconazol, levodopa, methyl dopa, metronidazol, penicillin G and V, piroxicam, rifampicin, salicylic acid, sotalol, sulfonamides and tetracyclines (...)
- Increasing absorption capacity: carbamazepine, chlorothiazide, diazepam, griseofulvin, hydralazine, labetolol, metoprolol, nitrofurantoin, phenytoin, propranolol and spironolactone (...).
- Not acting on absorption: prednisone and verapamil are a couple of known examples [6].

It should be mentioned that the intestinal absorption process is also very important. The involved mechanisms are passive or active through very specific transporters. For example, the salicylic acid, which is partly absorbed in the stomach (see above), is more completely absorbed by an active intestine transporter called monocarboxylic acid.

Long-term drug regimens can alter the gastro-intestinal digestive process [8]:

- Anorexia can be related to the long-term use of antibiotics, digoxin or theophylline.
- Agueusia can be the result of a long-term treatment with calcium-channel blockers, angiotensin converting enzyme inhibitors, iron supplements, metformin, metronidazole and also tricyclic anti-depressants.

- Dysphagia can be related to the long-term treatment with alendronate, anticholinergic medications (dementia), non-steroidal anti-inflammatory agents, prednisone or potassium supplements.
- An early satiety feeling can be provoked by anticholinergic or sympathomimetic agents.
- Reduced feeding abilities can correspond to drug prescriptions of sedatives, opiates or psychotropic agents.
- Diarrhoea is possibly related to the use of antibiotics, laxatives (over-the-counter drugs), SSRI's or theophylline.
- Hypermetabolism can be related to the use of thyroxine and/or natural supplements containing ephedrine.
- When geriatric patients suffer from unusual nausea and vomiting, it is important to verify their treatment. These digestive symptoms can be caused by the use of antibiotics, digoxin, nonsteroidal anti-inflammatory agents, opiates or the short/long-term use of theophylline.

To conclude this section, it seems fundamental to stress that gut integrity decreases rapidly. After 5 days without food intake, there is a noticeable negative impact on drug absorption and metabolism [9]. Here is a simple and practical statement to summarize this segment: "if the gut works, use it" [1].

11-1-2 The first metabolic pass

An important age-related change in drug metabolism is the reduced hepatic blood flow. Numerous drugs have a decreased first hepatic passage: labetalol, metoprolol tartrate, nifedipine, propranolol HCL and verapamil HCL (...). Moreover heart failure and hepatic insufficiency worsen this disturbed drug metabolism [6].

This well-known change in the first hepatic passage, as well as a better understanding of the specific roles of four different families of clinically significant cytochrome P450 (CYP2, CYP2D, CYP2D6, ...), explain some drug-interaction phenomena:

- Food intake increases hepatic blood flow and, through an increase of the first pass, the bioavailability of drugs (propranolol, for example).

- Inversely, in postprandial periods, food and drugs can be competing for activating the same enzymes (P450 cytochrome, for example).
- On the other hand, if food stimulates one sub-type of P450 cytochrome (CYP 3A4/2D6, for example), drug metabolism can be accelerated.
- More and more special interferences between certain food (grapefruit juice, for example) and drugs are now being discovered (see below).

11-1-3 Drug distribution

Age-related changes consist in a reduction in lean body mass, an increase in fat mass, a global decrease in total body water and lower plasma protein and albumin concentrations. These changes disturb the metabolism of:

- Fat- and water-soluble drugs (whose half-times are modified in opposite directions).
- High protein affinity drugs, such as antipyrine, diazepam, imipramine, imidazolam, phenytoin, warfarin sodium (...), show an increase in their drug fraction (active form). The same mechanism exists with alcohol.

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Multiple pathological conditions can reinforce these metabolic abnormalities: congestive heart failure, dehydration or oedema / ascitis, hepatic failure and indeed malnutrition, a condition that is often insufficiently identified and/or dealt with in the elderly.

11-1-4 Drug metabolism

All these aspects of drug/food interactions are closely intertwined and it is difficult to isolate one or another. Age-related changes, such as a decrease in liver mass with a reduction in liver blood flow and microsomal activities, are responsible for a decrease in hepatic clearance and contribute to an increase in the plasma half-life time of entero-hepatic-excreted drugs. Moreover, these modifications enhance the organism's susceptibility to develop drug-induced hepatitis.

Several drugs, often prescribed in geriatrics, that are influenced by these metabolic changes, include: levodopa, lidocaine, morphine, propranolol and nortriptyline. Once again, these age-related changes and their

consequences can be reinforced by pathological processes such as congestive heart failure, fever, malignancy, dysthyroidism and overall malnutrition.

11-1-5 Drug excretion

Although numerous drugs can be (partly) excreted by the entero-hepatic cycle (see above), excretion is often limited to the renal pathway. The size of the kidneys is reduced with age, as well as renal blood flow, the glomerular filtration rate and indeed the tubular secretion. The main and logical consequences are a decrease in renal clearance and an increased half-life of drugs excreted via the kidneys. A toxic accumulation of drugs can lead to hearing loss, balance impairment or repeated hypoglycaemia. All these drastic changes with ageing influence angiotensin-converting enzyme (ACE) inhibitors, cimetidine, furosemide, gentamycin and metformin (...).

In clinical geriatric practice, it is crucial to remember that plasma creatinine level is not related to kidney function, but to reduction of lean body mass. It is very important to calculate or estimate creatinine clearance before prescribing or adjusting drug dosages.

11-2 Specific food-drug interactions

Possible food-drug interactions should be kept in mind to assure a valuable drug prescription, dosage adaptation and follow-up of possible side effects that can seriously affect patient health (not exclusive to seniors).

- Grapefruit juice, which contains naringuine, naringenin and bergamotone, inhibits cytochrome CYP3A4. This leads to an a) increase in plasma concentrations of dihydropyridines (nifedipine) and an b) inhibition to the degrading enzymes such as triazolam, cyclosporine, saquinavir and lovastatin (...) [6].
- Bitter orange extract found in orange marmalade, fresh blood orange and herbal supplements generate the same effects.
- Cranberry juice interferes with warfarin [10].
- More information on the potential dangerous food-drug-cytochrome interactions can be found on this website: <http://medicine.iupui.edu/flockhart/table.htm>. The most appropriate advice to offer patients is to drink water when taking several pills simultaneously.

- Herbal teas reduce the absorption of both iron and neuroleptics.
- Caffeine interacts with 2 CYP450 isoenzymes systems and can modify the half-life of a drug metabolised by the same cytochrome, from 3-7 hours to 100 hours [11].
- Natural liquorice can induce arterial hypertension and interact with several drugs affected by CYP families [1].
- Fibres may have the same effects as resins, facilitating the entero-hepatic elimination of drugs.
- Fatty food consumption facilitates liposoluble drug absorption (such as vitamins A, D, E and K).
- Consumption of cheese containing tyramine may provoke arterial hypertension crisis in patients on long-term treatment with irreversible monoamine oxidase inhibitors (MAOIs). Today, this risk is decreasing with the better sanitation of food (cheese) and the more frequent use of the newer generation of MAOIs which are active at a lower dosage [1].

11-3 Specific diseases-drugs-food interactions

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Restabilising the nutritional well-being in cancer patients can be complicated as a malignancy challenged the weight balance. Most cancer drugs alter the taste of food which provokes a loss in appetite, ultimately causing a decrease in food intake. Moreover, these drugs very often induce nausea and vomiting [1].

Patients suffering from **heart failure** also very often lose their appetite due to their drug intake. Careful weight control is necessary and its interpretation presented in the clinical status evaluation [12].

- Long-term treatment with diuretics leads to a loss in sodium, potassium, magnesium and thiamine. The insidious deficiencies in these microelements are not always well compensated by food intake or nutritional supplements and contribute to acute deterioration of chronic heart failure.
- Digitalis and its derivatives can provoke nausea, anorexia and reduced food intake which contribute to status quo of protein energy malnutrition [13].

In treated **diabetes mellitus**, possible food-drug interactions exist with calcium antagonists, diuretics, antibiotics, and non-steroid anti-inflammatory

drugs (...), facilitating or precipitating hypoglycaemia (very often atypical, and difficult to diagnose particularly in very old and frail patients) [13].

The relationship between **osteoporosis** and a lifelong unbalanced diet is well established. Not only are calcium and vitamin D important for prevention from the disease, but protein intake is also essential to bone building. It is generally agreed that about 50 % of calcium intake comes from milk and its derivatives. Calcium is mainly absorbed in the proximal part of the small intestine; however, its absorption can be delayed by gastric alkalisation, as is frequently the case in old adults. Calcium excretion is influenced by salt or protein intake.

Numerous other interactions exist between food environment and drugs:

- Vitamin D is necessary to contribute to calcium fixation in the matrix of skeletal bones. Therefore, vitamin D supplements are required when there is a lack of sun exposure.
- Tetracycline chelates calcium in the gastro-intestinal tract, and consequently reduces calcium absorption.
- Alcohol and corticosteroids favour osteoporosis.
- A deficiency in estrogen or androgen facilitate osteoporosis [13].

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11-4 Food-drug interactions: classical clinical recommendations

The following are two basic principles that must be put in practice in order to avoid such interactions:

- Firstly, any experienced medical doctor has an obligation to systematically warn patients of all possible food-drug interactions as well as pure drug side effects, when the disease process cannot explain the short- and long-term unexpected clinical symptoms or laboratory changes presented by his patient.
- Secondly, during the long-term follow-up of a patient with a chronic disease, the general practitioner (GP) is responsible in determining whether drug dose adjustment or nutrient supplementation is necessary.

Moreover, the 4 types of pharmacological drug-food interactions, mentioned at the beginning of this chapter [5], support other clinical recommendations [7].

- The ex-vivo bio-inactivation of various agents by hydrolysis, oxidation or precipitation can be avoided by never mixing the nutrient and drug in the same device.
- The inhibition of biotransformation or transport imposes the separate administration of the drug and the nutrient, or a change of the drug administration route.
- The existence of systemic, physiologic or cellular competitive interferences can be prevented by avoiding foods inhibiting cytochrome functioning, such as grape fruit, or by adding adequate supplement such as niacin or folates (see above).
- Changes in the clearance of drugs can be partially offset by an adequate fluid intake and by a careful choice of drugs whose excretion pathway is tuned to a limited hepatic and renal function.

11-5 Coping with drugs for chronic conditions in patients with limited life expectancy

Every clinician, and particularly a geriatrician, is confronted with the dilemma of continuing or withdrawing drugs and/or food and/or liquid administration in terminally ill patients.

In any case, the patient's mental capability needs to be carefully evaluated. If the patient is able to decide, then decision remains his/hers, despite family members' strong opposition. However, if the patient is severely cognitively impaired and is unable to express valid consent, then the choice must be either to [14]:

- Continue the treatment of a chronic condition until the patient is unable to take the medication(s) or suffers from adverse reactions;
- Stop the treatment arbitrarily.

Clinicians are unable to calculate life expectancy with absolute precision, but they can accurately predict the remaining time of life in days, weeks or

months for their patients [14]. However, during this terminal phase, the pharmaco-kinetics and pharmaco-dynamics can rapidly change without notice. The patient suffering from a chronic condition, with a limited life expectancy, generally takes numerous drugs to which clinicians will have to add symptomatic treatment. But withdrawing a long-term treatment can also lead to serious conditions [14], depending on whether the terminal patient suffers from only one single very severe organ failure, or a multi-system organ failure. Therefore, co-morbid conditions as well as nutritional status will greatly contribute to the decision-making. The recommended attitude could be based on the answers to the following questions (adapted from [14]):

- What is the natural course of the disease?
- For this patient, what would be the probable course of the disease?
- What would be his/her expected survival time and life conditions?
- With our medical intervention (pharmacological/non-pharmacological treatments or nutritional support), what would be the expected changes of the course of the disease?
- What would be the likelihood of an acute deterioration if treatment is reduced or completely withdrawn or if the nutritional support is (is not) continued?

A general guideline in such situations is to go back to “the number to treat”, as stressed by J STEVENSON et al. even though this method is usually used to start rather than to withdraw a treatment [14]. However, this suggestion can be helpful in many circumstances. Mindful that a 10-year antihypertensive treatment of 25 patients prevents only one stroke, it is unlikely that an antihypertensive treatment in a patient who develops a small-cell lung cancer will protect him/her from suffering a stroke before death.

This simplistic way of thinking can be useful in many different situations, including decisions about nutrition and hydration support whereby several other considerations arise:

- What is the survival rate?
- How is the control of pain and other symptoms managed?
- What is the quality of the remaining lifetime?
- What is the patient’s will? What expectations does the family have?

All these questions seem to be somewhat unrelated from the main topic of this chapter, devoted to the interactions between food and drugs, but

they touch upon the next and last chapter of this book: Ethical issues at the terminal phase of life.

11-6 Summary

Geriatric medicine, which imposes a holistic approach on senior patients, has been successful in learning about food-drug interactions in old adults. Such knowledge of the physiological changes with aging is essential to better understand and interpret the pharmaco-dynamic and kinetic modifications linked to advancing age. Moreover, the numerous co-morbidities dictate a deep knowledge to offer the most optimal and beneficial prescription, dosage and regimen while avoiding side effects. This clinical expertise allows an anticipatory approach of very elderly and chronically ill terminal patients.

In addition to this ample complexity, the food-drug interactions contribute to the development of the geriatric concept with environmental, daily functioning and ethical issues (i.e. adding even more complexity to an exceptionally multifaceted discipline):

- Age-related physiological changes influence drug pharmacology, which is already compromised by other diseases and specific treatments.
- Daily nutrition can alter absorption and transform metabolism, distribution and excretion of drugs. Basic nutritional knowledge can avoid numerous food-drug interferences (e.g. adverse effects of grapefruit, tea, natural liquorice or coffee in certain circumstances).
- Long-term treatment can cause progressive nutritional deficiencies which may explain the deterioration of the initial disease. For example, during a long-term treatment with diuretics for chronic heart failure, the patient suffers from a 25 % of deficit of niacin.

If clinicians may predict the absolute life expectancy, they are quite accurate at predicting the expected survival. One of the main goals of geriatric medicine is also to manage this difficult end-of-life period by respecting the patients' will and assuring them the best nutritional well-being and quality of care. This remains a constant challenge for each of us (patients, family members and clinicians).

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12 – Nutrition in old patients with life-limiting illnesses

12-1 Geriatric medicine

Geriatricians are more and more assuming the role of medical specialists confronted with the end of life. Nowadays, 80 % of deaths occur in patients over the age of 70 in developed countries. Geriatric medicine has two main characteristics: geriatric core and geriatric care.

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12-1-1 Geriatric core

The geriatric core is based on internal medicine as well as other important insights such as the detailed medical history/diagnosis/treatment of patients with an emphasis on daily functioning, living conditions, family interactions, and social network. Moreover, geriatric medicine integrates ethical issues such as patients' will and their own notion of "quality of life".

12-1-2 Geriatric care

Geriatric care is based on two complementary issues. After the diagnosis and the treatment of the disease, the imperative continuity of care includes a strict follow-up consisting of either a rehabilitation or palliative program. In this phase, the patient discusses his/her advance directives and expresses his/her will, which is of great importance to the family and health professionals.

Palliative medicine and care correspond to an active and comprehensive care for patients suffering from a non-curable disease. The control of pain and other symptoms becomes the main goal of care including psychological, affective, social and spiritual considerations, all within a humanistic approach [1]. In this context, it is necessary to keep the patient and his/her family informed about changes in the patient-disease interaction.

At the end of life, artificial nutrition remains controversial: lay people as well as some health care professionals believe it is a fundamental component of care [2]. Informative communication and consistent support from family members before the death of their relative(s) is more and more considered to be particularly helpful in facilitating the mourning process of survivors. Death circumstances, the quality and adequacy of communication and a supportive relationship are all important in reducing those dark and sad moments of the survivors [3].

The second major component of geriatric care is the interdisciplinary teamwork. The balance existing between the patient's expressed will as well as the care priorities, determined by the geriatric team, is delicate. Interdisciplinary teamwork includes demonstrating professional skills and expertise as well as the proficiency of working, thinking and interacting to reach the same goal. Moreover, accepting individual differences and deeply respecting other's beliefs and opinions is essential [4]. Integrating the patient's wishes within the care plan, while simultaneously explaining to the patient's family the reasons and the importance of such an attitude is a real challenge. Normally, this 'team approach' leads to an ease of communication, an improvement of health outcomes and better quality of care which increases the satisfaction of both the patient and family members. [5-6].

12-2 Ethical issues of care in old patients suffering from life-limiting illnesses

Based on the above-mentioned concepts, the geriatrician has to take into account several ethical issues:

- High technology resources must be counter-balanced by the futility of certain aggressive interventions in the late period of life.

- Treatment withdrawal frequently appears to be an early defeat in opposition to therapeutic doggedness.

At the end of life, patients are often ambivalent and their decision-making process is compromised. Their physical, psychological and emotional status as well as numerous external pressures can interfere with the previous consensually decided mind-set.

The ethical issues of care are complex and provoke endless discussions. One such important discussion is the respect of the patient's wishes. Good communication is crucial in assuring the patient that the interdisciplinary team will follow his/her will.

In the case of the patient's loss of discernment, the existence of clear and applicable oral (or written) advance care planning becomes extremely important. If no such advanced directives exist, the former designation of a proxy will greatly facilitate decision-making. If not, the major problem will be to determine the patient's legal representative amidst divergent demands from family members. Hence the role of the geriatric team is very delicate [7-8].

A few years ago, Nicole LERY, from Lyon, proposed a "tool box" which includes a list of pertinent questions; each of these questions have to be successively discussed and answered as one ethical issue is raised after another:

- Is the proposed clinical action technically feasible and unharmed?
- Does this act respect the deontology of all the health care professionals belonging to the care team?
- Does the proposed technical act/treatment respect the law?
- Are the patient's culture, religion and beliefs respected if this technique/ treatment is applied?

If the answers to the above-mentioned questions are satisfactory, the clinical decision is likely to raise a true ethical issue. However, before discussing the ethical issue itself, it is always very important to be sure that all parties involved understand the clinical situation and/or safety of the intervention.

Unfortunately, in many clinical situations, another issue influences these pertinent questions; the cost of acute or long-term care conflict with the financial interest of the family members (depending on the health care system of the country).

Within this context, clinicians must practice ethically in an environment of significant technological complexity, where authority has unfortunately shifted to insurers. Ethnic, cultural and religious pluralism divide the health care profession and the public. Moral scepticism comes into play when law, economics and patient autonomy all demand to be heard at the bedside. Indeed, what must not change is the moral heart of medicine, that which gives the profession its ethical identity – the primary welfare of the patient [9].

12-3 Nutrition considerations in old patients with life limiting illnesses

Nutrition has many facets including biological, hedonic, social, religious and symbolic dimensions. Of course, nutrition is perceived differently by each person, explaining the difficulty of applying the same evidence-based nutrition rules to all patients in the terminal phase of life. The confrontation between the patient's nutritional habits, the life-limiting disease and the ethical grounds is very important to consider:

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- Patients can be suffering for years from a chronic disease such as diabetes, arterial hypertension, broncho-pulmonary chronic obstructive disease, polyarthritis, dementia, heart failure (...) or a combined complicated co-morbidity which imposes a long-term diet and/or treatment. These diseases ultimately lead to a long-term state of disability but rarely to foreseeable death.
- During the course of the previously mentioned diseases, another life-limiting disease (cancer, leukaemia) can occur and entirely modify the patient's life expectancy.
- Regardless of the presence of one or several underlying diseases, the immediate cause of death is linked to an acute cardiovascular event (myocardial infarction, pulmonary thrombo-embolism) or an acute infectious episode (in particular, cross infections linked to the care). Other possible and immediate causes of death are varied, but less frequent (hepatic or renal failures, metabolic coma) [10].

In any case, significant unintentional weight loss and/or cachexia and/or a wasting syndrome are rarely direct causes of death. Moreover, it is not really scientifically proved that the reversal of wasting improves the immediate outcome [11].

However, it is important to stress that the quality of the end-of-life period and death circumstances are dependent upon the ability to control the major symptoms that are present during the terminal stage of life. Uncontrolled nausea or vomiting, swallowing disturbances, intestinal occlusion or abdominal pain linked to dyspepsia, oesophagitis and gastritis or colonic inflammatory diseases will possibly limit oral feeding as well as bad oral hygiene, mouth pain (linked to dry mouth, reduced saliva flow, painful ulceration – denture, viral or mycosis infections, cancer) or drug side effects (taste alterations) (...).

In case of impossible oral feeding, family and staff members have different statements such as: “We can’t just let him starve to death”, “If we don’t put this tube in, he/she will get a pneumonia” or “Not feeding him/her is a kind of active euthanasia”. These statements are all quite common, even if the patient receives hydration from another route (rectal or subcutaneous route). In addition, it is important to realize that hydration alone may only prolong the dying process [2].

12-4 The possible nutritional supports

12-4-1 Enteral nutrition

Enteral nutrition corresponds to the delivery of nutrients by the gastrointestinal tract using nasogastric, gastrostomy or jejunostomy tubes which now offer the possibility of using an extensive range of commercial feeding regimens. However, before starting this enteral nutrition, several questions must be answered:

- Is the tube feeding being put in to surpass a critical phase of the disease, or to facilitate the cure of an opportunistic disease (cross infection)? In such cases, it is necessary to determine a fixed date to re-evaluate the patient. Moreover, the conscious patient, as well as family and staff members, should all be aware that in the absence of expected successful outcomes, the tube will be withdrawn.

- The expected outcomes of enteral nutrition need to be clearly understood by everyone (informal and formal carers):
 - Artificial nutrition may in fact prolong life, if it helps to cure the interfering disease.
 - Tube feeding is not considered a preventative measure against aspiration pneumonia. Even in the absence of an affirmative prospective trial, aspiration occurs in up to 50 % of patients with feeding tubes (*naso-gastric and gastric*) [12-13].
 - Feeding tubes do not protect against pressure sores and do not accelerate the healing of pre-existing pressure sores [14-15].
 - Tube feeding does not avoid the onset of infectious diseases. On the contrary, nasogastric tubes facilitate the occurrence of sinuses and middle ear infections, while gastrostomy tubes may be responsible for local infections and abscesses [14-15].
 - Moreover, tube feeding, in general, does not enhance the patient's comfort and raises the controversial problem of needed restraints for care [14-15].

12-4-2 Parenteral nutrition in end-of-life cancer and demented patients

Parenteral nutrition corresponds to the delivery of nutrients directly into the circulation by a catheter inserted centrally or peripherally. The use of complete nutrient solutions is possible. Unfortunately, in end-of-life patients, there was no noticeable change in resuming an oral diet, the recovery of ADL abilities or the quality of the last moments of life [16]. To facilitate the decision-making in such cases, various scientific societies established guidelines.

- **Guidelines of artificial nutrition vs. hydration in terminal cancer patients - established in 1996, by the European Association of Palliative Care [17]**

These guidelines include three steps which are sub-divided in several issues:

- The first important step concerns the inventory of the key elements which will facilitate decision-making:
 - The oncological conditions have to be precisely known – tumour site, histology, stage, slow- or fast-growing lesion, the possible oncological therapy – and integrated with the patient's characteristics - age, co-morbidity, cognition

status, prior nutritional habits and daily functioning.

- The present symptoms have to be inventoried and possibly explained/corrected - dehydration related symptoms, protein energy malnutrition symptoms, gastrointestinal and liver clinical and biological signs and oral health hygiene, mouth pain, nausea, eructation. Moreover, it is necessary to accurately assess the patient's mood (dysthymia or depression, willingness to live).
 - The length of survival in terminal patients is impossible to determine. However, it is known that artificial nutritional (AN), which is ineffective if delivered for a very short time, needs to be performed by experienced carers; if the patient stays at home, formal health care professionals and informal carers should be trained at least 1 or 2 weeks prior to starting the AN. Moreover, if the goal of AN is to keep the patient alive, his/her life expectancy has to be longer than 2 or 3 months.
 - A comprehensive nutritional assessment needs to be carefully performed. Is the patient's voluntary daily intake close to 100 % of the recommended daily allowances (RDA) or less than 75 % of RDA? Symptoms, clinical and biological signs of dehydration and of protein energy malnutrition must be identified, and if possible, corrected but always followed-up. Different combinations of these nutritional changes may greatly influence the decision-making process. After this complete nutritional assessment, we must determine that the enteral route is possible and if the gut is functioning well or not.
 - The patient's psychological attitude is another key element within the decision-making process. There are several possible scenarios: a) the patient is totally aware of his/her condition and actively interacts with the clinician for any decision, b) the patient is totally unaware of his/her condition thereby solely relies on the clinician's decision, or c) the patient is cognitively impaired and not able to participate in any decision.
 - In any case, and particularly in the last two situations, family members play major roles in the decision of management support (particularly in being trained to contribute to the AN care). The active participation of family members in the decision-making process, within a climate of truth, may avoid any secondary complaints and increase patient and family care satisfaction [17].
- The second step is the decision-making itself. Based on the multiple and fundamental evaluations of the patient's clinical status coupled with his/her family's involvement, it is possible to developing a care plan tailored to a feasible, ethically appropriate and efficient intervention to prolong the patient's survival with the best possible quality of life [17].
 - The third step consists of a careful follow-up of the patient's clinical changes under AN and oncological treatment. Regular comprehensive assessments

support the delivery of the best care, i.e. between therapeutic determination and premature withdrawal [17].

- **Are there guidelines of artificial nutrition versus hydration in terminal demented patients?**

The same initial questions need to be answered before discussing AN in severely demented patients:

- Are advance directives established by the patient before his/her cognitive deterioration?
- Is the patient's mouth hygiene good enough to pursue oral feeding?
- Is there any swallowing disturbance(s) imposing to stop oral feeding?
- Does a fluctuating consciousness state limit communication?
- What are the precise medical reasons to resort to AN?

Moreover, it is important to know whether any A contra-indications exist, such as critical illness, active cancer or major organ failure (...) [18]. The 1966-1999 Medline meta-analysis performed by FUNICANE et al. [19] found no positive arguments in favour of AN in severely demented patients. Moreover, no published data suggests that AN increases the patient's survival [19-21]. As no randomized studies are performed on these practical and ethical issues, clinicians should rely on regular comprehensive geriatric assessments to help them adapt their practice.

12-5 Summary

Death occurs more and more at advanced age, which explains why geriatricians are so often in charge of palliative and terminal care. Numerous symptoms alter the quality of the end of life, such as pain, fatigue, dyspnoea, depression; in fact, many of them are directly related to nutritional symptoms such as anorexia, nausea, vomiting, dehydration, weight loss and constipation (...). Patients, as well as their family and healthcare professionals, often believe that not feeding the patient can be considered as an "active euthanasia". Palliative medicine and care, which include physical, emotional, psychological, and spiritual approaches, must maximally favour mouth care in order to maintain a good oral hygiene thereby allowing to maintain oral feeding as long as possible.

Irrespective of the patient's will, collaboration and global capacities can highly modify the clinicians' attitude:

- Food rejection or hunger strikes may destabilize the care team (yet the patient's will has to be respected).
- The patient's advance directives are helpful, but very often difficult to follow without troubling the carers.
- Conscious patients, well informed of their personal medical situation, are able to participate in the decision-making.
- Conscious patients, unaware of their clinical situation, can ask the clinician to choose for them, which might prove to be very difficult (even impossible, if the family interferes with any therapeutical decision).
- The existence of guidelines for a few terminal diseases are very helpful for the clinicians who can gather the key elements necessary in the decision-making. Such inventory very often facilitates adopting the right attitude for each individual case. Artificial nutrition must enhance the efficiency of the treatment while maintaining the quality of the patient's survival. A comprehensive and regular follow-up of the patient's outcomes is fundamental in following the clinical evolution. These kinds of guidelines allow for a better choice between oral feeding and artificial nutrition, which can be used for multiple other diseases.
- Unfortunately, end-of-life for the severely demented patients requires more complex and interfering elements. Actually, no published data showed that artificial nutrition may neither prolong the survival nor improve the end-of-life quality and circumstances of death.

Death is part of life and to truly understand the suffering of dying, it is vital to understand the person.

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List of abbreviations

ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
AgRP	Agouti-Related Peptide
AIDS	Acquired Immuno Deficiency Syndrome
A.N.	Artificial nutrition
α -MSH	α -Melanocyte-Stimulating Hormone
bADL	Basic Activities of Daily Living
BAPEN	British Association of Parental and Enteral Nutrition
BASE	Berlin Age Study
BIA	Bio-impedence analysis
BMD	Bone Mineral Density
CART	Cocaine/Amphetamine Regulate Transcript
CHD	Coronary Heart Disease
CNS	Central Nervous System
CT	Computed tomography
DBP	Diastolic Blood Pressure
Dexa	Dual Xray absorptiometry
DFLE	Disability Free Life Expectancy
DHA	Dihydroandosterone
DHEAs	Dihydroepiandosterone sulfate
DPI	Dietray Protein Intake

EPSEN	European Society of Parenteral and Enteral Nutrition
FBM	Fat Body Mass
HDL	High Density Lipoprotein
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
IgF1	Insulin Growth Factor
IL2	Interleukine 2
IM	Intra Muscular
IL6	Interleukine
IMAO	Inhibitor of the mono amine oxydase
IU	International Unit
LAW	Lymphocytes/Albumin/Weight (assessment)
LBM	Lean Body Mass
LDL	Low Density Lipoprotein
MDD	Major Depressive Disorder
MNA	Mini Nutritional Assessment
MRI	Magnetic Resonance Imaging
MUST	Malnutrition Universal Screening
NPY	Neuropeptide Y
NSAI	Non-Steroid Anti-Inflammatory
PEM	Protein Energy Malnutrition
POMC	Propiomelanocortin
PPT	Physical Performance Test

LIST OF ABBREVIATIONS

RDA	Recommended Daily Allowance
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SC	
SGA	Subjective Global Assessment
TMJ	Temporo-mandibular Joint

