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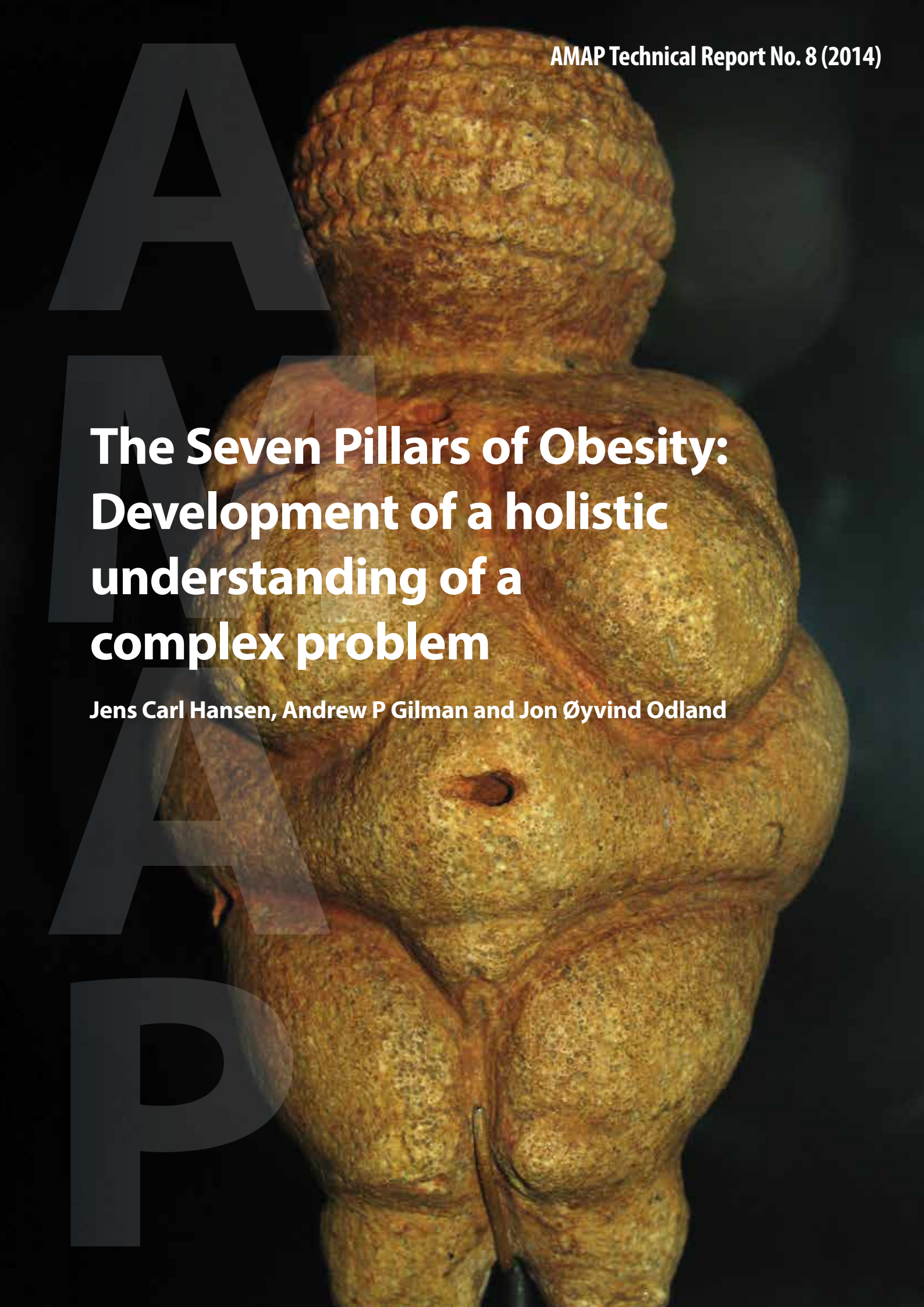

The Seven Pillars of Obesity: Development of a holistic understanding of a complex problem

Jens Carl Hansen, Andrew P Gilman and Jon Øyvind Odland

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The Arctic Monitoring and Assessment Programme (AMAP) was established in June 1991 by the eight Arctic countries (Canada, Denmark, Finland, Iceland, Norway, Russia, Sweden and the United States) to implement parts of the Arctic Environmental Protection Strategy (AEPS). AMAP is now one of six working groups of the Arctic Council, members of which include the eight Arctic countries, the six Arctic Council Permanent Participants (indigenous peoples' organizations), together with observing countries and organizations.

AMAP's objective is to provide 'reliable and sufficient information on the status of, and threats to, the Arctic environment, and to provide scientific advice on actions to be taken in order to support Arctic governments in their efforts to take remedial and preventive actions to reduce adverse effects of contaminants and climate change'.

AMAP produces, at regular intervals, assessment reports that address a range of Arctic pollution and climate change issues, including effects on health of Arctic human populations. These are presented to Arctic Council Ministers in 'State of the Arctic Environment' reports that form a basis for necessary steps to be taken to protect the Arctic and its inhabitants.

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Jens Carl Hansen (1938 - 2012)

Dedication

This report was essentially finished by the time that Jens C. Hansen became seriously ill and died. We, his two co-authors, promised our dear friend and colleague that we would finalise and publish this, his last intellectual exercise. Jens was a soft-spoken individual and very modest about himself. He was also a great leader, both in his academic life at the University of Aarhus and, especially, as the long-standing Chair of the AMAP Human Health Assessment Group. We served together with Jens in the AMAP Human Health group from the very beginning, and our respect for Jens steadily increased over those 30 years. Watching how effectively Jens would steer the production of Arctic assessment reports from a group of scientists with diverse interests in health and well-being was fascinating. Discovering Jens' enormous intellectual capacity and curiosity beyond the formalities and bureaucracy was inspiring. His knowledge of cultures and literature was formidable, as was his knowledge of French food and red wine. His kitchen table was the place for deep discussions and intellectual output for our papers, reports, and books. A journal like Medical Hypotheses was his preferred publishing site. We saw ourselves as pupils and sometimes scientific assistants as he expounded on the literature that he had read, integrated into knowledge, and developed further in his own writing.

Obesity and its huge impacts on health was a fascination for Jens; understanding how to solve the 'globesity' epidemic was a pressing priority. The Seven Pillars volume is built on many of his previous publications. We, the co-authors, are privileged to be his friends in life and death. We are proud to present this completed work to a skilled audience for reflection and new thought. We also know that Jens' intention was to dedicate his last intellectual work to his two dear daughters. Out of respect for Jens' wishes, we are delighted to dedicate this work to Mette and Frederikke.

Enjoy your read.

Jon Øyvind Odland & Andrew Gilman

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Preface

During the last four decades the world has experienced an epidemic of overweight individuals in affluent as well as developing countries. Currently, more people die from being overweight or obese than from undernutrition. The World Health Organization (WHO) has predicted a 'globesity' epidemic with approximately 2.3 billion adults being overweight and more than 700 million of these being clinically obese by 2015. Obesity among children and adolescents is of great significance. From a global population perspective, this epidemic in weight gain and its sequelae, such as metabolic syndrome, diabetes type 2, hypertension, cardiovascular diseases, and certain forms of cancer, has become the greatest public health problem identified to date and has significant adverse implications for population health, as well as comprising an increasing proportion of health care spending.

Prior to the 1950s, the prevalence of obesity had considerable geographical variation with the highest prevalence in the most affluent parts of the world. These geographical differences are no longer as pronounced, as obesity has become an increasing problem even in developing countries. However, the patterns differ according to socioeconomic conditions and are significantly affected by economic transition.

While genetic changes have been discussed as a cause of the epidemic, there has been too little time since the start of the epidemic to enable enough genetic adaptation to take place for this to be a valid explanation. Traditionally, positive energy balance and sedentary lifestyle have been regarded as the primary causal factors; however, these factors have so far failed to provide explanations for the entire problem. During the last half century numerous investigations have been carried out and articles published. A search in Pub Med provides more than 150 000 (March 2013) references on obesity, and still a definitive understanding of the causes of the epidemic is lacking.

In this book we provide a more holistic view of the complexity of the causal factors underlying the global obesity epidemic. As Wisdom built her house of seven pillars (see quotation, Chapter 4), we here introduce the seven pillars of obesity:

1. Genetics
2. Epigenetics
3. Energy balance
4. Composition of the diet
5. Thermogenesis and ambient temperature
6. Contaminant exposure
7. Psycho-social factors.

The seven pillars are discussed individually and in relationship to each other and are accompanied by detailed mechanistic explanations for their interactions.

Our analysis, based on a careful review of existing and recent literature, may help to better explain the complexity of the obesity problem and promote a more differentiated approach to a strategy to counteract this serious population health issue. Some statements may be provocative; this is intended. It is our hope to be able to contribute to an in-depth and ongoing discussion and understanding of the obesity epidemic, which has become a significant problem for the survival of the human race.

The target groups for this book are the educated reader as well as health professionals and health administrators. To meet the needs of these target groups, we have provided fully referenced text to enable further reading and verification and detailed information boxes on more technical biochemical aspects for those interested in more specific explanations.

1. Introduction

Proper exercise, food and drugs maintain or restore the body's economy, which is health.
Hippocrates c. 460–337 BC

During the last half century an epidemic of obesity[1] has been observed in the industrial world and is now also rapidly spreading to developing countries undergoing nutritional transition. Obesity has now developed into a major global public health problem (Mendez et al., 2005; Ogden et al., 2006; Popkin et al., 2006; WHO, 2012a) and is still increasing.

Excess body weight and obesity are abnormal or excessive fat accumulation that may impair health (WHO, 2012a). Body mass index (BMI) is a simple index of weight-to-height that is commonly used in classifying excess body weight and obesity in adult populations and individuals (definitions see **Box 1**). BMI provides the most useful population-level measure of excess body weight and obesity, as it is the same for both sexes and for all ages of adults. However, it should be considered as a rough guide because it may not correspond to the same degree of fatness in different individuals because of, for example, variations in bone density and muscle mass.

Box 1 Definition and classification of obesity

Obesity is defined according to the body mass index (BMI). BMI is calculated from the following equation (WHO, 2012b): BMI = kilograms body weight/height (in meters)^2. For example, a person weighing 77 kg and of 178 cm height has a BMI of: 77/1.78 × 1.78 = 77/3.17 = 24.3.

BMI	Classification
<18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
>40.0	morbid obesity

In children, healthy weight varies with age and sex. Obesity in children and adolescents is defined not as an absolute number but in relation to a historical normal group, such that obesity is a BMI greater than the 95th percentile. As Asian populations develop negative health effects at a lower BMI than Caucasians, some countries have a modified definition of obesity, for example, Japan has defined obesity as >25 and China as >28.

The World Health Organization (WHO, 2012b) defines 'overweight' as a BMI equal to or more than 25, and 'obesity' as a BMI equal to or more than 30 (see **Box 1**). These cut-off points provide a benchmark for individual assessment, but there is evidence that risk of chronic disease in a population increases progressively above a BMI of 21–22 (Ryan, 2009). The new WHO Child Growth Standards, launched in April 2006, include BMI charts for infants and young children up to age 5. However, excess body weight and obesity in children aged 5 to 14 years is challenging because there is not a standard definition of childhood obesity applied worldwide. The WHO is currently developing an international growth reference for children and adolescents (WHO, 2012b).

The WHO projects that by 2015 approximately 2.3 billion adults will be overweight and that at least 700 million will be obese (WHO, 2012b). According to data from the Global Database on BMI, there are wide variations in the prevalence of obesity throughout the world, ranging from India, where 1% or less of the population is obese, to the Pacific Islands, where the prevalence of obesity can reach up to 80% in some regions. The change in adult obesity prevalence over time was calculated for 28 countries that have two or more nationally representative surveys recorded in the Global Database on BMI. Overall, most countries were found to have rising trends of obesity. Only two of the 28 countries (Denmark and Saudi Arabia) showed a falling trend in the prevalence of obesity in men, and five of the 28 countries (Denmark, Ireland, Saudi Arabia, Finland, and Spain) showed a falling trend in the prevalence of obesity in women.

It has been predicted by Wang et al. (2008a) that all Americans will become overweight or obese by 2048, with black women and Mexican-American men being affected the most. The economic consequences of this progression in obesity will be huge. The health care costs attributable to an overweight/obese population are predicted to double every decade from a base value of 9.1% of the total US medical expenditure in 1998 (Wang et al., 2008a). A further addition to this alarming scenario is that it is not only total obesity that has increased, but also that abdominal obesity (fatty deposition in the abdomen) increased significantly in both men and women from 1999 to 2008 (Ford et al., 2011). Since subcutaneous fat, compared with the abdominal fat, has less impact on metabolic disturbances, the observation that abdominal fat proportion is increasing, especially in women, is a significant concern.

1.1 Evolutionary and historical aspects of obesity

The human phenotype is determined as an interaction between the genotype and the actual environment. The human genome has developed and adapted to the environment over hundreds of thousands of years during which environmental fluctuations were relatively small.

[1] The term obesity is from the Latin *obesus* which means stout, fat, or plump. *Esus* is the past participle of *edere*, to eat. The Latin word *ob* means over. The Oxford English Dictionary documents the first use of the term 'obesity' in 1611.

Box 2 Ketogenic diet

The Paleolithic diet was characterized by high protein and fat, and very low content of digestible carbohydrates; this is a typical ketogenic diet. The term 'ketone' refers to the compounds acetoneacetate, 3-hydroxybutyrate, and acetone. Acetoneacetate and 3-hydroxybutyrate can be used for energy production in several tissues, including the brain, and replace glucose as an energy source. Ketones are formed in the liver, predominantly from fatty acids. From the 1920s, the ketogenic diet was used in the treatment of child epilepsy, as it was empirically observed to relieve seizures. However, at that time there was no knowledge of different biochemical qualities of various fatty acids, and the common type of fat used was saturated fat. This practice led to an unfavorable serum lipid profile and consequently the idea was given up. The more recent understanding of the action of polyunsaturated fatty acid in lowering triglyceride (TG) and low density lipid (LDL) cholesterol levels has opened up a reconsideration of the ketogenic diet for treating epileptic children.

The ketogenic diet was a reality for Paleolithic populations and up to recent time, has continued to be the primary diet for Inuit populations in the Arctic.

The possibility, for non-Inuit, to also survive on a ketogenic diet has been documented through the diaries of polar expeditions. Frederic Swatka, the leader of the expedition in search of the Royal Navy's Franklin Expedition in 1878–1880, wrote as follows (cited by Phinney, 2004): "*When first thrown wholly upon a diet of reindeer meat, it seems inadequate to properly nourish the system, and there is an apparent weakness and inability to perform severe exertive fatiguing journeys. But this soon passes away in the course of two to three weeks*".

During early hominid evolution the ability to synthesize ascorbic acid was lost (around 15 million years ago). Later, in the mid-Miocene period, the ability to further metabolize uric acid was lost, a genetic characteristic shared by present-day humans and the great apes but not by most other mammals, which have conserved these genes. These mutations in the hominids have been described as an evolutionary benefit for survival under changing conditions of food supply (feast/starvation), as uric acid stimulates the forage response, while ascorbic acid counteracts it (Johnson et al., 2009).

The loss of ability to break down uric acid coincides with mid-Miocene global cooling, where great areas of tropical rain forests were transformed into savannahs. This forced the early hominids to adapt to the new environment; gradually they became hunters, they developed weapons needed for the hunt and they developed bipedal locomotion so they could use their arms to make better use of the weapons.

The mid-Miocene climate change forced the hominids into a transition to the hunter-gatherer state; this change was an important element in the development from hominids to *Homo*. The transition to hunting meant an increased dietary intake of long-chained fatty acids of the n-3 family (see Chapter 4). This has been related to the development of the human brain (Crawford et al., 1999).

The genus *Homo*, to which humans belong, appeared around 2.4 million years ago and developed into several species, for example, the Neanderthals. The present human species, *Homo sapiens sapiens*, first appeared 100 000 to 200 000 years ago. At that point, they still lived as hunters and gatherers. We have a fairly good knowledge of the Paleolithic diet; established through studies of differences in cranio-dental structure, stable isotopes, gut morphology, and calculations of energy needs for development of brain/bodyweight ratios. These studies are based on archaeological finds and comparisons with the few present-day hunter-gatherer cultures. These studies have indicated that during the transition from archaic *Homo* species to *Homo sapiens sapiens*, a shift from a plant-based diet to a diet dominated by foods of animal origin took place; man became partly carnivorous. This decrease in dependence on plants made it possible for them to move after the ice ages into more temperate zones and even to subarctic and Arctic areas, where they became almost fully dependent on food of animal origin – a ketogenic diet (for explanation see **Box 2**). Still there are distinct differences based on latitude between the plant/animal food ratios in human food (see **Figure 1**).

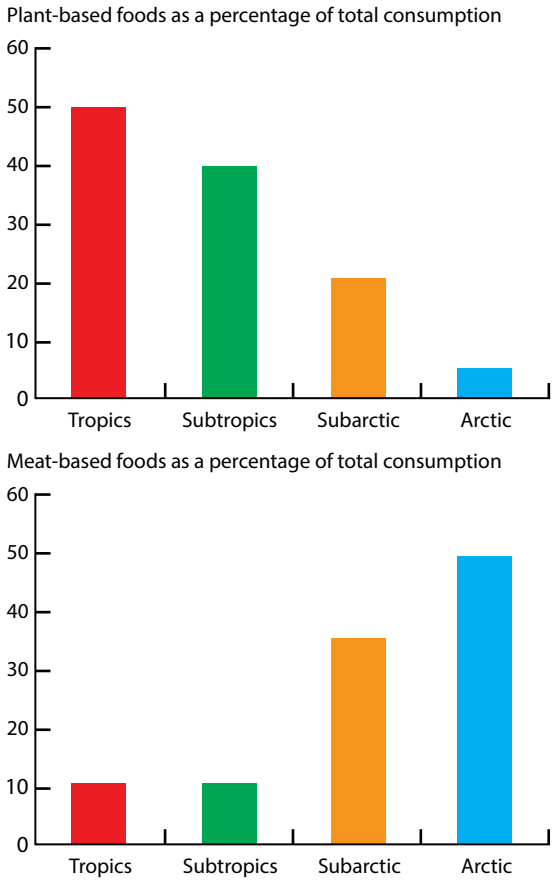

Figure 1. Dietary proportions of plant-based foods (upper) and marine (meat-based) foods (lower) consumed by human populations from different latitudes. After Cordain et al. (2000).

The problem for Paleolithic man was that the energy supply from carbohydrates was sparse and often of low digestibility. In addition, the intake of proteins was of limited value because of the poor capacity of the body to metabolize proteins without also creating toxic by-products, for example, rabbit starvation disease (see **Box 3**). The consequence for humans was that fat became an indispensable source of energy and consequently was cherished as a delicacy (see **Section 4.4.1**).

Life as a hunter/gatherer was harsh, especially in the temperate and Arctic climates and during periods of famine. It has been suggested that individuals with the greatest ability to store body fat to be utilized during periods of famine had a selective genetic survival advantage. This has been referred to as the 'thrifty gene' hypothesis by Neel (1962). This hypothesis has also been used to explain the present-day obesity epidemic, that is, the present abundant food supply in most parts of the world is a poor match for our inherited genes which were developed over millions of years to deal with famine.

The thrifty gene hypothesis has been widely accepted since it was proposed. However, Neel proposed in 1999 (Neel, 1999) that the hypothesis might be wrong. More recently, the thrifty gene hypothesis has been challenged by Speakman (2006, 2008) who argues that such thrifty genes have never been identified. Speakman indicates that if an advantageous thrifty gene arose during the evolution of Hominid ancestors over two million years, and the thrifty hypothesis is true, we should all have inherited these thrifty genes, and if these mutations and current diets now cause obesity, as the hypothesis suggests, we should all be obese. This is so far not the case for any population in any country. These conclusions are based on what happens to allele frequencies under positive selection pressure over time.

According to these arguments, if positive selection is negated, the alternative process is genetic drift, which occurs when the mutant alleles in question are neutral and not under selection. To better understand the problem, Speakman drew an analogy to animals living in the wild where body fat is regulated, with a lower and an upper limit for intervention. The lower limit is set by the risk of starvation, and the upper limit by risk of predation, that is, an obese animal would be an easy prey as it moves more slowly compared to a non-obese animal. To suppose that this is also true for humans would mean that obesity is not an advantage for an ancient hunter because he would have been less efficient and, like the obese animal, would be at a higher risk of becoming the prey rather than the predator.

Speakman proposed the 'predation release' theory in 2008. He postulated that humans two million years ago went through a transition in predation risk because at that time more social behavior, weapons and fire were developed. This effectively reduced the selection pressure and genes have been subject to random mutation and drift since this time. As a consequence, in modern societies where energy is freely available, individuals move towards their upper intervention point (Speakman, 2006). Speakman (2008) suggested abandoning the thrifty gene hypothesis and replacing it with the 'drifty gene' hypothesis. However, neither of the two hypotheses seem to provide the full solution, as both accept that obesity may have existed in Paleolithic times. The statue of Venus of Willendorf is proof that obesity did occur in early times (**Figure 2**).

Box 3 Protein intoxication, 'rabbit starvation disease', or starvation mimicking disease

Under starvation, the first thing to happen is that glycogen deposits are used for energy supply. When these are exhausted, fat deposits are utilized for a ketogenic energy supply. In the next step, where the fat resources are also depleted, protein becomes the ultimate source of energy for survival. The amount of protein tolerated by the mammalian organism is determined by the ability of the liver to up-regulate enzymes necessary for urea synthesis. Rudman et al. (1973) showed that the mean maximal rate of urea synthesis (MRUS) in normal subjects can be calculated by the following equation:

MRUS = 65 mg urea N/hour/kg bodyweight × 0.75

Protein intake that exceeds the MRUS results in protein intoxication with hyper-aminoemia and hyper-amino acidemia. For a 12.5 MJ energy intake, dietary protein intake would need to be 35% of the total energy intake (range 30–41%). The present day recommendation is <15%.

Rabbits have very small fat deposits and consequently under starvation will very quickly be forced to derive energy from their body's proteins and consequently develop elevated acidemia and aminoemia, a condition referred to as Rabbit Starvation Disease.

Figure 2. The figurine *Venus of Willendorf*, found in Austria and dated to between 28000 and 25000 BC. It has been regarded as a symbolic combination of obesity and fertility. Source: Wikipedia (CC-BY).

A minimum of body fat is essential for normal body function and when this minimum is not attained or lost it leads to the starvation limit. When this lower limit is approached the body will send strong signals to the brain. The resulting 'hungry' brain stimulates a preoccupation with food and strongly pursues a course that will avoid the starvation limit. The upper limit (obesity), which in wild life and in prehistoric humans can be considered a predation risk, appears to be a level of fat storage tolerated without development of significant metabolic change to reduce consumption. Contrary to the starvation limit, the upper limit is only weakly avoided (Zeng et al., 2009). The weak avoidance of the upper limit means that when food is plentiful the upper limit is easily surpassed and, especially in genetically prone individuals, metabolically-based 'stop eating' signals only appear later and are weak. As a consequence, there is a poorly-defined upper limit for pathological fat storage. This is a simple model that may generate a pattern of susceptibility to obesity that reasonably mimics the form of the present-day epidemic.

For the males in the hunter/gatherer societies, it was important to stay lean in order to be successful hunters. Women, however, could be obese and hunters could afford to have fat (and fertile) wives. This speaks for the drifty (drifting) gene hypothesis. Another factor of importance could be the genetically-determined gender difference in body fat distribution, with a tendency for men to accumulate visceral fat while women accumulate subcutaneous fat. From a Paleolithic context, it would be an advantage for hunters to have their energy reserves on their ventral region and to leave their arms more fat-free for hunting activities, while the female phenotype indicates energy reserves as fat for reproduction deposited subcutaneously on thighs and buttocks. This is the background for a connection between fatness and fertility. This speaks in favor of the thrifty gene hypothesis, and possibly that the genes determining the gender-differentiated fat deposition patterns which still prevail today, are the missing thrifty genes.

The controversy over *thrifty* or *drifty* has so far not been definitively solved. Both hypotheses agree that the obesity epidemic is a reality and both hypotheses agree that the actual obesity epidemic is rooted in the human genome evolved in ancient times.

In antiquity, obesity was recognized as a health problem, thus the Greek physician Herodicus (5th century BC and a tutor of Hippocrates) was the first to combine medicine with diet and exercise (Georgoulis et al., 2007). Although his works were lost, his teachings can be traced back through other ancient texts, making Herodicus the father of sports medicine. Later, the wisdom of the ancient world was forgotten and obesity became prized as an indication of wealth, as only rich people could afford gluttony (**Figure 3**).

This became accepted in the Roman Empire as expressed by Shakespeare in Julius Caesar Act 1, scene 2: *"Let me have men about me that are fat; sleek-headed men and such sleep o'nights"*. This general view of health and wealth associated with obesity was prevalent up to the end of the 20th century, and still today obesity is regarded as an ideal condition for young women in some northwest African cultures such as Mauritania where wealthy men frequently send their daughters to 'fattening-houses' (Polhemus, 1978) or their mothers force girls to eat fatty foods and to avoid exercise in order to gain weight.

Figure 3. The wealthy family patriarch. Source: Detail from the *Seven Deadly Sins and the Four Last Things* by Hieronymus Bosch.

1.2 Is obesity a disease?

> *Corpulence is not only a disease itself, but the harbinger of others.*
> Hippocrates, 460–357 BC

Since Hippocrates' recognition of obesity as a health problem, the acceptance of obesity as a medical problem during the centuries to follow has been slow. Some physicians have endeavored to address the problem (for a review, see Haslam, 2007). In the clinical sector of the medical world the problem of obesity was neglected up to the end of the 20th century and regarded as readily curable by simply reducing food intake.

When the World Health Organization (WHO) was established in 1948 it adopted the disease classification developed by the International Classification of Diseases (ICD) in 1900. It is notable that obesity was then specified as a disease and this has been retained throughout the updating process. Thus, the WHO has recognized obesity as a disease for more than 65 years. In the beginning, the problem was regarded as relevant only to adults in the affluent part of the world and as a result of overeating; obesity did not have a very high priority as a medical health issue.

In order to counteract the reluctance of the WHO to accept obesity as a serious health problem, the International Obesity Task Force (IOTF) was established in 1994 with the purpose of addressing the increase in the worldwide prevalence of obesity. The IOTF, which has a formal relationship with the WHO, has prepared documentation used by the WHO for its development of programs and guidelines to prevent the globesity epidemic (IOTF, 2013). Data gathered by the International Association for the Study of Obesity (IASO) on global obesity in adults and children and the policy status among countries related to marketing of obesigenic foods to children is readily available through a series of interactive global maps (IASO, 2013a,b).

From a scientific point of view, the question of whether or not obesity should be regarded as a disease is still controversial. This is not because of a lack of agreement or understanding about obesity, but rather because of the lack of a specific and scientifically accepted definition of the disease. The Obesity Society commissioned a panel to address this question. Their conclusion was that, although it cannot be scientifically proven whether obesity is a disease or not, a utilitarian approach supports the position that obesity should be declared a disease (Allison et al., 2008). This conclusion is based on the indisputable fact that obesity causes much suffering, functional impairments, reduced quality of life, an increased prevalence of co-morbidities, and higher mortality.

As an appendix to this discussion, we should mention the so-called 'obesity paradox' which has arisen from several cross-sectional, retrospective database studies where an inverse relationship between BMI and mortality has been found (**Figure 4**). However, when the data are adjusted for cardio-respiratory fitness the inverse relationship largely disappears (McAuley et al., 2010). The paradox has also been refuted by Ades and Savage (2010) because weight loss and physical frailty are often final events in patients with chronic diseases and in aging. Adipose tissue acts as a storage depot for energy in excess to the body's needs. Adipose deposits were an evolutionary strategy to store energy in periods of food abundance for use in periods of starvation. All mammalian species have the ability to differentiate pre-adipocytes throughout their lifespan in response to demands for fat storage capacity (Ntambi and Kim, 2000). Without the development of adipocytes, it is doubtful whether many of today's mammals could survive the cycles of famine that have always plagued them. Thus the relationship between BMI and mortality is U-shaped. So it seems better to be fat and fit than to be lean and unfit, although the very best is to be lean (within a physiological range) and fit.

The concept of obesity as a disease has been disputed by Unger and Scherer (2010), who argue that obesity should not be regarded as pathology or a disease, but rather as the normal, physiological response to sustained caloric surplus, without which the onset of metabolic syndrome would be accelerated. However, this is only true with some limitations. Adipocytes have evolved to store fat during periods with plentiful food supply, to be used during periods of famine, and as such they play an important physiological role. To be temporarily overweight is not a disease. However, for many populations today famine seldom if ever occurs, and so the temporarily stored surplus energy supply becomes permanent. The storage capacity of adipocytes has a maximum (see **Chapter 3**). As a result, when this storage capacity is reached the consequence is ectopic fat deposition defined as lipodystrophy. As obesity/overweight, *per se*, cannot definitively be categorized as a disease, it seems reasonable to state that lipodystrophy, a consequence of chronic surplus energy intake and obesity, is a disease or at least a cause of diseases. A parallel can be drawn from infectious diseases. Is influenza a disease during the incubation period? Or, are cancers considered diseases during early asymptomatic cell proliferation?

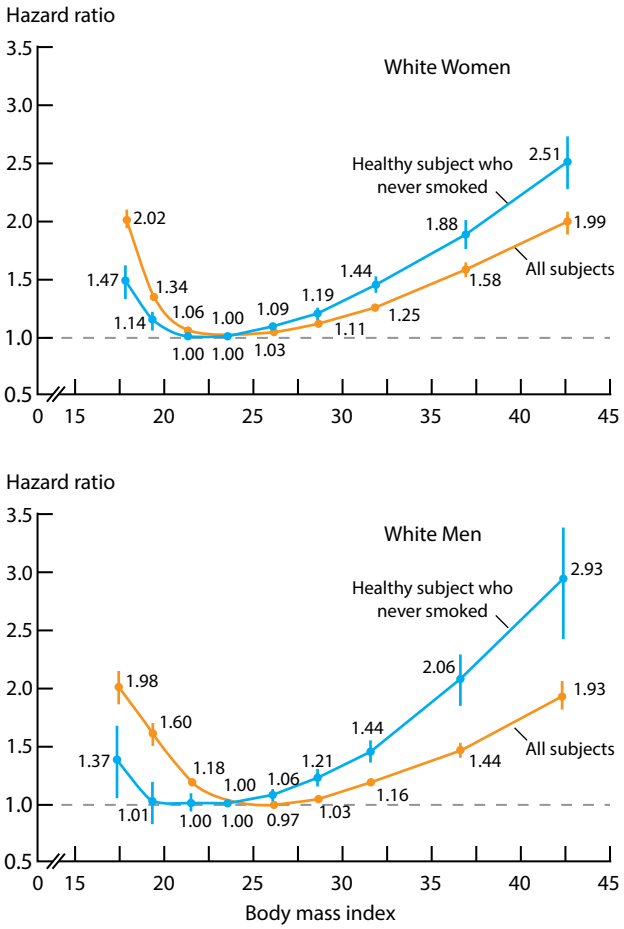

Figure 4. Mortality risk (expressed as a hazard ratio) in relation to BMI for white women (upper) and white men (lower). Source: McAuley et al. (2010).

2. Public health perspectives of the obesity epidemic

2.1 Global prevalence of obesity

The WHO reports that globally in 2008 approximately 1.4 billion adults (aged 20+) were overweight and more than 500 million adults (over 200 million men and nearly 300 million women) were obese (WHO, 2012b). The WHO predicts that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. Globally, 40 million children under the age of five were overweight in 2011. Excess body weight and obesity are also dramatically increasing in developing countries and countries with economies in transition, particularly in urban settings. The WHO reports that 65% of the world's population live in countries where overweight and obesity kills more people than underweight.

Excess body weight and obesity lead to serious health consequences. Risk increases progressively as BMI increases. An elevated body mass index is a major risk factor for chronic diseases such as cardiovascular disease (mainly heart attacks and stroke which kill 17 million people each year) and diabetes, both of which are rapidly becoming a global epidemic. The WHO projects that deaths related to diabetes will increase by more than 50% worldwide in the next 10 years. Some musculoskeletal disorders, especially osteoarthritis and some cancers (endometrial, breast, and colon), are also predicted to increase due to obesity. Childhood obesity is associated with a higher chance of premature death and disability in adulthood (WHO, 2012b).

Developing countries and countries with economies in transition are now facing a 'double burden' of disease (WHO, 2012b). While they continue to deal with the problems of infectious disease and undernutrition, they are experiencing a rapid increase in chronic disease risk factors such as obesity and excess body weight, particularly in urban settings. It is not uncommon to find undernutrition and obesity existing side-by-side within the same country, the same community and even within the same household. This double burden is caused by inadequate child nutrition followed by exposure to high-fat, energy-dense, micronutrient-poor foods and lack of physical activity.

The prevalence of obesity around the world is monitored by the WHO through the Global Database on BMI (WHO, 2006a). The survey data included in the database are identified from the literature or from a wide network of collaborators. However, high-quality data from systematic nationally representative samples are sparse. The prevalence of obesity in the United States has increased dramatically since 1980 both in adults and children. However, there is evidence of a possible recent stabilization in prevalence of obesity for children and adults in the United States based upon a comparison of data taken from 2003 to 2004 and 2005 to 2006 (WHO, 2006b). The epidemic of obesity is not limited to the United States but has been documented in several regions worldwide, with the prevalence of obesity rising in most countries. The highest rate of obesity has been reported in the Pacific Islands and the lowest rates have been seen in Asia (Ngyen and El-Serag, 2010). The rates in Europe and North America are generally high, whereas the rates in Africa and Middle Eastern countries are variable.

Obesity is affected by a complex interaction between the environment, genetic predisposition, and human behavior and economic factors; it is associated with an increased risk of numerous chronic diseases, from diabetes and cancers to many digestive diseases (Yach et al., 2006). These authors clearly indicate the global reality that obesity is as much an economic issue as it is a health issue. They identify five tipping points related to the cost of food and caloric intake which have accelerated the globesity crisis: (1) expanding labor market opportunities for women; (2) increased consumption of food away from home; (3) the rising costs of healthy foods relative to unhealthy foods; (4) the growing quantity of caloric intake with declining overall food prices; and, (5) decreasing requirements of occupational and environmental physical activity. In addition, the obesity epidemic exerts a heavy toll on the economy with its massive health care costs (Knai et al., 2007). The problem of excess body weight and obesity has therefore emerged as one of the most pressing global issues to be faced during the next several decades, and demands attention from the health care community, researchers, economists and policy-makers.

2.1.2 Prevalence of obesity in European societies in transition

Excess body weight and obesity in most countries of Europe show rising secular trends and are predicted to continue to rise if not addressed (**Figure 5**). Estimates of the costs to health services and to economic productivity indicate that some countries may find it hard to cope with the burden of obesity: up to 6% of total health care costs and as much in indirect costs of lost productivity can be attributed to obesity and its associated illnesses (Knai et al., 2007).

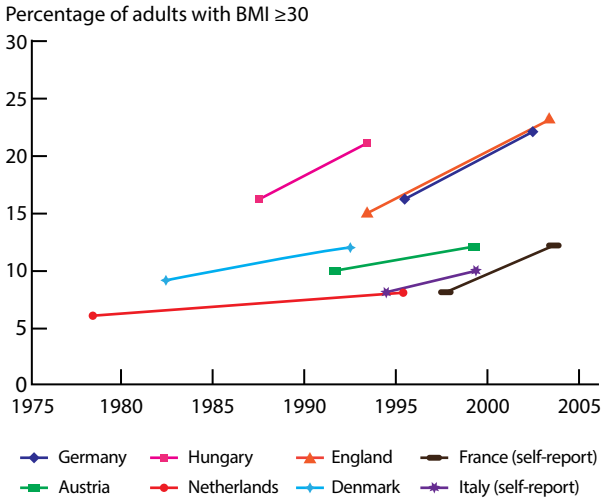

Figure 5. Trends in obesity prevalence among adults in European countries, 1977 to 2004 – percentage of the adult population with a BMI ≥30. Source: IASO (2013a). Note: definitions of 'adult' may differ between countries.

While most countries have benefitted from coming together to form the European Union (EU), there has been some collateral damage related to the fast-growing obesity challenge. Policy-makers in the new and candidate EU countries, as well as other countries of the European region, can learn from the negative experiences in Western Europe. The message is clear: act now to stem the obesity epidemic from developing further and in so doing, reduce the substantial economic impacts associated with this epidemic. Local, national and international strategies will be needed to combat the problem (Knai et al., 2007).

2.2 Global costs of medical care

Ryan (2009) reports that the increasing prevalence of obesity and type 2 diabetes mellitus (DM) among children and adults has posed important policy and budgetary considerations to government, health insurance companies, employers, physicians, and health care delivery systems. Obesity has been disproportionately prevalent among women and minorities, accompanied by an increased risk for diabetes (Yach et al., 2006) and the trend is expected to continue. Women have experienced an increased risk for metabolic syndrome, diabetes, and cardiovascular disease following the onset of menopause. Obesity has been related to an increased risk for breast cancer among women, and can be a barrier that prevents women from being screened for colon and breast cancers. Maternal obesity has been a risk factor for gestational diabetes.

Obesity and diabetes represent crises for the health care system and the health of the public. As the disease burden for adults and children increases, health care costs will increase (Ryan, 2009). About two-thirds of the costs from diabetes complications could be averted with appropriate preventive care. Unless there is a more coordinated effort to address the causes of these conditions at the local, national and regional level, the crises for public health and health care will continue to deepen.

2.2.1 Global economic burden on health care systems

The epidemics of obesity and diabetes impose a considerable economic burden on health care systems globally (Yach et al., 2006). There is a well-established body of evidence that the medical and treatment costs for these conditions take considerable resources from health systems. Developing countries have been undergoing rapid 'obesogenic' social and economic transformations and, as a result, the pace of nutrition transition is proceeding, even accelerating, at a rate never before seen in developed countries. Seven of the ten countries with the greatest number of diabetics are in the global south. Within the next two decades, the number of persons living with diabetes in Brazil, China and India is projected to increase at nearly twice the rate observed in the United States. As these costly conditions continue to strike with greater incidence at earlier stages of life within populations, the economic burden can only be expected to worsen.

The case of the United States demonstrates the explosive potential of the uncontained costs of obesity and diabetes. In the span of five years, the medical costs due to diabetes more than doubled, shooting from USD 44 billion to USD 92 billion (Ryan, 2009). Much of this growth relates to rising levels of obesity, estimated to impose health-system costs roughly equivalent to 20 years of natural aging. Yet despite this outpouring of resources, individuals are receiving only a fraction of the preventive and chronic care they need. The largest fraction of diabetes expenditures covered hospital admissions for the treatment of long-term complications such as heart disease, stroke, blindness, renal failure and lower-limb amputations. At least 7% of these diabetes-related hospitalizations could have been avoided. Nonetheless, only a small fraction of the resources devoted to the care of diabetes-related complications are spent for strategies that can help avoid obesity and diabetes in the first place. Today, the American epidemic seriously threatens to temper the gains achieved by reductions in the prevalence of cardiovascular disease. Although the epidemics are in the early stages of their upward trajectory in developing countries, the economic burden is already very important.

2.2.2 Societal costs of obesity – the US problem

The costs of diabetes mellitus (DM) in the United States have risen sharply: from USD 23 billion in 1969, to USD 132 billion in 2002 and to USD 174 billion in 2007 (Ryan, 2009). The actual 2007 expenditures surpassed that which was forecast for 2010 of USD 156 billion, and approaches that which was forecast for 2020 of USD 192 billion. Half of all direct medical costs in the United States were from inpatient care for DM complications (50% in 2007, up from 43.9% in 2002). Remaining costs were from DM medications and supplies (12%), retail prescriptions to treat complications of DM (11%), and physician office visits (9%). Medical expenditures by people with DM were estimated to be 2.3 times higher than medical expenditures by people without DM. Indirect costs included increased absence from work (USD 2.6 billion) and reduced productivity during work (USD 20.0 billion) for the employed population, reduced productivity for those not in the labor force (USD 0.8 billion), unemployment from disease-related disability (USD 7.9 billion), and lost productive capacity because of early mortality (USD 26.9 billion). Approximately two-thirds of the costs from DM complications may have been averted with appropriate preventive care for these conditions.

The total societal cost in the United States attributable to obesity amounted to USD 99.2 billion in 1995 (Ryan, 2009). Approximately USD 51.64 billion of those dollars were for direct medical costs for diseases attributable to obesity, equal to 5.7% of the national health expenditure of the United States. Obesity accounted for 62.6 million office visits to physicians. Employers in the United States have borne an enormous loss as a result of obesity. Estimates have ranged from USD 3.9 billion in lost productivity and 39.2 million days of lost work in 1994 to USD 45 billion in 2008 for obesity-related costs including lost work days, reduced functioning, obesity-related chronic diseases, and costs incurred from treating obesity including therapy, bariatric surgery, and medications. In a health plan with a co-insurance rate of 17.5%, obesity imposed a welfare cost of USD 150 per person per year. In 1994, there were 239 million restricted-activity days and 89.5 million bed days (days during

which an individual is confined to a bed or stays overnight in a hospital). Compared with 1988, physician visits attributable to obesity in 1995 increased by 88%; restricted-activity days increased by 36%; bed-days increased by 28%; and lost workdays increased by 50%. The opportunity costs, or indirect costs from obesity, were USD 47.6 billion in 1995, which are comparable to the economic costs of cigarette smoking.

2.2.3 The danger of globalizing US solutions

The importation of westernized lifestyles may not be the only threat to the health systems of developing countries. A second threat may be the importation of the westernized medical response to the increasing prevalence of diabetes and obesity. Yach et al. (2006) state that "*…as in the US, healthcare services for developing countries tend to be oriented toward acute, reactionary medical care rather than cost-saving preventive approaches. Many of the high-priced, tertiary- and specialist-care treatments driving the growth of medical spending are poorly suited for developing health systems. The race is on for the pill to control obesity, with pharmaceutical companies betting heavily on potential market prospects. While this occurs, bariatric*[2] *surgery is seen by many as the only proven means of reducing the impact of severe obesity. Evidence of how this view is spreading worldwide can be seen in the recent formation of the Asia-Pacific Bariatric Surgery Group by surgeons from 11 Asian countries*".

Research funding agencies favor medical and surgical solutions over health promotion and health prevention approaches (Yach et al, 2006). It is therefore not surprising that relatively few large-scale, community-based interventions have been undertaken that address excess body weight, obesity, food intake and physical activity together.

Yach et al. (2006) state that "*…the burden of obesity and diabetes on health systems only reflects a fraction of the financial disruptions they cause sick individuals, their families and communities. Empirical evidence shows that the full cost of diabetes to society is borne out through lower returns on education, decreased household wages, earnings and income, increased premature retirement and unemployment, and higher dependence on welfare. Over time, these indirect impacts can be more costly than the conditions themselves*". Individuals and their families in poorer countries often have to pay for their own healthcare, for example, diabetic individuals in India may have to pay 15–25% of household income to cover treatment costs. The cost for health care is often the greatest for those people who are the least able to afford it, deepening impoverishment and widening inequalities. Yach et al. (2006) report that a recent survey in China found that 30% of poor households attributed their poverty to health care costs. It is reasonable to assume that many individuals in this situation avoid some medical treatments related to diabetes because of their financial constraints. Furthermore, even when families are able to afford insulin, identified by the WHO as 'essential medicine', it may not be available.

2.3 Prospective visions for possible interventions

Concerned by the growing health and financial burdens amenable to primary and secondary prevention approaches, advocates have begun to call for vigorous public policy intervention for obesity and diabetes (Brownell and Yach, 2006; Yach et al., 2006; Ryan, 2009). These calls for action have met with resistance from some influential economists and policy analysts, according to Yach et al (2006) because obesity is considered to be a by-product of social progress. According to some economists and policy analysts, if consumers prioritize prevention of these diseases, the market should help them to achieve those objectives, as evidenced by the emerging health-food and weight-loss markets. To stimulate a multi-sectoral approach that can curtail the rise of obesity and diabetes, a sound economic argument is required which demonstrates (1) that the market, left uninhibited, will not produce socially desirable outcomes and (2) that early intervention and health promotion will lead to social gain and economic savings. These economic arguments, as they relate to obesity and disease, have not been addressed to the extent that they have been for tobacco use. Several lines of recent evidence suggest that the behavioral risk factors for diabetes and the lengthy latency period to disease onset give rise to suboptimal market behavior (Yach et al., 2006).

[2] Bariatric: a term introduced around 1965 to describe the medical branch dealing with causes, prevention and treatment of obesity. From Greek: *bar* (weight,) the suffix *iatr* (treatment) from *Iatros* (doctor), suffix *ic* (pertaining to).

3. From excess body weight to disease

3.1 Development of obesity-related co-morbidities

In general, the obesity-related co-morbidities are described as diabetes type 2, hypertension and cardiovascular diseases, as well as non-alcoholic fatty liver disease (NAFLD), gallbladder disease, osteoarthritis, and some cancers (Kopelman, 2000; Bray, 2004; Caterson et al., 2004). Hypertension, dyslipidemia, and atherosclerosis have also been mentioned as co-morbidities to obesity (Blüher, 2009). As the epidemiological aspects of the obesity-related co-morbidities have been extensively described in the literature, we will not go into depth with the epidemiological aspects of these diseases, but will instead concentrate on an analysis of obesity, the mechanistic background for its development, and its co-morbidities.

3.1.1 Who will develop the co-morbidities?

The co-morbidities noted above are observed in most (but not all) obese individuals and also some individuals who are not obese, that is, the same diseases can be seen in lean persons and the metabolically-obese (Ruderman et al., 1981). To understand this correctly it is necessary to look at individual variations in adipocyte number and adipocyte size (see **Box 4**).

Humans belong to genetically-determined phenotypes. The hyperplastic phenotype has many small adipocytes with the ability to store fat; the hypertrophic phenotype has many large cells, already filled up with fat, and only a few small cells, limiting fat storage capacity. In addition, there is the rare hypotrophic phenotype with few adipocytes and, consequently, limited capacity for fat storage and a susceptibility to lipotoxicity, as an adequate amount of adipose tissue is essential for maintenance of metabolic homeostasis (Kershaw and Flier, 2004).

In recent times, a constant abundance of food has led to continuous over-nutrition and the threat of development of adipose dysfunction. Individuals with the hyperplastic phenotype will be able to accumulate fat without showing signs of metabolic disturbances, however, a continuous fat overload will, in time, lead to formation of large, hypertrophic adipocytes and the storage capacity will be met. If the fat intake continues, dysfunctions will start to develop. In contrast, individuals with the hypertrophic phenotype who have reduced fat storage capacity will start to develop dysfunctions at an earlier stage, and especially the hypoplastic group will develop dysfunctions at a very early stage. For these reasons, BMI is not necessarily an indicator of adipose dysfunction.

The rare hypoplastic phenotype leads to lipodystrophy even at a low BMI (sometimes referred to as metabolic obesity). Since these individuals develop metabolic disturbances similar to overweight and obese individuals, they should be included in the discussion of the role of adipose tissue in metabolic disturbances.

Box 4 Cell size and number in adipose tissue

Adipose tissue contains both large adipocytes (hypertrophic adipocytes) and many small adipocytes (hyperplastic adipocytes). The total adipocyte number in fat is greatest when the cells are in pronounced hyperplasia, and smallest when cells are in pronounced hypertrophy (Arner et al., 2010). Increased adipocyte size correlates with serum leptin and insulin concentrations. The development of leptin and insulin resistance increases the risk of developing diabetes type 2 (Bjørntorp et al., 1971; Weyer et al., 2000; Lundgren et al., 2007).

Arner et al. (2010) found that the absolute number of new adipocytes generated per year was 70% lower in fat which contained predominantly hypertrophic adipocytes than in fat which contained predominately hyperplastic adipocytes. These authors also showed that the relative death rate of adipocytes (10% per year, or a mean age of adipocytes of approximately ten years) was not correlated with cell morphology. This means that the relative cell death rate is higher in hyperplasia than it is in hypertrophy.

These findings mean that two persons with identical BMIs, even below the overweight limit of 25, can either be, or not be, at risk for developing metabolic disturbances, according to their belonging to either the hypertrophic or the hyperplastic phenotype. This is demonstrated in its extreme in patients with partial familial lipodystrophy (PFLD), that is, persons who are adipo-hypoplastic and as a result cannot store fat and consequently develop lipotoxicity.

In humans, pre-adipocytes begin to differentiate into adipocytes during late embryonic development (Van, 1985; Ali et al. 2013) (see **Figure 6**), with a majority of differentiation taking place after birth (Burdi et al., 1985). This is contrary to rodents which do not start adipocyte differentiation until after birth (Ailhaud et al., 1992). The effect of dietary fat on adipose tissue development can be divided into effects on cell size and cell number. Increases in adipocyte cell numbers generally occur post weaning, whereas the increases in adipocyte size are associated with the late gestation and the pre-weaning period (Tulp et al., 1979).

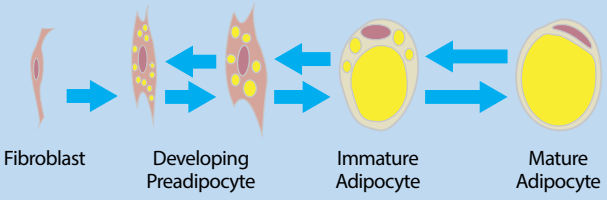

Figure 6. Adipocyte differentiation. Source: Ali et al. (2013).

Box 5 Definitions of the metabolic syndrome

WHO (Alberti and Zimmet, 1998)

Presence of diabetes or impaired fasting plasma glucose (FPG ≥5.6 mmol/L) and at least two of the following components:

- Diagnosed hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidemia (TG ≥1.695 mmol/L or HDLC in males ≤0.9 mmol/L, or in females ≤1.0 mmol/L
- Central obesity (WHR >0.90 in males; 0.85 in females, or BMI ≥30)
- Microalbuminurea (urinary albumin to creatinine ratio (ACR) ≥30).

Modified ATP III (Denke and Pasternak, 2001)

Presence of at least three or more of the following five components:

- Elevated WC (≥90 cm in males; ≥80 cm in females)
- Elevated TG (>150 mg/dL or 1.659 mmol/L)
- Reduced HDLC (<1.036 mmol/L in males; <1.295 mmol/L in females)
- Hypertension or elevated blood pressure (≥130/85 mmHg)
- Diabetes or elevated FPG (≥5.6 mmol/L).

IDF (Alberti et al., 2005, 2009)

Identical to ATP III, but requires the presence of central obesity (elevated WC) as an essential criteria. This has, however, recently been modified in such a way that WC should be evaluated on population- and country-specific definitions.

WHR: waist hip ratio; WC: waist circumference; HDLC: high density lipoprotein cholesterol; FPG: fasting plasma glucose; TG: triglycerides.

The term diabesity was coined by Sims et al. (1973) to demonstrate the close relationship between diabetes[3] type 2 and obesity. The current weight of evidence has led to the prevailing view that dysregulation of fat deposition and lipotoxicity are primary contributors to the diabesity pandemic (Unger and Orci, 2001).

3.1.2 Metabolic syndrome

Obesity and its co-morbidities are generally referred to as the metabolic syndrome, but so far no unifying pathogenic mechanism for all the elements in the syndrome has been accepted (Unger and Sherer, 2010). The existing definitions are given in **Box 5**.

From the various definitions, it appears that elevated fasting glucose is a common criterion. To place hyperglucosemia as a central criterion stems from the work of Oscar Minkowski (1858–1931), who was the first to connect pancreatic dysfunction to diabetes mellitus. As a consequence, insulin resistance in the pathogenesis of diabetes type 2 has traditionally been explained under the 'glucogenic paradigm'. More recently, the 'lipogenic paradigm' has gained increasing interest.

Xu et al. (2010) compared the three definitions in a study involving 5584 adults aged 20–79 from Shanghai, China and found that only 9.0% of males and 13.3% of females fulfilled the criteria in all three definitions. However, they found that the most prevalent component was dyslipidemia; this clearly points to lipotoxicity as the basic causal factor in the metabolic syndrome.

In recent years studies have supported that dysregulation of lipid homeostasis is the primary metabolic defect. The 'lipocentric paradigm' has now been generally accepted, as has cellular dysfunction due to lipid imbalance as an underlying problem associated with obesity and the ensuing co-morbidities (Garbarino and Sturley, 2009) (for further explanation see **Box 6**).

Box 6 From overweight to chronic disease

Sustained intake of surplus lipogenic calories (sugar and fat) is a *sine qua non* for developing obesity and its co-morbidities. A proposed flow sheet from over-nutrition to the metabolic syndrome, to relevant clinical outcomes is shown in **Figure 7**.

Fatty acids and glucose constitute the primary oxidative fuels for the body. In the context of physiological conditions there is a great potential, especially in muscles, to adjust fuel selection from the one to the other in order to match the actual demand for energy. Insulin is the principal regulator of these transitions. A high intake of glucose gives rise to a high postprandial insulin level caused by glucose stimulated insulin secretion (GSIS). High insulin levels will favor glucose uptake and glycolytic metabolism, whereas low insulin levels and elevated fatty acids, under circumstances such as

[3] Diabetes: from the Greek word siphon, *dia* (through) and *bainein* (to go). Mellitus: from the Latin word for honey sweet.

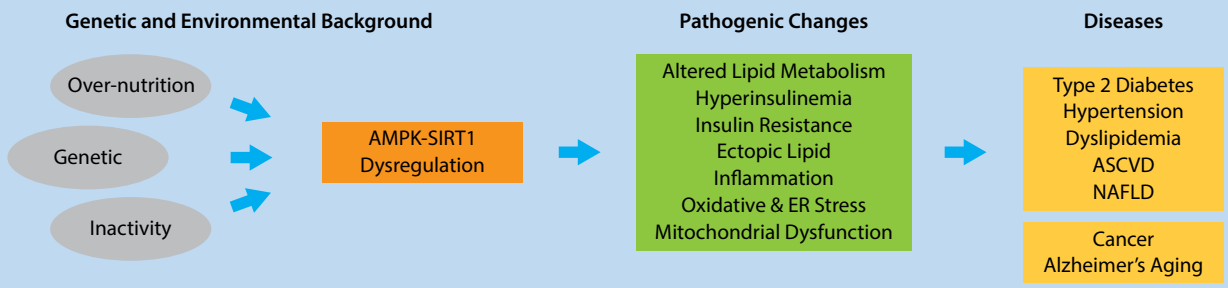

Figure 7. Flow sheet from over-nutrition to the metabolic syndrome, to relevant clinical outcomes. Source: Adapted from Ruderman et al. (2010).

fasting and exercise, will trigger metabolism that relies on fatty acid oxidation (Muoio and Koves, 2007). GSIS is regulated by peroxisome proliferator activated receptors (PPARs), such that it is stimulated by PPAR-γ and down-regulated by PPAR-α (see **Box 10**) and the level of fatty acids (Sugden and Holness, 2008).

Energy overload with lipogenic calories leads to hyperinsulinemia through GSIS. Insulin activates the sterol regulatory element binding protein (SREBP 1-c). SREBP promotes lipogenesis and as such a tendency toward fat accumulation and weight gain. When adipocytes store excess calories as triglycerides, the secretion of leptin will increase (hyperleptinemia) (Unger, 2003). In contrast to the effect of insulin, leptin inhibits SREBP. As long as this balance between insulin and leptin is maintained, a physiological compensation for over-nutrition is established. This is, in the evolutionary perspective, meant to be a temporary condition in order to promote survival. However, when over-nutrition becomes permanent, the compensatory mechanisms fail to work – they simply become exhausted.

The ability of adipocytes to store fatty acids as triglyceride is not infinite. Saturation of triglyceride biosynthesis and the resulting accumulation of free fatty acids (FFA) overwhelm the abilities of the adipocytes to maintain cellular homeostasis resulting in adipocyte dysfunction. This in turn leads to the release of FFA to the circulatory system and ectopic fat deposition and development of lipotoxicity. At the same time pro-inflammatory cytokines are released to the circulatory system and as a consequence obesity is now regarded as a chronic state of mild inflammation. The lipotoxic response elicited by ectopic FFA accumulation in skeletal muscle, heart, liver, and pancreas is an underlying key factor for development of insulin resistance, cardiomyopathy, steatosis and diabetes type 2 (Garbarino and Sturley, 2009).

The processes leading to chronic diseases are shown in **Figure 7**. An overweight condition leads to obesity which will result in insensitivity to leptin resistance, saturation of the storage capacity of the adipose tissue and consequently a spill over to non-adipose tissues, liver, muscles, heart, and pancreatic islets. This will have deleterious effects such as lipotoxicity and lipoapoptosis. When lipids accumulate ectopically they are ineffectively oxidized and form metabolites which can cause lipotoxicity, defined as lipid induced tissue dysfunction. Lipotoxicity leads to a cascade of lipid-induced programmed cell-death, lipoapoptosis. Together, these lipid-related processes will lead to insulin resistance and to the metabolic syndrome, with its cluster of chronic diseases (Kusminski et al., 2009).

When fat deposition has progressed to the state where leptin resistance has developed, the negative feed-back mechanism on SREBP is suspended and a dangerous cycle is established. Accordingly, the pathological processes will continue to accelerate unless a rigorous regime of caloric restriction is initiated; in advanced stages of obesity the process seems to become irreversible. This explains why the obesity epidemic, on a global scale, continues to accelerate, and why on the individual level it is so difficult to sustain weight loss obtained during a cure.

In obesity, not only is the concentration of FFA increased, but also the concentrations of reducing sugars such as glucose, fructose and others. These sugars react non-enzymatically with free amino groups of proteins to form unstable glycosamines which can, by oxidative reactions, be transformed into stable advanced glycation end-products (AGEs).

Some of the AGEs elicit toxic reactions and the level of circulating AGEs indicates obesity related health risks. Continuous hyperglycemia will lead to an increased formation of AGEs and is of importance for the pathogenesis of diabetic complications.

The level of circulating AGEs increases with age and in aged individuals with diabetes or cardiovascular diseases it is elevated, and even more so in individuals suffering from both conditions (Gul et al., 2008).

AGEs up-regulate enzymes (e.g. NADPH) which generate reactive oxygen species and as such introduce oxidative stress (Rodiño-Janeiro et al., 2010) resulting in increases in inflammation followed by increased risk for development of chronic diseases (Shalkwijk et al., 2008) and acceleration of the ageing process (Sick et al., 2010; Takeuchi et al., 2010). Furthermore AGEs have been related to cancer growth and metastasis (Yamagishi and Matsui, 2010).

3.1.3 The transition from overeating to disease

The process from overeating to development of chronic disease consists of several phases and involves a complicated network of biochemical interactions, which are described in **Box 6**.

In general terms, the development can be described as occurring during a two-phase process. The first phase is a non-pathogenic and reversible condition produced by temporary and/or moderate overeating. The metabolic reactions will be activated, but still the condition is fully reversible if the energy intake is reduced.

Over-nutrition increases the production of insulin from the pancreas which in turn triggers the synthesis of fat (see **Figure 7** in **Box 6**). The synthesized fat is stored in the adipose tissue. At a certain level of storage, the adipose tissue will increase the production of the hormone leptin (for a description see **Box 7**) which signals that fat deposition is approaching the tolerable limit and a reduction in appetite. This negative feedback system functions to regulate the temporary fluctuations in the naturally-occurring energy intakes without causing health problems. However, in the case where over-nutrition is sustained, the regulating system will be compromised and the increasing signal to produce more leptin cannot be met any longer. There creates a state of leptin resistance. This means that the increasing fat production surpasses the normal storage capacity of the adipose tissue and is accordingly accumulated in other tissues where it does not belong, for example, in muscle and liver. Fat occurring in these tissues in un-physiological concentrations (ectopic fat deposition) will lead to toxic reactions (lipotoxicity). Lipotoxicity will in turn induce insulin resistance and consequently metabolic syndrome. The proposed flow sheet (**Box 8**) for the development of metabolic syndrome explains why lipotoxicity and not insulin resistance is the basic problem, and that glucose dysregulation is secondary to lipotoxicity.

From the first phase, where a negative feedback mechanism regulates metabolism, the process will, in cases of sustained surplus energy intake, move through a grey zone (which is defined by individually-determined factors) into the second phase which is a state of no return. The negative feedback system is replaced by a positive feedback system, which means that the state of disease will be still in progress. Consequently, in the second phase, preventive measures are out of reach, and only pharmacological and/or surgical bariatric options are realistic means of treatment.

3.2 How to break the obesity cycle?

The primary causal factor for metabolic dysfunction is an oversupply of calories in relation to expenditure. Consequently, the precaution is either to reduce the intake of energy or to increase the energy expenditure, or even better, a combination of the two. The only opportunity to break the obesity cycle is in the

Box 7 Leptins

Leptin is a hormone produced by adipocytes, under regulation of the sympathetic nervous system. The amount formed is dictated by the development of hyperplastic adipocytes, hence, leptin is positively related to body fat mass and BMI (Hynes and Jones, 2001). Under physiological conditions leptin is an important regulator of lipogenesis and of satiation. Leptin expression is probably only seen in the sub-cutaneous fat and not in visceral fat (Unger, 2003).

Leptin down-regulates the sterol regulatory element binding protein SREBP (Shimomura et al., 1999) and as such the expression of lipogenic enzymes. Leptin also up-regulates perioxome proliferator-activated receptor γ (PPAR γ) coactivator 1α (PGC-1α) (Kakuma et al., 2000), probably through its activation of AMP-activated protein kinase (AMPK). In this way, leptin promotes fatty acid oxidation and prevents increased serum concentrations of FFA, thereby counteracting ectopic fat accumulation and lipotoxicity.

Circulating leptin is transferred to the brain, where the hypothalamus has the highest concentration of leptin receptors. Signals from the hypothalamus are transmitted to the body. Under physiological conditions, leptin regulates appetite and prevents ectopic fat accumulation. However, under a patho-physiological state such as obesity with over production of fat, these functions can no longer be maintained due to development of leptin resistance. How the resistance develops is not fully understood, but it has been suggested to be a result of the saturation of transport receptors in the blood-brain barrier.

Box 8 How to increase lipid oxidation

Caloric restriction, exercise, and reduced ambient temperature all act in concert to increase the oxidation of fat and to reduce fat deposition. When caloric restriction is put in place, the body will first utilize glycogen as an energy source. When this source is exhausted, fat oxidation takes over with the formation of ketone-bodies (see **Box 2**). In order to fulfill the body's energy demand, FFA concentrations in serum increase. This will activate the PPARβ/δ, now recognized as the major sensitizing nuclear receptor (see **Box 10**). Activation of PPARβ/δ will activate SIRT1 which is in cross talk with AMPK. Both SIRT1 and AMPK activate PGC-1α, which in turn activates PPAR-α, and fatty acid oxidation. For further explanation please see boxes on Sirtuins (**Box 9)** and PPARs (**Box 10**). Dietary components such as the polyphenolic compound resveratrol found in grapes (and in red wine) can also activate SIRT1 (see **Box 11**).

Co-morbidities associated with obesity accelerate the aging process (see **Box 13**); obese individuals have a shorter life-expectancy compared with lean individuals. This will be further discussed in **Section 4.2**.

first phase of development of excess body weight. In the second phase, where clinical obesity has already developed, preventive measures can only be a support to medical interventions.

3.2.1 Reduction of energy intake

As a consequence of its favorable influence on metabolic processes, caloric restriction (CR) is related to a prolonged life span in mammals and could also have profound public health impact by reducing incidences of diseases and possibly extending the quality and length of human life (Barger et al., 2008). The effect of caloric restriction in humans remains to be fully elucidated (Smith et al., 2010) but seems to be a crucial prerequisite to control obesity. The advice to reduce caloric intake seems to be easy: just eat less than usual by reducing portion size. How to increase expenditure is a little more complicated. Energy expenditure is not solely dependent on physical activity, but depends on of all seven pillars of obesity as will be explained in **Chapter 4.**

3.2.2 How to increase energy expenditure?

Increased energy expenditure can be obtained either by exercise or a reduced ambient temperature. In addition, these can be supported by dietary interventions, as not all nutrients are energy-producing to the same extent. Furthermore, the thermogenic capacity of nutrients varies greatly. These aspects are dealt with in detail in **Chapter 4.**

3.2.3 The combined effect of caloric restriction and an increase in energy expenditure

Caloric restriction, exercise, and a lower ambient temperature will, in concert, reduce the amount of energy available for the metabolic household of the body. In the case of a negative energy balance, the needed energy will be supplied through increased fat oxidation from the body's stores of energy found in adipose tissue. This is accomplished through a complicated cascade of biochemical reactions (see **Figure 7** in **Box 6**).

The sirtuins ('silent information regulators') play a central role in these processes (see **Box 9**). Sirtuins are a group of proteins which were identified about ten years ago in all living organisms from bacteria to humans. They are activated by a negative energy balance (caloric restriction, exercise and cold) and play a crucial role in fat oxidation (see **Boxes 9 and 10**). Sirtuins can also be activated by nutritional factors such as plant phenols, for example, resveratrol found in dark-skinned berries (see **Box 11**).

3.2.4 The importance of plant phenols

Dark-skinned berries contain a great number of phenolic compounds with anti-oxidative effects; among these resveratrol has recently gained great interest (see **Box 11**). It is present in the highest concentrations in blue grapes. Moderate daily consumption of red wine has been connected to The French Paradox, a term coined in 1992 to describe the relatively low incidence of cardiovascular diseases in the French population. This beneficial effect was later confirmed in several studies which have shown that red wine consumption produces a kaleidoscope of potential effects that reduce cardiovascular risk factors (Lippi et al., 2010). Recently it has been shown, in an intervention study, that a daily intake of 250 mL of red wine, but not beer or vodka, had a positive effect on risk factors for cardiovascular diseases (Huang et al., 2010). As a consequence, moderate daily intake of red wine has been recommended. The

Box 9 Sirtuins

Sirtuins are a family of proteins present in most organisms from bacteria to humans. They play key roles in the health and survival of an organism as regulators of metabolic homeostasis. One of the sirtuin families, the silent information regulator 2 gene (SIR2) was first found in yeast cells. Mammalian sirtuins consists of seven orthologs (SIRT1 to SIRT7) of SIR2 (extensively reviewed by Haigis and Sinclair, 2010). Of the seven sirtuins SIRT1 is the best characterized.

In humans, sirtuins are activated by starvation, caloric restriction, exercise and by a number of polyphenolic compounds, for example resveratrol, found in grapes and red wine. The same factors also activate AMP-activated protein kinase (AMPK) which acts together with SIRT1 in the SIRT1-AMPK metabolic control network. Both AMPK and SIRT1 activate peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1α) to induce mitochondrial biogenesis and fatty acid oxidation (Haigis and Sinclair, 2010).

In studies on human hepatocyte cultures, Okazaki et al. (2010) found that PPAR β/δ, a ubiquitous transcription factor of the PPAR family and a FFA sensor. PPAR β/δ is activated under starvation by lipolysis-derived FFAs which in turn increase the expression of the SIRT1 gene. This mechanism acts to protect cells against nutritional insufficiency. Interestingly, Okazaki et al. (2010) also found that PPARα was not involved in the regulation of the SIRT1 gene even if it acts as a promoter of β-oxidation of FFA and is activated, like SIRT1, by starvation, and exercise. This can, however, be explained by the findings of Purushotham et al. (2009) that PPARα is activated by PGC-1α via SIRT1. The PPARα/PGC-1α signaling axis is a major target for SIRT1 (see **Figure 8** in **Box 10**).

Long-chained polyunsaturated fatty acids of the n-3 family are known to lower serum lipids by promoting β-oxidation of fat and it has been speculated that n-3 fatty acids act as agonists to PPARα (Hansen et al., 2008). However, it has now been shown in rodent studies that n-3 fatty acids increase expression of the SIRT1 gene (Fernandes, 2008) through activation of AMPK (Lorente-Cebrián et al., 2009). As there is a cross-talk between AMPK and SIRT1, the SIRT1-AMPK metabolic control network is a central coordinator for environmental stimuli (e.g., physical exercise, nutrition, caloric restriction, or n-3 fatty acids) to enhance fatty acid oxidation.

Box 10 The PPAR System (revised and up-dated from Hansen et al., 2010)

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor super family. PPARs form obligate heterodimers with the retinoid-X receptor and bind to elements in the promoter region of target genes. The PPAR group consists of three related members: PPAR-α, primarily expressed in the liver; PPAR-γ, predominantly expressed in adipose tissue (PPAR-γ1 is expressed in a number of tissues including the pancreatic islets, while PPAR-γ2 is only expressed in adipose tissue); and PPAR-β/δ expressed ubiquitously but with a relatively high expression in the skeletal muscles. See **Figure 8**.

The PPARs recognize a variety of nutrients (e.g., fatty acids, fatty acid derivatives), act as metabolic sensors/transcription factors and regulate a variety of metabolic-related genes. In addition to their responses to natural agonists they can all be activated by synthetic agonists which are used clinically. They also play a role in the generation of ketone bodies to support energy needed during fasting. Thus PPAR-α, PPAR-β/δ and PPAR-γ act in a complementary way in anabolic and catabolic processes.

Among the three receptors, PPAR-γ is regarded as a 'feed sensor' and exerts an anabolic effect on excess carbohydrates by facilitating adipogenesis to store energy as triglycerides. This is facilitated by its ability to promote the conversion of pre-adipocytes to adipocytes with the ability to store triglyceride. In this way PPAR-γ lowers serum FFA and as such has a beneficial role in counteracting lipotoxicity. This is the rationale for using PPAR-γ agonists in the treatment of diabetes type 2.

In contrast both PPAR-α and PPAR-β/δ act as 'fast sensors' and switch the energy source from carbohydrates to stored triglyceride by inducing lipolysis/β-oxidation-related genes. PPAR-α agonists are used in the treatment of dyslipidemia.

The role of PPAR-β/δ has hitherto been obscure; however, it is now recognized as an important factor for metabolism of fat and adaptive thermogenesis. PPAR-β/δ seems to be the major sensor of plasma FFA (Sanderson et al., 2009) (see Figure 8). PPAR-β/δ is induced by starvation, caloric restriction and FFA; it promotes expression of SIRT1 and as such seems to play a central role in metabolic regulation during starvation and caloric restriction. Evidence is now emerging that PPAR-β/δ ameliorates pathologies related to the metabolic syndrome partly through its anti-inflammatory effect by preventing production of inflammatory cytokines by the adipocytes (Coll et al., 2010). So far, no synthetic agonist for clinical use has been developed for PPAR-β/δ, however, when it appears, it will have a great potential for treatment of obesity.

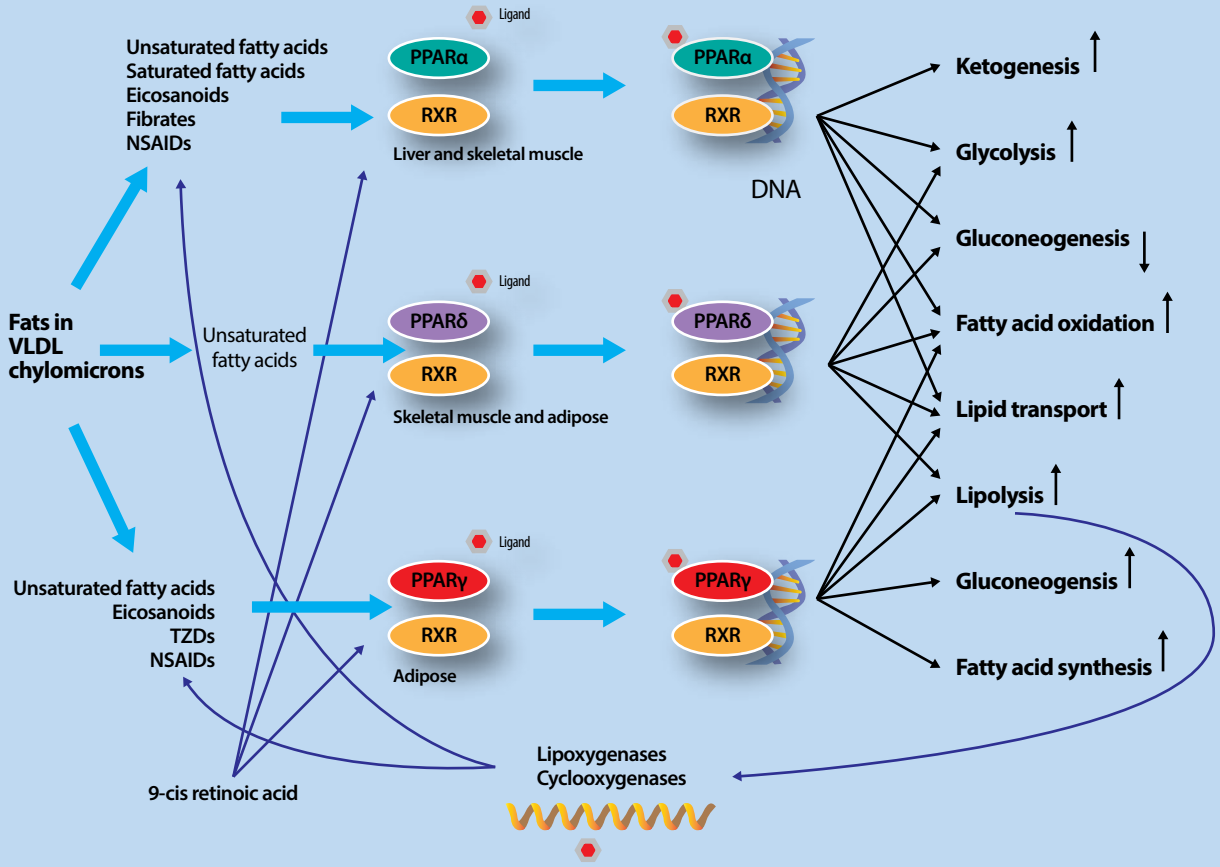

Figure 8. For each PPAR, the initial step involves the activation of the receptor through its binding to a ligand. Then, the retinoid-X receptor (RXR), a nuclear receptor activated by 9-cis retinoic acid, heterodimerizes with a PPAR prior to ultimate binding of the complex with DNA. NSAID: non-steroidal anti-inflammatory drug; TZD: thiazolidinedione, a class of drugs that bind to PPARγ and have insulin-sensitizing properties; VLDL: very low density lipoprotein (used to transport lipids in the blood). Source: Ament et al. (2012).

definition of a moderate intake has been suggested as one to three glasses per day, which probably is a conservative estimate. The advice to abstainers has been to take a resveratrol capsule or to consume fruits (or fruit concentrates) which contain resveratrol (see **Box 11**).

3.3 Conclusions

Surplus energy supply in relation to energy expenditure is a *sine qua non* for development of metabolic disturbances. Whether or not these disturbances will develop is highly influenced by individual characteristics, as is discussed in **Chapter 4.** A sustained positive energy balance will sooner or later lead to obesity and its co-morbidities. To alter this process, it is necessary to combine calorie restriction with a non-obesogenic diet and to increase energy expenditure.

Moderate excess body weight should not be regarded as a disease, but as an evolutionary approach to store energy. However, when this purpose is overruled by a constant intake of excess food energy, the excess weight becomes permanent and there is an almost inevitable risk of a progression into adverse patho-physiological processes. These include development of leptin resistance and the start of a cycle that is extremely difficult to break.

The best options seem to be caloric restriction (in extreme cases fasting) and exercise, however the problem is more complex than this (see **Chapter 4**). Weight corrections through lifestyle changes alone only appear to be relevant for overweight individuals with BMIs between 25 and 30. For individuals in obesity class I (see **Box 1**), lifestyle corrections, in combination with pharmacological intervention might be effective. For those in obesity class II and those who are morbidly obese, lifestyle corrections are of little value and only pharmacological intervention and surgery are realistic.

In general, it seems warranted to recommend that individuals with BMIs >18.5 and <25 regularly control their weight, as increasing or decreasing weight trends can indicate the early development of disease. For individuals with BMIs >25 there is an indication of a need for medical surveillance even if no clinical signs and symptoms are yet evident.

Box 11 Resveratrol

Resveratrol is a phytophenol which, together with other phenols, is found in dark colored fruits. Resveratrol is found in the highest concentrations in blue grapes and consequently in red wine. These phytophenols have for a long time been known to have anti-oxidative properties and have been regarded as the reason for the apparent beneficial health effect of red wine (the French Paradox). More recently, resveratrol has been of interest as an antioxidant, anti-inflammatory agent, anti-cancer agent and as a caloric restriction mimic and has been commercially introduced as a food-additive useful for promoting better health and longevity. In addition to its anti-oxidative properties, resveratrol activates SIRT1 and acts in synergy with caloric restriction and exercise to promote fatty acid oxidation.

The content of resveratrol in grapes is highly dependent on the type of grapes; Pinot Noir has the highest concentrations, followed by Cabernet Franc, Cabernet Sauvignon, Mouvèdre, and Grenache. The average concentration in Pinot Noir wines is 3.6 mg/L. Moderate daily consumption of this wine (three glasses per day) equates to a daily intake of 1.35 mg of resveratrol.

Is this enough to provide health effects? Commercial resveratrol food additive capsules contain 5 mg and recommended dosages are usually 1–4 capsules/day (5–20 mg resveratrol/person/d). This dose is based on the concept that you can eat as you want and take resveratrol capsules to counteract the consequences. Resveratrol acts in synergy with caloric restriction and physical activity, and amounts less than 5–20 mg/person/d might still be effective. Resveratrol is only one of several potential phytophenols in red wine; its polymers viniferin, and vaticanol are di- and tetramers respectively of resveratrol. The close interaction between caloric restriction and resveratrol has been demonstrated in animal experiments by Barger et al. (2008) and a beneficial effect of even low doses was demonstrated. Studies in humans are lacking but are certainly needed.

Daily moderate consumption of red wine is still recommended. Alternatively, one daily resveratrol capsule might be a reasonable alternative. However, to pretend that intake of high doses of resveratrol in capsules can be a means of avoiding caloric restriction is unethical and misleading. Resveratrol taken either through red wine or as a capsule is a valuable support for the effects of a negative energy balance but should never be regarded as a remedy for the effects of over-eating.

4. The seven pillars of obesity

Wisdom hath built her house; she hath hewn out her seven pillars.
Proverbs 9:1

We propose seven pillars which contribute to the problem and the solution of the globesity epidemic (**Figure 9**). While the pillars are dealt with separately in the following text, they are intimately linked. They work together. How they impact the structure and function of adipose tissue and alter the capture and storage of energy are key aspects of this chapter. As a result, we provide additional information in a box related to adipose tissue and energy (see **Box 12**).

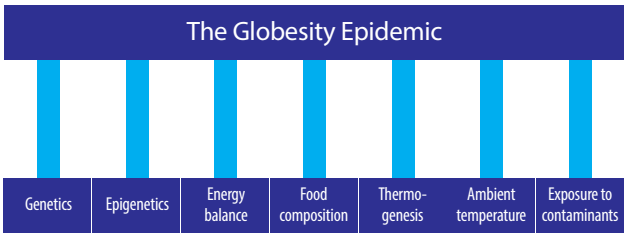

Figure 9. The seven pillars of obesity. Source: Hansen et al. (2010).

Box 12 Adipose tissue

Two different types of fat are present in the human body. White adipose tissue (WAT) is the main energy store of the body and is, in addition, the largest endocrine organ. Brown adipose tissue (BAT) is less abundant and is specific to the production of heat, that is, it is thermogenic; it is an energy-expending organ as it dissipates energy as heat. The development patterns of WAT and BAT are distinct. Recent studies have revealed that BAT and WAT develop from distinct different cellular lineages (Atit et al., 2006). BAT emerges earlier than WAT during fetal development. BAT is at its maximal size, relative to bodyweight, at birth. This is the time when the requirements for non-shivering thermogenesis are maximal. After birth, BAT involutes both in humans and rodents with age (Cannon and Nedergaard, 2004). The development of WAT begins in mid-gestation and increases gradually throughout life. Both in rodents and humans, BAT depots are replaced by WAT during aging. Although the number of fat cells can increase throughout life (Prins, 1997), individuals with adult on-set obesity, in general, exhibit increased size of adipocytes (hypertrophy). Individuals with early-onset obesity have both adipocyte hypertrophy and an increased number of adipocytes (hyperplasia) (Hirsch and Batchelor, 1976).

In human fetuses and newborns, BAT is found in axillary, cervical, perirenal, and periadrenal regions (Cannon and Nedergaard, 2004). It decreases shortly after birth and has traditionally been considered insignificant in adults, perhaps with the exception of workers in cold climates subjected to prolonged cold exposure (Huttunen et al., 1981). The evolutionary rationale for an abundance of BAT at birth, both in rodents and in humans, is based on the need to maintain body temperature after the abrupt reduction in ambient temperature after birth. Later in life other strategies for protection from cold become available and the need for BAT non-shivering thermogenesis is reduced. Consequently the amount of BAT is reduced. However, it has been observed in adult mice that reactivation of thermogenesis occurs within minutes of being exposed to cold (Coulter et al., 2003). Therefore, the transcriptional machinery must be conserved to be able to respond to an acute physiological need. This new insight has also been confirmed in humans through data from Fluoro-Desoxy-Glucose Positron Emission Tomography (FDG-PET) scans which in addition to identifying malignant tissue can also detect metabolically active BAT in the subclavicular, axillary, and paravertebral regions of normal individuals (Nedergaard et al., 2007). Experiences from the PET scans show that false positive readings caused by active BAT can be avoided if the patients are kept warm during the time between FDG injection and PET imaging, as this fully suppresses FDG uptake in BAT. Most individuals living in cooler climatic regions are only rarely exposed to cold outdoor temperatures because of the clothes they wear and the type of heated housing in which they live and work. As a result, it is unlikely that present-day humans become adapted to cold during the winter period (Nedergaard et al., 2007).

The extent of the role played by BAT in energy balance in adult humans is still unclear. However, recent research has indicated an important role for BAT in adult humans in the control of body temperature and adiposity, that is, the amount of BAT in human adults is inversely correlated with BMI (Cypess et al., 2009; Saito et al., 2009). Important questions in this connection are: does the lack of brown adipose tissue lead to obesity, or does obesity lead to a lack of brown adipose tissue? Even though paradoxical, both questions may be answered with yes! In the first case of lack of activated BAT such as would occur with high ambient temperatures, a minimum of energy is dissipated as heat and will be stored as fat. In the second case, in established obesity, subcutaneous fat will insulate the body against cold and consequently reduce the cold induced activation of BAT. In either case, there is a close connection between the amount of activated BAT and obesity. Rothwell and Stock (1979) estimated that as little as 50g of BAT could account for 20% of daily energy expenditure. These findings reject the notion that BAT is absent in adult humans; however, the variation between individuals is considerable (Nedergaard et al., 2007).

Brown adipocytes have also been observed in adults in classical white fat depots; the number of brown adipocytes increases dramatically during cold exposure or after

hormonal and/or pharmacological treatment (Diehl and Hoek, 1999). It is evident that white adipocytes can be transformed into brown adipocytes by the peroxisome proliferation activation receptors (PPARs) and their cofactors. For example, PGC1α (a PPAR γ cofactor) induces the expression of brown adipocyte genes in white adipocytes (Tiraby and Langin, 2003; Tiraby et al., 2003). Xue et al. (2007) have reported that the two types of brown cells are genetically distinct; the brown adipocytes in WAT are developed from white adipocytes while the 'classic' BAT develops from a distinctly different cell lineage than do the WAT adipocytes.

The potential to induce the production of even a small amount of BAT in adult humans could provide a new approach to the treatment and/or prevention of obesity and its metabolic complications (Gesta et al., 2007). Fat distribution, even in lean persons with a steady body mass index (BMI) changes with age, decreasing in retro-orbital and subcutaneous fat and increasing in intra-abdominal fat (Gesta et al., 2007).

Genetics play an important role in both obesity and distribution of WAT. Studies with twin siblings and other population studies have revealed that both BMI and waist/hip ratio are heritable traits with genetics accounting for 30–70% of the variability. Understanding the biological and environmental factors controlling the expression of the two brown adipocyte populations, in brown and white adipose tissue respectively, might provide new strategies by which enhanced thermogenesis can be used to reduce obesity (Kozak and Anunciado-Koza, 2008; Lidell and Enerbäch, 2010).

4.1 Pillar 1 – Genetics

The genetic contribution to obesity is well-established and extensively described in the literature. For this reason it will not be discussed here in detail. For a detailed review see Hetherington and Cecil (2010).

Genes are strongly implicated in the causality of excess weight gain in human beings, underlying both individual differences in susceptibility and the pathways by which excess weight gain occurs. Twin and adoption studies have suggested that approximately half of individual variation in total excess weight gain and fat distribution is genetic (Bouchard, 1997). This is in accordance with the findings by Fisher et al. (2007) in a study of Hispanic children.

Some individuals are genetically resistant and defend easily against a propensity to accumulate fat and do not develop obesity while others are genetically predisposed to be obese. In addition to common obesity, which is influenced by the environment, there are about 30 rare syndromes caused by discrete genetic chromosomal abnormalities leading to extreme obesity; these syndromes are most often related to mental retardation but have obesity as a clinical feature (Alfredo Martínez et al., 2007). The Prader-Willi syndrome is the best known (recently reviewed by Goldstone and Beales, 2008).

Common obesity, as observed in the majority of populations, is polygenetic, involving complex gene-gene and gene-environment interactions. The degree of environmental influence is determined by our genetic blueprint ranging from a strongly genetic to slightly genetic predisposition. At present, 135 candidate genes have been associated with obesity (Bellisari, 2008). The role of genetic factors is complex, involving the interactions of many genes, which individually may have relatively minor effects. Such 'susceptibility genes' work in combination with each other and help to explain why some individuals are more prone to developing obesity than others and why some individuals, in spite of weight loss regimens, fail to lose weight. However, genes alone cannot explain the developing obesity epidemic observed during the last half century (Wells, 2006).

A specific example of how genetics can promote obesity comes from the work of Keskitalo et al. (2007) who found that approximately 50% of individuals they studied had a liking for sweets (sugar-containing foods). Several studies on taste preferences have been performed in humans; however, the results have been conflicting. Preference for sweets has also been related to alcohol and drug dependence (Fortuna, 2010), although this has not been confirmed to date. Genetically-determined food preferences as well as alcohol dependency are areas of great interest, but more research is needed before definite conclusions can be drawn.

Environmental factors are thought to play an important role in the development of the obesity epidemic. Food is the environmental factor to which we all are exposed from conception to death. Therefore, dietary habits represent key environmental factors that modulate gene expression throughout life. This has introduced a new paradigm in nutritional science called nutritional genomics (see **Box 13**), aimed at developing a holistic understanding of gene/nutrient interactions. Within this concept, three terms are used: genomics (the total blueprint of an organism), nutriomics (the total chemical composition of nutrients, including components not yet recognized as nutrients), and metabolomics (the total metabolic network). These interact in such a way that nutriomics influence the genomic expression, which in turn determines the metabolomics.

The science of nutri-genomics is new and poses large methodological challenges. However, when the appropriate technologies are developed it may become the driving force in future research on the relationship between disease and nutrition on a population scale. Van Erk et al. (2006) have demonstrated that it is possible to measure responses to dietary exposure by profiling gene expression in white blood cells. While there is considerable intra-individual variation in gene expression profiles in blood leucocytes, there is a relatively constant gene expression over time within an individual

Box 13 Epigenetics and aging

Epigenetics are not solely a question of fetal programming; they can also take place in adult life. An example in relation to obesity is the environmental influence on telomeres[4] (non-coding repetitive sequences of DNA situated as caps at the end of the chromosomes to protect them from genetic instability).

The longer the telomeres the better the protection; however, in the extreme, the longevity of cells increases and consequently the risk of malignancy increases (Gancarcíková et al., 2010). A shortening of the telomere length weakens the protective effect, such that very short telomeres lead to early cell senescence and death. Shortening of telomeres is a normal process over a lifespan and is considered to be closely related to the aging process (Takubo et al., 2010; Wong et al., 2010).

The physiological aging process can, however, be accelerated by life-style factors. For example, a shortening of telomeres takes place with increasing BMI (Nawrot et al., 2010) and parallels increases of oxidative stress (von Zglinicki, 2002; Richter and von Zglinicki, 2007; Satoh et al., 2008; Moreno-Nawarrete et al., 2010). As oxidative stress is closely related to obesity and the metabolic syndrome, these disorders will accelerate the ageing process (Kim et al., 2009; Al-Attas et al., 2010) and lead to a shorter life expectancy in obese individuals compared with lean individuals.

(van Erk et al., 2006). This opens up a new technology called nutrigenetics, which focuses on generating recommendations about the risks and benefits of nutrients and may be a powerful tool to study individual reactions to diets and single nutrients. This may become an invaluable tool for providing specific advice to patients with metabolic diseases (Ordovas and Mooser, 2004).

4.2 Pillar 2 – Epigenetics

Genetics play a major role in the development of obesity; however, the recent increase in prevalence of obesity globally has been too rapid to be associated with major genetic changes. This has supported an interest in the studies of epigenetics.

The term epigenetics (*epi-* from Greek: after) is defined as 'heritable changes in gene expression that occur without changes in the DNA sequence'. Epigenetics deals with the study of how existing genes in a cell can be activated or silenced by environmental factors such as diet, lifestyle, exposure to

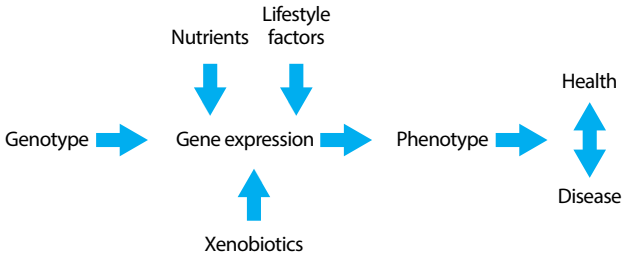

Figure 10. The influence of environmental factors on genetic expression. Source: Hansen et al. (2008).

contaminants and other factors to influence the phenotype (**Figure 10**). Epigenetics has been called neo-Lamarckism, after the French scientist, Jean Baptiste Lamarck (1744–1829) who in 1809 published *Philosophie Zoologique* where he claimed that abilities acquired through life could be inherited by offspring. Epigenetic processes, however, fit better with Darwin's theory of evolution expressed in *The Origin of Species by Means of Natural Selection* published in 1859, half a century after Lamarck´s *Philosophie Zoologique*. The difference between the two is that Lamarck thought that individually developed characteristics could be inherited, while Darwin's theory was that environmental factors could influence the general phenotype of populations in a heritable way.

In 1869, Gregor Mendel first characterized the laws of genetic inheritance. At first they were not recognized scientifically, but were rediscovered around 1900 by Hugo de Vries and Carl Correns and from then on regarded as the foundation of genetics. The science of genetics subsequently flourished; however, the problem of development of the phenotype was not taken into account. The Darwinian idea of an environmental influence on phenotype was neglected in classical genetics, and still is in some circles of society.

Towards the middle of the 20th century, there were a few leading biologists who realized that genetics and developmental biology were indeed related and should come together as one discipline. One of them was Conrad Waddington who, in the early 1940s, coined the term epigenetics. Recent research has shown that there are no contradictions between classical genetics and epigenetics. Rather, it has been shown that environmental factors are able to influence gene expression, that is, some promote expression of genes and others silence gene expression.

Epigenetic processes take place throughout life, from conception to death. From a public health point of view, the prenatal processes are of greatest interest, as they carry the trans-generational aspect. Epigenetic processes are closely related to the concept of 'fetal programming'. Fetal programming is an epigenetic phenomenon related to

[4] In 2010 Elizabeth H. Blackburn (professor at the University of California, San Francisco), Carol W. Greider (professor at the Johns Hopkins University School of Medicine, Baltimore), and Jack W. Sozostak (professor at Massachusetts General Hospital, Boston) were awarded the Nobel Prize in Physiology and Medicine for their discoveries of how chromosomes are protected by telomeres and the enzyme telomerase.

modification of certain physiological functions as a result of exposure to nutritional, hormonal, physical, psychological, and other stressful events during a critical period of the fetal life (de Moura and Passos, 2005). Maternal energy intake seems to affect offspring obesity through gene-environment interactions (Wu and Susuki, 2006). This has attracted much attention lately because there is increasing evidence to show that over-nutrition and under-nutrition during pregnancy may have an adverse effect on fetal development and the later development of obesity.

It has been clearly shown that fetal malnutrition resulting in low birth weight is associated with an increased risk of obesity in later life. However, newer studies have shown that fetal over-nutrition also increases susceptibility to future obesity (Lillycrop and Burdge, 2011). Therefore obesity is no longer an individual problem, but should be regarded as a trans-generational problem.

Two scenarios related to under- and over-nutrition during pregnancy are shown in **Figure 11**. In the case of fetal malnutrition, the fetus will adapt to a thrifty genotype, which will improve survival in the postnatal environment with food restrictions. However, if the postnatal period is rich in nutrition, the fetal programming will result in metabolic disturbances. On the other hand, fetal hypernutrition will program the fetus later in life to develop obesity.

Pregnancy causes metabolic stress, which leads to a progressive decrease in insulin sensitivity in normal weight women. Insulin sensitivity is accentuated with increasing BMI and as a result obese women have an increased risk for developing gestational diabetes (Catalano, 2010).

As the epidemic of obesity expands, it increasingly affects women of reproductive age. It has been estimated that one in four women of reproductive age is obese and have a significantly increased risk of maternal and neonatal complications (Chu et al., 2008). In these women the metabolic regulatory system will be incorrectly programmed, leading to an increased disposition for the obesity-related co-morbidities. Female offspring born to obese and/or diabetic mothers will, when they become pregnant, expose their offspring in the same way as they were exposed themselves, thereby creating an inter-generational cycle. This is referred to as an acquired epigenetic disposition to obesity and diabetes, which is passed on to future generations (Plagemann et al., 2010a,b).

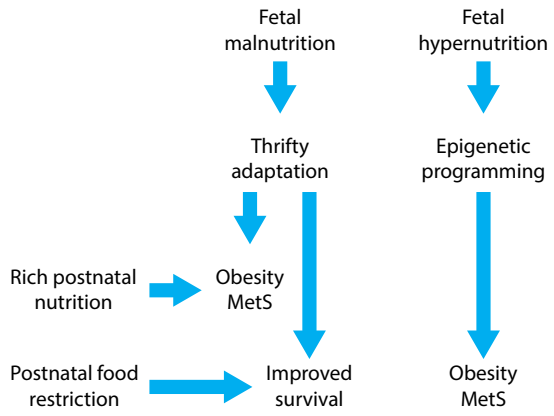

Figure 11. Consequences of fetal malnutrition or fetal hypernutrition. MetS: metabolic syndrome. Source: Hansen et al. (2008).

Generational epigenetic programming of the fetus plays a significant causal role in expanding the development of the global obesity epidemic. During periods of embryonic, fetal and infant development, the susceptibility to environmental hazards is high. Toxic exposures to chemical pollutants during these windows of susceptibility can cause disease and disability in later life, including certain cancers and obesity, and may even affect successive generations (see **Box 13**) (Grandjean et al., 2007).

4.3 Pillar 3 – Energy balance

Heart attack is born by the intake of fatty meals, overeating, excess of sleep, lack of exercise, and anxiety.
Charaka Sutra, 600 BC

The energy balance of the body is a delicate relationship between ingested energy and energy expenditure. Energy taken in by food will either be absorbed or excreted through feces, depending on the digestibility of food items, primarily carbohydrates. In this section, energy intake (EI) is defined as the energy absorbed from the diet.

Energy balance (EB) is determined by the equation:

EB = Energy intake (EI) – Energy expenditure (EE)

If EI is greater than EE, energy balance is positive and the excess energy will be stored as fat. If EI is equal to EE, energy balance is neutral. If EI is less than EE, energy balance is negative and the body's need for energy is taken first from stored fat.

Energy expenditure (EE) is affected by an individual's basal metabolic rate (BMR), their level of physical activity, facultative or adaptive energy expenditure, and general bodily energy loss, that is, heat loss through evaporated sweat, excreted urine and feces, expired air, skin surface loss and lost organic molecules. The BMR is the energy needed to maintain metabolic processes when an individual is at rest. The BMR in sedentary humans has been estimated to account for about 80% of total energy expenditure (Landsberg et al., 2009). While physical activity increases energy expenditure and is important for general health and well-being, the percentage of additional energy expenditure is generally far less than the energy consumed to maintain the BMR.

Achieving an appropriate energy balance requires more than a reduction in energy intake; it has to be combined with exercise. Physical activity will need energy, in addition to that accounted for by the BMR, muscle contraction and the dissipation of heat produced during physical activity. Exercise helps to maintain an optimal metabolism and it allows consumption of sufficient quantities of food to fulfill the physiological needs for micronutrients such as vitamins and minerals. Daily requirements for micronutrients may not be met during periods

of extreme dietary restriction, for example, self-imposed caloric restriction for weight loss without sufficient physical activity, or caloric restriction associated with anorexia.

Metabolic efficiency is another significant factor in maintaining energy balance. Individuals who dissipate excess calories as heat have a less efficient metabolism that those who store ingested calories as fat with less dissipated heat. Individuals with an efficient metabolism will better resist famine, but have a predisposition to fat-related weight gain in a situation of excess food availability.

Caloric intake, the nutritive value of the diet, metabolic efficiency and physical exercise all contribute to energy balance; however, the other pillars of obesity also exert a significant influence on overall energy balance.

4.3.1 Energy measurements

Energy is traditionally measured in calories. A calorie is defined as the energy needed to raise the temperature of 1 gram of water from 14.5 to 15.5 degrees Celsius. The unit Joule[5] (J) is more often used today; one calorie is equal to 4.2 Joules.

The daily energy intake is the sum of the energy contained in the food consumed. The energy originates from the three major macronutrients: carbohydrate provides 17 kJ/g, fat provides 38 kJ/g, and protein provides 17 kJ/g. These figures are determined based on calorimetric measurements of the various types of macronutrients. Their actual contribution to metabolic energy will vary from individual to individual and by food type due to the extent of digestibility and absorption of the ingested macronutrients.

4.3.2 Is a calorie a calorie?

A notion that has been widely accepted is 'a calorie is a calorie' regardless of whether it comes from fat, carbohydrate or protein. The rationale has been that to deny this would be a violation of the first law of thermodynamics about the constancy of energy. A consequence of this notion has been that low-fat diets have been recommended as the best for weight loss because fat has the highest energy density of the macronutrients. This view is now in dispute (Feinman and Fine, 2003, 2004; Fine and Feinman, 2004). Feinman and Fine have argued that to deny the notion does not violate the first law of thermodynamics, but it will violate the second law of thermodynamics (which relates to increasing entropy in open systems). A living cell needs fuel to produce effective energy (see **Box 14**). However, this efficiency is not 100%, as some energy is lost as bodily heat and also in eliminated waste products. Their conclusion is that, in open biological systems, the first law of thermodynamics is satisfied by properly accounting for the amount of high entropy molecules excreted (carbon dioxide, water and urea) and the amount of heat radiated. The second law dictates that there is an inevitable metabolic inefficiency in all biological processes with formation of heat and high entropy waste molecules, but is silent on the existence of a variable efficiency. The possibility of a variable efficiency of fuel utilization is important. A proper accounting of entropy and efficiency must be included if we are to understand the relationship between energy balance and obesity. This opens up for discussion whether or not there is a metabolic advantage of one or more of the macronutrients over the others. Feinman and Fine (2003, 2004) argue that such a metabolic advantage does exist, but conclude that the existence of variable efficiency and metabolic advantages is an empirical question rather than a theoretical question and needs to be proven. Recent research has clearly shown that a calorie is not a calorie in a metabolic sense, and consequently the qualitative aspect of nutrition is just as important as the quantitative aspect. The value of a calorie in a metabolic sense depends on what is used for thermogenesis, metabolic degradation, or fat deposition and what is left for production of energy in the body. Not all macronutrients, for example fats, are lipogenic. Further information on individual energy needs and the roles of macronutrients in thermogenesis are found in **Box 15** and **Box 16**. It seems clear that counting calories as a form of diet management is far from ideal; it is the macronutrient composition of the diet that is important.

4.3.3 Physical activity level

Energy demand in relation to physical activity is divided into exercise-activated expenditure coming from programmed physical activities such as work and sports activities and non-exercise activated expenditure defined as the cumulative energy

Box 14 Cellular energy metabolism

Energy conversion from macronutrients takes place in the mitochondria of the cell. Energy is captured as adenosine triphosphate (ATP) through the Krebs Cycle or Electron Transport System. Energy capture is an ongoing process because storage of ATP in cells is limited. The electron transport system generates a proton gradient over the mitochondrial inner membrane which causes protons to flow back across the membrane. This creates the energy needed to transform adenosine diphosphate (ADP) into ATP. The coupling between substrate oxidation and ATP formation is, however, less than 100% efficient. The proton gradient, built up by substrate oxidation, can be reduced by proton leaks, causing the ATP formation to be diminished and energy to be dissipated as heat, that is, thermogenesis (Schrauwen and Hesselink, 2002). Depending on the type of energy supply from the diet consumed, the amount of thermogenesis can negatively influence ATP formation, leaving less energy for formation of fat stores.

[5] The unit Joule is named in honor of the British physicist James Prescott Joule (1818–1889).

Box 15 Individual energy need and definitions

Energy needs of individuals vary considerably depending on age, gender, physical activity, body mass and ambient temperature. The energy needs of individuals are now better defined by energy metabolism rather than based on observed energy intake. Energy expenditure consists of the energy consumed through the basal metabolic rate (BMR) and from physical activity level (PAL). Basal metabolic energy expenditure is the body energy expenditure measured after 12–18 hours of fasting in an awake and resting individual at a room temperature of 23°C. In addition to energy for basal metabolism, the body needs energy for physical activities. This includes the 24-hour energy expenditure for physical activities of all kinds. PAL is thus a weighted mean of all activities during 24 hours, expressed as the total energy expenditure (TEE) divided by BMR. The total energy need is defined as the BMR multiplied by the PAL. Neither the BMR, nor the PAL, can be readily determined for a given individual because they can only be calculated after extensive laboratory testing. However, tabulated average values are available for a variety of body types in several textbooks on nutrition. In addition, there is an extra need for energy in order to maintain a constant body temperature if the ambient temperature is below the neutral point. There is considerable inter-individual variance in energy need due to differences in metabolic efficiency.

Box 16 Diet induced thermogenesis

Diet induced thermogenesis (DIT) can be defined as the increase in energy expenditure above basal fasting level divided by the energy content of the food ingested and is commonly expressed as a percentage (Westerterp, 2004). Thermal energy losses from mixed diets vary from 5–15%; the greatest loss arises from a high protein diet, a moderate loss from a high carbohydrate diet and the lowest loss from a high fat diet. Thus a high-protein diet seems to possess a metabolic advantage over high-carbohydrate or high-fat diets (see also **Section 4.3.1**). Johnston et al. (2002) have reported that postprandial thermogenesis is increased two-fold after a high-protein, low-fat meal compared to a high-carbohydrate, low-fat meal. In this context carbohydrates and fat are referred to as they appear in an average western diet. For more detailed evaluations, the digestibility and the glycemic index of various carbohydrate products should be taken into consideration. The type of fat consumed is also important as not all are lipogenic, for example, saturated fatty acids are lipogenic, n-6 PUFAs are lipogenic and n-3 PUFAs are anti-lipogenic. Mono-unsaturated fatty acid (MUFA) seems to be neutral in energy expenditure based on studies which compared a diet rich in MUFA to a low-fat, high carbohydrate diet (Rasmussen et al., 2007).

expended through all other activities of daily living (Kotz and Levine, 2005). Both are highly variable among individuals. Some authors have maintained that the primary cause of the obesity epidemic cannot be explained by increased energy intake as there has been little increase in energy intake from the 1970s to the 2000s. Moreover, fat consumption seems to have decreased (Binkley et al., 2000). Consequently theories of causation have focused upon the reduction of expenditure of energy resulting from reduced physical activity. This viewpoint has recently been challenged by Westerterp and Speakman (2008) who have argued that energy expenditure related to human physical activity has not declined since the 1980s and matches the energy expenditure of wild animals. Their calculations are based on average human physical activities and do not address the importance of individual physical activity and energy expenditure which are known to vary widely among individuals. Nevertheless, a general reduction of energy expenditure does not appear to explain increasing weight gain found globally. Data on energy intake are often uncertain as most of the information is based on self-reported food intakes. Data derived from food balance sheets, used as an indication of food consumption trends in Europe (national averages), have demonstrated a considerable increase in total energy availability and energy from fat over the past 40 years (Balanza et al., 2007). As a consequence, neither increased energy intake nor decreased physical activity can be ruled out as major factors in individual weight gain.

4.3.4 Weight conserving mechanisms

Recently it has been suggested that changes in thermogenesis away from the expected is an adaptation linked to both overfeeding and to decreased food intake. During overfeeding the observed thermogenesis is higher than expected and during food restriction the observed thermogenesis is lower than expected. This phenomenon has been described by Cannon and Nedergaard (2009) as the lipostatic hypothesis. The hypothesis implies that the body has an intrinsic mechanism that seeks to maintain the *status quo* relative to body weight. If correct, this explains why it is difficult for obese individuals who reduce their caloric intake to lose weight and, on the other hand, why it is difficult for underweight persons to gain weight.

Joosen and Westerterp (2006) scrutinized 16 overfeeding experiments that applied appropriate protocols and measurement techniques. They found that five studies claimed to have found evidence for adaptive changes in thermogenesis while eleven studies suggested that no changes in thermogenesis took place. These authors concluded that for humans, evidence of adaptation of thermogenesis occurring with overfeeding was still inconsistent; however, the possibility cannot be ruled out.

The conflicting results obtained in both overfeeding and weight loss studies may be a result of methodological inconsistencies between studies, including the absence of weight stability and lack of weight-matched controls. Other possible confounders are variations in diet composition and levels of physical activity (Heymsfield et al., 2007). In order to address these confounders which are frequently present in outpatient studies, Rosenbaum et al. (2008) conducted a study with subjects living in a clinical

research center, which enabled control of diet, monitoring of patient compliance, measurement of physical activity and stabilization of weight to levels of constancy. This study confirmed that a significant decline in energy expenditure occurs after weight loss and that it persists over an extended period of time – perhaps indefinitely. This study thus supports the existence of a weight-conserving mechanism, that is, the lipostatic hypothesis.

The human body is a very conservative organism which reacts to short-term changes by adapting its metabolism in a way to preserve a state of homeostasis. On the other hand, under continuous lifestyle changes the body will also adapt to a new balance and consequently defend this as its new level of homeostasis. The lengthy re-adaptation period needed to attain a new homeostatic equilibrium explains, in part, why short-term weight loss regimes often result in weight gain back to the original starting weight; what is needed is a life-long change with calorie restriction.

Siebel et al. (2010) have hypothesized that there may be a 'metabolic memory', based upon the observation that diabetic patients continue to develop vascular complications, even after achieving glycemic control. In a worst case situation, the metabolic memory hypothesis and the lipostatic hypothesis could imply that, even under pathological conditions, the homeostatic mechanisms of the body will dominate. Once obese, always obese!

4.4 Pillar 4 – Composition of the diet

4.4.1 Evolution of nutritional paradigms

Throughout human development diet has been dominated by three different paradigms of various lengths. The first was the hunter/gather period (the Paleolithic period) lasting from the first appearance of *Homo sapiens sapiens* 200 000 years ago until around 12 000 years ago. The second was the agrarian period, which lasted from the end of the hunter/gatherer period to the 19th century. The third period began with the Industrial Revolution and continues today. There are considerable overlaps in both time and geography between these periods. The hunter/gather paradigm has survived to the present day in a few hunter/gather societies. The agrarian paradigm which started in the so-called Fertile Crescent in the Middle East and spread successively to most of the world, has lasted to the present, but has been increasingly dominated by the industrial paradigm during the latest two centuries.

4.4.1.1 The hunter/gatherer diet

Knowledge about the Paleolithic diet stems from archeological finds and comparisons with the few present-day existing hunter/gatherer cultures. These studies have shown that there was a transition from plant-based diets to diets dominated by foods of animal origin. Man became partly carnivorous (a facultative carnivore, or omnivore). This transition to decreased dependence on plants made it possible for early man to move into temperate zones, and even into the subarctic and the high Arctic areas where there was almost total dependence on animals for food.

The Paleolithic diet is not clearly defined and several different opinions on the distribution of macronutrients have been published (for a review see Cordain et al., 2002). The composition of Paleolithic diets has varied enormously according to climate zone and latitude as shown earlier in **Figure 1** with considerable differences in plant-to-animal ratios and terrestrial animal-to-marine animal ratios. Consequently no absolute definition of the Paleolithic diet can be provided other than the following basic principles:

- a high supply of proteins, in some areas close to the toxic limit;
- a varying supply of fat, from medium to high, however, with a favorable fatty acid composition, that is, a very low content of saturated fat and an optimal ratio between n-3 and n-6 poly-unsaturated fatty acids, and;
- a varying supply of carbohydrates, all being of low digestibility (low glycemic load) and rich in fibers. Refined sugars were totally absent.

In addition it must be assumed that essential micronutrients were available in adequate amounts.

This diet must have been health-promoting and been a good fit with the human genome, developed through millennia. The Paleolithic diet has recently attracted interest as a means to improve metabolic homeostasis. It has been shown that patients adhering to an adapted Paleolithic diet over a three-month period had improved glycemic control and reduced several cardiovascular risk factors compared with patients receiving a diabetic diet designed according to conventional guidelines (Lindeberg et al., 2007; Jönsson et al., 2009).

4.4.1.2 The agrarian diet

When the last ice age came to an end about 13 000 years ago, an ecological catastrophe began to unfold. Ice cover decreased dramatically and moved north towards the polar area as the climate became warmer. The rise in temperature led to extensive grasslands south of the ice cap which gradually became forested. As a consequence there was no longer adequate forage for big game like bison and mammoths. As the human population increased and more efficient weapons were developed, many of the species that had become basic game for the human population were drastically reduced through overhunting. A dietary transition took place during the Mesolithic period to consumption of smaller forest animals, birds, aquatic species, and nuts and seeds. During the Neolithic period, agriculture began to appear; first in the Fertile Crescent (the southern part of Turkey, Iraq, Iran, Syria, Jordan, and Israel). Early agriculture in this area focused upon wild species of wheat, barley, peas, and lentils. In addition, there were animals suited for domestication such as sheep, goats, pigs, and cattle.

The development of an agricultural way-of-life meant that populations needed to live near their crops rather than follow their food, as was the case for the hunter/gatherers. Agriculturalists began to live together in small villages. They often shared their basic shelters with their animals. This new lifestyle impaired general health. The congregation of people and animals living in close quarters promoted the spread of pathogenic microorganisms between individuals, and

between animals and people (zoonoses[6]). Infectious diseases were introduced and became an increasing problem throughout human history until the 20th century when vaccinations and antibiotics were introduced that could reduce the spread of disease.

The nutritional value of the diet of the first agrarians was lower compared to the hunter/gatherer diet. In the first place the carbohydrate-to-protein ratio was increased. Meat was restricted, as the animals were important for breeding, for producing wool and milk, and for providing transportation and field labor (e.g., soil cultivation). Second, the domesticated animals were fed the grown grains, which introduced saturated fatty acids into the human diet.

4.4.1.3 The industrial diet

The industrial food paradigm started early in the 19th century and is characterized by industrial refinement of agricultural products. The first was the production of sugar (from sugar beets and sugar cane). Emperor Napoleon Bonaparte strongly supported the production of sugar from sugar beets for the French population because the supply of the traditional cane sugar was restricted by the Emperor's embargo of trade with England.

The next invention was margarine[7]. This invention also had a French imperial background. In 1867, Napoleon III ordered Mège-Mouriés, a chemist, to develop a new product, which would be a cheap and accessible butter substitute for the poor and would have a longer shelf life than butter for use by his army and the navy. The first product was based on bovine fat mixed with milk and water but it was not popular. The product was then refined and based on plant oils.

The next food product invention of public health importance was the conversion of cornstarch to fructose by Marchall and Kooi (1957). This project was subsidized by the US government to support corn production, and to counteract a tariff on foreign sugar. Fructose has a sweetening effect greater than that of glucose and corn syrup was increasingly produced from the mid-1960s for addition to many foods needing a sweet taste. The use of fructose sweeteners has spread globally.

All three food product inventions have had significant impacts on diets in the Western world. Beet sugar introduced a cheap source of high-energy carbohydrate, margarine contributed to a rise in the n-6/n-3 fatty acid ratio and fructose contributed to a hyper-physiological supply of a simple carbohydrate. In addition, the industrialization of agriculture and food production introduced a vast number of foreign chemicals to the food supply, for example, agricultural chemicals, industrial chemicals and food additives. Some chemicals such as persistent organic contaminants (POPs) can be directly associated with the obesity epidemic (see **Section 4.6**). Some food additives can contribute to decreased nutritional value, as they often are used to add flavor to food with poor nutritional quality. If the present development of population obesity under the industrialized paradigm continues, the result may be development of a new phenotype as shown in **Figure 12,** called *Homo sapiens obesus* (Chaldakov et al., 2007).

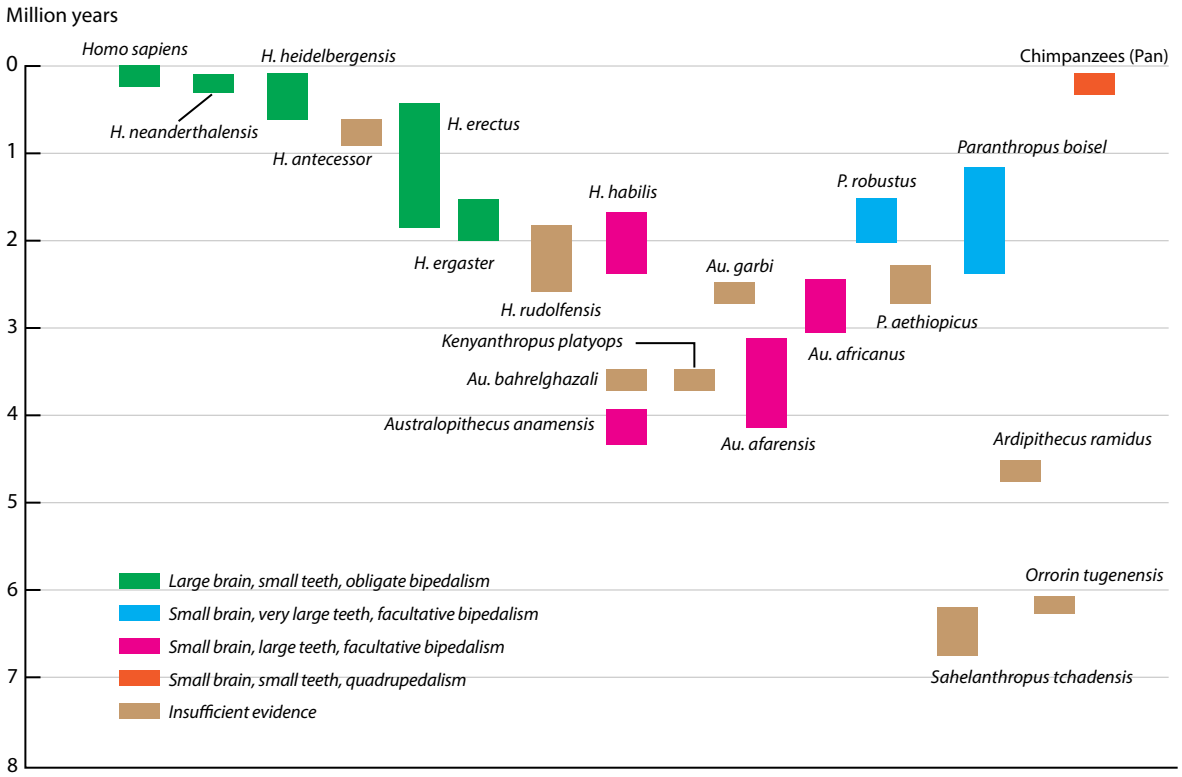

Figure 12. From Hominoid to *Homo sapiens obesus*. Source: Chaldakov et al. (2007).

[6] A zoonosis is a disease that can be transmitted from animals to humans and *vice versa*. One example among many is tuberculosis.

[7] Margarine comes from the Greek *margaron*, meaning a pearl, referring to the pearl-like color of bovine fat.

4.4.1.4 An emerging paradigm

A fourth paradigm could well be the nutriceutical paradigm with commercial development of nutriceuticals and functional foods to be prescribed by physicians based on individual nutrigenomic analyses. These preventive strategies, based upon genomic medicine and personalized nutritional advice, have been forecast as significant future possibilities (Choquet and Meyre, 2010). However, nutriceutical diets may impact social processes related to food enjoyment, for example, families or friends eating together, if eating becomes a matter of therapeutic intervention.

4.4.1.5 Major changes in food composition from the Paleolithic era to the present

As our genome is largely identical to that of Paleolithic man, our present-day metabolic pattern is governed by the same genome. Thus, it would be worthwhile to sum up the major changes in the actual food composition that have taken place.

In the first place, energy density (cal/g) has increased considerably; this is primarily because fiber content has dropped due to introduction of refined carbohydrates. The intake of total fat has probably not changed significantly; however, the quality of ingested fat has changed with a steep increase in saturated fat. Polyunsaturated plant oils (n-6) have increased, while the n-3 fatty acids have decreased. Also protein intake has declined.

It appears that the obesity epidemic cannot be solved by simply limiting a general category of macronutrients, although there may be a benefit to a protein-rich diet (see **Section 4.4.2.4**). This view has recently gained some support in the literature (Kerksick et al., 2009). There remains an urgent need to distinguish between different types of the three individual macronutrients because they play an active role in the metabolome. This is especially true for fats, as they are not only sources of energy but are highly active in gene transcription and play a role in the regulation of metabolic processes. In addition, not all fatty acids are lipogenic; saturated fatty acids and especially polyunsaturated fatty acids of the n-3 family seem to be anti-lipogenic (see **Section 3.2**).

4.4.2 Individual macronutrients

4.4.2.1 Fat

Dietary fat consists of triglycerides (three fatty acids attached to a glyceride molecule), a little cholesterol and some free fatty acids. Fatty acids are molecules consisting of a chain of carbon atoms to which are attached hydrogen atoms and a terminal carboxyl group. The length of the chains varies between 2 and 24 carbon atoms. Over 40 different fatty acids have been found in nature.

Fatty acids can be divided into three classes according to the number of double bonds between the carbon atoms. Saturated fatty acids (SFAs) have no double bonds, monounsaturated fatty acids (MUFAs) have one double bond; polyunsaturated fatty acids (PUFAs) have 2 to 6 double bonds. The PUFAs can be further divided into two families: the n-6 and the n-3 PUFAs (see **Box 17**).

Fatty acids are now classified into two additional groups; essential or non-essential. The essential fatty acids are the PUFAs with an 18-carbon chain of both the linoleic and linolenic acid families. They are considered essential as the body is unable to place a double bond in positions n-3 and n-6. Accordingly they have to be supplied in the diet.

There is an abundant body of literature describing the specific types and effects of fatty acids; they will only be summarized here.

Saturated fatty acids

Saturated fatty acid (SFA) intake comes primarily from consumption of farm animals; terrestrial game has a low content of saturated fat (Cordian et al., 2002). In addition, some plant oils such as coconut and palm oils are rich in saturated fat.

Dietary intake of saturated fat, a holdover from the early agricultural revolution, has been shown to increase low-density lipoprotein (LDL) cholesterol which is associated with increased risk of cardiovascular disease (CVD) and insulin resistance (Lovejoy, 2002). As a result, there has been a longstanding recommendation to limit the intake of red meat from farm animals as a means to reduce the risk of CVD. Increased risk for CVD is closely associated with pro-lipogenic activity and promotion of metabolic syndrome.

Animal experiments have shown that saturated fat decreases heat production by BAT (Bueno et al., 2008). As a result, less energy is dissipated as heat and more is available for fat storage. Furthermore, it has been shown that for animals kept on a diet containing Western-like fat (saturated fats), offspring gradually accumulated fat over four generations compared with animals kept on diets with similar energy but a more favorable fat composition (Massiera et al., 2010). This means that weight gain and adipose tissue expansion are not solely determined by the amount of energy ingested. Other macronutrients are also able to influence feed-efficiency and affect adipocyte function. For example, a high-protein diet will move a consumer into an anti-lipogenic state while a high carbohydrate diet, in particular a high-glycemic index carbohydrate diet, will induce a pro-lipogenic state and promote adiposity (Madsen and Kristiansen, 2010). This implies that when saturated fat is to be replaced, it is of the utmost importance that it is by non-lipogenic nutrients; otherwise no benefit will be obtained (Jakobsen et al., 2010). Consequently the substitutes must be a combination of:

- high-quality fats such as olive oil, fish oil and plant oils (such as rape seed oil and walnut oil) of which all have a high content of n-3 fatty acids;
- low glycemic index carbohydrates; and,
- lean meats (no marbling and stripped of visible fat).

The objective is not to eliminate all saturated fatty acids from the diet; this is impossible. Even olive oil contains 13.5% saturated fats (Assy et al., 2009). The problem with saturated fat has arisen as a consequence of the increasing supply through time from food originating from farm animals (especially meat, fat and dairy products); it is this component which needs to be reduced in order to achieve a healthier diet.

Box 17 Structural formulae and systematic names of some fatty acids

The carbon atoms are numbered starting from the carboxylic group as number one. The position of the first double bond is indicated by counting from the terminal methyl carbon atom. Here two notations are used, either 'n minus' or 'ω minus' where n or ω indicates the number of carbon atoms from the end where the first double bond occurs. The numbers indicate the total number of carbon atoms and the total number of double bonds in the molecule. For example, 18:2, n-6, linoleic acid has 18 carbon atoms, with 2 double bonds of which the first (counted from the back) is placed at the sixth carbon atom. See **Figure 13**.

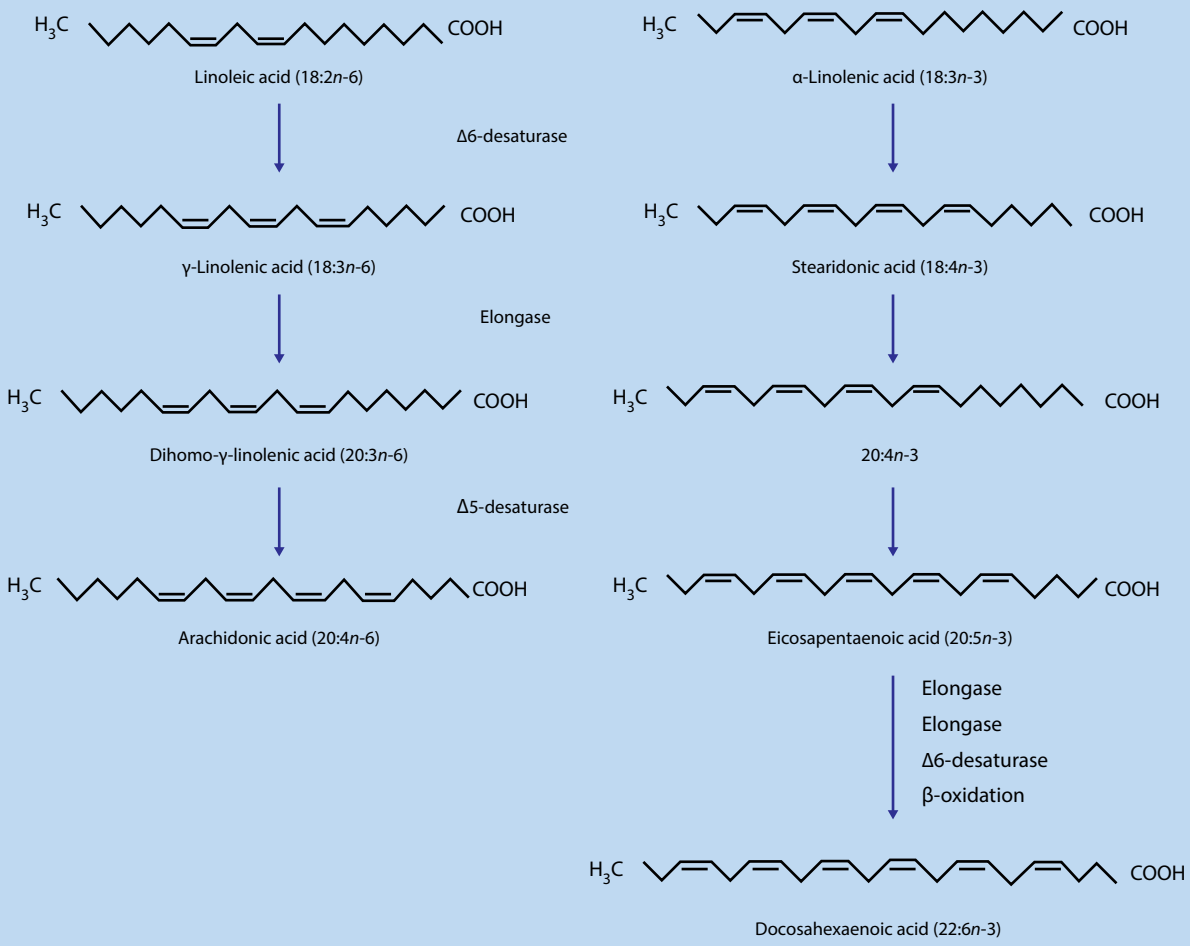

Figure 13. Structure and naming of three classes of fatty acids based on their total number of carbon atoms and the location of their double bonds. Source: Hansen et al. (2008).

Monounsaturated fatty acids

Common monounsaturated fatty acids are palmitoleic acid (16:1 n−7), cis-vaccenic acid (18:1 n−7) and oleic acid (18:1 n−9). The main dietary supply of mono-unsaturated fatty acids (MUFAs) is olive oil, although some marine species are also rich in MUFAs, for example, Greenlandic halibut.

The metabolic role of MUFAs has to some degree been controversial, but most often it has been regarded as a neutral fat. While some monounsaturated fatty acids (in the same way as saturated fats) may promote insulin resistance (Lovejoy, 2002), oleic acid (18:1-9) is considered an important MUFA in human nutrition. The Mediterranean diet, which has proven to be beneficial for glycemic control and normalization of metabolic disorders (for a review see Assy et al., 2009) contains olive oil, which is 74% oleic acid. Olive oil is also a significant source of anti-oxidative phytochemicals and vitamin E. This is true only for virgin olive oils because other poorer quality olive oils are produced with heat and pressure during the refining process and have lost much of their anti-oxidative capacity. Another characteristic of the Mediterranean diet is red wine, which also contains metabolically beneficial phytophenols (see **Box 11** on resveratrol). Both olive oil and moderate amounts of resveratrol-containing fruits (and red wine) appear to be beneficial.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) come from plant or marine species. The n-6 PUFAs are supplied by plant oils such as soy, corn and sunflower oils, and the long-chained n-3 PUFAs are

primarily supplied from marine fish. However some plant oils such as rapeseed oil and walnut oil contain the basic n-3 PUFA linolenic acid. This can be transformed in the body to the long-chained n-3 PUFAs. The problem is that it competes with the n-6 linoleic acid for the same enzymes, which means that in the case of a high n-6/n-3 ratio, as is found in most Western diets, the conversion of linolenic acid will be insignificant. For that reason it can be argued that a supply of long-chained n-3 fatty acids through marine food items is essential for better human nutrition.

PUFAs protect against cardiovascular disease by providing more membrane fluidity than monounsaturated fats and may be protective against insulin resistance (Lovejoy, 2002; Fukuchi et al., 2004); however, they are more vulnerable to lipid peroxidation (rancidity). The essential long-chained PUFAs of the n-6 and n-3 families are in metabolic competition. For example, the n-3 acids are anti-inflammatory and anti-obesogenic, while the n-6 acids are pro-inflammatory and obesogenic (Calder, 2006; Ailhaud et al., 2008). For this reason the balance between the two PUFA families becomes crucial (see **Box 17**).

Since the 1960s, indiscriminate recommendations have been made to substitute saturated fat (like butter) with vegetable oils, high in n-6 and low in n-3 fatty acids. This has unfortunately led to a general increase in intake of n-6 fatty acids, primarily due to increased consumption of high n-6 containing plant oils and margarine, and a decrease in intake of n-3 fatty acids (Ailhaud et al., 2008). The n-6/n-3 ratio in Western societies can be greater than 20, which is far above dietary recommendations. In traditionally-living Inuit, with a diet dominated by marine products, the same ratio is around 1. While the optimal ratio is difficult to determine, the current recommendation is a ratio of around 3. The increase of the n-6/n-3 ratio has, by time, turned the general Western diet toward a more obesogenic direction; this may be of specific importance as an early determinant of childhood obesity (Massiera et al., 2006; Ailhaud et al., 2007).

Despite recommendations to reduce the relative amount of dietary fat, the obesity epidemic has continued to accelerate (Walker et al., 2007). Based upon our current knowledge of fat metabolism and the different metabolic effects of various fatty acids, it seems appropriate to conclude that the specific type of fat, rather than the amount, is of greatest importance for curbing obesity (Storlien et al., 2001).

4.4.2.2 Carbohydrates

Carbohydrates are synthesized in green plants through photosynthesis. The basic components in the synthesis are carbon dioxide from the atmosphere and water from the soil. The energy needed for photosynthesis is delivered by sunlight and oxygen is formed as a waste product. The primary products are the sugars, which are readily soluble in water and easily transported in the plant tissues as fuel for the cells. Afterwards the sugars are polymerized to form polysaccharides, which are less soluble and can be stored as energy reservoirs. Plants also synthesize more complex and insoluble polymers such as cellulose and hemicelluloses as building blocks for cell walls.

From a mammalian perspective, carbohydrates can be grouped as either available or unavailable for metabolism. The available carbohydrates are:

- monosaccharides, with glucose and fructose being the most important;
- disaccharides (each molecule consists of two mono-saccharides), with sucrose (one glucose and one fructose molecule) dominating; and
- polysaccharides, with starch (long-chained molecules of glucose) dominating.

The unavailable carbohydrates consist of complicated and indigestible molecules usually termed fibers.

Carbohydrates can also be divided into refined and unrefined categories. Refined carbohydrates are industrial products such as sugars and flours in which the fibers, and unfortunately most of vitamins and essential minerals, are removed, leaving the carbohydrate as an energy source only. Refined carbohydrate products are often said to be suppliers of 'empty calories'. Unrefined carbohydrates are found in whole grain products, root vegetables, leafy vegetables, legumes and fruits where fibers and micronutrients are preserved.

The digestibility of a given carbohydrate is indicated by its glycemic index (GI). GI is a qualitative measure of carbohydrates; it is the measured increase in human serum glucose two hours after ingestion of a standard amount (50 g) of a given carbohydrate. Arbitrarily, the GI for glucose is fixed at 100 while other carbohydrates range from 20 to 80. The lowest GIs are for the high fiber containing products. Interestingly the monosaccharide fructose has a very low GI and was recommended to diabetics by nutritionists until the end of the 20th century. What is more important for evaluation of total diets is the glycemic load (GL), defined as the daily intake of a given carbohydrate multiplied by its GI.

The invention of mass production of refined fructose in the late 1960s led to a significant increase in its use as a sweetener in food products. Fructose has a higher sweetness effect compared with glucose and it was thought to be an alternative to glucose-based products for diabetics. The extensive use of refined fructose in Western diets led to a large increase in its daily intake from below 20 g per day (based on fruit consumption) to 80–100 g per day. In these amounts, fructose is able to increase serum triglyceride levels and is suspected to be a significant factor in the development of obesity. The question of fructose intake is still to some degree controversial, however, there is an increasing body of evidence to show that excessive intake of fructose is highly lipogenic and should be avoided. For further discussion see Hansen et al. (2008).

The importance of dietary fibers was only recognized about 40 years ago. A British textbook on nutrition published in 1956 stated, *The value of these unavailable carbohydrates or roughage in the diet has been, and still is, over-rated.* Burkitt (1969) noted that cancer and other diseases of the large intestine, common in the West, were rarely seen in tropical Africa. He suggested that

high intakes of dietary fiber protected Africans against these Western diseases. His observation has now been confirmed in numerous studies. The beneficial action of fibers is that they increase the bulk of feces and speed up the passage of material through the large intestine. They bind water and as such they support healthy intestinal function. Another beneficial effect of fibers is that they are functionally anti-obesogenic; their presence in the diet reduces the glycemic load.

4.4.2.3 Proteins

In relation to metabolic disorders, proteins have not attracted the same interest as have fats and carbohydrates. There are, however, some new data showing that different types of proteins may be of importance for a balanced metabolic system.

In general, nutritionists recommend a moderate daily intake of protein, that is, about 12% of daily energy intake. The advice to moderate protein consumption is partially based on the toxic effects of very high intakes, as described earlier. Very high intakes are unusual in the current typically varied Western diet.

The importance of dietary proteins lies in the fact that every cell in the body is partly composed of proteins, which are subject to continuous break down and replacement. As carbohydrates and fats contain no sulfur and nitrogen, two essential elements in proteins, cells are dependent on dietary protein for their maintenance and reproduction.

Proteins consist of sequences of 20 different amino acids; the relative amount and sequence of the individual amino acids differs according to species. Some amino acids are readily converted in the human body from one to another; others cannot be converted and have been designated as essential, that is, they have to be supplied through the food. The distinction between essential[8] and non-essential amino acids is, however, not clear-cut. Animal experiments have shown that some amino acids are essential at an early stage of development but not in adulthood. While this is probably true for humans as well, it is an area requiring more research.

Only recently has interest grown in the active role of proteins in metabolism. Probably due to epidemiological reports on negative influences of animal meat, interest in alternative sources, such as soy protein and casein has increased. Comparisons between intakes of types of protein have shown that soy protein and protein from fish have metabolic advantages over casein (Teixeira et al., 2004; Wergedahl et al., 2004).

Another reason for the advice to moderate intake of protein is based upon reports of a linkage between intake of meat from farm animals and development of CVD (Bernstein et al., 2010; Micha et al., 2010). In this connection it should be remembered that while meat from farm animals is high in protein, it also contains saturated fat. Studies have shown that lean meat, low in saturated fat, does not increase CVD risk factors (Li et al., 2005; Hodgson et al., 2007).

There is an ongoing dispute concerning the health benefits of eating red meat. Recent reports have indicated that a decreased intake would be of benefit to reduce the risk of cancers (Cross et al., 2011), heart disease (Ashaye et al., 2011), diabetes type 2 (Steinbrecher et al., 2011), and favor weight reduction (Vergnaud et al., 2010). However, these epidemiological studies were based on self-reported intake of red meat and did not include actual measured intakes, or information on type of meat and fat content.

Cordain et al. (2002) investigated fat content and fat quality in meat from wild ruminants compared with farmed beef. They found that the total fat content of meat from farmed beef, stripped of visible fat, was still two to three times higher than the total fat content of meat from wild game. Furthermore, the content of saturated fat was two to three times higher and levels of n-3 PUFA were three to four times lower. Interestingly, they also observed that pasture-fed cattle has a fat composition similar to wild ungulates. As a consequence it seems reasonable to question the reported negative health effects of red meat *per se*, and to postulate that the reported effects are a result of an increased intake of saturated fat.

The most apparent explanation for the metabolic effects of proteins seems to focus on their content of arginine. Both soy protein and fish protein have a relatively high content of arginine, compared with casein. Arginine is not recognized currently as being essential, but has, however, recently attracted a considerable amount of attention. Animal experiments have indicated clearly that arginine supplementation reduces white fat gain and enhances skeletal muscle and brown fat masses and as a result has a beneficial influence on metabolic homeostasis (Jobgen et al., 2009a,b; McKnight et al., 2010). McKnight et al. (2010) suggest that, despite the lack of corroborating human evidence, animal studies imply that protein is likely to influence metabolic systems in humans. The best approach for obtaining an optimal supply of essential and other proteins is to vary protein sources as much as possible, to retain fish protein as a substantial component of daily protein intake, and to avoid fatty (marbled) meat.

4.4.2.4 What is the best combination of macronutrients?

As the obesity epidemic has grown, a huge number of quick-fix weight reduction techniques and regimens have appeared on the market; most have little or no value. Short-term solutions do not work because they are poorly conceived and they do not address the basic need to change lifestyle and diet. Weight loss requires an informed, consistent and long-term commitment. Several long-term programs have been developed and some are

[8] The eight classically recognized essential amino acids are valine, leucine, isoleucine, threonine, lysine, phenylalanine, tryptophan, and methionine. Histidine has been added recently and probably more will follow as scientific investigation continues. Other additions may be termed 'conditionally essential' indicating that they are essential under certain conditions such as age and specific environmental exposures.

Table 1. Dietary composition of some weight loss programs and a suggestion for a more realistic dietary balance.

	'Atkins'	'Zone'	'LEARN'	'Ornish'	Our suggestions
Total carbohydrate, % of diet	very low	low	medium	high	medium (low GI)[a]
Total protein, % of diet	high	medium	medium	low	medium (fish)[b]
Total fat, % of diet	high	medium	medium	low	medium (n-3 fats+)[c]
Saturated fat, g/d	high	medium	medium	low	low
Total fibre, g/d	low	medium	medium	high	medium

[a] Low GI (carbohydrates with a low Glycemic Index); [b] fish (as a major source of protein); [c] n-3 fats+ (inclusion of dietary fats with n=3 or more).

shown in **Table 1**. One weight loss program, LEARN is based on the US national dietary guidelines and includes specific recommendations on daily exercise.

Gardner et al. (2007) compared the four diet types in overweight pre-menopausal women and found that those assigned to the Atkins diet experienced greater weight loss than those assigned to the three other regimens. They concluded that a low-carbohydrate, high protein, high fat diet may be considered a feasible alternative recommendation for weight loss. The main characteristics of the Atkins diet (Atkins, 2002) is the very low content of carbohydrate, but also a high fat content

Box 18 Thermogenesis in brown adipose tissue

Heat production is mediated through the action of uncoupling proteins (UCPs) which are mitochondrial transporters present in the inner mitochondrial membrane. The first member of this family, UCP1, is specifically expressed in BAT mitochondria and is the main reason that BAT has thermogenic capacity. UCP1 confers to the inner mitochondrial membrane an enhanced conductivity to protons, thus resulting in the decoupling of the electron transport system which leads to heat production (Villarroya et al., 2007).

After the discovery of UCP1, several other decoupling proteins have been described, that is, UCP2, UCP3, UCP4 and UCP5. It is unknown whether or not these new compounds are also involved in thermogenesis. There is, however, increasing evidence for a tissue-specific involvement in thermoregulation and metabolic changes associated with nutritional status (Yu et al., 2000). Although UCP3 is highly expressed in BAT, its main site of expression is in skeletal muscles (Villarroya et al., 2007). In order to produce heat, BAT has to be stimulated via the sympathetic nerve system. This leads to stimulation of thyroid hormone production and synthesis of free fatty acids (DHA, docosahexenoic acid, 22:6-3) through the action of the PPAR system (see **Box 10**, and **Figure 8**).

BAT is richly innervated with sympathetic nerves releasing noradrenalin under stimulation. It is generally accepted that noradrenalin is of primary importance for the peripheral activation of BAT thermogenesis.

Thyroid hormones (THs) have the potential to indirectly influence BAT thermogenesis by regulating the storage and supply of fatty acids (through lipogenesis and lipolysis) which serve as a substrate for BAT thermogenesis. However, BAT does not depend solely on de-novo lipogenesis; it also requires a supply through the blood. THs also influence BAT thermogenesis by regulating brown adipocyte respiration and membrane phospholipid composition (Saha et al, 1998). In rat experiments it has been demonstrated that the level of the PUFA DHA is closely related to the noradrenalin-stimulated *in-vitro* oxygen consumption of BAT cells, but not arachidonic acid (AA) and eicosapentaenoic acid (EPA) (Ohno et al., 1996, Saha et al., 1997). Together these findings show that suppression of normal thyroid function impairs BAT activity, possibly by modifying phospholipid fatty acid composition. Most likely it is done by depleting the DHA level. In conclusion, optimal levels of thyroid hormones (especially triiodothyronine) and a dietary supply of n-3 fatty acids, especially DHA, are necessary for maximum thermogenic activity of the brown adipocytes. Thus, the general declining dietary intake of n-3 fatty acids may play a role as a co-factor in the globesity epidemic.

Cold activated thermogenesis in BAT

In experiments of murine BAT exposed to cold, expression of genes encoding proteins involving glucose uptake and catabolism is significantly elevated. The levels of mRNA encoding proteins critical to *de novo* lipogenesis are also increased, as well as enzymes associated with procurement and metabolism of long-chain fatty acids. Based on these findings, Yu et al. (2002) proposed a model in which coordinated activation of glucose uptake, fatty-acid synthesis, and fatty-acid metabolism occur as part of the adaptive thermogenic processes in BAT. In adult mice, chronic stimulation of β-adrenergic receptors by exposure to cold results in increased UCP1 expression (Bouillaud et al., 1984; Jacobsson et al., 1985) followed by both hyperplasia of BAT and recruitment of brown adipocytes in WAT (Guerra et al., 1998). Rim et al. (2004) have found evidence that transcription factors are sequestered in the cytoplasm where they are functionally inactive. When the mice are exposed to cold, the transcription factors are translocated back into the nucleus where they can provide a rapid response to a physiological requirement.

without taking into account that different types of fat have different metabolic effects. Volek et al. (2009) have found that carbohydrate restriction had a more favorable impact on metabolic syndrome than a low-fat diet. During recent years a number of studies have appeared to show a beneficial role for a high protein diet (Merkling and Sherfey, 2007; Westerterp-Plantenga et al., 2009; Wycherley et al., 2010). The rationale for a high protein diet is its favorable influence on appetite regulation, thermogenesis, energy efficiency and body composition.

4.5 Pillar 5 – Thermogenesis and ambient temperature

Thermogenesis can be divided into obligatory and facultative thermogenesis. Obligatory thermogenesis is related to the basic metabolic rate (BMR) and as such almost exclusively related to lean body mass. Obligatory thermogenesis involves all metabolically active cells and is important in ensuring a constant body temperature. Facultative thermogenesis is related to physical activity level and environmental conditions; it is defined as energy dissipated as heat in response to external stimuli (temperature and diet) (Lowell and Spiegelman, 2000). Thermogenesis is dependent on the dietary composition of macronutrients. Macronutrients which produce the most heat are, in decreasing order: *Proteins = Alcohol > Carbohydrates > Fat.*

Thus at isocaloric regimes, a high protein diet produces more energy as heat than high carbohydrate or a high fat diets.

Ambient temperatures below 23°C (thermo-neutral) will increase thermogenesis in BAT and in skeletal muscles. In the event of an acute exposure to low temperatures, the first reaction will come from the muscles through shivering to quickly produce the necessary heat. With prolonged exposure to cold, shivering will be replaced by metabolic thermogenesis in both BAT and muscles. These mechanisms are explained in **Box 18** and **Box 19**. As a consequence of this, it seems reasonable to regard thermogenesis as an important player in obesity.

4.5.1 Ambient temperature

Observations of daily energy expenditure (DEE) in wild living mammals have demonstrated that body weight and ambient temperature are significant contributing factors for DEE; energy expenditure increases with higher body weight and lower ambient temperature. Westerterp and Speakman (2008) have described this relationship in animals mathematically. Based on the assumption that the Westerterp-Speakman equation might also be valid for humans, we have calculated DEE at different temperatures for an average 70 kg human (**Figure 14**, see also **Box 20**).

Figure 16 shows that the reduction of DEE is approximately linear at ambient temperatures between 10°C and 30°C. Based on these calculations, the mean reduction in DEE over the 20 degree drop in ambient air temperature is 0.3 MJ; which is equivalent to 15 KJ per degree of temperature reduction. This must be regarded as the maximum expenditure to be obtained.

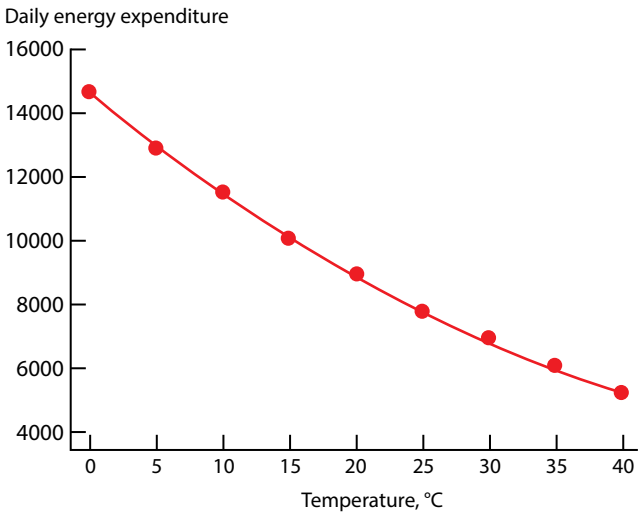

Figure 14. Relationship between change in daily energy expenditure (DEE) and ambient temperature in a 70 kg person as calculated by the equation given by Westerterp and Speakman (2008) in Joules and degrees Celsius. See also **Box 20**. Source: Hansen et al. (2010).

Several experiments have been carried out on humans (van Marken Lichtenbelt et al., 2002; Harris et al., 2006; Wijers et al., 2008) in which ambient temperatures were dropped 6°C below the thermo-neutral point of 23°C . These studies have indicated that energy expenditure did increase from

Box 19 Thermogenesis in muscles

Sander et al. (2008) have shown that human skeletal muscles have the capability to increase heat production in response to mild cold stress through mitochondrial decoupling. They found, however, that UCP3 expression was not up-regulated during cold exposure. As neither UCP1, UCP2, UCP4, nor UCP5 are present in human muscle, it has been suggested that other candidate actors have yet to be identified. See **Figure 15**.

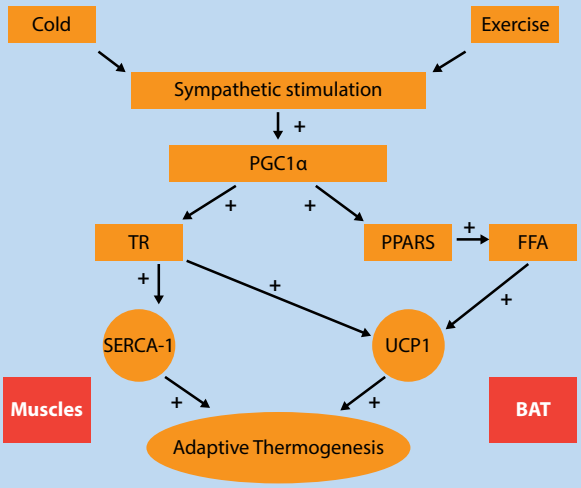

Figure 15. Heat production in brown adipose tissue (BAT) and muscles. FFA=free fatty acids; TR=thyroid receptor. Source: Hansen et al. (2010).

Box 20 Estimated efficacy of a 5°C reduction of ambient temperature

Weight loss due to a reduction of ambient temperature cannot be calculated precisely because the magnitude of the extra energy expenditure will depend on factors in all of the 'seven pillars'. However, a rough estimate can be made under some conditions, such as:

- unchanged intake of energy;
- all extra energy expenditure is used for burning of fat; and
- each degree of lower ambient temperature gives an extra energy expenditure of 100–150 kJ as indicated by Rintamäki (2007).

Based upon these prerequisites, the following estimate can be made: 500–750 kJ will be needed to maintain body core temperature if the ambient outdoor temperature is reduced from 23°C to 18°C. If 1 g of fat is needed to yield 37 kJ, then on a daily basis, 14–20 g of fat will need to be burned to maintain core body temperature if the ambient temperature is reduced to 18°C. This is equivalent to 5.1–7.3 kg of fat burned per year.

Even though this is a hypothetical estimate, from a population based perspective it indicates that, in concert with other lifestyle corrections, a reduction of ambient living temperature might significantly influence the obesity epidemic in a positive direction. Furthermore, it will save energy used for heating buildings and thus also counteract emissions of greenhouse gases.

5–110 KJ/d. This corresponds to 16–40% of the maximum predicted from the animal model. This does not necessarily mean that the animal model is not valid for humans; study subjects in the experiments may have had different amounts of subcutaneous fat (insulation effect), different diets and/or different clothing quality. The influence of diet is demonstrated in one study by van Marken Lichtenbelt et al. (2002), who found that test persons given an energy balanced diet had a higher change in DEE in comparison to test persons who were allowed to eat *ad libitum*. Finally, a genetic difference could also contribute to differences between individual DEEs.

Claessens-van Ooijen et al. (2006) compared the heat production in 10 overweight men and 10 lean men during mild cold exposure (15°C for one hour) and found that in both groups heat production increased significantly during exposure to cold. This increase was larger in the lean group compared with the overweight group, probably due to the insulating effect of subcutaneous fat in the overweight group. The same research team (Claessens-van Ooijen et al., 2004) also investigated seasonal changes in response to cold air. They found greater heat production in individuals in winter compared with measurements made at the same temperature during the summer, suggestive of some form of cold adaptation during winter. The magnitude of the cold responses was found to be subject-specific and was consistent for each subject throughout the seasons.

Overall, these results indicate that cold exposure might be beneficial in body weight regulation. Wijers et al. (2008) were the first to demonstrate in humans that skeletal muscle has the intrinsic capacity for cold-induced adaptive thermogenesis under physiological conditions. A small change in energy expenditure for a prolonged period might contribute significantly to weight gain or to weight loss depending on whether the ambient temperature rises or drops respectively.

Diminished facultative thermogenesis has indeed been identified as a risk factor for obesity.

Recent studies suggest that manipulation of facultative thermogenesis is a realistic tool for counteracting obesity (Diehl and Hoek, 1999; Cannon and Nedergaard, 2009; Wijers et al., 2009). In this connection it is important to look at the two types of BAT cells separately because they do not act identically. Classical iBAT (intramuscular BAT) cells have a myogenic expression while wBAT cells (those found in white adipose tissue) have a lipogenic expression. Both types are activated by cold and produce heat, but only wBAT is influenced by dietary thermogenesis. As a consequence wBAT plays an important role for whole body energy balance, while the only function for iBAT is to regulate body temperature (Kozak et al., 2010; Madsen et al., 2010).

The discovery of BAT in adults, based on PET/CT scans has led to retrospective studies on the prevalence of active BAT in patients (Jacene et al., 2011; Ouellet et al., 2011). The general finding has been that the number of BAT-expressing patients is about 6%. However, scans are normally performed under warm conditions, and this 6% figure is not likely to be representative of the population as a whole. If the scans were carried out under temperatures below the thermal neutral point, the results would probably show that the majority of the adult population has the ability to activate BAT in response to cold.

In the studies above, it was demonstrated that BAT expression correlated negatively with age, BMI and serum glucose. These findings have increased interest in finding methods to increase BAT activity in order to minimize metabolic disorders. PET/CT scans only indicate BAT activity, and the correlations to BMI and serum glucose might be confounding factors, that is, BMI, because of its insulating effects against cold exposure; and serum glucose, because of its relationship to BMI.

No effective pharmacological method has been developed to increase BAT activity, thus the only natural method would be through lifestyle changes such as a combination of caloric restriction to reduce BMI (and thereby increase glucose tolerance) and to lower ambient living temperature. In combination, these measures would increase cold-induced thermogenesis (see also **Box 21**).

Box 21 The mechanistic background for cold adaptation

When the ambient air temperature goes below the thermo-neutral set-point of 23°C, an organism will start to activate adaptive metabolic processes to maintain core body temperature and DEE will increase. In a cold exposure situation the first reaction will be a stimulation of the sympathetic nervous system, leading to vasoconstriction in the skin to minimize heat loss. The next step is increased sympathetic nerve stimulation which causes increased UCP1 activation in BAT to increase heat production. Due to the high demand for oxygen during this process (adaptive thermogenesis) the BAT tissue will tend to become hypoxic. To compensate for this hypoxia there is a requirement for increased blood perfusion to supply oxygen and substrates and to export heat. This is achieved through increased vascularization of the BAT in cold-exposed animals. In fact, a marked increased vascularization has been observed in both BAT and WAT in relation to cold adaptation (Xue et al., 2009).

Vascular endothelial growth factor (VEGF) plays a pivotal role in both vasculogenesis and angiogenesis and under both physiological and pathophysiological conditions (Dvorak et al., 1995). VEGF expression is regulated by AMP-activated protein kinase (AMPK) (Ouchi et al., 2005; Zwetsloot et al., 2008). Mulligan et al. (2007) found that AMPK activity is significantly increased by chronic cold exposure in both BAT and WAT. They also found that the increase in AMPK was not up-regulated by sympathetic nerve stimulation of BAT, which is contrary to the response of WAT. This is in agreement with the finding of Mulligan et al. (2007) that the increase in AMPK in BAT is delayed by several days after the start of cold exposure because of the increased sympathetic nerve activity in BAT, but not in WAT following cold exposure. Consequently AMPK activation must take place due to non-sympathetic nervous system pathways; however, these are still not understood (Mulligan et al., 2007). Obviously the vascularization process is triggered as a secondary response to the sustained hypoxia of the BAT induced by cold. The thermogenic capacity of BAT in cold acclimated animals is normally limited by the degree of vascularization (Xue et al., 2009). The negative health consequences of obesity are believed to be the result of inflammatory responses in WAT. There is evidence to show that one factor involved is hypoxia (Trayhum et al., 2008). Therefore the issue of vascularization in WAT may be of significance in the morbidity associated with obesity (Xue et al., 2009).

Most obesity is associated with low sympathetic activity in WAT (Bray and York, 1998). This will lead to low angiogenesis in WAT, consequently increased hypoxia, and thus aggravate the inflammatory processes. Physiologically, an easy way to counteract this condition is to lower ambient living temperature for a prolonged time. Lowering ambient living temperatures will also activate BAT to produce heat and energy expenditure will increase.

4.6 Pillar 6 – Contaminant exposure

The global chemical age began in earnest in the late 1940s. Chemistry not only created substances to treat significant insect pests (DDT was introduced for control of lice during World War I), but soon branched out into a broad range of other biocides (insecticides, rodenticides, herbicides, fungicides, bactericides, and molluscicides). At the same time, industrial use of chemicals expanded for production of synthetic materials (PCBs, SCCPs, PFOS) and led to emissions and distribution of wastes and unwanted by-products (PCDDs, PCDFs, HCB) (see **Box 22** and **Box 23**).

At first, the improvement seen in agricultural yields, public health benefits and product possibilities were considered the dawn of a global renaissance. Slowly however, biologists, toxicologists and then epidemiologists began to find insect resistance to several of the pesticides, effects on bird and mammalian reproduction, neurobehavioral effects and cancers. The story of the unraveling of the chemical age has been described in books such as Silent Spring (Carson, 1962) and Our Stolen Future (Colburn et al, 1996).

The contaminants of greatest concern are those that are persistent, bioaccumulative and toxic, often referred to as the PBT substances. Once produced and released, these substances are persistent (they resist degradation), they build up in the food chain (biomagnify) and they exert an array of adverse (toxic) effects on a wide range of avian, terrestrial and aquatic species. A summary of the toxic effects of several PBT substances on humans is provided in **Box 22**.

These environmental contaminants generally fall into three classes:

- metals such as mercury, lead and cadmium;
- organic chemicals which travel long distances via the atmosphere and water currents; and,
- organic chemicals which do not travel far from their areas of use.

Global regulation of twelve persistent, bioaccumulative and toxic substances which travel long distances began in 2001 with the signing of the Stockholm Convention (see **Box 23**). The list of persistent organic pollutants (POPs)[9] controlled

[9] POPs (persistent organic pollutants) generally refers to substances which are persistent in the environment, bioaccumulate or biomagnify in the food chain, are toxic to biota (animals, birds, aquatic species, insects, etc.) and travel long distances from their original source. The term is usually used for those substances which have been listed under the annexes of the Stockholm Convention (see **Box 23**).

Box 22

The most important contaminants of relevance for human health. See **Box 23** for acronyms. Source: UNEP (2011).

Population health effect	Legacy POPS likely involved in causing the effect	Sub-population at risk	Source
Cancer	DDT, toxaphene, 2,3,7,8-TCDD, mirex, HCH, PCBs, HCB	Primarily adult (breast cancer; prostate and testicular cancer)	IARC, 1987 (and updates)
		Some cancers reported in children	Prins, 2008
	Chlordecone (associated to date with prostate cancer)		Multigner et al., 2010
Reproductive effects	PCBs, some dibenzodioxins and dibenzofurans	Fetus (live births); newborns (genital and other birth defects); women of childbearing age (fecundity)	Gilman et al., 2009
	Penta BDE		Harley et al., 2010
Growth retardation	PCBs, some dibenzodioxins and dibenzofurans	Fetus, newborns and children (length, body weight, head circumference of newborns)	Dewailly and Weihe, 2003
Neurological impairment	PCBs, some dibenzodioxins and dibenzofurans (cognition, attention span)	Fetus and children (cognition, attention span, memory)	Gilman et al., 2009
		Adults (Parkinson's disease and Alzheimer's disease)	Landrigan et al., 2005; Weisskopf et al., 2010
Altered behavioural development	PCBs, some dibenzodioxins, Penta BDE	Children, into adulthood (attention deficit disorders, learning disabilities)	Herbstman et al., 2010; Roze et al., 2009
Immune system suppression	PCBs, some dibenzodioxins and dibenzofurans	Newborns, children (increased ear infections, colds and disease resistance), adults (immune suppression)	Gilman et al., 2009
Cardiovascular effects	PCBs	Children and adults (blood pressure and heart rate variability)	Dewailly and Weihe, 2003; Gilman et al., 2009
Effects on thyroid function	PCBs, PFOS and PBDEs	Perimenopausal women (hypothyroidism)	Gilman et al., 2009; Sowers et al., 2004; Canaris et al., 2000
Metabolic disorders	PCBs, POPs in general	Adult males and females (diabetes and obesity)	Longnecker and Daniels, 2001; Longnecker et al., 2001; Rylander et al., 2004; Vasiliu et al., 2006
Bone disease	PCBs, dioxin, and HCH	Adult females and males (osteomalacea, osteoporosis)	Alveblom et al., 2003; Côté et al., 2006

under the Convention has doubled in a decade and continues to grow (UNEP, 2012).

For the purposes of this book, we are interested in the relationship between exposure to several organohalogens, particularly several organochlorines[10] which have now been well-studied and characterized, and risk factors for development of metabolic disorders and their sequelae – obesity, metabolic syndrome (MS), thyroid dysfunction, diabetes type 2 and cardiovascular disease (CVD).

4.6.1 Thyroid dysfunction

Wang et al. (2005) demonstrated in the general Taiwanese population a significant relationship between *in utero* exposure to coplanar PCBs and altered thyroid function in newborn babies, and suggested routine screening of both thyroid hormone levels and thyroid function in newborns. The effects on thyroid hormone metabolism may be transient (ten Tusscher and Koppe, 2004).

In humans, BMI and fat mass have been positively related with plasma concentrations of organochlorine pollutants (Pelletier et al., 2002). Lee et al. (2007a, 2008) found that PCBs were linearly associated with waist circumference in non-diabetic persons with metabolic syndrome. During weight loss regimens, organochlorines (OCs) are mobilized to the circulatory system, resulting in increased plasma concentrations (Chevrier et al., 2000; Asawasinsopon et al., 2006). The release of OCs into blood during weight loss has been associated with decreased energy expenditure, and OCs have been shown to be the best predictors of a significant decrease in resting metabolic rate (Pelletier et al., 2002). The effects of OCs can be partly explained through the relationship between plasma OC concentrations and decreased levels of free thyroxin and total thyroxin in plasma (Toubro et al., 1996; Sala et al., 2001). Pelletier et al.

Box 23 National and international regulation of contaminant influx to the environment (UNEP, 2012)

Most developed countries and more and more developing countries have national legislation and regulations to manage chemical substances produced, imported or exported for commercial use. For example, the European Union uses legislation and regulations under Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), the USA makes use of the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Canada uses the Canadian Environmental Protection Act (CEPA) and the Pest Control Products Act (PCPA), Australia uses the National Industrial Chemicals Notification and Assessment Scheme (NICNAS).

The Stockholm Convention on Persistent Organic Pollutants, adopted 22 May 2001, is a global agreement which is designed to protect human health and the environment from the negative effects of persistent organic pollutants (POPs) by restricting and ultimately eliminating their production, use, release and unsafe disposal. POPs are chemical substances that have toxic properties, resist degradation in the environment, bioaccumulate through the food chain and are transported long distances through air, water and migratory species, within and across international boundaries. The Stockholm Convention entered into force in May 2004 and now includes over 160 signatory countries. It initially listed twelve chemicals; however, ten more substances have been added to the banned and severely restricted annexes up to 2013. The 22 POPs belong to three groups (some substances are listed twice because they belong in more than one category, for example, hexachlorobenzene, pentachlorobenzene, polychlorinated biphenyls).

Pesticides used in agricultural applications, for fungus control or for insect control: aldrin, chlordane, chlordecone, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), gamma-hexachlorocyclohexane (γ-HCH, lindane) and by-products of lindane (alpha-hexachlorocyclohexane (α-HCH) and beta-hexachlorocyclohexane (β-HCH)), mirex, toxaphene.

Industrial chemicals used in various applications: tetra- and pentabromodiphenyl ethers (PBDEs), hexa- and heptabromodiphenyl ethers (PBDEs), hexabromobiphenyl, hexabromocyclododecane (HBCD), perfluorooctane sulfonic acid (PFOS), its salts and perfluorooctane sulfonyl fluoride (PFOS-F), pentachlorobenzene (PeCB), polychlorinated biphenyls (PCBs).

Chemicals generated unintentionally as a result of incomplete combustion and/or chemical reactions: hexachlorobenzene (HCB), pentachlorobenzene (PeCB), polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs).

Specific attention is placed on the impacts of POPs upon the most vulnerable human population groups such as the fetus, newborns, children and women of reproductive age. The Stockholm Convention also emphasizes the strengthening of national capacities for the management of chemicals in developing regions, including through transfer of technology, the provision of financial and technical assistance and the promotion of cooperation and information exchange among the Parties (signatory countries).

[10] Organochlorine (OC) is a generic term for a group of substances which are made up of an organic chemical with chlorine atoms attached to some or all of the carbon atoms in the structure. In most cases the organic moiety is in the form of a ring structure. Polychlorinated biphenyls (PCBs) are a well-known type of organochlorine. Organohalogen is an even more generic term as the organic moiety may contain any halogen (such as chlorine, bromine or iodine) attached to some or all of the carbon atoms in the molecule.

(2002) found that the increase in plasma OC concentration during weight loss was inversely correlated with changes in triiodothyronine (T_3) serum concentrations. T_3 is a determinant of daily energy expenditure (Toubro et al., 1996). Alvarez-Pedrerol et al. (2008) and Abdelouahab et al. (2008) have reported that, even at a background level of exposure, PCBs affected the thyroid system negatively, especially total T_3 levels. These authors concluded that even low concentrations of these environmental contaminants can interfere with thyroid status.

The evidence related to PCB exposure and adverse thyroid function in adults is still, to some degree, controversial. Salay and Garabrant (2008) performed a systematic review of 22 publications and concluded that the epidemiological evidence for a relationship is not entirely clear. However, it is still warranted to include an evaluation of the exposure to OCs in metabolic studies which intend to address energy expenditure/thermogenesis. OCs are globally distributed, found consistently in populations around the world, and may contribute to the global nature of the obesity epidemic.

In addition to the mounting evidence for a direct interaction between exposure to POPs and metabolic processes, Porta (2006) has suggested an epigenetic mechanism as also being significant. Serum concentrations of OCs are positively correlated to global hypo-methylation of DNA. The latter is suspected to contribute to increased cancer risks. Methylation of DNA constitutes an essential epigenetic characteristic that influences a wide variety of biological processes including gene expression, chromosomal stability, imprinting, and cellular differentiation (Bernstein et al., 2007). Disturbances of epigenetic modulations are considered to be a key mechanism in many diseases (Ozanne and Constancia, 2007). Rusiecki et al. (2008) have reported that among Greenlandic Inuit, global DNA methylation is inversely related to several POPs. Greenlandic Inuit are probably the most exposed population in the world to several POPs (van Oostdam and Donaldson, 2009) due to their diet of marine mammals. In order to determine if the same relationship existed for a lesser exposed population Kim et al. (2010) examined an apparently healthy low-exposed Korean population and found that low levels of some OC pesticides were associated with DNA hypomethylation.

4.6.2 Diabetes

Longnecker et al. (2001) were the first to suggest that PCB and diabetes may be causally related. The adjusted mean serum level of PCBs among subjects with diabetes was 30% higher than the control subjects (p=0.0002) and the relationship of PCB level to adjusted odds of diabetes was linear. Fierens et al. (2003) have reported that the risk of diabetes was significantly increased in subjects in the top decile for adjusted concentrations of polychlorinated dibenzodioxins, coplanar PCBs, and the sum of 12 PCB congeners. Recently, Vasiliu et al. (2006), in a follow-up study with the Michigan polybrominated biphenyl cohort, found that in women (but not men) higher PCB levels (>10 µg/L) were associated with increased incidence of diabetes. Today around 80% of the adult Greenlandic population has serum values in excess of 10 µg/L.

Son et al. (2010) have reported a connection between exposure to OC pesticides and diabetes type 2 in randomly selected Koreans. Lee et al. (2006) have reported a strong dose-response relationship between serum concentrations of six POPs and diabetes among a subset of adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES) of 1999–2002. Also based on the NHANES study, Lee et al. (2007a,b) suggested that OC pesticides and non-dioxin-like PCBs may be associated with an increased risk of type 2 diabetes based on their ability to increase insulin resistance. This has now been substantiated in a prospective study lasting 29 years from 1985–2006 (Lee et al., 2010, 2011). Kristansen and Frøyland (2010) have also reported a causal relationship between exposure to POPs and insulin resistance syndrome.

4.6.3 Metabolic syndrome

Lee et al. (2007c) suggested that the prevalence of metabolic syndrome may be affected by background exposure to a mixture of POPs currently present in the environment. In non-diabetics with metabolic syndrome, PCBs were linearly associated with waist circumference (Lee et al., 2007c). These authors suggested that even if PCB exposure shows a decreasing trend while obesity prevalence does not, the toxicity of PCBs may synergistically increase as people become more obese. Lim et al. (2008) suggest that brominated flame retardants may also be involved in the pathogenesis of metabolic syndrome and diabetes (see **Box 24**).

4.6.4 Cardiovascular diseases

The first observations of a possible influence of organohalogens on development of risk factors for cardiovascular diseases were made at the beginning of the 1980s. Several human studies have observed a positive and significant correlation between serum PCBs and serum triglyceride concentration (TGs). This has been observed both in occupational exposures (Chase et al., 1982; Smith et al., 1982; Hara, 1985) and in environmental exposures from highly polluted areas (Baker et al., 1980; Stehr-Green et al., 1986; Steinberg et al., 1986). Elevated serum TG levels were also observed among the 'Yusho' victims of the 1968 contaminated Japanese rice oil episode[11]. The correlation between elevated TG and PCBs persisted for 20 to 30 years in the exposed individuals, following which the blood PCB level and serum TG returned to close to normal levels (Hirota et al., 1993; Masuda, 2001). In these early studies, no congener-specific information for PCBs was available. Furthermore, the Yusho patients were exposed to a mixture of dioxins and PCBs. Vietnam veterans from the United States who were exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) developed hyperinsulinemia (Cranmer et al., 2000) and probably also alterations of their blood lipid profile. Occupational exposure to 2,3,7,8-TCDD has been related to hypertriglyceridemia (Pelclova et al., 2002, 2006).

[11] Yusho disease (literally oil disease) refers to the mass poisoning by PCBs and polychlorinated biphenyls from contaminated rice oil, which occurred in Japan in 1968. About 14 000 people who had consumed the contaminated oil were affected. A similar case occurred in Taiwan in 1979 where the condition was known as Yu-Cheng disease, with similar symptoms and effects of PCBs and PCDFs as in the Yusho poisoning.

Box 24 A mechanistic explanation for a role of OCs in metabolic disorders

An attempt to provide a possible mechanistic explanation of the biochemical effects of PCBs in the cells is shown in **Figure 16**. Intracellular calcium homeostasis is of outmost importance for cell function; in the muscles cells (the myocytes) calcium is supplied when needed to the cytosol from the sarcoplasmic reticulum through the ryanodine channels. To avoid too high a concentration of calcium, sarcoplasmic endothelium reticulum calcium A (SERCA) will catalyze the return of the calcium ions back to the sarcoplasmic reticulum, and homeostasis is restored.

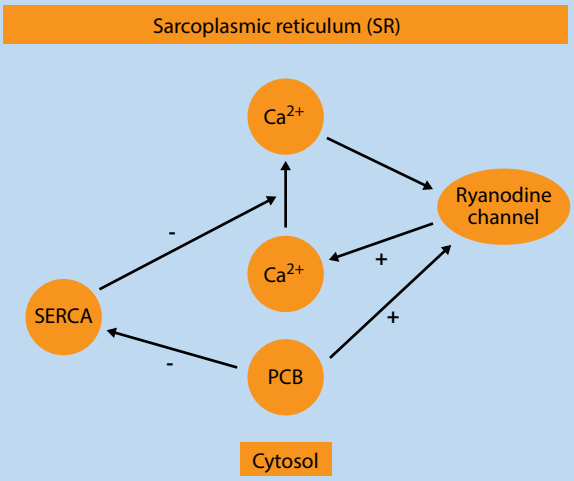

Figure 16. The influence of organochlorines on the intracellular transport of Ca^{2+} between the sarcoplasmic reticulum and the cellular cytosol in myocytes. Source: Hansen et al. (2008).

Non-coplanar PCBs may have a significant effect on intercellular Ca^{2+} homeostasis. Even though the ryanodine receptor (RyR) and its isoforms are widely expressed in most tissues (Pessah et al., 2006; Kobylewski et al., 2012), their presence in adipose tissue has not been demonstrated so far. Under physiological conditions, activation of the sarcoplasmic ryanodine receptor (RyR) leads to an increase in cytosolic Ca^{2+} concentration. Ca^{2+} is then pumped back to the sarcoplasmic reticulum by SERCA (Roux and Marhi, 2004) under hydrolysis of ATP and production of heat (Arruda et al., 2007). Non-coplanar PCBs induce Ca^{2+} release from the sarcoplasmic reticulum to the cytosol in myocytes through selective activation of the ryanodine-sensitive Ca^{2+} release channels (Wong and Pessah, 1996). Since PCBs also inhibit the backwards transport of Ca^{2+} to the sarcoplasmic reticulum, the SERCA activity is inhibited, resulting in inhibition of muscle thermogenesis. Kodavanti et al. (1993) demonstrated that non-coplanar PCBs increase cytosol Ca^{2+} in cultured cerebellar granule cells and inhibit Ca^{2+} transport over endoplasmic reticulum membranes in isolated mitochondria. This study suggests that general inhibition of SERCA may be responsible for part of the decreased ability of organelles to sequester Ca^{2+} when exposed to non-coplanar PCBs.

The major risk factor for development of CVD is elevated serum TGs. In a study of a North American fish-eating community, Goncharov et al. (2008) found significant associations between PCB levels, age, BMI and serum lipids. The same observation was made in a study among Greenlandic Inuit.

These findings are consistent with recent data from Greenland indicating associations between lifestyle-related obesity and contaminant-related increased risk of CVD (Gilman et al., 2009). Serum triglycerides were elevated in individuals with elevated serum PCBs but were only significant in persons with BMI >30. The effect was attenuated by n-3 fatty acids as shown in **Figure 17**. Hansen et al. (2008) has proposed some possible pathways and mechanisms by which mercury and PCBs could lead to signaling of pro-inflammatory responses and TG production. Goncharov et al. (2008) concluded that PCBs are directly involved in an increased synthesis of TGs.

Wang et al. (2008b) demonstrated the modulating effects of PUFAs in cell culture experiments. PCB congener 77 appears to increase oxidative stress and the effect can be potentiated by PUFAs of the n-6 family and attenuated by the n-3 fatty acids.

Ruzzin et al. (2010) showed that when salmon oil was substituted for corn oil in rats the effects of environmental concentrations of POPs in the salmon oil were not countered by the n-3 fatty acids in the salmon oil. Insulin resistance and associated metabolic disorders continued to be observed. As there is a difference in metabolism between rodents and

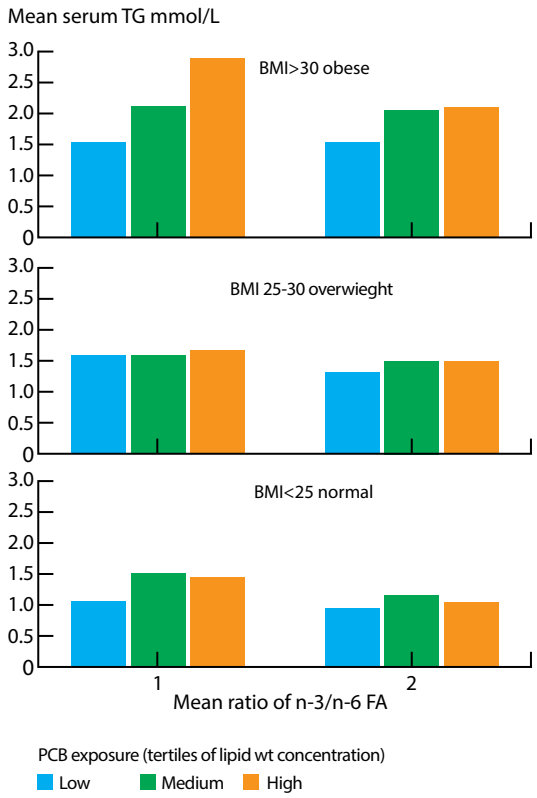

Figure 17. Effect of PCB exposure on serum triglyceride (TG) concentrations in relation to BMI categories and serum levels of n-3 fatty acids. Source: Hansen et al. (2008).

humans, these results in rats may not be directly applicable to humans and further research is needed.

4.6.5 Conclusions on contaminants

Even though connections between metabolic disorders and OCs are biologically plausible and have been demonstrated in several studies, not all epidemiological studies have found the same linkages. Discrepancies between studies might be caused by the fact that many studies report sum of PCB congeners, or worse, a single congener as a proxy for all PCBs. This will lead to misinterpretations as the toxic potential of congeners differs. Some congeners, which are present in significant amounts in the industrial mixture of PCBs, are not bioaccumulated significantly and over time, may have a lesser effect on organisms than those that do bioaccumulate. Since human exposure to several OCs is primarily through diet, what you eat (its relative level in the food chain) and where the food comes from will influence exposure with respect to both the levels and the types of OCs, especially to those which bioaccumulate.

Sorting out exactly which POPs or groups of POPs are causal agents in metabolic disorders is challenging. Humans are exposed to a variety of individual compounds, most of which are strongly inter-correlated. Human exposure is dependent on diet and dietary composition varies according to geography and the trophic level of individual food items. Several studies now indicate that organic contaminants such as PCBs, even as environmental levels decline, are still able at current exposure levels to act as aggravating factors in development of metabolic disorders and that their toxic potential is increased by obesity. Furthermore, organohalogen contaminants may well contribute to the onset of obesity in more highly exposed populations.

4.7 Pillar 7 – Psycho-social factors

Several psychosocial factors, such as inherited or learned social behavior, societal or community pressures, peer relationships, and mental health can have a significant influence on the development of obesity. The availability, quality, quantity and type of foods can also play a role in the development of obesity. Food choices are often influenced by advertising, peer pressure, tradition and awareness of product composition (nutrients, contaminants, etc.). Children and youth are often more vulnerable to peer and media influences on food choices. Life stress (relationships, work, financial, etc.) can also contribute to occasional overeating. Mental disorders, which contribute to compulsive eating or eating related to consolation for loss, grief, anxiety or loneliness can all contribute to obesity; however, these will not be considered further in this chapter as their root cause is beyond the scope of the seven pillars.

Hedonism is a philosophical school originating with the Greek philosopher Epicur (341–270 BC). Epicur argued that pleasure was the only intrinsic good and 'hedonists' strived to maximize pleasure and to avoid discomfort. Philosophically, hedonism is rarely discussed today; however, as a way of thinking, it still prevails. Common societal norms tend toward the notion that discomfort is no longer acceptable; if you are tired you rest, if you feel pain you take medication, if you are bored you contact someone, if you are hungry you reach for food. Immediate satisfaction of needs and cravings is accepted as a modern way of life.

For our early forefathers, hunger was a signal to go and find food and led to significant energy expenditure (hunting). For modern civilization, especially Western society, the hunger signal results in a walk to the refrigerator or cupboard and little energy expenditure. Foods chosen to relieve hunger in current Western society are often of poor nutritional value and contribute to excess energy intake relative to energy expenditure resulting in body weight gain (see **Section 4.4** for discussion of shifting historical food paradigms).

4.7.1 Cultural changes in food preferences

During the first half of the 20th century, food was prepared in the home by the female head of household based primarily on fresh, raw materials using traditional recipes handed down from generation to generation. Nutritional value was not always optimal; diets often contained large amounts of saturated fat and sugar and cooking methods, especially boiling of foods, stripped away many vitamins and minerals.

During the latter half of the 20th century, and especially immediately after World War II, the situation changed dramatically in some areas while in others it did not. In areas of intense warfare or occupation by invaders the problem was survival; simply finding enough of what was edible to survive. Butter (saturated fat) and sugar were scarce and were rationed. Exercise (labor) was also intense. After World War II a societal revolution took place, based on industrial acceleration. Increasingly women became part of the work force and family patterns changed. Children went to preschool and kindergartens and the time for home cooking was substantially reduced. The fast food industry grew to fill the food preparation gap and the use of precooked products and ready-to-serve meals expanded. Family taste preferences became less important as the food industry sought to provide products that would suit the tastes of the majority. Competition among producers led to lower prices but also lower quality and less nutritious products. This trend has continued and has played an important role in the globesity epidemic.

To counter the trend towards less nutritious foods, many developed countries have been providing better and more consistent labeling for domestic and imported foods to enable consumers to make informed choices about micro- and macronutrient contents. These initiatives can only be successful if the population is educated on what constitutes a nutritious product and if they apply their knowledge in making choices in the market place.

4.7.2 Advertising and its influence upon children

Children are more influenced by advertising than other age groups. Evidence indicates that there is an association between

food commercials and children's food-related behaviors, including their food preferences and food purchase requests (Lobstein and Dibb, 2005). As large numbers of children worldwide are exposed to advertising of unhealthy food, the advertising media have a role to play in the globesity epidemic. Internationally, television advertising is under scrutiny for its role in influencing children's health, diet and self-perception and several countries have banned advertisements for products considered harmful or have restricted times at which advertisements related to certain products can appear. Some products like carbonated soft drinks and sugar-based candy bars have been removed from school vending machines in some jurisdictions and replaced with more nutritious alternatives. Preventing childhood obesity is much more than restricting questionable advertising exposure. Heitmann et al. (2009) report that numerous studies have been carried out to identify the most efficient strategy for prevention and that there is still relatively little known about how to intervene most effectively.

4.7.3 Economic status and diet

A family's economic situation has a great influence on food choices. Low-income families are more likely to purchase lower cost foods which often means a greater consumption of highly digestible carbohydrate products (such as potatoes, pasta and polished rice) and fast food products which are often of low nutritional value. Minet Kinge and Morris (2010) report a strong negative correlation between socioeconomic status and BMI and health related quality of life. Economic pressure often leads to social stress, which is closely linked to personal stress (see definition in **Box 25**).

4.7.4 Stress

Stress is strongly associated with excess body weight and obesity. Societal, family and individual stress is caused by a multitude of external and internal factors; accordingly it is only defined based on a number of physiological or mental reactions, which are referred to as the general adaptive syndrome (see **Box 25**).

Stress can make it very difficult for an individual to maintain the self-discipline necessary over a long period of time to maintain body weight and/or to lose weight. Individuals under long-term stress are more prone to eating more than usual and often consume items high in carbohydrate, especially sugars. As a result, energy intake is too high and energy expenditure too low, resulting in weight gain.

4.7.5 Public policy and regulations related to preventing obesity

While obesity has often been regarded as an individual problem, the globesity epidemic is a significant and general public health issue, which demands the attention of policy makers. The conventional policy approaches have been:

- Support for information and education campaigns related to healthy food choices
- Labeling of food products
- Regulation of food/product advertising
- Subsidies for healthy products and fresh produce and/or increased taxation of the unhealthiest products
- Removal of some products from high visibility areas.

Nestle and Jacobson (2000) have reviewed several public intervention programs. Low success rates appear to be related to some generic components: inconsistent recommendations, lack of sustained funding for nutrition/exercise campaigns, overly complex food-labeling information, and taxation approaches and advertising restrictions in collision with the free market economy.

Obesity and smoking are the two leading public health problems in the most affluent parts of the world. Smoking has been successfully reduced through legislation, education, taxation, a curb on advertising and restricting smoking areas. Public policy related to obesity is still evolving, yet the WHO has predicted that the globesity epidemic will exceed smoking as the leading

Box 25 Definition of stress

Clinical stress, as a factor in biological systems, was coined by the Canadian endocrinologist Hans Selye and first described in the British Journal Nature in 1936. Stress is medically defined as: the sum of the biological reactions to any adverse stimulus (stressors), physical, chemical, social, mental or emotional (internal or external), that tends to disturb the organism's homeostasis.

These reactions can be united in the General Adaptive Syndrome (GAS) suggested by Selye. GAS is defined as: the total of all non-specific systemic reactions of the body to long-continued exposure to systemic stress. The organism possesses reactions to counteract these stimuli. A certain level of stress is essential to keep bodily functions alert, however, if these compensating reactions are inadequate or inappropriate, they may lead to disorders. According to Selye, stress appears in three stages: adaptation; resistance; and, exhaustion.

Under the adaptive state, with moderate stress, no symptoms are apparent and the effect may even be beneficial, as a certain low level of stress seems to be necessary to keep the bodily defense mechanisms, such as the immune system, alert. In a theoretical situation, without any stress, these functions would become ineffective and the organism would deteriorate.

At a higher stress level in the resistance stage, a balance will be established between the effects of stressors and the defense function of the organism. If, however, this balance is broken, either by a decreased efficiency of the defense or by an increased influence of stressors, the stage of exhaustion develops, resulting in a clinical stress syndrome.

cause of mortality. Recent data have shown that the societal costs of obesity already exceed those of cigarette smoking and alcoholism combined (Baum, 2009). Ironically, the success of public health initiatives to curb smoking may have made some contribution to the current globesity epidemic, as smoking and obesity are inversely related. The less people smoke, the less they experience appetite suppression and the more they turn to food snacks. Garson and Engelhard (2007) and Engelhard et al. (2009) have proposed that public health policy makers consider if the measures successfully enacted against smoking could be applied to the obesity problem as well.

Combating the globesity epidemic at the social and psychological level will require a multifaceted public health approach with adequate and sustained funding and strong national and regional leadership.

5. Conclusions on the seven pillars

Obesity is a complicated multi-factorial problem as illustrated in **Figure 7**. So far, there has been very little success in counteracting the global epidemic which began in the mid-20th century. Obesity is a major contributor to the global burden of chronic diseases and disabilities and is closely connected with serious social and psychological disorders affecting virtually all ages and socioeconomic groups. Of special concern is the increasing incidence of childhood obesity. The ultimate 'cause' of this epidemic appears to be a series of genetic, biological, and cultural adaptive responses developed over the long course of human evolution to energy scarcity. There exists now a mismatch between these long-standing adaptive responses and the more recent environmental influences of abundant food and thermic-neutral temperatures.

We propose that there are 'seven pillars' of obesity which all interact: genetics, epigenetic programming, positive energy balance, composition of the diet, thermogenesis and ambient temperature, contaminant exposure, and psycho-social factors.

5.1 Genetics

Obesity develops when energy intake exceeds energy expenditure for a prolonged time (positive energy balance). This energy imbalance, together with the sedentary lifestyle of many present-day populations, has traditionally been regarded as the main cause of obesity. The focus on these factors as the main causal agents has contributed to a neglect of other putative contributors to obesity. Recent research has revealed that the causality is much more complex. Genetics are likely to play a major role; body mass variations are known to have a large genetic component (30–70%). General obesity is polygenetic in origin, and is associated with metabolic reactions which can provide some explanation of inter-individual differences in body weight. However, genetic differences alone cannot provide an overall explanation for the rapidly increasing tendency. While some individuals, based upon their genetic blue print, will have a greater problem with weight control than others, for most individuals, weight control will primarily depend on environmental and lifestyle factors.

5.2 Epigenetics

Recent scientific attention has focused on epigenetic predisposition, where the maternal metabolic phenotype can be transferred to the fetus, resulting in increased risk for development of obesity and its co-morbidities later in life. This needs careful attention from a public health perspective as it indicates that being overweight is not only a question for the individual, but also for offspring via a trans-generational mechanism. There is evidence to show that maternal obesity or an unbalanced diet during pregnancy adversely affects the long-term health of the offspring. Several studies have demonstrated that both the *in utero* and early post-natal environments can influence body weight and energy homeostasis in adulthood. This has been demonstrated in both clinical studies and in rodent models. Although genetic factors can explain the etiology of some severe obesity syndromes, the recent increase in occurrence of childhood and adolescent obesity cannot be explained by genetic shifts alone or by epigenetic influences alone.

5.3 Energy balance

Positive energy balance is the major causal determinant of obesity. While 'energy intake' can be estimated quite reliably, 'energy expenditure' (EE) is much harder to estimate. EE consists of energy needed for basal metabolism and for physical activity. Both types of energy expenditure can be measured; however, there are often large individual variations. The majority of the variation is due to differences in thermogenesis which is determined by genotype, food composition and ambient temperature.

5.4 Composition of the diet

Food quantity and quality are central to this discussion. Overeating is closely associated with overweight in individuals because energy intake exceeds energy expenditure. Qualitative aspects of nutrition (micro- and macronutrient composition, type and availability) are also important. Hitherto, the discussion of management of food type has centered on low-fat or low-carbohydrate diets; however, these two choices have not contributed significantly to our understanding of the causal factors for the obesity/overweight epidemic. A much more nuanced view of available dietary macronutrients is necessary.

The individual metabolic characteristics of nutrients are of importance.

- Some nutrient components are lipogenic, i.e., saturated fatty acids and PUFAs of the n-6 family, and others are anti-lipogenic, i.e., PUFAs of the n-3 family.
- Increased intake of fructose, which has been added to many processed foods such as sweetened soft drinks and juices, over the past 50 years, leads to increases in serum triglyceride concentrations. In these quantities, fructose is both lipogenic and diabetogenic.
- Compared to intake of carbohydrates and protein, fat intake has been considered the biggest contributor to diet-based weight gain because of its high energy density. However, fat is more than a source of energy as individual fatty acids also regulate gene expressions and as such influence metabolic processes.
- It is important to distinguish between complex and simple carbohydrates, because they vary in their calorimetric energy and physiological fuel value. Thus, a simple carbohydrate like sucrose has a much higher physiological fuel value compared to starch even if the calorimetric energy values are identical.
- Proteins have not gained much attention in the obesity debate. Clearly, proteins are the nutrients demanding

the most energy for digestion and metabolism and furthermore have the highest thermogenic capacity. As such, they have a metabolic advantage over carbohydrate and fat. The more energy spent on heat production, the less is left for fat storage (metabolic efficiency). However, there is increasing evidence to show that metabolic processes can be influenced by the amino acid composition of proteins.

5.5 Thermogenesis and ambient temperature

Ambient living temperatures, both outdoors and indoors, affect energy expenditure. Most people in the developed world live and work in a rather narrow temperature range around the thermic neutral point (TNP) of 23°C. This means that little or no energy is needed to maintain the body's core temperature. It has been demonstrated that for each degree Celsius the ambient temperature is below the TNP point, an extra energy expenditure of 105–156 kJ per day is needed to maintain thermic homeostasis. Lower indoor temperatures will stimulate thermogenesis and could significantly reduce lipogenesis and increase fat metabolism in individuals. Outdoor temperatures are of importance for workers and inhabitants of areas with cold climates, as the low temperatures will also influence their energy expenditure.

5.6 Contaminant exposure

The increase in human exposure to environmental contaminants such as the organohalogen compounds has paralleled the increasing prevalence of obesity. Organochlorine contaminants have been suggested as co-factors in the development of obesity. This suggestion is supported by recent findings that OCs, even at current exposure levels, may aggravate lifestyle-induced metabolic disorders. For example, it has been found that serum concentrations of some OCs are positively related to obesity and negatively correlated to thyroxin levels and may therefore help to account for reduced energy expenditure and reduced thermogenesis during weight loss. The effects of OCs on CVD and diabetes may also exacerbate these same co-morbidity diseases of obesity.

5.7 Psycho-social factors

Modern lifestyles are often considered very stressful and stress has been linked to obesity (Bose et al., 2009). An obvious explanation for the association between stress and weight gain is that, regardless of the cause, stress often leads to a loss of self-control and consolation-related eating. Definitive causal links between stress and obesity have so far not been identified.

Obesity and its sequelae are growing problems with huge economic consequences. The problem is extremely complex, involving social, cultural, nutritional, environmental and genetic aspects. A successful approach to reducing local obesity and the globesity epidemic in general will require education campaigns at all levels of society, especially aimed at health professionals and children and their parents. A solution will also require political awareness and a willingness to implement effective policies including regulatory interventions.

6. Strategies to counteract the 'globesity' epidemic

Excess body weight and obesity, as well as their associated chronic diseases, are, in theory, largely preventable. The solutions rest with individuals (habits need to change), with the public health system (information campaigns and patient support programs), with social policy decision makers (advertising norms, reducing access to poor quality or obesogenic foods, sustained program funding) and with industry (responsible chemistry, reduction in contaminant emissions, production of nutritious and high quality foods). Governments, international partners, civil society and non-governmental organizations and the private sector have vital roles to play in shaping healthy environments and making healthier diet options affordable and easily accessible. This is especially important for the most vulnerable in society – the poor and children – who have limited choices about the food they eat and the environments in which they live.

6.1 Personal strategies

There is no cure for excess body weight, however there are two prerequisites for successful individual weight loss: a firm commitment to lose weight in order to improve health, longevity and quality of life; and recognition that this requires life-long lifestyle changes and that no short-term 'cures' are effective. Only a long-term commitment to weight loss and maintenance is effective. Mark Twain is quoted as saying: *"Quitting smoking is easy.... I've done it a thousand times"*. The same can be said about losing weight.

Why is it so difficult for individuals to lose weight? Genetic diversity and epigenetic programming mean that weight loss is easy for some but very difficult for others. External factors, such as insufficient information and advice, misleading advertising and personal stress add to the difficulties. However, following some simple recommendations based upon the seven pillars of obesity will in the long run be beneficial for all.

- Eat less – refrain from a second serving, eating snacks between meals; accept the feeling of being hungry between meals.
- Make food choices which are healthy and personably acceptable (taste, texture, appearance) – healthy eating should be pleasurable, not an ordeal.
- Limit energy intake from total fats; shift fat consumption away from saturated fats to unsaturated fats; limit intake of sugars; increase consumption of fruits, vegetables, legumes, whole grains and nuts.
- Exercise moderately every day – taking physical health and capability into account; endeavor to achieve a balance in energy intake and energy expenditure.
- Lower the indoor temperature in your home to 18–19°C – this is within a comfort range and adaptation is quite rapid; the resulting thermogenesis will burn fat.

6.2 Food industry and marketing strategies

Initiatives by the food industry to reduce the fat, sugar and salt content of processed foods and portion sizes, to increase introduction of innovative, healthy, and nutritious choices, and to review current marketing practices will contribute significantly to curbing obesity and accelerating health gains worldwide.

Market-driven responses are increasingly emerging from food companies that have increased their profitability by entering into 'healthy food' and 'healthy beverage' markets. Other companies have drawn lessons from the tobacco industry and have begun to voluntarily restrict the marketing of some products to children in response to mounting evidence that advertising increases childhood obesity (Yach et al., 2006).

Businesses are also increasingly becoming aware of the financial rewards that arise from investing in the health of their employees (Yach et al., 2006). A break-even scenario for one representative international company would require reducing health risks by 0.17% per year for 10 years. An international drug company recently decided to integrate workplace health promotion into its human resources strategy. As companies begin to comprehend the positive business case of such programs – an average savings of USD 3 for every USD 1 invested – employee health will improve and the company's bottom line will grow.

Brownell and Yach (2006) propose seven societal actions which would drive healthy food choices and promote improved energy balance: (1) support local farmers and promote the consumption of local foods; (2) regulate the marketing of unhealthy food, particularly to children; (3) teach individuals to evaluate media/advertising campaigns in order to help them avoid 'poor-food' marketing; (4) discourage the consumption of categories of foods known to contribute to poor diet and obesity (especially soft drinks); (5) focus on food norms which emphasize food quality and nutrient density over quantity and price; (6) monitor and modify economic conditions which support/subsidize unhealthy over healthy foods and create conditions where healthy foods are the logical economic choice; and (7) protect opportunities and incentives for physical activity.

In May 2010, the World Health Assembly (WHA), through resolution WHA63.14, endorsed a set of recommendations on the marketing of foods and non-alcoholic beverages to children (WHO, 2010). The main purpose of the recommendations was to guide efforts by Member States in designing new policies, or strengthening existing policies, on food marketing communications to children in order to reduce the impact of marketing foods high in saturated fats, trans-fatty acids, free sugars, or salt.

6.3 Public health/political strategies

The absence of definitive evidence of strategies that will work to reduce excess body weight and obesity should not delay action.

When several Nordic countries as well as Canada, New Zealand and Singapore pioneered comprehensive tobacco control in the early 1970s, they relied on sound economic and consumer theory. Over time, their research which demonstrated that smokers would respond to price, marketing, access to treatment and education programs, has proven correct. Adapting these basic principles to the much more complex areas of food, nutrition and physical activity will be tougher and will require broader alliances between public, private and civil societies.

The consequences of inaction on obesity – reversal of steady improvements in life expectancy and rising health and social costs – should be sufficient motivation for urgent action. Obesity and diabetes represent crises for the health care system and the health of the public, incurring costs and disease burden for adults and children. Increasing costs and prevalence can be expected unless more coordinated efforts to address the causes of these conditions at the national level are implemented. These conditions, which already affect a large and growing proportion of the population, create policy and budget dilemmas for governments, health insurance companies, employers, physicians, and the health care delivery systems. Obesity and diabetes also create significant physical and emotional burdens for individuals and their families who experience the effects of the disease and its complications.

6.4 An overall strategic approach

Obesity has evolved from a status symbol, signaling wealth and influence, to the greatest threat to human health. An effective overall strategy to combat the obesity epidemic can be based upon elements of the seven pillars of obesity.

Strategy 1: Inform the public of the role of genetics in obesity and encourage nutrigenetic studies.

New progress in the science of nutrigenomics, especially nutrigenetic evaluations on an individual level, could be a tool for developing advice based on knowledge obtained from nutrigenomic studies. A prerequisite for this would be that individual genetic testing becomes more acceptable among the general population. For this to occur, the value of genetic testing would need to be explained and discussed more thoroughly with the general public. As genetics is considered to account for about 60% of the causal factors in general obesity, it would appear to be urgent to establish a system where individuals can obtain nutrigenomic advice.

Strategy 2: Establish a science-based information program for doctors and midwives on trans-generational transfer of proneness to obesity.

Epigenetic inheritance is not widely known among health professionals or the general population. There remains an urgent need to inform overweight women of childbearing age to change their lifestyle before getting pregnant in order to avoid the transfer of a tendency toward obesity to their offspring.

Strategy 3: Educate health personnel, at all levels, to enable them to advise patients on realistic and relevant dietary and nutritional choices, and develop a more consistent science-based refinement of advice for the public on the nutrition/exercise relationship.

It is essential to balance food and dietary components with physical activity in order to maintain energy balance. The most trusted advice comes from health care professionals. Knowledge acquisition for health care professionals, based on sound research, must come first before knowledge transfer can take place to patients.

Strategy 4: Promote further study of the anti-obesogenic nutrients and provide science-based information to health care workers about diets which can reduce obesity.

It is essential to undertake further study of the metabolic advantages and disadvantages of individual macronutrients and to reach consensus on the ideal diet composition taking into account the different components of each of the three macronutrients (lipids, proteins and carbohydrates). Other micronutrients that can affect weight gain and loss also deserve more attention in research studies to be sure that patients can optimize all aspects of their diet.

Strategy 5: Lower temperatures below 23°C in homes, schools, and workplaces to promote more physiological energy expenditure and intensify research on cold adaptation as a factor in weight control.

Thermogenesis (heat production) comes from that part of the energy intake not used for production of ATP. The greater the use of energy for heat production, the less energy is available for fat formation under iso-caloric conditions. An increasing number of human beings are living in heated and air conditioned homes and workplaces that are maintained at close to the thermic neutral point of 23°C. This emerging lifestyle eliminates an important control factor against obesity, i.e., the need to expend energy for maintaining body temperature. Special emphasis should be placed on lowering the ambient temperatures in homes, schools and workplaces as this would be of benefit to health, save substantial amounts of global energy and decrease greenhouse gases which affect climate. This consideration has largely been ignored in discussions of the causes of obesity. Cold adaptation is also an almost forgotten issue in energy expenditure research.

Strategy 6: Strengthen international conventions on reduction of production, use, and distribution of persistent organohalogen compounds and other xenobiotics and promote research of their adverse effects on weight loss.

The 'western lifestyle' plays an important role in the obesity epidemic. As a sequela to industrialization, humans throughout the globe are exposed to a mixture of numerous contaminants. The persistent organic contaminants are of concern as they act additively and are likely to have negative effects on metabolism, increasing obesogenic potential and exacerbating some co-morbidities of obesity.

Strategy 7: Based upon the successful measures taken against smoking, develop and implement a multi-faceted campaign to reduce the desire for and use of low quality, obesogenic foods.

Stress has been introduced into modern societies and has developed into a significant factor for health and mental

well-being. Stress influences tendencies towards overweight as stressed persons very often are inclined to overeat, especially high-carbohydrate snacks of poor nutritional quality. In most cases, a person under stress will not be receptive to food advice, as their reactions are ruled by an internal, metabolic or mental disorder. Consequently, public and political intervention is necessary. The classical possibilities for public interventions include: better information, education, taxation of unhealthy foods, promoting/subsidizing healthy foods, and restrictions on advertising of unhealthy food (see **Section 6.2**). In spite of several public health interventions, the effects globally have not been convincingly positive. Political awareness of the problem has repeatedly been demonstrated, but the lack of results are probably due to conflicting attitudes between what is needed from a public health point of view and commercial interests of food-producing industries (including agriculture). Taking into consideration the seriousness for public health of the globesity epidemic and the enormous and increasing healthcare costs, it is time for a comprehensive, multi-faceted campaign to combat obesity.

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Abbreviations

AMPK	AMP-activated protein kinase
BAT	Brown adipose tissue
BMI	Body mass index
BMR	Basal metabolic rate
Ca	Calcium
CVD	Cardiovascular disease
DEE	Daily energy expenditure
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
FFA	Free fatty acids
GI	Glycemic index
GSIS	Glucose stimulated insulin secretion
OC	Organochlorine
PCB	Polychlorinated biphenyls
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1 α
POPs	Persistent organic pollutants
PPAR	Peroxisome proliferator activated receptors
PUFA	Polyunsaturated fatty acids
SIR2	Silent information regulator 2 gene
SREBP	Sterol regulatory element binding protein
TG	Triglycerides
WHO	World Health Organization

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