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Dietary transition and contaminants in the Arctic: emphasis on Greenland

Jens C. Hansen, Bente Deutch, Jon Øyvind Odland

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Einmal muß man von der Erklärung auf die bloße Beschreibung kommen.
(Ludwig Wittgenstein)

Dietary transition and contaminants in the Arctic: emphasis on Greenland

Jens C. Hansen
Bente Deutch
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List of abbreviations

AA: arachidonic acid
AhR: aryl hydrocarbon receptor
AMAP: Arctic Monitoring and Assessment Programme
BMI: body mass index
baPWV: brachial-ankle pulse wave velocity
CAM: Centre for Arctic Environmental Medicine
CAR: constitutive androstane receptor
CBMC: cord blood mononuclear cells
CBT: caffeine breath test
CMIT (or ITM): carotis media intima thickness
Cd: cadmium
CFA: confirmatory factor analysis
COX: cyclooxygenase
Cu: copper
CVD: cardiovascular disease
CRP: C-reactive protein
CYP: Cytochrome P450 enzymes
DDE: dichloro-diphenyl-dichloro ethylene
DDT: dichloro-diphenyl-trichloro ethane
DHA: docosahexaenoic Acid
DNA: deoxyribonucleic acid
DNL: *de novo* lipogenesis
E: elongase
EPA: Environment Protection Agency
EPA: eicosapentaenoic acid
ER: estrogen-receptor
FFA: free fatty acids
FAS: fatty acid synthetase
Fe: iron
FFQ: food frequency questionnaire
FMD: flow-mediated dilatation
GI: glycemic index
GLUT4: glucose transporter
GP_x4: phospholipids-hydroperoxide-glutathione-peroxidase
GSH-Px: glutathione peroxidase
HCB: hexachlorocyclobenzene
HCH: hexachlorocyclohexane
HDL: high density lipoprotein
Hg: mercury
IDF: International Diabetes Federation
IGFBP: insulin growth factor binding protein
iNOS: inducible-nitrogen-oxide-synthetase
ITM: intima-media thickness
LDL: low density lipoprotein
IL: interleukine
LA: linoleic acid
LOAEL: lowest observed adverse effect level
LHR-1: liver homolog-1 receptor
MCP-1: monocyte chemoattractant protein
MeHg: methyl mercury
MetS: metabolic syndrome
MJ: megajoule
mRNA: messenger ribonucleic acid
MRUS: maximal rate of urea synthesis
NF: nuclear factor
NF-ϰB: nuclear factor-KappaBeta
NNR: Nordic nutrition recommendations
NO: nitric oxide
Pb: lead
PBB: polybrominated biphenyls
PBDE: polybrominated diphenyl ethers
PCB: polychlorinated diphenyls
PCDD/Fs: polychlorinated bi-phenyl dioxin/furans
PCOS: polycystic ovarial syndrome
PGE: prostaglandine E
PON: paraoxonase
POPs: persistent organic pollutants
PPAR: peroxisome proliferator activated receptors
PUFA: polyunsaturated fatty acids
PXR: pregnane xenobiotic receptor
ROI: reactive oxygen intermediates
Se: selenium
SFA: saturated fatty acid
SHBG: steroid hormone binding globuline
SOD: superoxid dismutase
SREBP: sterol regulatory element binding protein
SXR: steroid and xenobiotic receptor
TCDD: tetra chlorodibenzo-p-dioxin
TBG: thyroid binding globuline
TEQ: toxic equivalents
TG: triglycerides
TNF: tumor necrosis factor
US EPA: United States Environmental Protection Agency
WHO: World Health Organization
Zn: zinc

Map of Greenland. Dotted lines represent community borders.

Content

Preface

In May 2006, the Greenlandic Minister of Health and Environment convened a meeting in Nuuk, Greenland to discuss health-environment relationships in Greenland. This meeting included participation of scientists from The Kingdom of Denmark, (Denmark, Greenland and the Faroe Islands), officials from the Greenland Home Rule, and representatives from the Danish Environmental Protection Agency. The background for the meeting was the evidence presented in the recent Arctic Monitoring and Assessment Programme (AMAP) Phase II assessment report on potential human health implications of pollution of the Arctic by persistent organic pollutants and toxic heavy metals.

As a consequence of the meeting, Danish scientists participating in the international AMAP Human Health Assessment Group (Eva Bonefeld-Jørgensen, Anders Carlsen, Bente Deutch, Jens C Hansen, Gert Mulvad, Henning Sloth Pedersen and Pal Weihe) were requested to prepare a 'memorandum' for the Home Rule Government of Greenland to aid the political decision-making process in addressing the question of how to handle the situation that exists. The document was drafted by Jens C. Hansen, director of the Centre for Arctic Environmental Medicine (CAM), University of Aarhus, Denmark and was finalized following discussion with the group members. The memorandum was sent to the Greenland Home Rule, via the Danish EPA, in 2006.

A prerequisite for preparing a document that has the potential to have profound influences on living conditions and cultural development within Greenlandic society, is that it is based on an in-depth ongoing scrutiny of recent scientific evidence. In order to present the evidence that formed the background for the memorandum and the basis for its conclusions, CAM decided to prepare a more detailed review of the science behind the memorandum. In this report the scientific evidence is presented in such a manner that the reader will hopefully be able to make an informed judgement on the groups consideration of these issues.

Contaminant issue in relation to human health have in recent decennia focused primarily on hormone mimicking effects of certain organochlorines, and their possible implications for fecundity and hormone-related cancers, and on methylmercury in relation to neurological development in children. There is now a considerable volume of literature on these issues. Rather than duplicating this, we have chosen to concentrate this review on a possible aggravating effect of pollutants on lifestyle-related metabolic disorders. This seems to us to be particularly relevant because in the Arctic, food choice and contaminant exposure are closely related, and there is a sound scientifically-based hypothesis that contaminants exert an additive effect on an otherwise obesitogenic lifestyle. In this way, contaminants may exert a negative health effect at much lower concentration levels than previously anticipated.

It is our hope that this report will provide understanding for our reasoning in the memorandum to the Greenland Home Rule Government, and also create understanding for the necessity that future studies combine toxicological and nutritional/lifestyle factors in order to create a holistic and meaningful health assessment.

The time has come where it is necessary to implement a general public health policy, which through proper education of the younger generations may improve living conditions for Arctic peoples within their cultural traditions, and still recognizing the value of local food resources.

Aarhus October 2007

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CHAPTER 1
INTRODUCTION

At an early stage, humans recognized the association between diseases and food supply. Hippocrates linking the development of medicine to that of nutrition is quoted as saying: "Let food be thy medicine and medicine be thy food".

Food is a basic necessity for life. It is therefore not surprising to find that interest in its nutrititional qualities has continued to grow throughout the ages, resulting, in the 20th century, in the recognition of nutrition as a distinct science with organisations and publications devoted to this specialist field of interest. Today, adequate nutrition is recognised as one of the major determinants of health. However, food is more than just a factor influencing physical health. In every human society food provides a means of expressing relationships between people. These relationships may be between individuals, or between members of social, religious or ethnic groups. Food is more than just a source of nutrition, it is an essential part of the way a society organises itself and views the world that it inhabits (Helman 2000).

'Globalisation' of the human diet is an area of growing importance. Social and economic changes have impacted on nutrition and health, especially in those communities that are undergoing urbanization, industrialization and 'westernization'. These societies have entered different stages of what has been called the 'nutrition transition'. Global diet is in a constant state of flux, and the cultural- and health implications of this are only now beginning to emerge. The indigenous minorities of the world and their respective cultures are particularly vulnerable. Not only is rapid technological development leading to changes in basic living conditions, but contaminants are also spreading through the food-chains, and together with climate change this poses a potential threat to the health of Indigenous Peoples and their cultures.

Catching wild animals, such as marine mammals, fish, terrestrial mammals and birds has always been central to the survival of Arctic Indigenous Peoples. As part of the global community, Arctic Indigenous Peoples

have repeatedly asserted their rights to utilize and benefit from the natural resources that have sustained them for centuries, and which are the basis for their culture and traditional way of life.

In recent years this traditional lifestyle has been threatened by events in other parts of the world, including human activities that have resulted in the release and spread of environmental contaminants at a global scale.

The mere suspicion that resources may be contaminated can be enough to prevent indigenous people using them for food. This fact has been recognised and (mis-)used by some environmental groups that would like to see indigenous people discontinuing their hunting of marine mammals. Social pressures from outside, such as increased exposure to western lifestyles as a result of television and development of Arctic mineral resources, etc., and the associated increased availability of western foods and its promotion through advertising are all factors that contribute to a non-directed dietary change, moving away from nutritious traditional food towards a non-balanced westernized diet.

A number of contaminants bio-accumulate, and some bio-magnify in marine food-chains. The fact that certain cultural groups, such as Inuit who consume large amounts of marine mammals and therefore occupy the position as top predators in these food-webs may be exposed to high levels of contaminants is of concern from a public health point of view (AMAP 1998). Some of these contaminants can also be passed from mothers to their children during breast-feeding.

At the same time, these foods are important sources of vitamins and other vital nutrients. Following its first assessment, in 1997, the Arctic Monitoring and Assessment Programme (AMAP) Human Health Expert Group therefore concluded that:

Weighing the well-known benefits of breast-milk and traditional food against the suspected but not yet fully understood effects of contaminants it is recommended that:

- Consumption of traditional food continues, with recognition that there is a need for dietary advice to Arctic peoples so they can make informed choices concerning the food they eat.
- Breast-feeding should continue to be promoted.

During its second assessment period (1998-2002), AMAP continued to monitor exposure levels, but also investigated the human health effects of contaminants in a more comprehensive manner. These programmes documented evidence of the existence of subtle health effects, related to contaminant exposure, including effects both in the Inuit and the Faroese populations. Although the measured exposure levels are unlikely to lead to overt diseases, they indicate that the presence of contaminants may initiate processes with a potential for transgenerational adverse health effects. These new data have increased the health concerns associated with environmental contaminants and led to a qualification of the above mentioned recommendation in the subsequent AMAP assessment report (AMAP 2003), as follows:

"At actual levels of exposure observed in some Arctic populations there are negative health effects related to the contaminant exposure; for this reason there is an urgent need to lower the level of exposure in some populations, through both national and international efforts."

An ideal diet is one that promotes optimal health and longevity. Throughout history, humans have developed a variety of dietary patterns based on available food plants and animals that successfully supported growth and reproduction. The dietary pattern developed by the Inuit in the hostile climate of the High-Arctic is an extreme pattern, based almost solely on animal food of marine origin. This traditional diet is characterized by a very high protein intake, a high fat intake, and an extremely low intake of carbohydrates and fibres, and as such appears to be far from what nutritionists today regard as a well-balanced diet. Nevertheless, it has sustained the Inuit population, and has gained scientific interest, in particular following the observations by Bang and Dyerbergs that marine fatty acids provide a protective factor against the development of cardiovascular diseases (Bang *et al*. 1971, Bang and Dyerberg 1972, Dyerberg *et al*. 1975). Later evidence has emerged that the relative intake of n-3 fatty acids can influence several pathological conditions. In addition to these positive qualities, however, recent studies have documented that the Inuit traditional marine food is the main source of human exposure in the Arctic to environmental contaminants such as the chlorinated organic compounds and methyl mercury (AMAP 1998, AMAP 2003).

The purpose of this review is to evaluate the nutritional qualities of the Inuit traditional food pattern seen in an evolutionary and historical perspective, and to describe the present day nutritional pattern as influenced by dietary transition. Observed exposure levels to contaminants, and their potential negative effects will be discussed. Finally, we attempt to indicate what could be the direction for future developments in order to conserve the cultural and nutritional values of the local diet, and at the same time reduce contaminant exposure levels.

CHAPTER 2

THE EVOLUTIONARY ASPECT OF HUMAN NUTRITION

The genus (Homo), to which humans belong, appeared around 2.4 million years ago, with the present human species, *Homo sapiens*, appearing 100 000 to 200 000 years ago. Prior to the development of agriculture in some parts of the world, about 10 000 years ago, our human ancestors lived as hunter-gatherers. They were dependent on fat and protein for their primary sources of energy, while the intake of carbohydrates was limited (see Table 1). This pattern has prevailed in the Inuit cultures up until recent times.

For some time, a number of anthropologists and nutritionists have considered that studies of the paleolitic diet might serve as a 'reference' for contemporary diets and as a model for use in studies of diseases related to the present day 'western' lifestyle, such as obesity, type 2 diabetes, MetS, and cardiovascular diseases. A fairly good knowledge of the paleolitic diet exists, established through studies of differences in cranio-dental structure, stable isotope studies, comparative studies of gut morphology, and calculations of energy needs for development of brain/body weight ratio. These studies are based on archaeological finds and comparisons with present day hunter-gatherer cultures. They have shown that during the transition from archaic Homo species to *Homo sapiens* a shift from a plant-based diet to a diet dominated by foods of animal origin took place; man became a carnivore. This decrease in dependence on plants made it possible for them to

Table 1. Distribution of macronutrients, % of total energy.

	Nordic nutritional recommendations 1996	Danish population averages	Alaskan Eskimos[a]
Protein	≤ 15	12	30-35
Fat	≤ 30	42	50
Carbohydrates	55	46	15-20[b]

[a] Ho *et al.* 1972; [b] largely as glycogen from meat consumed.

move, after the ice ages into more temperate zones, and even into subarctic and Arctic areas, where they became almost entirely dependent of food of animal origin.

The paleolitic diet was characterised by high protein and fat, and very low carbohydrate content (see Table 1); this is a typical ketogenic diet. The term 'ketone body' refers to three compounds: acetoacetate, 3-hydroxybutyrate, and acetone. Of these three, acetoacetate and 3-hydroxybutyrate can be utilized for energy production in several tissues, including the brain, and replace glucose, while acetone is regarded to be of little metabolic significance (Morris 2005). Ketone bodies are formed in the liver, predominantly from fatty acids, and act as alternative energy source to glucose. The paleolitic diet also contained higher concentrations of essential trace elements, with the exception of sodium, compared to the present-day western diet. The so-called 'traditional Inuit diet' is also a ketogenic diet, and this is what the Inuit have survived on, with success, for millennia. The general opinion prevailing among physicians and nutritionists today is that a high intake of fat leads to obesity (because fat has a higher energy density compared to protein and carbohydrate), and that it is necessary to consume carbohydrates in order to perform optimal physical activity. These concepts have been adopted to such a degree that today they also influence Indigenous Peoples who, while previously living in accordance with their inherited traditions, are now undergoing a transition between an 'old' and 'new' way of life. One consequence of this transition is that typical so-called 'civilisation diseases' are observed at increasing prevalence.

The possibility, for non-Inuit, to also survive on a ketogenic diet has been documented through the diaries of polar expeditions. Frederick Swatka, the leader of the Swatka 1878-1880 expedition in search of the lost Royal Navy Franklin Expedition, 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 appearant weakness and inability to perform severe exertive fatiguing journeys. But this soon passes away in the course of two to three weeks"

For the Inuit, the ketogenic diet was the only accessible food. It was, however, not consistently available, meaning that periods of plenty of food were followed by periods of starvation. In a state of starvation the glycogen depots are quickly depleted and a ketogenic metabolism is initiated, using body stores of fat as an energy source. As a consequence of this, the Inuit did not experience the problems described by Swatka – for this reason the ketogenic diet is also named the 'starvation mimicking' diet.

From the 1920s the ketogenic diet has been used in 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 saturated fat was used. This increased serum triclycerides and LDL cholesterol and, as a consequence the practice has been discussed. The recent understanding of the action of polyunsaturated fatty acids in lowering triglyceride and LDL cholesterol levels has opened for reconsidering the ketogenic diet for treating epileptic children.

In absence of glucose, free fatty acids are β-oxidised in the mitochondria, under formation of ketone bodies. This process is dependent on absence of glucose, and is inhibited by insulin (Denor *et al*. 1985). All types of fatty acids seem to be substrates for formation of keto-bodies, but the polyunsaturated n-3 fatty acids seem to be more ketogenic than the n-6 fatty acids or monounsaturated fatty acids, which are more ketogenic than saturated fatty acids.

The polyunsaturated fatty acids (PUFA) and a subset of their eicosanoid metabolites serve as ligands for a key metabolic regulating system; the peroxisome proliferator activated receptors (PPAR). PPARs belong to the nuclear steroid hormone receptor superfamily. To date, three related PPAR iso-types have been identified: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-α is highly expressed in liver, heart, kidneys, and skeletal muscle. Beta-oxidation of fatty acids is induced by PPAR-α (Fig. 1), which is primarily expressed in the liver.

The PPAR-α expression is increased by a ketogenic diet, by starvation, and by physical activity. The natural ligands for the receptor are free fatty acids. An increased expression of PPAR-α results in increased oxidation of fatty acids, decrease of serum triglycerides, and regulation of gluconeogenesis. The same effects have been observed in intervention studies with n-3 fatty acids. Even today there are diverging indications of which of the polyunsaturated fatty acids are the natural agonists of the PPAR-α, there seems to be evidence, that, under physiological conditions, the n-3 fatty acids play a dominant role when abundant.

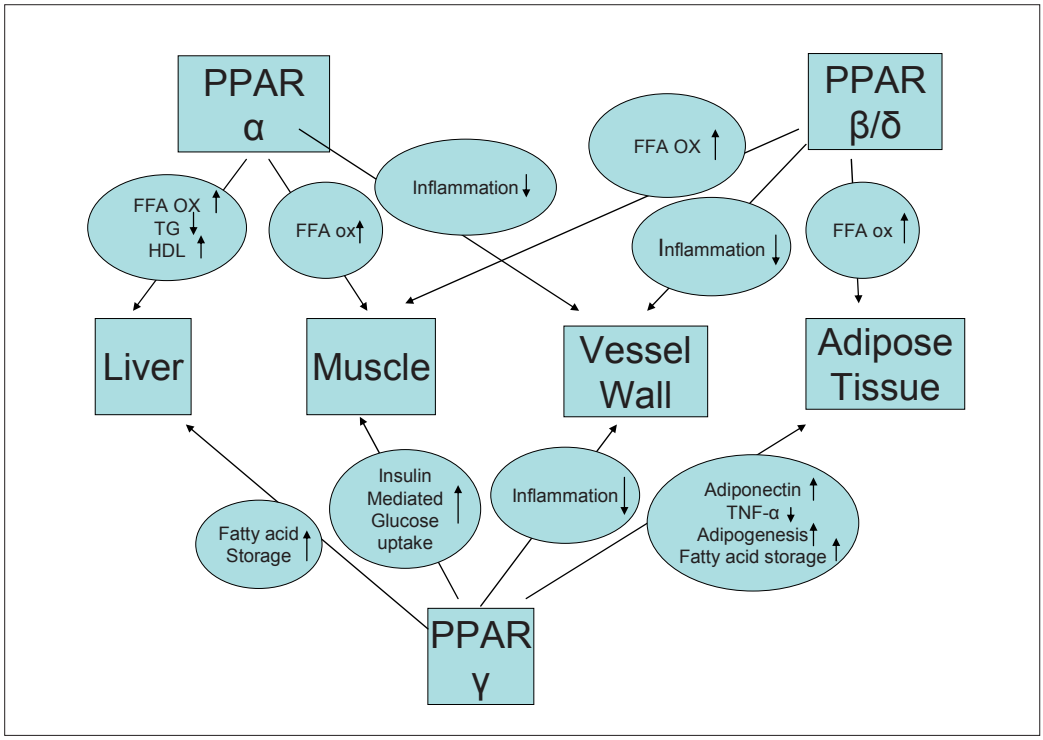

Figure 1. Activity of peroxisome proliferator activated receptors (PPARs).

The human genome has developed over more than 2 million years as an adaptation to the environment. The genetic set-up today is more or less identical to that in the Palaeolithic time. However, agriculture-based populations have acquired a number of adaptations to survive under their new conditions (Cavalli-Sforza and Cavalli-Sforza 1995). These small genetic differences observed between different populations are examples of what has been called microevolution; for example, herders of milk-producing domesticated animals in Europe and Africa have evolved the ability to digest lactose throughout life to better adapt to their new diet. Northern Europeans evolved to have lighter skin to allow more efficient synthesis of vitamin D in their sunlight-deficient environment, thereby preventing rickets. The same is not the case for Inuit living in the northernmost parts of the world, probably because of the abundance of vitamin D in their marine diet. Light skin is therefore most likely a recent adaptation to a dietary deficiency caused by agriculturilization.

As the Inuit have never practised agriculture, it is reasonable to assume that these populations still today are genetically very close to their hunter-gatherer forebearers. During the 20th century a dramatic societal change has taken place in Inuit communities, including the introduction of imported western food which has resulted in a rapid dietary transition from an almost 100 percent animal-based local diet to a diet that today typically contains around 75 percent imported agricultural products (Deutch *et al*. 2006). The most prominent changes are a decline in protein intake and increase in carbohydrates (see Fig. 2).

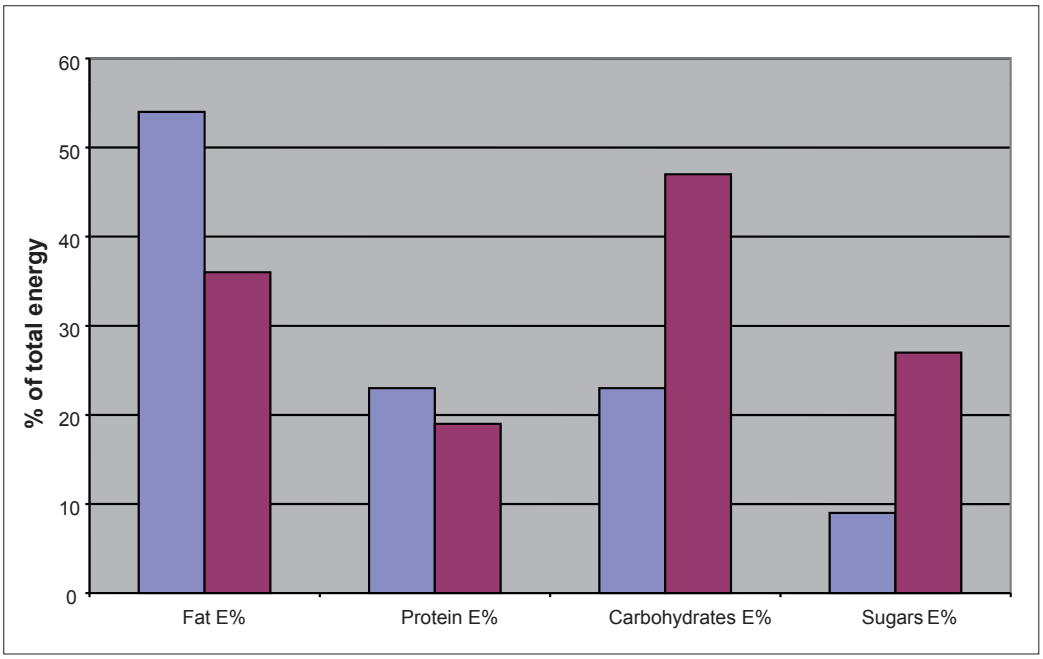

Figure 2. Energy % distribution of consumed macronutrients in Angmassalik 1945 (blue) and 1978 (red) (Helms 1982).

The microevolutions among agricultural groups took place over 10 000 years; the less than 100 years of dietary transition among Inuit is far too short for adaptation to have taken place and, as a consequence, an increased prevalence of chronic degenerative diseases such as CVD and type 2 diabetes as well as obesity are beginning to appear in Inuit populations. There is evidence that these conditions were rare among the Inuit in pre-colonial times, implying that the underlying genetic factors probably had minor adverse effects at that time. This highlights the fundamental principle that all phenotypes are formed by the interactions of a genotype with the environment, and likewise that degenerative diseases arise from one or other degree of genetic predisposition in interaction with the prevailing environmental conditions. Through human evolution, genetic adaptation was linked with environmental alterations. Now, however, cultural changes occur too rapidly for genetic accommodation to keep pace (Wilson 1998, Klein 1999). We still carry genes that were selected for their utility in the past, but which under the novel circumstances of contemporary life may imply increased susceptibility to chronic diseases. These alleles/genes are sometimes mentioned as 'defects'. This is a misinterpretation; they are not defects, but simply do not fit the present day way of life.

The 'Thrifty Gene' hypothesis was introduced by Neel (1962). This is one way to explain the effects of dietary transition among indigenous peoples. It is based on the suggestion that some population groups have a 'thrifty' genotype, which could have conferred a selective advantage under the traditional food regime, while today it would be detrimental because the recently adopted new types of foods are constantly available. This is an attempt to explain the emerging new disease patterns observed in some populations in rapid cultural transition. The rationale for the 'Thrifty Gene' hypothesis is that, in general, man has been genetically adapted through millennia to the available food situation. Under rapid transition, as experienced by many indigenous populations during the 20th century, a misbalance will occur between the genetic constitution and the food actually eaten, resulting in occurrence of new disease patterns.

Carbohydrates, especially glucose, are essential for brain function. When the natural diet was very low in these nutrients, it was important to save them for this function instead of using them for energy production. As a consequence a low glucose metabolism would be advantageous, and the energy from carbohydrates could easily be compensated for by the high supply of fat. Later, during the transition, when food changed to a carbohydrate rich diet, the impaired ability to metabolize glucose becomes evident as glucose intolerance, leading to increased prevalence of obesity and type 2 diabetes. The 'Thrifty Gene' hypothesis is regarded as controversial from a scientific point of view.

According to Eaton *et al*. (2002) the principal goals of evolution-based prevention are 1) to characterize differences of patterns of life in ancient and modern environments, 2) to identify which of these are involved in the initiation and progression of specific diseases, 3) to use this information to design innovative studies of the pathophysiology, and 4) to integrate epidemiological, mechanistic, and genetic data with evolutionary principles to create an integrated formulation upon which to base persuasive, consistent, and effective public recommendations.

CHAPTER 3

THE TRANSGENERATIONAL ASPECT

An area of increasing interest in relation to the gene/environment problem is foetal programming. When, as often was the case in prehistoric time, the foetus developed under restricted nutrition, it adapted to the thrifty genotype. After birth it was therefore better able to cope with food restriction and thus had better chances of survival (Langley-Evans 2006). On the other hand, if a fetus adapted to thrifty genes was well nourished after birth, it would develop obesity. In the opposite situation, where a foetus was overnourished, an epigenetic programming would occur and the result would be obesity in later life. The different situations are visualized in Figure 3.

The changing disease pattern in some populations in cultural and dietary transition should not, as is often the case, be regarded only as an inevitable consequence of the cultural change process, but should primarily be evaluated in the light of genetics. The thrifty human genome has not changed in any dicernable way through the period of human evolution; thrifty genes are therefore general and not a special phenomenon of indigenous peoples in dietary transition. The mechanism that triggers negative effects is not solely due to the genes, but rather a combination with an affluent lifestyle leading to foetal programming. By these epigenetic mechanisms (the study of heritable changes in gene function that occur without a change in the DNA sequence) maternal metabolic disorders can be transferred to the next generation.

Programming is an epigenetic phenomenon, by which nutritional, hormonal, physical, psychological and stressful events acting in a critical period of life, such as gestation and lactation, modifies in a prolonged way certain physiological functions (de Moura and Passos 2005).

Heredity plays a major role for development of obesity. However, the increase in prevalence of obesity globally has been too rapid to be associated with major genetic changes. Therefore, parental obesity seems to affect offspring obesity through gene-environment interactions (Wu and Suzuki 2006).

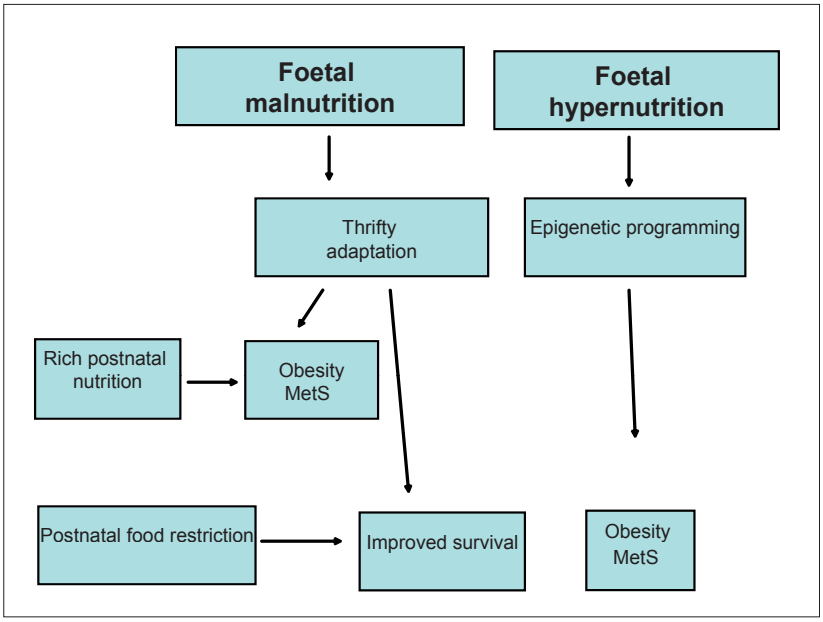

Figure 3. Consequences of foetal malnutrition or foetal hypernutrition.

The mechanism may be due to epigenetic inheritance. The increased knowledge concerning foetal programming supports the idea that epigenic marks are not always completely cleared between generations; it is also becoming evident that the establishment of epigenetic marks during foetal development can be influenced by environmental factors. These two processes in combination may provide a possibility for development of new phenotypes (Chong and Whitelaw 2004).

Dahlgren *et al*. (2001) have shown in rat experiments that prenatal exposure to cytokines TNF-α and IL-6 increased bodyweight of offspring in both genders and produced hyperandrogenicity in females. This suggests that prenatal exposure to cytokines can induce gender-specific programming of hormonal homeostasis, contributing to the development of somatic disorders at adult age. This experimental observation may be relevant for humans as well, where obese mothers produce obese children. (Sewell *et al*. 2006). Boney *et al*. (2005) showed that the risk for later development of MetS was significantly higher in offspring of obese mothers compared to non-obese mothers, (hazard ratio: 1.81, 95% CI 1.03-3.19). This partly explains why obesity and its sequelas are no longer mainly a problem of old age, but increasingly a problem among children and adolescents. The interactions between genes and nutrition and their possible role in foetal development have recently been reviewed by Maloney and Rees (2005).

Some major gene polymorphisms are published in non-Arctic populations in type 2 diabetes, obesity and cardiovascular diseases. Most of those relate to proteins discussed such as PPARγ polymorphism

(Pro12Ala) in diabetes and adiponectin receptor polymorphism in obesity (Minton *et al*. 2006).

Both nutrients and xenobiotics are able to influence the phenotype through effects on gene expressions. However, gene expression is not solely determined by DNA base sequence, but also depends on epigenetic phenomena, defined as gene regulating activities that do not involve a change to the base sequence (i.e. base-pairing is not altered) and which can persist through one or more generations (Pennisi 2001). Therefore inheritance should be considered on a dual level: 1) transmission of genes from one generation to the next in the somatic sense; and 2) epigenetic mechanisms involved in the transmission of alternative states of gene activity (Watson and Goodman, 2002). Epigenetic or metabolic programming occurs when an early stimulus or insult overlaps with the sensitive window of development of specific organs during early phases of life, resulting in a permanent alteration in the physiology and metabolism of target organs (Srinivasan *et al*. 2003). No direct mechanisms for metabolic programming are yet available, but cellular communication mechanisms (extra-, intra-, and gap junctional inter-cellular communication) may play a central role, as reviewed by Trosko *et al*. (1998), as, from the fertilized egg throughout life, they control cellular communication of endogenous and exogenous signals. The cellular communication system allows the organism to adapt to fluctuations in the exogenous signals and, as such, is an important factor for survival in a changing environment. However, prolonged unfavourable signalling may lead to metabolic programming and mal-adaptation, and finally dispose for development of chronic diseases such as MetS, obesity, cardiovascular diseases and probably some types of cancer.

Recent research of foetal programming is based on the observations that environmental changes can reset the developmental path during intrauterine development leading to hyperphagia, obesity, cardiovascular- and metabolic disorders later in life (Breier *et al*. 2001). This has been shown in studies on rats (Srinivasan *et al*. 2003, Harder *et al*. 1998) and epidemiological studies that suggest that foetal under- and over-nourishment induce metabolic programming in humans with development of adult-onset diseases (Barker 1995).

As some xenobiotics, such as methyl mercury and dioxin-like substances are toxic by themselves and interfere with the metabolism of nutrients, it is highly possible that a life-long low-dose exposure, such as that observed as present in parts of the Arctic may induce foetal programming as well; either indirectly as an aggravating factor in interaction with nutrient metabolism, or directly through receptor signalling.

The concept of foetal programming explains the difficulty experienced by obese individuals to loose weight, and highlights the need for early onset of nutrition and life-style advice and for a revision of risk assessment of certain contaminants. Wu and Suzuki (2006) have suggested a new paradigm for prevention of obesity which should be designed on occurrence of epigenetic inheritance and the notion that parental diet may influence lifelong health of the offspring.

CHAPTER 4

THE HISTORICAL DIET IN GREENLAND

Macronutrients

According to analyses of the 15th century Qilaqitoq mummies, using the stable carbon isotope technique, the traditional Inuit diet was dominated by marine animals (98%) and some small amount of berries (Tauber 1989). This means that the diet was very high in proteins, moderately high in fats, and low in carbohydrates. As seen in Figure 2, this pattern still prevailed during the first part of the 20th century. The Inuit have the highest protein content in their diet compared with other indigenous populations in the world (Saunders and Katzenberg 1992). This is consistent with the findings by Cordain *et al*. (2000) that there is a relationship between protein intake and latitude, with increasing protein intake towards the north; the same tendency is seen for fat intake while carbohydrate intake shows the opposite trend (see Fig. 4).

The amount of protein tolerated by the 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:

$$MRUS = 65 \text{ mg N} \times h^{-1} \times \text{kg body weight}^{-0.75}$$

The protein intake that exceeds the MRUS results in hyperammonemia and hyperaminoacidemia. For a 12.5 MJ energy intake the mean maximal dietary protein intake would be 35% of the total energy (range 30-41) (Cordain *et al*. 2000). As seen from Figure 1, the traditional Greenlandic diet came close to this limit, and due to the scarcity of carbohydrate containing food, fat became an indispensable source of energy and consequently was cherished as a delicacy.

In order to avoid protein poisoning the early hunter-gatherer populations had several options. They could 1) increase their plant-animal energy subsistence ratios by eating more plant-food energy; 2) hunt larger animals, because percentage body fat increases with

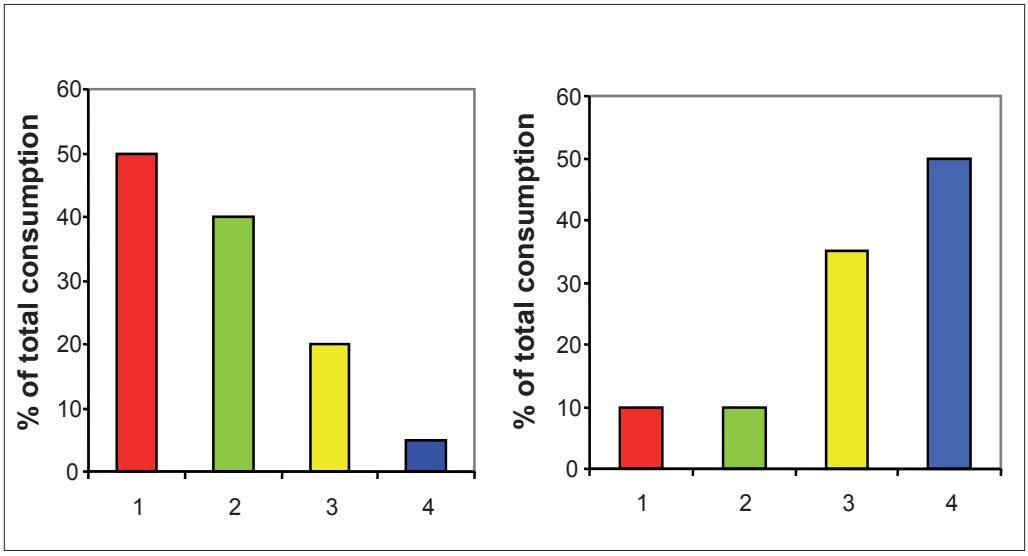

Figure 4. Relative amount (% of total consumption) of plant food (left figure) and marine food (right figure) related to latitude (after Cordain et al. 2000). 1 tropic, 2 subtropic, 3 subarctic, 4 arctic.

increasing body size (Pitts *et al*. 1968); 3) hunt smaller animals during the season in which body fat is maximized; 4) selectively eat only the fattier portions of the carcass and discard the rest; and 5) increase their intake of concentrated sources of carbohydrate, such as honey. In the Inuit case, only options 2 and 4 were applicable. This also explains why large marine mammals and not fish were the prey of choice for the Inuit.

The composition of the marine fat also provides advantages as it contains a low proportion of aetherogenic saturated fatty acids and a high proportion of long-chained polyunsaturated fatty acids, with a n-3/n-6 ratio approaching unity, similar to that in other pre-agricultural populations. This specific quality of the dietary fat is pertinent to several areas of current nutrition-related research, e.g., coronary heart disease (Lands *et al*. 1992, Kang and Leaf 1996), MetS (Giugliano *et al*. 2006), depression (Adams *et al*. 1996, Hibbeln *et al*. 1997, Stoll *et al*. 1999), dystocia (Roy 2003) and autoimmune diseases (Stamp *et al*. 2005).

Another feature of marine fat is the relatively low content of medium-chained fatty acids (e.g., linoleic and α-linolenic acid, which in herbivores are the precursors for the essential long-chained fatty acids. The conversion takes place through the enzymatic action of desaturases (δ-6 and δ-5 desaturases) and elongases. The processes are regulated in a negative feedback system (see Figure 5), in such a way that high concentrations of the long-chained acids inhibit the δ-6 desaturase. This means that the conversion of linoleic acid (18:2, n-6) and linolenic acid (18:3, n-3) to γ-linolenic acid (18:3, n-6) and 18:4, n-3, respectively, is inhibited if there is a high dietary intake of the long-chained acids, which is the case in a diet based on marine food. This has lead to the assumption that Inuit, like carnivore animals, have a genetic deficit in expres-

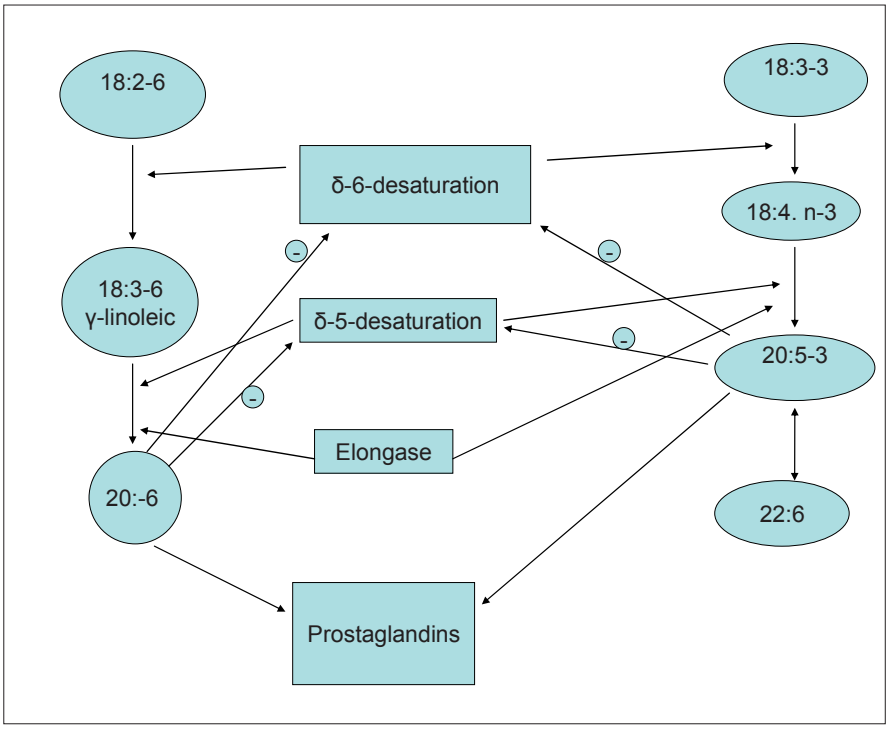

Figure 5. Negative feedback through the enzymatic action of desaturases. Catalysing and inhibitive actions (+ action if not marked on figure).

sion of δ-6-desaturase. However, enzymatic inhibition via the negative feedback system may be a plausible explanation.

The very low intake of carbohydrate in the traditional diet was, with regard to energy, compensated through the high intake of fat. However, there is evidence that an adaptation has taken place to preserve glucose, which now when sugar is available shows up as an impaired glucose tolerance with development of type 2 diabetes and obesity. Asp *et al*. (1975) demonstrated among Greenlanders multiple, but not generalized disaccharidase intolerance, e.g., 79% were found to have low lactase activity.

Micronutrients

The traditional diet will, in most cases, provide an ample supply of most vitamins and minerals needed for optimal human nutrition. Of these minerals, selenium is abundant, especially in muktuk, and in some areas the daily intake reaches a level where adverse effects, such as nail deformations, may be anticipated; however an adaptation to a high selenium levels in populations with a high intake has been suggested. Selenium plays an important role as part of the glutathione-peroxidases, the classic cytosol enzyme GSH-Px and the membrane bound phospholipid-hydroperoxide-glutathione-peroxidase (GPx4). GPx4 is the only known antioxida-

tive enzyme which directly reduces phospholipids hydroperoxides within membranes and lipoproteins, acting in conjunction with α-tocopherol. The expression and activity of the enzyme is modulated in a complex manner by lipids, proinflammatory cytokines and antioxidants. In the presence of adequate selenium, GPx4 may favour protection against potentially atherogenetic processes (Sneddon *et al*. 2003).

Contrary to selenium, the Inuit diet is low in calcium. However, a genetic adaptation to this dietary constraint has been found (Sellers *et al*. 2003), such that there is an increased absorption of calcium in Inuit compared to Caucasian populations. The same genotype has been found in other groups with a low calcium intake, such as the Chinese and Thai people. This also means that, in the event that western nutritional guidelines are applied to Inuit populations, it may result in iatrogenic hypercalciuria and renal damage. A cautious approach to such guidelines, with recognition of genetically distinct target populations, is thus necessary.

CHAPTER 5

CHANGING DIETARY HABITS IN GREENLAND

Traditional Greenlandic diets 1945-1980, composition and nutritional content

About a hundred years ago the Inuit lived almost entirely from local products, mainly marine mammals and fish (Bertelsen 1937; Uhl *et al*. 1955). Their traditional diet was composed of raw, boiled or dried meat, blubber and offal from several seal species (Greenland seal, Bearded seal, Ringed seal), dried meat and skin from baleen and toothed whale species, meat and blubber from Walrus, and Polar bear, a number of marine and freshwater fishes (fresh or dried), and sea birds. In the summertime, the diet was supplemented by leaves, roots and flowers from a number of plant species (e.g., Scurvy grass, Angelica, Sedum and Saxifraga species). In more recent times, the diet of Indigenous People in the circumpolar countries has consisted of both traditional food and imported (market) foods.

During the 20th century, the population of Greenland grew from about 10 000, which was regarded by Helms (1982) as the ecologically sustainable maximum population, to about 55000. This population growth coninncided with the import of more food to Greenland, and the population increase was probably a consequence of this improvement in food availability and sustainability. Population growth and the consumption of imported goods escalated significantly after the Second World War (Helms 1982). Over the course of this time, the dietary composition changed from comprising 75-80% local products and 20-25% imported products to almost the opposite. The changes occurred at different times and rates in different parts of the country, with on one hand hunting capacity and on the other the availability of imported foods as the determining factors.

Several Danish scientists were interested in these developments, and concerned about the dietary changes and possible adverse effects on the population health. On the other hand, there was also awareness that the traditional Greenlandic diet lacked certain vitamins,

e.g., vitamin C. There was also a special concern about high rates of infant mortality, infectious and respiratory diseases, such as tuberculosis, and diseases associated with vitamin deficiencies, such as scorbut and rickets (Uhl *et al*. 1955, Bang *et al*. 1976, Bang *et al*. 1980, Helms 1982, Helms 1987). Thus, several comprehensive population and food studies were undertaken to determine the nutritional content of various dietary compositions, and the possible health consequences of these. Uhl *et al*. (1955) reported on the high incidence of infant mortality in Greenland in 1951, where the mortality due to influenza, measles, and whooping cough were about 30 times the rate in Denmark.

Helms (1982) reported on the changes in disease pattern in Angmassalik, East Greenland, from 1948 to 1979, and compared the mortality and morbidity to Danish statistics. He found that infectious and respiratory diseases in Greenland were much higher than in Denmark, but that they were decreasing during the period of observation. On the other hand, (unspecified) heart diseases were very low but increased during the same period. In fact, the low rate of heart disease became the inspiration for many years of research into the proposed beneficial effects of the high content of n-3 fatty acids in traditional food based upon local marine animals and fish (Bang *et al*. 1976, Bang *et al*. 1980).

During those times the main questions were:

- Was the energy intake sufficient/adequate?
- Was the fat intake adequate/excessive?
- Was the protein intake adequate/excessive?
- Was the intake of key vitamins (A, D, B1, B2, C) sufficient and not toxic (A, D)?
- Was the intake of minerals sufficient (Ca, Fe) and not toxic (Fe, Se)?
- What were the major dietary sources of these nutrients (Uhl *et al*. 1955)?
- What were the health consequences of the special fatty acid composition of the local food (Bang *et al*. 1976, Bang *et al*. 1980)?

In 1953, Uhl and coworkers visited Greenland for approximately one year where they undertook an extensive study of the nutrient content of Greenlandic food items, sea animals, fish, birds, and local plants and berries (Uhl *et al*. 1955). The results were published as tables, and used in connection with three dietary surveys among local families living in the Disko Bay settlements; Ilulissat and Qaqortoq, respectively (see Table 2).

Meats and organs were collected from three species of seal, four species of whale, lamb, three fish species, and parts of four local plant species and analysed for energy, vitamin, and mineral content. In addition, since they were particularly interested in and concerned about the presumed low vitamin C intake, Uhl *et al*. analysed 17 plant species from different geographic locations. They also noted that offal and skin of the locally hunted animals contained vitamin C, particularly if eaten raw. Especially high in vitamin C were livers from seals, birds and fishes, and whale skin/fat (*muktuk*). Finally, they also documented that the fish Capelin was a very good source of Ca, especially when dryed.

Vitamin A is known to be very unevenly distributed in food, but all the analysed local

Table 2. Dietary surveys based upon comprehensive dietary interview or registration for 7-10 day or nutrient analysis of duplicate meals. Percentage of Greenlandic food items from total energy (E).

Population	Study group	n	E %	Local meat g/day	Local fish g/day	EPA[a] g/day	Reference
Disko Bay villages 1953	5 families	18 adults 13 children	54	362	891		Uhl *et al.* 1955
Ilulissat 1953	7 families	25 adults 20 children	25	60	367		Uhl *et al.* 1955
Qaqortoq 1953	4 families	14 adults 19 children	18	23	191		Uhl *et al.* 1955
Uummannaq district village, 1976	Married couples	32	40	430	90	3.0	Deutch *et al.* 2006, 2007
Ammassalik1945	Adults	?	74	500	145	6.3	Helms 1981
Ammassalik 1978	Adults	?	22	202	200	1.3	Helms 1981
Qaanaaq district villages 1987	Adults	63	27	307	45		Helms 1987
Qaanaaq district villages 1987	Children	16	16	150	22		Helms 1987
Uummannaq 2004	Married couples	30	21	66	47	1.3	Deutch *et al.* 2006
Narsaq 2006	Married couples	30	14	33	31	0.6	Deutch *et al.* 2006, 2007

[a]EPA, eicosapentaenoic acid, C20.3, n-3, a marker for marine animals and fishes.

Table 3. Nutrient adequacy of key vitamins and minerals in Greenlandic food with various energy percentages (E%) of local food items in comparison with Nordic Nutrient Recommendations (1996).

Population	E%	A	B1,B2,B6, Niacin	B12	C	D	E	Folic acid	Ca	Fe	Reference
Disko Bay villages 1953	54	+++	+		-	+++			+	+	Uhl *et al.* 1955
Ilulissat 1953	25	+	+		-	+			-	+	Uhl *et al.* 1955
Qaqortoq 1953	18	+++	+		-	+++			-	+	Uhl *et al.* 1955
Uummannaq district village, 1976	40	++	++	++	-	+	+	--	-	++	Deutch *et al.* 2006
Qaanaaq district villages 1987	27	+++	+	+	-	+			+	+	Helms 1987
Uummannaq 2004	21	+	+	++	-		-	-	-	+	Deutch *et al.* 2006, 2007
Narsaq 2006	14	-	+	+	-		-	--	-	+	Deutch *et al.* 2006,

Symbols: -- very low, - below NNR, + adequate, ++ above NNR, +++ very high, (borderline toxic in some individuals). The blank cells indicate missing data.

meats and organs were very high in vitamin A content. Vitamin D was only analysed from the fishes and birds, of which the livers had very high vitamin D content.

Using these results and a 10-day dietary registration they calculated the nutrient intake by 17 families in the three locations mentioned above.

The dietary and nutrient composition was referred to family or household units, which comprised different numbers of children and adults. Although this was a common method at the time, it is therefore difficult to compare with modern studies. We have therefore used the data of Uhl *et al*. (1955) to calculate the nutrient intake per standard energy intake 10 MJ (Table 3).

This calculation showed that, in general, intake of vitamins B1 and B2, and Fe were adequate, vitamin C was very low (12-20 mg), and Ca below recommendations except in one village. However, vitamin A and D intakes were very high (950-9150 and 5-62 micrograms, respectively) and borderline toxic. In addition, since vitamin D was only calculated for some food items, the true intake was probably higher.

Consumption of potatoes, vegetables and fruit was very low, and in the villages practically zero. This means that intakes of vitamin E, beta-carotin, and folate were presumably very low. Of particular interest is the fact that, for one family in one village, the daily energy intake per person during the 10-day registration period was 19.000 kJ, and the diet consisted only of fish- and seal-meat and organs (78%), bread (12%), and sugar (8%). This diet was adequate in vitamins A, B1, B2, D, and Ca and Fe, whereas vitamin C was 25 mg (the third highest in the survey). Vitamin D intake, however, was extremely high and borderline toxic. Helms observations from Ammassalik matched these general tendencies (Helms 1982). He observed that the average daily intake of local meat and fish was 645 grams, whereas the rest of the diet was made up of 104 grams of grain products (mainly bread) and 42 grams of sugar. This pattern has changed markedly since the 1970s. In 1978, Helms found that the intake of local food had decreased to 400 grams, and the intake of imported food increased to 925 grams, now including potatoes, fruit, and some vegetables, but also some meat, eggs and milk products imported from Denmark.

In several expeditions in the 1970s, Bang, Dyerberg and coworkers studied the diet in a hunter community in Uummannaq district (West Greenland). Their main aim was to analyse the fatty acid composition of the traditional diet and its possible relationship to low rates of cardiovascular diseases (Bang *et al*. 1980). In addition, in 1976 they performed dietary interviews and collected 177 duplicate meals from 16 men and 17 women. The duplicate meals were analysed for macronutrients and fatty acid content, and the interview results were used as a basis for micronutrient calculations; the results of this dietary study were not published at the time, but were included in a later retrospective study (Deutch *et al*. 2006). The diet in 1976 in this Uummanaq settlement was adequate in vitamins A, B1, B2, B6, B12, niacin, D, E, and the minerals Fe, Mg, P, Zn, and Se. That is, basically, all nutrients except vitamin C and folate. Vitamin A and D intakes were still very high, but less extreme than in the Disko Bay settlements in 1953 (Uhl *et al*. 1955).

In 2004 and 2006, comparative studies were conducted, using the same method of duplicate portions among similar groups of men and women in Uummannaq and in Narsaq (Deutch et al. 2006). In both cases, the energy (E) and nutrient content of the meals were determined by accredited chemical analysis. The average E of Greenlandic food was 20 and 14 %, respectively, and in the meal samples from both towns the general nutrient content was less than adequate, although there were slight, but still insufficient increases in vitamin C and folate.

All the available retrospective and modern studies show that the traditional food was adequate in most vitamins and minerals if it contained about 20-30 energy percent of local products. As the relative energy percentage from imported food increased, not only the mass but also the variety of local products decreased. In particular, not much heart, liver or other offal was found in the duplicate food portions in the studies in 2004 and 2006. This appears to have resulted in some deleterious effects on the nutritional content of the analysed Greenlandic meals, in particular with respect to vitamin A and Fe. The imported fruit and vegetables, which in principle should supply vitamin C, carotin, vitamin E and folate, were not eaten in high enough quantities to replace the previous sources. In addition, their long shelf-life or other storage problems could make these foods lose important antioxidants.

CHAPTER 6

THE PRESENT DIETARY SITUATION IN GREENLAND (1980-2006)

In common with many other societies, the dietary habits in Greenland are in transition. The direction of this transition is away from the traditional food based upon locally caught animals, birds, and fishes and towards a larger content of 'western' foods consisting of imported items. The imported food is mainly of Danish origin, but also includes various products such as fruits, spices and condiments from other countries. The reasons for the dietary changes may be associated with changing climatic conditions, economic circumstances, cultural changes or the general process of globalization, or most likely a combination of these.

Based upon a countrywide population study with Food Frequency Analysis among randomly selected 20-50 year old men and women (Deutch *et al*. 2004, Deutch *et al*. 2006, Deutch *et al*. 2007a, Deutch *et al*. 2007b) the following more specific results were observed. The mean weight percentage of Greenlandic local food in the diet (liquids excluded) ranged from about 10% among women in Nuuk to 22-25% in Uummannaq (North-West Greenland) and Qaanaaq (North Greenland). This distribution closely follows the intake of marine mammals (see Fig. 6 and 7), and interestingly, also intake of Danish meat which is highest in Qaanaaq. The intake of Greenlandic food is also age dependent; people below 30-years of age only consume about 13% local food, whereas people above 50-years of age consume 25% (see Fig. 8).

Thus, the dietary transition and development is, not surprisingly, occurring fastest in the larger towns and in the southernmost part of Greenland. In these areas the supply of imported goods is more widespread and constant, and associated with better shipping and airfreight access. This again may also reflect a better economic basis for selling and buying these products. According to Greenland Statistics, the average taxable income is highest in Nuuk, Sisimiut, Qaqortoq, and Narsaq (in that order), followed by the Disko Bay area, Uummannaq, Ittoqqortoormiit, Ammassalik and finally Qaanaaq. Thus, higher community average income levels are correlated with

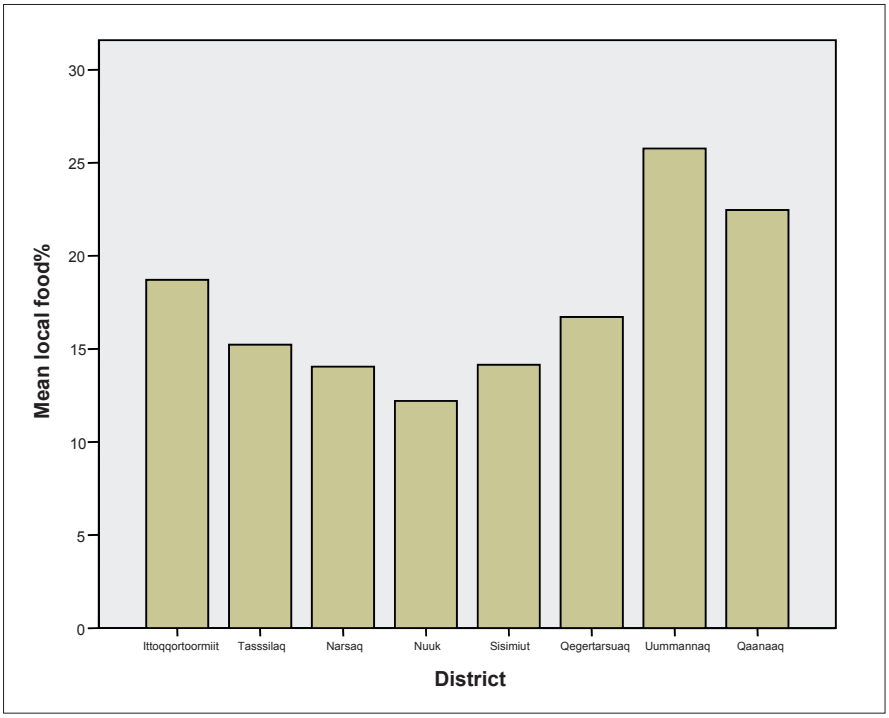

Figure 6. Mean use of local food by district in Greenland. Percent of total energy intake.

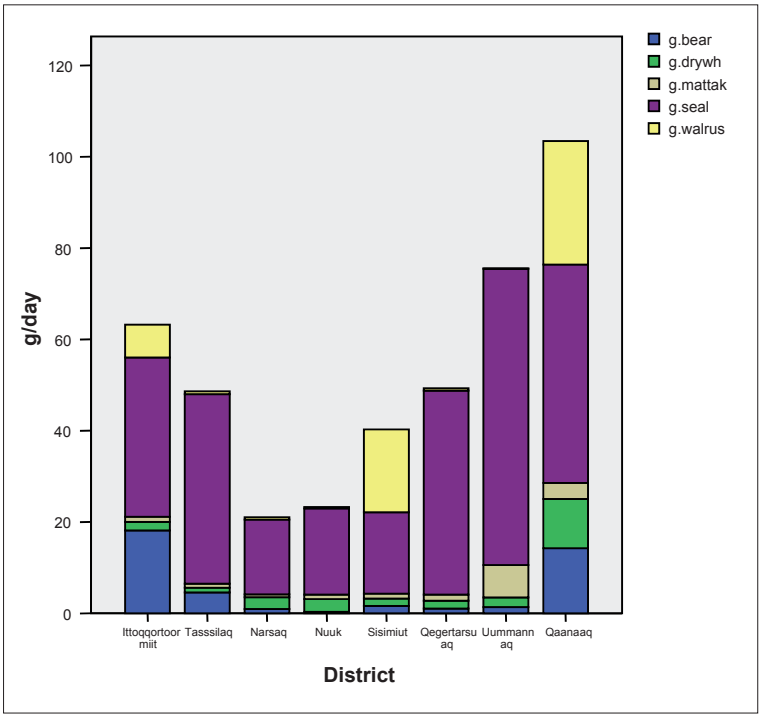

Figure 7. Intake of sea mammals by district in Greenland.

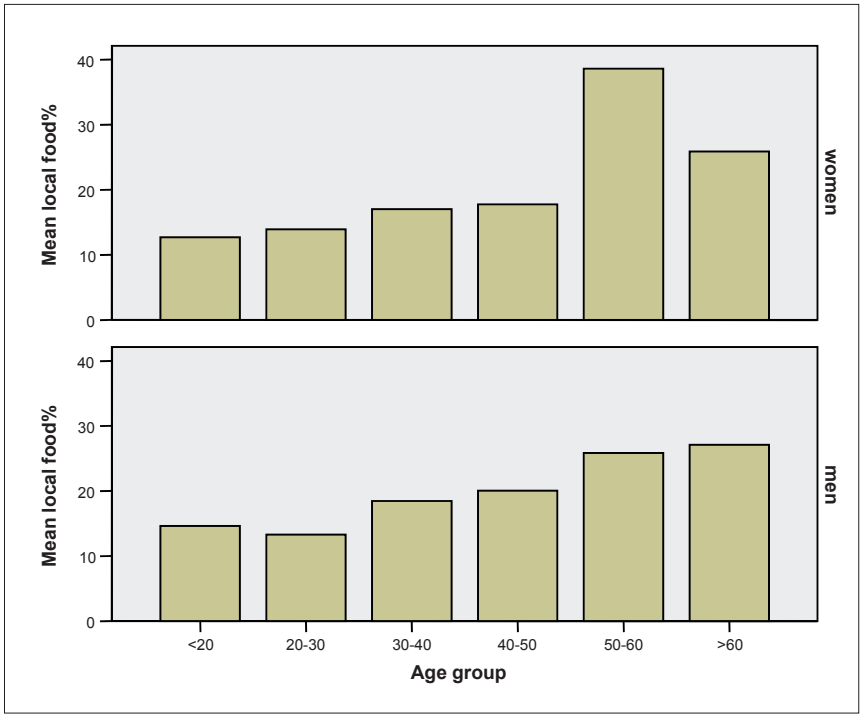

Figure 8. Intake of Greenlandic food by sex and age group. Percent of total food intake.

a broader and more varied food composition, especially reflected by fruits and vegetables (see Fig. 9).

In general, the intake of high protein food items such as meat is high in Greenland. On average, the total intake of meat (from local and Danish sources), amounts to 162 grams/day, compared with 135 grams/day in Denmark. Furthermore, the intake of fish amounts to 56 grams/day vs. 27 grams/day in Denmark. (Andersen *et al*. 1995).

Thus, meat intake does not seem to be limited by price or availability. However, meat intake today is much lower than in the past, having gradually decreased since the Second World War when it was 4-500 grams/day (Helms 1982, Deutch *et al*. 2006, Deutch *et al*. 2007a).

The change in dietary habits is also a matter of cultural influence and personal choice. This can be seen in the fact that especially younger women are the first to adapt to new habits. Younger women have reduced their intake of sea mammals and increased their intake of fish. Their intake of fruit, tomatoes, and assorted vegetables is 50-100% higher than that of men. In the larger towns in the south of Greenland, women's average fruit intake is 200-250 g/day (see Figure 10), which is higher than in Denmark (125 g/day) (Andersen *et al*. 1995). Vegetables are eaten less (mean intake only 38 g/day vs. 84 g/day in Denmark); are not evenly available, and probably also less popular. For example carrots, cabbages, and onions, which have a reasonably long shelf-life, are not eaten regularly. Potato consumption (55 g/day) is almost even throughout the country.

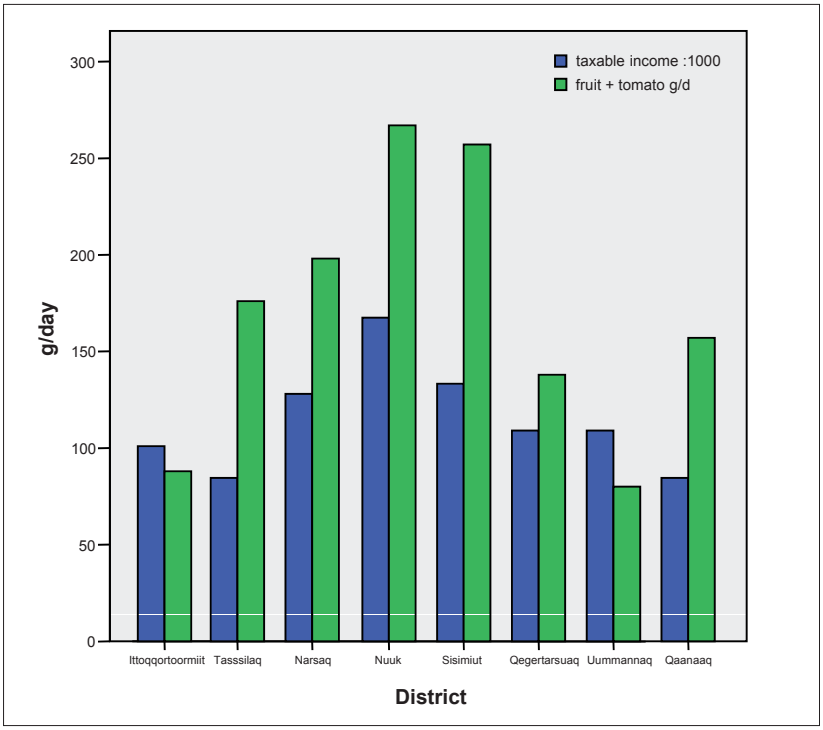

Figure 9. Intake of fruits and vegetables by district in Greenland.

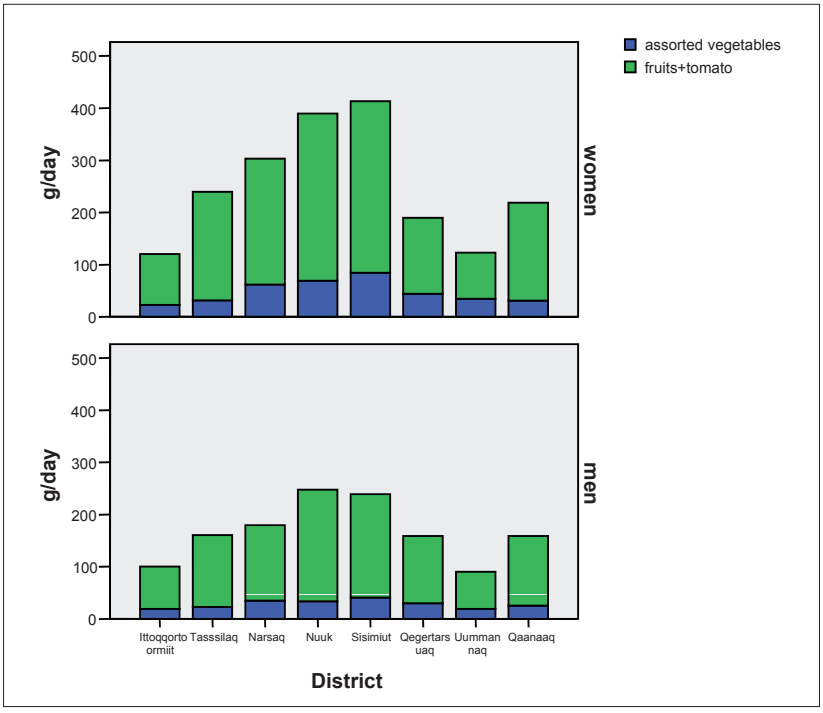

Figure 10. Assorted vegetables and fruit intake (g/day) by district in Greenland.

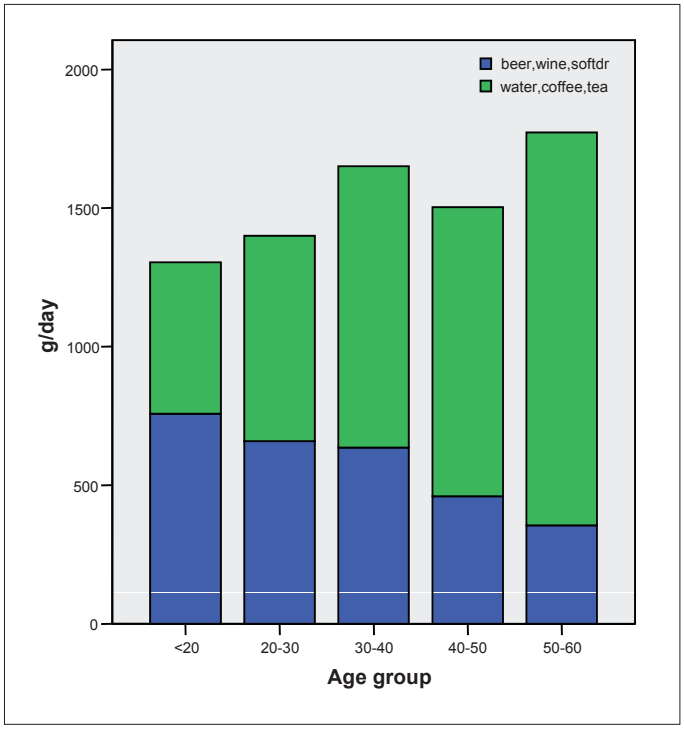

Figure 11. Intake of soft drinks and other liquids (g/day) by age group.

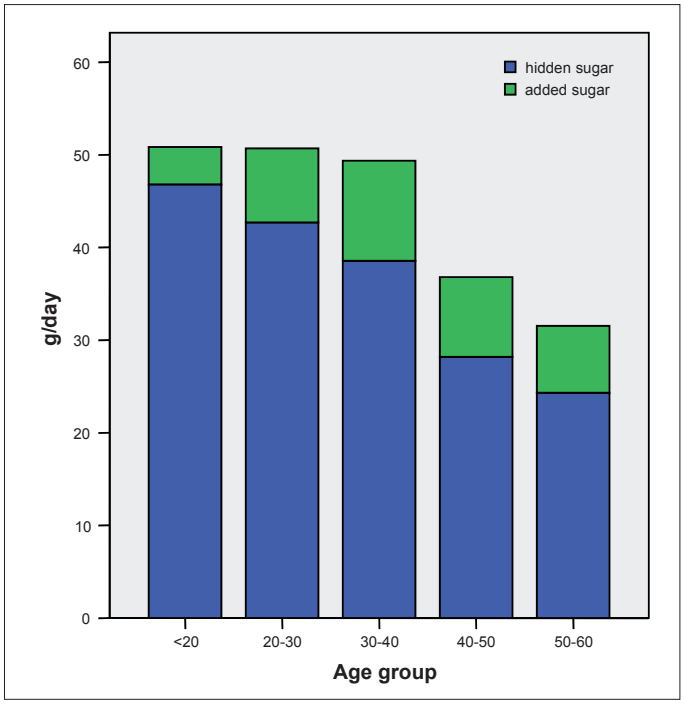

Figure 12. Intake of sugar (g/day) by age group.

As in other parts of the world, men are more conservative in their food choice, but even so, in Nuuk and Sisimiut they are also changing their dietary habits.

From a health point of view, meat, organs and blubber of marine mammals contain valuable nutrients, such as vitamins A, D, and B12, and iron and other minerals, and important fatty acids of the n-3 group, (Deutch *et al*. 2006, 2007a). However, the meat also contains high levels of methylmercury and the blubber high levels of organic pollutants, which introduces a level of caution into consumption levels. Compared to marine mammals, fish and terrestrial mammals do not have the same contaminant levels. From an exposure point of view it would therefore be a healthier choice to reduce, but not eliminate the consumption of marine mammals and increase the consumption of fish, reindeer and local lamb. This choice should not compromise the nutritional value if the versatility of the diet is maintained.

Another health issue in Greenland today is the increasing consumption of carbohydrates, including so-called 'hidden sugars' in candy, chocolate, cakes and especially soft-drinks. The intake of hidden sugars is highest in the poorest areas. In this less healthy transition, the younger part of the population has unfortunately taken the leading role (see Fig. 11 and 12).

During the past 20-30 years in particular, body weight and body mass index (BMI) have increased throughout Greenland, in small settlements as well as towns, resulting in a similar average BMI (27 kg/m^{-2}). The increase in BMI correlates significantly with age and higher income level, and is not statistically related to any particular food composition, whether modern or traditional (Deutch *et al*. 2005). The population survey conducted did not include children or teenagers, groups in which overweight characteristics may be different, and related to high intake of fast food and soft drinks.

Along with the dietary surveys and food analysis it is also important to measure and assess the nutrient status of key population groups using blood levels of nutrients or other biochemical markers. A study by Rejnmark *et al*. (2004) assessed vitamin D status among Greenlanders living on traditional or westen diets, compared to Greenlanders and Danes living in Denmark. They found that Greenlanders on a western diet (in Greenland) had significantly lower plasma 25-hydroxyvitamin D and Ca and significantly higher percentage of vitamin D insufficiency. Milman *et al*. (1992) measured serum ferritin among Greenland Iniut hunters. They found that ferritin increased with percent energy from traditional food, and found a continuous accumulation of large iron stores with age, which is different from results among Caucasians. With this high intake of iron from local meats and high ferritin blood levels it is possible that the Inuit don't require a high intake of vitamin C. One of the functions of vitamin C is to chemically reduce iron and facilitate its absorption. No recent studies have measured vitamin C status among Greenlanders.

In four districts in Greenland, blood mineral content of about 45 elements was measured. Some elements are more interesting than others from a nutritional point of view. Among these, selenium is considered

an essential mineral with antioxidant qualities. Blood levels of selenium are strongly correlated with traditional food intake, with meat from seals, whale, birds and reindeers being good sources. Even with a low percentage of Greenlandic food products in the diet (Nuuk and Narsaq), intakes of Se are more than 100% above the nutritional recommendations. In North and West Greenland, blood levels of selenium are high. About 33% and 12% of the participants, respectively, exceed a blood level of 560 µg/L, which corresponds to the maximum safe intake (Yang *et al*. 1989). The mean blood levels and ranges for Ca, Fe, Mg, and Zn can be considered to be within normal range (Iyengar *et al*. 1978).

Summarizing the dietary composition in Greenland today, the content of local, traditional food items are highest in the northernmost remote districts, where they also have a high intake of imported meats, breads, and sugar, but a low intake of fruits and vegetables, except potatoes. At the other end of the scale lie the larger towns in the south of the country, with lower intake of local marine mammals and Danish meat, higher intake of fish, reindeer, fruit, and vegetables, and lower intake of sugar. This means that, in general, the transition in the Greenland dietary habits is going in a reasonable direction. Especially women seem to take a responsible attitude, implementing a diet with sufficient coverage of vitamins and minerals. However, the quality of some imported fruit and vegetables is inferior, with too low antioxidant content. This is a logistic issue which can be solved. However, it is also important to keep the developments on the right track, especially among the young. A healthy diet is not just a matter of whether to eat traditional Greenlandic vs. 'western' foods; it also depends strongly on the composition of the mixed diet and the quality of the imported products. More important still is the need to follow the health of the population using sentinel markers for potential deficiencies and diseases.

CHAPTER 7

METABOLIC DISORDERS

Globalization, dietary and cultural transition has lead to an increasing prevalence of lifestyle induced metabolic disorders. Obesity and its co-morbid conditions, MetS, type 2 diabetes, and cardiovascular diseases have, during the latest 3 decennia, developed into pandemic proportions, also among the Indigenous peoples of the Arctic (Jørgensen *et al*. 2004). The general belief has been that this is caused by hypercaloric intake of nutritionally unbalanced diets in connection with an increasing sedentary lifestyle. The severity of this problem is underlined by the recognition that it is not only a question of individual lifestyle factors, but also that the risk to develop obesity and later MetS can be transferred from mothers to their babies by an epigenetic way (foetal programming).

Table 4. Criteria for clinical diagnosis of MetS (IDF 2005).

	Categorical cut points
Waist circumference	a) ≥90 cm in men , ≥80 in women b) ≥94 cm in men, 80 in women
Plus any two of the following:	
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglycerides
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or on drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥6.0 mmol/L or on drug treatment for elevated glucose

a) Asian and South and Central America b) others

There are several definitions of the MetS (WHO, EGIR (European Group for the Study of Insulin Resistance), ATPIII (the US National Cholesterol Education Program) and IDF (International Diabetes Federation). As the criteria in the various definitions deviate the estimated prevalences will also vary. This has recently been described by Cameron *et al*. (2007). In table 4 we demonstrate the IDF definition, as this allow for differences in waist circumference cut points between populations of different ethnicity, and consequently may be of highest relevance in studies of the Arctic.

Metabolic disorders and obesity

The classical view of adipose tissue as being mainly a storage organ for excess energy in the form of triglycerides has changed dramatically during the past 10 years. Today, it is clearly established that adipose tissue is a multifunctional organ that produces and secretes a large number of active substances, which act either in an auto/paracrine or an endocrine fashion (Hauner 2004). From this a new concept has arisen that adipose tissue is an active participant in an integrated network that maintains an intensive communication between various organs.

To date, more than 100 components called adipokines have been described to be produced and released by adipose tissue. However, the functional significance of most of the products is unknown or rather vague. Among the known are aromatase, steroid hormones, prostaglandins, TNF-α, angiotensin II, interleukins (IL-1β, IL-6, IL-8), inducible nitrogen-oxyde-synthetase (iNOS), leptin, and adiponectin (Goldfine and Kahn 2003). Some of the compo-

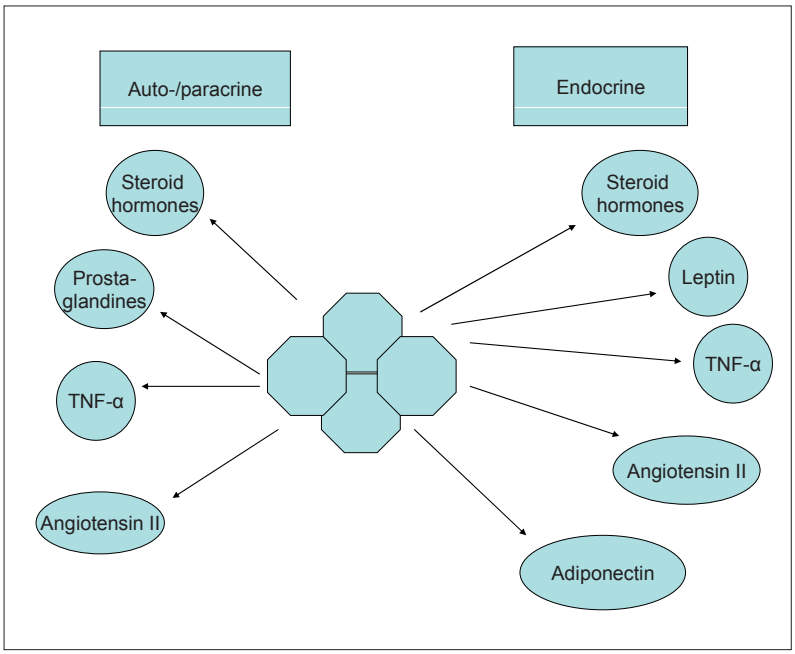

Figure 13. Secretory factors from adipose tissue.

nents are produced by the adipocytes others by pre-adipocytes or macrophages. These secretory products allow the adipocyte an important feedback role in the regulation of appetite, energy expenditure, development of insulin resistance, and to participate in the atherogenetic processes (Ahima and Flier 2000, Mora and Pessin 2002). The adipose tissue provides two hormones essential for normal insulin sensitivity: leptin and adiponectin (see Fig. 13).

Leptin is secreted predominantly by the adipose tissue and is a signal of sufficiency of energy. It decreases food intake and increases energy expenditure. Under normal conditions of weight maintenance, plasma leptin concentrations are positively correlated with total body mass. Reduction of body weight results in decreased leptin levels which again stimulates weight gain (Korner and Leibel 2003). In obesity, plasma leptin concentrations are increased and as exogenous administration has no effect on body weight (Kershaw and Flier 2004), this phenomenon has consequently been called leptin resistance (Meier and Gressner 2004). In addition, soluble leptin receptor concentrations, and hence the fraction of bound leptin are low in obesity, this is independently associated with abdominal obesity and insulin resistance. Soluble leptin receptors are thought to be of importance for transport to the brain, therefore in obese individuals the brain concentration of leptin is relatively low (Meier and Gressner 2004), and the neuroendocrine energy control regulated by the hypothalamus is consequently impaired.

Adiponectin, a novel adipose-specific protein, has recently attracted great interest as it is found to have insulin-sensitizing (Yamaushi *et al*. 2002) and anti-atherogenic actions (Kubota *et al*. 2002). Adiponectin is expressed by activation of PPAR-γ in concert with another responsive orphan nuclear receptor, liver receptor homolog-1 (LHR-1), also expressed in adipocytes, as LHR-1 augments PPAR-γ-induced transactivation of adiponectin promoter (Iwaki et al 2003) (see Fig. 1). As PPAR-γ down-regulates the expression of other adipokines such as TNF-α, PPAR-γ ligands promote the balance of these substances to enhance insulin-mediated glucose uptake and decrease inflammation and as such reverse the major defects of the (Hsueh and Law, 2003).

In humans, plasma adiponectine concentration exceeds those of any other hormones by a thousand times. Unlike other adipokines it decreases with increasing obesity and is positively associated with whole-body insulin sensitivity. Therefore, a low plasma concentration, hypoadiponectinemia, appears to be an important factor in the development of MetS (Stefan and Stumvoll 2002). Gilardini *et al*. (2006) found in Italian obese children and adolescents that hypoadiponectinemia was independently associated with MetS risk and conclude that adiponectin is the best predictor of MetS, and thus of higher cardiovascular disease risk. The strong association of adiponectin serum concentrations with obesity and metabolic parameters in children indicates epidemiological and pathophysiological relevance already in childhood (Böttner *et al*. 2004). Furthermore, there is increasing evidence that genetic variants in the adiponectin gene itself and/or in genes encoding adiponectin-regulatory proteins, such as PPAR-γ, may be associated with hypoadiponectinemia, insulin resistance and type 2 diabetes. Kadowaki *et al*. (2003) report

that more than 40% of the Japanese population has a genotype that increased the susceptibility to genetically decreased adiponectin. This is a much higher proportion than that found in Caucasians, and means that Japanese may be more prone to diabetes under a westernised life-style. Whether the same pattern of polymorphism is also found in other populations, such as the Inuit, is not known. This issue should be investigated to evaluate a possible genetic background for the rapid increase in BMI and prevalence of diabetes in indigenous populations under dietary transition.

There exists a sexual dimorphism in lipid metabolism resulting in a sex specific distribution of fat. Compared with women, men accumulate a considerably greater proportion of fat in the abdomen, whereas in women a greater percentage is accumulated in the subcutaneous tissue, leading to android and the gynoid fat distribution patterns, respectively. The reason for this dimorphism is largely unknown (Mittendorfer 2005). It may, however, be related to the observations that in healthy lean boys, adiponectin levels significantly decrease, parallel with pubertal development and increased production of androgens leading to reduced adiponectin levels in adolescent boys compared to girls (Böttner *et al*. 2004). In Japanese obese children, the adiponectin level was correlated inversely with visceral adipose tissue area. This correlation was significant after adjustment for percentage overweight, percentage body fat and gender (Asayama *et al*. 2003). The gender differences in adiponectin levels and its relation to visceral fat may explain why men have an increased tendency to accumulate visceral fat compared to women.

Under normal physiological condition the production of the compounds, produced in the adipose tissue, secure a balanced metabolism. However, in obesity the number of macrophages increases in adipose tissue (Xu *et al*. 2003, Weisberg *et al*. 2003), especially in the intra-abdominal fat, which contains more blood vessels and sympathetic nerve fibres than subcutaneous fat, indicating a greater metabolic activity (Bornstein *et al*. 2000). Weisberg *et al*. (2003) found a macrophage percentage below 10% in lean and 40% in obese humans, respectively. This is probably a result of conversion of preadipocytes into macrophages in obese individuals (Charriere *et al*. 2003). The strong relationship between adiposity and the content of macrophages provides a mechanism for the increased production of proinflammatory molecules and acute-phase proteins associated with obesity. Thus, obesity leads to a misbalance in the production of active components in adipose tissue which is the link to development of the MetS, type 2 diabetes and cardiovascular disease. As the android type of obesity is more active than the gynoid, men are at greater risk than women for development of these diseases.

Activated macrophages release cytokines and biological active molecules such as NO, TNF-α, IL-6, and IL-1 (Gordon 1998). These molecules are produced in direct proportion to adiposity (Weisberg *et al*. 2003) and have been suggested to be implicated in the development of the pathophysiological conditions associated with obesity (Sartipy and Loskutoff 2003, Pickup and Crook 1998). Obesity can thus be characterised as a state of chronic low-level inflammation (Wellen and Hotamisligil 2005). The way the macrophages are

activated is not fully understood, but studies have indicated that obesity related down-regulation of adiponectin (Hotta *et al*. 2000), up-regulation of leptin (O´Rourke *et al*. 2002), complement factor C3, the precursor of C3a (a potent activator of macrophages) (Koistinen *et al*. 2001) and MCP-1 (monocyte chemoattractant protein), an essential signal for macrophage activation (Huang *et al*. 2001, Dahlman *et al*. 2005) could all be involved. Suganami *et al*. (2005) have suggested a paracrine loop between adipocytes and macrophages as macrophage derived TNF-α increases the release of free fatty acids (FFA) from adipocytes. This in turn augments the inflammatory response in macrophages, thereby leading to increased production of TNF-α. They also found that the effect on macrophages was initiated by saturated fatty acids while PUFAs did not. Saturated fatty acids induce inflammatory markers in macrophages through the activation of toll-like receptors which are preferentially inhibited by PUFAs of the n-3 family, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Lee *et al*. 2003). This is in accordance with the concept of an anti-inflammatory effect of n-3 fatty acids. Metabolism of fatty acids is visualized in Figure 14.

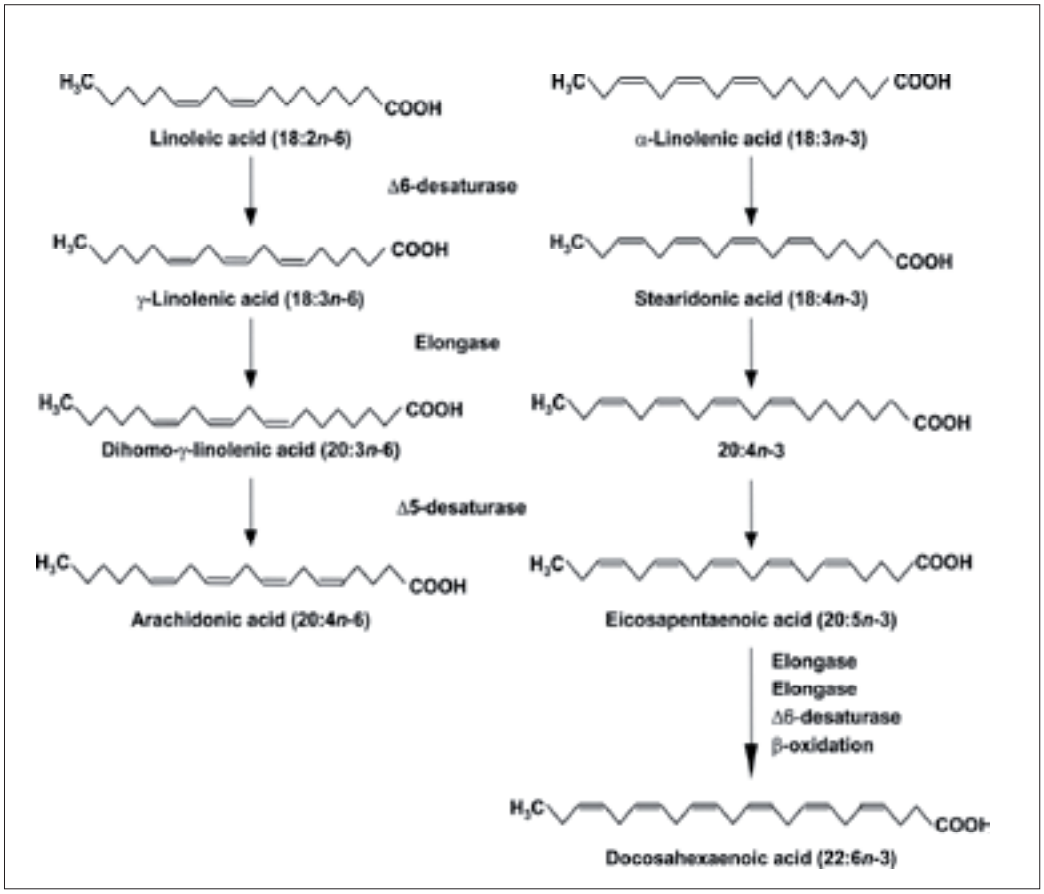

Figure 14. Metabolism of fatty acids.

There may be several signalling pathways involved in the induction of inflammatory changes in adipocytes and macrophages. Thus, Suganami *et al*. (2005) reported that inhibition of MAP kinase significantly abolished the inflammatory changes, and speculated that TNF-α activation of MAP-kinase in adipocytes and macrophages within the adipose tissue may contribute to the pathogenesis of obesity itself and MetS. With increasing BMI, this condition develops to a systemic inflammation as seen in the MetS, type 2 diabetes and in cardiovascular disease (Berg and Scherer 2005). TNF-α is highly expressed, not only in adipose tissue but also in skeletal muscles of rodents with diet-induced insulin resistance (Borst and Conover 2005). TNF-α seems to play a crucial role in development of insulin resistance, as it has been shown that neutralization of TNF-α reverses insulin resistance in skeletal muscle but not in adipose tissue (Borst *et al*. 2004). Skeletal muscle is primarily responsible for the removal of glucose, which is almost exclusively stored as glycogen. If TNF-α of adipose origin would cause the systemic effect, a significant increase in circulating TNF-α is to be expected. However, this is observed neither in rodents (Borst and Bagby 2002, Borst and Bagby 2004) nor in humans (Kern *et al*. 2001). The link between adipose and muscular expression of TNF-α is not fully understood, but might be mediated by circulating adipokines, e.g., MCP-1, so far the only known chemokine produced by adipocytes that is secreted into the extracellular space (Dahlman *et al*. 2005). Circulating levels of chemokine MCP-1 have been found to be elevated in diet-induced obese mice (Chen *et al*. 2005) and to be positively correlated with BMI in humans (Christiansen *et al*. 2005). Initially circulating MCP-1 may attract monocytes to fatty tissue surrounding muscles, where they are transformed to activated macrophages, which in turn, in a paracrine loop induce myocytes to produce TNF-α, as suggested by Borst *et al*. (2004). TNF-α induced insulin resistance is followed by hyper-insulinemia, which in turn down-regulates the hepatic production of sex hormone binding globulin, SHBG (Haffner *et al*. 1988, Nestler *et al*. 1991). Plasma levels of SHBG have been suggested as a predictor of MetS (Hajamor *et al*. 2003). This is supported by Bataille *et al*. (2005) who found SHBG to be a determinant of the serum lipid profile, as it correlates negatively with TG and positively with HDL. Cikim *et al*. (2004) concluded from a study on obese, but otherwise healthy pre-menopausal women that a low SHGB may indicate a severe degree of insulin resistance.

A major role for SHBG is the binding of free endogenous sex hormones, and thus regulation of the availability of biological active free testosterone and estradiol and their metabolic clearance rate (Rosner 1991). However, the sex hormones are more than reproductive hormones. Thus, estradiol (E2) is known, at physiological levels, to modulate insulin sensitivity, as it through the estrogen receptor alpha (ER- α) activates the glucose transporter GLUT4, and thus facilitates glucose uptake in skeletal muscles (Barros *et al*. 2006). However, a high level of E2 induces insulin resistance, probably by activation of the ER-β receptor (Garcia-Arencibia *et al*. 2005) which, contrary to ER-α, induces insulin resistance (Barros *et al*. 2006). ER-β requires approximately five- to tenfold greater concentrations of E2 than ER-α for maximal transcriptional activity to occur (Pettersson and Gustafsson 2001).

The influence of androgens on metabolic disorders has been debated. However, a number of studies indicate that androgens also have an influence. In men, a negative correlation between testosterone level and serum glucose, triglyceride, and BMI is described by Dunajska *et al*. (2004). They concluded that a low testosterone/estradiol ratio may be involved in the pathogenesis of coronary atherosclerosis in men. Several studies have demonstrated an inverse correlation between total- and free testosterone and insulin levels in men (reviewed by Kapoor *et al*. 2005) and with adiponectin levels (Böttner *et al*. 2004). Aging *per se* results in decreased bioavailable testosterone levels in men, and aging is also associated with an increased prevalence of type 2 diabetes (Kapoor *et al*. 2005).

In postmenopausal diabetic women Korytkowski *et al*. (2005) found evidence of androgen excess compared to non-diabetics and suggest a role of androgens in development of cardiovascular risk profile. Earlier studies found increased serum levels of estrone and estradiol in obese men (Schneider *et al*. 1979). This may contribute to the insulin resistance in obese men, as observed by Phillips *et al*. (2003), this is supported by the fact that both total and free testosterone correlated inversely with insulin levels, that the estradiol/testosterone ratio was positively correlated with insulin levels, and that E2 correlates positively with TG in men (Bataille *et al*. 2005).

In postmenopausal women hyperandrogenism is related to MetS. This is also the case in premenopausal women with polycystic ovary syndrome (PCOS) (Golden *et al*. 2004). Premenopausal women with type 2 diabetes also seem to have biochemical and clinical hyperandrogenism when compared with non-diabetic controls, and PCOS is more prevalent in diabetic women compared with non-diabetics (Tok *et al*. 2004). The estrogen/androgen balance is determined by the enzyme aromatase (P450arom, CYP-19) responsible for the irreversible conversion of C-19 androgens to C-18 estrogens in men and women. McTernan *et al*. (2000, 2002) demonstrated intrinsic gender differences in the regulation of aromatase which may explain the male hyperestrogenic and the female hyperandrogenic metabolic pattern in relation to obesity and obesity related diseases.

There seems to be an important link between sex hormone balance and MetS. Obese individuals have a higher level of oxidative stress compared to non-obese persons. This has been demonstrated both in women (Davi *et al*. 2002) and men (Urakawa *et al*. 2003). Ceriello and Motz (2004) indicate oxidative stress and inflammation as a key for development of metabolic disorders. This has been further substantiated experimentally by Houstis *et al*. (2006). The causal web for development of MetS and its co-morbidities are shown in Figure 27.

Influence of nutrients

Recent studies have demonstrated that very low-carbohydrate diets are equal to or even more efficient than low-fat diets in obtaining weight loss (Sondike *et al*. 2003, Samaha *et al*. 2003, Brehm *et al*. 2003, Noakes *et al*. 2006). However, the type of dietary fat consumed has substantially different effects on lipoproteins. Saturated fat raises serum cholesterol and the relative content of plasma saturated fatty acids

(SFA) is associated with features of the MetS independently of body fat mass (Klein-Platat *et al*. 2005). In contrast, PUFAs, and in particular n-3 PUFAs, raise HDL cholesterol, lower TG and have favourable effects on insulin resistance and inflammation (Samaha 2005). This indicates that the quality of dietary fat is more important than the energy % of total fat.

Fats

The three categories of fat: saturated (SAT), monounsaturated (MONO), and polyunsaturated (PUFA) act differently in the metabolism. The polyunsaturated fats of both families; n-6 and n-3 are essential, as the precursor molecules for the long-chained metabolites; linoleic acid (18:2, n-6) or α-linolenic acid (18:3, n-3), which cannot be synthesized in the human body.

PUFAs and a subset of their eicosanoid metabolites serve as ligands for a key metabolic regulating system; the PPARs. The PPARs belong to the nuclear steroid hormone receptor superfamily. To date, three related PPAR iso-types have been identified: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-α is highly expressed in liver, heart, kidneys, and skeletal muscle. PPAR-γ is primarily expressed in adipose tissue, while PPAR-β/δ is expressed ubiquitously. In skeletal muscle PPAR-α is most abundant. Activation of all three types has an anti-inflammatory effect (see Fig. 1).

PPAR-α activation primarily induces β-oxidation of fatty acids and, as such, lowers serum triglyceride. Consequently synthetic agonists (fibrates) are used to treat dyslipidemia. PPAR-β/δ also induces β-oxidation in skeletal muscle (Tanaka *et al*. 2003). So far, no synthetic agonist has been developed. PPAR-γ regulates cell differentiation and lipid storage. Beside this it regulates glucose homeostasis. Synthetic agonists (rosiglitazone and others) are used to treat type 2 diabetes (for a comprehensive review of the PPAR system see Li and Palinski 2006).

The ability to regulate fatty acid pools is essential for normal metabolic homeostasis. Thus, the overall balance between fatty acid catabolism (PPAR-α, and PPAR-β/δ) and storage (PPAR-γ) may be regulated by the relative levels of endogenous ligands. The PPARs appear to be much more promiscuous in their interaction with ligands than other members of the nuclear receptor family. *In vitro* assays have not resulted in identification of the most important ligands *in vivo*. They may not be determined simply through a single high-affinity ligand, but may instead be a function of the sum concentration of a variety of free fatty acids and their metabolites that interact with the receptors.

Both synthetic PPAR-α agonists and dietary intake of n-3 fatty acids produces a decrease in serum triglyceride concentrations. It seems appropriate to speculate that n-3 fatty acids, when abundant, serve as effective agonists for PPAR-α. This has experimentally been supported by Sekiya *et al*. (2003) who found that n-3 fatty acids, both in wild-type and in ob/ob mice induced mRNA of PPAR-α. They also found that fish oil has a more potent effect than EPA (eicosapentaenoic acid: 20:5, n-3) alone, and concluded that n-3 fatty acids ameliorate obesity-associated symptoms in ob/ob mice through activation of PPAR-α. PPAR-α in turn down-regulate sterol-regulatory element binding protein (SREBP-1c), a key regulator of fatty acid and triglyceride synthesis (Osborne 2000)

through promotion of free fatty acid synthetase (FAS), the key enzyme in *de novo* lipogenesis (DNL). Contrary to PPAR-α, PPAR-γ, one of the master regulators of adipocyte differentiation, up-regulates SREBP-1. Up- regulation of PPAR-γ will thus favour *de novo* lipogenesis. (Schadinger *et al*. 2005).

Experimentally, both *in vitro* and *in vivo*, it has been shown that arachidonic acid (AA), the precursor for prostacycline is adipogenic. Prostacyclin acts through a series of ligand-receptor reactions which leads to activation of PPAR-γ2, the master gene of terminal differentiation of preadipocytes to adipocytes (adipogenesis). This is not the case for eicosapentaenoic acid (EPA) and docosahexaenoic Acid (DHA) (Massiera *et al*. 2003, Massiera *et al*. 2006).

As the content of linolenic acid (18:2, n-6) in breast milk has increased in US women from 6-7% of total fat in the early 1950s to 15-16% in the mid-1990s (Ailhaud and Guesnet 2004) it has been suggested that the increased dietary intake of n-6 polyunsaturated fat is an important factor for the increasing childhood obesity (Massiera *et al*. 2003, Massiera *et al*. 2006).

Several studies have shown that different types of fat have different immunomodulating effects, either pro- or anti-inflammatory effects. Ajuvon and Spurlock (2005) showed (*ex vivo*) that the saturated fatty acid palmitate, but not laureate, activate pro-inflammatory pathways both in myotubes and in adipocytes and induce expression of TNF-α and IL-6. This is in agreement with the observation by Suganami *et al*. (2005) who found that saturated, but not unsaturated fatty acids induced TNF-α in macrophages.

The association of physiological levels of PUFA's with pro- and anti-inflammatory markers has been described by Ferrucci *et al*. (2005) in a community-based study in Tuscany, Italy comprising 1123 persons aged 20-98 years. This study concluded that both n-6 and n-3 fatty acids were independently associated with low levels of pro-inflammatory markers (IL-6, IL-Ira, TNF-α, and CRP) and with higher levels of anti-inflammatory markers (sIL-6, IL-10, and TGF-β) being independent of confounders. Interestingly, they also noted that the immunomodulatory effect of PUFA's is influenced by the n-3/n-6 ratio, which gave the strongest correlate to IL-10, and TGF-β. This may explain the importance of the n-3/n-6 ratio (Wijendran and Hayes 2004) as it is experimentally (*ex vivo*) shown that linoleic acid (18:2 n-6) can generate oxidative species that can trigger oxidative stress-sensitive pro-inflammatory signalling pathways (Hennig *et al*. 2002), while n-3 fatty acids have an anti-inflammatory effect (see Table 5 for overview).

Table 5. Dietary fat effects.

		PUFA[a]	Sat	Mono
	n-6	n-3		
Essentiality	+	+	-	-
Adipogenic effect	+	-	+	(+)?
Proinflammatory effect	+	-	+	-
CNS development and function	+(AA)	+(DHA)	-	-

[a]PUFA=polyunsaturated fatty acids

In a study by Pischon *et al*. (2003) it was also shown that dietary intake n-3 and n-6 fatty acids in American men and women were inversely associated with plasma levels of sTNF-α receptors 1 and 2. These observations are important as they show that physiological levels of fatty acids are able to modulate inflammation, and further that the composition of dietary fat can influence the pathological sequels of obesity. It also indicates that the type of dietary fat is more important than the energy percentage of dietary fat. Klein-Platat *et al*. (2005) have shown that normal-weigh adolescents had lower SFAs and higher DHA in plasma phospholipids and cholesterol esters compared with overweight adolescents.

A sequel of obesity, in particular the central obesity, is hypertension which is a diagnostic criterion for the diagnosis of MetS. The link between obesity and hypertension is at the moment not fully understood. Recently Mukherjee *et al*. (2006) have suggested adipocyte secreted leptin as a link. However, this is not supported by a study by Almeida-Pititto *et al*. (2006), who concluded that waist circumference is a better determinant for central obesity related hypertension than BMI. Li *et al*. (2005) have suggested hypertension also to be an inflammatory disease. There is also evidence that PUFAs influence the hormonal balance, as it has been shown that the arachidonic acid (AA) derived eicosanoid PGE2 stimulate the activity of aromatase (CYP-19) (Noble *et al*. 1997), which converts 19-steroids to estrogens. The analogue PGE3, a product of eicosapentaenoic acid, does not activate CYP 19 (Larsson *et al*. 2004). The formation of eicosanoids is visualized in Figure 15.

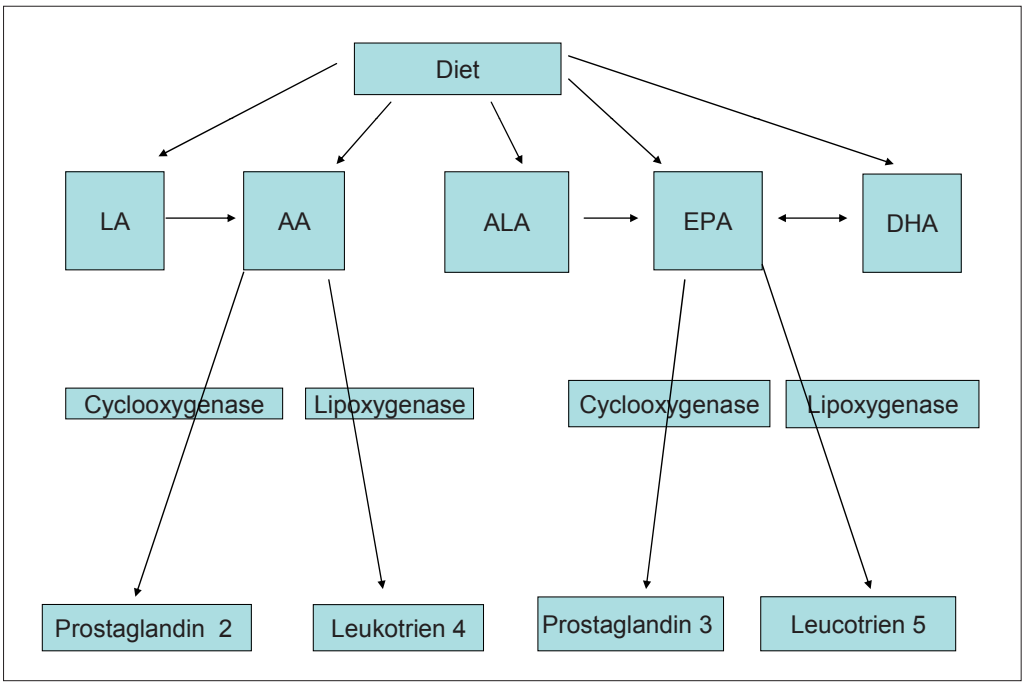

Figure 15. Formation of eicosanoids.

Dietary Guidelines for Americans released in 2005, recommended that less than 10% of the daily energy intake come from saturated fat, and 20-35% from total fat. The minimum for small children is 30% and 25% for children >4 years, respectively. This is an increase in total fat from previous recommendations.

Carbohydrates

In order to prevent metabolic disorders, it is recommended to reduce intake of refined carbohydrates with a high glycemic index (GI), to avoid easily absorbed, high energy sugars, such as glucose. The glycemic index is a measure of individual nutrients to induce glucose load compared to glucose itself (Gl for glucose =100). The glycemic load is the G1 multiplied by the amount of nutrient eaten daily.

The question weather or not glucose can be transformed to fat in the human body through *de novo* lipogenesis (DNL) has been controversial, primarily due to lack of appropriate methods to measure DNL. As a consequence of this, DNL has been largely neglected until recently. Schwartz *et al*. (2003) showed that obese individuals with hyperinsulinemia had significantly higher DNL than normoinsulinemic lean subjects on the same diet. They also demonstrated that lean subjects on a high carbohydrate diet had a significantly higher DNL than normoinsulinemic lean subjects on a high fat diet. This was found to be mainly due to content of refined sugars in the high carbohydrate diet. Finally, they found that when the refined sugars were below 40% of the total carbohydrate energy the DNL was minimal.

Fatty acid synthethase (FAS) is the central enzyme in DNL (Wang *et al*. 2004) and its gene transcription in humans is increased by insulin (Claycombe *et al*. 1998). For this reason hyperinsulinemic subjects will have a higher DNL than normoinsulinemic subjects. PUFA, especially of the n-3 family, attenuates FAS expression and as such, lipogenesis (Kim et al 2003).

Apart from glucose, another simple sugar, fructose, is supplied from the diet. It originates from fresh fruit and from sucrose (a disaccharide consisting of one molecule of glucose and one molecule of fructose). Historically, the daily intake of fructose is estimated at 16-20 grams per day. This physiological intake seems to be advantageous as it improves glucose homeostasis (Vaisman *et al*. 2006). Industrialisation of food production during the last century has, however, resulted in significant increases in added fructose (from corn syrup which can contain up to 90% fructose) leading to a daily consumption amounting to 85-100 grams per day (Basciano *et al*. 2005).

Gross *et al*. (2004) examined the correlation between consumption of refined carbohydrates and the prevalence of type 2 diabetes in the United States. They concluded that increasing intakes of refined sugar (corn syrup) concomitant with decreasing intakes of fibres parallelled the observed upward trend in the prevalence of type 2 diabetes.

Faeh *et al*. (2005) showed in a human study that a high fructose diet significantly increased fasting glucose (7%), triglycerides (79%), and DNL (600%). Supplements of fish oil partly reversed the dyslipidemia, but had no influence on insulin resistance. Unlike glucose, which is widely utilized by tissues throughout the body, the metabolism of fruc-

tose takes primarily place in the liver. Exposure to large quantities leads to simulation of lipogenesis and TG accumulation, which in turn contributes to reduced insulin sensitivity and hepatic insulin resistance/glucose intolerance (Basciano *et al*. 2005). In an *in vivo* study in rats, Nakagawa *et al*. (2006) compared diets with 60% glucose and 60% fructose, and found that only the fructose fed rats developed hyperuricemia, hypertriglyceridemia, and hyperinsulinemia. Based on this observation it was suggested that uric acid has a causal role in fructose induced MetS in rats, due to the observation that allopurinol, a xanthine oxidase inhibitor lowering serum uric acid, was able to both prevent and reverse features of MetS in fructose fed rats (see Fig. 16).

Nagai *et al*. (2002) have, in animal experiments, shown that fructose induced hyperglyceridemia reduces the hepatic expression of PPAR-α which down-regulated the expression of fatty acid oxidation enzymes, which again lead to an up regulation of sterol regulatory element binding protein (SREBP) (Yoshikawa *et al*. 2003, Nagai *et al*. 2002). SREBP is a key transcription factor responsible for regulating fatty acid and cholesterol biosynthesis. Also, in humans, increased uric acid levels are linked to obesity, dyslipidemia, hypertension and insulin resistance, all of which are related to cardiovascular disease (Nakamura *et al*. 1994). Matsubara *et al*. (2002) described that serum leptin was the significant independent variable for uric acid values, which indicates an independent relationship between leptin and uric acid and supports the concept that both are causally involved in the pathogenesis of the MetS. However, Bedir *et al*. (2003) suggested that leptin might be a regulator of serum uric acid concentrations in humans as they found that the serum leptin level was independently accociated with uric acid in both sexes, but only in overweight or obese individuals. Contrary to leptin there was a reverse rela-

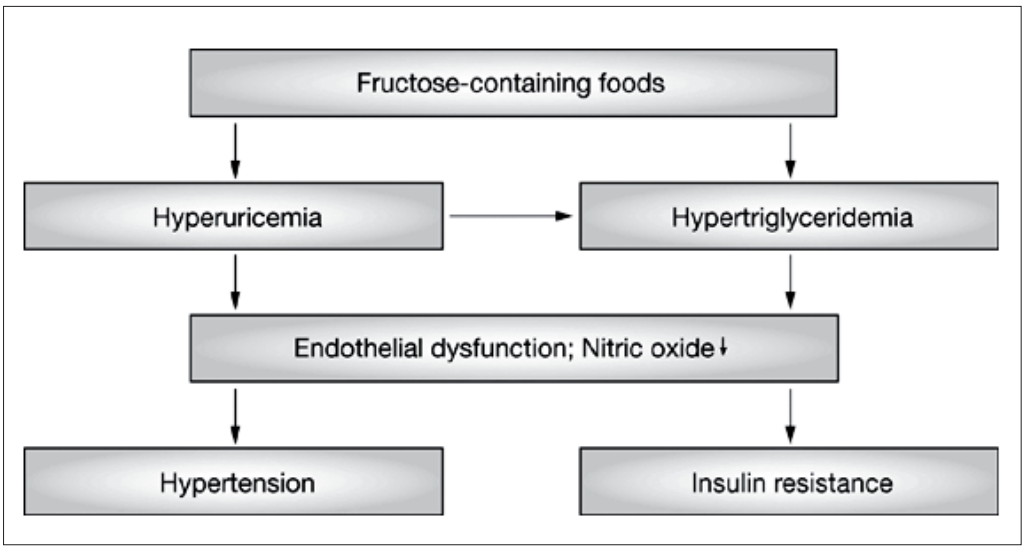

Figure 16. High fructose-containing foods and possible effects (Nakagawa et al. 2005).

tionship between adiponectin and serum uric acid (Gilardini *et al*. 2006, Böttner *et al*. 2004, Asayama *et al*. 2003).

In a randomized prospective trial, Seber *et al*. (2006) demonstrated that activation of PPAR-α and PPAR-γ by synthetic ligands both significantly decreased serum uric acid. Thus, it seems likely that also in humans high fructose consumption will lead to PPAR-α inhibition and hyperuricaemia.

Wu *et al*. (2004) found in a cross-sectional study among 1999 healthy women that circulating C-peptide, which is positively related to insulin resistance and development of type 2 diabetes, was significantly higher in the highest quintile of energy-adjusted fructose intake (p=0.01) compared to the lowest quintile.

Ishizaka *et al*. (2006) observed in a Japanese population, that serum uric acid levels in both genders were associated with increased brachial-ankle pulse wave velocity (baPWV), a marker of arterial stiffness which is a surrogate marker of early atherosclerosis. Erdogan *et al*. (2005) found in healthy subjects that increased serum uric acid, even in physiological range (<420 μmol/l for men and <350 μmol/l for women), is a risk factor for increased carotid artery intima-media thickness (ITM), reduced brachial artery flow-mediated dilatation (FMD), and increased arterial stiffness independent of other cardiovascular risk factors, and other factors related to MetS. In a recent review, Corry and Tuck (2006) conclude that there is a growing body of evidence, both experimental and clinical, that points to a mechanistic role for uric acid in cardiovascular disease.

These observations are all consistent with a recently published paper by Pladevall *et al*. (2006) who, by using confirmatory factor analysis concluded that the MetS is likely to be a distinct entity, with evidence to support leptin resistance and uric acid playing a causative role. However, the authors stress that further investigations are needed to determine whether the underlying factor is genetic or environmental.

CHAPTER 7

CONTAMINANT STATUS IN GREENLAND

Introduction

Epidemiological studies in Greenland have shown that human blood levels of various anthropogenic contaminants are very high compared to those in northern Europe and other Arctic areas (AMAP 1998). In Ittoqqortoormiit (Scoresbysund), East Greenland the population shows the highest blood levels of several persistent organic pollutants found in Arctic countries, especially PCB (Deutch and Hansen 2000). As in other Arctic countries, the direct source of these contaminants is the diet, and it is therefore important to monitor both the diet itself and other factors which may influence uptake and metabolism of the contaminants in question.

Correlations between the intake of traditional food items as determined by dietary surveys, and blood levels of anthropogenic substances, have been demonstrated for both heavy metals and organochlorines. Chemical analyses of food items of animal origin have provided ample evidence that traditional food is the major source of exposure for most persistent organic substances and for heavy metals including mercury (Hg) and in some cases cadmium (Cd) and lead (Pb) (Johansen *et al*. 2000, Johansen *et al*. 2002). Furthermore, since many persistent organic pollutants (POP) are biomagnified through the food chain, animals (including man) at higher trophic levels generally have higher levels of organic contaminants, although age, size, and gender also have an influence. Exposure estimates for heavy metals calculated from dietary intake show good correlations with human tissue concentrations (Hansen and Pedersen 1986, Hansen 1990). Dietary exposure estimates of POPs have been compared with human body burdens of POPs and several studies have shown very significant positive associations between n-3 fatty acids in human lipid fractions and blood levels of both Hg (Hansen and Pedersen 1986, Dewailly *et al*. 2001) and POPs (Deutch and Hansen 2000). This makes the connection between the intake of marine mammal fat (i.e. blubber) and

organic pollutants, and the intake of meat and mercury highly probable.

As part of the ongoing AMAP study covering 8 locations in Greenland, levels of heavy metals and a number of lipophilic persistent organic pollutants, including 10 pesticides, 14 PCB congeners, and 5 toxaphenes have been measured in human tissues (n=600), and the associations between self reported monthly food frequencies and the levels and ratios of plasma phospholipid fatty acids (FA) as indicators of local food have been assessed.

The dietary survey was measured by a semi-quantitative food frequency questionnaire (FFQ), which concerned consumption patterns during the previous year. The resulting relative amounts (by weight) and energy intake of local products ranged from about 25% in Qaannaq and Uummanaq to about 12% in Sisimiut, Narsaq and Nuuk. It was found, not unexpectedly, that the intake of local Greenlandic products was relatively higher in the north and that the intake and versatility of imported Danish products was higher in the south (see Chapter 5 and 6).

The reported food intakes by men and women were found to be very similar in the smaller towns, but in the larger towns women appeared to have a more 'westernized' diet than men. The diets of smokers and non-smokers were compared, but there were no significant differences in dietary patterns. The results of the dietary survey are presented in more detail elsewhere (Deutch 2003; Deutch *et al*.2004, Deutch *et al*. 2006, Deutch *et al*. 2007 a,b).

The relative intake of local food was strongly correlated with plasma n-3/n-6 levels of the study subjects, and this ratio can be used as an indicator of marine food intake. Individual n-3 fatty acids were all mutually (and highly significantly) correlated, and were also significantly correlated with the n-3/n-6 ratio. Therefore any correlation found with one of these fatty acids would also apply to the others. The highest n-3 intakes were found in Uummannaq, Qaanaq, and Tassiilaq with plasma n-3/n-6 ratios equal to 0.70, 0.48, and 0.45, respectively. This finding was also consistent with the highest relative intake of marine food.

Plasma n-3 fatty acids and heavy metals are, in general, also strongly correlated (see Table 4), for Hg in particular ($r=0.54$ $p<0.0001$). Blood Hg levels were extremely high in Uummannaq and Qaanaaq in Northwest Greenland, where the ratio between Hg levels and n-3/n-6 was significantly higher than in all other districts. This indicates that dietary sources in these districts have higher Hg levels than in other districts, and therefore points to a special environmental Hg problem in Northwest Greenland, which cannot yet be fully explained. Blood Hg levels were also significantly correlated with selenium levels ($p<0.001$), indicating the same external source, most likely whale and seal meat. Animal data are not entirely consistent between locations or species. However, in Qaanaaq, Riget *et al*. (2006) found a significant increasing trend of 7.8 % per year for concentrations of inorganic Hg in ringed seal liver. In polar bear hair, Dietz *et al*. (2006) also found significant increasing trends of Hg measured in East Greenland (1885-2004) and in Northwest Greenland 1915-1994. In human blood, Se levels were always higher than mercury, with a mean molar (Se/Hg) ratio ranging from 22 to 200 and individual molar ratios ranging from 6 to 800.

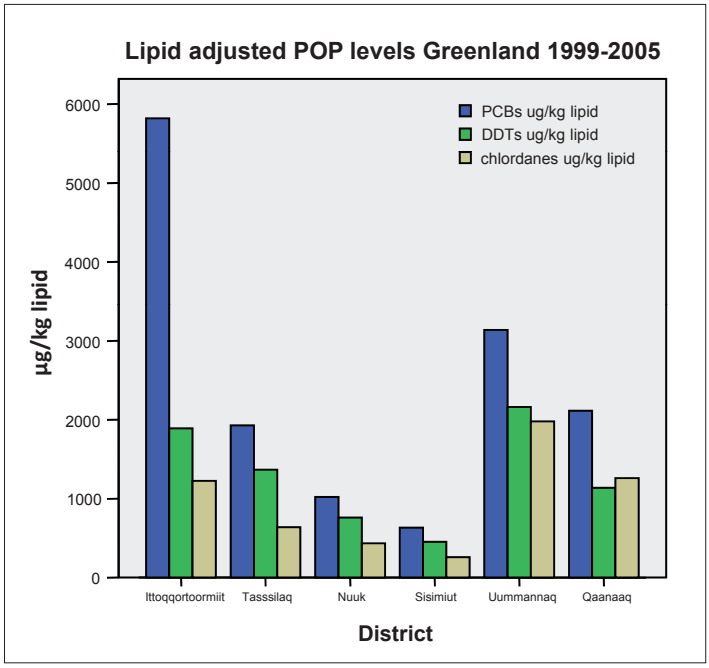

Figure 17. Plasma POP levels (µg/kg lipid) in Greenland 1999-2005 by district.

Lipid adjusted blood levels of some organic contaminants in different districts of Greenland are presented in Figure 17. This figure shows that the overall concentrations of contaminants in blood follow the same pattern as marine food intake. However, there were specific differences between compounds. For chlordanes (as sum of chlordanes), dichlorodiphenyl-dichloro ethylene (DDE), hexaclorobenzene, mirex and toxaphenes, levels were significantly higher in Uummannaq $p<0.001$ and Qaanaq $p<0.01$ than on the east coast. Concentrations of polychlorinated diphenyls (PCB), however, were extremely high in Ittoqqortoormiit (East Greenland), being significantly higher than all other districts ($p<0.0001$); levels of beta- hexachlorocyclohexane (HCH) were high in both Ittoqqortoormiit and Uummannaq. Concentrations of all the POPs were in general lower in Tasiilaq, and the lowest in Sisimiut Nuuk, and Narsaq. Different levels were found between men and women, but this is not equally pronounced in all districts, but predominates in the larger towns. The men from Nuuk stand out as having higher POP levels than men from other districts, this being attributed to their higher average age.

All the POP's were positively associated with the reported monthly intake of 'traditional meals' and, not surprisingly, several of them were inversely correlated with intake of meals of food imported from Denmark. Meals including seal meat were correlated with PCB, chlordanes, hexachlorobenzene and mirex, and meals that included seal products (meat, blubber, and liver) were significantly correlated with plasma levels of all POPs, except DDE. Polar bear intake was significantly correlated with all POPs except DDE and mirex, as was

was intake of muskox. Intake of muskox is only common in Ittoqqortoormiit and may be a proxy variable for intake of polar bear. Intake of birds correlated with PCB and toxaphene; fish intake only correlated with DDE and Mirex. Among women from Nuuk and Sisimiut who only ate seal and whale once or twice a month, PCB and Hg exposure levels were as low as those of young Danish women (Deutch 2003 a,b). It was also found that smoking, independent of the other factors, was significantly correlated with the plasma levels of POPs. The magnitude of this effect was even relatively large, to the extent that a typical 50-year old male smoker could have double the PCB level of a comparable individual that had never smoked.

Multiple linear regression analysis, performed using natural logaritms of lipid adjusted POP concentrations as dependent variables (see Table 6) showed that age, gender, district, and in particular plasma n-3/n-6 ratio were all highly significant predictors of human plasma levels of POP's. Smoking status (present, previous, or never), and plasma cotinine level indicating present nicotine exposure were also significantly correlated with POP levels. Plasma cotinine levels were mainly used to confirm reported present smoking status; since cotinine levels decrease close to zero on cessation of smoking, it is not a good indicator of lifetime smoking exposure.

Table 6. Multiple linear regression analysis of predictors of lipid adjusted plasma levels of persistent organic pollutants (logarithmic) in Greenland 1999-2005 (n=475).

Dependent variable	R-square	Independent variables	Standardized β-coefficients	p-value
PCB	0.44	Age	0.23	<0.0001
		District	-0.27	<0.0001
		n-3/n-6	0.40	<0.0001
		Smoker or	0.19	<0.0001
		Cotinine	0.15	0.006
		Sex	-0.26	<0.0001
DDT[a]	0.37	Age	0.37	<0.0001
		District	-0.33	<0.0001
		n-3/n-6	0.29	<0.0001
		Smoker or Cotinine	0.15	<0.0001
		Sex	-0.19	<0.0001
Chlordanes[b]	0.45	Age	0.23	<0.0001
		District	-0.03	ns
		n-3/n-6	0.43	<0.0001
		Smoker or Cotinine	0.16	<0.0001
		Sex	-0.28	<0.0001
Mirex	0.48	Age	0.24	<0.0001
		District	-0.19	<0.0001
		n-3/n-6	0.45	<0.0001
		Smoker or Cotinine	0.17	<0.0001
		Sex	-0.31	<0.0001

[a]Lipid adjusted β-HCH) shows similar correlation pattern. [b]Lipid adjusted HCB and lipid adjusted toxaphene show similar correlation patterns.

Blood levels of heavy metals, Hg and Pb were also significantly correlated with meat from seal and whale, and in multiple linear regression analysis with age, gender, district, plasma n-3 and smoking. Cadmium was not correlated with seal and whale consumption, but in multiple linear regression analysis it was correlated with n-3/n-6, gender, district and smoking, though not with age.

Spatial and temporal trends

The results of human tissue monitoring show that not all POPs have the same geographical distribution and that the external sources of POPs may vary from place to place. This reflects differences in dietary composition as well as different contaminant levels in animals used as food. The uneven contaminant levels in the local predators (which have yet to be fully explained) make the 'district' an important predictor of POPs levels in humans. Polar bear is an important food source on the east coast, particularly during the winter months, and levels of POPs, especially PCB, are extremely high in polar bear (AMAP 1998). High PCB levels observed in humans in Ittoqqortoormiit are highly significantly ($p<0.0001$) correlated with polar bear consumption (Deutch *et al*. 2004).

PCB tissue concentration guidelines for pregnant and fertile women are exceeded by 100% of the study participants in East and Northwest Greenland, and by about 50% of participants in West and South Greenland (see Fig. 18). Animal contaminant data show that PCB and DDT levels are about twice as high in seals, birds, fishes and mussels caught in Ittoqqortoormiit than on the west coast (Johansen *et al*. 2000, Johansen *et al*. 2002). This means that for the same intake of seals (or other marine animals),

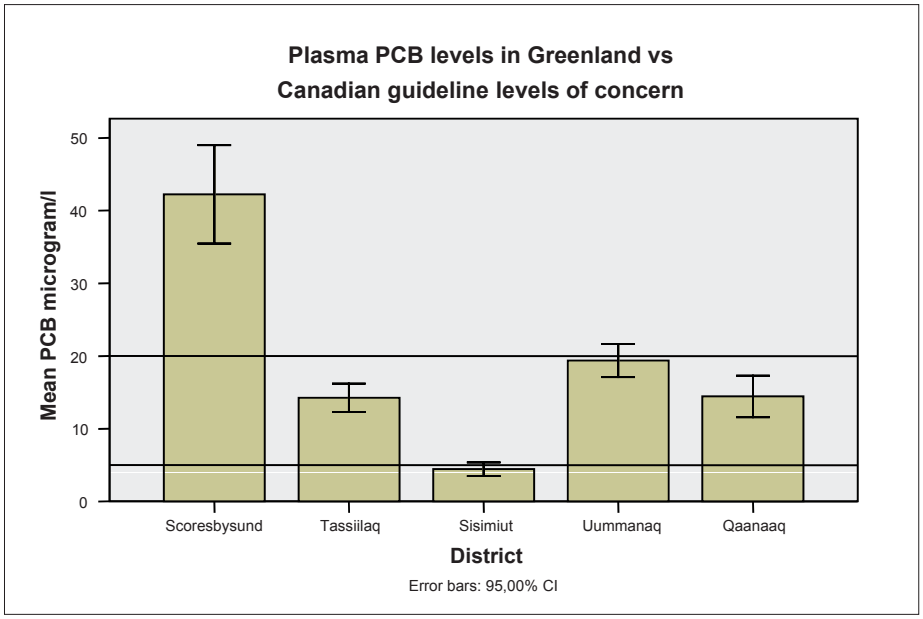

Figure 18. Plasma PCB levels in Greenland vs. Canadian guideline levels of concern. Concern level for fertile women 5 µg/L, other adults 20 µg/L (y-axis).

the exposure to contaminants is higher on the east coast than on the west coast. From analysis of consumed animals and food samples (Deutch *et al*. 2006) it appears that PCB exposure is decreasing. We have less documentation of a temporal trend in human tissue. However, among pregnant women from Disko Bay area over a 12 year period (1994-2006) we found significant decreases in plasma of oxychlordane, p,p-DDE, and PCB153. These decreases may partially be explained by different dietary and smoking habits (Deutch unpublished observation).

The findings reported here are in accordance with other Greenlandic studies concerning POP exposure estimates from various subsistence animals (Deutch et al. 2003 b); Johansen *et al*. 2000, Johansen *et al*. 2002). Although these theoretical exposure estimates should be regarded as provisional, they identify seal blubber (followed by whale blubber) as the predominant contributor to human PCB, DDT, chlordane, and HCH intake in West Greenland. Compared with this exposure from consumption of marine mammals, exposure via fish intake is negligible. Regarding polar bears, insufficient animal contamination data is currently available from the east coast of Greenland. However, data from other comparable locations, such as Svalbard (AMAP 1998) indicate levels of contaminants sufficiently high to make polar bear the predominant source of at least PCB in areas where it is consumed (Deutch 2003 b). This is in accordance with the correlation between reported polar bear intake and POP levels in human blood.

Exposure estimates for bioavailable mercury show that seal and whale meat are the largest contributors. In contrast to this, the high levels of inorganic Hg in liver and kidney tissue of animals are much less bioavailable and therefore not important sources (Deutch 2002). The latest US EPA blood guideline value for mercury of 4.2 microgram/litre is exceeded by 100% of study participants in all districts (see Fig. 19), except for women from Nuuk (not shown).

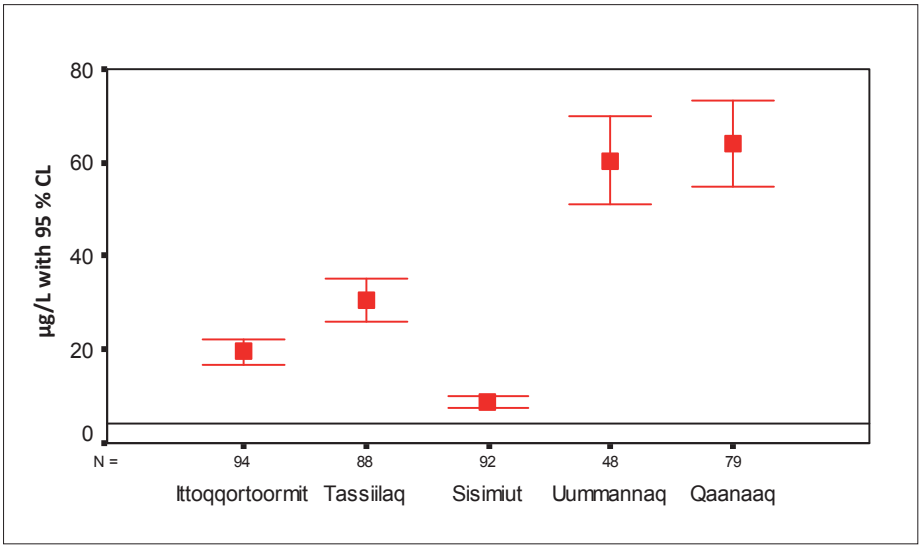

Figure 19. Mercury blood levels (µg/L with 95 % CL) by district in Greenland .The line in the figure indicates the blood concentration (4.2 µg/L), corresponding to an intake at the US EPA reference dose level (RfD).

In contrast to POPs, monitoring of heavy metals in human tissue has taken place in Greenland since the late 1970s (Hansen 1990). Already at that time, high Hg levels were observed in Northern Greenland. Blood Hg levels found in the present study in Uummannaq are, however, even higher, about 50 -100% greater than those found in the early 1980s. In these studies, the molar ratio between Se and Hg has always been found to be greater than one. This increase in Hg levels is in contrast to a general decrease in traditional food intake over the same period. At present there is no explanation for the high Hg levels and these contradictory trends.

During the same time span, Pb levels have decreased significantly, following the widescale introduction of unleaded petrol in North America and Europe, and Cd levels have decreased due to reductions in industrial emissions. However, the major Cd source to humans in Greenland remains smoking.

Age and gender

Age is a predictor of human tissue concentrations of POPs that are bioaccumulated over time, BMI is an (inverse) but not significant predictor. The latter effect probably reflects the fact that lipophilic substances are distributed in a smaller volume of tissue in slim people, resulting in higher concentrations. As an illustration of this, Chevrier *et al*. (2000) found that the concentration of POPs in body fat increased in obese people who lost weight over a short time period.

Gender is also a predictor, but mainly in the larger towns, where women appear to eat a more 'westernized' diet, resulting in lower contaminant levels. In smaller settlements, where the diets of men and women are very similar, POP levels are as high in women as in men. Thus, the influence of gender appears to be a behavioral effect rather than physiological.

N-3/n-6 as an indicator of marine food

At present, the best indicators available for intake of (traditional) food of marine origin are the relative concentrations of n-3 fatty acids in various human lipid fractions. The plasma phospholipid fatty acid (FA) fractions, e.g., n-3/n-6 indicate recent intakes over a period of weeks (Tjønneland *et al*. 1993, Marckmann *et al*. 1995, Deutch *et al*. 2000). Unless people have recently dramatically changed their habitual intake of n-3 FA the phospholipid n-3 is usually strongly correlated with a more long-term intake, and also shows a strong relationship with accumulated POPs. There also exists a highly significant correlation between blood mercury concentrations and the n-3/n-6 ratio.

Smoking

Smoking is a predictor where the higher levels of all measured POPs among smokers in Greenland indicate that nicotine or other substances in tobacco smoke influence the metabolism of these xenobiotic substances (Deutch and Hansen 2000, Deutch *et al*. 2003, Lagueux *et al*. 1999). Tobacco itself is not a source of organochlorines. The effects of smoking on POP accumulation have in general not been supported in other studies, where no relationship has been observed (Apostoli *et al*. 2005, Glynn *et al*. 2003, Ayotte *et al*. 2005). However, one study

by Lackmann *et al*. (2000) concluded that both active and passive maternal smoking increases the neonatal burden with PCBs and HCB. In the Russian Arctic, significantly higher POP levels were observed among smoking pregnant women than among non-smokers, Klopov V.P (personal communication, July 2002).

Cadmium and lead concentrations in blood are both significantly correlated with smoking since tobacco is a direct source of these elements. This is further discussed in Chapter 10.

Genetics

Human tissue levels of POPs are also influenced by genetic factors due to polymorphism in gene coding for various enzymes involved in the metabolism and excretion of organochlorine compounds, e.g., CYP1A1 (Lagueux *et al*. 1999). Furthermore, tissue levels are influenced by various lifestyle factors, as indicated by their relationship with BMI (Deutch *et al*. 2003) and smoking (as discussed in Chapter 10) (Deutch and Hansen 2000, Deutch *et al*. 2003). Therefore, identification of individuals at risk of accumulating a high POP burden is not just a simple question of dietary exposure, but is complicated by other behavioral and interacting genetic and biochemical factors. These should receive more attention in future studies, with the ultimate intention of enlarging the basis for public health advice regarding dietary habits and behaviour.

Conclusions

Levels of both mercury and several POP contaminants in certain groups of humans in Greenland exceed international safety guidelines. The multiple regression analysis applied in this study demonstrates that the main predictors of a high human burden of POPs are age, 'district' (i.e., locality in relation to various food sources), plasma phospolipid concentration of n-3 FA and smoking status (as indicated by plasma level of cotinine). Gender is also a predictor, but mainly in the larger towns, where women appear to eat a more 'westernized' diet, resulting in lower contaminant intakes.

These results imply that public health measures are urgently needed to bring exposures down to acceptable levels. Abstention or a reduction in smoking is an effective and non-harmful measure to reduce exposure. Dietary changes are more complex and controversial because of the cultural aspects and the risk of compromising nutrient intake and status. Meat and organs from local marine mammals are very important sources of vitamin A and D, iron and selenium. Blubber is a good source of n-3 FA, but fatty fish could substitute for this. However, it is non-contestable that consumption of blubber from large, older, predatory animals is the most important contributor to POP exposure, and that meat and organs from the same animals are the main contributors to Hg (especially methylmercury) exposure. Moderating intakes of these foods could bring blood concentrations down to acceptable levels in the general population, as is the case for women from Nuuk, Sisimiut and Narsaq who only eat seal and whale once and twice a month. In this context, it is a question of limiting, not eliminating the use of marine mammals for food, including choice of species and age of the selected animals. As part of the AMAP Programme, the monitoring and assessment of the human exposure to persistent contaminants will be continued, including efforts to reveal possible time trends.

CHAPTER 9

CONTAMINANTS AND METABOLIC DISORDERS

The traditional concept of the causal complex underlying metabolic disorders has, to date, not produced a satisfactory explanation of this major public health problem, thus less than 50% of variation in HDL cholesterol between and within individuals, is explained by established predictors (Jeffs *et al*. 2006). Recently, there has been an increasing awareness of global environmental pollution (i.e., pollution by contaminants that are distributed around the globe) as a causal or, aggravating, factor in the development of metabolic disorders. Longnecker *et al*. (2001), and Longnecker and Daniels (2001) stated, based on a study of pregnant women that "The possibility exists that PCB and diabetes are causally related" and "that the relationship of PCB level to adjusted risk of diabetes was linear". The lipid adjusted mean serum level of PCBs among subjects with diabetes was 30% higher than the control subjects (p=0.0002).

In agreement with this, Fierens *et al*. (2003), in a Belgian study report that the risk of diabetes was significantly increased in subjects in the top decile for adjusted concentrations of dioxins (odds ratio 5.1, 95% confidence interval l.1-21.8), coplanar PCBs (odds ratio 13.3, 95% CI 3.31-53.2), or Σ-12 PCB markers (odds ratio 2.6, 95% CI 1.58-36.3). Recently, Vasiliu *et al*. (2006) found, in women (but not in men) in the Michigan polybrominated biphenyls (PBB) cohort that higher PCB levels (>10 μg/l) were associated with increased incidence of diabetes. Today around 80% of the adult Greenlandic population has PCB serum values in excess of 10 μg/l.

The first observations of a possible influence of halogenated organic compounds on development of risk factors for cardiovascular diseases were made in the beginning of the 1980s. Several human studies have observed a positive and significant correlation between serum PCBs and serum triglyceride (TG) concentration. This has been observed both in occupational (Chase *et al*. 1982, Smith *et al*. 1982, Hara 1985) and in environmental exposures from local highly polluted areas (Steinberg *et al*. 1986, Baker *et al*. 1980,

Stehr-Green *et al*. 1986, Stark *et al*. 1986). Steinberg *et al*. 1986 also found an effect of DDE, and furthermore noted that only the less chlorinated PCBs (Aroclor 1242) correlated significantly and negatively with HDL cholesterol. Also, among the 'Yusho' victims an elevated serum TG was observed. The correlation to PCBs persisted for 20-30 years although the blood PCB level and serum TG at that time were relatively close to the normal levels (Hirota *et al*. 1993, Masuda 2001). In these early studies, no congener specific information was available and furthermore the 'Yusho' patients were exposed to a mixture of PCDD/F's and PCB's. Wang *et al*. (2005) demonstrated in the general Taiwanese population a significant association between *in utero* exposure to coplanar PCBs and thyroid function in newborn babies, and suggested routine screening of both thyroid hormone levels and thyroid function in newborns, however the effects on thyroid hormone metabolism seems to be transient (ten Tusscher and Koppe 2004). Vietnam veterans exposed to TCDD developed hyperinsulinemia (Cranmer *et al*. 2000) and thus probably also alterations of the blood lipid profile; occupational exposure to 2,3,7,8-TCDD has also been related to hypertriglyceridemia (Pelclova *et al*. 2002).

There is some epidemiological evidence for a connection between exposure to dioxin-like compounds and diabetes. The possibility for this linkage lies in the fact that these compounds, as AhR agonists, increase the production of TNF-α, which in turn reduces the production of PPAR-γ, which again induces insulin resistance (Remillard and Bunce 2002).

Perinatal exposure to background levels of dioxins in Europe and the USA cause persistent effects into childhood (for review see ten Tusscher and Koppe 2004) These effects include deficits in IQ and behaviour, interference in haematopoiesis, and reduced lung function.

Epidemiological studies have also added to the increasing evidence for a link between cardiovascular diseases and halogenated organic contaminants. One study found an increased mortality from cardiovascular diseases among Swedish capacitor manufacturing workers exposed to PCB's for at least five years (Gustavsson and Högstedt 1997). Another study made the same observation in workers exposed to phenoxy herbicides and PCB's from waste transformer oil (Hay and Tarrel 1997).

Increased prevalence of atherosclerosis may be associated with the ability of PCB's to modulate plasma and tissue lipids to an atherogenic profile, an event that can result in compromised lipid metabolism and lipid dependent cellular signalling pathways (Hennig *et al*. 2005). A pro-atherogenic plasma lipid profile is also a sequel of obesity, regarded as the main risk for developing of the MetS, type 2 diabetes and cardiovascular diseases; a triad causally founded in metabolic disorders.

Recent data from Greenland generated under the AMAP Human Health programme have indicated the association between lifestyle related obesity and contaminant related increased risk for development of cardiovascular diseases (see Fig. 20).

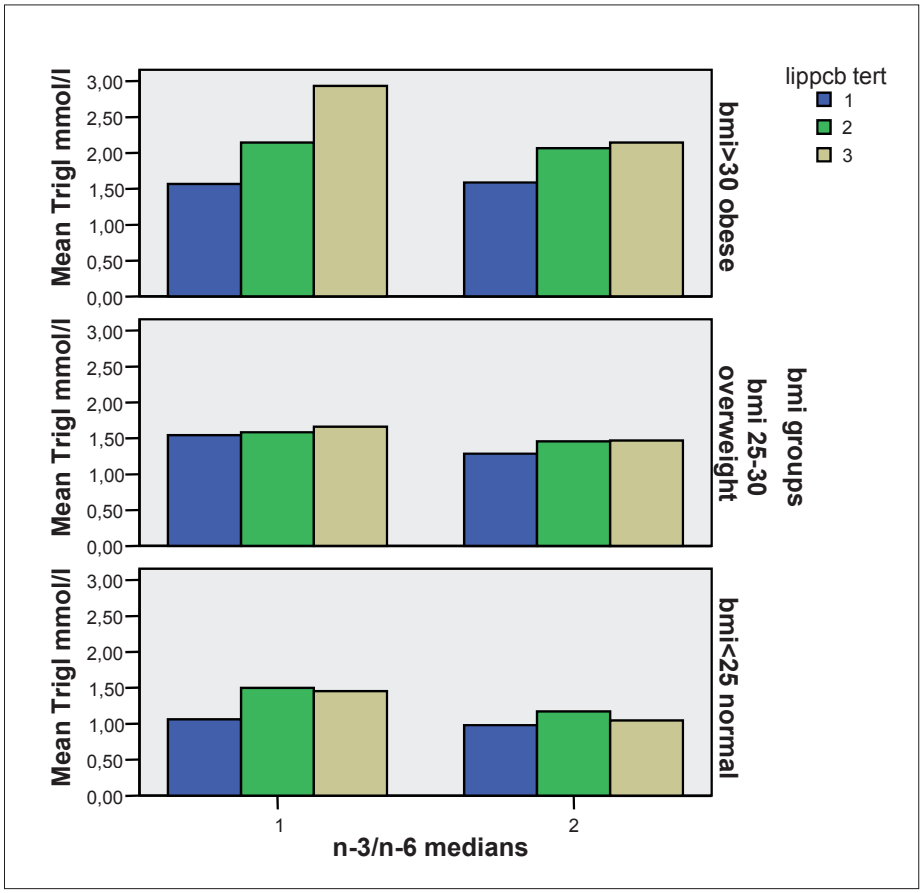

Figure 20. Effect of PCB exposure levels on serum triglyceride concentrations in relation to BMI groups and plasma levels of n-3 fatty acids.

There are several processes related to development of metabolic disorders where contaminants may play an aggravating role:

- Pro-inflammatory effect through formation of reactive oxygen species, oxidative stress and formation of pro-inflammatory cytokines.
- Modulation of fatty acid metabolism.
- Influence on nuclear receptors
- Influence on steroidogenesis.
- Influence on uric acid levels

Proinflammatory effects

One feature common to several persistent contaminants is their pro-oxidative properties; as such they act as pro-inflammatory substances. Hennig *et al*. (2002a) have shown in *in vitro* on porcine endothelial cells that the co-planar PCBs 77, 126 and 169 produce oxidative stress in a dose dependent manner; PCB126 was the most effective, with maximal response at 0.5 μM. They also suggested (Hennig *et al*. 2002b) that the effect is mediated through their

role as AhR agonists, that an intact AhR may be necessary for the observed PCB effect, and that activation of the AhR can be an underlying mechanism of atherosclerosis mediated by certain environmental contaminants. Choi *et al*. (2003) also reported that PCB104 is a potent stimulant of inflammatory mediators in human vascular endothelial cells. They suggest the action to be mediated through induction of the macrophage activating agent MCP-1 and adhesion molecules. The pro-oxidative action of co-planar PCBs is supported by *in vivo* tests on rats where it was found that PCB77 significantly reduced the level of the selenium containing antioxidative enzyme glutathione-peroxidase (GPX), while the higher halogenated PCBs were inactive (Twaroski *et al*. 2001).

While Hennig *et al*. (2002a) did not find any effect of CB153, Kwon *et al*. (2002) reported that CB153 induces cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in a study using the human leucemic mast cell line. The expression of the cytokines was found to occur through activation of NF-ϰB. Also, Fadhel *et al*. (2002) report that PCB153 produces oxidative stress in rats, but suggest a different mechanism from the co-planar PCBs. The described pro-inflammatory effect of PCB153 may, however, be indirect. Zhou *et al*. (2006) demonstrated a mutual repression of both steroid and xenobiotic receptors (SXR) and the NF-ϰB signalling pathway (See Fig. 21). Tabb *et al*. (2004) showed that the higher chlorinated PCBs block the action of SXR in humans and consequently the

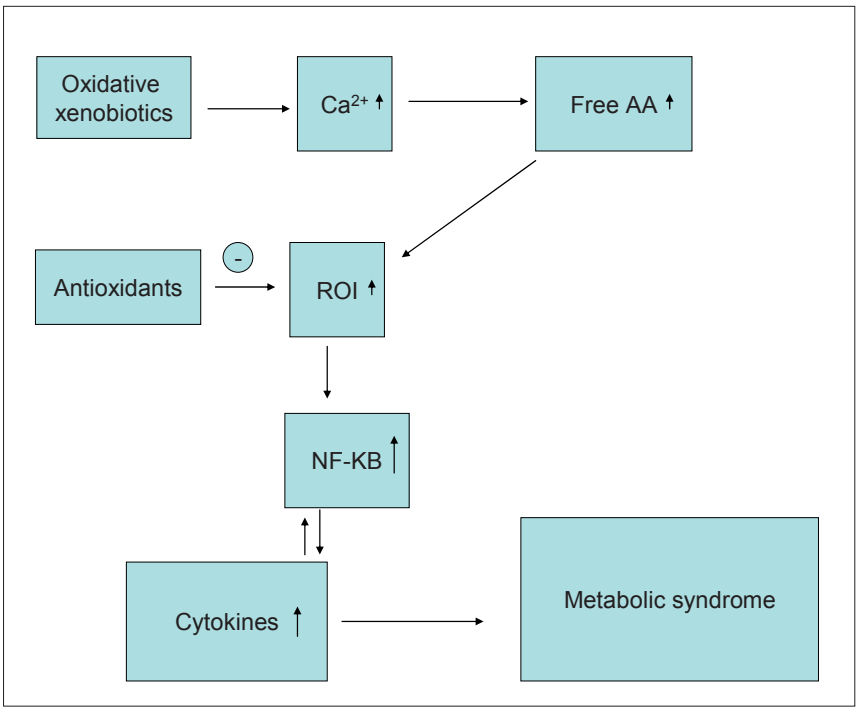

Figure 21. Interactions between pro-oxydative Xenobiotics and antioxidants. AA= Arachidonic acid; ROI= Reactive oxygen intermediates; NF-KB=Nuclear factor-KappaBeta

NF-κB will be upregulated, leading to formation of pro-inflammatory cytokines. The pro-oxidative effects of co-planar PCBs was supported by Ramadass *et al*. (2003) who found that dietary flavonoids modulate PCB induced oxidative stress in cultured endothelial cells, and *in vivo* that vitamin E and C administrated concomitantly with PCBs ameliorated the oxidative effects of PCB (Murugesan *et al*. 2005).

The evidence for a pro-oxidative and, as such, also pro-inflammatory effect of several PCB congeners, especially the lower halogenated co-planar congeners, seems experimentally to be well supported. However the evidence from human studies does not seem to provide a clear picture, thus Ahne and Jarre (2002) reported impaired release of TNF-α in *in vitro* tests of human blood after addition of CB77, and CB126 in concentrations of 50 and 500 ng/ml. In agreement with this, Bilrha *et al*. (2003) found an inverse correlation between TNF-α secretion in *ex vivo* phytohemoagglutinin stimulated cord-blood mononuclear cells (CBMCs) isolated from cord-blood samples, and the cord blood plasma concentrations of PCB, p,p,DDE and HCB. Samples were collected in a population exposed to organochlorines and methylmercury via food, and from an unexposed control population. Also, Bélanger *et al*. (2006) conclude from a study among Canadian Inuit that the contaminated traditional diet seems to have no direct oxidative effects in adults. Nevertheless they report that plasma oxidised-LDL is predicted by PCBs ($p = 0.006$), even if the level of oxidised-LDL was low. This indicates that there is an oxidative load from PCBs which partially is counteracted by the n-3 fatty acids which were found to be positively correlated to the contaminant level. There is no immediate explanation to the discrepancy between these data; it may, however, partly be explained by differences in experimental methodologies and the congener tested individually and in mixtures, different exposure levels, and also that concomitant intake of n-3 fatty acids could through their antioxidative properties counteract the contaminant effect (see Fig. 20).

An indication of a long lasting pro-oxidative effect is reported by Shimizu *et al*. (2003) who, in 'Yusho' victims, more than 30 years after the accidental poisoning, found lower serum concentrations of copper (Cu), zinc (Zn) superoxid dismutase (SOD) and higher Mn-SOD in victims compared to age-matched controls, indicating an imbalance of redox-regulation mechanisms. Also, methylmercury has pro-oxidative properties involving calcium homeostasis as suggested by Hansen and Danscher (1997) (see Fig. 22).

This has been supported experimentally by Gassó *et al*. (2001) who, in cultured rat cerebellar granule cells found that disruption of redox equilibrium and Ca^{2+} homeostasis contribute equally to $HgCl_2$ toxicity, whereas oxidative stress is the main cause of methylmercury (MeHg) neurotoxicity. As PCBs and methylmercury originate in the same dietary sources, they may have an additive effect, which is supported in studies by Bemis and Seegal (1999), Voie and Fonnum (2000), Roegge and Schantz (2006).

While the immunotoxicity of the coplanar PCBs is well documented, the effects by the non-coplanar PCBs have received less attention. Levin *et al*. (2005) demonstrated that the non-coplanar PCBs 138, 153, and 180, but not the coplanar 169 suppress human leukocyte phagocytosis, The authors regard this as a cause for concern as the results suggest an AhR-independent pathway through which the

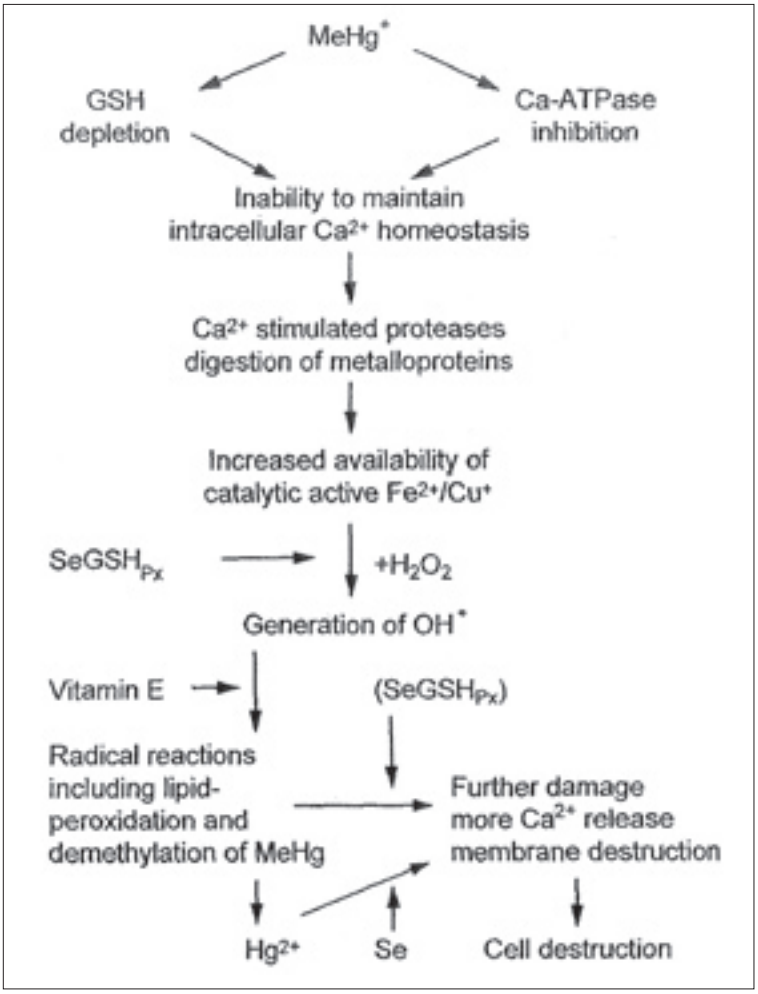

Figure 22. Toxic reactions of methylmercury; possible interactions of antioxidants (Hansen and Danscher 1997).

most abundant non-coplanar PCBs modulate phagocytosis, the immune system's first line of defence, and thus possibly will increase susceptibility to infectious diseases. They also found that this effect could not be predicted by either the toxic-equivalence approach or the mouse model. This undermines the use of these traditional methods in risk assessment of mixtures containing non-coplanar congeners, which always will be the case in human exposure situations.

Effects on fat metabolism

There seems to be ample epidemiological evidence, that PCBs, especially the co-planar congeners, modulate fatty acid metabolism resulting in increased serum levels of triglyceride. The exact mechanisms are not known, but one suggestion is that PCBs inhibit Δ-6, and Δ-5 desaturases (Matasusue *et al*. 1999). As a consequence the conversion of linoleic acid (LA) (18:2-6) to arachidonic acid (AA)

(20:4-6), AA will be inhibited and LA will be allowed to accumulate. This is supported by Grandjean and Weihe (2003) who, in a Faroese birth cohort found that an increased PCB exposure was associated with a modest decrease in arachidonic concentrations both in maternal and cord serum. In data from Greenland (n=353), the LA/AA ratio was found to be inversely associated to serum PCB concentrations. The dietary intake of LA originates from the 'western' part of the diet while AA is supplied through the traditional part, mainly from meat of marine mammals. As a consequence, both a low LA/AA ratio and a high PCB level are directly related to the amount of traditional food regularly consumed. Thus, the correlation does not provide information on a possible effect on the desaturases. However, when the LA/20:3-6 is used there is a significant positive correlation with PCB exposure, which indicates an inhibition of Δ-6 desaturase (Deutch unpublished observation). 20:3-6, eicosatrienoic acid, is a metabolite of LA after elongation and Δ-6 desaturation and, for that reason, related to the intake of LA and not to the proportion of traditional food eaten.

Hennig *et al*. (2002a) have experimentally shown that both LA and PCB 77 – and more markedly when applied in combination - can generate reactive oxidative species which trigger proinflammatory signalling pathways under formation of pro-inflammatory cytokines, which in turn promote formation of triglycerides (see Figure 23). Hennig *et al*. (2005) have suggested an inhibitory effect of PCBs on PPAR-α. If this can be confirmed it would explain the pro-inflammatory effects, as well as the triglyceride increasing effect of PCBs.

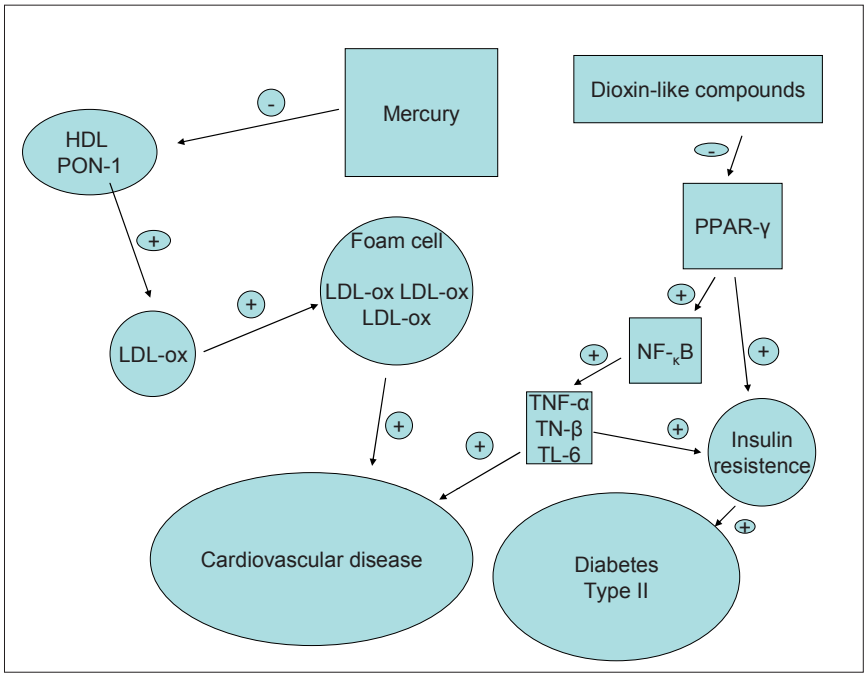

Figure 23. Hypothetical influence of contaminants on the induction of cardiovascular disease.

Influence on nuclear receptors

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that mediates a spectrum of toxic and biological effects of dioxins and dioxin-like compounds. Activation of AhR by the agonists has been shown to inhibit PPAR-γ (Alexander *et al*. 1998), which leads to impaired adipocyte differentiation and regulation of glucose homeostasis (Fig. 1 and 23). Exposure to dioxin and dioxin-like compounds has consequently been linked to development of type 2 diabetes. Experimentally it is demonstrated that dioxin, in an AhR dependent manner, induces insulin growth factor binding protein (IGFBP-1) in human hepatocytes and that this may contribute to the disruptive effects of dioxin on glucose homeostasis (Marchand *et al*. 2005). Due to lack of longitudinal studies it remains unclear whether background exposures to dioxin-like compounds are associated with increased risk of diabetes (Arisawa *et al*. 2005).

Beside inhibition of PPAR-γ, activation of AhR also inhibits PPAR-α (Shaban *et al*. 2004). Shaban *et al*. (2005) have also shown that AhR agonists down-regulate the PPAR-α induced expression of CYP2B and CYP3A, while both receptors down-regulate expression of CYP2C11 in an additive way, when activated. CYP 2B, CYP 3A, and CYP2C11 all function as testosterone hydrolases (You 2004). This is an indication that dioxin-like compounds also may have an effect on sex hormone balance beside the negative cross-talk with the estrogen receptor (ER).

In rodents, both CYP2B and CYP3A are, via the constitutive androstane receptor (CAR) and the pregnanexreceptor (PXR), readily induced by a variety of environmental contaminants, such as DDE, some PCBs (You *et al*. 1999) and polybrominated diphenyl ethers (PBDEs), (Sanders *et al*. 2005). Beside the induction of CYP enzymes, CAR and PXR also induce detoxification enzymes and will in this way play a role in protection against toxic effects of contaminants. Tabb *et al*. (2004) demonstrated that in humans, contrary to rodents, the higher chlorinated PCBs inhibit the steroid and xenobiotic receptor SXR (the human ortholog to the rodent PXR) and thus its target gene CYP3A (which metabolises most of the non co-planar PCBs in non-human mammals). In humans, the higher chlorinated congeners seem to inhibit their own metabolism, introducing a caveat not to rely on rodent models in human risk assessment. An extensive review of the influences of xenobiotics on CAR and PXR is given by Kretschmer and Baldwin (2005).

Effect on steroidogenesis

Hitherto, most interest on contaminants has been devoted to their hormone disrupting properties in relation to reproductive disorders. However, recent research has documented that sex hormone balance is also important for the development of MetS; this issue must be considered as a contributing risk factor. Several experimental studies on single compounds or groups of compounds have been carried out with respect to their effects on the individual steps in the steroidogenetic process which is illustrated in Figure 24.

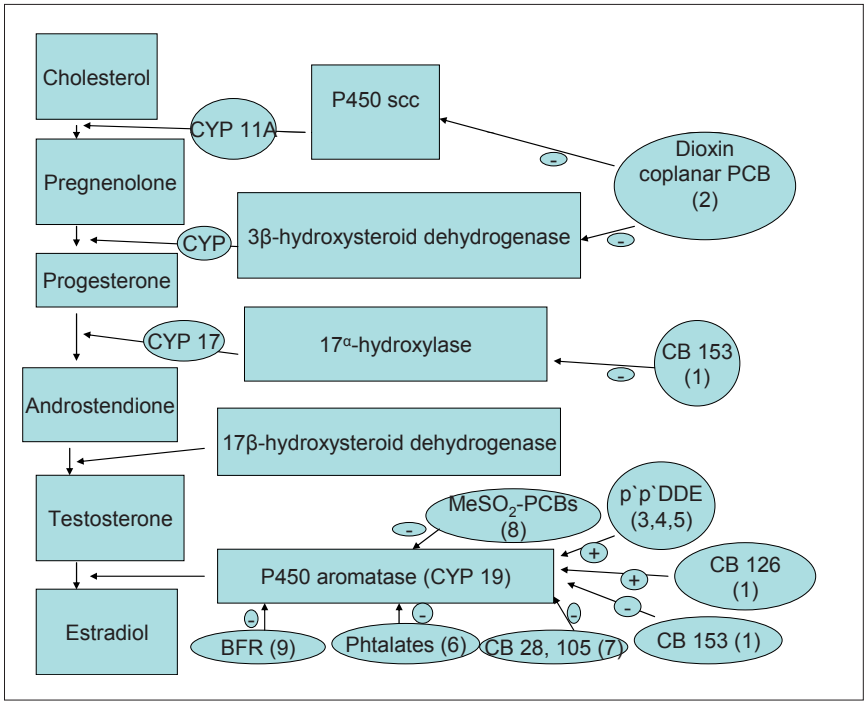

Figure 24. Steroidogenesis and possible influences by contaminants. (1)Wojtowicz *et al.* 2005; (2) Augustowska *et al.* 2003; (3) Holloway et al. 2005; (4) You *et al.*. 2001; (5) Younglai *et al.*. 2004; (6) Lowekamp-Swan and Davis, 2003; (7) Woodhouse and Cooke 2004; (8) Letcher *et al.* 2002; (9) Canton et al. 2005.

From these single component studies it is not possible to draw conclusions with regard to the human exposure situation as the resultant effect will depend on the exposure level, and above all on the relative concentration of single components in a given exposure situation. As this will vary from one population to another, there is a need to study the combined effects on steroidogenesis of mixtures of contaminants representative for the actual composition of contaminants in specific high exposure populations.

Some epidemiological studies have used one or a few compounds, e.g. PCB153 as the most abundant PCB congener, and DDE as the most abundant pesticide metabolite, as proxies for the exposure situation in a population. This is, however, not scientifically justified as the hormone disrupting effects vary according to the exposure situation, depending on the relative occurrence of the active congeners and, as such on the trophic level from which the food is obtained. In an Arctic Inuit population, where the contaminants originate from a very long passage though the marine food-chain, the higher, slowly metabolised, higher chlorinated PCBs will dominate over the lower chlorinated and more readily metabolised congeners. This will create a specific effect on the hormonal balance, distinct from populations exposed more directly to the sources of these contaminants. Pliskova *et al*. (2005) found in a human study that the lower chlorinated

PCBs act as estrogens, while the higher chlorinated congeners act as antiestrogens. This is in accordance with results from Greenland, where a lower estrogen/androgen ratio was found, compared to European populations (E.C.Bonefeld-Jørgensen, personal communication August 2007).

Another, and possibly more serious caveat to the use of single compounds as proxy, is that the influence of industrial compounds, such as phtalates and bisphenols are neglected. Phtalates belongs to the peroxisome proliferators, which activate PPAR-α and thereby inhibit aromatase (CYP 19 arom), and as such exibit an antiestrogenic effect. On the other hand, bisphenol, widely used as coatings for the inner surface of food and beverage cans, is reported to have a connection to insulin resistance at doses much lower than the lowest observed adverse effect level (LOAEL) used upto now (50 mg/kg/day) (Alonso-Magdalena *et al*. 2006).

In summary, at the moment it is not possible to draw conclusions about the actual exposure to environmental hormone disrupting chemicals with regard to their influence on risk for developing the MetS, as the resulting effect of an exposure will depend on the distribution between estrogenic and antiestrogenic/androgenic and antiandrogenic compounds present in an actual exposure. The influence of xenobiotics on setroidogenesis in relation to metabolic disorders is important, and needs further attention.

Influence on uric acid

During the recent period, uric acid has increasingly been associated as a pivotal factor in the development of MetS, and related to the increasing dietary intake of fructose through industrialised food items. One animal study, in rats, has demonstrated that exposure to PCBs increased serum uric acid concentrations, regardless of their degree of chlorination (Kutlu *et al*. 2007). If this also applies for humans, it may indicate that PCB exposure can be an aggravating factor which adds to the negative influence from the increasing dietary fructose intake through industrialised food production.

CHAPTER 10

SMOKING AND CONTAMINANTS

We have previously reported a significant positive correlation between smoking and serum PCB levels in the Greenlandic data (Deutch and Hansen 1999, Deutch and Hansen 2000, Deutch *et al*. 2003, Deutch *et al*. 2004) (see Fig. 25). The association was significant in study populations of non-pregnant women and men, pregnant women and in cord-blood, after correction for age, alcohol intake, and intake of marine food, plasma lipids, n-3/n-6 ratios, BMI, and district. Similar relationships were found for DDE, chlordanes, HCB, mirex, and toxaphenes.

In general this has not been supported in studies of other populations, where no relationships have been observed (Apostoli *et al*. 2005, Glynn *et al*. 2003, Ayotte *et al*. 2005), or it was not investigated as smoking together with BMI were considered covariates (Bloom *et al*. 2005). However, one study by Lackmann *et al*. (2000) concluded that both active and passive maternal smoking increase the neonatal burden of PCBs and HCB. In the Russian Arctic, significantly higher POP levels were observed among smoking pregnant women than among non-smokers (V.P.Klopov, personal communication July 2002).

Ayotte *et al*. (2005) measured the caffeine breath test as an indicator of smoking, and induction of CYP1A2, and related this to the ratios of PCB 105/153 and 118/153. They found a significant inverse relationship between both ratios and CBT. A logical deduction from a decreasing ratio is either a relative decrease in the numerator or a relative increase in the denominator. The latter condition would appear to be inconsistent with the presumption that external exposure level is the same in smokers and non-smokers, Ayotte *et al*. (2005) therefore concluded that smoke induced CYP1A2 degrade PCB 105 and 118.

In the dataset from Greenland, there are no CBT measurements; however, serum cotinine (a nicotine metabolite) levels were measured as an alternative indicator of smoking status. Correlating the same congener ratios with cotinine levels, a significant inverse relationship with cotinine was observed.

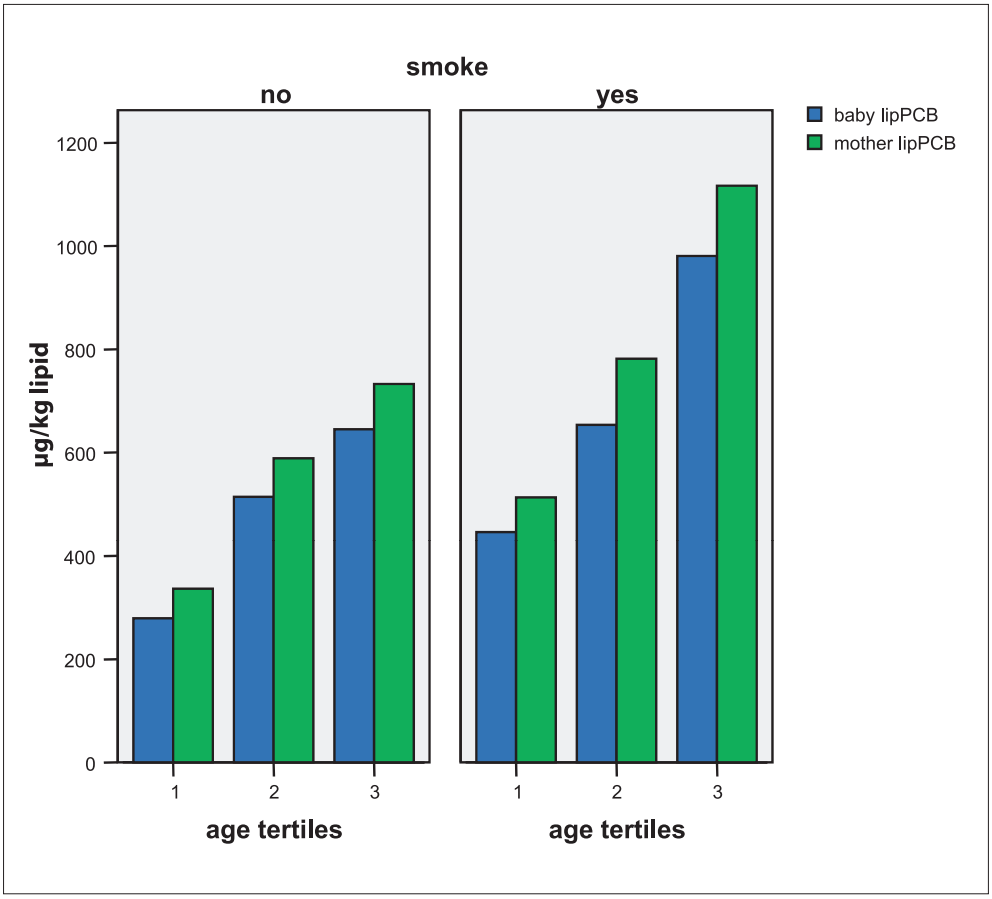

Figure 25. Lipid adjusted PCB levels in maternal and cord plasma as a function of the mothers present smoking status in Disko bay, Greenland 1994-97.

Considering the regression analyses between cotinine and the individual congeners, there were no significant associations found between PCB 105 or 118 and cotinine, but there was a highly significant direct relation between PCB 153 (and other highly chlorinated PCBs) and cotinine (see Table 6). As a consequence we are back to the paradox that highly chlorinated PCBs (153 and others) are increased in smokers compared with non-smokers.

Tabb *et al*. (2004) demonstrated that, contrary to results for rodents, in humans the higher chlorinated PCBs inhibit the steroid and xenobiotic receptor SXR and thus its target gene CYP3A. These enzymes metabolise most of the non co-planar PCBs in mammals, but these compounds seem to inhibit their own metabolism in humans. Raunio *et al*. (2005) found that smoking markedly represses CYP3A5 in human alveolar macrophages.

Table 7. Partial correlation coefficients between plasma cotinine and PCB congener ratios, after adjusting for age, district and plasma n-3/ n-6 ratio.

	Cotinine vs. PCB105/PCB153	Cotinine vs. PCB118/PCB153
r-value	-0.237	-0.294
p-value	<0.0001	<0.0001

Table 8. Partial correlation coefficients between plasma cotinine and single PCB congeners adjusted for age, district and plasma n-3/n-6.

	Cotinine vs. PCB 105	Cotinine vs. PCB 118	Cotinine vs. PCB 153	Cotinine vs. PCB 180
r-value	0.009	0.001	0.10	0.10
p-value, 2-tailed	0.860	0.979	0.048	0.053

Based on these observations, it can be hypothesised that, in smokers, the xenobiotic metabolizing CYP3A is almost entirely blocked and higher chlorinated PCBs are not metabolized; while in non-smokers, the system is only partly blocked and PCB metabolism will take place, even at a low metabolic rate. This may provide an explanation for the observed difference in plasma concentrations of the higher chlorinated PCBs in smokers and non-smokers. It may also explain why sum of PCBs levels are higher. If this is the case, the concentration pattern of PCB metabolites should show the opposite tendency.

The inconsistency in observations on smoking related PCB levels may well be related with the polymorphic nature of the P-450 enzymes. As this question seems to have public health implications, we suggest that all relevant data from the eight Arctic countries to be collected for a statistical scrutiny, with special emphasize on the different exposure levels.

CHAPTER 11

DISCUSSION AND CONCLUSIONS

The conceptual view that a hypercaloric, unbalanced diet will result in obesity is well-established, with the energy balance playing a key role beyond discussion. The remaining controversy centers on the question of whether low fat or low carbohydrate diets are the most efficient for weight reduction. Recent research has tended to conclude that as long as the diet is hypo- or eucaloric, the relative amounts of the macro-nutrients are of minor importance. Raatz *et al*. (2005) compared obese subjects on three different hypo- and isocaloric diets: 1. A high glycemic-index diet; 2. A low glycemic-index diet; 3. A high-fat diet. After 12 weeks, weight loss from baseline, and improvement in insulin sensitivity were significant for all groups, but not different between groups. This underlines that energy restriction is conditio sine qua non in weight control. Maintenance of a good metabolic health goes, however, beyond weight control. In this connection the quality of the macro-nutrients play a pivotal role. Especially the dietary fat composition is important. Some saturated fatty acids, e.g. palmitate, induce inflammation in adipocytes and will, as such, promote and exacerbate obesity and insulin resistance (Ajuwon and Spurlock 2005). Polyunsaturated fatty acids of both the n-6 and n-3 families are essential. The two families of fatty acids interact in regulation of pro- and anti-inflammatory processes. A low n-3/n-6 ratio will tend to be proinflammatory, while a high ratio on the other side will induce an immuno-suppressive state. Furthermore, there is evidence to show that n-6, but not n-3 fatty acids have a lipogenic action. For these reasons a balanced dietary intake of the two PUFAs is very important. The optimal ratio is, however, still under debate. The precolonial traditional Inuit diet provided a ratio around 1, while in a present day westernised fast-food diet the ratio could be as low as 0.05. In a review of the n-3/n-6 balance in relation to cardiovascular health Wijendran and Hayes (2004) recommend a ratio of 0,16.

Compared to PUFAs, carbohydrate quality seems not to play an important role as, unlike PUFAs, carbohydrates do not interfere with

gene expression of metabolic regulating enzymes. Carbohydrates serve as energy source, and as long as the total energy supply is eucaloric, even the GI seems to be of minor importance. An exception is the unphysiologically high intake of fructose prevalent today as a result of the increasing industrialisation of food production. Existing literature provides convincing evidence that this is a major contributor to the increasing prevalence of obesity and MetS, which is being experienced today on a global scale.

A common feature of dietary induced obesity and MetS is the induction of oxidative stress at a cellular level, and consequently development of inflammation. This is also a characteristic of environmental xenobiotica to which humans are exposed through the diet. As a consequence, it is reasonable to speculate on an interaction between an unbalanced diet and concomitant exposure to xenobiotics, where the contaminants may play a role as aggravating factors. The early findings, from the 1980s, of a PCB-related and persistent increase in serum triglyceride concentrations clearly support a connection to xenobiotic exposure, as do the recent findings from Greenland, where the risk factor for cardiovascular diseases, TG/HDL was, as expected, increased by increasing BMI, but further increased according to exposure level to POPs. This seems to be a clear indication that, in relation to obesity and MetS, neither dietary imbalances nor exposure to contaminants should be evaluated separately, but should be considered in combination.

With the exception of certain populations, such as the Inuit consuming large quantities of marine mammals, the general levels of contaminant exposure in the Arctic are below guidelines for safe exposure. A question, however, remains as to whether these relatively low exposures can still have an influence on metabolic disorders. Based on the existing literature, it seems reasonable to speculate that, in an already susceptible organism, predisposed to develop metabolic disorder as a result of life-style factors, a concomitant exposure to dietary contaminants will, even at a relatively low level, accelerate the inflammatory processes and thus act in an additive way. At the moment there is little epidemiological evidence for this, however the available experimental results provide a justification for taking this into account in future studies examining this public health problem (see Fig. 26).

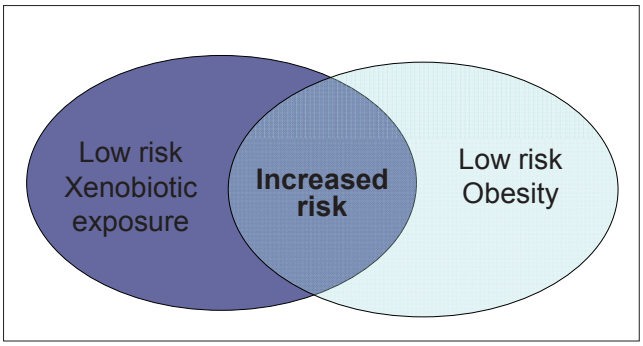

Figure 26. Interface between low xenobiotic exposure and obesity.

The origin of obesity and its sequelae is rooted in a complicated causal web, where genetic-, epigenetic, and environmental and life-style factors all play pivotal roles. This is illustrated in Figure 27.

The notion that nutrition can modulate the toxicity of environmental pollutants, and *vice versa*, represents a new way of thinking in the field of environmental health. Nutritional awareness in environmental toxicology is critical, because of the need to develop guidelines which specifically target exposed populations. In this way, nutrition may provide the most sensible means of developing primary prevention strategies for diseases associated with environmental toxicology (Hennig *et al*. 2004).

In conclusion, in order to improve our understanding of the health effects associated with exposure to contaminants in the Arctic, it is recommended that circumpolar studies, including both nutritive and toxicological aspects should be implemented on a larger scale. Methylmercury- and POPs- related effects are still the key issues. However, the role of more recently observed contaminants, such as polybrominated diphenyl ethers (PBDEs), polychlorinated naphtalenes (PNCs), phtalates, and bisphenyls, should also be investigated. For exposure estimates, mixtures and nutritional benefits of foods should be incorporated in risk-assessment profiles. There is a need for a better understanding of the interactions between nutrients and xenobiotics, and risks should be evaluated in accordance with this interaction. A conceptual model is presented in Figure 28.

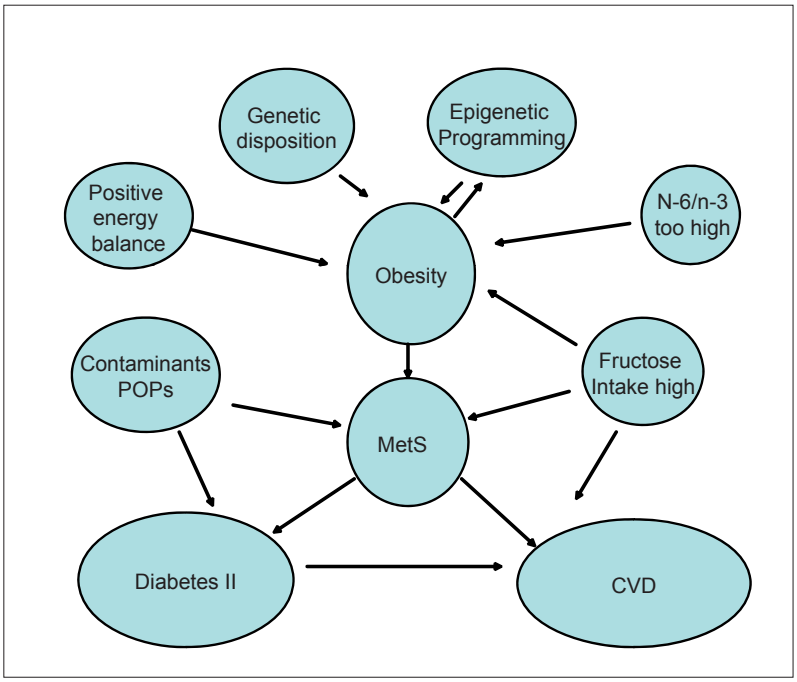

Figure 27. The causal web for the metabolic syndrome and its co-morbidities.

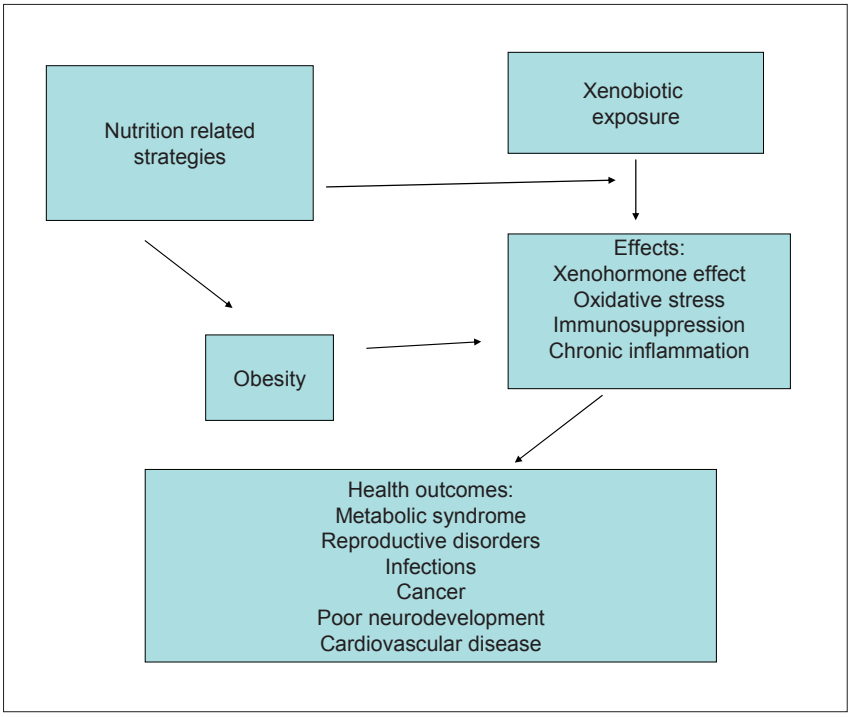

Figure 28. A conceptual model for dietary intervention strategies to reduce effects of environmental xenobiotics.

It is essential that a better understanding of the health consequences of nutritional transition in Arctic populations is achieved, as well as of the nutrient/contaminant interaction, and that this information is communicated to Arctic populations in a correct, responsible and understandable manner.

CHAPTER 12

PLAIN LANGUAGE SUMMARY

Human nutrition

Generally speaking, health is determined by a combination of the genetic fingerprint and environmental exposures. The human genome was created in response to environmental conditions over the several hundreds of thousands years it took for the modern man (*Homo sapiens*) to develop from his primitive ancestors. In prehistoric times, man lived as hunter-gatherers, with a diet characterised as being high in protein and fat, low or very low in carbohydrate (depending on geographical location), and devoid of dairy products, refined sugars and starches. In Inuit cultures, this dietary pattern prevailed well into the 20th century.

Around 12,000 years ago, man began to cultivate plants and domesticate animals, adopting an agricultural-based lifestyle in most parts of the world. Consequently, the amount of carbohydrate in the diet increased, and dairy products were introduced. This tendency has continued, with increasing amounts of refined food items entering the diet during the industrial period. As the human gene is essentially unchanged over this time, the change in food has resulted in an unbalanced gene/food relationship, which is the main cause for what have been called 'diseases of civilisation', such as obesity, diabetes, and cardiovascular diseases.

In Greenland, however, the hunting culture continued well into the 20th century, with meat and organs from marine mammals, especially seals, being staple foods. In pre-colonial times, local hunting products were the only food available. During the colonial period, this gradually changed, with import of food items, primarily from Denmark. This tendency has continued, paralleling (and supporting) the increase in the size of the Greenlandic population. Consequently, the relative amount of local food in the Greenlandic diet has decreased. Shortly after World War 2, local food accounted for 50% or more in the Greenlandic diet. Since then, this percentage has declined drastically, and

is now on the average of around 25 % in districts with the highest intake of traditional food, while in districts with the lowest intake of traditional food it is now below 10%. The rapid transition during the last 50 years has been influenced by increased access to outside information and resulting exposure to the 'western' lifestyle, together with the general trend in modern society towards 'globalisation'. This has transformed Greenland into a modern society, and altered eating habits to a more 'western' style, especially among young women in the larger towns. The transition has also introduced the Greenlandic society to the 'pit-falls' of unbalanced nutrition, well known in industrialised parts of the world. For these reasons it is important that guidance on dietary changes is made available, especially in a society under such rapid transition from one culture to another.

Obesity

Obesity is, today, of epidemic proportions in most areas of the world, including the Arctic, and the tendency is increasing. Obesity increases the risk for development of type 2 diabetes and cardiovascular diseases, and is therefore an immense health problem on a global scale. In addition to the previously mentioned gene/food imbalance, a number of other factors play an important role.

Overeating, when more energy is consumed than used and the surplus is stored as fat is a primary factor for obesity. Also, people have an increasingly sedentary lifestyle and consequently lower need for energy, thus exacerbating the overeating problem. It is not only the amount of food eaten that matters; the quality of the food is also of great importance. A high intake of refined sugars provides a high amount of energy which, if not compensated for, will lead to obesity and stress the production of insulin, ultimately leading to the development of diabetes. Fructose is a simple sugar which occurs naturally in fruits. However, as fructose tastes sweeter than glucose it has been industrially produced and used as an additive in numerous commercially prepared foods, including soft drinks. As a result, intake of fructose has increased from a natural and healthy intake of few grams per day to around 100 grams per day in extreme cases. An unnaturally high intake of fructose presents a health risk as it increases the level of blood lipids and uric acid, both of which are strong indicators of increased risk for cardiovascular diseases.

The fat fraction of the diet represents another problem. Per gram, fat contains more energy than protein or carbohydrates. Consequently low-fat diets have been widely recommended; but in spite of this, people continue to become more obese. It is therefore not only a matter of the amount of fat that is consumed, but also the kind of fat that is present in the food. Saturated fat is characteristic for foods derived from domesticated animals; wheras wild-living herbivorous mammals tend to have a fat composition that reflects the food they eat, with a relatively high content of polyunsaturated fatty acids. If eaten in too high amounts, saturated fat is lipogenic and pro-inflammatory, and as a consequence should be restricted in the daily diet. Monounsaturated fats, e.g. olive oil, are in general neutral fats and, as such are an acceptable substitute for saturated animal fat. Of particularly interest, however, is the polyunsaturated

fat (PUFAs). Two families of PUFAs are identified, according to their chemical composition, as n-6 and n-3. For simplicity, (although not totally correct) these are referred to in the following as plant oils and fish oils, respectively. Both are essential to human nutrition and have to be supplied through the diet as they are needed for optimal development of the brain and the nervous system during foetal life and infancy. A constant supply in later life is also necessary to maintain a vital balance in biochemical body function.

Around 50 years ago, it was observed that plant oils reduced blood cholesterol levels, and for that reason they were recommended as a substitute for animal saturated fat in order to protect the heart. However, the expected effects on health did not appear and the prevalence of heart diseases continued to increase. An explanation for this may well lie in the fact that, at the time, fish oils were not recognised as essential; this first happened later in the 20th century. In several respects, the two families of polyunsaturated fats have different ways of action in the human body. The main differences are that the plant oils are pro-inflammatory, while the fish-oils are anti-inflammatory. Plant oils are also lipogenic, while fish oils are anti-lipogenic. As these opposite effects are equally important, it is clearly understood that the balance between the two families of fats is essential; a dominance of plant oils will favour inflammation and obesity, while an excess of fish oil will suppress the immune defence and contribute to increased susceptibility to bacterial and viral infections, but on the other hand will combat obesity. By studying our ancestors diet, is appears that the ratio of the two types of polyunsaturated fat was close to one, which can be regarded as the optimal ratio. In 'westernized' societies, with a fast-food culture, there has been a shift to a higher plant/fish fat ratio, in some as high as 20 in some cases. This will certainly contribute to the health problems, and responsible nutritionists have now begun to recommend a reduction of plant oil intake relative to fish oil. The obesity problem is difficult to deal with for a number of reasons. Firstly, among these is the complexity of the causal web; secondly is the lack of consistency and relevance of many advisory programmes; thirdly, some people are reluctant to permanently change their lifestyles in order to maintain a normal weight. The global epidemic seems likely to continue in a vicious circle, not least because obese mothers will, through foetal programming, give birth to babies with increased risk of developing obesity (and consequently also diabetes and cardiovascular diseases) later in life.

Contaminants

Environmental contamination on a global scale is essentially a post World War 2 phenomena, with the problems continuing to grow until the mid-1970s when it became evident that many of the chemicals concerned were potentially harmful to animals and humans. Furthermore, it was recognized that many chemicals were also very resistant to degradation both in the environment and in living organisms following uptake. As a consequence, bans and restrictions were introduced in many countries, culminating in the recent entry into force of international conventions that ban or control the use of some of these toxic compounds. However, due to their persistence, considerable quantities of the main chemicals of concern

remain in the environment, and they continue to be transported around the globe by ocean currents and through the atmosphere. In the marine environment, chemicals are taken up by organisms and enter the marine food web. Some (in particular some lipophilic) chemicals biomagnify, such that concentrations may increase by several orders of magnitude from the lowest to the highest organisms in long marine food chains, resulting in especially high levels of accumulation in top predators, such as polar bears. When man utilises these species for food, he occupies the top level in the food chain, and as a consequence may have very high dietary exposures to contaminants. This explains why contamination of traditional foods is such a concern in the Arctic, despite the fact that the region is far from those areas where the chemicals are produced and used.

Marine food webs may be long, involving several trophic levels, unlike the terrestrial environment where the connections tend to be a shorter, with perhaps three levels from plants to herbivores to predators. For this reason, food contamination is primarily a problem linked to intake of predatory marine mammals and seabirds. Contaminants of highest concern include PCBs, pesticides, and mercury. In addition, a number of organic compounds, such as PCBs and a several pesticides are soluble in fat and therefore concentrate primarily in fatty tissues such as the blubber, whereas mercury (as methylmercury, the chemical form that is most prevalent in living organisms) is found primarily in the muscle tissue. Such factors need to be taken into account when developing dietary advice.

Due to the fact that marine mammals still play a relatively large role in human nutrition in several districts in Greenland, human contaminant exposure remains high and, in a number of cases exceeds internationally accepted guidelines for safe exposure. The same applies to other Arctic communities that have similar situations to those in Greenland. Although this information has now been available for more than ten years, few official recommendations concerning changing lifestyle or eating habits have been issued.

The resons for this are several. Firstly, an exposure that moderately exceeds guidelines does not in itself imply an increased risk of developing specific diseases; such guidelines include built-in uncertainty factors (typically applying a factor of 10 or 100 to identified effects levels) to account for differences in individual susceptibility. Secondly, the fact that the exposure originates from traditional marine food sources which contain essential and health promoting nutrients means that over-simplistic advice may do more harm than good.

This dichotomy is the reason behind the conclusion in the 1997 AMAP human health assessment that the known beneficial nutritional qualities in the traditional diet probably overweigh the potential negative effects due to contaminants. In the most recent AMAP human health assessment report, from 2003, it was concluded that present levels of exposure to contaminants do have negative health effects in some Arctic populations. Since its publication, this conclusion has been further substantiated.

In Greenland, a relationship between contaminant exposure and sperm motility and activity of sex hormones has been demonstrated which may have implications for human fecundity. In the Faroe Islands, recent investigations have indicated that prenatal

exposure to PCBs impair the ability to produce antibodies. These studies, in children at age 7, indicate an increased susceptibility to infectious diseases. Furthermore, both in the Faroe Islands and in Greenland, recent data indicate that risk factors for developing cardiovascular diseases are increased by contaminants, both by organochlorines and mercury. Interestingly, in the data from Greenland it was shown that the risks were most pronounced in the obese group while practically absent in normal weight individuals. This indicates that a contaminant exposure moderately in excess of international guidelines, while not an immediate health risk, may, in combination with lifestyle induced metabolic disturbances be capable of aggravating the effects associated with obesity. For this reason, it is not possible to separate the contamination problem from life-style effects, and the two health aspects should therefore be assessed in an integrated health policy.

What needs to be done?

In order to improve the quality of food and reduce the exposure to contaminants there seems to be an immediate need for some degree of intervention in Arctic populations experiencing rapid dietary and cultural transition. One particular issue concerns life-style/dietary advice to reverse the development of increasing bodyweight. This is a global health issue, which is also an increasing problem in Greenland and has developed to be the major public health concern. Another is to decrease contaminant exposure, to address the negative health effects which have been related to contaminants at the levels of exposure currently found in several Arctic populations. These two activities need to be integrated as they are inter-related. A final plan for intervention also needs to include appropriate consideration of the possible consequences on cultural and dietary traditions in the regions.

As mentioned above, the observed increase of prevalence in obesity is primarily related to the quantity of food eaten in relation to energy expenditure. Therefore, energy balance also needs to take into account a certain level of physical activity, which is also important for an optimal metabolism.

Equally important as the quantitative aspect, is the qualitative aspect of the food and the balance between individual nutrients. Taking energy balance for maintaining normal body weight (or a negative balance in the case of a weight loss regime) as a prerequisite, the following recommendations can be given:

- With regard to fat, the intake of saturated fat should be restricted to a minimum and if possible replaced with monounsaturated fat, e.g. olive oil. Also the intake of plant oils (n-6) should be restricted in relation to fish oil (n-3) to ensure an n-3/n-6 ratio of above 0.2, but blubber intake from marine mammals should be reduced.
- With regard to carbohydrates, the intake of refined sugars, especially fruit sugar (fructose) should be restricted to a minimum, and refined starches should be eaten in moderation, vegetables and fruit intake should be increased.
- With regard to protein, the main part should be derived from lean red meat from terrestrial game and from fish. Because of their contaminant load meat, blubber and organs from marine mammals should be eaten in moderation, especially by children and people in the fertile age group.

A reduction in the level of dietary exposure to environmental contaminants is necessary due to the fact that several Arctic populations have been shown to have exposures in excess of internationally accepted guidelines for safe intake. High exposure levels are closely related to intake of food derived from marine mammals. In Greenland, this exposure has been shown to be related to occurrence of negative health indicators, such as disturbed sex-hormone balance/activity and to a reduced sperm quality. Furthermore, recent data generated under the AMAP programme have indicated that exposure to POPs (PCBs) is related to an increased level of blood lipids, an indicator of increased risk for development of cardiovascular diseases. The effect was not noticeable in normal weight, but only in obese persons. This underscores that even if exposure levels *per se* are not high enough to induce measurable changes in the risk factors in normal weight individuals, in obese individuals with an increased risk, contaminants can aggravate the risk.

This clearly demonstrates that the two problems, contaminant exposure and lifestyle related obesity cannot be separated, and should be addressed simultaneously in a general food policy.

Human exposure to hazardous contaminants can be reduced in two ways:

- Agreement of measures such as international conventions to eliminate or reduce production and use of the most dangerous chemicals. This is, however, a very slow and time consuming process.
- Implement intervention strategies locally, in order to protect the highest exposed populations, as a quick and effective first action.

In the Arctic, the main source of most contaminants of concern in highly exposed groups is from consumption of marine mammals. Consequently, the most efficient way to reduce human exposure is to replace consumption of highly contaminated marine mammals with fish and terrestrial mammals. Since World War II, the proportion of marine mammals in the traditional diet has steadily declined, from being a major staple food to accounting for, on average, less than 10% of the energy intake at the present time in the larger communities. This development is especially pronounced among young people. Some older people still regard marine mammals as part of the traditional food and their cultural integrity. However, the risk to normal weight persons over reproductive age of continuing their traditional eating habits is negligible and they should therefore not be recommended to change this. It is the younger generation who need to be guided into a healthy life style through relevant education.

Eating traditions are an integrated part of a culture. Cultures are not static but must constantly develop and adapt to the changing world – as must dietary habits. Nowadays no generation eats exactly as their parents did and eating habits change with the changing culture. The present tendency to follow a 'western' lifestyle, with increasing consumption of fast food products will by no means promote an improvement in the general health situation. The time has come where it is necessary to implement a general public health policy, which through proper education of the younger generations may improve living conditions for Arctic peoples within their cultural traditions, and still recognizing the value of local food resources.

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