

NUTRITION AND HEALTH COLLECTION

NUTRITION AND SUCCESSFUL AGEING



Éditions John Libbey Eurotext

127, avenue de la République
92120 Montrouge, France
Tél. : 33 (0) 1 46 73 06 60
e-mail : contact@john-libbey-eurotext.fr
<http://www.john-libbey-eurotext.fr>

John Libbey & Compagny Ltd
Collier House
163-169 Brompton Road
Knightsbridge
London SW3 1 PY, England
Tel. : 44 (0) 20 75 81 24 49

CIC Edizione Internazionali
Corso Trieste 42
00198 Roma, Italia
Tel. : 39 06 841 26 73

© John Libbey Eurotext, 2002
ISBN : 2-7420-0424-6

Il est interdit de reproduire intégralement ou partiellement le présent ouvrage
sans autorisation de l'éditeur ou du Centre Français d'Exploitation du Droit de Copie (CFC),
20, rue des Grands-Augustins, 75006 Paris.

NUTRITION AND
SUCCESSFUL AGEING



Scientific Committee

Cameron CHUMLEA, *Wright State University of Medicine, Yellow Springs, USA*
Gino DORIA, *University of Rome, Italy*
Bruno VELLAS, *CHU Toulouse, Hôpital de Casselardit, France*
Irene LENOIR-WIJNKOOP, *Danone Vitapole, Paris*

Contributors

J. AMES, *United Kingdom*
R. ASPINALL, *United Kingdom*
G. BIRO, *Hungary*
J-P. BONJOUR, *Switzerland*
C. BOULEY, *France*
K. CHARLTON, *South Africa*
D. COMMENGES, *France*
V. DE LA GUERONNIERE, *France*
P. DUCIMETIERE, *France*
A. FAZEL, *France*
S. GUO, *USA*
B. JACOTOT, *France*
S. KALMIJN, *The Netherlands*
D. LANZMANN, *France*
B. LESOURD, *France*
D. LINDSAY, *United Kingdom*
M. LYNCH, *Ireland*
J. MILLWARD, *United Kingdom*
H. PAYETTE, *Canada*
E. POSTAIRE, *France*
G. ROTH, *USA*
D. SCHMUCKER, *USA*
J. SELHUB, *USA*
A.J. SINCLAIR, *United Kingdom*
R. SOLANA, *Spain*
N. SOLOMONS, *Guatemala*
L. SZPONAR, *Poland*
P. SUTER, *Switzerland*
K. THOREUX, *USA*
M.C. VAN NES, *Belgium*
R. WEINDRUCH, *USA*
M. WEKSLER, *USA*
J.W. WONG, *Hong Kong*

Scientific Coordination

Irene LENOIR-WIJNKOOP, *Danone Vitapole, Paris*

CONTENTS

Introduction

Successful ageing or functional decline, The impact of nutrition	3
---	---

Chapter 1 - Nutrition, ageing, and functional decline

Sarcopenia	6
Nutrition and osteoporotic fractures in the elderly	8
Water and ageing	9
Anti-ageing effects of caloric restriction	9

Chapter 2 - Nutrition and cognitive function

Aluminium, silicon and Alzheimer's disease	15
Dietary fat intake and cognitive decline	16
Dietary manipulation and animal studies	18
Diabetes and cognitive function	20

Chapter 3 - Nutritional impact on immune response and life span

Immune deficiency and dysregulation	21
Micronutrients and immune response in the elderly	22
Role of genes in immune response in the elderly	25
NK and NK/T cells, nutrition and immune regulation	26
Ageing and the impairment of intestinal immunity	27

Chapter 4 - Nutrition and the cardiovascular system	
Nutritional fat supply and cardiovascular disease	29
Ageing, oxidative stress and atherosclerotic cardiovascular disease	31
Selected studies on diet and heart disease	31
The Chinese diet and heart disease	33
Chapter 5 - Nutritional impact on cancer	35
Chapter 6 - Type 2 diabetes and the nutritional balance	
Epidemiology	37
The relationship with nutrition	37
Suggestions for studies	39

INTRODUCTION

In the past, studies on ageing and functional decline were exclusively cross-sectional, focusing on different groups of people of ages 20, 40 and 70. Recently, researchers were able to follow the same people over an extended period of time, in cohorts. These longitudinal studies reveal that the effects of ageing are less important than formerly believed.

"Usual" ageing is defined as a process involving frailty, functional, cognitive and muscular decline and possible loss of autonomy. The ageing rate is expressed by the maximum life span potential of the longest living member of a mammalian population; it varies from 3 years in rodents to about 120 years in humans. The mean life span has been enhanced greatly in humans since Antiquity. Though people live longer today, they still age at the same rate and the maximum life span remains the same for different populations at various periods of times. The ageing rate is under genetic control.

In France, life expectancy for women is 82 years, as compared to 74 years in men. The two categories of people who are considered to be ageing "successfully" are those who remain very healthy even beyond 90, and those who live without requiring medicine. Here, successful ageing is defined as avoiding disease and disability, having an active social life and maintaining high cognitive and physical functions. Scientists are currently very interested in understanding whether nutrition has played any role in this success.

Finally, "bad" ageing is that in which disease occurs. The three major categories of diseases involved are: degenerative diseases, cardiovascular diseases and malignant diseases. Coronary diseases occur more frequently in people aged 45 to 70 as do cerebro-vascular accidents. The rate of malignancies and, in particular, the mortality linked to cancers, also increases with age.

Recently, four large longitudinal studies addressed successful ageing and showed

interesting conclusions: the Manitoba Study (Canada), the MacArthur and New Mexico Studies (USA) and the Toulouse Study (France). The MacArthur Study followed more than 1000 participants from 1988 to 1990 while the Toulouse Study focused on nearly 500 people. The 20-year follow-up data of the New Mexico Study, which began in 1979, were recently published.

In all of these studies, the majority of participants maintained stable health. The MacArthur Study noted functional decline in 15% of the subjects two years after the beginning of the study. Six years after the initial study, the Toulouse research group found that 40% of the subjects had experienced functional decline. At the same time, improvement was seen in 13% in the former study and in 6.5% of the latter study. One of the most important findings was that ageing is not always associated with functional decline. In these studies, healthy subjects had an active social life without cognitive or functional decline.

High protein intake seemed to decrease the likelihood of frailty in both women and men. Nonetheless, it has been suggested that the answer is not so much to increase protein or calcium intake, but to ensure that the overall diet is balanced. Many elderly people are still at risk of frailty as they consume only 1 000 calories per day.

CHAPTER I

NUTRITION, AGEING AND FUNCTIONAL DECLINE

One of man's greatest fears in growing older is becoming frail. Most elderly people over 85 are usually frail. People between 70 and 85 years old are more likely to experience functional impairment, which is defined as problems with vision, gait, balance or hearing. The most commonly found characteristic among frail people is the inability to perform instrumental activities in daily life. Since frailty is most likely dynamic, as opposed to unrelenting, it may be possible to prevent or alleviate its effects.

Sarcopenia is a major component of frailty. It describes the loss of lean body mass and, more generally, is defined by the gradual loss of skeletal muscle with advancing age. In the New Mexico Study from 1998, the prevalence of sarcopenia among the healthy elderly was 13% in men under 70 and 52% in men over 80; the prevalence in women was 23% and 43%, respectively. This loss of muscle mass can impair mobility (gait, balance, strength) in otherwise healthy people. Although more studies are needed on this topic, current data show that low protein and calorie intake are possible causes of sarcopenia. Testosterone is among the hormones being tested for possible use since it has relatively few side effects and has proved effectiveness.

Sarcopenia can be measured in a number of ways. It can be expressed as a relationship between age and creatinine excretion, or by the dual-energy X-ray absorptiometry (DXA) that measures the whole body composition (lean and bone masses) and regional body composition (appendicular skeletal muscle mass [ASM]). Sarcopenia is associated with a loss of muscle fibres, especially type II fibres. Cut off values for sarcopenia in each sex were defined as values of two standard deviations below the sex-specific means of the Rosetta Study reference data for young adults:

- $ASM/height^2 < 7.26$ in men;
- $ASM/height^2 < 5.45$ in women.

Osteoporosis is defined as a generalised skeletal disease resulting in low bone mass and impairment of bone tissue. It brings about fragility and increased susceptibility to fracture. However, it is important to remember that fractures are not a necessary component of osteoporosis. Common fracture sites are the spine, the neck of the femur and the wrist. Thanks to recent technological progress, it is now possible to accurately measure bone mass over time and at different sites.

The number of hospital days per year required by osteoporosis patients is higher than that of patients with coronary heart disease, while the cost amounts to nearly USD 1 billion per year.

SARCOPENIA

One may ask whether it is necessary to be concerned about muscle loss with age. Indeed, it is, as humans cannot expect to be as strong in old age as in their prime. Sarcopenia does matter: the disability rate in patients with sarcopenia is significantly higher where gait abnormality, need for assistance in walking or after falls, etc. are present.

Although scientists are certain that age is the main determinant of sarcopenia, it can also depend on a variety of other factors, including hormones (estrogen, testosterone, insulin) and cytokines (interleukin-6, interleukin-1 β , TNF- α). The latter can also have an effect on dietary intake, since they can influence the resting metabolic rate, protein and fat metabolism. Some influential factors are not modifiable: gender, genetic height (reduced height is associated with lower muscle mass). Physical activity, on the other hand, can be adjusted and has subsequent effects on appetite and dietary intake.

Exercise would appear to be the proper solution. In reality, the positive effects of exercise on the cardiovascular system seem to have little impact on leg strength. Adults who are aerobically fit and who have had a lifetime of physical activity are no less vulnerable to sarcopenia than sedentary adults who spend their lives watching television and have lower aerobic activity. The only way to prevent or reverse sarcopenia through physical activity is by performing progressive resistance exercises, otherwise known as strength training. This is valid even for frail individuals over 100 years of age. When exercise is combined with nutrition, the magnitude of increase in strength can be more important. Furthermore, the increase in strength leads to an increase in spontaneous physical activity and an increase in food intake. The populations of certain poorer countries, such as Guatemala, enjoy these effects because exercise and physical activity are integral parts of their lives. It is possible that, once maximal muscle size has been attained as a result of bone length, the absence of further active stretching must be compensated by changes in lifestyle in order to maintain the muscle size.

Since muscle function is associated with muscle protein, it is natural to assume that sarcopenia patients suffer from inadequate protein status. Two studies focused on this subject. The first involved a group in Boston in the 1980s, and examined a group of men and women with adequate levels of protein. The study aimed to determine the relationship between protein intake and nutritional status by measuring anthropometry and blood biochemistry. At least four parameters were measured, one of which was a surrogate measure for sarcopenia. It

showed that protein intake was inversely related with indicators of nutritional status.

The second study was conducted in Southampton in the 1980s. It attempted to study nitrogen balance in two groups of elderly people. The first was healthy, mobile and consumed Recommended Dietary Allowances (RDA) levels of protein, while the second was housebound, suffered from a variety of chronic diseases and consumed low levels of protein. The latter group tended to show a negative nitrogen balance in intake versus excretion, whereas the healthy individuals showed a zero balance. Most interestingly, there was no relationship between the level of intake and actual success in achieving balance. Individuals in both groups were just as likely to exhibit characteristics of the group as a whole.

Both of these studies seem to indicate that it is difficult to find causal relationships between protein intake, nitrogen balance and muscle mass as measured by muscle circumference.

There is no convincing evidence indicating that the elderly have higher protein requirements. However, it is important to bear in mind that none of the studies performed thus far used functional indicators. An attempt is now underway to address this question and to identify the biological basis of protein requirements. C13 glycine oxidation was used in this study to model the metabolic demands for protein by measuring post-absorptive losses. Post-pancreatic protein gain of C13 glycine balance was used to calculate the efficiency of protein gain. These two parameters were then used to calculate the apparent protein requirement, expressed as demand divided by efficiency of utilisation. Again, this study examined protein requirements for balance.

The first set of data was published recently. It involved ten young and ten elderly, mobile, fit men and women. The metabolic demand falls with age; there was no difference at all in efficiency of utilisation. The protein requirement as measured with this protocol is thus lower in the elderly than in other age groups. The fall in itself is less significant than the fact that protein requirements do not rise with age. In other words, no detrimental effects were identified with age.

Sarcopenia is a major cause of disability in the elderly. It is unlikely that this condition is caused by protein deficiency. Unfortunately, aerobic exercise does not appear to protect against loss of muscle. Progressive resistance exercise, however, can work to this end. Thus, adequate intake of food can be combined with such exercise to prevent the onset of sarcopenia.

However, recent studies are now exploring the effects of protein when taken as a supplement. One French study noted that, when taken as a daily supplement, protein could increase overall bone mass. Likewise, it is necessary to study the relationship between bone and muscle mass. What has yet to be established is the existence of any interaction between nutrition and strength training in relation to the prevention of sarcopenia.

NUTRITION AND OSTEOPOROTIC FRACTURES

Many of the risk factors associated with osteoporotic fractures cannot, in fact, be treated. Among others, they include age and previous fractures. Today, scientists are attempting to determine whether those risks could be diminished through proper nutrition, increased physical activity, weight loss or other long-term solutions. The decrease in bone mass following the onset of osteoporosis makes fractures resulting from falls all the more dangerous. It has already been proven that the incidence of falls increases with poor nutrition. At the current time, scientists are studying whether protein can play some positive role. Protein intake below RDA levels could be particularly detrimental for both the acquisition of bone mass and the conservation of bone integrity with ageing. Low calorie and calcium intake have also been linked with osteoporotic symptoms.

In order to determine the role of each of these elements in the development of osteoporosis, physicians provided patients with vitamin D, calcium and protein supplements. The normalisation of protein intake, independent from that of energy, calcium and vitamin D, was clearly responsible for a more favourable outcome in patients who had suffered from hip fracture. This is due to protein's ability to stimulate the production of IGF-1 (Insulin-like Growth Factor), which enhances the growth of bone metabolites. Experimental studies show that IGF-1 *in vivo* stimulates bone formation both directly, as described above, and indirectly, by influencing renal functions important for calcium-phosphate homeostasis.

In vitro exposure of osteoblastic cells to some amino acids (e.g., arginine) leads to a stimulation of the production of IGF-1 within the bone. Thus, low protein intake decreases IGF-1, bringing bone mass and muscle mass levels down. In undernourished elderly subjects, an increase in protein intake, from a low to a normal level, induces a significantly greater gain in plasma prealbumin, IGF-1 and IgM than isocaloric placebo after six months of administration. Moreover, protein-supplemented patients experienced an increase in proximal femur areal bone mineral density (aBMD) after one year. This favourable response was associated with a shorter stay in rehabilitation hospitals.

These studies contradict data obtained in the United States, which initially prompted physicians to discourage protein intake or, at the very least, to keep it to a minimum. In order to gain confirmation of these somewhat new principles, scientists developed an animal model using adult female rats. Isocaloric protein undernutrition was shown to mimic osteoporosis observed in elderly women, in whom both cortical and trabecular skeletal sites were affected. Decreased protein intake led to a decrease in IGF-1 production and action as well as in bone production. In addition, some cytokines were found to have an effect on sex hormone production, a topic which is currently under study.

Based on these data, a series of recommendations have been issued to the general population, physicians and future researchers. The two most relevant to this topic are:

- 1) Undernutrition and malnutrition, which are characterised by low calcium and protein intakes, can favourise osteoporosis;
- 2) Calcium, vitamin D and protein supplementation can prevent the onset of osteoporosis and maintain bone health.

In addition, exercise is not only good for overall muscular and cardiovascular health, it can improve bone strength.

WATER AND AGEING

Little information is available on the topic of body water in adults. One of the problems inherent to such studies resides in the impossibility to separate water from fat-free mass and total body fat. Thus, the supposed correlation between body water and age is in fact a relationship between fat and fat-free mass. The women studied also showed a slight age-related decline in total body water. The only significant negative trend that was independent from results on body composition was found in the population of Black men.

According to the results of longitudinal studies, there is no change in total body water until age 65 in men and until age 40 or 50 in women, probably due to the effects of menopause. Even then, body water levels do not vary significantly.

There exists only a limited amount of information on total body water and extracellular fluid, whatever the age group studied. This is particularly true for the elderly and minority groups. There is no change in total body water or extracellular fluid independent of fat levels. The extent of these relationships after age 75 is unknown. Once these relationships are elucidated, they will be valuable in the treatment of kidney failure and renal disease through dialysis, as well as in developing a better approach to heart failure and oedema. Clinical pharmacologists lend great importance to water balance. Recommended water intake has been set at eight glasses (2 litres) a day and should apply to all populations, whether old or young. It is difficult to ingest too much water.

ANTI-AGEING EFFECTS OF CALORIC RESTRICTION

Dietary caloric restriction (CR) is the only intervention conclusively and reproducibly shown to slow ageing and maintain health and vitality in mammals. This mechanism is most effective when initiated early in life and continued thereafter. Laboratory rodents submitted to 25% to 50% reduction in caloric intake without malnutrition display delayed onset of age-associated pathological and physiological changes, as well as extension of maximum life span. CR postpones age-related immune dysfunctions and retards the onset of cancer, nephropathy and myocardial degeneration.

One of the basic effects of dietary CR is the delay of age-associated decline of DNA repair. The maintenance of DNA integrity in long-lived and actively-dividing lymphocytes is instrumental for normal functions of the immune system, which may, in turn affect life span. It has recently been shown that CR prevents the degeneration of gene expression in ageing. Whether CR has an effect on the level and activity of DNA's PK components is an interesting possibility and should be explored. CR might also be capable of modifying auto-immune reactivity.

Since the introduction of the concept of CR 60 years ago, two burning questions

have prevailed in the minds of scientists: what is the biological mechanism of action? Can CR work in humans? Since any experiments on humans would be extremely difficult, studies have been started with primates, to identify possible areas in which CR can be relevant to humans. One longitudinal study involved 60 male and 60 female rhesus monkeys, divided into three groups according to their age at the start of the study: juvenile, young adult (3-5 years), older (>17 years). The diet administered contained only 5% fat in order to ensure that the control animals are not obese. Restriction begins at 10%, then rises to 20% and, finally, to 30%.

The measurements taken to test the general health included: energy metabolism, age-related disease (osteoporosis, diabetes, cardiovascular disease), vital markers of ageing, oxidative stress. Physiologically, CR monkeys are smaller and shorter than their control counterparts, and show less adiposity at the waistline. They are also healthier than fully-fed monkeys. One of the first metabolic changes observed in CR monkeys is a drop in body temperature. Initially, temperatures were lowest in the morning and highest in the evening, as in humans. This pattern was sustained throughout the experiment, but was consistently 0.5°C to 1°C lower in CR animals. Although this drop does not account for all of the metabolic benefits, it is symptomatic of an overall change in strategy, from a reproductive aim to a life maintenance aim. All of the body's mechanisms are geared towards keeping the animal alive. Energy expenditure dropped as caloric restriction was phased in, confirming the above hypothesis. However, as soon as body weight caught up with lower energy expenditure, there was no difference between control and restricted groups at any age.

Based on this information, ageing appears to be a series of events where biological processes become deregulated. With time, animals go from an orderly state to a disordered state. Many forces impact this biological disordering (oxidative damage, stress, changes in gene expression) and ultimately result in the death of the organism. The metabolic shift resulting from CR seems to give the monkeys more leverage, making it possible for them to add 30% to 40% more years to their lives.

When intravenous glucose tolerance tests are performed on CR monkeys, peak levels increase with age in both monkeys as we know they do in humans, but the level itself is markedly reduced in CR monkeys. The lowering rate of glucose level back to normal is not affected by restriction, although it does increase with age. Insulin sensitivity falls with age, but is less prominent in CR animals, whose response is clearly better.

The protective cardiovascular effects of CR include: reduction in blood pressure, lower circulating levels of triglycerides, lower LDL-cholesterol levels and, interestingly, an increase in HDL-2B, a substance that has a protective effect against cardiovascular diseases. All of these findings suggest that CR animals are less likely to develop diabetes and cardiovascular problems as they grow older.

One of the best biological markers identified thus far is dehydroepiandrosterone (DHEA), which has often been mentioned in the context of studies on the elderly in the United States. It has been reported to have beneficial effects on a variety of age-related diseases, from immune response to cancer and cardiovascular disease. Scientists were interested in this because, in contrast to normal age-related decline, CR animals experience much slower decrease in DHEA levels without having to benefit from endogenous supplements.

All of the findings made in CR monkeys agree with what has been shown in CR rodents; the only remaining uncertainty lies in the field of longevity, which will require further studies.

CR is probably not easy to respect for most people. It is therefore important for scientists to mimic this effect by restricting energy, without making dieting a necessity. The leading compound at the current time is 2-deoxyglucose, which is structurally similar to glucose. It is insulin-responsive and a competitor in the inhibition of glycolysis: it allows glucose to undergo phosphorylation once, but then metabolises further until 2-deoxyglucose is excreted from the cell. This possibility must be tested with care as high doses of this compound are toxic. The first experiments were therefore devoted to achieving the correct doses and determining the toxic doses.

In rats, 2-deoxyglucose lowers body temperature and has an anti-tumour effect. In humans, it raises the level of glucocorticoid hormones. This is one of the hypotheses that made CR appear beneficial to humans. A six-month pilot study on rodents examined three groups, feeding them diets containing either 0.2%, 0.4% or 0.6% 2-deoxyglucose. Food intake was unchanged, except in the early stages and in the highest groups, which needed time to grow accustomed to the taste of the chow. Body weight was slightly reduced. However, since the animals were not eating less food than normal, this was interpreted to be more weight stabilisation than weight reduction.

More importantly, insulin levels fell, starting at week 13 in the 0.4% and 0.6% groups. Glucose levels did not appear changed, but are not as important a marker as insulin.

The same was true for body temperature over the course of the study: the higher 2-deoxyglucose-groups showed lower body temperature than the control animals. Thus, these two important components of CR can be mimicked using 2-deoxyglucose. Reduction in tumours and effects on stress and apoptosis were other common points found between CR and the mimetic mechanism.

Concerning the manifestations of sarcopenia, there is a slight decrease in lean body mass at the very end stages of life. CR animals did not prove to be any different from *ad libitum* fed animals in that respect. It is difficult to compare these results to those of wild animals, which tend to die younger, victim to predators.

Future studies will attempt to determine whether these animals can indeed live longer while still eating the same amount of food. If that proves true, the beneficial effects of CR can be taken to the next level.

The philosophical implications of CR must always be kept in mind. Is it the responsibility of scientists to increase both median and maximum life span or rather to increase the former, while leaving the latter as is. Similarly, should one aim to lengthen life or to improve its quality? Quite clearly, no one wants to live 120 years if the last 20 years must be spent in a nursing home.

CHAPTER II

NUTRITION AND
COGNITIVE FUNCTION

Cognitive function declines with age. It ranges from simple complaints of memory loss to Alzheimer's disease. After having devoted much of its attention to the prevention of cardiovascular disease in previous years, it is important that the medical community now looks into prevention methods for Alzheimer's disease which affects 8% of people over 65 and 30% of people over 85. In addition to the heavy human cost, the financial cost of the disease amounts to 100 billion USD in both the US and Europe. Therefore, it is very important to search for modifiable risk factors. In particular, anything that can be learned about the effects of nutrition will be valuable in preventing cognitive decline.

Currently, two main hypotheses for the onset of Alzheimer's disease are being examined. Neuronal death is thought to be due to:

- 1) the cumulative consequences of free radical reactions, leading to atherosclerotic lesions, neuronal DNA damage, β -amyloid plaque deposition, glutamate secretion and lipid peroxidation,
- 2) the rise in homocysteine levels, as an independent risk factor for CHD.

Some data suggest that these two hypotheses may in fact be only one since antioxidants are believed to interact in the prevention of hyperhomocysteinemia-related complications.

It has been ascertained that vascular problems and Alzheimer's disease are deeply intertwined. In the past, it was believed that 30% of dementias were vascular in nature while 70% were degenerative. Today, it is estimated that the incidence of true vascular dementia amounts to only 10%.

Mild cognitive impairment (MCI) is characterised by memory complaints on the part of the patient without any disorders being detected in tests. The difference between normal

memory disorder and abnormal memory disorder is the ability to remember words upon receiving hints. Even when people prove to have normal memory disorder, it is still important that they be examined on a regular basis.

If the transition from memory complaints to MCI were better understood, scientists could define a role for nutrition in the prevention of further decline. Intervention studies are necessary in order to prevent the development of MCI or Alzheimer's disease in populations with memory complaints, which are thought to be at high risk. Reviews of several studies indicate that individuals with MCI have a 10-15% increased risk of developing Alzheimer's disease.

Absence of Alzheimer's disease in poorly nourished older Africans

The proportion of elderly in African populations is much smaller than in developed countries (less than 6% of the general population), but the absolute number of older Africans is rapidly rising and is estimated to double within 17 years.

Data on older Black Africans are sparse. One of the largest studies took place in Zimbabwe and showed that anaemia was present in 23% of the population, serum vitamin B12 level was low in 13% and red blood cell folate was low in one-third. Three-quarters of the people in a Cape Town survey had eaten fruit and vegetables in the 24 hours prior to the survey; few of these were rich in either vitamin C or carotene; folate and vitamin B6 levels were equally low in the diet.

Despite a low reported caloric intake of 1 300 calories in women, over half of the elderly women in Cape Town are obese, as compared to only 13% in the rural areas. The change of lifestyle due to the rural exodus includes an increase in fat intake and a decrease in carbohydrate intake.

The incidence of Alzheimer's disease (AD) is believed to be rare, extremely rare or absent in Black Africans. Community, hospital-based or pathological surveys throughout the continent have concluded that it is difficult to find dementias at all.

Comparative insights

A Zimbabwe study compared the severity of neurological affection to haemoglobin levels in people with a low vitamin B12 status, but the authors had the surprise to find that, the worse the neurological score, the better the blood sample. Normally, people with vitamin B12 deficiency are supposed to have anaemia. Instead, good blood samples may be associated with an impaired neurological state. Another study came to similar conclusions.

Most assessments of cognitive function require numeracy and literacy skills. The most commonly used cognitive screening instrument, the Mini-Mental Status Examination (MMSE), has been disputed as it was originally designed for English-speaking literate populations. An attempt in Zimbabwe to adapt and abbreviate this test proved that it remained inadequate, as this assessment tool still included some parameters related to educational

status: based on this test, 48% of the subjects would have been classified as cognitively impaired. A national survey of 4 400 older South Africans showed that 80% of elderly in rural areas have never received schooling and can neither read nor write. This figure falls to 50% in urban areas.

Survey results

A study performed in a rural part of South Africa used rapid appraisal techniques, interviewing psychiatric patients, traditional healers, psychiatric nurses and community representatives. With the exception of the psychiatric nurses, 98% of the group described mental impairment as a manifestation of bewitchment, or "possession by spirits".

Another Cape Town survey of two elderly groups focused on constructive mental illness. There, too, a large gap existed between health care providers and the elderly themselves. Getting lost, forgetfulness and suspiciousness are almost always referred to as "bewitchment" by the latter, but as dementia by the former. If mental illness is observed in younger people, indigenous populations usually ascribe it to consumption of alcohol.

Data from 1996 show that 52% of elderly people live in cities or at their outskirts. When compared to other areas around the world, the slum area in this study showed prevalence of depression three times higher than elsewhere.

Diabetes and hypertension have been proven to predispose to cognitive impairment. In Africa, the situation regarding hypertension is not always clear as prevalence varies widely. Nonetheless, it is clear that half of hypertensives are not diagnosed. Of those who do receive treatment, 80% have blood pressure over 160/95 mm Hg due to lack of primary care services.

ALUMINIUM, SILICON AND ALZHEIMER'S DISEASE

A number of studies and in vitro tests have demonstrated that aluminium is neurotoxic and can therefore induce neurofibrillary degeneration. Naturally, given the ubiquity of aluminium, there are many ways in which it can be ingested and reach the brain. Animal experiments have allowed scientists to confirm the cerebral neurotoxicity of aluminium. In dialysis, the aluminium comes in contact with the blood. In addition, aluminium can penetrate through the lungs (dust in the air), the skin (anti-perspirants, cosmetics) and the gut (food, water). Most of this aluminium is eliminated through urine.

The remaining aluminium can cross the blood-brain barrier. Accidents or lack of awareness involving aluminium can therefore be all the more dangerous. For example, in recent years, workers who were treated against silicosis using aluminium powder now show signs of cognitive impairment. In Camelford, England, a large amount of aluminium compounds were poured into the water distribution network, understandably causing public upheaval. No studies have been performed on the effects of this huge accident. Only a few instances of memory complaints have been noted.

A number of questions must be answered: is aluminium toxic in "normal" situations, such as consumption of food or drinking water? Is aluminium a risk factor for Alzheimer's disease? This is all the more important, because aluminium remains within the brain and can accumulate to dangerous levels. Silicon is thought to be an essential element because of its ability to protect against aluminium. A variety of surveys have been carried out, but opinions diverge.

In a sense, it is not surprising that the results are contradictory: such studies are extremely difficult to carry out, as they involve long questionnaires and depend on a number of variables. In addition, aluminium is present at higher amounts in food than in water but these sources are difficult to dissociate. One possible alternative or complement is the study of diseased brains of Alzheimer's patients. Some argue that the issue is not a priority in public health research, while others believe that the danger is too significant to ignore. The general trend is toward carrying out research on all possible risk factors in order to constitute an epidemiological body of knowledge that was totally non-existent just 40 years ago; the concept of Alzheimer's disease in elderly people did not exist then.

The Paquid study, part of a French population-based survey of subjects 65 year-old and over, focused on water. The study began in 1985 and included eight-year follow-up data. A complementary study, Alma, was designed to study the aluminium-Alzheimer's disease hypothesis. The 4000 people included in the non-invasive Paquid study were representative for two French administrative areas: Gironde and Dordogne. Based on the eight-year follow-up data, it was found that people, regularly exposed to concentrations of more than 100 µg of aluminium, have a twice greater risk of developing Alzheimer's disease. Silicon does appear to be a protective factor.

The main difficulty in all studies of this kind is the length of time required. The Paquid study was a prospective study. Studying cognitive decline first might allow for better progress on the understanding of Alzheimer's disease at a later time. Intervention, for example through taking a blood sample, might also provide clearer results. The biochemistry of aluminium and its relationship with silicon needs to be better understood. One might also measure the distribution of non-radioactive isotopes of aluminium silicates in humans coming from water so as to calculate their half-life. Long interventional studies on several elements, similar to those carried out in cardiovascular field, might add credibility to the study.

DIETARY FAT INTAKE AND COGNITIVE DECLINE

Research on the relationship between dementia, cognitive decline and dietary fat (saturated fatty acids [SFA], mono- and polyunsaturated fatty acids [MUFA, PUFA], and cholesterol) is very limited; some animal studies show that SFA intake increases the risk of cognitive impairment while two immunological cross-sectional studies show an association between SFA or cholesterol intake and cognitive impairment. There are three mechanisms by which fat intake could influence cognitive ability: atherosclerosis, thrombosis and oxidative metabolism.

Diets that are high in cholesterol and SFA lead to an unfavourable lipid profile and

thereby increase the risk of cardiovascular disease. This, in turn, may increase the risk of cognitive decline and dementia. Omega-3 PUFA, which are present in fish, influence the production of thromboxane and prostaglandins in such a way that they reduce the risk of thrombosis. Thus, fish consumption may reduce the risk of cardiovascular disease and cognitive impairment.

Linoleic acids, the most commonly found in Western diets, have the opposite effect and could increase the risk of both thrombosis and cognitive impairment. Yet at the same time, these acids lead to a rise in HDL cholesterol and a more favourable fat profile.

Oxidative stress could lead to dementia and cognitive impairment by affecting LDL cholesterol, but also by damaging the cell membranes, leading to selective cell death, for example, in the hippocampus. These relationships were studied in two longitudinal studies: the Zutphen Elderly Study and the Rotterdam Study. The former included men born between 1900 and 1920 from a rural town in the Eastern part of the Netherlands. The conclusions were based on measurements of dietary intake, obtained in 1985 and 1990, and measurements of cognitive function taken in 1990 and 1993. Cognitive impairment, defined as a MMSE-score below 26, was found in 32% of the population studied. Subjects who showed a drop of more than two points from 1990 to 1993 were thought to have experienced cognitive decline. This was the case in 15% of the subjects. The threshold score of 26 may seem high, especially since the UK has established its threshold at 24. However, it reflects the high level of education and social status in the Netherlands; a lower rate might falsely exclude certain people.

The Rotterdam Study focused on dietary intake in men and women of over 55, living in a suburb of Rotterdam. Baseline examination began in 1990 and extended until 1993. Follow-up examinations were carried out from 1993 to 1994. More than 5 000 non-demented subjects with information on dietary intake were tested using a three-step process. All subjects were screened by the MMSE and underwent a geriatric mental evaluation. Those who had normal results were interviewed, while those who were suspected of dementia were examined by a neurologist.

In the Zutphen study, dietary history was explored using a questionnaire. Low total calorie but high linoleic acids intake were associated with cognitive impairment. These data are not age-adjusted. The Rotterdam Study excluded people with cognitive impairment or dementia from the dietary assessment. The resulting data, which are age-adjusted, show that total fat as well as saturated fat intake was higher in those who became demented. However, fish consumption was lower. After adjustment for age, sex, education and total calorie intake, intake levels in the highest tertiles of the total fat and saturated fat were associated with an increased risk of dementia. Linoleic acid intake increased the risk of cognitive impairment, but not cognitive decline. Risk of dementia apparently decreased. This may indicate that linoleic acid has a harmful effect in the short term (on lipid profile, cardiovascular disease), but a protective effect in the long term (on thrombosis). Note that since BMI levels are lower in demented people, all functions drop. This is the result of both, declining biological ability and lessened mental awareness. These studies were carried out on people who were healthy and non-institutionalised at the outset.

Fish consumption of 20 grams per day, or one portion per week, decreased the risk

of cognitive impairment by 40% and the risk of cognitive decline by 50%. It decreased the risk of dementia by 60%. Future studies will distinguish between oily fish and white fish.

Fat intake seems to be associated with pure Alzheimer's disease or vascular dementia. However, since only a few of such cases arose in these studies, one cannot be sure. Fish consumption is protective against vascular dementia. It has proved to slow down cognitive decline. The association between high linoleic acid intake and cognition or dementia is not clear. These affirmations may be expressed through vascular or inflammatory processes.

It is very important to study diet and dementia in longitudinal studies since dementia may change dietary intake. The follow-up period must be long because other forms of dementia may not be revealed until later. It is too early to perform intervention studies at this time.

DIETARY MANIPULATION AND ANIMAL STUDIES

In an animal model study, the objective was to determine what sort of cellular changes occur in the brain with age. This research is intended to help the understanding of changes contributing to the impairment of cognitive function.

The model used here was Long-Term Potentiation (LTP) in the hippocampus, describing a long-lasting increase in synaptic efficiency following a relatively modest stimulus. This property of persistence as well as some of its other characteristics have led to the proposal that LTP might represent a biological marker for learning and/or memory. In aged animals (here, 22 month-old rats), LTP is impaired. This impairment has been associated with a number of parameters including impaired glutamate release and increased interleukin-1 β concentration. Aged animals also show a decrease of 25 to 50% in concentrations of arachidonic acid and docosahexanoic acid in hippocampus as compared with young animals.

A significant number of experiments has been carried out to determine what influences fatty acid concentration. They have found that it is always linked to an increase in peroxidation, which is itself caused by an increase in production of reactive oxygen species (ROS). These changes are linked with an increase in interleukin-1 β . Thus, in aged animals, the real problem was the decrease in PUFA of the membrane, and the problems with LTP and glutamate release could be reversed by storing the PUFA and reinjecting them in the diet through supplements.

Similarly, if it is true that ROS are the root of the problem, one could provide a diet that is enriched with ROS scavengers. In the last few years, several diets have been studied. In this study, animals between 18 and 20 months were given four diets enriched in either a) arachidonic acid, its precursor and α -linoleic acid; b) docosahexanoic acid; c) combinations of vitamins E and C or d) the proposed antioxidant α -lipoic acid for eight to ten weeks. A group of young animals was fed on either a control diet or an experimental diet. In all cases, the animals were examined for their ability to sustain LTP and a variety of other factors.

In one study, young animals were given either the control diet or the proposed antioxidant α -lipoic acid. They received either 20 mg or 10 mg of lipids per day for the two months. When animals were given the experimental diets, there was hardly any difference between the 22-month old and four-month old animals: the 22-month old mice fed with α -lipoic acid were in fact better at sustaining LTP than the previous group. The animals' tissue showed a characteristic decrease in arachidonic acid concentration with age. However, this could be decreased with either of the diets. The opposite changes were seen in lipid peroxidation: lipid peroxidation increased with age, but could take on the reverse tendency when the mice were fed specific diets. In addition to the change in arachidonic acid, researchers noted a decrease in docosahexanoic acid, which could not be reversed to the same extent as the other elements using diet. Note that the protein-enriched diets contained small amounts of both of these fatty acids.

There is an age-related increase in ROS production. This increase can be partially reversed by α -lipoic acid enriched diets. This production increases through oxidative phosphorylation and the action of other pollutants. However, the brain deals with reactive oxygen species production through specially-devised pathways, which can be either enzymatic or non-enzymatic. In the former case, the three most important enzymes are superoxide dismutase, glutathione peroxidase and catalase. Non-enzymatic elements include vitamins E and C as well as carotenoids.

Aged tissue presented an increase in superoxide dismutase and therefore had the potential to create hydrogen peroxide. Glutathione peroxidase and catalase both have the properties necessary to metabolise hydrogen peroxide. However, since they do not increase, hydrogen peroxide might accumulate in the brain and later become damaging hydroxy ions. These elements fall back to near-normal levels when animals are fed one of the aforementioned diets. Furthermore, the age relationship decreases for catalase and glutathione peroxidase. Superoxide dismutase may well be a major contributor to the increase in reactive oxygen species found in the brain. The only change found in scavengers was a decrease in vitamin E in the aged brain. The α -lipoic acid diet reversed this effect. Thus, the reason for which reactive oxygen species might accumulate in the aged brain is the increase in superoxide dismutase, the concomitant increases in other enzymes and the decrease in vitamin E, a major scavenger.

A number of studies have shown that there exists a clear negative correlation between interleukin-1 β and arachidonic acid concentration. There exists a positive correlation between LTP levels and the concentration of arachidonic acid. In contrast, docosahexanoic acid did not correlate significantly with LTP levels. This suggests that the arachidonic concentration is more important in this model. A number of parameters have been studied in the aforementioned acids. Contrary to what has been found in the past, the arachidonic acid and α -linoleic acid diets appeared to act as antioxidants. Young weaning animals, which were fed on a docosahexanoic acid enriched diet, sustained less LTP than control animals. Upon studying the brains of these animals, researchers found that reactive oxygen species had actually increased. Neither of these were found in aged animals.

The brains of aged animals contain higher levels of interleukin-1b concentration. The reasons for this are not yet known: interleukin-1 β usually increases with stress, injury or insult of any sort. Data indicate that the increase in cytokine concentration is associated with a

decrease in the concentration of PUFAs in the membrane, more specifically in arachidonic acid and docosahexanoic acid. These obviously affect membrane fluidity and, therefore, lead to a decline in receptor or channel function. This clarifies the long-term impairment. Evidence here suggests that if science is able to overcome the reason for change in PUFAs with age, it will be able to reverse at least some of these changes. This may well have an impact on memory learning processes, if it can be shown or proven that long-term potentiation is a reasonable model for studying cellular events.

DIABETES AND COGNITIVE FUNCTION

Recently, it has been discovered that diabetes and high cholesterol are not only risk factors for vascular dementia, but also for degenerative diseases such as Alzheimer's. A recent epidemiological study in Baltimore has shown that patients with type 2 diabetes have a higher risk for developing Alzheimer's disease four to six years after the onset of diabetes.

When children develop type 1 diabetes before the age of five, they often enter adolescence with a number of subtle, yet undeniable cognitive impairments. These can result in their failure to reach certain academic milestones. Repeated hyperglycaemia is likely to be the reason for this. Type 2 diabetes, which occurs later in life, has been said to have no effect on cognitive function. However, the tests that showed this were non-representative, using varying methodologies. Their findings are challenged by those of an American group, which identified a link between type 2 diabetes and changes in verbal fluency and motor dysfunction. Another study reached similar conclusions, adding that, if metabolic control were regained within two to three months, an improvement in cognitive function could be noted.

European population-based studies showed that type 2 diabetes is associated with cognitive dysfunction, using either MMSE or other tools. Subjects with impaired glucose tolerance also seem to have cognitive dysfunction. In the United Kingdom, a study included 400 subjects, with age and sex match controls; it confirmed through cross-sectional analysis that type 2 diabetes patients (mean age 75 years) have a clear deficit in cognitive function. This study used both MMSE and the Clock Test. It has not only shown differences, but also demonstrated that those differences have consequences on the daily life style: people with diabetes and cognitive impairment demand care or support, cannot manage their disease on their own and must go to the hospital.

Currently, the actual link between diabetes and cognitive function remains unknown. It is possible that they share common clustering factors, such as blood pressure, depression or high levels of insulin. A prospective study will probably be required. CT-scans of patients with type 2 diabetes and cognitive impairment show atrophy in the temporal lobe, which may also be linked with development of Alzheimer's disease. The prevalence of Alzheimer's disease and diabetes being very high, it is almost unavoidable that some patients will have both clinical conditions.

CHAPTER III

NUTRITIONAL IMPACT ON IMMUNE RESPONSE AND LIFE SPAN IN THE ELDERLY

Ageing is associated with a variety of changes in the immune system. Nutrition can influence health, immunity and ageing and play a role in human capacity to age successfully.

IMMUNE DEFICIENCY AND DYSREGULATION

T-cells in elderly people do not have the same ability to proliferate as those in younger people. A variety of infectious diseases cause more difficulties in the elderly than in the young. Excess death rates from influenza, for example, are rare in very young children, but become significant in individuals as young as 45. Susceptibility increases threefold in the oldest group (65-85 year-old). Similarly, only 1% of deaths with pneumonia occur in the young age range, but more than 40% occur in the older age group. This marked increase in death rate suggests that there is an association with impaired immune function. The number of naive T-cells declines with age, in order to maintain the level of T-cells in the body. But the immune system depends on its ability to replicate T-cells when facing an antigen.

Although it is encouraging to see that about 50% of elderly people have a healthy "young" immune response to influenza vaccine, the same vaccine manages to protect over 95% of young individuals. The failure of 50% of the elderly patients explains much of their increased morbidity and mortality following infection.

Data in animals have shown that the age-associated thymic atrophy probably results from a defective thymic environment. A part of the defect in naive T-cell production might be found in a defect of interleukin-7 production. The later thymus atrophy occurs, the longer the immune system will be able to produce naive T-cells and protect against diseases. A recent study has shown that children born in Gambia in the hunger season had a shorter life span compared to children receiving normal caloric intake, related to a nutritional thymectomy: the

thymus of children who do not receive adequate nutrition when very young, does not produce a normal peripheral T-cell pool. A large number of these children died of infections. As a conclusion, nutrition might play a role in the beginning of thymic atrophy.

In addition to immune deficiency, ageing also brings immune dysregulation. Whereas the antibody response to a foreign antigen in the blood decreases in ageing people, a concurrent increase in the percentage of individuals with auto-antibodies can be noted. The specificity of the immune response that is thought to be typical in all humans is, in fact, considerably diminished in the elderly. Exposure to a foreign antigen generates a modest antibody response, but also a number of irrelevant auto-antibodies.

Humoral dysregulation is not the only form of dysregulation in the immune system. T-cells do not produce antibodies, but a variety of cytokines. While interleukin-2 decreases dramatically with age, thereby giving the illusion of being a simple impairment, it is accompanied by a vigorous antibody response in other cytokines. Interleukin-6, which has been associated with osteoporosis and sarcopenia, dramatically increases when lymphocytes from old donors are stimulated, but does not vary in younger donors. Some cytokines, including interferon- γ , seem to change rather little with age.

MICRONUTRIENTS AND IMMUNE RESPONSE IN THE ELDERLY

A large percentage of elderly hospital patients (20% to 60%) enter the hospital malnourished. This state has been clearly related to decreased immune competence, impeded wound healing, lengthened hospital stays and a rise in mortality. However, the distinction between malnutrition and immunodeficiency with age as causes and consequences cannot be clearly defined: one can argue that malnutrition leads to these events just as one can argue that patients are malnourished due to a disease.

One difficulty lies in defining appropriate nutrient intake. Various organisations have issued requirements on micro- and nutrients, macronutrients. However, it is difficult to lend credence to these endorsements since they may not be optimal for elderly people with health problems. Thus, the distinction between "required" and "optimal" levels must be made. Further studies are still needed to determine which micronutrients and which doses are indicated for what type of patient.

Micronutrient deficiencies, especially in B vitamins and zinc, are common in the elderly, present in 25% to 33% of self-sufficient home-living elderly. Some studies have concluded that, although trace elements and vitamins cannot bring immune response in healthy elderly to the same level as that of a young control group, they do bring about significant improvement in capacity of T-lymphocytes, hypersensitivity reactions and antibody response following influenza vaccine. Most importantly, micronutrients were found to alter the course of infectious illness (e.g., pulmonary disease requiring a hospital stay) which results in a shorter stay for the micronutrient recipients as compared to the placebo group.

One controlled study with a 12-month supplementation of micronutrients showed

an increase in CD3+ cells (decreasing with age) and CD4+ cells, decreasing in frail elderly subjects, and a booster response for lymphocyte proliferation. The number of days with infection over that year of supplementation was significantly lower in the treated group. Another French study showed a similar decrease in aged patients living in nursing homes during 2 years of supplementation.

In addition to the B vitamins and zinc, other micronutrients, studied in recent years, include vitamins conveying antioxidant properties such as vitamin C and vitamin E.

In general, micronutrient supplements increase IL-2 secretion, antibody and delayed-hypersensitivity skin test (DHST) responses. Part of the effects normally attributed to ageing, might in fact be rooted in micronutrient levels.

Vitamin B6

Vitamin B6 has been demonstrated to influence greatly the immune response. Thirteen years ago, Talbot reported that a decline in T-cell function and antibody synthesis could be restored by vitamin B6 supplementation in self-sufficient aged persons. The restoration that occurred thanks to vitamin B6 resulted from the elimination of the deficit, but no change was observed in subjects with normal levels of vitamin B6. In another study, an important decline was noted in IL-2 production after six weeks of vitamin B6 deprivation.

Folic acid

A French study examined the relationship between immunosenescence and micronutrient intake in a very healthy elderly population, the main criteria being absence of disease in the five years prior to the study. The subjects accepted for the study showed immune systems that were minimally affected by age. Neither IL-2 levels nor proliferation capacity had diminished. The main change noted with age related to subsets of T-cells in peripheral blood lymphocytes. The segment of the population in whom decline is small, was considered exceptional.

One part of this study separated subjects into two groups according to whether their blood folate levels were low. When folate levels were below 5 mg/l (and albumin levels below 38 g/l), lymphocyte proliferation was also lower, even though the individuals were otherwise perfectly healthy. In a group of elderly people with normal high folate levels, a lower proliferation of T-cells was observed in a subgroup of subjects with albumin levels < 38 g/l compared to elderly with 42 g/l. One month of folic acid supplements on such elderly rose the levels of folates, IL-2 and lymphocyte CD24 to normal levels. This proves that, even in a very selected group of elderly, micronutrients may influence immune response.

Zinc

It has been demonstrated that people showing high zinc levels also showed increased immune responses at 70 years of age, in comparison to people who did not receive any zinc supplements. A study on trace elements and vitamins carried out by a large number of geriatric centres concluded that trace elements increase antibody response following antibody vaccine.

Zinc deficiency is quite common in aged people, even if they are entirely self-sufficient. Although the elderly have very few thymic functions, neutropenia appears and T-cell function does decline. Zinc supplementation (50 to 100 mg/d) can restore immune response and also acts on monocyte function. However, it is important to note that zinc supplementation can lead to decrease plasma copper levels, in order for the system to achieve a kind of balance. That balance is certainly very important: patients, receiving only a multiple supplementation but without zinc supplementation, show a boost in the immune response whereas patients having a multiple supplementation including zinc show an improvement in their immune response that is no better than with placebo after three months.

Vitamin E

Vitamin E deficiency may induce cell-mediated immunodeficiency as well as non-specific immunodeficiency, probably due to the increased number of free radicals in the remaining cells.

Vitamin E deficiency is associated with a very important decline of the immune function and a rise in PG2 production. The latter has been identified as a possible factor of depressed immune response. When animals are supplied with vitamin E supplements, their immune function is restored and PG2 production returns to normal. In humans, there is no vitamin E deficiency in aged persons. The immune response, however, can be increased using 200 to 800 IU of vitamin E (10 to 20 times the RDA) per day.

In a non-European study, it has been proven possible to enhance the immune response by vitamin E supplements, in people who were made vitamin E deficient. No change in the immune response has been induced in the placebo group and the plasma lipid peroxides levels remained unchanged; but in a group of patients having received a vitamin E supplementation, a sharp decrease in the plasma lipid peroxides was observed. These data suggest that vitamin E acts as an immuno-stimulant, mainly by removing the free radicals from the cells; this anti-oxidant property might then boost the immune system.

Mice were infected with a virus through nasal spray, while given diet supplements of vitamin E (30 ppm or 500 ppm). The results of the study showed that the performance of the immune system was dependent on the age of the animals, regardless of the size of their supplement. The young mice had succeeded in inhibiting the action of the virus and would presumably have managed to eliminate it entirely with time. In the older mice, the higher levels of vitamin supplement were not associated with a response different from that of the younger groups. In contrast, the "recommended" dose of 30 ppm led to improvement. Nonetheless, the rate of improvement or elimination of the virus was significantly inferior to that of both groups of young mice.

Immune competence can be improved in healthy elderly adults through supplements. This has been demonstrated by extending the experiment to humans, by giving healthy adults 200 mg of vitamin E. This rather large dose managed to raise vitamin E levels in the serum. Vitamin E supplementation increased delayed hypersensitivity and antibody responses to two of the four vaccines tested (hepatitis B and tetanus). Response to diphtheria and pneumococcus remained the same. There was no increase in auto-antibodies.

RDA levels for the elderly

The micronutrient intake in ageing is very important. There is a decline in immune response with ageing, but its effects are borderline in very healthy persons: they appear only after the age of 90 years. Micronutrient supplementation in healthy elderly at two to three times the RDA does improve immune response, but it is sometimes necessary to use very high doses to achieve any significant effect. Based on this information, several countries have recently proposed an increase of RDAs. In order to assuredly relate ageing to nutrition, it is necessary to define how healthy the subjects are and to clearly establish their nutritional status.

ROLE OF GENES IN IMMUNE RESPONSE IN THE ELDERLY

The following observations support the idea that ageing rate is controlled by genetic factors: all animal species have a characteristic rate of ageing; the progeny from the crossbreeding of two inbred mouse strains has a longer life span than either parental strain. In humans, females live longer than males, as in most animal species. The genetic control of the ageing rate makes stochastic processes due to random events less likely and favours programmed events encoded in part of the genome, as in a master clock. These genes regulate molecular mechanisms accounting for the synchrony of structural and functional changes in different cells and tissues of each member of a given species.

Identification of the genes and processes, that set the ageing rate differently in several species, has been attempted by several approaches. Different regions of chromosomes have been found to interact between themselves and with environmental factors to influence the median life span in recombinant mice of 20 inbred strains. A limited gene theory of ageing has considered the role of the major histocompatibility complex (MHC), which controls immunoregulatory cell functions and interactions. The reason for this gene theory is that most of the diseases observed in senescence have an immunological pathogenesis associated with the decline of immune responsiveness to exogenous antigens and increased tendency to autoimmune reactivity.

Experiments with congenic mice have shown that, although genetically identical except for a short MHC region, the mice within each set display considerable variation in mean life span. However, evidence has been given of a complex interaction between a particular allele and the complete genetic background, as a single allele promotes either longer or shorter life span, depending upon the background. Studies on genetically selected mice have showed that genes expressed in the immune system play a significant role in conditioning life span and diseases.

The hypothesis that age-related immune dysfunctions have significant impact on life span and diseases is also supported by the study of centenarians, showing that healthy individuals who have reached the extreme limit of human life in good clinical condition are equipped with well-preserved and efficient immune defence mechanisms.

The role of the MHC in ageing is not restricted to immune mechanisms. It has been postulated that MHC-related genes, which regulate superoxide dismutase and mixed-

function oxidases, influence the ageing process by protecting from the free radical-induced damage inherent to the ageing process. The association between oxidative stress response and life span has recently been reinforced by results published on the role of a single-transduction pathway (p66shc). The p66 protein is involved in cellular responses to stress and leads to apoptosis. Ablation of p66 in knock-out mice enhances cellular resistance to apoptosis resulting from environmental stress (UV, etc.) and brings about a 30% increase in life span.

Mitogen-activated PBMC show increased DNA repair capacity as compared to unstimulated PBMC, suggesting the existence of a relationship between proliferation and repair capacity. It is not known whether age-related impairment in proliferative activity leads to reduced DNA repair potential or if reduction of DNA-repair capacity with ageing affects the proliferation of PBMC from elderly subjects. Maintenance of DNA integrity is fundamental for normal immune functions. The reduced DNA repair capacity in human lymphocytes with ageing could play a key role in the deterioration of immune reactivity and contribute to the development of age-associated immune dysfunctions, which, in turn, may affect life span.

The link between immunity and ageing is stressed by thymic involution, a prominent phenomenon that leads to major alterations in T-cell population (replacement of naïve cells by memory cells, accumulation of cells with signal transduction defects, changes in the profile of TH1- and TH2-type cytokines). However, the possible link between genetic factors and life span through the performance of the immune system remains to be demonstrated.

NK AND NK/T CELLS, NUTRITION AND IMMUNE REGULATION

A significant role has been ascribed to natural killer (NK) cells: the regulation of all aspects of antigen-specific T-cell response, mainly by the secretion of immunoregulatory cytokines. NK cells also express cytokine receptors and can therefore be stimulated by different cytokines. Interleukin-15 plays the most important role in NK cell differentiation.

It has been demonstrated that these cells play a role in defence against infection, mainly viral infections, in the elderly. A low number or decreased function of NK cells has been associated with severe infection and higher mortality risks. In contrast, centenarians almost always have well functioning NK cells and healthy old people have higher levels of NK cells, even if the cell cytotoxicity mediated by peripheral blood lymphocytes is well preserved (it has been considered that the number of NK-cells could be a marker for healthy ageing). This indicates that NK cytotoxicity calculated on a per cell basis is significantly impaired with age. NK cell proliferation, expression of CD69 and killing of NK-resistant cell lines in response to IL-2 or other cytokines are also decreased in ageing. On the contrary, other NK cell functions such as TNF- α production or perforin synthesis are not significantly altered. Furthermore early IFN- γ and chemokine production in response to IL-2 or IL-12 is decreased in healthy elderly. Taken together, these results indicate that senescence is associated with a defective functional capacity of NK cells that is partially compensated by an increased number of mature NK cells.

Patients under haemodialysis who are deficient in vitamin D show increased NK cell cytotoxicity. People, aged 90 and over, with high vitamin D levels are also more likely to live

autonomous lives, have better metabolism and better NK cell activity. Thus, nutrition is somehow involved in NK cell numbering activity. A correlation between the number of NK cells and levels of zinc and selenium has also been shown.

A population of T-cells expressing NK cell markers has been found in mice. They have been referred to as NK/T cells and present several unique characteristics: they express T-cell receptors, recognize CD1 and bound non-peptidic ligands; they express and produce IFN- γ , IL-4; regulate a variety of infections, play a role in anti-tumoural response. It has been postulated that these NK/T cell subsets belong to an entirely different population, which lies between the innate and adaptive immune responses. In particular, NK/T cells increase in the secondary lymphoid organs of aged mice and in peripheral blood of aged rats.

In humans, a similar T-cell subset expressing these NK cell markers has been defined. These cells are particularly abundant in the liver but not in the peripheral blood, co-express CD3 and NKRP1 (the equivalent of NK 1.1) and show the inhibitory receptor characteristics of NK cells. It has been suggested that they recognize CD1, can be cytotoxic and produce TH1 and TH2 cytokines. They are very heterogeneous in the expression of CD4 and CD8 antigens. The subsets containing V-a24 are thought to be absent at birth, developing only with age. Their growth can also be stimulated in culture. It is still not known whether these NK/T cells are the same as those defined as CD3-positive cells.

NK/T cell levels have been found to be particularly high in animals with low vitamin A intake. In addition to the other changes in the classic T-cell response, this increase in NK/T cell is thought to be a compensatory mechanism of the deficit in classic T-cell response.

Therefore, immunotherapy, or the modulation of the immune system in the elderly, has to include not only vaccination, but also treatment with antioxidants and dietary supplementation, to avoid the changes observed in adult immune systems.

AGEING AND THE IMPAIRMENT OF INTESTINAL IMMUNITY

There is a large amount of data illustrating systemic immunosenescence. Much of the focus has been placed on T-cells, often at the expense of mucosal immune function, an area that deserves more attention. Until a few years ago, scientists had not carried out many studies on mucosal immune response as a function of age. A growing database has been developed since that time. Although it is often epidemiological or circumstantial, it convincingly shows that mucosal immunity is compromised with age. Some of the data show increased morbidity and mortality as a result of gastrointestinal infections, increased progression rates of infectious diseases and reduced responsiveness to mucosal vaccines. Subsequent studies have shown that the intestinal mucosal response to specific antigens is markedly reduced as a function of age, both in the rodent model and in primates (rhesus macaque).

The mucosal immune system is quite unique, in that it has its own immunoglobulin (IgA) and requires the co-operation of mucosal epithelial cells to express a satisfactory response. Moreover, the immune response consists of a series of steps that may be

susceptible to age-related perturbation:

- The uptake of antigens by specific epithelial cells (M cells) of the small intestine;
- The presentation of antigens by antigen presenting cells to immune competent cells and the subsequent processes which include isotope switching;
- The maturation and migration of putative IgA plasma cells from the Peyer's patches through the intestinal lymphatic drainage and into the systemic circulation and, finally, homing back to the lamina propria of the intestine.

Once the final maturation of the immunoblasts has been completed, they begin secreting specific IgA antibodies. The intestinal epithelial cells are responsible for delivering the antibodies (IgA or IgM) through receptor-mediated endocytosis and vesicular transport, to the mucosal surface, where they can be effective against pathogens.

In an American study comparing this process in senescent and younger rats, local antibody production and their transport to the intestinal mucosa seem to be unaffected by age. However, migration from the Peyer's patches back to the intestinal wall appears to be compromised in old rats. This last step implies a co-operation with the epithelial cells. A thorough understanding of the aetiology of intestinal mucosal immunosenescence is essential for the development of successful interventions such as adjuvants, vaccine delivery systems and, perhaps, probiotic organisms and nutritional factors.

CHAPTER IV

NUTRITION AND THE
CARDIOVASCULAR SYSTEM**NUTRITIONAL FAT SUPPLY AND CARDIOVASCULAR DISEASE**

Coronary heart disease (CHD) prevention has so far not been a major public health issue in the elderly. This is probably based on the belief that heart disease is part of a continuous evolution. For example, the Atherosclerosis Society's book shows it as a linear process, which spans from birth to old age. Starting at approximately age 50, it is assumed that one's fate is sealed; one can only wait for complications to arise. Yet, biological processes prove that nothing is static in heart disease. It is thus possible to reverse certain tendencies. Notwithstanding, it is understandable that prevention in the elderly has not gained much recognition. Indeed, there is little empirical evidence in favour of it. Given that the elderly population is extremely heterogeneous, the lack of experimental data is characteristic.

When discussing dietary lipids and cardiovascular disease, most epidemiologists refer to the "diet-heart hypothesis", which developed between the 1950s and the mid-1980s. It states that dietary lipids and dietary cholesterol modulate the risk of heart disease. This association is said to be causal and can be at least partly explained by the role of cholesterol. It is now widely accepted that dietary lipid intake affects serum glycoprotein levels. Studies and meta-analyses from around the world definitively and consistently show predictable changes at the group level. In contrast, individual responses can vary greatly, particularly in the adult population.

In the elderly, scientists have not reached consensus regarding differential effects with age. However, it is important to remember that no specific studies have ever been carried out on the effects of dietary intake on serum glycoprotein levels. Circumstantial evidence shows that people in their sixties, who are the "youngest of the elderly", react to improved diet in the same way as average adults do. In post-menopausal women, for example, LDL cholesterol clearly decreased with age when the percentage of fat in the diet was reduced. Interestingly,

the decrease noted in HDL cholesterol was exactly the same in 60 year olds and adults. This indicates that, in order to maintain high HDL levels in spite of decreasing fat levels, one must aim for weight loss. When total calorie levels were reduced, LDL cholesterol remained the same whereas HDL cholesterol levels rose. This relationship is exactly the same as in average adults. Studies also found that the serum-cholesterol association in elderly adults, concerning mortality and morbidity, is sometimes the inverse of what has been observed in adults. After 70 years of age, there is no significant correlation between total cholesterol and CHD mortality.

A French cohort study focused on over 10 000 people at the time of their annual health check-up. In men under 60 and over 75, the relationship between total cholesterol levels and all types of mortality was found to be weaker. Cancer and cardiovascular disease increased with cholesterol levels, but were not dependent on age. The inverse association, which was found in men over 75, might be explained by the fact that they constitute a particularly heterogeneous population. It might also be attributed to lower susceptibility to atherosclerosis from circulating cholesterol. Mortality and BMI were also found to be negatively related. The only way to attenuate this negative relationship is by selecting groups who have recently experienced disease. All of these patterns are the same in men and in women.

Five prospective studies compared the prevalence of CHD in vegetarians as compared to non-vegetarians in four age groups. The former were indeed less likely to develop heart disease, but only until age 80. Two short-term studies, one in Denmark and one in Greece, investigated the association of diet and heart disease in people over 77y. Individuals were scored on the composition of their diet on the basis of intake of SFA, sugar, sodium, overall food and a variety of ingredients. SFA were found to be an important component of heart disease in both studies, despite the very different lifestyle of the countries.

The limits of epidemiological associations must be recognised, particularly when looking at the elderly. The unpublished results of the EVA study (study on arterial ageing) involved men and women from Nantes in very good health. All of the subjects, who participated on a voluntary basis, were under age 73. Researchers focused on a very specific category of SFAs, whose presence in adipose tissue and membranes is a marker of fat uptake from ruminants. It was shown that people in the third tertile, who ate more dairy fats, had lower body mass index, healthier overall condition and were less likely to smoke. By studying images of these people's arteries over a four-year period, researchers also found that they had less risk for developing atherosclerosis. Although these data are still unpublished and involved only a small number of people, their implications regarding dairy fat are very important.

Currently proposed dietary advice for the general population is associated with lower risk of CHD, at least in the elderly above 75. The literature's affirmations on adults can thus also be applied to younger elderly who are in good general health. There is no evidence that other elderly should follow this same advice. Further research must be carried out on dietary intake and overall health. Measurements of biological markers on dietary intake and atherothrombosis should be included in such studies, as should evidence from vascular imaging. Epidemiological observations and bio-genetic data must be combined if sound, thorough conclusions are to be drawn in the future.

AGEING, OXIDATIVE STRESS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Cardiovascular ischaemic diseases are a major obstacle to increasing life expectancy and to good quality of life in the elderly. These diseases occur mainly in men above 45 and in women above 55. Their frequency increases with age. Atherosclerosis and atherothrombosis are common problems among the elderly. Oxidative stress is involved at all levels of the atherosclerotic process, from the formation of fatty striations to the fissure of atherosclerotic plaques. This process involves inflammatory phenomena.

The role of nutrition is very important in the prevention of oxidative stress. Research over past decades has demonstrated the role of oxidative modifications in lipoproteins (particularly those of low density) in the pathogenesis of atherosclerosis and in plaque fissure. Studies have shown that the essential step in atherogenesis is the transformation of monocyte macrophages into foam cells within the arterial intima. Modified LDL, most of which are oxidated, are taken up by unregulated scavenger macrophage receptors. This process leads to the accumulation of cholesterol in the macrophages and, subsequently, to the formation of atherosclerotic plaque.

Several mechanisms lead to lipid peroxidation and oxidation of LDL, particularly during ageing. Lesions in endothelial cells and smooth muscle cells are responsible for the modification of LDL. Endothelial dysfunction, frequent in the elderly (as seen through hypertension, diabetes, etc.) increases oxidated LDL levels and strengthens the link of LDL with the proteoglycan found in connective tissue. Finally, the increase of residence time in plasma fosters LDL oxidation in patients with hypercholesterolemia.

This tendency to lipid peroxidation may be reduced by antioxidants, such as vitamin E, β -carotene and phenolic compounds, found in an adequate diet. At this time, there is no epidemiological proof of this. Thus, scientists do not know whether cardiovascular disease can be prevented through supplements of antioxidants, particularly vitamin E. The only prevention studies that exist, indicate a reduction in myocardial function, but no reduction in cardiovascular mortality. This possibility is currently being investigated by several new studies.

According to their content in fatty acids, LDL are more or less susceptible to oxidation. LDL enriched in PUFA are more oxidisable. In contrast, those enriched in MUFA are able to resist oxidation. These data are important in the development of nutritional recommendations for the elderly. They indicate that physicians should encourage a diet traditionally rich in antioxidants and in MUFA. The Mediterranean diet is a good example of this favourable diet.

SELECTED STUDIES ON DIET AND HEART DISEASE

The Seven Country Study

The first large-scale study on ageing and nutrition involved seven countries and

spanned 25 years. Subjects were between 65 and 84 years old and were examined for CHD and cancer, in particular lung, colorectal and stomach cancer. The lowest overall mortality rate (31.4%) was recorded in Crete (Greece) while the highest were found in Croatia (61%) and Finland (59.7%). The main nutritional factor studied was consumption of SFA.

The Lyon Diet-Heart Study

The Lyon Diet-Heart Study, a secondary prevention study, applied the diet observed in Crete to people who had experienced one myocardial infarction. After 27 months, the study was stopped for ethical reasons: the differences between the experimental and control groups were so significant that it was not possible to continue. Sixteen people suffered cardiac death in the control group as compared to 3 in the experimental group. As regards overall mortality, 20 people died in the control group, as compared to 8 in the experimental group. The latter group experienced a 70% decline in mortality. The recommendations resulting from this study were very general in nature. It encouraged people to eat more bread, more vegetables, more fish and less meat. If meat had to be consumed, chicken should be preferred. Individuals should eat one fruit per day and replace butter and cream with rapeseed margarine. All oils should be replaced either by olive oil or rapeseed oil.

The North Karelia Project

Another study that focused on diet was the primary prevention intervention study in North Karelia, Finland. It was in this region that mortality related to heart disease was particularly high. Local authorities were very motivated by this study and decided to intervene in public health, changing the diet and discouraging smoking. Between 1972 and 1992, the following changes were observed. Instead of whole milk, low-fat milk became the choice of 80% of male inhabitants. Butter was replaced by vegetable margarines (mainly rapeseed) in most households. Rapeseed oil is widely used, initially for economic reasons (it was the only oil which the country could produce). The meat consumed is now mainly lean pork. Fish and cheese consumption have risen significantly, fruit consumption has doubled and vegetable consumption had a three-fold increase.

Thanks to these efforts, mortality from heart disease has fallen by 70% in North Karelia. Even mortality from cancer has dropped by 45%. Overall mortality fell by 48%. These levels are continuing to fall, even beyond the levels predicted by experts. The older the people, the less they were able to change their habits; this is particularly important to remember when designing public health policy. In the young, mortality from heart disease fell by 75% in men and 65% in women. This compares to 35% and 50% in men and women aged 65 to 74.

The methods used in Finland to change individuals' habits were very innovative as public authorities knew how difficult it is to bring about change. For example, competitions were held between villages to achieve the lowest cholesterol levels. Public campaigns and activities were organized and both local and public leaders were trained to stimulate the population. Supermarkets monitored customer purchases and the food industry took part in this effort, providing skim milk and margarine and encouraging their consumption.

THE CHINESE DIET AND HEART DISEASE

The prevalence of coronary and arterial disease in Hong Kong is 25% lower than in the US, both in men and in women. Diet, as expressed through percentage of total energy from fat, amount of saturated fats, the amount of folic acid, antioxidant vitamins, omega-3 fatty acids, may provide some explanation of this.

Although caloric intake is similar between Americans and Chinese, the latter have a lower fat intake. They consume more PUFA and less SFA. The Chinese eat far less meat and more fish, have a low milk consumption and eat more fruits and vegetables. This diet can vary from one region to another. Questionnaires distributed to Chinese people in rural China, Hong Kong, San Francisco and Sydney show marked differences.

Green tea, often consumed by the Chinese, was shown to lower cholesterol and reduce the oxidation of LDL in vitro. A Japanese study also indicates that green tea has hypocholesterolemic effects. A wide variety of Chinese herbs, including ginseng, are probably a mixture of antioxidants. Chinese mushrooms, with which the Chinese make soup, have been shown to have cholesterol-lowering effects as well as antioxidant properties. There are no randomised clinical control trials to prove this, but the interest is no lesser. Wine, an antioxidant containing beverage, is a growing industry in China. Wineries in Tsingtao are particularly successful as they are at the same latitude as California and produce well-appreciated products.

The Chinese diet has one disadvantage: a high salt content which induces age-related hypertension in people who consume more than 100 mg of sodium per day. In Northern China, salt intake can reach 15 g per day since much of the food eaten during the winter is preserved. In addition, vegetables cannot grow during that season. With time, individuals grow accustomed to the strong taste and cannot eat foods that do not have so much salt. As a result, the incidence of stroke is rather high.

CHAPTER V

NUTRITIONAL IMPACT
ON CANCER

Research on nutrition and cancer has developed substantially over the past 20 years, initially stimulated by a number of epidemiological studies which drew attention to the large world-wide variations in cancer incidence, suggesting that these variations could be related to differences in diet and lifestyle between populations. Hundreds of epidemiological studies have been conducted so far on the relation between diet and the risk of developing different types of cancer, particularly cancers of the digestive and respiratory tracts, breast, female reproductive organs and prostate. The most consistent result so far is that a diet rich in vegetables and fruit is associated with a lower cancer risk. The epidemiological evidence is particularly consistent for a protective effect of vegetables on cancers of the colon, and of vegetables and fruit on cancers of the mouth, pharynx, larynx, lung and stomach.

Various hypotheses have been put forward to explain why consumption of vegetables and fruit is associated with a reduced risk of cancer; among others, these include the biological effects of natural antioxidants, various vitamins and minerals, dietary fibres, resistant starches and certain natural components such as coumarins, flavonoids, isoflavones, isothiocyanates, lignans and phytosterols.

During the past 15 years, in parallel to laboratory research aimed at identifying potential anticarcinogens, several large randomised trials were initiated to test whether high pharmacological doses of various combinations of vitamins, minerals and dietary fibre could reduce cancer risk or recurrence of preneoplastic lesions. The results of several randomised studies have been published recently, and the results have so far been quite disappointing, indicating that supplementation either had a very modest effect, or did not reduce cancer risk, or even increased cancer risk in the case of two β -carotene trials.

These results suggest that the biological mechanisms behind the vegetable and fruit effect are likely to be much more complex than the "one molecule, one effect" biological

model underlying some of the chemoprevention trials conducted so far. A strategy combining observational epidemiology, laboratory research and randomised intervention studies on diet and lifestyle is likely to be a more appropriate means of tackling such a complex issue.

However, other studies have shown convincingly the protective effects of B vitamins against certain types of cancers. A study at Tufts University focused on the synthesis of nucleic acid and its stability. When folate levels are not high enough, DNA proliferation produces uracil instead of the required thymine acid. Since uracil resembles cytosine, the result of metabolism is guanidine instead of thiamine and leads to an error in DNA replication. In addition, uracil's instability can lead to other types of anomalies that can bring about cancer. Finally, low B vitamin levels can also give rise to hypomethylation. Indeed, low folate levels cause S-adenosylmethionine (SAM) levels to be higher and increase the risk of cancer. In 60% of the cases studied, hypomethylation of DNA was found to be a sign of cancer.

A study performed at Harvard examined the relationship between folate intake and colorectal cancer. Subjects were divided into five categories according to their folate levels. Those who showed high folate levels had the lowest risk of developing cancer. Some of the studies carried out at Tufts University with the National Cancer Institute studied vitamins in the blood of people who later developed cancer. Those who had high vitamin B6 levels had 50% less risk of developing cancer than those with low B6 levels. The same was true for folate levels. Similar markers have been observed for lung cancer among smokers. Another study proved that B12 levels also showed protective effects.

A large European project was initiated 8 years ago with the aim of clarifying the role of diet in the aetiology of cancer. The project, named EPIC (European Prospective Investigation into Cancer and Nutrition), is a multi-centre prospective cohort study designed to investigate the relationship between diet, nutritional and metabolic characteristics, various lifestyle factors and the risk of cancer. The study is based in 22 collaborating centres in nine European countries and includes populations characterised by large variations in dietary habits and cancer risk.

Detailed data on diet, lifestyle and anthropometry have been collected from all study subjects and stored for further laboratory and statistical analyses. The study was initiated in 1992, and by 1999 about 480 000 subjects had been included with questionnaire data.

It is expected that about 17 000 cases of cancer will occur in the cohort by the year 2002. Follow-up is done through cancer registers and national mortality registers. Studies are being planned on the role of prediagnostic levels of steroid hormones, insulin-like growth factors and their binding proteins in the aetiology of cancers of the breast, prostate and colorectum. These studies on metabolic factors will be paralleled by genetic investigations into susceptibility to cancerogenesis, focusing initially on polymorphisms of genes involved in known metabolic functions (metabolism of hormones, some vitamins, exogenous carcinogens, etc.).

CHAPTER IVI

TYPE 2 DIABETES AND THE NUTRITIONAL BALANCE

EPIDEMIOLOGY

Diabetes is a major chronic disease with an extremely high prevalence. For example, in Northern Europe and in North America, one out of three individuals above the age of 65 has type 2 diabetes. Much higher prevalences are found in North American Indian populations. This reinforces the fact that type 2 diabetes is not only induced by the environment, but also by heredity. Prevalence in the United Kingdom reaches only 10%. This may be due to differences in measurement of BMI or diagnosis methods. .

The disease is associated with a considerable amount of disability. Taking into account all of the factors that are related to diabetes, it is possible that nutritional impediments (not necessarily obesity) are related to this disability. Like many chronic states, diabetes takes its toll on patients' health. A number of benefits can be derived from achieving nutritional balance, whether pharmacological or therapeutical. In obese individuals, a body weight loss can bring about improved instrumental sensitivity and better response to oral anti-diabetic agents. Nutritional well-being promotes overall health and therefore reduces overall cardiovascular risk factors. Finally, economic benefits, such as a decrease in hospital stay, can also be influenced by nutritional factors. Several studies have suggested that poor foetal development and nutrition may be associated with the development of major disorders, including type 2 diabetes. This is an interesting potential relationship between early life and diabetes.

THE RELATIONSHIP WITH NUTRITION

It has been known for some time that malnutrition may be related to glucose intolerance. In tropical countries, it has been shown that a diabetes-like state can develop as a result of malnutrition. Malnutrition-related diabetes, which can be either protein-deficient

pancreatic or fibrocalculous pancreatic, generally occurs in tropical regions. The first studies were performed on this type of diabetes in 1955. The various transformations of the pancreas throughout this illness raise the difficult question of how nutrition can affect the course of diabetes. Some believe that tapioca and cassava, staple products in the diet of local populations, are converted into cyanogenic glycosides. They may cause pancreatitis and lead to a diabetic state.

Oxidative stress

Experimental models of diabetes show evidence of increased lipid peroxidation and decreased pancreatic antioxidant reserves. When patients are given vitamin C, antioxidant levels rise initially, but reach a steady state relatively quickly. This suggests that there may be a defect in the metabolism of vitamin C in these subjects. Oxidative stress and diabetes are clearly linked. There may thus be a relationship between core antioxidant reserves and subsequent development of diabetes.

Leptin

Leptin has been found to regulate food intake and energy expansion and to be associated with diabetes. Elevated or increasing leptin levels were correlated to fat cell numbers. Most importantly, there appears to be a relationship between leptin and insulin levels.

A 12 years follow-up study, including over 400 Japanese-American patients aged 52, was performed in Seattle and recently published. Among these subjects who had a baseline normal glucose tolerance, 40 (17 of whom were women) developed diabetes. Leptin was found to be an independent risk factor in men, but not in women. The relationship between leptin, insulin and diabetes deserves further study. Studies thus far have concentrated mainly on the sex difference associated with leptin. The possible correlation between age, leptin and obesity has not yet been discovered.

Metformin

Metformin, recently introduced in the American market, is a common type of oral agent used in the treatment of type 2 diabetes. Over the last two years, it has become one of the most commonly prescribed agents in this context. In 30% to 40% of cases, it is associated with adverse gastric symptoms, including nausea, diarrhoea, etc. A number of studies have demonstrated that when metformin is given in clinical trials, subjects' caloric intake changes.

A St. Louis research team worked with a small group of markedly obese diabetic women. They showed that the amount of calories consumed declined significantly after the administration of increasing doses of metformin. This led the authors to question whether adverse circumstances had intervened or whether other mechanisms were involved. One hypothesis was that metformin might have some part in nitric oxide synthesis. Subsequent studies on mice (*ob/ob* and *ob/c*), showed a biphasic effect of metformin on the regulation of hypothalamic nitric oxide synthesis. The molecular structures of metformin and aminoguanidine might provide an answer as to the complex relationships involved here.

SUGGESTIONS FOR STUDIES

Diabetes imposes a considerable amount of physical disability, which greatly exceeds that of normal ageing or even other diseases related with ageing. The aetiology of this functional decline has been explored by many authors, who have identified the following influences: the presence of macrovascular complication in the limbs; cognitive impairment; depression; visual impairment; peripheral neuropathy; hypoglycaemia; repeated infections, etc. Nutritional impairment should also be added to this list. One tends to think that type 2 diabetes patients are obese or overweight, but, in fact, approximately 30% of them, mostly men, are undernourished. Nutritional impairment may thus be directly related to functional decline.

In any modern health system, prevention may be of far more value than specific pharmacological strategies for treatment of disorders. The process of biological ageing, the presence of chronic disease, such as diabetes, and the concept of urbanisation converge to lead to the impairment of physical capacity, disability and functional decline. Urbanisation, a new notion in this context, has given rise to what can be called the hypokinetic adult. Depending on their socio-economic circumstances, hypokinetic adults are either over- or undernourished. They have a low body discipline, do not exercise and are generally overprotected. Physical activity, exercise and social activity have all proved instrumental in lowering the impact of disability. Improved nutrition should now be incorporated as part of a healthy life. British authorities have recommended that 50% of daily intake come from carbohydrates and that 8% to 25% of that should come from polysaccharides.

Despite being a highly prevalent disorder, diabetes is generally overlooked in nutritional research. The wider scientific community must look into this disease and develop new ideas and insights on the issues raised above. Aspects such as the immune function or trace elements, though not mentioned here, are highly relevant.

Successful aging

- Rowe J, Kahn R: Successful aging.

The Gerontologist 1997;37:433-440

- Seeman T: Successful aging: reconceptualizing the aging process from a more positive perspective. Facts and Reserach in Gerontoly 1994;429-441

Frailty

- Fried LP, Waltson J

Frailty and frailure to thrive. In: Hazzard WR, Blass JP, Ettinger WH, Halter JB, Ouslander JG (ed): Principles of Geriatric Medicine and Gerontology. 4th ed. New York, McGraw Hill, 1998, p:1387-1402

Bone mass and osteoporosis

- Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP
Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 128:801-9
- Nordin BE, Need AG, Steurer T, Morris HA, Chatterton BE, Horowitz M
Nutrition, osteoporosis and aging. Ann NY Acad Sci 1998;854:336-51
- Beaufriere B, Boirie Y
Aging and protein metabolism. Curr Opin Clin Nutr Metab Care 1998;1:85-9

Muscle mass and sarcopenia

- Baumgartner R, Waters D, Gallagher D, Morley J, Garry P
Predictors of skeletal muscle mass in elderly men and women. Mech Age Dev 1999;107:123-136
- Baumgartner R, Koehler K, Gallagher D, Romero L, Heymsfield S, Ross R, Garry P, Lindeman R: Epidemiology of sarcopenia among elderly in New Mexico. Am J Epidemiol 1998;147:755-63

Body water

- Chumlea WC, Guo SS, Zeller CM, Reo NV, Siervogel RM
Total body water data for white adults 18 to 64 years of age: the Fels Longitudinal Study. Kidney Int 1999;56:244-52
- Fukagawa NK, Bandini LG, Dietz WH, Young JB
Effect of age on body water and resting metabolic rate. J Gerontol A Biol Sci Med Sci 1996;51:M71-3

Immune function

- Lesourd B, Mazari L
Nutrition and immunity in the elderly. Proc Nutr Soc 1999;58:685-95
- Han SN, Meydani SN
Vitamin E and infectious diseases in the aged. Proc Nutr Soc 1999;58:697-705
- Chandra RK
Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet 1992;340:1124-7

Cognitive functions

- Selhub J, Bagley LC, Miller J, Rosenberg IH
B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71 (2 part 2):614S-20

- Launer LJ, Kalmijn S
Antioxidants and cognitive function: a review of clinical and epidemiologic studies. *J Neural Transm* 1998;53:1-8
- Kalmijn S, Feskens EJM, Launer LJ, Kromhout D
Polyunsaturated fatty acids, antioxidants and cognitive function in very old men. *Am J Epidemiol* 1997;145:33-41
- Jacqmin-Gadda H, Commenges D, Letenneur L, Dartigues JF
Silica and aluminium in drinking water and cognitive impairment in the elderly. *Epidemiology* 1996;7:281-5

Cancer

- Young KJ, Lee PN
Intervention studies on cancer. *Eur J Cancer Prev* 1999;8:91-103
- Lee IM
Antioxidant vitamins in the prevention of cancer. *Proc Assoc Am Physicians* 1999;3:10-5
- Jacobs DR, Marquart L, Slavin J, Kushi LH
Whole-grain intake and cancer: an expanded review and meta-analysis. *Nutr Cancer* 1998;30:85-96

Cardiovascular diseases

- Carlsson CM, Carnes M, McBride PE, Stein JH
Managing dyslipidemia in older adults. *J Am Geriatr Soc* 1999;47:1458-65
- Buring J, Hennekens C
Antioxidant vitamins and cardiovascular disease. *Nutr Rev* 1997;55:53-58

Diabetes

- Sinclair AJ
Diabetes in the elderly: a perspective from the United Kingdom. *Clin Geriatr* 1999;15:225-37
- Salonen JT, Nyyssönen K, Tuomainen TP, Maenpää PH, Korpela H, Kaplan GA, Lynch J, Hemrich SP, Salonen R
Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a four-year follow up study in men. *BMJ* 1995;311:1124-7

Free radical theory of aging

- Ashok BT, Ali R
The aging paradox: free radical theory of aging. *Exp Gerontol* 1999;34:293-303
- Vendemiale G, Grattagliano I, Altomare E
An update on the role of free radicals and antioxidant defense in human disease. *Int J Clin Lab Res* 1999;29:49-55
- Pitchumoni S, Doraiswamy P
Current status of antioxidant therapy for Alzheimer disease. *JAGS* 1998;46:1566-72

Caloric restriction

- Roth G, Ingram D, Lane M
Calorie restriction in primates: will it work and how will we know? *JAGS* 1999;47:896-903
- Yu BP
Aging and oxidative stress: modulation by dietary restriction. *Free Rad Biol Med* 1996;21:651-68



Achevé d'imprimer par Corlet, Imprimeur, S.A.
14110 Condé-sur-Noireau (France)
N° d'Imprimeur : 56998 - Dépôt légal : juillet 2002

Imprimé en U.E.

NUTRITION AND SUCCESSFUL AGEING

The world's population is growing and life expectancy is increasing. In light of these facts, it is natural to want to use nutrition, education and other alternatives to alleviate or eliminate some of the problems related to ageing. Scientific data show that many diseases, including cancer and osteoporosis, may be age-related.

Is it possible to help a population to age successfully via food management and nutrition, given that successful ageing means remaining active and mentally lucid at a late age? Some data already indicate that, today, the nutritional impact is both, compensatory and preventive. What will be the best approach to maintain optimal lifestyle while we grow older?

With this workshop, bringing together international and multi-disciplinary scientists, Danone Vitapole would like to contribute to increasing awareness of the importance of good nutrition to the well-being of elderly and raise the priority given to research and education in this field.



ISBN : 2-7420-0424-6