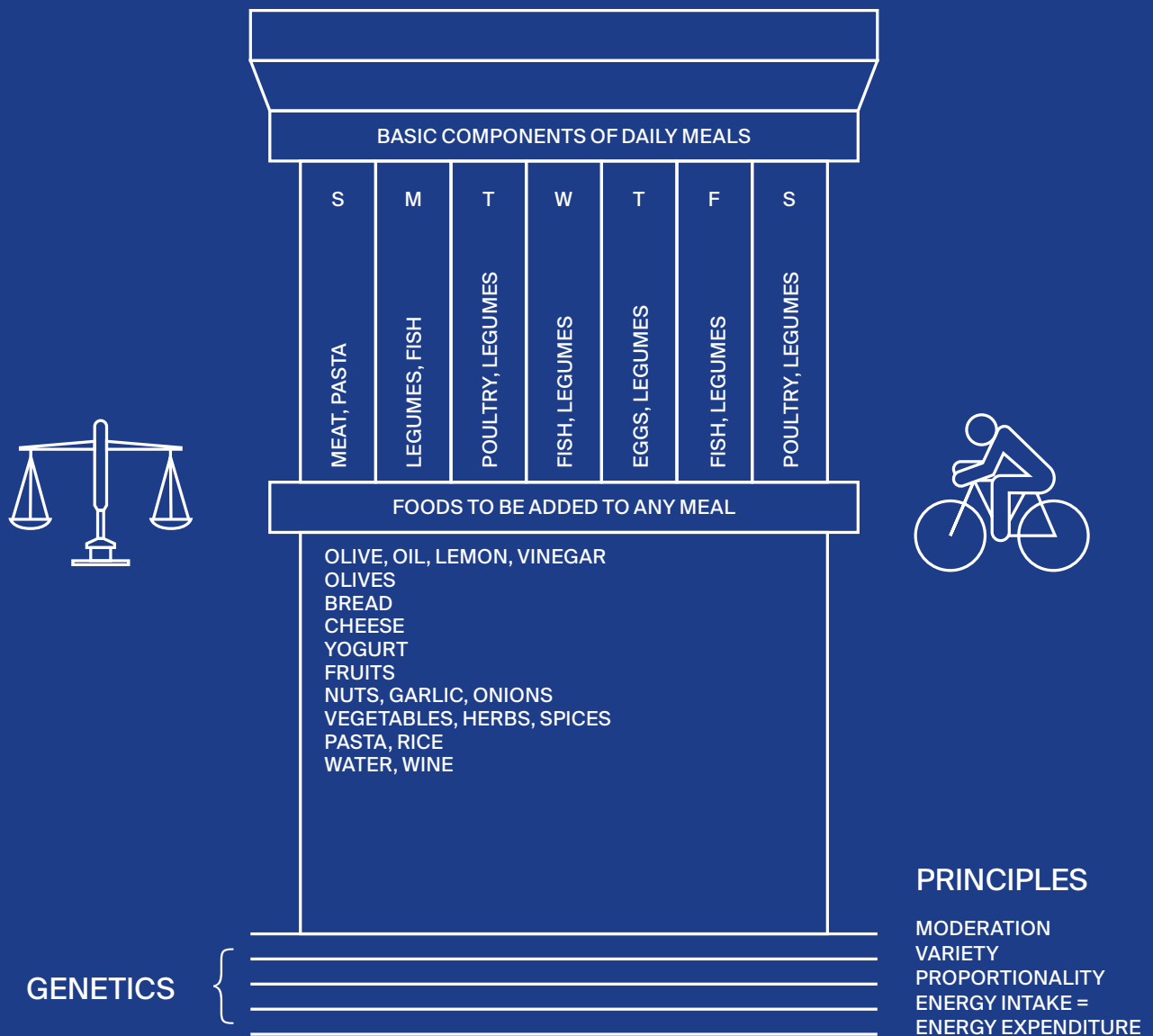


THE HEALTHIEST DIET FOR YOU: SCIENTIFIC ASPECTS

ARTEMIS P. SIMOPOULOS

GREEK COLUMN FOOD GUIDE



The Healthiest Diet for You: Scientific Aspects

Praises for

The Healthiest Diet for You: Scientific Aspects

"If a healthier life is important to you and your family, this book is a must read. From the clinician-scientist that gave us the scientific basis for success of the Mediterranean Diet, Dr. Simopoulos now gives us the science behind the Healthiest Diet in easy-to-read everyday terms in this exceptional book. Excessive inflammation is widely agreed to be a key component to many diseases from COVID-19 to heart disease to obesity. Dr. Simopoulos explains the resolution of inflammation from molecules needed in the body, genes to nutrition and healthy Aging. A careful read of this book will prolong lives, shorten recovery for many and keep us healthy, if we practice what she provides in this book for us all."

–Charles N. Serhan, Ph.D., DSc, Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School

"The book titled *The Healthiest Diet for You: Scientific Aspects* by Artemis P. Simopoulos is a goldmine of information and makes very interesting reading. In the initial part of the book, the author very effectively links human evolution with the evolution of dietary patterns over time and the transition they have undergone with the advent of agricultural development and subsequently with the introduction of food processing methods. She has raised an important question directed at food manufacturers regarding healthier options in processed foods which also contribute to early satiety and prevent people from overeating. She underscores the imperative need to improve cooking methods from the standpoint of Nutrition Policy. She goes on to draw the attention of the reader to the importance of the desirable ratio of omega-6 to omega-3 fatty acids in maintaining optimum health, the need for precision nutrition and the role of genetic influences as contributors to nutritional outcomes. She reminds the reader of the crucial role played by the gut microbiome in contributing to health and disease, the interesting association between obesity and inflammation and factors contributing to healthy ageing. In a nutshell, this book is a "MUST READ"."

–Sarith Gopalan, M.D., Director of Medical Affairs, Reckitt, South Asia

"This book engagingly provides actionable guidelines for individuals backed up by well-documented scientific detail for professionals. It applies emerging personalized nutrition principles to a vital but often neglected issue that underlies so many chronic health conditions – the balance of omega-3 and omega-6 fatty acids in our diets and how that depends on genetic factors. If individuals, healthcare professionals, and policymakers focus on this one issue, it will make a dramatic difference in health and quality of life."

–Dana Reed, MS, CNS, CDN, Board Director, American Nutrition Association

"Artemis Simopoulos, who pioneered the original Omega-3 fatty acid studies and the Omega-3/Omega-6 ratio, has written a beautifully nuanced account replete with useful tables and graphics of the science underlying healthy food. Meticulous research into genetic variation and pathways, biochemical connections and endocrine signaling reveals how vital nutrients benefit long term health by decreasing the risk of disease. Scientific evidence has added the subtle influence of the intestinal microbiota on brain and behavior and the profound effects of regular physical activity on

healthy function.”

–Regina C. Casper, M.D., Professor, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

“This is an absolutely unique, science-based description of practically every facet of nutrition and health. I know of no other author who has the range and the ability to integrate so many fields of science to write such a book than Dr. Artemis P. Simopoulos. In a field where there is so much advocacy of half-truths or even falsehoods, this is a monograph that you can count on. I know that I learned a lot even after many decades of working and research in this field. And I am going to modify my own diet in accordance with the traditional Crete diet!”

–Norman Salem, Ph.D., Nutritional Biochemist

Thoughts about the Book

Cholesterol (in food or in the body) has remained a favored metric for training and studying cardiovascular disease since the 1960's until today. In the book "The Healthiest Diet for You: Scientific Aspects", Dr. Simopoulos illuminates the complex debates, both scientific and political, especially the misinterpretation of the data from the Seven Countries Study, which ignored the important role of essential fatty acids, and the importance of their balance (omega-6/omega-3) and metabolism for health.

The importance of the evolutionary aspects of diet and the incompatibility with the current food supply is highlighted, as is the importance of genetic variation in the development of inflammation, which is the basis of chronic diseases (obesity, diabetes, cardiovascular disease, hypertension, some forms of cancer, and aging), all of which are increasing in prevalence around the world. The need to avoid developing foods that have not previously been part of our diet, and the dire consequences of ultra-processed foods, is discussed. The current Dietary Guidelines for Americans are discussed, and references and quotations are provided, based on comments made by many outstanding scientists regarding the weak scientific basis upon which many of the guidelines are created. As emphasis is placed on the prevention of disease and the maintenance of good health, the importance of knowing your "family history", developed by the U.S. Surgeon General, is referenced on the Centers for Disease Control and Prevention (CDC) website, and the reader is advised to know their family tree and their predisposition to disease.

The book is an epistemological provocation, a reminder that science is a political enterprise and an invitation for each one of us to educate ourselves about our family history, understand the science behind food technology, evolution, and the fact that our genes are programmed to respond to a diet and food supply that have been part of human evolution. Currently, 72% of calories come from foods that have not been part of our diets during evolution. The book is also an invitation and provides you with enough scientific information to select the healthiest diet for you. Scientific knowledge is essential for the selection of the healthiest diet for you.

Artemis P. Simopoulos

The Healthiest Diet for You: Scientific Aspects



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Dedication

To my three daughters, Daphne Anne Pinkerson, Lee Harrie Pinkerson, Alexandra Pinkerson, MD and to my two granddaughters Emma Rose Kirby and Edith Fan Leaver, whose enthusiasm and interest in scientific truth sustained me during the writing of this book; and to the memory of my late husband Alan Lee Pinkerson, MD, who always supported me in all my scientific endeavors.

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Preface

I decided to write this book, *The Healthiest Diet for You: Scientific Aspects*, because major advances have taken place in the last 40 years in the role of nutrition in development and in the prevention and management of chronic diseases, as well as the role of nutrients in gene expression. The general public is fascinated with personalized nutrition and “what the genes can tell you about your nutrition”, and what you should eat to stay healthy and to delay the aging process. The book includes factors, players, and conditions that led to the current food supply, which is not consistent with the composition of foods that human beings evolved through the ages. The application of technology to agriculture following the Second World War, including the active role of Food technologists, who developed foods that tasted good, led to a very tasty palatable food supply high in fats, sodium, added sugar, and omega-6 fatty acids, but low in omega-3 fatty acids, fruits, vegetables and grains. The changes in agriculture and food production led to a proinflammatory diet in the US and practically all the developed countries and now spreading throughout the world. Yet although we know what a healthy diet is and for whom, world politics, economics, and the food industry make it difficult to implement.

Today, 54% of foods are ultra-processed and contain ingredients that are not found in whole foods. Furthermore, 72% of calories are coming from foods that have not previously been part of our diet. In addition, 70% of the junk food (junk food is generally understood to include processed foods and beverages that are high in calories, added sugars, sodium, and saturated fat) consumed by children and adults is purchased at the grocery store.

As Chair of the Nutrition Coordinating Committee (NCC) at the NH, I participated at Hearings during the Select Committee on Nutrition and Human needs Chaired by Senator McGovern and developed research programs and Clinical Nutrition Research Units throughout the US, which helped nutrition attain its Golden Age. Today, however, the FDA is 25 years behind in food regulation, particularly refusing to recognize the opposing roles of the omega-6 and omega-3 fatty acids, listing them together on the label as polyunsaturated fatty acids (PUFAs) despite all the knowledge, based on research from taxpayers money, that these two families (omega-6 and omega-3) are physiologically and metabolically distinct. Furthermore, during evolution humans ate foods that were balanced in the omega-6 and omega-3 fatty acids and had a ratio of 1–2/1. Today’s diet has a ratio of 20/1, which makes the US diet the most proinflammatory diet in the world. Inflammation is at the base of all chronic diseases.

The COVID-19 pandemic revealed the health disparities that exist in the US population with African Americans, Hispanics, Native Americans, and those with Arctic (Inuit) ancestry. These populations have higher morbidity and mortality due to COVID-19. In evaluating the reasons for the increased morbidity and mortality to COVID-19, there were many publications indicating that these populations also had more cardiovascular disease (CVD), diabetes, obesity, high blood pressure, lower socioeconomic status, and were over 65 years of age. What is missing are publications that show the dietary and genetic variants of these populations, particularly in the metabolism of omega-6 and omega-3 fatty acids that may account for the increased susceptibility to COVID-19, along with their pro-inflammatory diets and lack of physical activity. The book deals with these issues.

Knowledge is power. This book focuses on the science of nutrition and foods to provide you with information and enable you to choose healthy foods. It is the only way to overcome misinformation provided through marketing, especially to children on television. Only a well-informed person can make informed and wise decisions.

I believe there is a need for a book to provide scientific information for a healthy diet, which takes into consideration the evolutionary aspects of diet, its interaction with genetic variants, and the high inflammatory and oxidative state of the modern Western Diet and the uncontrolled expansion of ultra-processed foods.

The last chapter of the book lists foods and ingredients that are consistent with a healthy diet and foods and ingredients that are bad for you. I am not providing recipes. Each one of you has your own food recipes. By providing lists of healthy foods and ingredients, you can modify your own recipes, and doing so you practice personalized nutrition.

The aim of this book is to provide readers with the basic factual information necessary to comprehend the enormity and potential effects of nutrients and foods on overall health and well-being. As such, the audience for this book is the educated public, teachers, health professionals, physicians, medical students, agriculturists, nutritionists, dietitians, historians, and policy makers.

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Chapter 1. Introduction

The world has been going through a dramatic Nutrition transition that started about 50 years ago. In fact, the International Union of Nutritional Sciences (IUNS) Congress held 19–23 September 2005 in Durban, South Africa had the title “Nutrition Safari for Innovative Solutions”. Since 2005, obesity and expanded waistlines have been a common characteristic of the middle class worldwide, no longer limited to Western cultures. In developing countries, obesity coexists with severe malnutrition in the form of undernutrition. Wealth, industrialization, and rapid urbanization have led to:

- Increased production and consumption of ultra-processed foods, processed meat, and dairy products high in omega-6 fatty acids because the animals are fed grains high in omega-6 fatty acids instead of grazing (grass contains omega-3 fatty acids)
- Vegetable oils high in omega-6 fatty acids, and ultra-processed foods, and the most recent imitation or fake foods high in omega-6 oils, fat, sugar, and salt, and sugar-sweetened beverages high in sugars, especially fructose

Although there are a number of additional factors such as sedentary life style, and environmental pollutants in the form of toxins and endocrine disruptors (substances that behave like hormones and take over the functions of normal human metabolism believed to lead to chronic diseases), dietary change is the main cause of an exponential rise in obesity and many chronic diseases such as cardiovascular disease (CVD), diabetes, high blood pressure, cancer and osteoporosis (thinning of the bones) also known as diseases of civilization. The World Health Organization (WHO) Report on Obesity and Overweight, January 2015 stated that in 2014 about 1.9 billion adults were overweight worldwide, of which 600 million were obese.

Production and overconsumption of unhealthy food leads to detrimental agricultural changes in the earth system, which affect not only the land but oceans, waterways, the atmosphere in general, and a rich diversity of life that supports the current world population of 7.3 billion people. The global food system is one of the most important drivers of detrimental change of the Earth System, influencing climate change, loss of forests, biodiversity loss, and nitrogen and phosphorus use in fertilizers, and is a major producer of greenhouse gases. Another WHO Report on Global Strategy, Physical Activity and Health in 2016 states that modifying four risk factors, namely:

- Unhealthy diets;
- Physical inactivity;
- Tobacco use;
- Excess alcohol consumption,

could prevent up to 80% of cardiovascular disease and type 2 diabetes, and at least 1/3 of all common cancers. These four risk factors (unhealthy diets, physical

inactivity, tobacco use, and excess alcohol intake) are not only detrimental to health, but it has also been estimated that they will cost the global economy USD 47 trillion over the next two decades, with unhealthy diets being the most important. We know what healthy diets are ever since the Seven Countries Study showed that the people in Crete (Greece) lived the longest and had the lowest rate of coronary heart disease (CHD) and Cancer. The traditional diet of Crete prior to 1960 is indeed the healthiest diet, followed by the Japanese diet. In general, all traditional diets everywhere in the world are healthier and better than the Western diets formulated by food technology since World War II. The diet of Crete, and other traditional diets including the diet of Okinawa, the Paleolithic diet, and the diets of Southern Europe—the Mediterranean Diets—generally have minimally processed foods and are rich in fruits, legumes, vegetables (especially green leafy vegetables), whole grains, nuts, and seeds high in fibers, with little meat and more fish and, most importantly, fewer vegetable oils high in omega-6 fatty acids and a balanced dietary omega-6/omega-3 ratio. However, out of all the traditional diverse healthy diets, only the traditional diet of Crete (Greece) prior to 1960 resembles the Paleolithic diet in having a balanced dietary omega-6/omega-3 fatty acid ratio of 1–2/1, which is the ratio that humans evolved, and to which our genes are programmed to respond. People today are concerned about their health and look for healthy diets. A concern for health is a powerful driving force for changing the way that we produce and consume food, and generally live.

The concept of food security needs to be updated to include nutrition security, which means healthy foods that contribute to environmental sustainability, not what is being produced today, but foods whose composition is consistent with the way we evolved over thousands of years and that our genes are programmed to respond to. Therefore, the concepts of personalized nutrition based on genetic variation and the role of nutrients in gene expression are included practically in all the chapters in addition to the chapter on “What your genes can tell you about Nutrition”. Genes vary in frequency in many parts of the world and people’s bodies have learned to adapt to them. However, in a “global supermarket” where Western Diets are:

- High in sugars, especially fructose and other refined carbohydrates;
- High in omega-6 fatty acids and very low or depleted in omega-3 fatty acids;
- High in energy intake, ultra-processed foods, and processed foods high in refined carbohydrates, and meat, but low in green leafy vegetables, fruit, grains and fish (omega-3 fatty acids) and;
- Low in energy expenditure due to sedentary lifestyles,

Coronary heart disease (CHD), cancer, obesity, and diabetes lead to (1) early death and (2) increases in expenditures in healthcare delivery. All the above dietary factors and sedentary lifestyles are not consistent with the diets or lifestyles of our ancestors, to which our genes are programmed to respond. The frequency of genetic

variants that interact with nutrients vary around the world, and recent studies on the metabolism of omega-6 and omega-3 fatty acids show that the Western diets high in omega-6 fatty acids lead to a proinflammatory state, particularly in populations with Genetic Variants at FADS1 and FADS2.

Food production and agricultural development have led to a world where more people are obese than undernourished. Both obesity and undernutrition are manmade. Our planet can produce adequate amounts of food for everyone, if it were not for the devastating political decisions that lead to wars, refugees, political instability, and greed. For the current situation to be remedied we are going to need to develop Educational Programs about Healthy Agriculture, Healthy Nutrition, and Healthy People for the general public and for all kinds of health professionals, agriculturists, nutritionists, dietitians, nurses, physicians, and hopefully politicians. Knowledge is power and now is the time to begin. The characteristics of diets consistent with good health and of low environmental impact include:

- Balanced omega-6/omega-3 fatty acids by decreasing vegetable oils high in omega-6 fatty acids such as corn oil, sunflower oil, safflower, cottonseed, and soybean oil, and increasing olive oil, macadamia nut oil, flaxseed oil, canola, other forms of seed oil, such as hazelnut oil that are rich in monounsaturates (olive oil, macadamia nut oil, hazelnut oil), and omega-3s (flaxseed, canola, perilla, chia, camelia tree oil), palm oil produced from the fruit, and small amounts of organic coconut oil.
- More fruits, nuts, vegetables, and grains high in fiber;
- Moderate quantities of sustainably sourced fish;
- Moderate consumption of unprocessed or minimally processed meat;
- Very limited consumption of foods high in salt, fat and sugar, especially fructose and ultra-processed foods.

We must develop ways to reach and empower people. Farmers must develop food products that are consistent in composition with the foods our bodies are familiar with, as we adapted through thousands of years of evolution, and to which our genes learned to respond, and not products that are produced now in large amounts because the technology and chemical fertilizers make them possible. This approach has led to an expanded food processing industry that manufactures foods (that are ultra-processed and have a high omega-6/omega-3 ratio of 11:1), based on how cheap they are and not how healthy they are or their adverse effects on the environment.

This book provides scientific evidence and defines what is a healthy diet for you by taking into consideration evolutionary aspects of diet, genetic variation, and physical activity. The book consists of 13 chapters in the following order, in addition to the preface:

List of Chapters in order

- 1 Introduction

Part I.

- 2 Evolutionary Aspects of Diet
- 3 Paleolithic and Mediterranean Dietary Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Stress in Adults
- 4 Ultra-Processed and Imitation Foods

Part II.

- 5 The Importance of the Omega-6/Omega-3 Balance for Health
- 6 What Your Genes Can Tell You about Nutrition

Part III.

- 7 The Human Intestinal Microbiome in Health and Disease
- 8 Obesity
- 9 Healthy Aging

Part IV.

- 10 Evolutionary Aspects of Exercise
- 11 The Diet of Crete: The Healthiest Diet
- 12 Dietary Guidelines for Americans

Part V.

- 13 So How Can You Have the Healthiest Diet Today?

At the end of each chapter, except the chapters on “Dietary Guidelines for Americans” and “So how can you have the healthiest diet today?”, important statements are grouped together, so the reader will retain at a glance what each chapter is about. I hope that the contents of this book will inform the interested audience to follow the scientific evidence and change their diet and become physically active. The last chapter serves as a stimulus on how to do that. I expect each one of you will know which is the healthiest diet for you. You should be able to modify your own recipes by changing the oils, have a balanced omega-6/omega-3 ratio, eat seasonal and local foods, enjoy cooking, and get to “know thyself”. Socrates preached the concept of “know thyself” which by the way was at the entrance of the Temple to Apollo at Delphi, where the Ancient Greeks went to obtain advice about their future.

We should remember what Aristotle said about Truth.

“The search for Truth is in one way hard and in another easy. For it is evident that no one can master it fully nor miss it wholly. But each adds a little to our knowledge of Nature, and from all the facts assembled there arises a certain grandeur.”

Therefore, scientific truth should be the cornerstone for Nutrition and Health.

Part I

Chapter 2. Evolutionary Aspects of Diet

1. Wild Vegetable Foods
2. Wild Game
3. Nutritional Properties of Foods Introduced after Agricultural Development
4. Dairy Foods and Commercial Meat
5. Energy Expenditure

“Nothing in Biology Makes Sense Except in the Light of Evolution.”

~Theodosius Dobzhansky

The dietary intake and nutritional patterns of modern-day humans differ in many important ways from those of our preagricultural human ancestors, but our genes have not changed significantly. We still have the genes of our Stone Age ancestors. The genetic constitution was selected through evolutionary experience for life circumstances of the past, not those which exist at present (Table 2.1) [1].

Table 2.1. The main events of human evolution.

Years Ago	Epoch	Development
7,500,000		hominid–pongid divergence
2,000,000	Pliocene	<i>Homo habilis</i> present
1,700,000	early Pleistocene	<i>Homo erectus sapiens</i> appears
45,000	late Pleistocene	<i>Homo sapiens</i> (anatomically modern) appears
10,000	Late Pleistocene	agriculture revolution
200	Holocene	Industrial revolution

Source: Adapted from reference [1].

Although major changes have taken place in our diet over the past 10,000 years since the beginning of the Agricultural evolution, our genes have not changed. The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Therefore, over the past 10,000 years there has been time for very little change in our genes; perhaps 0.005%. In fact, our genes today are very similar to our ancestors during the paleolithic period 40,000 years ago, at which time our genetic profile was established [1,2]. Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected.

The dietary differences between our ancestral and current food supply, along with “old” genes and certain genetic variants in the metabolism of essential fatty acids, have serious implications for human growth, development, and health [3]. Ancestral human nutrition was derived mostly from wild game and uncultivated plant foods. Depending on the geographic location, season of the year and time, honey, fish, and, in times of shortage, wild grains made varying contributions [4].

Today we eat smaller amounts of the foods for which evolution has influenced the function of human biochemistry and physiology. This is because we consume less energy overall, consistent with less physical exertion, and because we have developed and/or adopted a variety of new energy sources, foods which were not available or at

least utilized little by our human ancestors, and which displace original, fundamental foods from our own daily intake pattern. Second, the “new foods” which make up over half of what we eat now include cereal grains, dairy products, prepared, processed, and more recently ultra-processed foods, commercial meat from grain fed animals high in omega-6 fatty acids, salt, refined flours, sweeteners, and recently all kinds of meat, fish, and chicken imitation products based on plant proteins. Altering the mix of dietary constituents is detrimental to health because of what they add as well as what they take away, resulting in nutrients detrimental to human health. That is, in addition to their passive effect of displacing much of the food which comprised nearly all Paleolithic human nutrition, the “new” foods have an actively adverse influence resulting from constituents which have been shown to be harmful.

1. Wild Vegetable Foods

The uncultivated fruits and vegetables consumed by hunters and gatherers usually contain high levels of micronutrients, except for sodium. The potassium content is much higher than sodium in practically all cases examined [4]. Nuts, beans, and seeds provide a substantial amount of fat, but this fat is mostly unsaturated and provides little saturated fat. Wild plants contain a considerable amount of (largely soluble) dietary fiber, which partly explains why their nutrient/food energy ratio is relatively great. Studies of the phytochemical content of wild plants are considered in line with their high average concentrations of vitamins and minerals [5].

2. Wild Game

Game animals are typically lean, containing on average only one-fifth of the fat and about half the energy provided by commercially produced meat [6]. Game also has less cholesterol. Furthermore, fat from wild animals contains a high proportion (25–30%) of polyunsaturates, including the essential fatty acids: arachidonic, eicosapentaenoic, docosapentaenoic, and docosahexaenoic long-chain fatty acids [7]. Because of its lower fat content and lesser food energy, the nutrient/energy ratio of game meat, like that of wild plants, is high.

3. Nutritional Properties of Foods Introduced after Agricultural Development

Cereal grains such as wheat, rice, corn, millet, and other grains led to dramatic population growth as they became major dietary resources. They increased the total food energy per given land area, and whereas whole grains are good fiber sources, especially for insoluble fiber, finely milled flours contain hardly any fiber at all [8]. Furthermore, grains have little cancer-preventive effect, relative to fruits and vegetables, suggesting that their phytochemical content is lower and their omega-6 fatty acid content is higher.

4. Dairy Foods and Commercial Meat

Today about half the energy in whole cow's meat is derived from fat, most of which consists of saturated and omega-6 fatty acids because the animals are grain fed. Prior to agricultural development, the animals ate mostly grass, and their meat contained omega-3 fatty acids, which by the way were found throughout the food supply. During the late 19th Century and most of the 20th Century, animals intended to provide meat were bred and raised to maximize their fat content. The much-prized marbling effect and the price structure for prime choice, and good beef, which vary step wise in their fat content, are manifestations of this practice [7]. This increase in fat content is mostly saturated fat, and since these animals are grain fed they have a high omega-6/omega-3 ratio leading to inflammation and to chronic inflammatory diseases [9]. The separation of fats, lard, and dairy fats led to high intake of saturated fats and cholesterol. Cooking methods such as frying increase the intake of fats from vegetable oils. This led to a higher proportion of omega-6 fatty acids than that of the fat typically available to our ancestral humans [10]. Refined flours, sweeteners, salt, prepared and processed and ultra-processed foods, and alcohol took over and became very prominent in Western diets and eventually throughout the world. These "new foods" led to a reversal of the ratio of energy/nutrients.

Fruits and vegetables contributed a higher proportion of total energy for Stone Ages: typically about two-thirds of their intake as compared with roughly one-fifth to one-fourth for Europeans and Americans [4]. The foods we consume at present are often fortified with known vitamins and minerals, otherwise the discrepancy seen in Paleolithic and current micronutrient intake would be even greater. In addition to the high fat intake of modern Western diets, a major change has taken place in the amount of the essential fatty acids, specifically the omega-6 and omega-3 fatty acids, their long-chain fatty acid derivatives, and metabolites. There has been an enormous increase in the omega-6 fatty acid content of the Modern Western Diet (MWD) following the Second World War, due to advances in technology in developing oils from corn, sunflower, safflower, and cottonseed oil, all of which are high in omega-6 fatty acids (Table 2.2).

Table 2.2. Sources of omega-6 fatty acids (linoleic acid).

Oils High in LA	Amount of LA
Safflower oil	78%
Sunflower oil	71%
Corn oil	59%
Soybean oil	56%
Cottonseed oil	53%

Thus, for the first time in the history of human nutrition, the omega-6/omega-3 ratio increased to 16–20/1 whereas during evolution this ratio of omega-6/omega-3 was 1–2/1. The balance of omega-6/omega-3 is important to health, for normal development, and for the prevention of chronic diseases and decreasing the rate of the aging process (Figure 2.1) [11].

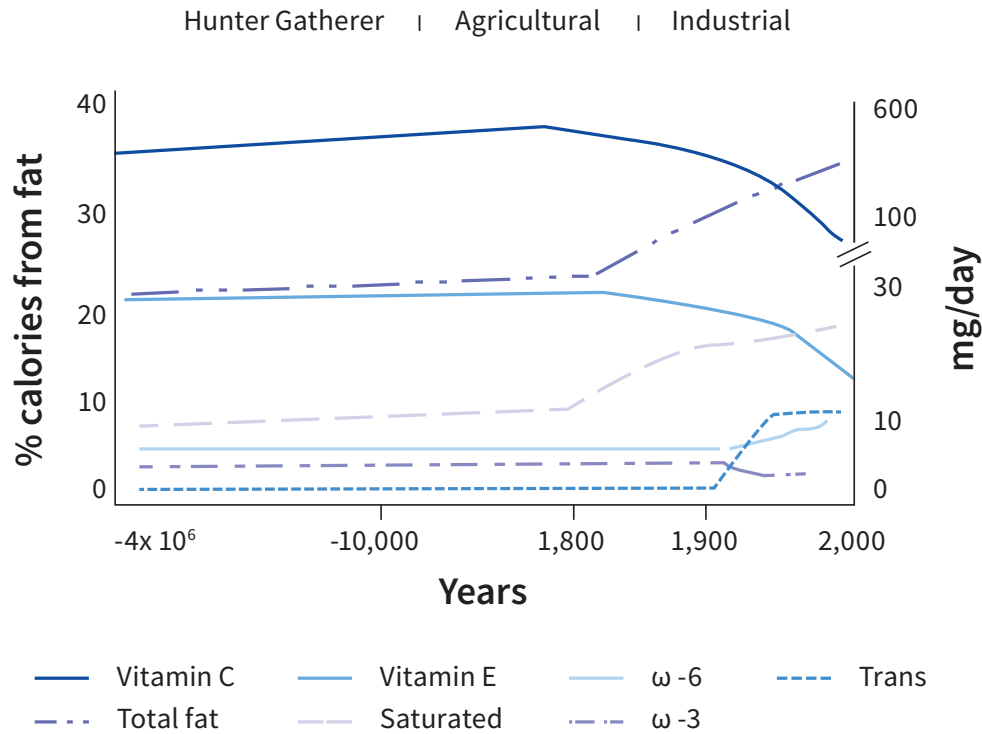


Figure 2.1. Hypothetical scheme of fat, fatty acid (ω -6 and ω -3, trans and total) in [11].

5. Energy Expenditure

In addition to dietary differences, physical activity was much higher due to the absence of motorized equipment. The level of physical activity exceeded that of the present, and the caloric expenditure was about 50% more each day than at present [12]. Until the late 19th Century, the circumstances of human existence demanded adult physical exertion, which equaled resting metabolic needs. Thus, if resting metabolic rate (RMR) was 1500 K cal/day, the total daily calorie expenditure was around 3000 K/cal [12]. This relationship characterized both Paleolithic and Agricultural populations. However, in the late 20th century the requirement for physical exertion over RMR has decreased by 60% or more [13]. For persons with an RMR of 1500 K cal/day, the total daily caloric expenditure is now 2000 K cal/day or even less. At the same time, the energy/nutrient ratio of our food supply has increased. It is now possible to achieve and often exceed our energy needs, while our intake of nutrients other than energy is much lower than that which would

be provided by “natural” foods, those that were consumed prior to agriculture. In the Paleolithic, when humans expended more energy through physical activity, the increase in nutrient intake would have provided a source, above currently established requirements.

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BOX 1

Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected.

BOX 2

Grains have little cancer-preventive effect relative to fruits and vegetables, suggesting that their phytochemical content is lower and their omega-6 fatty acid content is higher.

BOX 3

Prior to agricultural development, the animals ate mostly grass, and their meat contained omega-3 fatty acids, which by the way were found throughout the food supply.

BOX 4

The separation of fats, lard, and dairy fats led to high intake of saturated fats and cholesterol.

BOX 5

Refined flours, sweeteners, salt, prepared and processed and ultra-processed foods, and alcohol took over and became very prominent in Western diets, and eventually throughout the world. These “new foods” led to a reversal of the ratio of energy/nutrients.

BOX 6

Fruits and vegetables contributed a higher proportion of total energy for Stone Agers: typically about two-thirds of their intake as compared with roughly one-fifth to one-fourth for Europeans and Americans.

BOX 7

There has been an enormous increase in the omega-6 fatty acid content of the Modern Western Diet (MWD) following the Second World War, due to advances in technology in developing oils from corn, sunflower, safflower, and cottonseed oil, all of which are high in omega-6 fatty acids.

BOX 8

Physical activity was much higher due to the absence of motorized equipment, the level of physical activity exceeded that of the present, and their caloric expenditure was about 50% more each day.

BOX 9

Altering the mix of dietary constituents is detrimental to health because of what they add as well as what they take away, resulting in nutrients detrimental to human health. That is in addition to their passive effect of displacing much of the food which comprised nearly all Paleolithic human nutrition, the “new” foods have an actively adverse influence resulting from constituents which have been shown to be harmful.

Chapter 3. Paleolithic and Mediterranean Dietary Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Stress in Adults

1. Important Components of the Mediterranean Diet
2. The Question Is: Do the Olive Oils' "Hearty" Antioxidants Endure Heat?
3. Where Do You Buy Real Extra-Virgin Olive Oil?

Chronic inflammation and oxidative stress are associated with poor diet quality and a higher risk of cardiovascular disease (CVD), cancer and other chronic diseases. Both chronic inflammation and oxidative stress endanger our health due to the fact that current diets (Western Diets) are not consistent with the diet humans evolved to have and to which our genes are programmed to respond. In a recent study [1] instead of dietary histories to assess the quality of diet, the scientists chose to measure biomarkers in the blood because they are specific and accurate. For inflammation they measured the blood's levels of high-sensitivity C-reactive protein (hsCRP) which is an acute inflammatory protein whose level increases in the blood in the presence of inflammation, and F2-isoprostane which is a reliable marker of in vivo lipid peroxidation, a major indicator of oxidative stress. Oxidative stress can increase inflammation and vice versa. As mentioned above, both chronic inflammation and oxidative stress have been associated with cardiovascular disease (CVD), cancer and other chronic diseases. Several dietary factors influence a person's chronic inflammation level, such as a higher ratio of omega-6 to omega-3 fatty acids and a high intake of saturated fat; also, foods with a high glycemic load and lower dietary fiber intake are associated with higher inflammation levels [2]. In the past, investigations into which foods alter systemic inflammation and oxidative stress led to several clinical trials of nutritional supplementation to prevent CVD [3] and cancer [4,5], most finding limited effects and even harm in some instances [6–9]. Although there are many reasons why these trials might not have found the expected benefits, it may be that at least in part, the nutritional supplements used in the trials cannot sufficiently address the relevant complex and likely interacting components of diet [10–12]. To better capture the potential synergistic effects of food components in a complex diet, nutrition researchers have used dietary patterns, thus quantifying a person's entire diet rather than its individual components. One such pattern that is of increasing interest is a Paleolithic Diet Pattern. The Paleolithic diet of preagricultural hunter-gatherer humans—that is, more than 10,000 years ago—has been estimated from anthropologic evidence from fossils and a few surviving hunter-gatherer groups [13]. The diet pattern is characterized as a predominantly plant-food-based diet with a wide diversity of fruits, nuts and vegetables, small amounts of fish and meat from animals in the wild, and very little to no grains, dairy products, legumes, or sugar, and certainly no vegetable oils high in omega-6 fatty acids. It is also high in calcium and other minerals, which are found in various wild plant foods [13]. The consequences of the discrepancies between the diets and lifestyles of Homo sapiens before the agricultural revolution, and those during the modern, postindustrial revolution era are referred to as “evolutionary discordance”, and they have been proposed to account for some of the dramatic increases in chronic diseases in the 20th century [14,15]. There have been only a few clinical studies on the Paleolithic diet, with some indication that it may improve cardiovascular

and metabolic biomarkers [16–22], even more so than a Mediterranean diet. The Mediterranean diet is considered to be one of the healthiest diets for the prevention of many of the chronic diseases, and especially the traditional diet of Crete (Greece) prior to 1960 has been shown to be the healthiest diet for the prevention of cardiovascular disease, cancer and is associated with the highest longevity [23]. A number of studies on the Mediterranean diet have shown that it is associated with lower concentrations of biomarkers of inflammation and oxidative stress [24–26]. The Mediterranean diet is similar to the Paleolithic diet in that it emphasizes a high consumption of fruits, vegetables, fish, nuts, lean meats, olive oil instead of vegetable oils high in omega-6 fatty acids, and less processed foods, therefore the Mediterranean diet has little added sugar (fructose). Out of all the Mediterranean Diets that have been studied, only the traditional diet of Crete prior to 1960 had an omega-6/omega-3 ratio between 1–2/1 which is close to that of the Paleolithic diet of 0.72/1 [15], but unlike the Paleolithic diet is characterized by a moderate intake of grains, dairy (in Greece mostly yogurt and cheese), legumes, and alcohol in moderation. The balanced ratio of omega-6/omega-3 in the diet of Crete (Greece) and the Paleolithic diet is unique among all diets. Feart et al. [27] showed that the highest (best) Mediterranean score is consistent with a lower omega-6 fatty to omega-3 fatty acid ratio, because due to eating fish and olive oil, instead of processed meat and vegetable oils, the Mediterranean diet is lower in omega-6 fatty acids. Current Mediterranean diets are very different than the diets of 1960 when the first studies were performed as a part of the Seven Countries Study, which clearly showed that the diet of Crete was associated with the lowest mortality and the highest longevity, having less CVD and cancer, followed by the diets of Japan, Italy, then Yugoslavia (Croatia and the Adriatic Coast), Holland, the United States, and Finland. Additionally, not all Mediterranean diets are the same. The Mediterranean diet of Italy is high in pasta whereas the Mediterranean diet of Crete (Greece) is high in legumes that are higher in protein than pasta and contain omega-3 fatty acids. A balanced ratio of omega-6/omega-3 is the most important factor and therefore a major characteristic of the Cretan Mediterranean diet and the Mediterranean diets of the 1960s. In spite of this, recent studies carried out in Spain did not pay attention to the ratio of omega-6/omega-3 or the level of omega-6 fatty acids of the diet before intervention. The omega-3 intake was only recently looked at and of course, as expected, the higher the omega-3 fatty acids, the smaller the waistline gain and overall weight gain [28]. Although the 2016 US Dietary Guidelines recommended the Mediterranean Pattern, they forgot to mention the importance of olive oil and the need to avoid vegetable oils high in omega-6, such as corn oil, sunflower, safflower, cottonseed, and soybean oil. The true Mediterranean diet did not and must not include vegetable oils high in omega-6 fatty acids. It is a matter of changing FDA's current policies that fail to distinguish between the functions of omega-6 and omega-3 fatty acids. The FDA must move forward with

regulation and nutrition labels that do not state PUFA, but omega-6 and omega-3 fatty acids separately in terms of grams and percent of energy.

The Mediterranean Diets of today are very different from the Mediterranean Diets of the 1960s, at which time US processed food products began to flood Europe. Following the establishment of the European community, which Greece joined forty years ago, vegetable oils high in omega-6 began to replace olive oil as cooking oils, although in salads Greeks continue to use extra-virgin olive oil or just olive oil. Yet the omega-6/omega-3 ratio is no longer balanced, nor does the Greek egg have a balanced ratio. Unfortunately, today the omega-6/omega-3 ratio is 10/1 instead of 1-2/1 and obesity, CVD and cancer have increased, although Greeks continue to have better health statistics than the rest of Europe due to strong family ties, Greek culture, and general healthier attitudes that influence the diets of the young. A lower omega-6/omega-3 ratio or a higher intake of omega-3 fatty acids leads to improvements in mood, vigor, strength, and an overall positive attitude, which improve mental health [29]. When the Paleolithic Diet and the Mediterranean Diet scores were compared with the inflammatory markers of hsCRP and the oxidative stress marker F2 isoprostane, they showed that diets that are more Paleolithic or Mediterranean-like are associated with lower levels of systemic inflammation and oxidative stress in humans [1].

1. Important Components of the Mediterranean Diet

The Greeks consume more olive oil than any other population in the Mediterranean. In Greek mythology, the Goddess Athena gave the olive tree to the city of Athens as a gift and the population named their City of Athens after the Goddess. Olive oil is produced everywhere in Greece, but the two best-known olive oils come from Crete and Kalamata, the capital of the county of Messenia. I come from Kalamata, so I was brought up on Messinian olive oil and continue to use it to this day. Greek olive oil is a major component of the diet of Crete. In fact, the men in Crete began their day with a shot of olive oil in a wine glass. Olive oil is used to cook everything in baking, roasting, frying, in salads, and in making many of the traditional deserts such as kourabiethes, melomakarona and koulourakia. Melomakarona were served in the first Olympic Games in 776 BC and were a favorite of the athletes, and still are today.

Olive oil comes in different categories: extra virgin; virgin; extra light, and light. Extra virgin olive oil is of the highest quality because it is cold pressed and is rich in antioxidants, such as polyphenols. Overall natural polyphenols have anti-inflammatory properties, preventing oxidation and inflammatory expansion of blood vessels. These compounds account for the reduction in oxidative stress- or inflammatory-related sequelae associated with chronic degenerative diseases.

The fatty acid composition of olive oil is unique in a sense that it is mostly monounsaturated; about 80% has 1% ALA and only 6.1% LA and about 12% saturated fatty acids. Table 3.1 shows the composition of extra-virgin olive oil produced in our farm “Ampelistra”, which has been in our family for many generations.

Table 3.1. Fatty acid composition of Ampelistra olive oil.

Fatty Acids	C	%
Palmitic	(16)	10.8%
Palmitoleic	(16)	0.3 %
Stearic	(18)	0.8%
Oleic	(18)	81.6%
Linoleic	(18)	6.1%
Linolenic	(18)	0.3%

We studied the composition of the squalene content of olive oil. Squalene concentrations vary with the highest concentrations in oil from Kalamata. Squalene has antioxidant, anti-inflammatory, and anticarcinogenic properties. None of the other vegetable oils contain Squalene except rice oil. Greek olive oils contain the lowest amount of omega-6 fatty acids compared to other Mediterranean olive oils. Many scientific studies have shown that olive oil is the most important oil for health. In Greek mythology olive oil was considered so precious that the accidental waste of olive oil, for example due to the breakage of a container, was considered to be an omen of bad luck, because the olive oil was much more expensive than other cooking ingredients.

Olive Oil blocks COX-2 and potentiates the effects of omega-3 fatty acids in controlling inflammation. In addition to its healthy fatty acid composition and squalene content, olive oil is rich in other compounds that have anti-inflammatory and antioxidant properties. Oleocanthal is one of these components. Its properties are similar to classical non-steroidal anti-inflammatory drugs, i.e., aspirin. Olive oil is a non-selective inhibitor of cyclooxygenase (COX). Fifty grams (about three and a half tablespoons) of a typical extra-virgin olive oil per day contains an amount of Oleocanthal with similar in vitro anti-inflammatory effect to 1/10 of the adult ibuprofen dose [30]. It is therefore suggested that long-term consumption (as is carried out in Crete) of small quantities of olive oil may be responsible in part for the low incidence of heart disease and Alzheimer’s disease that is associated with the Mediterranean diet. Oleocanthal is responsible for the burning sensation we feel in our mouth and throat when we consume extra-virgin olive oil.

Hydroxytyrosol is a type of phenolic phytochemical with antioxidant properties in vitro. In nature, hydroxytyrosol is found in olive leaf and olive oil. Hydroxytyrosol

is a metabolite of Oleuropein. Oleuropein, along with oleocanthal, is responsible for the bitter taste of extra-virgin olive oil. Oleuropein in its pure form is a colorless, odorless liquid. The olive trees' leaves and olive pulp contain large amounts of hydroxytyrosol (compared to olive oil), most of which can be recovered to produce hydroxytyrosol extracts. However, it was found that black olives such as the common canned variety, containing iron (II) gluconate, contained very little of the original hydroxytyrosol because the iron salts are catalysts for its oxidation.

2. The Question Is: Do the Olive Oils' "Hearty" Antioxidants Endure Heat?

Extra-virgin olive oil is rich in antioxidants, has an aromatic taste, and an emerald-green color. "Pure"-grade olive oil is misleading. This olive oil has virtually no antioxidants and just virgin-grade olive oil has fewer antioxidants. So how do you know the olive oil you are buying is first quality—in other words, extra-virgin olive oil? The University of California at Davis has carried out many studies on the purity and quality of olive oil. Top-quality olive oil—extra-virgin olive oil—smells and tastes fresh, has aromatic notes—such as grass, apple, green banana, artichoke and herbs—and will typically have bitter and spicy notes, which indicate healthy levels of antioxidants.

Remember: extra-virgin olive oil's health benefits depend on its high antioxidant content and low omega-6 fatty acid content. The potent phenol-type antioxidants in extra-virgin olive oil mentioned above, such as oleuropein, hydroxytyrosol, and tyrosol, deliver powerful cardiovascular, anti-inflammatory, and other health benefits. Many studies have shown that regular consumption of extra-virgin olive oil is associated with a reduced risk of developing chronic degenerative disorders in addition to cardiovascular disease, such as type 2 diabetes and cancer [31], including alleviating autoimmune conditions such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, lupus, and psoriasis.

Although it is the extra-virgin olive oil that has the highest amounts of antioxidants, remember all olive oils regardless of quality grade have the lowest amount of omega-6 fatty acids compared to all other seed oils. In fact, out of all extra-virgin olive oils, the olive oil from the area near Kalamata in Greece, famous for its black kalamata olives, has the lowest content of omega-6 fatty acids. I was brought up on Kalamata Olive Oil and continue to use it to this day. The cheapest, most commonly used vegetable oils at home and in restaurants—soybean, corn, safflower, sunflower, peanut, and cottonseed oil—are very high in omega-6 fatty acids, which readily oxidize when exposed to heat and air.

Among all commonly used cooking oils, olive oil, macadamia, hazelnut oil, and canola oil are high in monounsaturated fatty acids, which do not oxidize during cooking, except for the canola oil which is 10% omega-3s and 20% omega-6 fatty acids and therefore should not be used in frying foods. Studies performed years

ago suggested that cooking with extra-virgin olive oil at a temperature of 300–350 degrees Fahrenheit does not produce excessive oxidation of its fats and preserves much of the oil's antioxidants. More recent studies show that extra-virgin olive oil is remarkably resistant to damage when heated even as high as 400 degrees Fahrenheit, such as when frying foods, largely because its high antioxidant content helps the oil resist oxidation. I enjoy making fried potatoes with Kalamata extra-virgin olive oil, cut into rounds, or making a potato omelet with omega-3 eggs and a salad with extra-virgin Kalamata Olive oil, with Kalamata's famous Balsamic Vinegar, black olives, and feta cheese that contains omega-3 fatty acids because Greek feta is made with milk from grass-fed goats. Frying with extra-virgin olive oil, however, will diminish the antioxidant content, but it is still better than all other oils. Despite the decrease in the total concentration of polyphenols during cooking, extra-virgin olive oil has properties that protect against oxidation of LDL cholesterol particles. In Crete at the time of the seven countries study prior to 1960, the men began their day with an ounce of extra-virgin olive oil and then had fruit, bread, cheese, and coffee for breakfast.

3. Where Do You Buy Real Extra-Virgin Olive Oil?

I am sure you are familiar with newspaper articles that every so often report the adulteration of olive oil with other vegetable oils. Each scandal intimidates many consumers. However, the best assurance of getting extra-virgin olive oil products/organic oils and vinegar or black olives is to buy from a trusted retailer or pick an extra-virgin-certified organic olive oil. Organic certification requires that the farm of origin, the production facility, and the supply chain undergo regular inspections. Olive oil should be kept in a dark bottle or a cupboard at room temperature. In the refrigerator it thickens and becomes semisolid. You can make a mixture of half butter and half olive oil, keep it in a butter dish and use it on toast, or to fry eggs. It is healthier than plain butter and delicious. The diet of Crete was the first Mediterranean Diet that was shown to decrease the death rate from coronary heart disease [32]. Although originally the emphasis was on olive oil, studies by researchers and others emphasized aspects of the diet that were not recognized by Keys and his associates in the Seven Countries Study [33]. One is the fact that the diet of Crete contained equal amounts of omega-6 and omega-3 fatty acids—that is, a balanced omega-6/omega-3 ratio—and the omega-3 fatty acids were found in every meal they ate. Second, the people in Crete ate wild plants, mostly green leafy vegetables and some fibers such as wild onions that were rich in ALA—the land-based omega-3 fatty acids—and in vitamins and minerals with antioxidant and antithrombotic properties. So far, I have emphasized the composition of extra-virgin olive oil and olives which provide the majority of calories of any other single food in the Greek diet up to 40 g/d (40x9=360 cal/d). Another very popular

fruit with a long history from antiquity are the figs—either fresh or dry—and black raisins (either fresh or dried). The raisins are high in polyphenols, their level being similar to the level of polyphenols in blueberries.

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BOX 1

Several dietary factors influence a person's chronic inflammation level, such as a higher ratio of omega-6 to omega-3 fatty acids and a high intake of saturated fat; also, foods with a high glycemic load and lower dietary fiber intake are associated with higher inflammation levels.

BOX 2

The Paleolithic diet of preagricultural hunter-gatherer humans—that is, more than 10,000 years ago—has been estimated from anthropologic evidence from fossils and a few surviving hunter-gatherer groups.

BOX 3

The consequences of the discrepancies between the diets and lifestyles of *Homo sapiens* before the agricultural revolution and those during the modern, postindustrial revolution era are referred to as “evolutionary discordance”, and they have been proposed to account for some of the dramatic increases in chronic disease in the 20th century.

BOX 4

The Mediterranean diet is considered to be one of the healthiest diets for the prevention of many chronic diseases, and especially the traditional diet of Crete (Greece) prior to 1960 has been shown to be the healthiest diet for the prevention of cardiovascular disease and cancer and is associated with the highest longevity.

BOX 5

The Mediterranean diet is similar to the Paleolithic diet in that it emphasizes a high consumption of fruits, vegetables, fish, nuts, lean meats, olive oil instead of vegetable oils high in omega-6 fatty acids, and less processed foods, therefore the Mediterranean diet has little added sugar (fructose).

BOX 6

The balanced ratio of omega-6/omega-3 in the diet of Crete (Greece) and the Paleolithic diet is unique among all diets.

BOX 7

A balanced ratio of omega-6/omega-3 is the most important factor and therefore a major characteristic of the Cretan Mediterranean diet and the Mediterranean diets of the 1960s.

BOX 8

Although the 2016 US Dietary Guidelines recommended the Mediterranean Pattern, they forgot to mention the importance of olive oil and the need to avoid vegetable

oils high in omega-6, such as corn oil, sunflower, safflower, cottonseed, and soybean oil. The true Mediterranean diet did not and must not include vegetable oils high in omega-6 fatty acids.

BOX 9

FDA must move forward with regulation and nutrition labels that do not state PUFA, but omega-6 and omega-3 fatty acids separately in terms of grams and percent of energy.

BOX 10

When the Paleolithic Diet and the Mediterranean Diet scores were compared with the inflammatory markers of hsCRP and the oxidative stress marker F2 isoprostane they show that diets that are more Paleolithic or Mediterranean-like are associated with lower levels of systemic inflammation and oxidative stress in humans.

BOX 11

Olive oil is used to cook everything, in baking, roasting, frying, in salads and in making many of the traditional deserts such as kourabiethes, melomakarona, and koulourakia. Melomakarona were served in the first Olympic Games in 776 BC, and were a favorite of the athletes and still are today.

BOX 12

Olive oil comes in different categories: extra virgin, virgin, extra light, and light. Extra-virgin olive oil is of the highest quality because it is cold pressed and is rich in antioxidants, such as polyphenols. Overall natural polyphenols have anti-inflammatory properties, and prevent oxidation and inflammatory expansion of blood vessels.

BOX 13

Olive oil blocks COX-2 and potentiates the effects of omega-3 fatty acids in controlling inflammation. In addition to its healthy fatty acid composition and squalene content, olive oil is rich in other compounds that have anti-inflammatory and antioxidant properties. Oleocanthal is one of the components. Its properties are similar to classical non-steroidal anti-inflammatory drugs, i.e., aspirin.

BOX 14

It is therefore suggested that long-term consumption (as is carried out in Crete) of small quantities of olive oil may be responsible in part for the low incidence of heart disease and Alzheimer's disease that is associated with the Mediterranean diet. Oleocanthal is responsible for the burning sensation we feel in our mouth and

throat when we consume extra-virgin olive oil.

BOX 15

The olive trees' leaves and olive pulp contain large amounts of hydroxytyrosol (compared to olive oil), most of which can be recovered to produce hydroxytyrosol extracts. However, it was found that black olives such as the common canned variety, containing iron (II) gluconate, contained very little of the original hydroxytyrosol, because the iron salts are catalysts for its oxidation.

BOX 16

Top quality olive oil/extra-virgin olive oil smells and tastes fresh, has aromatic notes such as grass, apple, green banana, artichoke, and herbs, and will typically have bitter and spicy notes, which indicate healthy levels of antioxidants.

BOX 17

Although it is the extra-virgin olive oil that has the highest amounts of antioxidants, remember all olive oils regardless of quality grade have the lowest amount of omega-6 fatty acids compared to all other seed oils. In fact, out of all extra-virgin olive oils, the olive oil from the area near Kalamata in Greece, famous for its black kalamata olives, has the lowest content of omega-6 fatty acids.

BOX 18

More recent studies show that extra-virgin olive oil is remarkably resistant to damage when heated even as high as 400 degrees Fahrenheit, such as when frying foods, largely because its high antioxidant content helps the oil resist oxidation.

BOX 19

Despite the decrease in the total concentration of polyphenols during cooking, extra-virgin olive oil has properties that protect against oxidation of LDL cholesterol particles. In Crete at the time of the seven countries study prior to 1960, the men began their day with an ounce of extra-virgin olive oil and then had fruit, bread, cheese, and coffee for breakfast.

BOX 20

Olive oil should be kept in a dark bottle or a cupboard at room temperature. In the refrigerator it thickens and becomes semisolid. You can make a mixture of half butter and half olive oil, keep it in a butter dish and use it on toast, or to fry eggs. It is healthier than plain butter and delicious.

Chapter 4. Ultra-Processed and Imitation Foods

1. Who Eats Ultra-Processed Foods?
2. From Ultra-Processed to Imitation Foods
3. The Van Vliet Study
4. The Question Remains: Can Food Manufacturers Create Healthier Processed Foods That Do Not Make People Overeat?
5. Nutrition Policy: The Need to Improve Cooking Processes

Ultra-processed foods are “formulations mostly of cheap industrial sources of dietary energy and nutrients, plus additives, using a series of processes” high in omega-6 fatty acids and containing minimal whole foods [1–3]. Ultra-processed foods make up more than half of the calories consumed by Americans. In fact, 72% of calories in Western diets come from foods that were not part of the diet during evolution. They are typically packaged or fast foods and contain many ingredients such as:

- Added sugars;
- Refined carbohydrates;
- Industrial oils high in omega-6 fatty acids;
- Sodium and synthetic flavors, preservatives, etc.

As an alternative to traditional approaches that focus on the nutrient composition of the diet, the NOVA diet classification system considers the nature, extent, and purpose of processing when classifying foods and beverages into four groups [1]:

- (1) Unprocessed or minimally processed foods;
- (2) Processed culinary ingredients;
- (3) Processed foods;
- (4) Ultra-processed foods.

While there might be various ways to define ultra-processed foods, usually they come in a box or carton or as fast foods that contain many many ingredients. Just reading the label, the enormous number of names should give you a lot of concern as to why there are so many names. You know that a recipe for a meal prepared at home does not have so many ingredients. These foods contain added sugars, refined carbohydrates, all kinds of industrial oils, mostly vegetable oils high in omega-6 fatty acids, sodium, all kinds of preservatives and synthetic flavors, imitating practically all the natural product’s flavors. Many epidemiological studies have shown that eating high amounts of these foods is associated with early death from cardiovascular disease and all-cause mortality [4,5]. Table 4.1 includes examples of ultra and minimally processed foods.

Table 4.1. Ultra-processed foods make people eat more and lead to rapid weight gain.

Ultra-Processed Foods
<ul style="list-style-type: none">● Breakfast Cereals● Muffins● White bread● Sugary yogurts● Low-fat potato chips● Canned foods● Processed meats● Fruit juices● Diet beverages
<hr/>
Minimally Processed Foods
<ul style="list-style-type: none">● Fruits and vegetables● Eggs● Fish● Grilled Chicken● Beef● Whole Grains● Nuts and Seeds

1. Who Eats Ultra-Processed Foods?

People from the lower socioeconomic brackets buy the most ultra-processed foods because they are cheap and tasty. These are the same people who smoke more, exercise less, and drink more alcohol and participate in other unhealthy behaviors. So, the combination of ultra-processed food and unhealthy lifestyle and behaviors makes it difficult to separate the effects of the ultra-processed food from the unhealthy lifestyles that influence disease risk.

The study by Hall et al. at the National Institutes of Health (NIH) was designed to avoid this problem by recruiting 20 healthy adults 31 years of age with a BMI of 27, which classifies them as overweight, but BMI of 27 is the average BMI of the US population [3]. These twenty persons were assigned to eat both an unprocessed and an ultra-processed diet and spent four weeks at the research facility of the Clinical Center at the NIH eating only their prescribed diets. All their meals were prepared by the metabolic kitchen including their snacks, which were carefully tracked—every piece of food they ate was accounted for. The effects of these foods were analyzed relative to their weight, body fat, hormones, and the omega-6/omega-3 ratio of both the unprocessed and the ultra-processed foods. The ultra-processed diet did not contain only obvious junk foods because the investigators wanted the ultra-processed diet to be similar to the diet a typical American might eat daily and which many Americans have been brainwashed to consider nutritious. So, the ultra-processed diet included cheerios, blueberry muffins, and orange juice for breakfast, cheese and turkey sandwiches with Baked Lay's potato chips and diet lemonade for lunch, and steak, canned corn, mashed potatoes from a box, and a diet beverage for dinner. Snacks included low-fat chips, Pepperidge Farm Goldfish, crackers, and

other packaged foods typically found in vending machines. In the unprocessed diet, breakfast consisted of Greek yogurt (Fage), parfait with strawberries, banana, walnuts (Diamond), salt and olive oil, apple slices with fresh squeezed lemon. Lunch included spinach salad with chicken breast, apple slices, bulgur (Bob’s Red Mill), sunflower seeds (Nature’s Promise), and grapes; vinaigrette made with olive oil, freshly squeezed lemon juice, apple cider vinegar (Giant), ground mustard seed (McCormick), black pepper (Monarch), and salt (Monarch), and for dinner Beef tender roast (Tyson), rice pilaf (basmati rice (Roland) with garlic, onions, sweet peppers, and olive oil), steamed broccoli, a side salad (green leaf lettuce, tomatoes, cucumbers) with balsamic vinegar (Nature’s Promise), orange slices, pecans (Monarch), salt, and pepper (Monarch). Table 4.2 lists the foods the participants ate in one day at breakfast, lunch, and dinner.

Table 4.2. Foods eaten in the Hall et al. study.

<u>Ultra-Processed</u>	<u>Minimally Processed</u>
Breakfast: Honey Nut Cheerios (General Mills); bananas, whole milk (Cloverland) with NutriSource fiber; with blueberry muffin (Otis Spunkmeyer); margarine (Glenview Farms)	Breakfast: Greek yogurt (Fage) parfait with strawberries, walnuts (Diamond), salt and olive oil; apple slices, fresh squeezed lemon.
Lunch: Beef ravioli (Chef Boyardee); Parmesan cheese (Roseli); white bread (Ottenberg); margarine (Glenview Farms); diet lemonade (Crystal Light) with NutriSource fiber; oatmeal raisin cookies (Otis Spunkmeyer)	Lunch: Spinach salad with chicken breast, apple slices, bulgur (Bob’s Red Mill), sunflower seeds (Nature’s Promise) and grapes; vinaigrette made with olive oil, fresh squeezed lemon juice, apple cider vinegar (Giant), ground mustard seed (McCormick), black pepper (Monarch) and salt (Monarch).
Dinner: Steak (Tyson), gravy (McCormick), mashed potatoes (Basic American Foods) margarine (Glenview Farms), corn (canned, Giant), diet lemonade (Crystal light) with NutriSource fiber, low-fat chocolate milk (Nesquik) with NutriSource fiber.	Dinner: Beef tender roast (Tyson), rice pilaf (basmati rice (Roland) with garlic, onions, sweet peppers and olive oil), steamed broccoli, side salad (green leaf lettuce, tomatoes, cucumbers) with balsamic vinegar (Nature’s Promise), orange slices, pecans (Monarch), salt and pepper (Monarch).

In the unprocessed diet fiber, sugar, and carbohydrates came from fresh produce, beans, oatmeal, sweet potatoes, grains and other whole foods, seeds, and nuts, whereas on the ultra-processed diet the subjects ate mostly refined carbohydrates and added sugars that are found in bread, bagels, juices, tater tots, sauces, chips, pasta, French fries, and canned foods. Because these foods are usually low in fiber

the subjects were given fiber supplements while on the ultra-processed diet. Table 4.2 shows the type of foods eaten, so you can actually see the foods in the ultra-processed menu vs. the minimally processed.

The two diets were designed so that they contained equal amounts of calories, fats, carbohydrates, and sugars, and the subjects were allowed to eat as much as they wanted. Of interest is the fact that while on the ultra-processed diet the subjects took in 500 more calories and gained weight (2 lbs) whereas on the unprocessed diet, the same subjects ate fewer calories and lost weight (2 lbs) and the appetite-suppressing hormone PYY increased while ghrelin, the hormone that stimulates hunger, decreased. What is of great interest to me is the fact that the omega-6/omega-3 ratio was higher in the ultra-processed diet and much lower (half as much) in the unprocessed diet. Table 4.3 shows the actual values for omega-6, omega-3 fatty acids and their ratio, added total sugar, fiber, and the percent quantity of saturated fat to total fat in their ultra-processed and unprocessed diets [3].

Table 4.3. Diet composition.

	Ultra-Processed		Unprocessed
Omega-3	0.6 gm/1000 Kcal		2.2 gm/1000 Kcal
Omega-6	8.1 gm/1000 Kcal		11.5 gm/1000 Kcal
Omega-6/Omega-3 Ratio	11:1	vs.	5:1
Added total sugar	54%	vs.	1%
Insoluble total fiber	77%	vs.	16%
Saturated to total fat	34%	vs.	19%

Source: Author's compilation based on data from [3].

On the ultra-processed diet, the omega-3 fatty acids were very low at 0.6 g/1000 Kcal, and the omega-6 fatty acids were high at 8.1/1000 Kcal, whereas in the unprocessed diet the values were 2.2 and 11.5, respectively. Further analysis on the source of the extra 500 calories showed that they came from carbohydrates and fat, not protein. Sodium was higher during the ultra-processed vs. the unprocessed diet. There were no significant differences in fiber or sugars. The higher energy density of the ultra-processed diet accounted for the extra 500 calories rather than the beverages.

- There were no differences in palatability or appetite between the two diets.
- There were differences in eating rate—ate faster on the ultra-processed diet; therefore they ate more.
- There were no differences in liver fat.
- The higher 24 h respiratory quotient seen with the ultra-processed diet suggests that fat oxidation was decreased in comparison to the unprocessed diet.
- Insulin and glucose levels were higher in the ultra-processed diet.
- There was no significant difference in energy expenditure measured by the accelerometer.

- There was no difference in glucose tolerance or insulin sensitivity—perhaps due to exercise—20 min, three times a day.

Thus, the ultra-processed diet is a proinflammatory diet increasing the risk of chronic diseases, obesity, diabetes, CVD, and cancer. This is not a diet fit for human health and everyone should avoid the ultra-processed foods used in this study. Of course, the diet was cheaper, and people liked it, ate more of it, and gained weight. Changes need to be made by the processed food industry to modify the composition of processed foods to be consistent with the evolutionary aspects of diet and health. Table 4.4 shows the differences in the type and quantity of foods between ultra-processed foods and the diet of Crete, which is the healthiest among the Mediterranean diets in decreasing the risk for coronary heart disease (CHD) and cancer [6]. (See the chapter on the diet of Crete).

Table 4.4. Comparison of the nutrient composition between ultra-processed foods and the diet of Crete.

	Ultra-Processed Foods	Diet of Crete
Fruits and vegetables	Canned or frozen (long shelf life)	Freshly picked
Salt	High	Moderate
Added sugar	High	No added sugar
Fat, saturated	High	Moderate in saturated fat
Omega-6	High	Low in Omega-6
Omega-3s	Low	High in Omega-3s
Omega-6/Omega-3 ratio	High (unbalanced) in omega-6/omega-3	Low (or balanced)
Fiber	Low	Rich
Additives	High	Low
Vitamins	Low (usually added)	High (natural)
Carbohydrates	Ultra refined (also added in beverages)	Complex
Protein	Low or average	High or within the normal range
Minerals		Normal range
Zn	Low (unless fortified)	Normal range
Mg	Low	Normal range
Ca	Low	Normal range
K	Low	High or normal range
Se	Low	High or normal range
Appetite, satiety	High and hungry	Good—satiated

The question is can food manufacturers create healthier processed foods that do not make people overeat?

A recent study by Drewnowski [7] examined the characteristics of plant-based beverages (PBBs) that are marketed as “milks” in the United States and included in the USDA Branded Food Products Database (BFPDB). Most PBBs (90.1%) and 95% of almond milks met the NOVA criteria for ultra-processed foods. They were created from food components and contained multiple substances not used in normal cooking. Rising consumption of ultra-processed foods has become a matter of public health concern [8].

2. From Ultra-Processed to Imitation Foods

Agriculture is having strong global impacts on both the environment and human health, often driven by dietary changes. Global agriculture and food production release more than 25% of all greenhouse gases (GHGs) [9–11]. In addition, the global transition towards diets high in processed foods, refined sugars, refined fats, oils, and meat has contributed to 2.1 billion people becoming overweight or obese [12–20]. As is well known, relative to animal-based foods, plant-based foods have lower GHG emissions. This difference can be large. Beef and lamb (ruminant animals) have emissions per gram of protein that are about 250 times those of legumes. Eggs, dairy, non-trawling seafood, traditional aquaculture, poultry, and pork all have much lower emissions per gram of protein than meat from ruminant animals [21]. From an environmental standpoint, the current food system is unsustainable. Worldwide, the Food and Beverage sector is responsible for roughly one-third of global GHG emissions according to FAO. Within the European Union, the sector contributes to approximately 30% of total emissions.

These types of data led food technologists and other industry groups to develop products from vegetable proteins, such as peas, that look and taste like beef burgers, chicken nuggets, and fish fingers. This way the products can be advertised as being of plant origin and less damaging to the environment in terms of CO₂ production. These foods from plant proteins are presented to the consumer as being vegan, and healthier for people and the environment. These alternative meats (beef and poultry) and fish are imitation foods and are not interchangeable in composition and health contributions with the real meat from animals and fish as shown by the study by Van Vliet et al. [22].

3. The Van Vliet Study

Van Vliet et al. [22] carried out a metabolomics comparison of plant-based meat and grass-fed meat to evaluate the nutritional composition. Metabolomics is a very precise science that distinguishes the various molecules that are involved in human and animal metabolism and evaluates the cell-to-cell communication that keeps us

healthy. His studies showed that there are large nutritional differences between the plant-based meat and the grass-fed meat despite comparable Nutrition Facts panels. Plant-based meat is an imitation meat product, but is it food? Just because food technology can make a food product look and taste like the “real thing” does not make it food. The FDA has developed food labels that are called Nutrition Facts. As you can see, in terms of what the FDA requires, the Nutrition Facts label of Ground Beef is similar to the Nutrition Facts label of the plant alternative (Figure 4.1).

Ground Beef		Plant Alternative	
Nutrition Facts		Nutrition Facts	
Serving size	(113g)	Serving size	(113g)
Amount Per Serving		Amount Per Serving	
Calories	220	Calories	250
% Daily Value*		% Daily Value*	
Total Fat 14g	18%	Total Fat 14g	18%
Saturated Fat 5g	25%	Saturated Fat 8g	40%
Total Fat 0g		Total Fat 0g	
Cholesterol 60mg	20%	Cholesterol 0mg	0%
Sodium 70mg	3%	Sodium 370mg	16%
Total Carbohydrate 0g	0%	Total Carbohydrate 9g	3%
Dietary Fiber 0g	0%	Dietary Fiber 3g	11%
Total Sugars 0g		Total Sugars 0g	
Includes 0g Added Sugars	0%	Includes 0g Added Sugars	0%
Protein 23g	46%	Protein 19g	38%
Vitamin D 0.1 mcg	0%	Vitamin D 0mcg	0%
Calcium 12mg	0%	Calcium 180mg	15%
Iron 2mg	10%	Iron 4.2mg	25%
Potassium 289mg	6%	Potassium 610mg	15%
Thiamin 0.05mg	4%	Thiamin 28.2mg	2350%
Riboflavin 0.2mg	15%	Riboflavin 0.4mg	30%
Niacin 4.8mg	30%	Niacin 4.8mg	30%
Vitamin B6 0.4mg	25%	Vitamin B6 0.4mg	25%
Folate 6mcg	2%	Folate 115mcg	30%
Vitamin B12 2mcg	80%	Vitamin B12 3mcg	120%
Phosphorus 175mg	15%	Phosphorus 180mg	15%
Zinc 4.6mg	40%	Zinc 5.5mg	50%
The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.		The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.	

Figure 4.1. Nutrition Facts panels of grass-fed ground beef and the plant-based meat alternative. Source: [22].

However, that is where the similarities stop. Further analysis of the components of each product using precision evaluation through mass-spectroscopy analysis annotation of metabolomics determined major differences in abundance of metabolites between beef and plant-based meat alternatives. The metabolic analysis showed that a total of 171 out of 190 annotated metabolites (90%) were different ($p < 0.05$) between beef and plant-based alternatives. Several compounds were found

either exclusively (22 metabolites total) or in greater quantities in beef (51 metabolites total). The authors concluded “While several of these nutrients are considered non-essential or conditionally essential based on life-stages (e.g., infancy, pregnancy, or advanced age) and are often less appreciated in discussions of human nutritional requirements [23], their importance should not be ignored, as their absence (or presence) can potentially impact human metabolism and health.”

The Van Vliet et al. [22] study shows, the plant-based alternative and grass-fed beef have largely similar Nutrition Facts panels and may appear nutritionally interchangeable to consumers [24]. Yet despite these apparent similarities based on Nutrition Facts panels, metabolomics analysis found that metabolite abundance between the plant-based meat alternative and grass-fed ground beef differed by 90%. Substantial differences in metabolites within various classes (e.g., amino acids, dipeptides, vitamins, phenols, tocopherols, odd-chain saturated and unsaturated fatty acids, omega-3 fatty acids, and antioxidants) indicate that these products should not be viewed as nutritionally interchangeable. This study is very important and indicates that the current production of “foods” by industry may be detrimental to the health of the people.

Just as ultra-processed foods increased food intake and led to weight gain [3] and continue to contribute to overweight and obesity worldwide [25] the new plant-based imitation products are not fit for human consumption. Consumers should focus on eating whole foods and not ultra-processed foods or imitation foods that actually are not foods. If consumers are truly interested in eating less meat, they can increase the consumption of legumes in soups and seeds and nuts in salads as protein sources. Consumers can adopt the diet of Crete and eat meat less often and legumes, nuts, seeds, and eggs more often.

4. The Question Remains: Can Food Manufacturers Create Healthier Processed Foods That Do Not Make People Overeat?

It appears that so far, food manufacturers have failed. In fact, in his viewpoint paper “Processed Food—An Experiment that Failed” [26] Dr. Lustig reviewed the events that began 50 years ago and led to today’s unhealthy food supply. In 1965, 10 food and drink companies—namely Coca-Cola, Pepsico, Kraft, Unilever, General Mills, Nestlé, Mars, Kellogg, Proctor & Gamble, and Johnson & Johnson—posed the hypothesis that “processed food is better than real food”.

Processed Food is defined by seven food engineering criteria:

- It is mass produced;
- It is consistent batch to batch;
- It is consistent country to country;
- It uses specialized ingredients from specialized companies;
- It consists of prefrozen macronutrients;

- It stays emulsified;
- It has as long shelf or freezer life [9].

How can consumers be empowered to eat healthy and sustainable foods? The European Consumer Organization (BEUC) says that consumer education is important but not enough, because current diets are not healthy and not sustainable. From the environmental standpoint, the current food system is also not sustainable. The trend of the food manufacturers to develop imitation foods that are not interchangeable nutritionally with real foods is a big problem that scientific and consumer organizations will have to tackle. The current regulation set up—i.e., the FDA's Nutrition Facts panel—is inadequate and cannot distinguish the nutritional differences between plant-based beef and grass-fed beef. Yet the two are not interchangeable and cannot substitute plant-based beef nutritionally for grass-fed beef since they are metabolically different as shown by Van Vliet's metabolomic study [22].

The movement on the part of Food Manufacturers to produce plant-based imitation products or add insect protein to pasta is being marketed aggressively. Plant protein from peas, soy, or wheat proteins are used in products labeled vegan. Meat from mycelium is made into burgers and nuggets by using a naturally occurring strain of mycelia, which are the filamentous-like root structures of mushrooms. Meat grown from cells taken from an animal is another way to manufacture meat that looks and tastes like meat. However, is it food, or interchangeable with steak from an animal? A recent advertisement reads "From fishless fingers to the world's first vegan supermarket Scotch Egg" created by a plant-based brand Squeaky Bean. The Scotch Egg alternative is made from breadcrumbs, wheat, and pea protein, but is it an egg? A new vegan Kit Kat produced by Nestlé and labeled Vegan is sold in the UK. The bar is made with a rice-based alternative to milk. I wonder what a metabolomic study will show about the Kit Kat's nutritional and health value. Vegan burgers are sold in US supermarkets and a plant protein-based chicken meat is sold in Singapore. All this hurry to develop alternative products that unfortunately are not interchangeable with real food is not leading to a more sustainable food supply, since they are made with all kinds of substitutes and emulsifiers that have been shown to increase CO₂ production. Therefore, these imitation products will not benefit the environment. The greatest environmental benefits can be achieved by wasting less food, eating less meat as in the traditional diet of Greece and more sources of plant-based proteins, such as pulses and nuts, only eating what you need (eat less) and replacing alcohol, fruit juices, and soft drinks with tap water, tea, or coffee and whole fruit, not its juice which is deprived of the fiber that is in the whole food.

On 20 February 2020, in her City Food lecture in London, Professor Louise Fresco proclaimed that meat is part of a sustainable world, and that the future of food would be characterized by people eating less meat [27]. Taking meat out of

people's diets is not a solution. She further stated "Even if we did away with all the animals for meat production, that land will be taken over by wild animals, which would have a carbon footprint of their own. So the anti-meat debate is not straight forward" and gave additional reasons why we need animals in the food system.

- 1 Grazing animals offer the planet its best hope for cutting GHG emissions by drawing carbon out of the atmosphere and storing it in the soil.
- 2 A large proportion of the world's surface is either too dry, too hot, too cold, too strong, or too steep to do anything else but have animals grazing. Grasslands are probably the best possible way to capture CO₂ and leave it in the soil: a permanent way of capturing CO₂.
- 3 Animals can potentially help address the problem of food waste. If the food waste can be used to feed animals, people are going to be better off.
- 4 Alternatives to meat proteins—we need more sources of plant proteins to add to meat products. About three-quarters of the meat in the world is processed meat. Proteins from plants can be added up to one-third (1/3 plant protein, 2/3 meat protein).
- 5 All these vegan burgers, she said, have a big problem and that is that they are ultra processed. From the nutritional point of view, they are not the best solution.
- 6 Insects are too unstable. If you want to rear them they require a lot of energy, which emits GHG. Food safety may also be an issue.

5. Nutrition Policy: The Need to Improve Cooking Processes

A number of specific foods (either highly processed or imitation foods) are associated with excess weight gain. These include potato chips, refined grains, processed meats, and soda [25]. The authors suggested that certain characteristics or cooking processes, rather than the actual foods themselves, may be behind their association with weight gain and obesity. For example, liquid calories have been shown to be more obesity promoting than calories from solid foods. Studies do show beverages are less satiating than solid food. Dong et al. [25] stated that while both potato chips and French fries are on the bad list, potatoes themselves when boiled or mashed without using too much butter or oil, are highly satiating and contain many essential nutrients. Furthermore, uncoated chicken and fish are not associated with weight gain, while those that are coated are. Therefore, Nutrition Policy should focus on reducing the intake of specific food items, and efforts should aim to change methods of cooking and processing of food. For example, chefs on cooking shows add sugar to everything they cook, even when making sauces, particularly with tomatoes "because tomatoes are acidic". In addition, they add vegetable oils high in omega-6 fatty acids (corn, soybean, sunflower, etc.), thus adding "insult to injury". Chefs should emphasize whole grains and high-fiber cereal, both of which are associated with weight loss.

Van Vliet states “The new generation of plant-based meat alternatives such as the Impossible Burger and Beyond Burger are becoming increasingly popular with consumers. Their success has led other international food companies—including traditional meat companies—to invest in their own product versions” [22]. The global plant-based meat alternative sector has experienced substantial growth and is projected to increase from USD 11.6 billion in 2019 to USD 30.9 billion by 2026, with a compound annual growth rate (CAGR) of 15% (Figure 4.2). In contrast, the meat sector is expecting a CAGR of 3.9% during this time and to reach a market value of USD 1142.9 billion by 2023 [28].

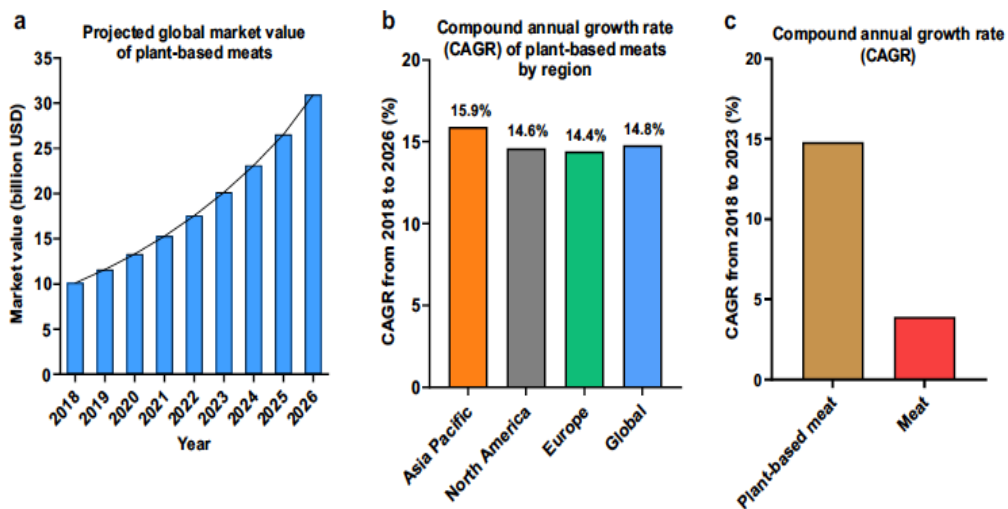


Figure 4.2. The global market value of plant-based meat alternatives and meat. Market data on plant-based meat alternatives and meat were obtained from STATISTA. (a) The projected global market value of plant-based meats from 2018 to 2026 in billion US dollars; (b) the compound annual growth rate (CAGR) of the plant-based meat sector globally and by region; (c) the relative growth of the global plant-based meat sector (+14.8%) is expected to exceed the relative growth global animal meat market (+3.9%). Despite growth in absolute terms, the value share of the global animal meat sector as a percentage of the overall food industry is expected to remain more or less similar during 2018–2023. Source: [22].

It is now 2022. It is expected that by 2050, global food systems will need to meet the dietary demands of almost 10 billion people in a healthy and sustainable manner. This can be accomplished by eating less meat and more vegetable protein as whole foods without changing the composition of the food supply through ultra processing and developing imitation foods that are not nutritionally interchangeable with the real meat from grass-fed beef [22]. Food technology, fake foods, imitation foods, and ultra-processed foods have led to proinflammatory diets that led to increases in all-cause mortality and are indeed an experiment that failed [26].

The typical Western diet is growing in prevalence around the world, despite the fact that it is both unstable and unhealthy, being excessive in food energy, high in animal products, low in fish, low in fruits and vegetables, high in ultra-processed foods, and high in omega-6 fatty acids, with a high omega-6/omega-3 ratio and food waste.

The characteristics of healthier and more sustainable diets include high dietary diversity, balanced food energy, low in animal products, moderate in fish, high in fruits and vegetables and whole grains, balanced in omega-6/omega-3 fatty acids, and low in food waste, and processed foods are avoided. In essence, this diet is consistent with the traditional diet of Crete that has been shown to be associated with longevity and less cancer and CVD than other Mediterranean and non-Mediterranean diets studied so far.

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BOX 1

Ultra-processed foods are “formulations mostly of cheap industrial sources of dietary energy and nutrients, plus additives, using a series of processes” high in omega-6 fatty acids and containing minimal whole foods. Ultra-processed foods make up more than half of the calories consumed by Americans. In fact, 72% of calories in Western diets come from foods that were not part of the diet during evolution.

BOX 2

As an alternative to traditional approaches that focus on the nutrient composition of the diet, the NOVA diet classification system considers the nature, extent, and purpose of processing when classifying foods and beverages into four groups.

BOX 3

While there might be various ways to define ultra-processed foods, usually they come in a box or carton or as fast foods that contain many many ingredients. Just reading the label the enormous number of names should give you a lot of concern as to why there are so many names. Many epidemiological studies have shown that eating high amounts of these foods is associated with early death from cardiovascular disease and all-cause mortality.

BOX 4

The ultra-processed diet did not contain only obvious junk foods because the investigators wanted the ultra-processed diet to be similar to the diet a typical American might eat daily and which many Americans have been brainwashed to consider nutritious.

BOX 5

The omega-6/omega-3 ratio was higher in the ultra-processed diet and much lower (half as much) in the unprocessed diet.

BOX 6

Thus, the ultra-processed diet is a proinflammatory diet increasing the risk of chronic diseases, obesity, diabetes, CVD, and cancer. This is not a diet fit for human health and everyone should avoid the ultra-processed foods used in this study. Of course, the diet was cheaper, and people liked it, ate more of it, and gained weight. Changes need to be made by the processed food industry to modify the composition of processed foods to be consistent with the evolutionary aspects of diet and health.

BOX 7

From an environmental standpoint, the current food system is unsustainable. Worldwide, the Food and Beverage sector is responsible for roughly one-third of global GHG emissions according to the FAO. Within the European Union, the sector contributes to approximately 30% of total emissions.

BOX 8

These alternative meats (beef and poultry) and fish are imitation foods and are not interchangeable in composition and health contributions with the real meat from animals and fish, as shown by the study by Van Vliet et al.

BOX 9

Yet despite these apparent similarities based on Nutrition Facts panels, metabolomics analysis found that metabolite abundance between the plant-based meat alternative and grass-fed ground beef differed by 90%. Substantial differences in metabolites within various classes (e.g., amino acids, dipeptides, vitamins, phenols, tocopherols, odd-chain saturated and unsaturated fatty acids, omega-3 fatty acids, and antioxidants) indicate that these products should not be viewed as nutritionally interchangeable.

BOX 10

Just as ultra-processed foods increased food intake and led to weight gain and continue to contribute to overweight and obesity worldwide, the new plant-based imitation products are not fit for human consumption.

BOX 11

How can consumers be empowered to eat healthy and sustainable foods? The European Consumer Organization (BEUC) says that consumer education is important but not enough, because current diets are not healthy and not sustainable.

BOX 12

The current regulation set up—i.e., the FDA's Nutrition Facts panel—is inadequate and cannot distinguish the nutritional differences between plant-based beef and grass-fed beef. Yet the two are not interchangeable and plant-based beef cannot nutritionally substitute grass-fed beef.

BOX 13

All this hurry to develop alternative products that unfortunately are not interchangeable with real food is not leading to a more sustainable food supply, since they are made with all kinds of substitutes and emulsifiers that have been shown to increase CO₂ production. Therefore, these imitation products will not

benefit the environment.

BOX 14

The greatest environmental benefits can be achieved by wasting less food, eating less meat as in the traditional diet of Greece and more sources of plant-based proteins, such as pulses and nuts, only eating what you need (eat less), and replacing alcohol, fruit juices, and soft drinks with tap water, tea, or coffee, and whole fruit, not its juice which is deprived of the fiber that is in the whole food.

Part II

Chapter 5. The Importance of the ω -6/ ω -3 Balance for Health

1. Biosynthesis of Omega-6 and Omega-3 Essential Fatty Acids (EFA)
2. Imbalance of Omega-6 and Omega-3 Fatty Acids
3. How Omega-3 Fatty Acids Fight Inflammation: Specialized Pro-resolving Mediators (SPMs)
4. Genetic Variation in the Metabolism of Omega-6 and Omega-3 Fatty Acids, Inflammation, and COVID-19 Infection
5. The COVID-19 Pandemic
6. The Need for Precision Nutrition

The rapid nutritional changes that have taken place in developed countries after World War II have led to maladaptations and related human diseases never before seen in such frequencies over a short period of time [1,2]. In fact, up to 72% of dietary calories consumed in the present Western Diet did not exist in hunter–gatherer diets [1]. These changes were driven by technological changes in food production and processing that provide high calories and refined grains.

Human beings evolved on a diet that was relatively balanced in linoleic acid (18:2n-6; LA) n-6 PUFA and alpha-linolenic acid (18:3n-3; ALA) n-3 PUFA [3]. Both LA and ALA are found in similar amounts in nature [3]. Humans obtained LA from seeds and nuts with the exception of flax seeds, rapeseed, chia, and perilla, which are rich in ALA. ALA is also plentiful in green leafy vegetables [4]. Both LA and ALA are essential for health, cannot be made by humans, and must be obtained from diet (Tables 5.1 and 5.2).

Table 5.1. Sources of omega-6 fatty acids (linoleic acid).

Oils High in LA	Amount of LA
Safflower oil	78%
Sunflower oil	71%
Corn oil	59%
Soybean oil	56%
Cottonseed oil	53%

Tables 5.2. Sources of omega-3 fatty acids (alpha-linolenic acid).

Oils High in ALA	Amount of ALA
Chia oil	64%
Perilla oil	58%
Flaxseed oil	55%
Canola oil	12%
Rapeseed oil	10%

The concept of a balanced ratio of the ω -6 and ω -3 fatty acids for health (normal development) and in the prevention and management of chronic diseases has attracted many researchers. As a result, there are now many studies that clearly show its importance. When we talk about balance of ω -6 and ω -3 fatty acids, we mean a balance at two levels at the 18 and 20 carbon atoms of the fatty acid chain. The parent fatty acids consist of two families of 18 carbon atoms. The ω -6 18C atom is called linoleic acid or LA and its formula is written 18:2 ω -6, and the ω -3 18C atom is called alpha-linolenic acid or ALA and is written 18:3 ω -3. These two fatty acids, LA and ALA, are called essential fatty acids because our body cannot make them, and they must be obtained from our diet. These two families of essential fatty acids have

different and in fact opposing physiological, biochemical, and functional properties. These fatty acids are distinct and except for the fact that they are both essential, they have very little else in common. You must remember because they have opposing properties, their balance is essential for health [5].

The LA and ALA are found in the seeds of oils. In other words, they come from the land and therefore they represent the “terrestrial” sources of the omega-6 and omega-3 essential fatty acids (Tables 5.1 and 5.2).

1. Biosynthesis of Omega-6 and Omega-3 Essential Fatty Acids (EFA)

In the body, LA and ALA are metabolized to longer chain fatty acids (Figure 5.1).

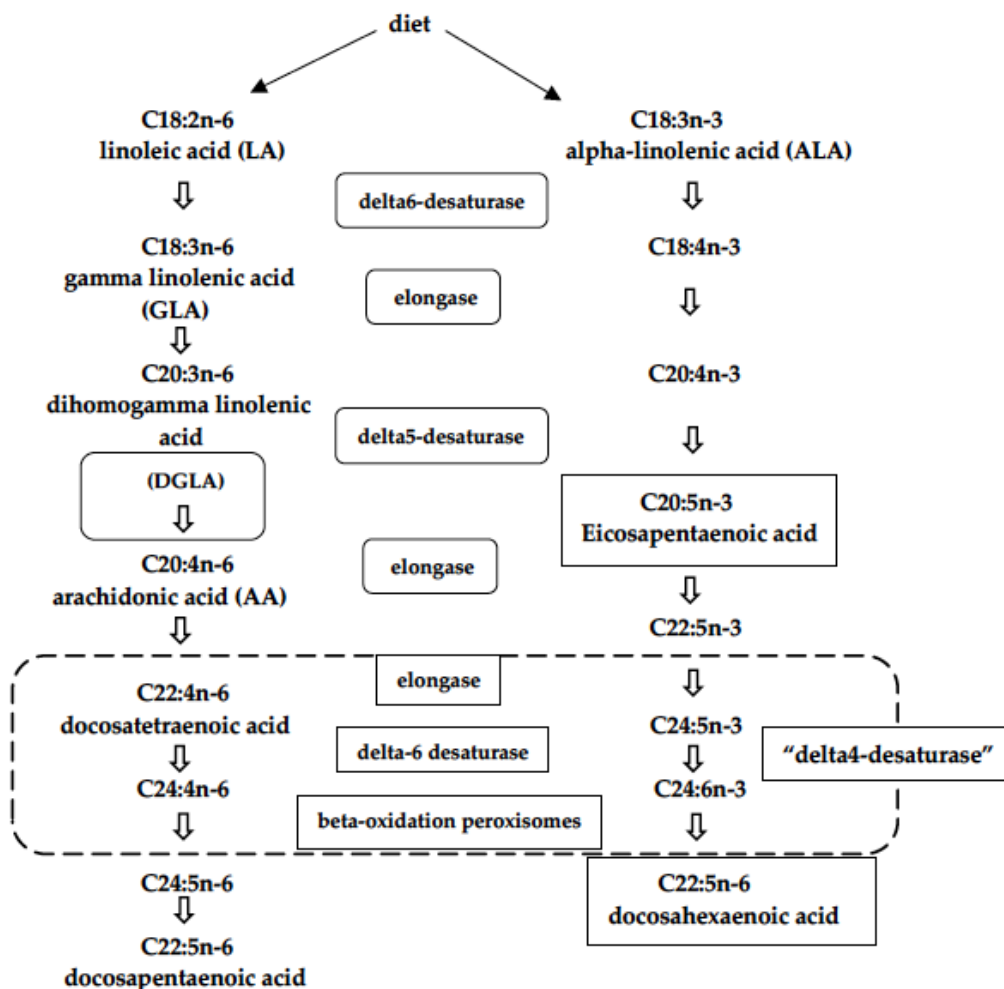


Figure 5.1. Elongation and desaturation of n-6 and n-3 polyunsaturated fatty acids. Source: Adapted from [3], used with permission.

LA and ALA are the parent PUFA that in the body are metabolized to arachidonic acid (20:4n-6; ARA) or eicosapentaenoic acid (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3; DHA), respectively (Figure 5.1). ARA, EPA, and DHA are precursors found in tissues of all organs in the body, which are mobilized

and enzymatically converted to potent local chemical signals of 20 carbon atoms (eicosanoids), involved in many physiologic and pathologic processes in humans. The eicosanoids biosynthesized from ARA include prostaglandins, thromboxanes, leukotrienes, as well as lipoxins. Prostaglandins, thromboxanes, and leukotrienes are also produced from EPA that in general display diminished activities (Figure 5.2).

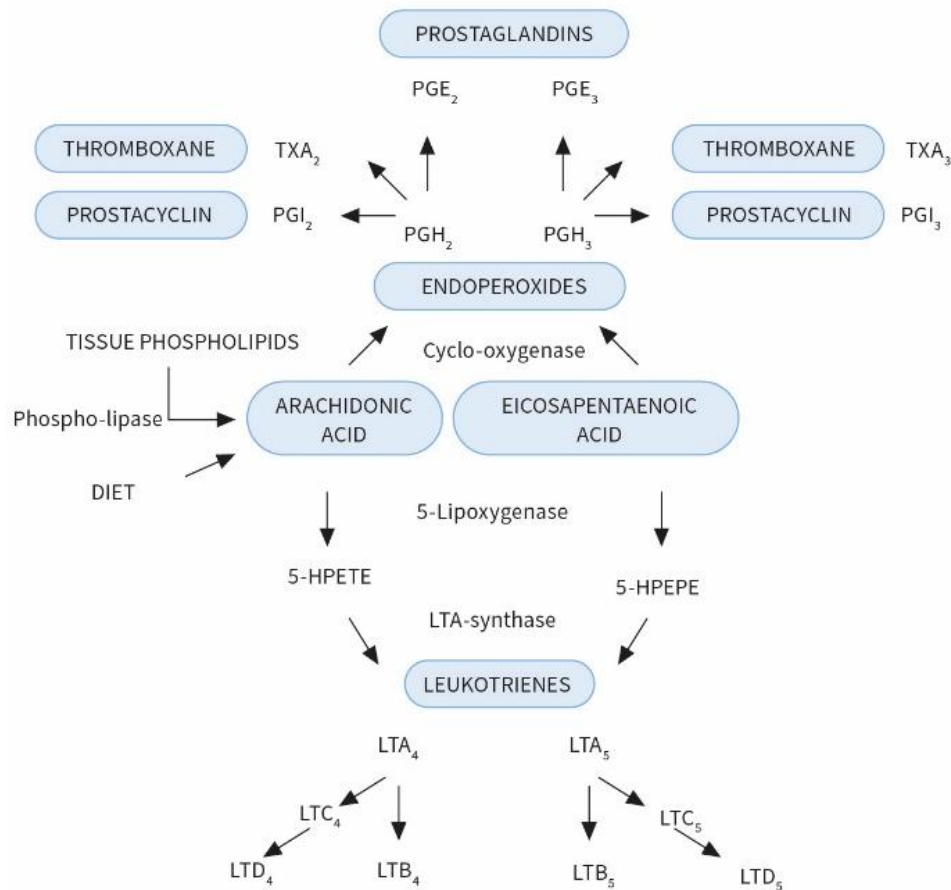


Figure 5.2. Oxidative metabolism of arachidonic acid and eicosapentaenoic acid by the cyclooxygenase and 5-lipoxygenase pathways. 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-HPEPE, 5-hydroxyeicosapentaenoic acid. Source: Modified from [3].

EPA and DHA are each biosynthetic precursors that are enzymatically converted in inflammatory milieu to novel lipid mediator autacoids, termed resolvins and protectins/neuroprotectins (Figure 5.3) [6]. ARA is found in meat, eggs, and dairy products, whereas EPA and DHA are enriched in fish and marine oils [3].

LA and ALA and their desaturation and elongation products use the same enzyme systems for their metabolism, have opposing properties, and are metabolically and physiologically distinct. The ALA pathway is the preferred pathway and up until the 1960s, there was a balance in the amounts of LA and ALA that humans obtained from their diet. However, things began to change in

the 1960s after Keys did not consider that the diet of Crete was balanced in n-6 and n-3 PUFA in the Seven Countries Study for the prevention of heart disease [7,8]. Soon after, the American Heart Association (AHA) declared cholesterol levels must be lowered to prevent heart disease, and the whole country was exposed to an enormous campaign to replace saturated fat with vegetable oils rich in LA such as corn, sunflower, safflower, soybean, and cottonseed to lower cholesterol. Almost overnight the amounts of vegetable oils and trans fats high in n-6 PUFA replaced butter, despite the fact that there was no evidence from randomized controlled trials demonstrating that LA prevented heart disease [9,10]. In fact, Ramsden et al. showed that LA will lower cholesterol by 30 mg/dL but will increase cardiovascular disease death by +22% [10]. This dietary advice continues despite the increase in chronic diseases such as obesity, type 2 diabetes, hypertension, and cardiovascular disease, all of which lead to a pro-inflammatory state due to high amounts of LA and ARA and their metabolites.

The LA pathway going to ARA and the ALA pathway going to EPA, DPA, and DHA and their metabolites are involved in the metabolism and physiology of every cell in the human body, influence the growth and development of human beings, and play important roles in inflammation and in the prevention and management of chronic diseases. These two metabolic pathways of LA + ALA use the same enzymes, but nature is partial to the ALA pathway. We call it the preferred pathway. When LA and ALA are in balance, how much ARA and EPA and DHA they make depends on the dietary intake and the genetics of the individual or populations. We want a diet like the diet of Crete balanced at two levels, at LA/ALA and at ARA/EPA, DPA +DHA. Under these conditions, the ARA and EPA, DPA, and DHA are further metabolized into compounds that are called eicosanoids because they consist of 20 carbon atoms (Figure 5.2). In the diet of Crete, where there was an overall balance of the ω -6 and ω -3 fatty acids, the body maintained a healthy state that led to normal development of the children, delayed the aging process and decreased the risk for cardiovascular disease and cancer.

2. Imbalance of Omega-6 and Omega-3 Fatty Acids

In Western Diets such as the US diet, there is no longer a balance of the ω -6 and ω -3 fatty acids. There are many reasons for this imbalance. Following the World War II there was an increase in the production of high ω -6 oils and their incorporation into the food supply. Originally it was mostly sunflower and corn oil, but today it is mostly soybean oil (Figure 5.4) [11].

The high ω -6 consumption was promoted by the American Heart Association (AHA) because LA lowers cholesterol and the AHA expected that it will lower the death rate from coronary heart disease (CHD). However, you already know that the Lyon Heart Study by de Lorgeril et al. [12] showed that the AHA-prudent diet,

which is high in ω -6 and low in saturated fat and cholesterol, did not decrease total death, because high LA leads to high ARA, which leads to high eicosanoids that are prothrombotic and proinflammatory, which lead to increased risk of CHD and death. Now you have heard of statins that decrease death from CHD. At first statins were used because they were found to lower cholesterol, but actually their most important function is that they are anti-inflammatory. There are many important studies using EPA + DHA from fish (fish oil) that show that EPA and DHA from the ω -3 family are anti-inflammatory and also protect against thrombus formation and decrease total death [12,13]. Furthermore, in persons with one heart attack 4 g of EPA and DHA led to faster healing of the heart muscle and a decrease in death [14].

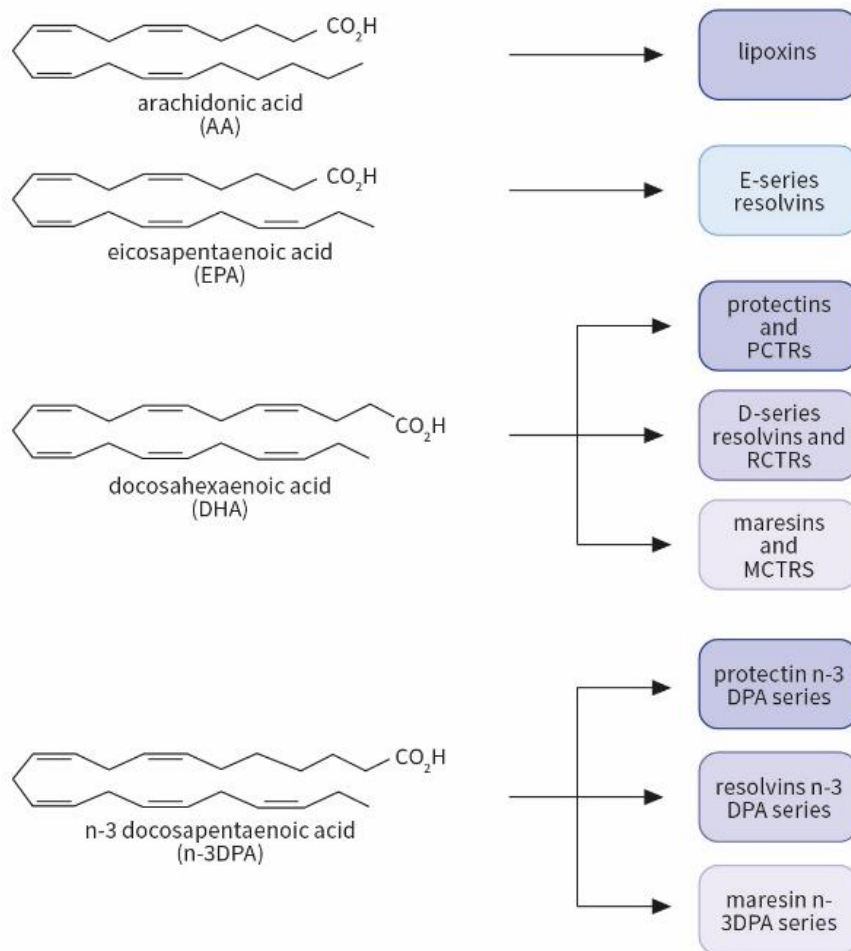


Figure 5.3. The chemical structures of AA, EPA, DHA, and n-3 DPA and an outline of the individual families of SPMs biosynthesized from these PUFAs. Source: [15].

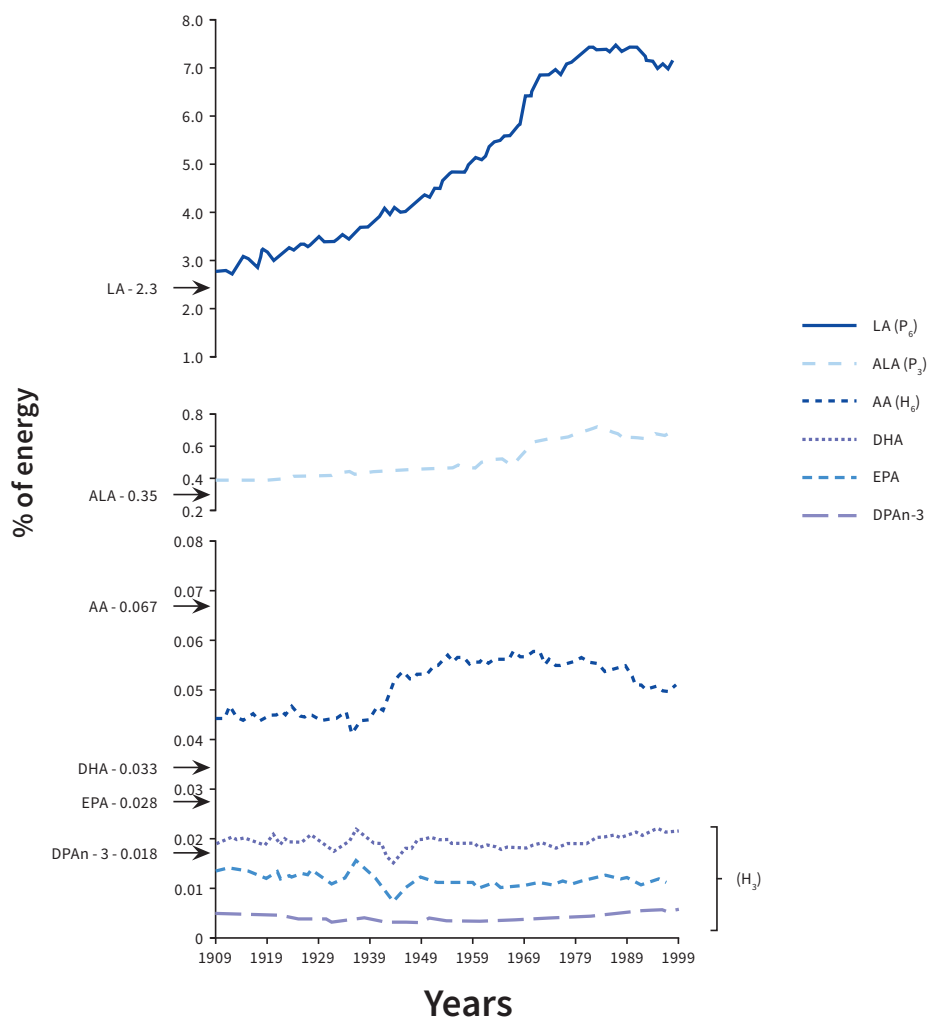


Figure 5.4. Essential Fatty Acid intake in the 20th Century. Availability of essential fatty acids from 1909 to 1999. 1909-T data are indicated by solid arrows for LA (2.23% of energy), ALA (0.35% of energy), arachidonic acid (AA) (0.67% of energy), docosahexaenoic acid (DHA) (0.033% of energy), eicosapentaenoic acid (EPA) (0.028% of energy), and docosapentaenoic acid (DPAn23) (0.018% of energy). Source: [11].

In addition to the increase in ω -6 oils, there were changes in animal feeds following World War II, which led to further increases in ω -6 fatty acid, especially the long-chain ARA. Animals were grain fed instead of grazing in the fields. Grains increase ω -6 fatty acids at the level of 18-C atoms that is LA, which metabolizes to the 20 carbon atom that is ARA, leading to enormous changes in the composition of the food supply in oils and meat, dairy and eggs. Additional changes in the food supply also occurred as a result of food processing. As discussed in the Chapter “Ultra-processed and Imitation Foods” ultra-processed foods have an ω -6/ ω -3 ratio of 11:1 [15]. Thus, over a short period of time, over one generation’s time, the whole country was exposed for the first time to a food supply that was not consistent

with the foods we were exposed to during evolution and to which our genes were programmed to respond. This new Western diet was rich in calories, but poor in nutrients, high in ω -6 fatty acids and low or depleted in ω -3s at both ALA and EPA and DHA levels. Furthermore, a high ω -6 and low intake of fruits and vegetables made the diet pro-inflammatory, exactly the opposite of the diet of Crete. Inflammation is the worst condition to be in because inflammation is at the base of all chronic diseases (obesity, diabetes, cardiovascular disease, some forms of cancer, arthritis, and osteoporosis).

3. How ω -3 Fatty Acids Fight Inflammation: Specialized Pro-Resolving Mediators (SPMs)

Activated cells release ARA from cellular stores that are converted to high amounts of prostaglandins and leukotrienes, notable pro-inflammatory mediators that amplify inflammation, with the exception of Lipoxins that are pro-resolving and anti-inflammatory, providing an environment enabling SARS-CoV-2 to thrive (Figures 5.2 and 5.3). Ultra-processed diets that are poor in fruits and vegetables and fish are the main foods available to poor neighborhoods of people of color (food deserts). EPA- and DHA-derived products are less thrombotic and less inflammatory than those produced from ARA. EPA and DHA are precursors to potent new autacoids that are anti-inflammatory as well as pro-resolving and participate in the resolution of inflammation and infections, preventing the development of full-blown uncontrolled inflammation (Figures 5.2 and 5.3)

In our bodies the immune system plays a very important role in toning down inflammation and works hard to clear inflammation and prevent inflammation from becoming chronic as it is in obesity, diabetes, and other chronic conditions. Inflammation is a normal part of the human body's healing process. When we get hurt, either from falling or other forms of injury, inflammation helps heal those injuries and fight off infection from bacteria. White cells and various types of immune cells travel rapidly to the injured part to thwart microbial invaders and repair the damage [16] (Figure 5.5).

Part of the fixing process causes some pain, swelling and redness in the injured area. This type of response against expansion of the inflammation is essential to our health. However, sometimes inflammation happens even when there is no obvious ailment to heal. This usually happens when we are in situations that are stressful, are overweight or obese, or have a poor diet such as the current US diet, which is high in ω -6 fatty acids and low in omega-3 fatty acids, fruits and vegetables. In other words, we have a proinflammatory diet, lack of sleep, and sit around snacking all the time and not exercising; all these situations can lead to low chronic inflammation that wreaks havoc throughout the body. This chronic form of inflammation can lead to heart disease, arthritis, Alzheimer's, diabetes, obesity, some forms of cancer,

and mental illness such as depression and anxiety, and hastens the aging process. This type of inflammation is also sort of “secret” and cannot be seen, does not cause swelling or pain, yet it seems to play a role in most chronic diseases known as “diseases of civilization” meaning that they are related to our current diet and various lifestyles that we have adopted, such as night work, exposure to lights longer than sunlight, and being sedentary, and are not consistent with the way we evolved as humans. Remember our genes have not changed over the same time as our diet and environment. Therefore, our genes are in a foreign environment to which they are not programmed to respond.

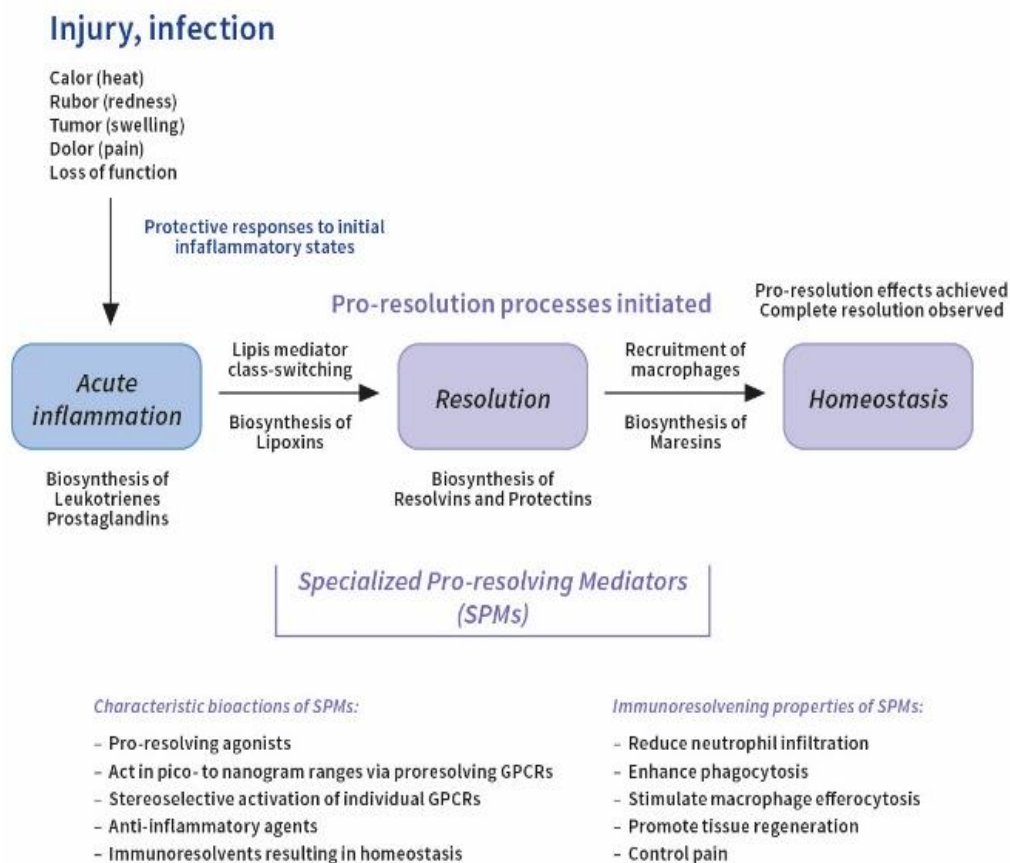


Figure 5.5. A general outline of the lipid mediator class switch involving SPM biosynthesis from EPA and DHA. Source: [16].

Out of all the nutrients that occur naturally in our foods, the ω -3 fatty acids, ALA, EPA, DPA and DHA, are the most potent anti-inflammatories, especially EPA and DHA found in fish and fish oils. In addition, ALA in the body metabolizes to EPA, DPA and DHA. Some people have genes that “encode”—tell the enzymes to make more EPA and DHA. These genes are very important. However, what is more important is that ω -6 and ω -3 fatty acids are in balance, otherwise those persons with the high ω -6/ ω -3 dietary ratio will be producing too much ARA that makes

very potent inflammatory substances: the thromboxanes and leukotrienes that lead to “diseases of civilization” characterized by inflammation. Therefore, you must know your ratio of omega-6/omega-3 and make sure that your diet is rich in fish, fruits, and vegetables; avoid vegetable oils high in LA (Table 5.1) such as sunflower oil, safflower oil, corn oil, soybean oil, and cottonseed oil; and instead use olive oil, macadamia nut oil, hazelnut oil, a combination of olive oil and canola, or olive oil and flaxseed, or perilla and olive oil, or small amounts of butter and any of these mixtures of oils (Table 5.2). EPA and DHA are found in the membranes of all cells in the body. Think of them as building blocks for cell membranes throughout our body. DHA is found especially in high amounts in our brains, eyes, and testes. Both EPA and DHA are essential from conception to old age, being essential for normal growth, helping fetuses develop and seniors remain healthy, as well as in the prevention and management of chronic diseases.

After you eat fish or take fish-oil supplements, both EPA and DHA find their way in every cell membrane in the body and produce the various substances we mentioned earlier in fighting inflammation (Table 5.3) (Figures 5.2 and 5.3).

Table 5.3. Effects of ingestion of EPA and DHA from fish or fish oil.

Decreased Production of Prostaglandin E2 (PGE2) Metabolites
A decrease in thromboxane A2, a potent platelet aggregator and vasoconstrictor
A decrease in leukotriene B4 formation, an inducer of inflammation, and a powerful inducer of leukocyte chemotaxis and adherence
An increase in thromboxane A3, a weak platelet aggregator and weak vasoconstrictor
An increase in prostacyclin PGI3, leading to an overall increase in total prostacyclin by increasing PGI3 without a decrease in PGI2 and PGI3 are active vasodilators and inhibitors of platelet aggregation
An increase in leukotriene B5, a weak inducer of inflammation and a weak chemotactic agent

The resolvins, maresins, and protectins produced by EPA, DPA, and DHA are powerful inflammation controllers and are known collectively as “specialized pro-resolving mediators” or SPMS as we mentioned earlier (Figure 5.3). These are the compounds that “neutralize” inflammation and eventually stop it, leading to “resolution” of inflammation. Think of the SPMS as the body’s peacekeepers calming down defensive forces after a threat has been handled. These substances have been shown to have a helpful role in a variety of disorders and conditions connected with inflammation, from inflammatory bowel disease to arthritis to allergic conditions, and even decrease the development of asthma in the children of mothers who have asthma when their mothers take 4 g of EPA and DHA during pregnancy.

Resolvins are produced from DHA and EPA. In fact, both aspirin and ω -3s lead to the production of the same resolvin-D3 (Figure 5.3). The discovery of resolvins led to the use of ω -3s as safer anti-inflammatory agents for the management of CVD, prevention of Type 2 Diabetes, rheumatoid arthritis, weight loss, and lowering blood pressure.

Maresins are made from macrophages, the white blood cells of the immune system, that “eat”, so to speak, cellular debris and even cancer cells. After we eat seafood or take supplements, the macrophages consume DHA and transform it to maresins, which help in the healing of wounds, resolve inflammation, and control pain and allergic reactions. Maresins work like a traffic cop to stop some of the healing processes at the right time, which redirect other immune responses.

Protectins have an important role in controlling inflammation and protecting our brains. That is why the term “neuroprotectins” has been used in research studies with animal models for Alzheimer’s disease or stroke. It appears that neuroprotectins reduce the inflammation that is associated with these diseases and might even delay some of the damage. SPMS can even stop flu in its tracks. In a study of flu patients omega-3 derived SPMS prevented the influenza virus from replicating ending the spread of illness [17]. The functions of SPMs arise from the chemistry inherited from their omega-3 PUFA precursors in our diet. The SPMs each counter-regulate cytokine storms, as well as proinflammatory lipid mediators, and control the killing and clearance of microbes.

4. Genetic Variation in the Metabolism of Omega-6 and Omega-3 Fatty Acids, Inflammation and COVID-19 Infection

As can be seen in the figure (Figure 5.1) on the biosynthesis of omega-6 and omega-3 fatty acids, both families use the same enzymes for their desaturation and elongation, but the ALA pathway is the preferred pathway. During evolution the food supply had equal amounts of LA and ALA with a ratio of LA/ALA of 1-2/1, whereas today, this ratio is about 20/1 due to large amounts of LA from vegetable oils, ultra-processed foods, and animal meats and eggs because today animals are grain fed. Grains are high in LA, whereas grass is high in ALA.

High amounts of LA lead to the production of high amounts of ARA, which is proinflammatory. In fact, the current American diet has one of the highest ratios of omega-6/omega-3 fatty acids. In addition to the high dietary intake of omega-6 fatty acids, another important factor that leads to an imbalance of omega-6 and omega-3 fatty acids is the genetic variation that exists in the biosynthesis of LA and ALA to ARA and EPA + DPA + DHA at the level of desaturases FADS1 and FADS2 (Figure 5.1). Within the population, desaturase II is what is called the limiting factor that controls the desaturation of both LA and ALA. During evolution, as they moved from seashore, lakes, and rivers into inland areas, humans in Africa needed

to have longer-chain fatty acids (ARA, EPA, DPA, and DHA) for normal growth and brain development, which in the past they obtained from their diet that was abundant in ARA, EPA, DPA, and DHA from fish and green leafy vegetables. In adapting to new environmental conditions inland, humans evolved genes in the form of desaturases that increased the production of the longer chain fatty acids, namely ARA, EPA, DPA, and DHA. Recent studies by Ameer et al. [18] show that today in Africa the population has two haplotypes. One is called ancestral haplotype or haplotype A and the other is called derived haplotype or haplotype D. The majority of the African population has haplotype D. This is the haplotype that has the most efficient biosynthesis from LA to ARA and from ALA to EPA, DPA, and DHA. The people with haplotype D benefited the most and survived. However, what was helpful to them during evolution has become a problem because today, with very high LA in the diet, more efficient biosynthesis to ARA leads to higher production of thromboxanes and leukotrienes, and to a proinflammatory state that increases the risk of inflammation and coronary heart disease. Table 5.4 shows the frequency of haplotype A and haplotype D in the various populations.

Table 5.4. Frequencies of Haplotypes A and D in various populations.

Haplotype A	Less than 1% in Africans 25-50 % in Europe West, South & East Asia Oceania 97% Native Americans Arctic people
Haplotype D	80% African Americans 43% Europeans 50% Latinos

Ameer et al. studied the frequencies of haplotypes A and D in native populations distributed all over the world. The most common haplotype D was associated with high lipid levels, whereas the less common haplotype A was associated with low levels. Persons homozygotes for haplotype D had 24% higher levels of DHA and 43% higher levels of ARA than those homozygous for haplotype A. The two FADs haplotypes differ both in transcription levels and in their ability to synthesize ARA and DHA from their precursor LA and LNA, respectively [18].

In the African Human Genome Diversity Project (HGDP) population, haplotype A is essentially absent (less than 1% of the chromosomes, whereas in Europe; West, South, and East Asia; and Oceania, it occurs at a frequency of 25–50%. Among the 126 Native Americans included in HGDP, haplotype A accounts for 97% of the chromosomes. A complementary analysis of haplotype frequencies for population samples from HapMap [19] and the 1000 Genomes Project [20] confirmed that

haplotype A occurs at a very low frequency among individuals of African descent, whereas it is present at moderate high frequencies in populations of European and Asian ancestry. Among individuals of African ancestry, 49% carry mixed FADS haplotypes with a higher resemblance to haplotype D than to haplotype A, consistent with a decay of haplotype D by recombination in African populations. The FADS region is among the top five candidate-gene clusters that have been under positive selection in African populations [21].

Individuals with haplotype D have a rapid biosynthesis from LA to ARA and therefore have higher amounts of ARA circulating in the blood, far and above the amounts expected from the high intake of LA in the diet. During evolution, as the populations in Africa moved from marine environments to inland areas, the gene with the rapid biosynthesis was essential to obtain DHA from ALA for brain development. This same gene is found in 80% of African American ancestry and in about 43% of Europeans. It is the higher frequency of genes and the current US diet high in LA that causes African Americans and Hispanics to have a higher susceptibility to obesity, type 2 diabetes, high blood pressure, and heart disease—all of which have inflammation as a basis for their development. It is possible that the combination of an ultra-processed Western type of diet plus the higher frequency of haplotype D magnifies vulnerability of African Americans and Hispanics to COVID-19. In Africa there are fewer deaths due to COVID-19 despite having the same genetic variants, possibly because their diet is not as high in n-6 PUFA and ultra-processed foods [22].

There are also other populations that carry genes that have lower biosynthesis of ARA from LA or EPA and DHA from ALA, such as American Natives. These populations have high LA and ARA because of the US diet and are relatively low in ALA and DHA, putting them at risk of a proinflammatory state and COVID-19. The Indigenous people of Arctic regions are another group, but they eat a lot of fish and thus do not become deficient in n-3 PUFA [23] and are not at risk of an inflammatory state [23].

5. The COVID-19 Pandemic

Beyond individual deaths, the pattern of mortality among population groups can reveal both those at higher risk and the groups who bear a disproportionate burden of the pandemic. The expression of disease in patients with COVID-19 varies from asymptomatic to fatal, with more severe outcomes for individuals of advancing age. In the US, COVID-19 has disproportionately affected African Americans, Hispanics, Native Americans, and Alaskan Native persons. There have been many papers on the cause/relationship of COVID-19 and the populations involved. A significant number of these papers have been published. The fact that certain groups—African Americans, Hispanics, Latins, Native Americans, and

Alaskan Natives—have been infected and have succumbed to the coronavirus in larger numbers has led to the consideration of various reasons for health disparities such as social, economic, healthcare delivery issues, etc. What is missing specifically are papers that focus on the genetic variation of these populations and the interaction of their genes with dietary components that have not been part of our diet during evolution but occur in high amounts today, such as the n-6 PUFA, or low amounts such as the n-3 PUFA, as well as lacking adequate amounts of fruits and vegetables, both of which are needed for proper absorption of n-3 PUFA [24]. These dietary patterns lead to a high n-6/n-3 ratio and to a proinflammatory and prothrombotic state, as well as increases in fat cell size and number increasing the risk of obesity, type 2 diabetes, hypertension, and heart disease [25], which increase vulnerability to COVID-19.

In SARS-CoV-2 activated human macrophages, Resolvin D1 and Resolvin D2 each dramatically reduce the cytokine storm diminishing the levels of key pro-inflammatory cytokines including TNF- α , IL-8, and MIP-1 [26]. SPMs also reduce eicosanoids that amplify and are mediators of inflammation, namely prostaglandins and leukotrienes from ARA that are each present in the peripheral blood of COVID-19 patients along with resolvins that dynamically change with disease severity [27]. Bronchoalveolar lavages from severe COVID-19 patients show high amounts of ARA-produced pro-inflammatory and pro-thrombotic eicosanoids such as thromboxane metabolite (TXB₂), prostaglandin E₂ as well as the potent leukocyte chemoattractant leukotriene B₄ compared to healthy subjects, indicating their origins in lung tissues of these COVID-19 patients and marking the dynamic pro-coagulant and inflammatory environment within the lungs of patients with severe COVID-19 [28]. These lavages demonstrated the presence of lipoxin A₄ and many of the resolvins of the D-series notably resolvin D1, resolvin D2, resolvin D4, resolvin D5, and the precursor intermediates, 18-HEPE and 17HDHA (the intermediate precursors of SPMs) that are also known to be bioactive, whereas other SPMs, e.g., resolvin E1 and maresins, were absent in these lavage samples. The presence of proinflammatory eicosanoids, and specifically resolvins and other SPMs in lung lavages at biologically active concentrations from severe COVID-19 patients, suggests these mediators may have functional roles in the lipid mediator storm of SARS-CoV-2 infections [28].

In a recent randomized double-blind placebo-controlled study in healthy volunteers, oral administration of marine oil enriched with 17-HDHA, 18-HEPE and 14-HDHA showed a time- and dose-dependent increase in peripheral blood SPMs likely from endogenous enzymatic conversion of these precursors [29]. This increase in SPM correlates with rapid reprogramming of blood cells that include rapid changes in the leukocyte transcriptome and increased bacterial phagocytosis [29]. These changes were apparent within hours, increasing SPMs that in turn enhance

both neutrophil and monocyte ability to phagocytose *E. coli* as well as regulate leukocyte transcripts of interest in infections. Hence, the nutritional availability of dietary n-3 PUFA and marine oils enriched with the SPM intermediate precursors (e.g., 17-HDHA, 18HEPE), along with increasing local biosynthesis of SPMs [30] to functional concentrations may be an approach of value during COVID-19 as well as in prevention and shortening their recovery phase from infections.

6. The Need for Precision Nutrition

It is evident that populations differ in their genetic variants and their frequencies and in their interactions with the food they eat. Gene/nutrient interactions is a very important area of study that provides specific dietary advice for individuals and subgroups within a population in the form of precision nutrition. The current recommendation of the American Heart Association to increase LA intake to 10% of energy could be detrimental for those in the US population that are fast metabolizers, specifically African Americans and Hispanics. Under natural conditions of dietary intake of no processed foods and a balanced n-6/n-3 ratio, the fast metabolizers will do well because they start their metabolism with balanced n-6 and n-3 PUFA. In a “melting pot” type of population such as the US, what the AHA recommends might actually be harmful. Importantly, new research is also identifying enzymatic metabolites from LA that may regulate nociception [31], and initial clinical trials testing if lowering dietary LA can alter nociceptive lipid mediators in a manner that decreases headache pain are underway [32].

There is no scientific basis or evidence for the AHA statement to increase LA to 10% of energy for all Americans. Nutritional science needs to focus on precision nutrition, genetic variants in the population, and a food supply composed of nutrients that have been part of our diet throughout evolution, which is the diet that our genes are programmed to respond to. In today’s diet, 72% of calories come from foods that were not present during evolution [1]. In the meantime, physicians should consider measuring PUFAs and their potent cellular effectors, both the eicosanoids and SPMs, in patients with COVID-19 and in patients with chronic diseases as in refs [27–29], specifically obesity, type 2 diabetes, hypertension, and CHD, by measuring LA, ALA, the LA/ALA ratio, and the ARA + EPA + DHA and ARA/EPA + DHA ratio in red blood cell membrane phospholipids (RBCs) and aim for balance in the dietary intake of n-6 and n-3 PUFA. The FDA should not continue to list PUFA on the food label and should replace the term “PUFA” with actual amounts of the individual molecules, namely LA, ALA, ARA, EPA, and DHA, and eventually industry should adopt an n-6/n-3 “ratio” per serving in all processed foods [33].

To put precision nutrition into practice, targeted LC-MS/MS-based lipidomic profiling of fatty acids and SPMs combined with genetic variation and markers of inflammation would identify candidate targets for intervention. Interventions,

especially of the dietary variety, should be monitored to confirm that both substrates and SPMs reach functional concentrations and could be considered in the management of patients with COVID-19, as well as in preventing and shortening their recovery phase from infections.

In terms of research priorities, the emphasis should be on measuring validated biomarkers and understanding the mechanisms and the effects/impact of gene–nutrient interactions in growth and development and in the prevention and management of diseases. Precision nutrition must be the driving force in making dietary recommendations. There is no scientific basis or evidence for the AHA statement to increase LA to 10% of energy for all Americans.

Ramsden et al. [34] carried out a study to determine whether dietary interventions that increase omega-3 fatty acids with and without a reduction in omega-6 LA can alter circulating lipid mediators that are implicated in headache pathogenesis and decrease headache in adults with migraine. The results of the study showed that the addition of EPA and DHA to their diet as well as the addition of EPA and DHA in a low-omega-6 LA diet led to the reduction of headaches and an increase in bioactive oxylipins blood levels. Migraine is among the largest cause of disability worldwide [35–37].

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BOX 1

The rapid nutritional changes that have taken place in developed countries after World War II have led to maladaptations and related human diseases never before seen in such frequencies over a short period of time.

BOX 2

Human beings evolved on a diet that was relatively balanced in linoleic acid (18:2n-6; LA) n-6 PUFA and alpha-linolenic acid (18:3n-3; ALA) n-3 PUFA. Both LA and ALA are found in similar amounts in nature.

BOX 3

When we talk about a balance of ω -6 and ω -3 fatty acids, we mean a balance at two levels at the 18 and 20 carbon atoms of the fatty acid chain.

BOX 4

These two fatty acids LA and ALA are called essential fatty acids because our body cannot make them, and they must be obtained from our diet. These two families of essential fatty acids have different and in fact opposing physiological, biochemical, and functional properties.

BOX 5

These fatty acids are distinct and except for the fact that they are both essential, they have very little else in common. You must remember because they have opposing properties, their balance is essential for health.

BOX 6

LA and ALA and their desaturation and elongation products use the same enzyme systems for their metabolism, have opposing properties, and are metabolically and physiologically distinct. The ALA pathway is the preferred pathway and up until the 1960s there was a balance in the amounts of LA and ALA that humans obtained from their diet.

BOX 7

However, things began to change in the 1960s after Keys did not consider that the diet of Crete was balanced in n-6 and n-3 PUFA in the Seven Countries Study for the prevention of heart disease.

BOX 8

Soon after, the American Heart Association (AHA) declared cholesterol levels must be lowered to prevent heart disease, and the whole country was exposed to an enormous campaign to replace saturated fat with vegetable oils rich in LA such as

corn, sunflower, safflower, soybean, and cottonseed to lower cholesterol.

BOX 9

In fact, Ramsden et al. showed that LA will lower cholesterol by 30 mg/dL but will increase cardiovascular disease death by +22%. This dietary advice continues despite the increase in chronic diseases such as obesity, type 2 diabetes, hypertension, and cardiovascular disease, all of which lead to a pro-inflammatory state due to high amounts of LA and ARA and their metabolites.

BOX 10

We call this the preferred pathway. When LA and ALA are in balance, how much ARA and EPA and DHA they make depends on the dietary intake and the genetics of the individual or populations.

BOX 11

In the diet of Crete, where there was an overall balance of the ω -6 and ω -3 fatty acids, the body maintained a healthy state that led to normal development of the children, delayed the aging process and decreased the risk of cardiovascular disease and cancer.

BOX 12

In Western Diets such as the US diet, there is no longer a balance of the ω -6 and ω -3 fatty acids. There are many reasons for this imbalance. Following World War II, there was an increase in the production of high ω -6 oils and their incorporation into the food supply.

BOX 13

However, you already know that in the Lyon Heart Study de Lorgeril et al. showed that the AHA prudent diet, high in ω -6 and low in saturated fat and cholesterol did not decrease total death, because high LA leads to high ARA, which leads to high eicosanoids that are prothrombotic and proinflammatory, which lead to increased risk of CHD and death.

BOX 14

Furthermore, in persons with one heart attack 4 g of EPA and DHA led to a faster healing of the heart muscle and a decrease in death.

BOX 15

In addition to the increase in ω -6 oils, there were changes in animal feeds following World War II, which led to further increases of ω -6 fatty acid, especially the long-chain ARA. Animals were grain fed instead of grazing in the fields. Grains

increase ω -6 fatty acids at the level of 18-C atoms, which is LA, which metabolizes to the 20 carbon atom, which is ARA, leading to enormous changes in the composition of the food supply in oils and meat, dairy, and eggs.

BOX 16

Thus, over a short period of time, over one generation's time, the whole country was exposed for the first time to a food supply that was not consistent with the foods we were exposed to during evolution and to which our genes were programmed to respond. This new Western diet was rich in calories, but poor in nutrients, high in ω -6 fatty acids and low or depleted in ω -3s at both ALA and EPA and DHA levels.

BOX 17

Furthermore, a high ω -6 and low intake of fruits and vegetables made the diet pro-inflammatory, exactly the opposite of the diet of Crete. Inflammation is the worst condition to be in because inflammation is at the base of all chronic diseases (obesity, diabetes, cardiovascular disease, some forms of cancer, arthritis, and osteoporosis).

BOX 18

EPA- and DHA-derived products are less thrombotic and less inflammatory than those produced from ARA. EPA and DHA are precursors to potent new autacoids that are anti-inflammatory as well as pro-resolving, and participate in the resolution of inflammation and infections preventing the development of full-blown uncontrolled inflammation.

BOX 19

In other words, we have a proinflammatory diet, lack of sleep, and sit around snacking all the time and not exercising; all these situations can lead to low chronic inflammation that wreaks havoc throughout the body.

BOX 20

This type of inflammation is also sort of "secret" and cannot be seen, does not cause swelling or pain, yet it seems to play a role in most chronic diseases known as "diseases of civilization" meaning that they are related to our current diet and various lifestyles that we have adopted, such as night work, exposure to lights longer than sunlight, and being sedentary, and are not consistent with the way we evolved as humans.

BOX 21

Some people have genes that "encode", telling the enzymes to make more EPA and DHA. These genes are very important. However, what is more important is that ω -6

and ω -3 fatty acids are in balance. Otherwise those persons with the high ω -6/ ω -3 dietary ratio will be producing too much ARA that makes very potent inflammatory substances: the thromboxanes and leukotrienes that lead to “diseases of civilization” characterized by inflammation.

BOX 22

EPA and DHA are found in the membranes of all cells in the body. Think of them as building blocks for cell membranes throughout our body. DHA is found especially in high amounts in our brains, eyes, and testes. Both EPA and DHA are essential from conception to old age, being essential for normal growth helping fetuses develop and seniors remain healthy, as well as in the prevention and management of chronic diseases.

BOX 23

The functions of SPMs arise from the chemistry inherited from their omega-3 PUFA precursors in our diet. The SPMs each counter-regulate cytokine storms, as well as proinflammatory lipid mediators, and control the killing and clearance of microbes.

BOX 24

In fact, the current American diet has one of the highest ratios of omega-6/omega-3 fatty acids. In addition to the high dietary intake of omega-6 fatty acids, another important factor that leads to an imbalance of omega-6 and omega-3 fatty acids is the genetic variation that exists in the biosynthesis of LA and ALA to ARA and EPA + DPA + DHA at the level of desaturases FADS1 and FADS2.

BOX 25

In adapting to new environmental conditions inland, humans evolved genes in the form of desaturases that increased the production of the longer-chain fatty acids, namely ARA, EPA, DPA, and DHA.

BOX 26

Recent studies by Ameur et al. show that today in Africa the population has two haplotypes. One is called an ancestral haplotype or haplotype A and the other is called a derived haplotype or haplotype D. The majority of the African population has haplotype D. This is the haplotype that has the most efficient biosynthesis from LA to ARA and from ALA to EPA, DPA and DHA. The people with haplotype D benefited the most and survived.

BOX 27

Ameur et al. studied the frequencies of haplotypes A and D in native populations distributed all over the world. The most common haplotype D was associated with

high lipid levels, whereas the less common haplotype A was associated with low levels. Persons homozygotes for haplotype D had 24% higher levels of DHA and 43% higher levels of ARA than those homozygous for haplotype A. The two FADs haplotypes differ both in transcription levels and in their ability to synthesize ARA and DHA from their precursor LA and LNA, respectively.

BOX 28

Individuals with haplotype D have a rapid biosynthesis from LA to ARA and therefore have higher amounts of ARA circulating in the blood, far and above the amounts expected from the high intake of LA in the diet.

BOX 29

It is the higher frequency of genes and the current US diet high in LA that causes African Americans and Hispanics to have a higher susceptibility to obesity, type 2 diabetes, high blood pressure, and heart disease—all of which have inflammation as a basis for their development.

BOX 30

It is possible that the combination of an ultra-processed Western type of diet plus the higher frequency of haplotype D that magnifies vulnerability of African Americans and Hispanics to COVID-19. In Africa there are fewer deaths due to COVID-19 despite having the same genetic variants, possibly because their diet is not as high in n-6 PUFA and ultra-processed foods.

BOX 31

There are also other populations that carry genes that have lower biosynthesis of ARA from LA or EPA and DHA from ALA, such as Native Americans. These populations have high LA and ARA because of the US diet and are relatively low in ALA and DHA, putting them at risk of a proinflammatory state and COVID-19. The Indigenous people of Arctic regions are another group, but they eat a lot of fish and thus do not become deficient in n-3 PUFA and are not at risk of an inflammatory state.

BOX 32

What is missing specifically are papers that focus on the genetic variation of these populations and the interaction of their genes with dietary components that have not been part of our diet during evolution but today occur in high amounts, such as the n-6 PUFA, or low amounts, such as the n-3 PUFA, as well as lacking adequate amounts of fruits and vegetables, both of which are needed for proper absorption of n-3 PUFA.

BOX 33

These dietary patterns lead to a high n-6/n-3 ratio and to a proinflammatory and prothrombotic state, as well as increases in fat cell size and number increasing the risk of obesity, type 2 diabetes, hypertension and heart disease [24], which increase vulnerability to COVID-19.

BOX 34

SPMs also reduce eicosanoids that amplify and are mediators of inflammation, namely prostaglandins and leukotrienes from ARA that are each present in peripheral blood of COVID-19 patients along with resolvins that dynamically change with disease severity.

The presence of proinflammatory eicosanoids, and specifically resolvins and other SPMs, in lung lavages at biologically active concentrations from severe COVID-19 patients suggests these mediators may have functional roles in the lipid mediator storm of SARS-CoV-2 infections.

BOX 35

Hence, the nutritional availability of dietary n-3 PUFA and marine oils enriched with the SPM intermediate precursors (e.g., 17-HDHA, 18HEPE), along with increasing local biosynthesis of SPMs [29] to functional concentrations may be an approach of value during COVID-19 as well as in prevention and shortening their recovery phase from infections.

BOX 36

It is evident that populations differ in their genetic variants and their frequencies and in their interactions with the food they eat. Gene/nutrient interactions is a very important area of study that provides specific dietary advice for individuals and subgroups within a population in the form of precision nutrition. The current recommendation of the American Heart Association to increase LA intake to 10% of energy could be detrimental for those in the US population that are fast metabolizers, specifically African Americans and Hispanics.

BOX 37

Under natural conditions of dietary intake of no processed foods and a balanced n-6/n-3 ratio, the fast metabolizers will do well because they start their metabolism with balanced n-6 and n-3 PUFA. In a “melting pot” type of population such as the US, what the AHA recommends might actually be harmful.

BOX 38

There is no scientific basis or evidence for the AHA statement to increase LA to 10% of energy for all Americans. Nutritional science needs to focus on precision

nutrition, genetic variants in the population, and a food supply composed of nutrients that have been part of our diet throughout evolution, which is the diet that our genes are programmed to respond to.

BOX 39

In the meantime, physicians should consider measuring PUFAs and their potent cellular effectors, both the eicosanoids and SPMs, in patients with COVID-19 and in patients with chronic diseases as in refs [26–28,32], specifically obesity, type 2 diabetes, hypertension, and CHD by measuring LA, ALA, and the LA/ALA ratio, ARA + EPA + DHA and ARA/EPA + DHA ratio in red blood cell membrane phospholipids (RBCs), and aim for balance in the dietary intake of n-6 and n-3 PUFA.

BOX 40

Interventions, especially those of a dietary nature, should be monitored to confirm that both substrates and SPMs reach functional concentrations and could be considered in the management of patients with COVID-19, as well as in preventing and shortening their recovery phase from infections.

BOX 41

Precision nutrition must be the driving force in making dietary recommendations. There is no scientific basis or evidence for the AHA statement to increase LA to 10% of energy for all Americans.

BOX 42

The results of the study showed that the addition of EPA and DHA to their diet as well as the addition of EPA and DHA in a low-omega-6 LA diet led to the reduction of headaches and an increase in bioactive oxylipins blood levels. Migraine is among the largest causes of disability worldwide.

Chapter 6. What Your Genes Can Tell You about Nutrition

1. Single-Gene Defects
2. Multigenic Multifactorial Diseases
3. Genetic Individuality and Polymorphisms
4. Genetic Variation and Nutrition
5. Genetic Variation, Dietary Cholesterol, Plasma Cholesterol Levels, and Obesity Risk
6. Protective Gene Variants
7. Dietary Sodium, Genetic Variation, and the Response of Blood Pressure
8. Dietary Calcium, Genetic Variation, and Bone Density
9. Omega-6 and Omega-3 Fatty Acids, Nutritional Requirements, and Genetic Variation
10. Ethnic Differences and Gene Variants
11. Genetic Risk, Adherence to a Healthy Lifestyle and Coronary Heart Disease
12. The role of Nutrients and Physical Activity in Gene Expression
13. Concept of Positive Health by Hippocrates
14. Genetic Testing
15. Direct-to-Consumer Genetic Testing

Each one of us is unique, made so by our individual inheritance, the thousands of genes found on our forty-six chromosomes and the interaction of our genes with many environmental factors, the most important environmental factor being our Nutrition. Although many changes have taken place in many aspects of our environment, our genes have not changed over the past 10,000 years since the beginning of the Agricultural revolution, which led to the domestication of animals for food consumption and work and the cultivation of seeds from plants in the wild and trees that bear fruit.

The human genome project determined that our genome consists of 22,000 genes and three billion genetic variants. There are two different kinds of nutritionally linked genetic diseases. The first are those that can be observed in utero or at birth, for which there is a clear pattern of inheritance. The second are the chronic diseases affected by what we eat, how physically active we are, and other environmental factors that have an underlying genetic component and take a long time to appear—or, as geneticists say “to be expressed” only doing so at some time in our adult life. For the latter conditions, we use the term “genetic predisposition” to describe individuals and families who have the potential to develop a disorder eventually based on the interaction of genes and various environmental factors, with diet being the most important environmental factor.

1. Single-Gene Defects

Phenylketonuria (PKU) is the best example of a disease in the first category, due to a single-gene defect that can be defined prenatally or at birth and can be prevented through a low-phenylalanine diet. In this condition, due to the absence of a specific liver enzyme, the body cannot handle phenylalanine, an essential amino acid present in all proteins, which everyone needs to make his or her protein. In untreated persons, phenylalanine piles up in the body, causing severe mental retardation, eczema, and neurological problems. We now test all newborns for PKU to find the very few 1 in 14,000 infants who have this genetic abnormality. The test is not scary for parents. Indeed, it is reassuring because the overwhelming number of infants do not have PKU. For those who do, there is an effective treatment that prevents retardation: using a low-phenylalanine diet. Genetic screening for diseases due to a single-gene defect such as PKU has been carried out for about 50 years in the US and other parts of the world as part of the Newborn Screening Program that each state carries. Single-gene defects such as PKU, Galactosemia, hypothyroidism, and cystic fibrosis have led to prevention of mental retardation due to PKU and galactosemia by eliminating phenylalanine-containing foods and galactose-containing foods, respectively.

2. Multigenic Multifactorial Diseases

Over the past 10 years, genome-wide association studies (GWAS) have shown associations between certain diseases such as coronary heart disease (CHD), cancer, diabetes, obesity, arthritis, etc., and certain genetic variants. However, these studies only occasionally include gene–nutrient interactions. Furthermore, for those chronic diseases there are many genes involved. In fact, the larger number of genes involved the better the association with disease. Most people think that for chronic diseases each genetic association contributes a small risk. The frequent genes identified through GWAS each contribute a very small risk to the disease. As a result, scientists are now looking for rare genes that might have a large effect in causing heart disease, cancer, obesity, diabetes, and other chronic diseases. In addition to discovering genes that contribute to disease, scientists have also discovered genes that are protective [1]. The science of genetics and chronic diseases is such that it is important to know your family history, discuss it with your physician, and decide about undergoing screening and proper management. The Surgeon General’s report on Family Health History is available from the Center of Diseases Control and Prevention [2]. For those interested in pursuing the information contained in the Surgeon General’s report, you will learn the basics of (1) What is Family Health History? (2) How to collect your Family Health History; (3) why it is important for your health, and (4) how to use your Family Health History to improve your health.

Chronic diseases such as CHD, cancer, obesity, diabetes, hypertension, and alcoholism are due to many genes (multigenic) and many factors (multifactorial), and are all examples of adult-onset disorders in which nutrition can play an important role, either to increase or reduce expression of genes and the severity of the disease. These are the diseases that involve more than one gene and many environmental exposures. Physical activity and diet can play a significant role in their development as well as in their prevention and management. Therefore, the health of the individual and the population in general is the result of the interaction between nature, which is our genetic blueprint, and nurture, all the environmental factors, the most important of which is diet (Figure 6.1) [3].

Humankind has always known that family history is important. That is one of the reasons matchmaking was popular in earlier societies. The concern of our clever ancestors was not merely territorial and financial; they were looking at health as well. Without modern scientific knowledge, with only their eyes and ears and oral history to guide them, ancient societies understood that family patterns repeat themselves, and that both positive and negative characteristics turn up in each generation. In the Greek culture, for example people were very sensitive about drinking and would refuse to marry their daughters to the sons of a father overly fond of wine. The Greeks also were wary of alliances with families where obesity was a problem, taking Hippocrates’ observations that “fat people die young” seriously.

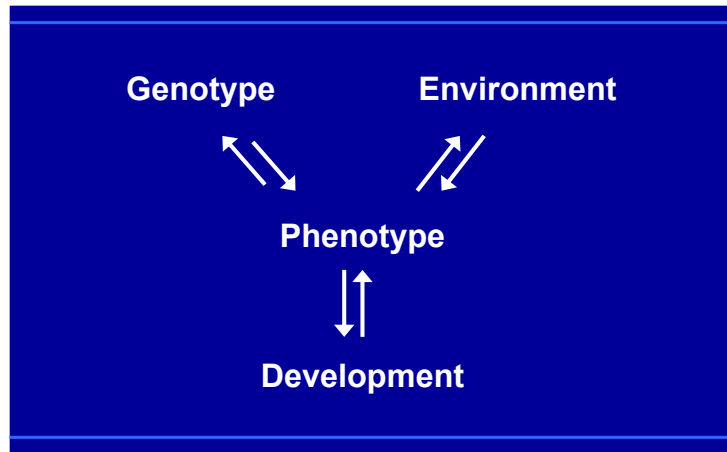


Figure 6.1. Relationships between genes, environment and development are dynamic. Source: [3].

3. Genetic Individuality and Polymorphisms

Genes may appear in more than one form. The different forms of a gene are called alleles. Common alleles (variants of a single locus) or polymorphisms form the basis of human diversity, including the ability to handle changes in the nutritional environment. All humans have polymorphic variants, defined as two or more alleles with a frequency of at least 1% or more in the population. An average individual that is heterozygous has at least one allele at about 10% of the loci. Alleles that contributed to health in the past are found at higher numbers in the population, due to what is called positive selection.

Individuality or our uniqueness is based on:

- Genes (both major genes and modifiers);
- Constitutional factors (age, sex, developmental factors, parental factors; and
- Environmental factors (time, geography, climate, socioeconomic status, occupation, education, diet, and physical activity).

All sorts of interactions among these three sources of variation are possible. It is for all these factors interacting with genes that genetic screening for chronic diseases should not be carried out “Direct-to-Consumers” in isolation, but within a health or medical setting, where all these factors are taken into consideration for diagnosis, and treatment. Such a setting consists of a team that includes geneticists, genetic counselors, nutritionists, dietitians, exercise physiologists, and physicians.

4. Genetic Variation and Nutrition

Genetic studies have shown enormous genetic diversity in human populations, and greater variations have been described at the DNA level. Therefore, both the incidence (new cases) and prevalence (the number of persons with disease

at a time) of chronic diseases vary among individuals, families, and nations. Furthermore, genetic predisposition, diet, other environmental factors, and quality of care contribute to variations in both the incidence and prevalence of chronic diseases. Advances in both genetics and molecular biology tell us that susceptibility to chronic diseases such as cardiovascular disease (CVD), hypertension, type 2 diabetes, obesity, osteoporosis, alcoholism, and cancer are genetically determined to a great extent. Such genes have been called predisposition genes. Genetic factors determine susceptibility to disease, and environmental factors (such as nutrition, an environmental factor of major importance) determine which among the genetically predisposed individuals will be affected and develop disease.

In the past, genetics and nutrition were considered to be two competing forces—nature versus nurture—influencing the development of the individual. Today we know that it is the interaction of genes and nutrients, physical activity, along with other environmental factors that determine phenotype (the way we look and function metabolically) in the development of the individual.

The rapid changes in our diet, particularly the last 75–100 years, are strong promoters of chronic diseases. In addition to diet, sedentary lifestyles and exposure to noxious substances interact with genetically controlled biochemical processes that lead to chronic diseases. CVD, hypertension, diabetes, obesity, cancer, and other chronic diseases in adults tend to occur in greater numbers in families and the risk of relatives is much higher than that in the general population.

Because families share both genes and environments, it is important to know how much of the similarity is due to genes and how much is due to the environment. What we inherit in our genes from our parents is defined by the term “heritability”, which tells us the amount of variance between people that is explained by the genes. Studies in the US have shown that 50% of the variance in plasma cholesterol level is genetically determined, whereas the variance in the blood pressure is between 30–60%, for fibrinogen which is an independent risk factor for CVD, the variance is between 15–50%. However, in the UK the variance for fibrinogen is 15%, and in Hawaii it is 50%, which shows differences in the various populations, and when we calculate heritability it is specific to that population and is not applicable to other populations. In fact, calculations of heritability are relevant only to the specific population and environment from which information was gathered, both in terms of the genetic predisposition and the various environmental factors, including diet and physical activity, that interact and influence the health of individuals and populations. Heritability may vary between populations, if they differ in the prevalence of the types of genes affecting the disease under consideration. Populations therefore should not copy each other’s dietary recommendations for the prevention of CVD and cancer, or any other disease for that matter. This is a major reason that global

health is an incorrect concept, which has not been possible to implement: in essence it is a political concept, without a strong scientific base.

5. Genetic Variation, Dietary Cholesterol, Plasma Cholesterol Levels, and Obesity Risk

I am sure you are familiar with the term Apolipoprotein E4, which increases the risk for Alzheimer's disease. It varies in frequency in various populations, and is higher in Northern Europe, Norway, Sweden, and Finland than in Mediterranean countries in Southern Europe. The population of Greece has the lowest frequency of ApoE4 at 6%, while Northern Europe has a frequency of 20–24%. In addition to being related to Alzheimer's disease, ApoE4 is associated with higher cholesterol levels and CHD.

We now have enough information to look at the plasma cholesterol level both in terms of genetics and diet. It has been known for at least 40 years that the response of plasma cholesterol concentration to cholesterol feeding depends on genetic variants of apolipoprotein E (APoE). On a low-fat/high cholesterol diet, persons with Apo E4/4 phenotype raise their blood cholesterol, whereas those with Apo E2/2 or 3/2 do not. When the diet changes to low fat/low cholesterol, the LDL is lowered and the HDL lowering is twice as great in men as in women. Women of the Apo 3/2 phenotype stand to benefit the least from a high-polyunsaturate/saturate (P/S) diet because of the lowering of the more "protective" HDL cholesterol, whereas men of the Apo 4/3 phenotype showed the greatest improvement in the LDL/HDL ratio. Therefore, a general recommendation to increase the polyunsaturated content of the diet to decrease plasma cholesterol level and the risk for CVD is not appropriate for women with the Apo 3/2 phenotype [4].

Oat bran has been shown to decrease serum cholesterol levels in some studies but not in others. Recently it was shown that only subjects with Apo E3/3 phenotype had a lowering of their serum cholesterol to oat bran at 4 weeks, but no change was noted in individuals with Apo E4/4 or 4/3 type. Thus, specific genetic information is needed to define the optimal diet for an individual. General recommendations usually lead to inconclusive studies or show a lack of benefit.

Genetic variants of APOA2 interact with saturated fat and this interaction is only associated with obesity at a high intake of saturated fat. The functional genetic variant –265T > C (rs5082) within the APOA2 promoter has shown consistent interactions with saturated fatty acid intake to influence the risk of obesity only at high saturated fat intake, due to epigenetic changes. The same variant at a low saturated fat intake does not increase the risk of obesity. A high saturated fat intake is a recent phenomenon since the Second World War and a prominent characteristic of Western diets. The traditional diet of Greece prior to 1960 was characterized by a saturated fat intake of less than 10%, whereas US diets contained double this amount

(22%). The frequency of the variant occurs in 20–40% depending on the population. The APOA2 variant is associated with a methylation variant that, in the presence of high saturated fat (22%), only leads to metabolic changes of increasing appetite and lower energy expenditure. In the presence of a low saturated fat intake there is no increased risk of obesity. Again, the presence of a gene in the absence of high saturated fat intake does not increase the risk of obesity. To prevent the increase in the risk of obesity, the physician could either recommend to decrease saturated fat intake to less than 10% or check for the presence of the APOA2 variant and give specific advice to the person carrying the gene to lower their saturated fat intake to less than 10% in order to decrease the risk of obesity [5].

6. Protective Gene Variants

Not all mutations lead to disease. Rare mutations that disrupt Apolipoprotein C3 (APOC3) function have beneficial effects. They are associated with lower triglyceride levels and the risk for heart disease is lower. About 1 in 150 participants in a study by The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute [1], was a heterozygous carrier of at least one of four mutations. Triglyceride levels in the carriers were 39% lower than levels in non-carriers, the circulating level of APOC3 in carriers was 46% lower than the levels in non-carriers, and the risk of CHD among 498 carriers of any rare APOC3 mutation was 40% lower than the risk among 110,472 non-carriers. This study shows that owing to mutations in the gene encoding apolipoprotein C3 (APOC3), lifelong low levels of non-fasting triglycerides are associated with a reduced risk of CVD in the general population.

Medicine is now entering the era of sequencing-based screening of healthy populations, such as the MyCode Community Health Initiative cohort [6] and the *All of Us* cohort [7]. In order to be able to answer clinical questions about genetic penetrance and prognosis, it will require a broader spectrum of the genetic contribution to risk, including pathogenic and protective variants. For example, loss-of-function alleles in the PCSK9 gene are known to be protective against coronary artery disease (CAD) [8].

Once DNA sequence is obtained, the next step is to interpret how a sequence variant relates to human health. The American College of Medical Genetics and Genomics 2015 Guidelines for sequence variant interpretation have been an important step toward standardization of the interpretation process for genetic variants [9]. The guidelines classify genetic variants into five classes:

- (1) Pathogenic.
- (2) Likely Pathogenic (associated with increased risk for disease).
- (3) Uncertain significance.
- (4) Likely benign (not associated with increased risk for disease).

(5) Benign.

However, there is no guidance on reporting protective variants associated with decreased risk of disease. Schwartz et al. [10] propose to correct this imbalance of not including protective variants, and recommend that variant classification guidelines should be modified to determine the evidence required to classify a genetic variant as protective.

Better understanding and attention to protective variants will improve the practice of medicine and would be especially important in refining risk assessments in asymptomatic individuals found to have a genetic risk for disease from family testing or general population screening initiatives. Many well-studied single-gene predisposition syndromes can manifest differently in individuals with the same variant, and some individuals that carry pathogenic variants never develop disease. Over 50 years ago I remember Dr. Charles Scriver emphasizing over and over again that “the gene is not the disease”. For the disease to develop you need to have genetic predisposition that interacts with environmental factors such as diet, sedentary lifestyle, pollutants, environmental toxins, etc. By identifying pathogenic variants and protective variants, it will make it easier to plan both preventive and therapeutic measures.

A good example of a protective genetic variant are PCSK9 loss-of function variants that are associated with very low levels of low-density lipoprotein cholesterol (LDL-C) and decreased risk for CAD. More common PCSK9 variants with partial loss of function (e.g., R46L) are associated with both lower LDL-C levels and CAD risk, but the effects are reduced. Before protective variants become a routine part of clinical care, it is essential that a strong scientific evidence base is established that characterizes the effect of variant on disease-health related outcomes. The magnitude of risk reduction must be determined by including the existence of protective variants. It will be necessary to develop standards for the classification and reporting protective variants in the practice of precision medicine. Using knowledge of protective variants to guide clinical decision making will lead to shared decision making by patients and their clinicians, in sort of a new way of practicing medicine and delivery of healthcare in the 21st century.

7. Dietary Sodium, Genetic Variation, and the Response of Blood Pressure

Essential hypertension is a common disease. Association between parental blood pressure and a high tracking profile in their children has been confirmed [11]. Genetic, nutritional, and other environmental factors (obesity, sodium, chloride, alcohol, low potassium, low calcium, low omega-3 fatty acid intake, stress, and physical inactivity) interact in the development of hypertension. Variations in blood pressure are due to the combined effects of many genes. As a result, different individuals, even within the same family, may have high blood pressure due to

different combination of genes. Patients with low plasma renin respond to a low-salt diet. Genetic differences are most likely responsible for salt sensitivity. Only half of the patients with high blood pressure are salt sensitive. Therefore, a general recommendation to reduce salt intake is not appropriate. The most effective intervention or prevention of high blood pressure would occur with targeted changes in environmental factors (nutrients, physical activity, weight loss) matched to an individual's specific genetic susceptibility.

8. Dietary Calcium, Genetic Variation and Bone Density

Osteoporosis is a metabolic disorder with strong genetic predisposition shown by twin and parent–offspring studies. The daughters of osteoporotic mothers have a higher incidence of osteoporosis [12]. Osteoporosis affects 1 in 4 postmenopausal White women, but also occurs frequently in men and women of all ethnic groups. One in three women over 65 years of age will suffer an osteoporotic fracture. The risk of fractures in patients with osteoporosis depends on both the peak bone mass in early adulthood and the rate of bone loss later in life. However, of the two, bone density achieved in early adulthood is the major determinant. Bone mass decreases with age. The factors that determine bone mass are genetic and nongenetic (nutrition, smoking, exercise, hypogonadism, etc.). The factors that increase the rate of bone loss in later life are aging, menopause, and various lifestyle factors including drugs and alcohol.

Bone mass has a genetic component, which is a simple allelic change in the Vitamin D receptor (VDR) that controls calcium metabolism. The presence of a site within the gene, which is consistent to the enzyme Bsm I and designated b, correlated strongly and positively with bone density. Absence of the site is the homozygous genotype BB, which is associated with the greatest risk for osteoporosis. In studies with twins [13], higher bone density was associated with the bb allele of the VDR gene, whereas the BB genotype is associated with lower mean bone density, and it was overrepresented in Australian women with osteoporosis in comparison to young normal women. Functionally distinct VDR alleles may contribute to the differences in bone and calcium homeostasis and bone mass between different ethnic groups, such as Whites, African Americans, and Hispanics. Use of this genetic marker should allow earlier intervention in those at increased risk of osteoporosis, provide insight into the physiological mechanisms of the whole population variance in bone density, and open the way to development of specific targeted therapy. One of the important nutrients in fracture prevention are the omega-3 fatty acids, which build bone whereas the omega-6 fatty acids increase bone breakdown.

9. Omega-6 and Omega-3 Fatty Acids, Nutritional Requirements, and Genetic Variation

As described in the chapter on “The Importance of the Omega-6/Omega-3 Balance for Health” genetic variants in the metabolism of omega-6 and omega-3 fatty acids influence blood levels. Linoleic acid (LA) and alpha-linolenic acid (ALA) are essential for the normal growth and development of human beings. The two families of omega-6 (LA) and omega-3 (ALA) fatty acids are physiologically and metabolically distinct, cannot be synthesized in the human body, and must be obtained from the diet. Both LA and ALA use the same enzymes (desaturase 1 + 2 and elongases), and compete with each other for enzyme availability. During evolution, there was a balance in the intake of LA and ALA with a ratio of omega-6 to omega-3 of 1–2/1, whereas today in Western societies, the ratio of omega-6 to omega-3 is about 16–20/1 due to the high intake of vegetable oils, such as soybean, corn, sunflower, safflower and linseed oil, which are high in omega-6. LA is found in high amounts in grains, with the exception of flaxseed, perilla, chia, rapeseed, and walnuts, which are rich in ALA. The green leaves of plants, particularly wild plants, are higher in ALA than in LA.

There are important differences in the capacity of different populations to synthesize LC-PUFAs [14]. These differences may provide a genetic mechanism contributing to health disparities among populations of African American, Asian, Hispanic, and European descent. Considering that human beings evolved on a diet that was balanced in the omega-6/omega-3 essential fatty acids, the increased consumption of vegetable oils high in omega-6 fatty acids such as LA, corn oil (66% omega-6), safflower and sunflower (77% omega-6), and soybean oil (56% omega-6) puts populations with genetic variants in the metabolism of omega-6 and omega-3 fatty acids that carry the FADS1 and FADS2 variants, which increase the production of arachidonic acid (AA), at an increased risk for CVD, diabetes, and kidney disease [15–18]. Studies have shown that there is large genetic variability in the rate of conversion of LA to ARA. LA accounts for the majority of fatty acids in Western diets. Importantly, genetic variants that are associated with higher levels of ARA are also associated with elevated levels of markers of systemic inflammation and the incidence of certain inflammatory disorders [19]. Studies have shown that there are differential effects of high concentration of LA in African and European American populations in the United States, and caution should be exercised with regard to dietary recommendations that assume that the omega-6 PUFA metabolome is uniform in all human populations [20].

The FADS1 and FADS2 gene cluster involved in the metabolic pathway of LA and ALA, as well as the enzymes involved in the production of eicosanoids, i.e., 5-lipoxygenase (5-LO) and cyclooxygenase from ARA and eicosapentaenoic acid (EPA), are polymorphic. Recent studies on their polymorphisms indicate that

the minor alleles of the genetic variants in FADS1 and FADS2 are associated with higher LA and lower ARA levels in red blood cell (RBC) membranes and plasma phospholipids that may influence the estimation of dietary requirements, particularly during pregnancy and lactation, as well as the infant's IQ [17], whereas an increase in the activity of the desaturase increases the ARA to LA ratio and the risk of coronary heart disease (CHD) [18]. Furthermore, genetic variants in the 5-LO and cyclooxygenase-2 (COX-2) genes have been associated with an increased risk of CHD and cancer [17,21,22].

Single genetic variants in the FADS1 and FADS2 region have previously been associated with lipid-related traits and phenotypes. A recent analysis has shown the presence of two common human haplotypes with dramatic differences in their transcription levels and their ability to synthesize essential omega-3 and omega-6 LC-PUFAs. These two haplotypes D (derived) and A (ancestral) account for all of the genetic effect seen in FADS activity, and none of the rare SNPs in the region appear to have any additional effect. In Africa, haplotype D appears to have continued to increase until it reached the present dominating position. Therefore, in the FADS region today, the derived allele haplotype D is more frequent in Africa than in other continents. As expected, it has been shown that the FADS genetic variants have a stronger effect on PUFA metabolism in African Americans than in Americans of European descent as a result of differences in genotype frequencies. Of interest is the fact that in women who carry genetic variants predisposing to breast cancer, the risk relates to the amount of LA in their diet [23]. Therefore, epidemiological studies on dietary fat and breast cancer should take into account the genetic predisposition related to omega-6 fatty acid metabolism. The background diet, when poor in green leafy vegetables and fruits, is associated with lower levels of omega-3 PUFA in the blood following supplementation [24]. Furthermore, the pattern of consumption does affect the incorporation of EPA and docosahexaenoic acid (DHA) into cells used as biomarkers of intake. For example, continuous supplementation with fish oils leads to higher blood levels of EPA and DHA than equivalent amounts obtained from fish intake once or twice a week [25]. These differences need to be considered in the design of studies and when extrapolating results from continuous capsule-based intervention studies to dietary guidelines for oily fish consumption.

10. Ethnic Differences and Gene Variants

Although man has evolved to be able to feed on a variety of foods and to adapt to them, certain genetic adaptations and limitations have occurred in relation to diet. Because there are genetic variations among individuals, however, changes in the dietary patterns impact a genetically heterogeneous population, although populations with similar evolutionary background have more similar genotypes.

Therefore, to be successful, dietary interventions must be based on knowing the frequency of genes whose effects we are attempting to control or modify.

In northwest Europe the frequency of phenylketonuria (PKU) is approximately 1 in 10,000 live births, but it is much lower in Africans and Native Americans [26]. Some disorders which are rare in most populations are not so rare in some isolated populations. For example, hereditary tyrosinemia occurs in about 1 in 1000 births in a French–Canadian Group, and hypertyrosinemia is more common in those of Finnish descent [26].

Hereditary fructose intolerance in Switzerland occurs in 1 in 20,000 [27] and essential pentosuria in people of Jewish origin occurs in 1 in 2500 in some groups [26].

Populations whose diet does not include wheat, barley, rye, or oats manifest gluten sensitivity upon the introduction of those foods in their diet. Celiac disease, triggered by the presence of gluten in the diet, occurs at 1 in 3000 live births in the US but 1 in 200 in Ireland. Removing gluten from the diet improves the general condition [26].

Compared to Caucasians (15%), extremely high frequencies of the Apo E4 allele have been found in African and Asian populations such as New Guineans (35%) and Nigerians (30%). Among European populations, northern countries have higher frequencies (Finland, 22.7%; Sweden, 20.3%) than southern countries (Italy, 9.4%; Greece, 4–6%), which suggest that Apo E4 may in part account for the differences in cardiovascular disease prevalence in the two European regions, along with dietary differences. The relationship between LDL cholesterol levels and Apo E genetic variation is not independent of environmental and ethnic factors. The association of the Apo E4 isoform with elevated serum cholesterol levels is greater in populations consuming diets rich in saturated fat and cholesterol than in other populations. Recent data indicate that the higher LDL cholesterol levels observed in subjects carrying the Apo E4 isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies, and that the response to saturated fat and cholesterol differs among individuals with different Apo E phenotypes [28].

Racial differences have been noted in osteoporotic fracture risk. Fracture rates in Africans and Asians are considerably lower than in White populations despite low dietary intakes of calcium [29]. Alleles of the VDR gene have been related to bone mineral density, bone turnover, and osteoporotic fracture risk [30]. Age-related changes in bone mass and the influence of calcium intake on bone status have also been related to VDR alleles. Recent studies on the distribution of the VDR alleles show a higher frequency of the b allele in The Gambia and China, where osteoporotic fractures are rare, and a much lower distribution in Cambridge, England. The bb distribution was 37.2% in England (similar to other reports of Northern Europe ancestry), 76.1% in The Gambia, and 85.3% in China, suggesting that the high frequency of the bb genotype in China and The Gambia may be associated with

the low fracture incidence in these countries [31]. Of interest is the fact that the bb distribution in African Americans in Boston was 43.1%, which is much lower than in The Gambia but higher than England [31].

An individual's health status is the product of the interaction of his genetic endowment, age, nutrition, physical activity, and other aspects of his physical and cultural environment. Family history (including demographic and ethnic aspects) is an important predictor of disease. In developing Dietary Recommendations, genetic variants in the population should be taken into consideration. Normal individuals have the ability to adapt to a wide range of nutrients, whereas genetically predisposed individuals should be given specific recommendations for the control of the disorder in question rather than the currently used general dietary recommendations. For example, a low-fat/high-carbohydrate diet is not appropriate for women with the Apo E3/2 type, since such a diet would lower HDL cholesterol as well, thus removing the protection from HDL. On the other hand, individuals with Apo E2/2 with a frequency of 8% in the US population and those with Apo A-IV-1/2 with a frequency of 13% in the US population have an attenuated response to a high-cholesterol diet and do not need to restrict their dietary fat and cholesterol intake.

In summary, the most effective intervention or prevention of chronic diseases would occur with targeted changes in environmental factors, including a diet matched to an individual's specific genetic susceptibility. It is mentioned earlier in this chapter that there are tests to identify susceptibility to coronary heart disease, hypertension, obesity, diabetes, osteoporosis, arthritis, and some forms of cancer. In situations where specific biochemical tests are not available, family history evaluation is one of the most useful and practical ways of identifying persons within a population who are at high risk for a particular disorder [2].

Since genetic variants are expressed in a specific environment, populations should not copy each other's dietary recommendations. Furthermore, because of genetic variability, individuals, families, and subgroups within a population have different susceptibilities to chronic diseases. The early identification of the individual at risk for chronic disease and appropriate treatment with nutritional and/or pharmaceutical means should lead to prevention amelioration or a delay in disease manifestation.

Universal dietary recommendations have been used by nutritionists who were concerned with undernutrition, but universal dietary recommendations are not appropriate when the problem is one of overnutrition. Individual dietary recommendations taking into consideration genetic predisposition and energy expenditure are in order.

11. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Heart Disease

We have known for over fifty years that both genetic and lifestyle factors contribute to individual level risk of coronary artery disease (CAD). It is the interaction of our genes with various environmental factors that leads to disease. However, the extent to which increased genetic risk can be offset by a healthy lifestyle has not been extensively investigated until recently. In 2016 Amit V. Khera and his group [32] carried out a study to evaluate the genetic risk, adherence to a healthy lifestyle, and coronary disease. The scientists quantified genetic risk score for CAD in three large groups that were followed prospectively—7814 participants in the Atherosclerosis Risk in Communities (ARIC) study, 21,222 in the Women’s Genome Health Study (WGHS), and 22,389 in the Malmö Diet and Cancer Study (MDCS)—and in 4260 participants in the cross-sectional BiImage Study for whom genotype and covariate data were available. The participants’ adherence to a healthy lifestyle was determined using a scoring system that consisted of four factors: no obesity, no smoking, regular physical activity, and a healthy diet. The study showed that a relative risk of coronary events was 91% higher among participants at high genetic risk than in those with low genetic risk. In the presence of three out of four factors that define healthy lifestyle there was a much lower risk of coronary events than an unfavorable lifestyle—(only one healthy lifestyle factor present), regardless of the genetic risk category. In all studies of those at high genetic risk, a favorable lifestyle was associated with a 46% lower relative risk of coronary events than an unfavorable lifestyle. This is a very important outcome across the four studies involving 55,685 participants from Europe and the US. Genetic and lifestyle factors were independently associated with susceptibility to CAD. Among participants at high genetic risk, those with a favorable lifestyle had a 50% lower risk of CAD than those with an unfavorable lifestyle. These findings are consistent with the Concept of Hippocrates about positive health and Dr. Charles Scriver’s concept that “the gene is not the disease”, but the interaction of genetics and environmental factors interacting throughout development. In this study, genetic risk was decreased by the favorable lifestyle showing that genes are not deterministic but both genetic factors and baseline adherence to a healthy lifestyle contribute independently to the risk of coronary events, and the prevalent subclinical burden of atherosclerosis. The authors derived a polygenic risk score from an analysis of up to 50 single-nucleotide polymorphisms (SNPs) that had achieved genome-wide significance for association with CAD in previous studies. A healthy diet was defined as being consistent with an increased amount of fruits, nuts, vegetables, whole grains, fish, and dairy products, and a reduced amount of refined grains, processed meats, unprocessed red meats, sugar-sweetened beverages, trans fats, and sodium (salt) consistent with the diet of Crete. A healthy lifestyle should be recommended for everyone at all levels of

genetic risk, and intensive lifestyle modification should be targeted at those at high genetic risk.

12. The Role of Nutrients and Physical Activity on Gene Expression

Omega-3 fatty acids blunt the expression of genes associated with increased risk of cardiovascular disease (CVD). Dwyer et al. [33] showed that persons who carry genetic variants in the metabolic pathway of omega-6 and omega-3 fatty acids for the enzyme lipoyxygenase, which increases the production of proinflammatory metabolites, have a higher risk of heart disease in the presence of high amounts of arachidonic acid (ARA)—the omega-6 fatty acid in their blood. By increasing the dietary intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the amount of EPA and DHA (both omega-3 fatty acids) increased in their blood, and the expression of the gene was blunted. Since then, there have been many examples in which gene expression and disease can be blunted through diet and exercise. These effects of diet and exercise have been shown in many different ethnic groups. The reason is that the high amounts of omega-6 fatty acids in our diets are a totally new phenomenon, so that people who carry genetic variants in the metabolism of the omega-6 and omega-3 fatty acids, in the current food environment, are finding themselves in an inflammatory state and, depending on their genetic predisposition, are at high risk for obesity, diabetes, CVD, and cancer.

In the case of obesity, animal studies show that changes in the gut bacteria due to a high omega-6/omega-3 ratio as a result of formula feeding high in omega-6 fatty acids leads to obesity. The use of antibiotics early in life, during the first four months of life, also changes gut bacteria that predispose or program infants to obesity later on in life. Just think then of all the environmental changes, not just to nutrition, that have taken place over the last 100–150 years that are in total opposition to the environment that our genes have been programmed to respond to.

Physical activity has been shown to lead to weight loss in many but not all clinical intervention studies, due to an inadequate number of persons in the study or to the fact that BMI was not actually based on body measurements but on self-reported weights. Similarly, physical activity in terms of energy expenditure was not actually measured. However, in studies carried out properly, physical activity leads to weight loss in most but not all subjects, due to genetic differences among the participants. The FTO gene and its variants is the gene most commonly identified as increasing the risk for obesity, and physical activity has been shown to decrease the effect of certain FTO variants in increasing obesity risk. In a recent large multiethnic study from six ethnic groups (South Asian, East Asian, European, African, Latin American, Native North American) followed for a period of 3.3 years, increased physical activity blunted the genetic effect of FTO rs 1421085 on adiposity by 36–75% [34]. This study is an excellent example of genes by environment

interaction, which shows that current sedentary lifestyles potentiate the effects of genes which are detrimental to health in the present environment. It is obvious that both the current increases in omega-6 fatty acids in the food supply and the lack of physical activity lead to increases in inflammation and in the expression of genes that increase the risk for CVD or obesity.

13. Concept of Positive Health by Hippocrates

“Positive health requires a knowledge of man’s primary constitution (which today we call genetics) and of the powers of various foods, both those natural to them and those resulting from human skill (today’s processed food). But, eating alone is not enough for health. There must also be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the season of the year, the changes of the winds, the age of the individual and the situation of his home. If there is any deficiency in food or exercise the body will fall sick.” (5th Century BC)

Hippocrates emphasized that the term diet includes the effects of nutrition, lifestyle (physical activity), and the overall environment in which a person lives and his or her relationship with family and community. The word “diet” as used today is limited to nutrition, which is the food we eat. It is not enough to focus only on Nutrition in order to have positive health. The time has come to think like Hippocrates on what we mean by diet and its various components. Focusing on nutrition (food) and drugs has not led to the prevention of the diseases of civilization—CVD, hypertension, obesity, diabetes, and cancer. Hippocrates said, “If there is any deficiency in food or exercise, the body will fall sick.” If we are going to seriously commit ourselves to positive health, we will need to change our current nutrition to be similar to the Paleolithic nutrition or the diet of Crete or to the traditional nutrition of Greece prior to 1960, without high amounts of fructose and omega-6 fatty acids, become physically active, cut down on environmental pollutants—not only methane and CO₂ but also toxins and endocrine disruptors—and make changes in agricultural production that will balance omega-6/omega-3, increase fruits and vegetables, and decrease sugar production and chemical fertilizers. Studying genetic variation and identifying genetic predisposition to disease are important and will contribute to specific identification of the individual at risk, but this is more in the future, whereas we can begin now to change our own diet and all its components by implementing the Hippocratic concept of positive health.

14. Genetic Testing

Genetic susceptibility influences which individuals within a particular group experience a particular disorder. Genetics can help explain why some African Americans, Native Americans, or Latino individuals develop diabetes, heart disease, or other common conditions, whereas others living in similar environments do not. Research to clarify the genetic contributors to disease etiology has many potential benefits. It may help explain disease mechanisms and lead to development of genetic tests, dietary changes, and/or drug development. Genetic variation and genetic testing provide information on disease susceptibility, but it is the interaction of genes with environmental factors (diet, exercise, work environment, etc.) that determine disease development.

15. Direct-to-Consumer Genetic Testing

Direct-to-Consumer Genetic Testing has been promoted by various groups as a way to enhance primary prevention of chronic diseases without going through a physician, although some consumers share their results with their primary healthcare provider. A recent study [35] showed that among 1026 participants, 63% planned to share their results with their primary healthcare provider. At a 6-month follow-up, 27% reported having done so, and 8% reported sharing with another healthcare provider only. Common reasons for not sharing results with a healthcare provider were that the results were not important enough (40%) or that the participant did not have time to do so (37%). Among participants who discussed their results with their primary healthcare provider, 35% were very satisfied with their healthcare provider's response and discussion, and 18% were not at all satisfied. Some of the issues that surface from this study are the fact that some of the results could not be acted upon or be used in healthcare, or lack of intent or involvement from the primary healthcare provider. These results suggest that direct-to-consumer genetic tests may create expectations that are unlikely to be met by healthcare providers, especially with busy clinicians trying to make the most of a less than 15 min clinical encounter.

Genetic tests are very different when you compare them to other "screening" tests, such as prostate-specific antigen (PSA) screening or whole-body scans in healthy people. Studies show that direct-to-consumer genetic tests deliver uncertain information and create patient expectations that may align poorly with evidence; clinical priorities; or, in some cases, the patient's best interests. Genetic information is complex and its interpretation is probabilistic, depending on many factors such as health status, family health history, ethnic background, lifestyle, and environmental factors, among which diet and/or nutrition is most important. For decades, the field of genetic counseling has sought to develop scientifically valid processes of helping people understand and adapt to the medical, physiological, and familial implications of genetic contributions to disease. In the genomics era, the role of

genetic counseling may yet undergo major changes as counseling for genetic diseases merges with health education and communication. The question is who should take on public educational challenges in genomics. Already, societies such as the American Society of Human Genetics provide educational material for high school students. Teachers of biology certainly could provide information on how to develop a family history tree. This should be part of every high school graduate's education. In addition to schools, communities could get involved in expanding interest in obtaining a family history, and depending on the information gathered one should discuss his or her findings with their physician. The medical team is the best avenue to proceed with genetic testing if indicated. Public health has a long history of taking on many challenges in educating the public and delivering communication messages to improve health and prevent disease. Genomics is the latest in hot scientific topics in health commercials. In the past two years, public health has begun to craft public educational and empowerment messages in genomics around hereditary breast and ovarian cancer, and the role of genetics in breast cancer in young women. It may be timely to expand public health educational approaches from a few genes related to cancer to a genome-wide approach to health education. A public health approach will look for many teachable moments, not only in clinical encounters but in homes, schools, and communities. One very good example in the past 10 years or so has been the Surgeon General's Family History Initiative [2], which has encouraged the public to collect family health history information, especially around holidays such as Thanksgiving Day [36]. Public health and healthcare should join forces to empower the general public with credible health information about genomics, using the expertise of many specialties such as health educators, genetic counselors, and others. This effort should assess what and how to communicate about genetic testing, and ultimately empower all of us to make well-informed personal decisions about the use of direct-to-consumer genetic tests in improving health and preventing disease.

For most people, including most Americans, the question is whether genetic testing can contribute to preventing the common complex diseases that are the leading causes of death and disability. Several studies have shown genetic contributors to coronary heart disease, asthma, diabetes, obesity, and most other common diseases, leading to the suggestion that genetic information can motivate healthy choices about diet and exercise, thereby preventing disease [37,38].

Crafting the best policy response to DTC genetics is a challenge. The US. Food and Drug Administration has signaled that it will increasingly use regulatory requirements to ensure that products and claims are supported by evidence. This approach makes sense but raises difficult questions about how evidence thresholds are defined and how claims should be monitored. As a complement to regulatory policy, professional organizations could consider providing educational resources. Such an initiative could offer explanatory materials about DTC genetic testing, as

well as other health products that are heavily marketed to consumers. Persons with a good understanding of the limitations of DTC genetic testing might still wish to pursue it, perhaps out of interest in learning about their ancestry or the genetic contributors to such traits as earwax and earlobe type! Some might feel comfortable placing information about genetic health susceptibilities into a larger context that takes into account absolute risk and the effect of non-genetic risk factors [39].

On 22 November 2013, the US Food and Drug Administration (FDA) ordered 23andMe, a genomics company, to stop marketing its flagship Personal Genomic Service (PGS). The PGS is a DNA sequencing product marketed directly to consumers that claims to “help individuals and their doctors identify health areas that they need to keep an eye on”. By determining the presence of certain single-nucleotide polymorphisms, the PGS estimates risk for more than 250 diseases and health conditions by extrapolating from research studies. After initially continuing to sell its product, 23andMe heeded the FDA’s warning letter and stopped offering health-related genetic tests on 6 December 2013. On 26 February 2014, Nicholas S. Downing AB and Joseph S. Ross MD commented in the *Journal of the American Medical Association* [40] “Additional data characterizing the accuracy of the PGS, including that of its sequencing process and estimates of risk, could facilitate its reintroduction. When it becomes clear that the sequencing process used by the PGS is accurate, the use of this product could be allowed under the supervision of a physician. Direct-to-consumer and office-based genomic testing will only become more common in clinical care with physicians playing a critical role by contextualizing test results. Physicians can help to inform patients about decisions regarding approaches to address any increased risk for clinical disease, which is an especially important responsibility in light of the FDA’s concerns about the potential adverse effects of unsupervised use of the PGS. In addition, this approach would allow continued empowerment of patients to seek out additional health information. However, resumption of direct-to-consumer sales should only be permitted once meaningful data have been generated confirming that the estimates of disease risk made by the PGS are accurate and that the product can be used safely without medical supervision.”

On 6 April 2017, FDA gave consumer genetics firm 23andMe of Mountain View, California, permission to market a saliva-testing kit that can test for genetic mutations strongly associated with ten conditions:

- Hereditary Thrombophilia;
- Alpha-1 Antitrypsin Deficiency (AATD);
- Late-Onset Alzheimer’s Disease;
- Parkinson’s Disease;
- Gaucher Disease;
- Factor XI Deficiency;

- Celiac Disease;
- G6PD Deficiency;
- Early-Onset Primary Dystonia (DYT1/TOR1A-Related);
- Hereditary Hemochromatosis.

These genetic tests provide information on risk for disease susceptibility and could help people make decisions about lifestyle choices or inform discussions with their physicians; they are not diagnostic tests and cannot be used alone for treatment decisions or other medical interventions (in contrast, for example, to BRCA gene testing for hereditary breast and ovarian cancer). The pros and cons of personal genomics direct-to-consumer tests have been discussed for years. People ought to think critically about the health utility of these types of tests, as well as the potential harm, and unnecessary follow-up healthcare costs that could result from testing. Over the past few years research shows that for the most part, data on personal genomics testing have revealed little or no harms, but also little or no health benefit. Additionally, evidence of the ability of genetic information to change health behavior has been lacking. It is important to emphasize the finding of a genetic variant does not mean an individual has a disease or is certain to develop it, and the absence of a variant does not guarantee that someone will not get that particular disease or condition. The FDA said “the tests are intended to provide genetic risk information to consumers” but the tests “cannot determine a person’s overall risk of developing a disease or condition”; they are just one piece of the bigger puzzle. In clinical medicine, genetic risk is used only occasionally as supportive evidence. A concern is that people will make decisions based on these results, and they may never get the disease in question. Therefore, the FDA has mandated that the company’s reports and prepurchase pages include information explaining the estimations of the tests. 23andMe said it would explain to customers before and after purchase what the test can and cannot confirm and add context to the results.

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BOX 1

Therefore, the health of the individual and the population in general is the result of the interaction between nature, which is our genetic blueprint, and nurture, all the environmental factors, the most important of which is diet.

BOX 2

Genetic factors determine susceptibility to disease, and environmental factors (Nutrition is an environmental factor of major importance) determine which among the genetically predisposed individuals will be affected and develop disease.

BOX 3

Calculations of heritability are relevant only to the specific population and environment from which information was gathered, both in terms of the genetic predisposition and the various environmental factors, including diet, that interact and influence the health of individuals and populations.

BOX 4

Populations therefore should not copy each other's dietary recommendations for the prevention of CVD and cancer, or any other disease for that matter. This is a major reason that global health is an incorrect concept, which has not been possible to implement—in essence, it is a political concept, without a scientific base.

BOX 5

It is for all these factors interacting with genes that genetic screening for chronic diseases should not be carried out “Direct-to-Consumers”, but within a health or medical setting, where all these factors are taken into consideration for diagnosis and treatment.

BOX 6

Therefore, a general recommendation to increase the polyunsaturated content of the diet to decrease plasma cholesterol level and the risk for CVD is not appropriate for women with the Apo 3/2 phenotype.

BOX 7

Therefore, to be successful, dietary interventions must be based on knowing the frequency of genes whose effects we are attempting to control or modify.

BOX 8

Recent data indicate that the higher LDL cholesterol levels observed in subjects carrying the Apo E4 isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies, and that the response to saturated

fat and cholesterol differs among individuals with different Apo E phenotypes.

BOX 9

The most effective intervention or prevention of chronic diseases would occur with targeted changes in environmental factors, including a diet matched to an individual's specific genetic susceptibility

BOX 10

In situations where specific biochemical tests are not available, family history evaluation is one of the most useful and practical ways for identifying persons within a population who are at high risk for a particular disorder.

BOX 11

Since genetic variants are expressed in a specific environment, populations should not copy each other's dietary recommendations. Furthermore, because of genetic variability, individuals, families, and subgroups within a population have different susceptibilities to chronic diseases.

BOX 12

Universal dietary recommendations have been used by nutritionists who were concerned with undernutrition, but universal dietary recommendations are not appropriate when the problem is one of overnutrition. Individual dietary recommendations taking into consideration genetic predisposition and energy expenditure are in order.

BOX 13

Thus, specific genetic information is needed to define the optimal diet for an individual. General recommendations usually lead to inconclusive studies or show lack of benefit.

BOX 14

This study shows that owing to mutations in the gene encoding apolipoprotein C3 (APOC3), lifelong low levels of non-fasting triglycerides are associated with a reduced risk of CVD in the general population.

BOX 15

Functionally distinct VDR alleles may contribute to the differences in bone and calcium homeostasis and bone mass between different ethnic groups, such as Whites, African Americans, and Hispanics. Use of this genetic marker should allow earlier intervention in those at increased risk of osteoporosis, provide insight into the physiological mechanisms of the whole population variance in bone density,

and open the way to development of specific targeted therapy. One of the important nutrients in fracture prevention are the omega-3 fatty acids, which build bone whereas the omega-6 fatty acids increase bone breakdown.

BOX 16

Recent data indicate that the higher LDL cholesterol levels observed in subjects carrying the Apo E4 isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies, and that the response to saturated fat and cholesterol differs among individuals with different Apo E phenotypes.

BOX 17

An individual's health status is the product of the interaction of his genetic endowment, age, nutrition, physical activity, and other aspects of his physical and cultural environment. Family history (including demographic and ethnic aspects) is an important predictor of disease. In developing Recommended Dietary Recommendations, genetic variants in the population should be taken into consideration.

BOX 18

Among participants at high genetic risk, those with a favorable lifestyle had a 50% lower risk of CAD than those with an unfavorable lifestyle. These findings are consistent with the concept of Hippocrates about positive health and Dr. Charles Scriver's concept that "the gene is not the disease", but the interaction of genetics and environmental factors interacting throughout development.

BOX 19

Genetic risk was decreased by a favorable lifestyle, showing that genes are not deterministic but both genetic factors and baseline adherence to a healthy lifestyle contribute independently to the risk of coronary events and the prevalent subclinical burden of atherosclerosis.

BOX 20

A healthy lifestyle should be recommended for everyone at all levels of genetic risk, and to target intensive lifestyle modification to those at high genetic risk.

BOX 21

It is obvious that both the current increases in omega-6 fatty acids in the food supply and lack of physical activity lead to increases in inflammation and in the expression of genes that increase the risk for CVD or obesity.

BOX 22

Public health and healthcare should join forces to empower the general public with credible health information about genomics, using the expertise of many specialties such as health educators, genetic counselors, and others.

Part III

Chapter 7. The Human Intestinal Microbiome in Health and Disease

1. Personalized Nutrition and the Microbiome
2. Microbiota Gut–Brain Axis
3. Depression and Constipation
4. Chemical Transformation of Xenobiotics by the Human Gut Microbiota
5. Microbiota and Omega-3s
6. The Microbiome in Disease
7. Type 2 Diabetes
8. Obesity
9. Atherosclerosis
10. Alzheimer’s Disease
11. Select Diets
12. Diet, Microbiome, and Immunity
13. Metabolic Diseases—Microbiome
14. The Metagenome
15. Probiotics and Prebiotics
16. The Role of Fermented Foods
17. Fecal Microbiota Transplantation

The human gut microbiota consist of various microorganisms such as bacteria, viruses, fungi, and protozoa that coexist in harmony with the human intestinal tract. Overall the predominant bacterial groups in the microbiota are Gram-positive firmicutes and Gram-negative Bacteroidetes. Recent studies suggest that the intestinal microbiota play an important role in modulating risks of several chronic diseases, inflammatory bowel disease, obesity, type 2 diabetes, cardiovascular disease, and cancer. We now understand that diet plays a significant role in shaping the microbiota. Experiments show that the dietary changes alter the composition of the microbes in just 24 h [1].

Glossary

Microbiome	The collection of all genomes of microbes in an ecosystem.
Metabolites	The means by which the microbiome communicates.
Metagenome	Refers to the collection of metabolites that the microbiome and host produce and interact with.
Microbiota	The microbes that collectively inhabit a given ecosystem.
Enterotype	Type of gut bacteria.
Homeostasis	Normal body metabolic balance or physiological state.
Dysbiosis	Microbiota imbalance.
Prebiotics	Nutritional substrates that promote the growth of microbes that confer health benefits in the host. (Host = humans or animals)
Probiotics	Live microbes that confer health benefits when administered in adequate amounts in the host.
Synbiotics	Formulations or mixtures consisting of a combination of prebiotics and probiotics.

I begin this chapter with definitions because the microbiome is a new area of research with possibilities of improving public health. The majority of microorganisms live inside the more distal parts of the digestive tract from the mouth to the anus, where their total biomass surpasses 10^{11} cells per gram content. In other words, we have more microorganisms than cells in our body. Gut bacteria in the distal part of the gut contribute to the health of the host by synthesizing vitamins and essential amino acids, as well as producing important metabolic byproducts from dietary components that were not digested in the small intestine. Short-chain fatty acid (SCFA) byproducts that go by the names such as butyrate, propionate, and acetate from the general circulation act as a major energy source for the intestinal epithelial cells that line the inside of the gut, which is important in keeping us healthy. The microbiota promote local intestinal immunity through their effects on many factors, thus influencing systemic immunity and systemic antibody production. These benefits have led to growing interest in the ability to modify the composition of the gut microbiota and find ways to avoid diseases (Figure 7.1).

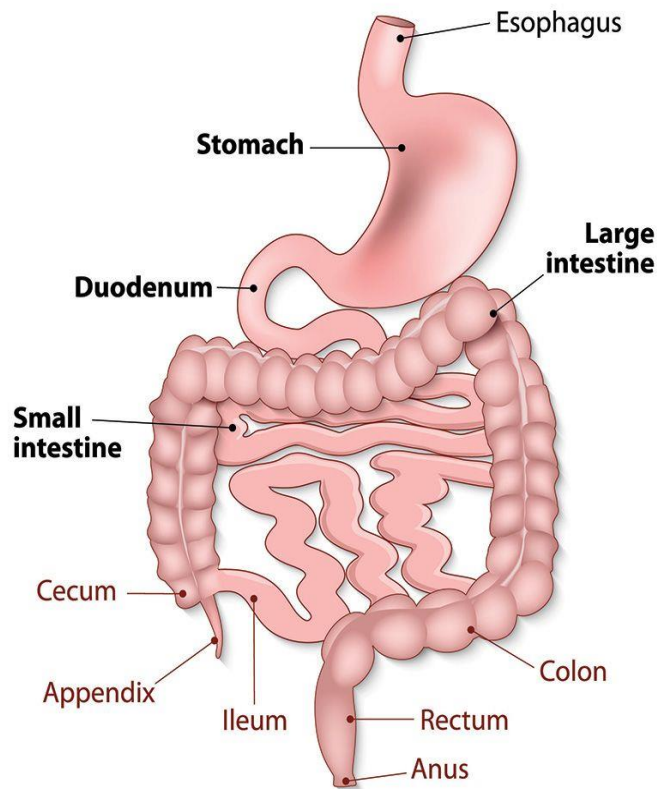


Figure 7.1. The various components of the gastrointestinal system.

1. Personalized Nutrition and the Microbiome

Diet is very important in maintaining beneficial microbiota. For example, an acute change in diet from one that is strictly animal-based to a plant-based diet changes the composition of the microbes in just 24 h and returns to baseline within 48 h after changing the diet. Furthermore, the gut microbiome of animals fed a high-fat or high-sugar diet is more prone to the disruption of circadian rhythm—our 24-h cycle that maintains our body in balance—and metabolic changes. Other studies show that stress and inflammation, such as that which occurs with severe burn injury, can lead to acute changes in the gut microbiota within one day after the injury. So, the composition of our gut depends on our diet and metabolic health.

The composition of the gut microbiota in rodents has been shown to influence how well certain microbiota, having extra energy from what we eat, influence the secretion of gastrointestinal hormones affecting appetite. Therefore, it seems as if the human gut microbiota have the potential to have a pivotal role in personalized nutrition.

Clustering of the human gut microbiota-designated enterotypes (types of gut bacteria) was first described in 2011. (1) The Bacteroidetes (Gram negative) bacteria predominate in individuals that eat more protein and animal fat (Western diet), (2) whereas the Prevotella predominate in persons who eat more carbohydrates and fiber. However, the type of gut bacteria of an individual remains stable. A recent

study by Hjorth et al. [2] compared the ratio of *Prevotella* to *Bacteroides* (P/B) as a prognostic marker for successful body-fat loss on two diets differing greatly in dietary fiber and whole-grain content. A total of 62 participants with increased waist circumference were randomly assigned to receive an ad libitum New Nordic Diet (NND) high in fiber and grains or an Average Danish Diet (ADD) for 26 weeks. The participants were grouped into two discreet enterotypes based on the relative amounts of *Prevotella* divided by *Bacteroides* P/B ratio. Among the participants with high P/B, the NND resulted in a 3.15 kg larger body fat loss compared with ADD. No changes were seen with low P/B ratio. The participants with the high P/B ratio appeared more susceptible to losing body fat on diets high in fiber and whole grains than participants with a low P/B ratio. These results could be due to various mechanisms involving:

- (1) Efficacy of energy harvest from different foods by the bacteria;
- (2) Differences in fiber utilization capacity;
- (3) Gut brain signaling behavior;
- (4) Secretion of GI hormones affecting appetite.

Recently, dietary fiber-induced improvements in postprandial blood glucose and insulin were found to be positively associated with the abundance of *Prevotella*. The recent breakthrough in personalized nutrition, showing the importance of pretreatment fasting glucose and insulin to determine the optimal diet for weight management [3], might also be linked to gut bacteria profiles. However, independent of these mechanisms the P/B ratio may serve as a biomarker to define and even predict future weight loss success on specific diets.

Numerous small molecules are known that are produced by the human microbiome, but fewer amino acid metabolites are synthesized by the microbiota. Gut bacterial species convert common dietary amino acids into distinct end products, such as tryptophan to indoxyl sulfate, indole propionic acid, and tryptamine, indicating that humans with the same diet but different gut colonists can have widely varying gut metabolic profiles.

2. Microbiota Gut–Brain Axis

There have been many studies on the so-called Microbiota gut–brain axis as a modulator of host metabolism and appetite. A number of studies have shown that the gut microbiota influence the bidirectional communication between the gastrointestinal tract and the brain. At any one time, the bacterial composition of the GI tract depends on:

- The type of bacteria present and the composition of the diet.
- Each bacteria species in the gut aims to increase its own bacterial fitness habitat and survival through specific fermentation of the dietary nutrients and secretion

of metabolites. These metabolites influence nutrient sensing and appetite, which then influence eating behavior and satiety-regulating systems.

- Animal experiments clearly show that microbiota produce neuroactivity and short-chain fatty acids, manipulate intestinal barrier function, interact with bile acid metabolism, manipulate the immune system, and influence host antigen production, influencing eating behavior.
- The importance of the intestinal microbiota composition has now been shown in obesity, anorexia, nervosa, and forms of severe acute malnutrition.

The homeostatic control of energy balance is highly regulated by a complex neuronal network where the hypothalamus plays a key role connecting to the brainstem and various forebrain regions (Figure 7.2). The role of gut microbiota in host metabolism and appetite has been primarily investigated in regard to obesity and metabolic syndrome. The importance of the gut microbiota in obesity is also emphasized by the fact that interventions targeting obesity, including bariatric surgery, and Roux-en-Y gastric bypass surgery in particular, induce substantial weight loss and are associated with alterations in gut microbiota composition [4–6].

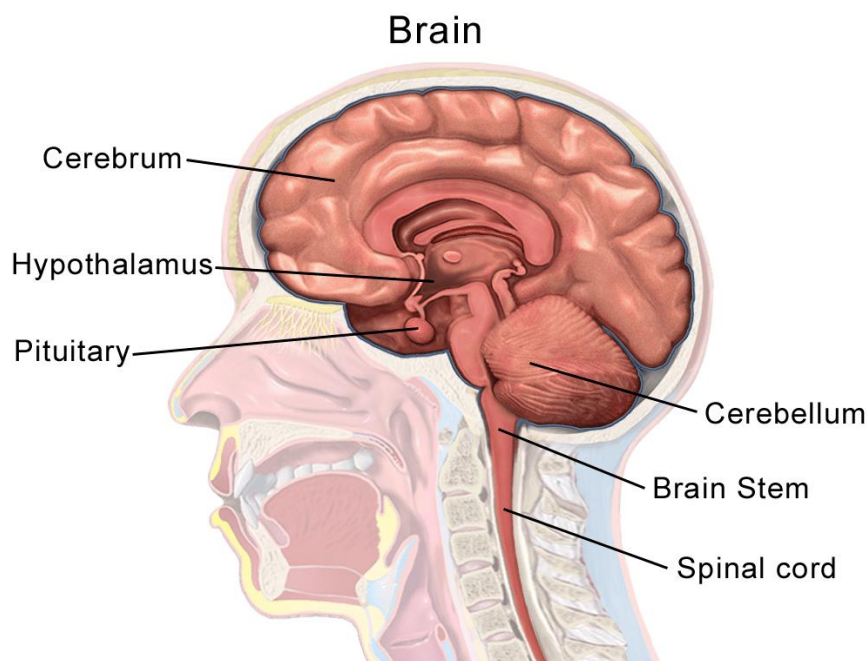


Figure 7.2.Brain and its regions.

Gut microbiota and its metabolites as therapeutic targets in host metabolism and appetite control can be modulated by the following:

- (1) The administration of live beneficial bacterial strains (probiotics);
- (2) The administration of host-indigestible dietary fibers, which undergo bacterial fermentation and subsequently stimulate the growth of certain types of bacteria (prebiotics);

- (3) The administration of targeted antibodies and;
- (4) Fecal microbiota transplantation.

3. Depression and Constipation

Depression and constipation coexist in both patients and animal models, and are associated with low serotonin levels. In animal experiments using the Adipose model of depression, Margolis et al. [7] showed that mice who were depressed due to a genetic variant were also constipated. Giving 5-Hydroxytryptophan (5HTP), a precursor of serotonin, led to improvements in both depression and constipation and an increase in serotonin. The gut is also called the body's second brain. It contains more neurons than the spinal cord and uses the same neurotransmitters as the brain.

4. Chemical Transformation of Xenobiotics by the Human Gut Microbiota

Humans ingest a multitude of small molecules that are foreign to the body (xenobiotics), including dietary components, environmental chemicals, and various drugs (pharmaceuticals). The trillions of microorganisms that live in our gastrointestinal tract (the human gut microbiota) can directly alter the chemical structures of such compounds, thus modifying their lifetimes, bioavailabilities—which are taken up by the body—and biological effects. Over the past several decades, studies of gut microbiota and modification of xenobiotics have revealed that these organisms collectively have larger metabolic abilities than human cells. The chemical differences between human and microbial transformations of ingested compounds arise not only from the increased diversity of enzymes present, but also from the distinct selection pressures that have shaped these activities throughout our evolution. Gut microbes modify many classes of dietary compounds, including complex polysaccharides, lipids, proteins, and phytochemicals. Fueled by findings underscoring the relevance of microbial xenobiotic metabolism to human health, scientists are increasingly seeking to discover and manipulate the enzymatic chemistry involved in these transformations. Revealing the full scope of microbially mediated transformations in the gut may give us new insights into the many variable and contradictory studies regarding the effects of diet, pollutants, and drugs on human health. Microbial genes and enzymes will provide both specific targets for manipulation and diagnostic markers that can be incorporated into clinical studies and practice. Eventually the molecular understanding of gut microbial xenobiotic metabolism will provide the information essential for personalized nutrition, toxicology risk assessment, precision medicine, and drug development [8].

5. Microbiota and Omega-3s

Omega-3 fatty acids have been shown to be important to health, including the growth and development of children, and the prevention and management of many

chronic diseases such as in cardiovascular disease, hypertension, arthritis, obesity, diabetes, and some forms of cancer. Gut bacteria can be thrown out of balance because many factors influence a person's unique microbial mix, such as antibiotics, dietary sugar and starch, low-fiber diets and, as recent research shows, diets low in omega-3s, especially diets low in seafood and DHA. In 2017, Menni C et al. [9] compared the amount of omega-3 fatty acids EPA and DHA in the blood of women involved in a large study in the UK. Menni et al. analyzed data collected from 876 middle-aged and elderly female twins (average age 65) who had previously been studied to look for links between their genetic profiles and gut microbiomes as they relate to weight gain and disease. They found that higher blood levels of omega-3s, especially DHA, were associated with healthier and more diverse microbiomes with higher levels of a friendly bacteria called *Lachnospiraceae*. These findings suggest that the women's estimated omega-3 intakes influenced the health/diversity of their microbiomes as a result of the higher blood levels of omega-3s.

There have been animal studies and small human studies, some of which do not show an effect of omega-3s on better gut health and diversity due to the fact that the omega-3 intake was only estimated through Dietary History questionnaires that are very inaccurate and their blood levels had not been measured. In addition, the omega-3 blood levels were associated with high fecal levels of N-carbamylglutamate (NCG) a compound that exerts antioxidant effects in the gut and may lower inflammation, which is at the base of practically all chronic diseases. Animal studies show that high amounts of omega-6 fatty acids are harmful to gut health. Dr. Jing X Kang at Harvard Medical School found that diets with a lower omega-6/omega-3 ratio lowered the amounts of harmful bacteria while boosting the amounts of beneficial bacteria and led to improvements of the animal's gut biomes. This healthy balance of omega-6 and omega-3s also led to lower levels of inflammation.

"Therefore, dietary strategies that lower the high omega-6/omega-3 ratio found in Western diets to a balanced omega-6/omega-3 ratio would optimize gut microbiota. By reducing intakes of vegetable oils, high in omega-6 fat, processed foods and grain-raised livestock, and increasing intake of fish and green leafy vegetables, could prove effective for managing chronic diseases."

6. The Microbiome in Disease

Studies that examine the composition and role of the intestinal microbiome in different disease states have uncovered associations with inflammatory bowel diseases (IBD), inflammatory skin diseases such as psoriasis, atopic dermatitis, autoimmune arthritis, type 2 diabetes, obesity, cancer, and atherosclerosis. For example, IBD patients tend to have less bacterial diversity as well as lower numbers of Bacteroidetes and Firmicutes, which together contribute a smaller amount of

microbial-derived butyrate. Butyrate and other small-chain fatty acids (SCFAs) have a direct anti-inflammatory effect in the gut. The relative abundance of different bacteria influence and control intestinal inflammation and Crohn's disease activity. Recent studies show that enzymes enriched in IBD microbiomes are more frequently involved in membrane transport, which could support a "leaky gut hypothesis" contributing to the disease state.

7. Type 2 Diabetes

The gut microbiota of patients with type 2 diabetes has been functionally characterized with diabetes-associated markers, showing enriched membrane transport of sugars and branched-chain amino acids, xenobiotic metabolism, and sulphate reduction, butyrate synthesis, and metabolism of cofactors and vitamins and decreased bacterial chemotaxis (Chemotaxis is the movement of an organism in response to a chemical stimulus).

8. Obesity

Obesity has been characterized by an altered intestinal Bacteroides/Firmicutes ratio, with greater relative abundance of Firmicutes that are Gram positive. Furthermore, studies involving microbiota transplantation from obese to lean mice have shown that the obese phenotype is transmissible and may be promoted by microbiota that have an increased capacity to harvest energy from the host's diet.

9. Atherosclerosis

Risk of atherosclerosis has similarly been linked to the gut microbiota, in particular due to enhanced metabolism of choline and phosphatidylcholine that produces the proatherogenic compound, trimethylamine-N-oxide (TMAO).

10. Alzheimer's Disease

A recent study also showed that gut bacteria can produce significant amounts of amyloid and lipopolysaccharides, which are key players in the pathogenesis of Alzheimer's disease.

These studies show the important role of microorganisms in human health and suggest that manipulating the microbiota through diet could influence disease activity. While the microbiome of a healthy individual is relatively stable, gut microbial dynamics can certainly be influenced by the host's lifestyle, including physical activity and dietary choices.

11. Select Diets

Several popular diets, such as Western, gluten free, omnivore, vegetarian, vegan, and Mediterranean diets, have been studied for their ability to modulate the intestinal microbiota. In several studies a Western diet (high in animal protein and fat; low in fiber) led to a marked decrease in numbers of total bacteria and beneficial Bifidobacterium and Eubacterium species [10,11]. Consumption of a Western diet has also been associated with production of cancer-promoting nitrosamines [12,13].

Sanz et al. [14] had 10 healthy subjects consume a gluten-free diet for 30 days. Populations of “healthy bacteria” decreased (Bifidobacterium and Lactobacillus), while populations of potentially unhealthy bacteria increased in parallel to reductions in gluten intake after beginning the diet. In particular, increases were detected in numbers of *E. coli* and total Enterobacteriaceae, which may include further opportunistic pathogens [14]. Bonder et al. [15] similarly investigated the influence of a short-term gluten-free diet, noting reductions in *Ruminococcus bromii* and *Roseburia faecis* with increased Victivallaceae and Clostridiaceae.

Vegan and vegetarian diets are enriched in fermentable plant-based foods. One study compared vegan and vegetarian diets to an unrestricted control diet, and found that both vegans and vegetarians had significantly lower counts of Bifidobacterium and Bacteroidetes species [16]. Yet another study found a very modest difference in the gut microbomes of vegan versus omnivorous subjects [17]. The different results in these studies may be due to methodological problems and or the genetics of the participants. More precise studies will be needed to define the different effects of a vegan vs. an omnivorous diet.

Out of all the diets, the Mediterranean diet, especially the diet of Crete, is highly considered as a healthy balanced diet. It is distinguished by a beneficial fatty acid profile, low in saturated fatty acids, high in monounsaturated fatty acids, a balanced omega-6/omega-3 ratio, high levels of polyphenols and other antioxidants, high intake of fiber and other low glycemic carbohydrates, and relatively greater vegetable than animal protein intake. Specifically, the high intake of olive oil, assorted fruits, vegetables, whole grains, legumes, and nuts, moderate intake of fish, poultry, and red wine, and a lower intake of dairy products (mostly yogurt and cheese instead of milk and cream), red meat, processed meat, and sweets contribute to its recognition as the healthiest diet, among all other diets of the countries around the Mediterranean Sea [18,19]. De Filippis et al. [20] investigated the potential benefits of the Mediterranean diet by comparing habitual omnivores, vegetarians, and vegans. They observed that the majority of vegans and vegetarians, but only 30% of omnivores, had high adherence to the Mediterranean diet. There were significant associations between degree of adherence to the Mediterranean diet and increased levels of fecal small-chain fatty acids (SCFAs), Prevotella bacteria, and other Firmicutes. At the same time, low adherence to the Mediterranean diet

was associated with elevated urinary trimethylamine-N-oxide (TMAO), which is associated with increased cardiovascular risk [20]. Several other studies have shown that foods that are part of the typical Mediterranean diet also improve obesity, the lipid profile, and inflammation.

Artificial sweeteners were originally marketed as a health-conscious, no-calorie food option that could be used to replace natural sugar. Recent evidence from Suez et al. [21] suggests that consumption of all types of artificial sweeteners is actually more likely to induce glucose intolerance than consumption of pure glucose and sucrose. Interestingly, artificial sweeteners are thought to mediate this effect through alteration of gut microbiota. Saccharin-fed mice were noted to have intestinal dysbiosis with increased relative abundance of *Bacteroides* and reduced *Lactobacillus reuteri* [21]. These microbial shifts directly oppose those induced by intake of natural sugars (glucose, fructose, and sucrose), which suggests, contrary to popular belief, artificial sweeteners may actually be healthier to consume than natural sugars.

12. Diet, Microbiome, and Immunity

In the past 15 years, studies on the microbiome in general and the gut microbiome in particular have been shown to play an important role in a wide range of human diseases. The close relationship between the gut microbiome diet and health suggests that there is an opportunity to improve our health by making dietary changes. One of the major ways in which microbiota can influence host health is by modulating host immunity. Studies in germ-free animals show that the gut microbiome is essential for immune cell recruitment and differentiation [22], and that certain types of bacteria have more specific roles in influencing host immunity and immunologic diseases. Although their exact mechanism is still not understood of how these gut microbiota modulate immune responses, several studies suggest that microbial-derived SCFAs may be contributing via G-protein-coupled receptors and epigenetic mechanisms [23,24]. Our gut microbiome has diverse effects on host immunity and a balanced gut microbiome is critical for a healthy immune system. In addition to affecting immunity our gut microbiome has been shown to impact the metabolic health of the host.

13. Metabolic Diseases—Microbiome

Persons with metabolic disorders and diseases such as obesity and diabetes have gut microbiomes that are different from those of healthy persons. In obesity, several bacterial groups may specifically contribute to the disease. People who are obese have a higher ratio of Firmicutes to Bacteroidetes, and reduction of caloric intake lowers that ratio [25]. Most important, hosts with a gut microbiome dominated by Firmicutes have different methylation in the promoters of genes that are linked

to CVD and obesity. Furthermore, *Lactobacillus* spp. decreases obesity-associated metabolic complications [26,27].

Another bacterium that improves obesity metabolic problems is *A. muciniphila*, which breaks down mucus. Obese persons with high amounts of this bacterium have greater improvements in obesity-associated metabolism, such as insulin tolerance, plasma triglycerides levels, and body-fat distribution after changes in diet [28]. These studies show the important role of gut microbiota in keeping the host in a good and healthy metabolic state. We then can conclude that diet can bring about important changes in the gut microbiome, which has an important impact on human health. This impact can be beneficial or bad depending on the type and abundance of the constituent bacterial population. For example, a high-fat diet reduces *A. muciniphila* and *Lactobacillus*, which are both associated with healthy metabolic states [29]. This is a good example of how changes in diet may be used to manage complex diseases, such as obesity and diabetes.

14. The Metagenome

Scientists treat the human microbiome as its own organ with its own unique, but necessary functions. The study of the microbiome's genome through genetic sequences—the metagenome—has allowed scientists to characterize and catalog the entire microbiome and gain a general understanding of how it supports human health. The only way to understand how the microbiome's presence affects the body at any given time is through studying the comprehensive or global metabolome, which is the collection of metabolites that the microbiome and host produce and interact with. Metabolites are the means by which the microbiome communicates. For metabolomics to be most effective, many different classes of metabolites, including xenobiotics, bacterial, and host, need to be measured simultaneously. Studying both the microbiome and metabolome of infants at risk for asthma and allergy, scientists discovered distinct predictive biomarkers for these conditions. The researchers compared the microbiomes and metabolomes of infants with varying levels of susceptibility to asthma and allergy. Among the most susceptible infants, they found deficiencies of several native bacterial species in the gut and had high concentrations of pro-inflammatory T-cells and relatively low concentrations of T-cells that protect against asthma and allergy. These findings in the immunological differences suggest that along with the gut microbiome, an infant's metabolome can be used as a biomarker to predict one's susceptibility to allergy and asthma. Metabolomics has elucidated the link between the microbiome and many other conditions ranging from periodontal disease to obesity, and its relevance is only bound to increase as we learn more about the role of our indigenous microbes in disease. Cataloging the human microbiome has advanced biomedical research by revealing the importance of the microbiome to human health.

15. Probiotics and Prebiotics

Probiotics are “live microorganisms that when administered in adequate amounts, confer a health benefit on the host”. *Prebiotics* are “selectively fermented ingredients” that result in specific changes in the composition or activity of gut microbiota, providing health benefits to the host. Probiotics and prebiotics are disseminated widely in our daily lives, particularly by the food industry, as ingredients in biscuits, cereals, chocolates, and dairy products. For example, most infant formulas are supplemented with probiotics and prebiotics, with the goal of creating a gut-microbiota composition similar to that of the breastfed infant.

16. The Role of Fermented Foods

So far we have seen that the microbiota contribute to many aspects of human health and the types of bacteria are influenced by diet—gut dysbiosis (microbial imbalance) of the intestine is associated with inflammatory and immune-mediated diseases such as inflammatory bowel disease and asthma.

Fermented foods that are commonly eaten include yogurt, cheese, pickles, olives, Kimchi (fermented cabbage), milk, soymilk, wine, and coffee. These foods are fermented predominantly by *Lactobacillus* spp., LAB, streptococcus, thermophiles, Bifidobacteria spp, and in the case of red wine and coffee, saccharomyces yeasts. These bacteria modify host metabolism and immunity. Furthermore, saccharomyces yeasts have anti-inflammatory properties, which may contribute to the immune system supporting characteristics of modest wine consumption. Eating fermented foods is beneficial to health and brings about a balance of the microbiota. We can think of the fermented foods as mediators or ambassadors between their consumption and health outcomes. It is interesting that practically all cultures have fermented foods as part of their traditional diets [30].

17. Fecal Microbiota Transplantation

There is a procedure known as stool transplantation in which stool from a healthy donor is placed into another patient’s intestine. There are different ways to transplant stool, but in most cases, patients have a colonoscopy during which a healthcare clinician puts small amounts of liquified and filtered stool into the colon. Other methods are through enema, capsules, or a feeding tube. Candidate patients for stool transplantation are persons who are difficult to treat or have recurrent infection (three or more episodes) with *Clostridium difficile*. When the numbers of healthy bacteria decrease, i.e., after antibiotic use, harmful *C difficile* bacteria usually increase and cause diarrhea. Although some antibiotics may treat diarrhea, certain individuals do not respond; such patients may be helped by transplants from healthy subjects, which restores the balance of healthy bacteria and clears infection. Stool

transplantation is being studied for treatment of other disorders such as inflammatory bowel disease. The US Food and Drug Administration permits stool transplantation after adequate donor screening and a thorough discussion about risks and benefits between doctors and the recipients.

Advances in microbiome research suggest novel therapeutic possibilities for diseases that have traditionally been difficult to treat. For example, the fecal microbiota transplant has been used successfully to manage several different conditions, such as ulcerative colitis, *Clostridium difficile*-associated colitis, irritable bowel syndrome, and even obesity [31–35]. In these studies, new methods have been developed (metagenomics) that provide information about both microbial identity and gene composition. Knowing which genes are encoded by the bacteria present in a sample permits researchers to better understand their roles in human health. It is important to recognize that the host genotype plays a role in shaping the microbiome, and that this host–microbe interaction is crucial for maintaining human health [36]. This brings us to precision medicine and personalized nutrition, which are therapeutic approaches for many diseases with strong genetic associations. A better understanding of the interplay between genes, phenotypes, and the microbiome will provide important insights into the utility of precision medicine and eventually making specific dietary recommendations to patients, which is known as personalized nutrition.

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BOX 1 The microbiota promote local intestinal immunity through their effects on many factors, thus influencing systemic immunity and systemic antibody production. These benefits have led to growing interest in the ability to modify the composition of the gut microbiota and find ways to avoid diseases.

BOX 2

Diet is very important in maintaining beneficial microbiota. For example, an acute change in diet to one that is strictly animal-based to a plant-based diet changes the composition of the microbes in just 24 h, and it returns to baseline within 48 h after changing the diet.

BOX 3

Other studies show that stress and inflammation, such as that which occurs with severe burn injury, can lead to acute changes in the gut microbiota within one day after the injury. So the composition of our gut depends on our diet and metabolic health.

BOX 4

The composition of the gut microbiota in rodents has been shown to influence how well certain microbiota, which have extra energy from what we eat, influence the secretion of gastrointestinal hormones affecting appetite. Therefore, it seems as if the human gut microbiota have the potential to have a pivotal role in personalized nutrition.

BOX 5

Numerous small molecules are known that are produced by the human microbiome, but fewer amino acid metabolites are synthesized by the microbiota. Gut bacterial species convert common dietary amino acids into distinct end products, such as tryptophan to indoxyl sulfate, indole propionic acid, and tryptamine, indicating that humans with the same diet but different gut colonists can have widely varying gut metabolic profiles.

BOX 6

Each bacteria species in the gut aims to increase its own bacterial fitness habitat and survival through specific fermentation of the dietary nutrients and secretion of metabolites. These metabolites influence nutrient sensing and appetite, which then influence eating behavior and satiety-regulating systems.

BOX 7

Animal experiments clearly show that microbiota produce neuroactivity and short-chain fatty acids, manipulate intestinal barrier function, interact with bile acid

metabolism, manipulate the immune system, and influence host antigen production, influencing eating behavior.

BOX 8

The role of gut microbiota in host metabolism and appetite has been primarily investigated in regard to obesity and metabolic syndrome. The importance of the gut microbiota in obesity is also emphasized by the fact that interventions targeting obesity, including bariatric surgery, and Roux-en-Y gastric bypass surgery in particular, induce substantial weight loss and are associated with alterations in gut microbiota composition.

BOX 9

The gut is also called the body's second brain. It contains more neurons than the spinal cord and uses the same neurotransmitters as the brain.

BOX 10

The chemical differences between human and microbial transformations of ingested compounds arise not only from the increased diversity of enzymes present, but also from the distinct selection pressures that have shaped these activities throughout our evolution.

BOX 11

Revealing the full scope of microbially mediated transformations in the gut may give us new insights into the many variable and contradictory studies regarding the effects of diet, pollutants, and drugs on human health.

BOX 12

Microbial genes and enzymes will provide both specific targets for manipulation and diagnostic markers that can be incorporated into clinical studies and practice. Eventually the molecular understanding of the gut-microbial xenobiotic metabolism will provide the information essential for personalized nutrition, toxicology risk assessment, precision medicine, and drug development.

BOX 13

Gut bacteria can be thrown out of balance because many factors influence a person's unique microbial mix such as antibiotics, dietary sugar and starch, low-fiber diets and, as recent research shows, diets low in omega-3s, especially diets low in seafood and DHA.

BOX 14

It was found that higher blood levels of omega-3s, especially DHA, were associated

with healthier and more diverse microbiomes with higher levels of a friendly bacteria called Lachnospiraceae. These findings suggest that the women's estimated omega-3 intakes influenced the health/diversity of their microbiomes as a result of the higher blood levels of omega-3s.

BOX 15

Animal studies show that high amounts of omega-6 fatty acids are harmful to gut health. Dr. Jing X Kang at Harvard Medical School found that diets with a lower omega-6/omega-3 ratio lowered the amounts of harmful bacteria while boosting the amounts of beneficial bacteria, and led to improvements of the animal's gut biomes. This healthy balance of omega-6 and omega-3s also led to lower levels of inflammation.

BOX 16

Dietary strategies that lower the high omega-6/omega-3 ratio found in Western diets to a balanced omega-6/omega-3 ratio would optimize gut microbiota. Reducing intakes of vegetable oils high in omega-6 fat, as well as processed foods and grain-raised livestock, and increasing intake of fish and green vegetables, could prove effective for managing chronic diseases.

BOX 17

Obesity has been characterized by an altered intestinal Bacteroides/Firmicutes ratio, with greater relative abundance of Firmicutes that are Gram positive. Furthermore, studies involving microbiota transplantation from obese to lean mice have shown that the obese phenotype is transmissible and may be promoted by microbiota that have an increased capacity to harvest energy from the host diet.

BOX 18

These studies show the important role of microorganisms in human health and suggest that manipulating the microbiota through diet could influence disease activity. While the microbiome of a healthy individual is relatively stable, gut microbial dynamics can certainly be influenced by host lifestyle, including physical activity and dietary choices.

BOX 19

In several studies a Western diet (high in animal protein and fat, low in fiber) led to a marked decrease in numbers of total bacteria and beneficial Bifidobacterium and Eubacterium species. Consumption of a Western diet has also been associated with production of cancer-promoting nitrosamines.

BOX 20

The different results in these studies may be due to methodological problems and/or the genetics of the participants. More precise studies will be needed to define the different effects of a vegan vs. an omnivorous diet.

BOX 21

At the same time low adherence to the Mediterranean diet was associated with elevated urinary trimethylamine-N-oxide (TMAO), which is associated with increased cardiovascular risk. Several other studies have shown that foods that are part of the typical Mediterranean diet also improve obesity, the lipid profile, and inflammation.

BOX 22

Saccharin-fed mice were noted to have intestinal dysbiosis with increased relative abundance of *Bacteroides* and reduced *Lactobacillus reuteri*. These microbial shifts directly oppose those induced by intake of natural sugars (glucose, fructose, and sucrose), which suggests that, contrary to popular belief, artificial sweeteners may actually be unhealthier to consume than natural sugars.

BOX 23

The close relationship between the gut microbiome diet and health suggests that there is an opportunity to improve our health by making dietary changes. One of the major ways in which microbiota can influence host health is by modulating host immunity. Studies in germ-free animals show that the gut microbiome is essential for immune cell recruitment and differentiation, and that certain types of bacteria have more specific roles in influencing host immunity and immunologic diseases.

BOX 24

Persons with metabolic disorders and diseases such as obesity and diabetes have gut microbiomes that are different from those of healthy persons. In obesity several bacterial groups may specifically contribute to the disease. People who are obese have a higher ratio of Firmicutes to Bacteroidetes, and reduction of caloric intake lowers that ratio. Most important, hosts with a gut microbiome dominated by Firmicutes have different methylation in the promoters of genes that are linked to CVD and obesity.

BOX 25

We then can conclude that diet can bring about important changes in the gut microbiome, which has an important impact on human health. This impact can be beneficial or bad depending on the type and abundance of the constituent bacterial population. For example, a high-fat diet reduces *A. muciniphila* and *Lactobacillus*,

which are both associated with healthy metabolic states. This is a good example of how changes in diet may be used to manage complex diseases, such as obesity and diabetes.

BOX 26

These findings in the immunological differences suggest that along with the gut microbiome, an infant's metabolome can be used as a biomarker to predict one's susceptibility to allergy and asthma.

BOX 27

Eating fermented foods is beneficial to health and brings about a balance of the microbiota. We can think of the fermented foods as mediators or ambassadors between their consumption and health outcomes. It is interesting that practically all cultures have fermented foods as part of their traditional diets.

BOX 28

By knowing which genes are encoded by the bacteria present in a sample, permits researchers to better understand their roles in human health. It is important to recognize that the host genotype plays a role in shaping the microbiome, and that this host–microbe interaction is crucial for maintaining human health, which brings us to precision medicine and personalized nutrition, which is a therapeutic approach for many diseases with strong genetic associations.

BOX 29

A better understanding of the interplay between genes, phenotypes, and the microbiome will provide important insights into the utility of precision medicine and eventually making specific dietary recommendations to patients, which is known as personalized nutrition.

Chapter 8. Obesity

1. Historical Aspects
2. Definitions
3. Obesity Is a Chronic Low-Inflammatory State
4. A High Omega-6/Omega-3 Ratio Increases the Risk for Obesity
5. The NIH Women's Health Study
6. The Fat-1 Mouse
7. Obesogenic Effects of Fructose and the Concept That a Calorie Is Not a Calorie
8. Fructose Increases Appetite and Obesity
9. How Fructose Turns into Fat and Obesity
10. Obesity and Its Impact on COVID-19
11. The Role of the Food Industry
12. Policy Change Is Needed to Focus on Prevention of Obesity

1. Historical Aspects

Evidence of obesity in humans can be found in primitive art that dates back to the Paleolithic period [1]. Two thousand five hundred years ago, Hippocrates cautioned that sudden death is more common in those who are naturally fat than lean [2]. Obesity treatments date as far back as Hippocrates, who recommended lifestyle changes to obese patients [3,4].

In 1980, as chair of the Nutrition Coordinating Committee at the National Institutes of Health, Dr. Van Itallie and I co-chaired a workshop on Body Weight, Health and Longevity, the purpose of which was to standardize the measurements for obesity in order to define obesity for the scientific community, so everyone could use the same measurements in their studies and in taking care of patients. In 1980 a significant portion of the US population was already overweight or obese. The workshop concluded:

“In the United States, the weight associated with the greatest longevity tends to be below the average weight of the population under consideration, if such weights are not associated with a history of significant medical impairment. Overweight persons tend to die sooner than average-weight persons, especially those who are overweight at younger ages. The effect of being overweight on mortality is delayed and may not be seen in short-term studies. Cigarette smoking is a potential confounder of the relationship between obesity and mortality. Studies on body weight, morbidity, and mortality must be interpreted with careful attention to the definitions of obesity or relative weight used, preexisting morbid conditions, the length of follow-up, and confounders in the analysis. The terminology of body weight standards should be defined more precisely and cited appropriately. An appropriate database relating body weight by sex, age, and possibly frame size to morbidity and mortality should be developed to permit the preparation of reference tables for defining the desirable range of body weight based on morbidity and mortality statistics.” [5]

2. Definitions

Following the publication of the paper, the National Institutes of Health (NIH) and the World Health Organization (WHO) both adopted body mass index (BMI) as a criterion for defining obesity (BMI is a measure of body weight in kilograms adjusted for height in meters squared, $BMI = \text{kg}/\text{height} (\text{m}^2)$). The use of BMI eliminated the need for sex-specific height/weight tables and provided a measurement that is better correlated with other estimates of adiposity or fatness.

Healthy body weight	BMI	between 18.5 and 24.9 kg/m ²
Overweight	BMI	between 25.0 and 29.9 kg/m ²
Obesity	BMI	between 30.0 and 40.0 kg/m ²

In children and adolescents, the Centers for Disease Control (CDC) have developed BMI for age growth charts that define overweight as a BMI above the 90th percentile of standard weight, and obesity as a BMI above the 95th percentile of standard weight–growth curves. BMI provides the most useful population-level measurements of overweight and obesity, and many large population studies across many continents have shown its utility as an estimate of risk for chronic diseases such as type 2 diabetes, CVD, and high blood pressure.

Current Western diets are poor-quality diets that cause predisposition to all of the major chronic diseases: obesity, diabetes, cardiovascular disease (CVD), and cancer, and increase the rate of the aging process. What has happened in the last four decades is instead of trying to prevent these chronic diseases through proper nutrition and exercise, unfortunately an array of drugs, fad diets, and medical and surgical treatments were developed that increased medical-care expenses, while at the same time the treatments did not eradicate or prevent the recurrence of obesity and its associated illnesses.

The US Preventive Services Task Force recommends referral of all obese adults to intensive, multicomponent interventions, including behavioral interventions, drug treatment, and surgical weight-loss procedures [6]. Five medications have been approved for the management of obesity by the FDA; orlistat, lorcaserin, naltrexone-bupropion, phentermine–topiramate, and liraglutide. Among overweight or obese adults on any of these five drugs compared with placebo, each were associated with achieving at least 5% weight loss after being on the drug for 52 weeks. Phentermine-topiramate and liraglutide were associated with the highest odds of achieving at least 5% weight loss [7].

To delay disease progression in CVD, millions of individuals in the United States depended on medications to lower levels of cholesterol for years, whereas now the new guidelines of the American College of Cardiology do not recommend measuring cholesterol for the prevention or management of CVD, except for those who are genetically predisposed. High blood pressure and blood glucose surgical procedures for the management of morbid obesity, to open or bypass blocked arteries, and dialysis consume time, money, energy, and effort of the US Healthcare Delivery System. As the data from the CDC show, we have now reached a tipping point beyond which technological advances may no longer compensate. Throughout the United States life expectancy was lowest in areas (states or counties) where obesity was highest.

Modern medical care may prevent premature death among adults who develop obesity at age 45 years, diabetes at 55 years, and heart disease at 65 years. However,

today obesity begins at a much earlier age than in the last century (20th Century) and this downward trend in longevity will almost certainly accelerate as the current generation of children with higher body weights reaches adulthood. Already type 2 diabetes occurs in early adolescence.

Although many factors influence body weight, the obesity epidemic is, at least in part, related to the following factors:

- First, the influence of special interest groups, mostly the food industry which continues to produce foods high in omega-6 fatty acids and fructose, both of which were never part of our diet in such high amounts until very recently (about 70 years ago).
- Secondly, foods being high in salt is another factor that contributes to obesity and high blood pressure in those who are genetically predisposed: about 50% of the population in European Americans and much higher than that among African Americans.
- Thirdly, industry continues to push the concept that “a calorie is a calorie” and has developed all kinds of low-fat, low-calorie products, none of which have been shown to lessen obesity or maintain weight loss.

In fact, to date, except for bariatric surgery no country or nation has reversed the obesity epidemic, or has been able to maintain weight loss after it is lost. This insistence on the part of the food industry to continue to develop foods and beverages high in fructose and omega-6 fatty acids, both of which have been shown to increase body weight, fatty liver, and type 2 diabetes, is inexcusable. The reason lower calorie intake does not lead to permanent weight loss is because people develop hunger and feel uncomfortable while at the same time the metabolic rate decreases, so hunger leads to higher intake of food and regain of weight loss. I think it is against medical ethics to carry weight-loss programs on TV such as *The Biggest Loser*, which show and parade these poor people when fat, then when they lose weight and regain it. Only very few people can maintain long-term weight loss through calorie restriction alone because of the antagonizing physiological responses, including increasing hunger levels and slowing metabolic rate over time [8,9].

3. Obesity Is a Chronic Low-Inflammatory State

- Obesity is accompanied by the development of chronic low-grade inflammation that is promoted by expanding adipose tissue.
- Expansion of fat mass characterized by adipocyte enlargement fuels the infiltration of macrophages into the adipose tissue, instigating the production of cytokines (IL-1b and IL-18) that contribute to the development of insulin resistance.
- Both IL-1b and IL-18 have been linked to the development of obesity-induced insulin resistance.

- Studies in mice indicate a major role for the inflammasome in modulating obesity and reveals its critical function in obesity-induced insulin resistance.
- Detailed metabolic and molecular phenotyping demonstrated that the inflammasome controls energy expenditure and adipogenic gene expression during chronic overfeeding.
- These findings reveal a critical function of the inflammasome in obesity and insulin resistance and suggest inhibition of the inflammasome as a potential therapeutic strategy.

4. A High Omega-6/Omega-3 Ratio Increases the Risk for Obesity

In the past three decades, total fat and saturated fat intake as a percentage of total calories has continuously decreased in Western diets, while the intake of omega-6 fatty acids increased to very high levels for the first time in the history of humans and the omega-6 to omega-3 ratio, from 1–2/1 during evolution increased to 16–20/1 or even higher. This change in the fatty acid composition parallels a significant increase in the prevalence of overweight and obesity. Experimental studies in animals have suggested that omega-6 fatty acids and omega-3 fatty acids have different and opposing effects on body fat gain through mechanisms of white fat cell formation (adipogenesis) (omega-6) and decrease proliferation (omega-3). Omega-6 fatty acids prevent the formation of brown adipose tissue, which is associated with energy expenditure, overall lipid homeostasis, brain–gut adipose tissue axis, and most importantly omega-6 fatty acids increase systemic inflammation. Diets high in omega-6 fatty acids are proinflammatory, and inflammation is at the base of all chronic diseases, including obesity and its comorbidities.

Obesity is a complex condition that involves the dysregulation of several organ systems and molecular pathways, including adipose tissue, liver, pancreas, the gastrointestinal (GI) tract, the microbiome, the central nervous system (CNS) (various parts of the brain that deal with emotion, cognition, memory, etc.) and of course genetics. The role of the CNS in obesity is receiving more attention as obesity rates rise and treatments continue to fail. While the role of the hypothalamus (part of the brain) in the regulation of appetite and food intake has long been known, the role of the CNS reward systems are beginning to be studied as the role of environmental influences on energy balance are explored. Furthermore, omega-3 fatty acids hold great promise in the prevention and management of obesity.

Animal experiments clearly show that a high amount of corn oil, a predominantly omega-6 oil (67% omega-6 fatty acids), during pregnancy and lactation leads to offsprings that are obese or become obese, while omega-3 fatty acids prevent the development of obesity. The omega-6 fatty acids metabolites, which are hormone-like substances called prostaglandins, lead to the formation of white adipose tissue on the one hand and also prevent the formation of brown adipose

tissue, which increases energy expenditure and is associated with leanness. The omega-6 fatty acids can be thought of as agents of promoting obesity because they lead to proliferation of white fat cells which store energy in the form of triglycerides, whereas the omega-3 fatty acids promote brown fat cells that dissipate energy and increase energy expenditure by producing heat.

In animal experiments during the perinatal period, where high amounts of omega-6 fatty acids were part of their diet, similar to Western diets, increases in percentage of body fat occurred across generations, which is consistent with the fact that in humans, overweight and obesity have steadily increased in the last decades and appear earlier in life. In human studies the level of ARA in adipose tissue is associated with BMI and overweight status of children. A high omega-6/omega-3 ratio in the red blood cell membrane phospholipids (a biomarker of omega-6 and omega-3 levels) of the umbilical cord was associated with high subscapular skin-fold thickness (a measure of fatness) at 3 years of age. It appears that the fetus is programmed in utero to become a fat child when the mother's diet is high in omega-6 fatty acids. Animal and human studies have shown that supplementation with EPA and DHA (omega-3 fatty acids) may be protective against obesity, and may reduce weight gain in already obese animals and humans. Studies show a reduction in visceral fat, which is belly fat, and the effect of reduction was bigger with the higher amount of omega-3 fatty acids. The reduction in belly fat was associated with smaller fat cells as well as a reduction in their number. High-fat diets rich in omega-6 fatty acids, as it is today in the US and other Western diets, increase obesity, type 2 diabetes, and resistance to leptin, a hormone that is high in obese individuals who are leptin resistant.

5. The NIH Women's Health Study

An important study was carried out as part of the NIH's Women's Health Initiative [10]. The purpose of the study was to examine the relationship between the amounts of the red cell membrane phospholipids of ARA (which is the omega-6 fatty acid) and EPA and DHA (which are the omega-3 fatty acids), to the risk of weight gain 10 years later in women who had normal body weights at the beginning of the study. The study showed that the higher the ARA, the higher the risk for weight gain while the higher the omega-3s, the lower the risk for weight gain. Then the scientists looked at the omega-6/omega-3 ratio. They found that the higher the ratio, the higher the risk for weight gain. The reason this study is very important is because it is one of the very few studies where actual levels of both omega-6 and omega-3 fatty acids were measured accurately in the red blood cell membrane phospholipids that reflected both the dietary intake of omega-6 and omega-3s and endogenous production; that is, whatever was produced by the body of these women which is based on genetics. About 1/3 of white Americans are what is called active metabolizers and make about

30% more ARA from LA from the vegetable oils found in the food supply of Western diets. In African Americans, about 80% of the population are active metabolizers and this fact increases their risk for obesity, insulin resistance, metabolic syndrome, and cancer of the breast, which increases with obesity.

Many epidemiological studies and clinical intervention trials have produced conflicting results on the relationship of omega-6 and omega-3 fatty acids and weight gain or obesity due to the fact that the scientists only measure or take a history of dietary intake and many of them fail to measure both omega-6 and omega-3 fatty acids in the blood, especially at the beginning of the trials. Furthermore, very few studies actually measure body weight or skinfold thickness, and only rely on self-reported body weights. These studies contribute to confusion instead of clarifying the relationship between omega-6 and omega-3 fatty acids and overweight or obesity. NIH funding attributed to obesity is only USD 900,000. NIH must develop precise protocols for randomized clinical trials to accurately evaluate the relationship between genetic predisposition and dietary factors that increase susceptibility to overweight and obesity. It should be part of the precision medicine initiative, precision nutrition. The time has come to move away from epidemiological studies, which do not tell you anything about disease causation. Many of these studies have been going on for years with manipulation of data from the same persons. In other words, when a new function by a nutrient is discovered the data from the same people (based on dietary history or self-reported body weights) are again examined for an association. We do not need any more association studies. Instead we need human clinical intervention studies to define the environmental factors and dietary factors that lead to overweight or obesity through the establishment of a precision network in centers for genetics nutrition and fitness for health [9].

6. The Fat-1 Mouse

There are many animal studies on the factors and mechanisms that cause weight gain. One of the most important animal models is the so-called fat-1 mouse developed by Dr. Jing Kang at Harvard Medical School [11]. Dr. Kang was able to develop his model by transferring one of the enzymes that makes omega-3 from omega-6 fatty acids. This enzyme is called delta-3 desaturase. Humans and all mammals have lost this enzyme during evolution because we get the omega-6 and omega-3 fatty acids directly from our diets. However, Dr. Kang got the enzyme from a worm called *C. elegans* and transferred it first in cell culture and then in the whole animal in the mouse and pig. The enzyme in the animal made omega-3 from omega-6 and did not stop making omega-3s from omega-6s until the ratio of omega-6/omega-3 was one. This is a perfect model to study mechanisms by manipulating the ratio directly instead of depending on feeding studies in animals that are grossly inaccurate. A balanced ratio in the fat-1 mouse is consistent with our results from the study on the

diet of Crete and the Greek egg, which under natural conditions where hens are free to move around to fetch their own food and produce eggs that are balanced in the omega-6/omega-3 ratio. In fact, the amount of omega-3s in one Greek egg is equal to the amount of DHA in the mother's breast milk at one month of age. In old cultures such as Greek and Chinese cultures the grandmothers would wait for the chickens to "announce" that they just had an egg and right away the grandmother would fetch the egg and while still warm she would separate the egg yolk from the white of the egg. Only the egg yolk was given to the baby after one month of age, as the first food, thus increasing the amount of omega-3s that the baby would consume and making them available to the brain. Contrast the composition of such a diet for the baby who is breastfed and also gets more DHA from the egg yolk after one month of age to that of a baby in the US fed formula based on cow's milk and baby food, both of them high in omega-6 fatty acids. It was not until about 30 years ago or so that omega-3s were introduced in infant formula after the NIH Workshop recommendations that I chaired [12]. However, like all processed food in the US, baby foods continue to be high in omega-6 fatty acids, and until 10 years ago were also high in trans fatty acids. In fact, many of the vitamin supplements still contain hydrogenated soybean oil.

I think that the fat-1 mouse was a major breakthrough to study the mechanisms by which high amounts of omega-6 fatty acids increase the risk of overweight, obesity, diabetes, insulin-resistant CVD and cancer, relative to lower amounts of omega-6 and a balanced omega-6/omega-3 ratio. The results of these studies have contributed to our understanding of inflammation, which is at the base of many of the chronic diseases and the reasons why the traditional diet of Greece that is similar to the Paleolithic diet, more so than any other Mediterranean Diet, is best for humans.

7. Obesogenic Effects of Fructose and the Concept That a Calorie Is Not a Calorie

Uncertain science, poorly constructed clinical trials, and other factors listed in Table 8.1 have contributed to the current situation characterized by data leading to conflicting results from the various intervention clinical trials [13].

Table 8.1. Factors that affect outcomes in obesity studies leading to conflicting results in clinical intervention trials. Source: [13].

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- Inability to determine the composition of the background diet in terms of omega-6 and omega-3 fatty acids and inflammatory markers, i.e., US, UK, and Northern European countries have the highest amount of LA + ARA in their diets, which competes with omega-3 PUFAs; they also have the lowest amount of vegetable and fruit intake, which is needed for optimal absorption of omega-3 PUFA from supplements
 - Background inflammation
 - Some studies are using fish and others omega-3 supplements; studies show that a continuous daily intake of omega-3 supplements leads to higher concentrations in the blood than eating fish two times/week
 - Variation in the dose of omega-3 fatty acids
 - Variation in the number of subjects
 - Variation in the severity of disease
 - Variation in the pharmacologic treatment
 - Genetic variants predisposing to cardiovascular disease
 - Dietary intake by means of questionnaires instead of actual measurements of omega-3 PUFAs in the red blood cell membrane phospholipids or plasma is a major problem that leads to conflicting results
 - Length of intervention
 - Genetic variants in the metabolism of omega-6 and omega-3 fatty acids
 - Low dose of EPA and DHA against a high intake of LA and ARA of the background diet
-

However, the advent of Nutrigenetics—defined as the role of genetic variation to dietary response—and Nutrigenomics—defined as the role of nutrients in gene expression—and Epigenetics—defined as genetic variation without structural DNA changes—has made major contributions to the scientific base of nutritional studies at the molecular level, and well-constructed clinical intervention trials. For example, contrary to the conventional perspective, research has shown that food affects hunger, hormones, and gene expression in ways that cannot be explained by consideration of caloric balance alone. In a crossover study consisting of normal volunteers, those on a low-fat diet had a decrease in energy expenditure of 325 Kcal per day compared to when they consumed an isocaloric diet that was low in carbohydrates. This study showed that the type of calories from fat or carbohydrates consumed affects the number of calories burned. If this were to continue on daily basis it could explain the obesity epidemic, even with no other changes in food intake [14].

8. Fructose Increases Appetite and Obesity

The effects of fructose vs. glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways has been studied in view of the obesogenic aspects of fructose. A calorie of fructose is not the same as a calorie of glucose when it comes to appetite control. In animal experiments in the brain, fructose injected into the ventricles of the animal provokes feeding,

whereas glucose decreases food intake because fructose and glucose have different effects in the hypothalamus (part of the brain) in terms of signaling pathways. Now new technologies are available to ease the translation of animal to human studies. Functional magnetic resonance imaging (fMRI) provides a non-invasive way to assess the effects of fructose and glucose ingestion on regional cerebral blood flow (CBF), which is an indirect marker of activation of neurons (brain cells). It is known that glucose ingestion decreases hypothalamic activity in humans. Increases in fructose intake have been associated with the increasing prevalence of obesity, and high-fructose diets, sugar-sweetened beverages (SSBs), and processed food promote weight gain and insulin resistance in both animal models and human beings due to the high amount of added sugars coming mostly from high-fructose corn syrup. When you eat processed food or drink beverages high in fructose, there is a much smaller increase in hormones that cut your appetite (satiety hormones) compared to glucose intake. Furthermore, central administration of fructose in the ventricles of the brain provokes feeding in rodents, whereas centrally administered glucose promotes satiety. However, you may ask, what about humans? Here is the answer. Page et al. [15] studied neurophysiological factors that might underlie associations between fructose consumption and weight gain by studying twenty healthy adult volunteers involving magnetic resonance imaging (MRI) while being given a fructose or glucose drink in a blinded, random-order, crossover design, and examined relative changes in the hypothalamic regional blood flow after glucose or fructose ingestion. This is a very precise way to carry out experiments in humans. The scientists also examined function and responses in the hypothalamus and other parts of the brain and hormone responses to fructose and glucose ingestion. In a series of exploratory analyses, consumption of fructose compared with glucose resulted in a distinct pattern of regional cerebral blood flow and a smaller increase in glucose and insulin. The consumption of glucose but not fructose reduced cerebral blood flow and activity in specific brain regions that regulate appetite and reward processing. The results of the study show that consumption of glucose, but not fructose, produced increased ratings of satiety and fullness. In the whole-brain analyses, glucose intake produced a reduction in cerebral blood flow in the brain regions that act in concert to “read” the metabolic state of an individual and drive motivation and reward. Fructose ingestion increased cerebral blood flow in the hippocampus, the part of the brain that plays an important role in memory function, but also influences emotional responses to food intake leading to increased appetite and food intake.

In the NIH-American Association of Retired Persons (AARP) Diet and Health Study [16], of all the investigated sugars, fructose, and added fructose were more often associated with an increased risk of all-cause cancer and CVD mortality. Fructose is a potent reducing agent and can produce Advanced Glycation End

Products (AGES), which are involved in type 2 diabetes and may be involved in the development and progression of cancer and CVD.

9. How Fructose turns into Fat and Obesity

Fructose and other caloric sweeteners have negative metabolic effects, such as dyslipidemia with decreased low-density LDL particle size—that is, small LDL particles. These small, dense LDL particles have been associated with increasing the risk of heart disease and increasing the risk of type 2 diabetes. Consumption of even moderate amounts of fructose results in smaller LDL particle size and increased insulin resistance in healthy young men, as do high amounts of omega-6 fatty acids. When consumed in moderate amounts by healthy young adults, fructose, but not sucrose or glucose in sugar-sweetened beverages (SSBs), increases fatty acid synthesis and decreases fatty acid b-oxidation, which means that fructose turns into fat and causes obesity. Increased fatty acid synthesis occurs even after consumption of moderate amounts of fructose in SSBs, such as 6.7% of total energy intake, showing that even small amounts of free fructose that are lower than the average daily consumption in the US (which is 10% of total calories), when consumed daily during 3 weeks added to SSBs, have distinct effects on the synthesis of fatty acids in healthy young men, when compared with SSBs containing sucrose or glucose [9,17]. Furthermore, this effect is completely abolished when sucrose instead of fructose is added to SSBs, providing the same amount as fructose (40 g). This is a very important study showing the deleterious effects of fructose in healthy young men, providing further evidence that fructose containing SSBs are harmful to health. Drinking SSBs has been shown, mostly in American populations, to increase incidence of type 2 diabetes. Similar results have been shown in the European study by the Inter Act Consortium [18]. Their study also showed the association between increased incidence of type 2 diabetes and high consumption of SSBs (336g, which is equal to 12 ounces/day). Despite being calorically equivalent, that is contribute the same amount of energy, fructose and glucose are metabolically distinct; that is, they affect human metabolism differently. Fructose increases food-seeking behavior and increases food intake, while only weakly stimulates the production of insulin and decreases the circulation of hormones that lead to satiety. In other words, fructose makes you eat more because it does not allow the hormones that tell your brain “enough”—you do not need to eat any more. Prevention of long-term weight gain through dietary changes such as limiting consumption of SSBs is more important than short-term weight loss in reducing the prevalence of obesity in the population.

Once an individual becomes obese, it is difficult to lose weight and even more difficult to keep it off. Body weight is clearly far from being entirely within an individual’s control. Genetic predispositions, and the development of food environments that facilitate overeating, and built environments requiring

minimal energy expenditure may help explain the increase in obesity in Western Societies, and its expansion to the rest of the world that accepts Western processed foods, environment and overall culture that is so very different from the foods and environment that our genes were programmed to respond to during human evolution. Food technology bears a lot of responsibility for the current state of affairs of processed foods and drinks that are injurious and do not promote health.

10. Obesity and Its Impact on COVID-19

In 2020 the US faced two major epidemics, obesity and COVID-19. Among those admitted to hospitals and died the majority of the people were over the age of 65. The most vulnerable were obese and/or diabetic. African Americans, Hispanics, Native Americans, and Alaskan Natives were in the majority of patients. These populations have the highest number of obese individuals, and have very poor diets lacking in fresh fruits and vegetables, but high in ultra-processed foods that are high in omega-6 fatty acids. They also have a low socioeconomic status. We already know that obesity is an inflammatory state, which is enhanced by the high amounts of omega-6 fatty acids in the diet. About 80% of African Americans and 50% of Hispanics are fast metabolizers of the omega-6 fatty acids and as such have higher amounts of the long-chain omega-6 fatty acids, while they are deficient in omega-3 fatty acids. In other words, they are in a high inflammatory state in which SARS-COV2 can replicate itself and lead to a cytokine storm [19] affecting the lungs, heart, liver, and brain. The presence of obesity in the majority of the US population is the most important factor in the large number of deaths due to COVID-19, more so than any other developed country.

11. The Role of the Food Industry

The Institute of Food Technology (IFT) was established in 1939 but did not come into full force until 1942 and expanded after World War II ended in 1944. During the war, the chemical industry developed all kinds of technology that was later adopted for food processing by the IFT. The emphasis was on calories and taste rather than health. Food that could be made cheaply (mostly from corn) had a long shelf life and provided calories was what the IFT and industry promoted. The result was a food supply that could feed the post-war populations, who suffered hunger and true famine in Europe during the war and needed calories. There was enormous production of vegetable oils from corn, sunflower, safflower, soybean, and cottonseed oils that were made into margarines as a substitute of butter and plain white bread that was made into toast and sandwiches, along with other highly processed foods made mostly from corn. There was enormous production of bakery products made with white flour, margarines, and sugar for snacking. Due to enormous marketing, all these awfully unhealthy products took over the US and the rest of the world.

No one thought of what they might do to health. In the meantime, the Department of Agriculture promoted the growth of corn wheat and other seeds for animal consumption in addition to human consumption. In fact, 40% of seeds went to animal feeds. By 1980 the US population was the fattest in the world followed by Canada and the UK, the countries that followed the US example of processed foods. In addition to obesity and diabetes, CVD and cancer followed, as well as increases in the rate of the aging process leading to sick elderly people despite increases in life expectancy. Smoking was found to cause lung cancer. However, the effects of a diet consisting mostly of processed food high in dairy and meat (high in omega-6 fatty acids from corn-fed animals) and high in vegetable oils high in omega-6 fatty acids was difficult to study. It was not simply one isolated factor such as smoking. The proponents of the lipid hypothesis made the situation more difficult, because they put the emphasis on saturated fat and cholesterol, and ignored the fact that the processed food, both meals and snacks, were high in sugar, salt, trans fat, omega-6 fatty acids, and depleted in omega-3 fatty acids (25% of the US population did not eat any fish), antioxidants, vitamins, and minerals were very low due to low intake of fruits and vegetables. This continues to date.

12. Policy Change Is Needed to Focus on Prevention of Obesity

The obesity epidemic continues in the United States and it seems unstoppable, costing more than USD 190 billion per year in healthcare expenditures [20]. NIH, the major Federal Agency for Research spent USD 900 million on obesity research, which is about the cost of bringing one drug to the market. The food industry is not particularly interested in supporting research into foods that will show that the current food supply contributes to obesity—it is not good for business, therefore the food industry supports the concept of eating less and exercising more, low-calorie snacks, and promoting the concept that all calories are the same. This approach suggested by the food industry has also been used as a mantra by the various programs to treat obesity, despite the fact that all these programs have failed in treating obesity and maintaining weight loss permanently. There are all kinds of books, some authored by scientists, others by journalists, others by persons reporting on their personal experiences. Some blame sugar, especially added sugar; others blame saturated fat (fat makes you fat); others blame foods that lead to insulin resistance as the main cause of obesity, and others want to change metabolism through various foods that could lead to a “fat burner” instead of a “sugar burner” as shown on public television, etc. In the meantime, no country or government in the world has been able to cure obesity, and industry continues to develop low-calorie foods based on their concept that all calories are the same and people need to lower their calorie intake to lose weight rather than eating less processed foods and maintaining a balanced omega-6/omega-3 ratio. Industry marketers have made

money on that, and they are not interested in any change or study. Obesity and its management is a big enterprise. As a result, the public health approach to obesity remains focused on advice that has changed little in the last century. For instance, the first recommendation in the 2015 Dietary Guidelines for Americans [21] is to “choose an appropriate calorie level to help achieve and maintain a healthy bodyweight”. In the middle of all this confusion, the food industry takes advantage to maintain the status quo by lobbying with its political influences against sensible regulations such as taxing sugary beverages and lowering omega-6 fatty acids in the food supply by changing oils high in omega-6 fatty acids such as corn, sunflower, safflower, cottonseed, and soybean. The time has come to put public health over special interests and politics as usual.

So far, I have described what is going on in terms of the continuous increase in the number of people that become obese. The distressing part is that obesity now occurs more and more at younger ages, and there is scientific evidence that obese adolescents have deficits in executive function. Furthermore, new research over the last 10 years clearly shows that the quality of fat in the US diet is characterized by high amounts of omega-6 fatty acids from vegetable oils and their inclusion in processed foods and an absolute and relative decrease or deficiency in omega-3 fatty acids. As mentioned earlier, these two families of fatty acids are physiologically and metabolically distinct and have opposing properties. Their balance is important for normal growth and development, and in the prevention of chronic diseases, including obesity. It is unacceptable from the scientific point of view that the FDA continues to use the term polyunsaturated fatty acids or PUFA on the food panel label and does not distinguish between omega-6 and omega-3 fatty acids. Furthermore, the new label for nutritional information includes added sugars; the fatty acids have been ignored. Certainly, a new approach is needed for both research and regulation to improve public health.

Among the harmful components of the food supply, the omega-6 fatty acids in current high amounts in the food supply need to be decreased, along with added sugars, especially fructose, and refined grains, all of which contribute to obesity and come from corn and wheat. New national policies are needed that shift away from low-quality commodities such as corn and wheat, and instead encourage production of high-quality proteins, fruits and vegetables, grains, legumes, nuts, fish, olive oil, or other monounsaturated oils such as oil from avocados, hazelnuts, or macadamia nuts and other whole foods, and lean meats, including meats from grass-fed animals. Today the meat of chickens contains a much higher amount of fat in comparison to 50 years ago and so does meat from pigs, sheep, and cattle.

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BOX 1

Two thousand five hundred years ago, Hippocrates cautioned that sudden death is more common in those who are naturally fat than lean. Obesity treatments date as far back as Hippocrates, who recommended lifestyle changes to obese patients.

BOX 2

BMI provides the most useful population-level measurements of overweight and obesity, and many large population studies across many continents have shown its utility as an estimate of risk for chronic diseases such as type 2 diabetes, CVD, and high blood pressure.

BOX 3

Current Western diets are poor-quality diets that cause predisposition to all of the major chronic diseases: obesity, diabetes, cardiovascular disease (CVD), and cancer, and increase the rate of the aging process.

BOX 4

The US Preventive Services Task Force recommends referral of all obese adults to intensive, multicomponent interventions, including behavioral interventions, drug treatment, and surgical weight-loss procedures.

BOX 5

As the data from the CDC show, we have now reached a tipping point beyond which technological advances may no longer compensate. Throughout the United States life expectancy was lowest in areas (states or counties) where obesity was highest.

BOX 6

Modern medical care may prevent premature death among adults who develop obesity at age 45 years, diabetes at 55 years, and heart disease at 65 years. However, today obesity begins at a much earlier age than in the last century (20th Century) and this downward trend in longevity will almost certainly accelerate as the current generation of children with higher body weights reaches adulthood. Already diabetes type 2 occurs in early adolescence.

BOX 7

This insistence on the part of the food industry to continue to develop foods and beverages high in fructose and omega-6 fatty acids, both of which have been shown to increase body weight, fatty liver, and type 2 diabetes, is inexcusable.

BOX 8

Expansion of fat mass characterized by adipocyte enlargement fuels the infiltration

of macrophages into the adipose tissue, instigating the production of cytokines (IL-1b and IL-18) that contribute to the development of insulin resistance.

BOX 9

Experimental studies in animals have suggested that omega-6 fatty acids and omega-3 fatty acids have different and opposing effects on body-fat gain through mechanisms of white fat cell formation (adipogenesis) (omega-6) and decrease proliferation (omega-3).

BOX 10

Omega-6 fatty acids prevent the formation of brown adipose tissue, which is associated with energy expenditure, overall lipid homeostasis, brain-gut adipose tissue axis, and most importantly omega-6 fatty acids increase systemic inflammation. Diets high in omega-6 fatty acids are proinflammatory; and inflammation is at the base of all chronic diseases, including obesity and its comorbidities.

BOX 11

Obesity is a complex condition that involves the dysregulation of several organ systems and molecular pathways, including adipose tissue, liver, pancreas, gastrointestinal (GI) tract, the microbiome, the central nervous system (CNS) (various parts of the brain that deal with emotion, cognition, memory, etc.) and of course, genetics.

The omega-6 fatty acids can be thought of as agents of promoting obesity because they lead to proliferation of white fat cells which store energy in the form of triglycerides, whereas the omega-3 fatty acids promote brown fat cells that dissipate energy and increase energy expenditure by producing heat.

BOX 12

In animal experiments during the perinatal period, where high amounts of omega-6 fatty acids were part of their diet, similar to Western diets, increases in percentage of body fat occurred across generations, which is consistent with the fact that in humans, overweight and obesity have steadily increased in the last decades and appear earlier in life.

BOX 13

In human studies the level of ARA in adipose tissue is associated with BMI and overweight status of children. A high omega-6/omega-3 ratio in the red blood cell membrane phospholipids (a biomarker of omega-6 and omega-3 levels) of the umbilical cord was associated with high subscapular skin-fold thickness (a measure of fatness) at 3 years of age. It appears that the fetus is programmed in utero to

become a fat child when the mother's diet is high in omega-6 fatty acids.

BOX 14

High-fat diets rich in omega-6 fatty acids, as it is today in the US and other Western diets, increase obesity, type 2 diabetes and resistance to leptin, a hormone that is high in obese individuals who are leptin resistant.

BOX 15

The study showed that the higher the ARA, the higher the risk for weight gain while the higher the omega-3s the lower the risk for weight gain. Then the scientists looked at the omega-6/omega-3 ratio. They found that the higher the ratio, the higher the risk for weight gain.

BOX 16

The reason this study is very important is because it is one of the very few studies where actual levels of both omega-6 and omega-3 fatty acids were measured accurately in the red blood cell membrane phospholipids that reflected both the dietary intake of omega-6 and omega-3s and endogenous production; that is, whatever was produced by the body of these women which is based on genetics.

BOX 17

Many epidemiological studies and clinical intervention trials have produced conflicting results on the relationship of omega-6 and omega-3 fatty acids and weight gain or obesity due to the fact that the scientists only measure or take a history of dietary intake and many of them fail to measure both omega-6 and omega-3 fatty acids in the blood, especially at the beginning of the trials.

BOX18

NIH must develop precise protocols for randomized clinical trials to accurately evaluate the relationship between genetic predisposition and dietary factors that increase susceptibility to overweight and obesity. It should be part of the Precision Medicine Initiative, precision nutrition.

BOX 19

We do not need any more association studies. Instead we need human clinical intervention studies to define the environmental factors and dietary factors that lead to overweight or obesity through the establishment of a precision network in centers for genetics nutrition and fitness for health.

BOX 20

A balanced ratio in the fat-1 mouse is consistent with our results from the study on

the diet of Crete and the Greek egg, which under natural conditions where hens are free to move around to fetch their own food, produce eggs that are balanced in the omega-6/omega-3 ratio. In fact, the amount of omega-3s in one Greek egg is equal to the amount of DHA in the mother's breast milk at one month of age.

BOX 21

However, like all processed food in the US, baby foods continue to be high in omega-6 fatty acids, and until 10 years ago were also high in trans fatty acids. In fact, many of the vitamin supplements still contain hydrogenated soybean oil.

BOX 22

Contrary to the conventional perspective, research has shown that food affects hunger hormones and gene expression in ways that cannot be explained by consideration of caloric balance alone.

BOX 23

A calorie of fructose is not the same as a calorie of glucose when it comes to appetite control. In animal experiments in the brain, fructose injected into the ventricles of the animal provokes feeding, whereas glucose decreases food intake because fructose and glucose have different effects on the hypothalamus (part of the brain) in terms of signaling pathways.

BOX 24

Increases in fructose intake have been associated with the increasing prevalence of obesity, and high fructose diets sugar-sweetened beverages (SSBs) and processed food promote weight gain and insulin resistance in both animal models and human beings due to the high amount of added sugars coming mostly from high fructose corn syrup. When you eat processed food or drink beverages high in fructose, there is a much smaller increase in hormones that cut your appetite (satiety hormones) compared to glucose intake.

BOX 25

The results of the study show that consumption of glucose, but not fructose, produced increased ratings of satiety and fullness.

BOX 26

Fructose ingestion increased cerebral blood flow in the hippocampus, the part of the brain that plays an important role in memory function, but also influences emotional responses to food intake leading to increased appetite and food intake.

BOX 27

In the NIH-American Association of Retired Persons (AARP) Diet and Health Study, of all the investigated sugars, fructose, and added fructose were more often associated with an increased risk of all-cause cancer and CVD mortality. Fructose is a potent reducing agent and can produce Advanced Glycation End Products (AGES), which are involved in type 2 diabetes and may be involved in the development and progression of cancer and CVD.

BOX 28

Fructose and other caloric sweeteners have negative metabolic effects, such as dyslipidemia with decreased low-density LDL particle size—that is, small LDL particles. These small, dense LDL particles have been associated with increasing the risk of heart disease and increasing the risk of type 2 diabetes.

BOX 29

Consumption of even moderate amounts of fructose result in smaller LDL particle size and increased insulin resistance in healthy young men, as do high amounts of omega-6 fatty acids.

BOX 30

When consumed in moderate amounts by healthy young adults, fructose, but not sucrose or glucose in sugar-sweetened beverages (SSBs) increases fatty acid synthesis and decreases fatty acid b-oxidation, which means that fructose turns into fat and obesity.

BOX 31

Drinking SSBs has been shown, mostly in American populations, to increase type 2 diabetes incidence. Similar results have been shown in the European study by the Inter Act Consortium.

BOX 32

Despite being calorically equivalent, that is, contributing the same amount of energy, fructose and glucose are metabolically distinct; that is, they affect human metabolism differently. Fructose increases food-seeking behavior and increases food intake, while it only weakly stimulates the production of insulin and decreases the circulation of hormones that lead to satiety.

BOX 33

Prevention of long-term weight gain through dietary changes such as limiting consumption of SSBs is more important than short-term weight loss in reducing the

prevalence of obesity in the population.

BOX 34

Once an individual becomes obese, it is difficult to lose weight and even more difficult to keep it off. Body weight is clearly far from being entirely within an individual's control. Genetic predispositions, the development of food environments that facilitate overeating, and built environments requiring minimal energy expenditure may help explain the increase in obesity in Western Societies, and its expansion to the rest of the world that accepts Western processed foods, environment, and overall culture that is so very different from the foods and environment that our genes were programmed to respond to during human evolution.

BOX 35

Food technology bears a lot of responsibility for the current state of affairs of processed foods and drinks that are injurious and do not promote health.

BOX 36

By 1980 the US population was the fattest in the world followed by Canada and the UK, the countries that followed the US example of processed foods. In addition to obesity and diabetes, CVD and cancer followed, as well as increases in the rate of the aging process, leading to sick elderly people despite increases in life expectancy.

BOX 37

The food industry is not particularly interested in supporting research on foods that contribute to obesity—it is not good for business, therefore the food industry supports the concept of eating less and exercising more, low-calorie snacks, and promoting the concept that all calories are the same.

BOX 38

For instance, the first recommendation in the newly released 2016 Dietary Guidelines for Americans is to “choose an appropriate calorie level to help achieve and maintain a healthy bodyweight”. In the middle of all this confusion, the food industry takes advantage to maintain the status quo by lobbying with its political influences against sensible regulations such as taxing sugary beverages. The time has come to put public health over special interests and politics as usual.

BOX 39

Their balance is important for normal growth and development and in the prevention of chronic diseases, including obesity.

BOX 40

It is unacceptable from a scientific point of view that the FDA continues to use the term polyunsaturated fatty acids or PUFA on the food panel label and does not distinguish between omega-6 and omega-3 fatty acids. Furthermore, the new label for nutritional information includes added sugars; the fatty acids have been ignored. Certainly, a new approach is needed for both research and regulation to improve public health.

BOX 41

Among the harmful components of the food supply, the omega-6 fatty acids in current high amounts in the food supply need to be decreased along with added sugars, especially fructose, and refined grains, all of which contribute to obesity and come from corn and wheat.

Chapter 9. Healthy Aging

1. Trends in Life Expectancy and Late-Life Survival
2. So What Is Healthy Aging?
3. Geroscience: The Science of Aging
4. Caloric Restriction (CR)
5. Time-Restricting Feeding (TRF)
6. Intermittent and Periodic Fasting (IF)
7. Fasting-Mimicking Diets (FMD)
8. Can You Delay the Aging Process?

Life expectancies in developed countries are projected to continue to increase, with women's life expectancy potentially surpassing 90 years old in South Korea by 2030 according to a study published in the Lancet [1]. The study predicts life expectancy is likely to be highest in:

I. For Women

- South Korea (90.8 years old);
- France (88.6 years old), and;
- Japan (88.4 years old).

II. For Men

- South Korea (84.1 years old);
- Australia (84.0 years old), and;
- Switzerland (84.0 years old).

Out of 35 developed nations, South Korea is expected to have the largest increase in life expectancy, with females surpassing 90 years by 2030, whereas UK life expectancy is estimated to reach 85.3 for women and 82.5 for men, and in the US 83.3 for women and 79.5 for men.

As recently as the turn of the century, many researchers believed that life expectancy would never surpass 90 years. The current predictions of increasing life span highlight public health and healthcare successes. These successes point to the need to both strengthen the health and social care systems and establish alternative models of care, such as technology-assisted home care and food and nutrition delivery systems. Furthermore, policies will have to be in place to enhance healthy aging, increase investment in health and social care, and possibly changes to retirement age. Unfortunately, in the US life expectancy is already lower than most other high-income countries, and is expected to potentially fall further behind in 2030 as a result of the large inequalities, absence of universal health insurance, having the highest homicide rate, obesity (BMI), and higher death rates for children and mothers of all high-income countries.

Human life expectancy increased greatly since the 19th century. Data show an ongoing reduction in old-age mortality and a rise of the maximum age at death, which may gradually extend human longevity. Studies in various animal species show that life span is flexible and can be increased by genetic or pharmaceutical intervention. These types of studies led to suggestions that longevity may not be subject to strict, species-specific genetic constraints.

In 2016 Dong et al. [2] analyzed global demographic data and showed that improvements in survival with age tend to decline after age 100, and that the age of death of the world's oldest person has not increased since the 1990s. Therefore, Dong et al. concluded that the maximum life span of humans is fixed and subject to natural constraints.

Maximum life span is, in contrast to average lifespan, generally assumed to be a stable characteristic of a species [3]. For humans, the maximum reported age at death is generally set at 122 years, the age at death of Jeanne Calment of France, still the oldest documented human person who ever lived.

1. Trends in Life Expectancy and Late-Life Survival

Life expectancy in France has increased over the course of the 20th and early 21st centuries. Survival has increased since 1900, but the rate of increase appears to be slower for ages over 100. Gains in survival peak around 100 years of age and then rapidly decline. The age with most rapid gains has increased over the century, but its rise has been slowing and it appears to have reached a plateau.

In a recent study by Barbi et al. [4] the authors estimated hazard rates from data on all inhabitants of Italy aged 105 and older between 2009 and 2015 (born 1896–1910), a total of 3836 documented cases. They observed level hazard curves, which were essentially constant beyond age 105. These data provide the best evidence to date for the existence of extreme-age mortality plateau in humans. Are there limits to the rise in risks of death by age?

After 1990, as data improved, studies began to build a case for genuine deceleration of mortality rates from about age 80 onward, in contrast to the clearly exponential curves observed in younger adults. When a mortality curve levels out, it is said to reach a plateau. However, in this study the increasing number of exceptionally long-lived people and the fact that their mortality beyond 105 years is seen to be declining across cohorts—lowering the mortality plateau or postponing the age at which it appears—strongly suggest that longevity is continuing to increase over time and that a limit if any, has not been reached. Enhanced care for the extremely old may help to lesser increases in mortality. Evolutionary theories of senescence, including the mutation accumulation theory and age-dependent effects of genetic load, also offer promising ingredients toward a joint explanation of both the phases of exponential increase and extreme-age plateaus.

2. So What Is Healthy Aging?

Studies now define that healthy aging is more than the absence of disease or functional impairment. Several recent studies have shown that multiple genetic, lifestyle and environmental factors (nutrition), including cognitive and physical capacity, as well as active participation in social activities, including exercise, affect healthy aging. Studies in which successful aging is based on self-reporting successful aging (subjective measurements of successful aging) tend to yield higher percentages compared to studies based on objective measures of successful aging, which suggests that while most older people may not meet the objective definitions of successful aging, they may nonetheless think of themselves as having aged successfully. This

of course raises the question: who should define successful aging? Some people think that “successful aging” is living even if you have an illness and diseases: you bypass that, and you live. Witness the statement how many celebrities diagnosed with cancer state “I will fight” or “win the battle”. Physical function (as measured by walking, speed, strength, etc.) and living independently (as measured by social engagement) are two aging process markers of particular practical significance.

Thus worldwide today, for the first time in history, most people can expect to live into their 70s and beyond. In less developed countries, this longer life span is largely the result of reduced mortality at younger ages due to the control of infections and improvements in sanitation and malnutrition. In high-income countries, continuing increases in longevity are now mainly due to rising life expectancy among those who are 60 years or older. When combined with falling fertility rates, these increases in life expectancy are leading to the rapid aging of populations around the world.

Longer life is an incredibly valuable resource. It provides the opportunity to reconsider not only what older age might be, but also how our whole lives might unfold. For example, in high-income countries, there is evidence that many people are rethinking rigid notions of what older age might consist of and are looking to spend these extra years in innovative ways, such as a career, continuing education, or pursuing a neglected passion of study or work. Additionally, as young people start to expect longer lives, they too might plan their lives differently. Yet, the extent of the opportunities that arise from the extra years of life will be very heavily dependent on one key factor: health. Although increasing longevity is often assumed to be accompanied by an extended period of good health, little evidence exists that older people today have better health than their parents did at the same age (Table 9.1).

Table 9.1. In the World Report on Aging and Health, the following 10 conditions have been identified as decreasing life expectancy.

-
- Ischemic heart disease;
 - Stroke;
 - Chronic obstructive pulmonary disease;
 - Cancer;
 - Diabetes mellitus;
 - Hypertension;
 - Heart disease;
 - Cirrhosis of the liver;
 - Stomach cancer;
 - Colon and;
 - Rectum cancer.
-

Source: Adapted from: [5].

As you can see, practically all ten causes are associated and can be influenced by nutrition and physical activity, in addition to genetic predisposition and socioeconomic factors. Healthy aging is defined by the World Report on Aging and Health as the process of developing and maintaining the functional ability

that enables well-being in older age. Healthy aging thus reflects the ongoing interaction between individuals and in the environment in which they live. Nutrition is an environmental factor of major importance. There is little consensus about what healthy aging might be, although research is also focusing on the absence of disease. For the past 50 years oxidative stress has been increasingly recognized as a contributing factor to aging and in the pathophysiology of the aging process. What is oxidative stress? Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products.

Lifespan = maximum age at death. Some of the factors that prolong lifespan include lifestyle-related activities such as studying and embracing new activities. Up to 25% of the variability in human lifespan has been estimated to be genetic [6]. The power of big data and genetics allows the comparison of the effect of different behaviors and diseases in terms of months and years of life lost or gained, and to distinguish between mere association and causal effect. The study by Joshi showed that longevity is partly determined by predisposition to common diseases and, to an even greater extent, by modifiable risk factors. Giving up smoking, educational attainment, openness to new experiences, and high-density lipoprotein (HDL) cholesterol levels are most positively genetically correlated with lifespan, while susceptibility to coronary artery disease (CAD), cigarettes smoked per day, lung cancer, insulin resistance, and body fat are most negatively correlated. The level of omega-3 fatty acids in the red blood cells of persons eating fish or taking fish oils, thus having higher amounts of EPA and DHA, are good mortality risk predictors. Higher levels increased life expectancy by almost five years [7].

From the end of the Civil War until the late 20th Century, lifespan increased rapidly in the United States, a tremendous public health triumph brought about by a more dependable food supply, improved sanitation, and advances in medical care. In 1850, life expectancy among Whites was 38 years for men and 40 years for women. By 1980, life expectancy had increased to 71 years for men and 78 years for women. The epidemic of obesity started in the late 1970s and at about the same time the trend of increased life expectancy began to slow down, leading some people to predict that life expectancy (how long one is expected to live) would decline in the United States by the mid-21st Century [8]. Preliminary data from the Centers for Diseases Control and Prevention provide new evidence in support of this prediction [9]. Age-adjusted death rates for the first 9 months of 2015 increased significantly compared with the same period in 2014. Thus, mortality rates increased in 1 year by 1% for heart disease, 1% for diabetes, 3% for chronic liver disease, 4% for stroke, and 19% for Alzheimer's disease, all of which are related to obesity [9]. These data are alarming and signal the need to more effectively manage obesity and other chronic diseases related to obesity and diet.

We want to maximize the number of years that we live free of chronic diseases, cancer, and cognitive decline. Biological age is defined by how rapidly a person's body is aging, regardless of their chronological age, which is the age in years. Scientists do not agree whether "biological age" can be measured. Despite some company claims, there is no way that you can take a sample of someone's skin or blood and tell them what their biological age is. Aging is the greatest risk factor for nearly every major cause of mortality in developed nations.

3. Geroscience: The Science of Aging

The major focus of biomedical research has traditionally been the pathogenesis and treatment of individual diseases, particularly those with substantial effects on morbidity and mortality. This disease-specific focus has substantially had a profound effect on medical care and human health. Many new treatments have been developed that are helping people live longer today than ever before. However, despite notable advances in management, we have been largely unsuccessful at postponing ameliorating or preventing the accumulation of morbidities during aging. As a consequence, people are living longer but often suffer from multiple diseases or disabilities caused by aging. The big question is, can we delay aging or the aging process?

Geroscience (the science of aging) has demonstrated that biological aging is modifiable and has provided approaches and ways to enhance healthy longevity. Biological age is defined by how rapidly a person's body is aging, regardless of his or her chronological age. Telomere length is a marker of biological aging that may provide a cellular memory of exposures to oxidative stress and inflammation. Telomere length at birth has been related to life expectancy. Martens et al. from Belgium assessed the association of prenatal exposure to particulate matter (PM) with newborn telomere length as reflected by cord blood and placental telomere length, in a prospective birth control study [10]. Air pollution was determined by maternal exposure during pregnancy to particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$. The study showed that mothers who were exposed to higher levels of PM $2.5 \mu\text{m}$ gave birth to newborns with a shorter telomere length. The telomere loss, leading to shorter telomeres in newborns by prenatal air pollution exposure, shows less buffer for postnatal influences of factors decreasing telomere length during life. Of interest is the fact that in animal studies the loss of telomere length can be prevented by supplementing the animal's diet with EPA and DHA. Of course, it is well known from both animal and human studies that both EPA and DHA have a positive effect. Therefore, improvements in air quality and dietary EPA and DHA supplementation may promote longevity from birth onwards. The shorter telomeres occurred during mid pregnancy.

More than 46 million people over the age of 65 years were living in the US in 2014 and more than 70 million are predicted by 2060. Among health risks, poor diet quality is very prominent, followed by physical activity levels, which are quite low. Although time spent on leisure activities increases with age, most leisure time among older adults is spent watching television, so old age is characterized by poor diet quality and a sedentary lifestyle. Yet all national and global studies show that good nutrition is the most important factor for health and the avoidance of chronic diseases. Everyone agrees healthy aging is what we need to focus on, which means “living a long life in good health”. In 2013 the average American life expectancy was 77 years, but the average American “healthy life expectancy” was estimated at only 67 years. Of course, healthy aging begins from the moment of conception. The mother’s diet during pregnancy and even before pregnancy influences both survival and the development of chronic diseases later on in life. A poor maternal diet, or famine as occurred in Holland during World War II, led to increased rates of obesity and chronic diseases in their children when they reached adulthood. Studies in The Gambia also show that maternal diet can influence the methylation of genes in the newborn. DNA methylation and inflammation and oxidative stress influence the expression of genes, which lead to aging-related metabolic diseases.

A number of studies differentiate between chronological age—the number of years one has lived—and biological age, which is the age that you look and at which your body functions. Some people look younger than their chronological age. Phenotypic change (the way you look) over time occurs very quickly early in life, as newborns grow into young children, then stabilizes for a while until it accelerates again. How this point of acceleration occurs is very different for different people. There are four areas of the body that change with age:

- (1) Changes in body composition;
- (2) Energy imbalance;
- (3) Homeostatic dysregulation;
- (4) Aging of the brain.

Homeostatic dysregulation of inflammation can have devastating results and nutrition plays an important role. There is very good evidence that the impact of nutrition is very potent. Inflammatory cytokines such as interleukin (IL)-6 are influenced by both fat and protein intake. The omega-3 fatty acids from fish and/or fish oil are the most potent anti-inflammatory agents, whereas diets high in saturated fat double the levels of IL-6 within 2 h after a meal. Furthermore, a higher protein intake is required to maintain muscle mass stability in individuals with higher IL-6 levels. Current Western American diets are notoriously proinflammatory diets due to high amounts of omega-6 fatty acids from vegetable oils and high saturated fats, and are low in fruits and vegetables, and hence low in antioxidants. Current diets are not healthy for anyone regardless of age. Obesity is a much stronger predictor

of disease at younger ages. Healthy nutrition plays a very important role over the lifespan in the development of cardiovascular disease, osteoporosis, sarcopenia, lower grip strength, loss of teeth, gastrointestinal (GI) tract, and microbiota, which are all nutrition dependent. A healthy diet benefits all these systems and there is no need for the term “heart healthy diet”, etc. The microbiome can be modified by diet. For example, plant-based vs. animal-based diets in humans have been shown to affect microbial gene expression and activity differently. The relationship has a two-way nature; that is, the microbiome is not only impacted by the diet, but it can also generate new metabolites from dietary components, i.e., butyrate from fiber. Many of the bacterial metabolites have been associated with health effects, but bacteria can also produce metabolites detrimental to health (see the chapter on microbiome).

Studies on brain aging and neurodegeneration, including delaying the development of diseases such as Parkinson’s and Alzheimer’s, show that anti-inflammatory diets, such as the Mediterranean diet, decrease the rate of the aging process in the brain [11] due to a balanced omega-6/omega-3 ratio and the high amounts of antioxidants. Progress in the understanding of genetic associations, particularly via genome-wide association studies, has shown a substantial contribution of genes to human aging and age-related diseases [12]. Recent studies showed that human genes are programmed for a lifespan of 120 years [4]. Longevity depends on our genes, but 70% of longevity needs to be conquered every day through a healthy diet and exercise.

As we age, our brains change and undergo a slow process of atrophy, which decreases the communication between various brain regions leading to declining memory and various aspects of cognitive functions. However, there are differences among people in this process. What is remarkable is a rare group of older individuals called “superagers” have been shown to learn and recall novel information as well as a 25-year-old. Investigators at Mass General Hospital (MGH) have now identified the brain activity that underlies superagers’ superior memory [13]. They have images of the function of superagers’ brains as they actively learn and remember new information. The scientists found, using fMRI, that the structure of superagers’ brains and the connectivity of their neural networks more closely resemble the brains of young adults. Superagers had avoided the brain atrophy typically seen in older adults.

During aging, neural differentiation diminishes, and the group of neurons that once responded primarily to faces now activates for other images. The brain now has difficulty creating unique neural activation patterns for different types of images, which means it is making less distinctive mental representations of what the person is seeing. That is one reason older individuals have trouble remembering when they may have seen a television show, read an article, or eaten a specific meal. A major

question is whether superagers' brains were always more efficient than their peers, or whether over time they developed mechanisms to compensate for the decline of the aging brain. Previous studies have shown that training can increase the selectivity of brain regions, which may be a potential intervention to delay or prevent the decline in neural differentiation in normal aging adults and make their brains more like the superagers'.

Aging does not begin at 50, 70, or 90 years; rather, it starts in utero. Therefore, thinking about healthy aging requires thinking about the lifespan from the very beginning of conception. Moreover, people age differently, some faster than others. When thinking about interventions it is important to keep in mind the socioeconomic context of aging and define certain aspects that are simple and easy to comprehend. For example, maintaining a certain walking gait is something that everyone can understand (e.g., being able to walk 1 mile in 15 min). Most people think of the elderly as adults with gray hair and wrinkles, but they are not. If someone's goal is for his or her 90 to be the new 70 then the traditional biomarkers of successful aging are the right targets to focus on. Of course, it takes a lot of work to be 70 at 90, and many people do not want to work that hard. Instead of a doctor telling an elderly person "This is how you should be at 90 or 85," it is really "What you think you should be at 90 or 85." Goal setting is very important and goal attainments are even more important. A healthy diet such as the Omega Diet based on the diet of Crete is associated with healthy aging [14]. Prior to 1960, the people in Crete lived the longest, had the lowest rate of CVD and cancer, and the healthiest diet (see the chapter on "The Diet of Crete: The Healthiest Diet"). The grandparents were highly respected in the community and gave advice to the younger ones. They maintained their social activities, danced at weddings of their grandchildren, and walked everywhere for their activities, such as shopping, visiting family, etc.

People and their doctors are looking for biomarkers for healthy aging. There are a number of ongoing studies. An early determinant of an inappropriate aging process is inflammation, which is associated with an inflammatory diet (high omega-6/omega-3 ratio), obesity and its comorbidities. Improving diet and weight loss both lower inflammation and restore health. However, personalized markers based on individuals' perceptions of their own healthy aging must always be taken into consideration. One of the most important markers of successful aging is being proud of how old you are.

4. Caloric Restriction (CR)

Caloric Restriction (CR): defined as energy intake reduced below ad libitum (AL) intake, increases life span in many animal models. This area of research is about 100 years old. Dr. Rous [15] discovered that limiting food intake in animals (rodents) decreased cancer development. Later on, McCay [16] and his associates showed that

rats fed a limited amount of food lived much longer than their littermates who ate as much as they wanted. Today, a century later, the positive effect of caloric restriction on health span and lifespan has been shown in many model organisms including fruit flies, mice, and primates (monkeys) suggesting a strong evolutionary conservation of common mechanisms connecting food intake to longevity, bringing about metabolic changes in lowering metabolic rate and oxidative damage, improvements in cellular turnover, protein homeostasis, and improvements of age-related metabolic disorders that include central obesity, insulin resistance, dyslipidemia, and high blood pressure.

Ravussin et al. [17] carried out a study in humans aged 21–51 years that were not obese to determine the feasibility and safety of a caloric restriction diet and its effects on predictors of longevity, risk factors, and quality of life. The CR diet was a healthy diet that did not have any deficiencies in vitamins or essential minerals, and lasted for two years. A total of 218 persons were randomized and the intervention group was designed to achieve 25% CR. The control group was on an ad libitum diet. The investigators evaluated changes from baselines of resting metabolic rate and core temperature, thyroid function (plasma triiodothyronine (T_3)), and tumor necrosis factor α ($TNF\alpha$) (that increases inflammation), and other physiological and psychological measures. At the end of 2 years the CR group achieved $11.7 \pm 0.7\%$ CR and maintained $10.4 \pm 0.4\%$ weight loss, whereas weight change in AL was negative. Of interest is the fact that resting metabolic rate (RMR) decreased significantly more in CR than AL at 12 months but not at 24 months, T_3 decreased more in CR at 12 and 24 months, whereas $TNF\alpha$ decreased significantly more on CR at 24 months. CR had larger decreases in cardiometabolic risk factors, and in daily energy expenditure adjusted for weight change, without adverse effects on quality of life. This study clearly showed that in non-obese subjects CR leads to improvements of human survival and disease risk factors and suggests potential benefits for aging-related outcomes.

Other studies have focused on the effect of CR on mood, quality of life, sleep and sexual function in healthy non-obese adults. Again, studies showed that CR had many positive effects and no negative effects in quality of life. So, the conclusion should be to eat less. Cut the number of calories by 25% and make sure that such a diet is not deficient in essential nutrients. It will be necessary to consult your physician along with a dietitian who will define a CR diet without deficiencies for you. This is a type of personalized nutrition.

Caloric restriction can be accomplished without provoking malnutrition by chronically reducing energy intake by 15–40% from the usual caloric intake for that individual, while maintaining adequate intake of vitamins and minerals. In mice this approach can extend life span by 50%. Traditionally, diet composition and genetic background have been thought to have a marginal impact on life-span extension brought about by caloric restriction. In humans short-term trials, such

as the multicenter CALERIE (comprehensive assessment of long-term effects of reducing intake of energy) study, the observational study of centenarians residing in Okinawa, who have been exposed to CR for most of their lives, and observations of the members of the CALORIE RESTRICTION SOCIETY (CRONies—Calorie Restriction with Optimal Nutrition) who self-impose CR have shown the occurrence of many of the same physiological, metabolic, and molecular benefits typically seen with long-lived animals on caloric restriction. These studies support the fact that CR preserves more youthful functions by improving several markers of health, including lower body weight, metabolic rate, oxidative damage, lower incidence of CVD and cancer, and decreased activity of the insulin-Akt-FOXO signaling pathway. However, there is a lack of clinical data showing consistent effects of caloric restriction in older populations and lack of complete understanding of the age-specific effects of these interventions such as bone thinning (osteoporosis) and lack of reserve in fighting infections. For these reasons, researchers are looking for alternative feeding regimes that have the beneficial effects of Caloric Restriction by controlling feeding–fasting patterns with little or no reduction in caloric intake.

5. Time-Restricting Feeding (TRF)

TRF refers to daily limitations in the timing of food intake from 4 to 12 h without reduction in caloric intake. The results of TRF trials in humans appear to depend both on the distribution of meals during the day, and the duration of fasting. When food intake was limited to the middle of the day, there was a decrease in body weight or body fat, fasting glucose and insulin levels, insulin resistance, hyperlipidemia, and inflammation, it and produced mild caloric restriction and weight loss without counting calories. In another study, metabolic markers were improved in a group of people eating an isocaloric diet with a bigger breakfast and a smaller dinner. Patients with type 2 diabetes on a hypocaloric diet had better metabolic results by eating most of their daily allotment in the first half of the day, rather than dividing their food into six meals throughout the day, whereas restricting food intake to the late afternoon or evening, either had no effect or worsened glucose levels after eating, blood pressure, or lipid levels. Two studies found that a fasting period of more than 13 h resulted in lower risk of breast cancer recurrence than in the women who fasted less than 13 h. Overall, these studies show that both the amount of time spent eating during each day and the time at which food is eaten relative to circadian rhythm are critically important to the effects of diet on health and longevity [18,19].

6. Intermittent and Periodic Fasting (IF)

In this situation no or few calories are consumed for periods of time that range from one to several days followed by ad libitum feeding (eating as usual) on the rest of the days. From an evolutionary perspective, fasting is a natural phenomenon to

which both animals and humans were regularly exposed. Even today animals in the wild are exposed to periods of famine, since food is not available to them at all times. Humans have evolved over time when they had to hunt for their food, which was not available at all times. Therefore, periods of fasting were a natural phenomenon, whereas today food is easily available practically at all times. Several short-term clinical trials have shown that alternate-day fasting can deliver benefits similar to caloric restriction in terms of weight loss and cardiometabolic health, improved lipid profiles, lower blood pressure, and increase insulin sensitivity [20–22]. In cancer patients, fasting selectively protects normal cells, but not cancerous cells, against toxicity related to chemotherapy and fasting up to 5 days, followed by a normal diet appears to be a safe, feasible, and effective strategy in reducing common side effects associated with chemotherapy [23].

7. Fasting-Mimicking Diets (FMD)

To make fasting acceptable, Longo and his associates conceived a low-carbohydrate high fat diet that improves compliance by avoiding complete deprivation of food [24]. The diet is low in calories and provides for plant-based soups, herbal tea, energy bars, nut-based snacks and supplements to be gradually implemented in a 5-day cycle each month for 3 months [25]. The main goal of the FMD is to maintain low-circulating concentrations of IGF-1 insulin and glucose while increasing concentrations of IGF binding protein 1 and ketone bodies. The rejuvenating effects of FMD are created by increasing the number of progenitor stem cells. Despite the positive results in health span the FMD did not increase maximum longevity in mice, and when administered to very old animals it may have been detrimental.

Dietary intervention studies based on long periods of fasting are promising to tackle metabolic syndrome, CVD, cancer, and even neurodegenerative diseases. The intermittent absence of caloric intake appears to improve multiple risk factors and, in some cases, to reverse disease progression in mice and humans. However, because of its experimental nature, although promising, it should be conducted under the guidance of a health professional.

8. Can you Delay the Aging Process?

Aging is a universal process. In laboratory animals, scientists have been able to alter both the onset and progression of aging by restricting daily total caloric intake. These same studies have also shown redirections in age-related cancers, as well as other age-related phenotypes. However, these lab-tested longevity interventions are life-long interventions. It would be very hard to convince a human to eat 30–50% of fewer calories every day for the rest of their lives. Energy restriction in the mouse

model shows a connection between energy restriction and the maintenance of optimal brain function and resistance to aging and disease.

There are enormous differences in the elder population with respect to health and risks associated with malnutrition barriers to good nutrition (i.e., medications that interfere with appetite), variations in nutritional health, and problems among subpopulations (i.e., individuals who live in the county as opposed in assisted-living facilities or nursing homes).

The following diets have been extensively studied in older individuals:

- (1) The Mediterranean diet;
- (2) The Dietary Approaches to stop Hypertension DASH diet, and;
- (3) The Mediterranean-DASH intervention for Neurodegenerative Delay (MIND) diet.

All three diets have shown significant decreases in several adverse health outcomes, including CVD mortality, overall mortality, cancer, stroke, Parkinson's and Alzheimer's, and cognitive functioning. Actually, the DASH diet is similar to the diet of Crete, described in my book *The Omega Diet* [14]. Although the authors of the DASH diet did not acknowledge it, Dr. Michael DeBakey, then Editor of the *Journal of Vascular Surgery*, asked me to write a paper on the nutritional aspects of hypertension [26]. In that paper I constructed a table in which I pointed out the similarities between the Omega Diet and the DASH Diet. Just like the Omega Diet, the DASH diet had more omega-3s, less salt, and more fruits and vegetables than the controlled diet, which was the Western diet.

Older people must be carefully followed when on low-calorie diets or other special diets in which the types of foods are limited, because they might be at a point where they need the calories. Surveys in the US show that among older adults (71 and older) vegetable and fruit intakes are low, while added sugars and sodium are not as great a concern in older adults as in adolescents. Total grains and protein intakes are near recommended levels. A majority of men and women do not meet the estimated average requirements for calcium and vitamin D, and have low omega-3 fatty acids from fish or fish oils and excessive amounts of omega-6 fatty acids due to high consumption of vegetable oils. A high omega-6/omega-3 ratio of 16–20/1 instead of 2–1/1 contributes to the inflammatory effects of US and other Western diets.

All over the world there has been an increase in life expectancy; however, this increase in life expectancy has not been accompanied by an increase in healthy aging. This has resulted in an increase in chronic diseases, which is seen in both developed and developing countries. Yet scientists and physicians that specialize in the elderly and the factors that influence both the aging process and the rate have provided knowledge and understanding of the consequences and processes that underlie aging from many points of view, including clinical, social, mental, physical and biological viewpoints. The emphasis has been to improve the health of older

persons, but most importantly to design and test interventions in order to prevent or delay age-related diseases. Such studies include, in addition to socioeconomic status, energy, the quality of the environment, physical activity, genetics and diet, all of which are the most powerful determinants of health and longevity. Although environmental quality and genetics are not under our direct control, energy intake and food selection are. Proper nutrition influences health throughout the human life cycle from conception to death. Diet or nutrients sustain life and allow growth, repair, and reproduction. Adequate dietary intake and physical activity influence health and survival and delay the aging process or may prevent the occurrence or progression of chronic diseases.

Research has shown that manipulation of a nutritionally balanced diet by changing the food intake either by lowering total energy or caloric intake, or meal timing, can lead to a delay in the onset, development, or progression of disease in many animal models and some epidemiologic studies. Reduction in food intake over weeks or months in prolonged and periodic fasting cycles have been shown to be able to delay the onset of the disease or increase lifespan. However, chronic caloric restriction is detrimental to health in some animal models, whereas in human studies it leads into an anorexic state. Changes in meal size (caloric intake) or frequency of meals (by controlling the time of feeding and fasting) have been an important research area and have led to the decrease or improvement of many age-related diseases, such as cardiovascular disease, diabetes, cancer, and dementia. The answer to the question “Can we delay the Aging Process?” is yes, and eat less.

The risk of dementia increases with aging. The JAMA patient page suggests the following actions to reduce the risk of dementia in older age [27]. In order to possibly decrease the number of people with new dementia diagnosis, there are currently three main areas of focus in prevention of dementia: lifestyle habits, medical conditions, and mental and social well-being.

Lifestyle Habits

- Increase physical activity. Physical activity is a key factor for brain health. Regular exercise as simple as brisk walking for as little as 15 min a day protects brain structure and function.
- Eat healthily. A Mediterranean diet consisting of fish, olive oil, nonstarchy vegetables, and nuts has been related to lower risk of dementia.
- Get a good night’s sleep. Adequate and uninterrupted sleep helps the brain repair itself. Good sleep hygiene improves the function of brain cells.
- Do not smoke. Smoking damages brain cells and vessels.

Medical Conditions

- Treat heart problems. Whatever is bad for the heart is bad for the brain. Heart attacks and heart failure have close links with dementia. Treating heart problems may protect the brain.
- Control blood pressure and blood-sugar levels. High blood pressure and diabetes, especially in middle age, can damage the brain. Control of blood pressure and blood-glucose (sugar) levels in midlife can improve brain health and may lower the risk of dementia in older age.
- Protect the head. Head injury increases the chance of developing memory and thinking problems. Wearing helmets and/or avoiding behaviors that increase the risk of head injury can decrease the risk of dementia.
- Test hearing. Hearing loss is linked to dementia.

Mental and Social Well-being

- Stay involved, curious, interested, and willing to learn new things. Being an active learner keeps the brain engaged and has beneficial effects on memory and information processing.
- Stay socially engaged. Engagement in social activities including sports, cultural programs, and support groups has a positive effect on brain structure and function and is associated with a lower risk of dementia.

Dementia has several causes and develops over decades of life. Therefore, prevention should start as early as possible and be maintained across the life span.

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BOX 1

As recently as the turn of the century, many researchers believed that life expectancy would never surpass 90 years. The current predictions of increasing life span highlight public health and healthcare successes. These successes point to the need to both strengthen the health and social care systems and establish alternative models of care, such as technology-assisted home care and food and nutrition delivery systems.

BOX 2

Studies in various animal species show that life span is flexible and can be increased by genetic or pharmaceutical intervention. These types of studies led to suggestions that longevity may not be subject to strict, species specific genetic constraints.

BOX 3

Enhanced care for the extremely old may help to lessen increases in mortality. Evolutionary theories of senescence, including the mutation accumulation theory and age-dependent effects of genetic load, also offer promising ingredients toward a joint explanation of both the phases of exponential increase and extreme-age plateaus.

BOX 4

Studies now define that healthy aging is more than the absence of disease or functional impairment. Several recent studies have shown that multiple genetic, lifestyle, and environmental factors (nutrition), including cognitive and physical capacity, as well as active participation in social activities including exercise, affect healthy aging.

BOX 5

Physical function (as measured by walking, speed, strength, etc.) and living independently (as measured by social engagement) are two aging process markers of particular practical significance.

BOX 6

Healthy aging is defined by the World Report on Aging and Health as the process of developing and maintaining the functional ability that enables well-being in older age. Healthy aging thus reflects the ongoing interaction between individuals and in the environment in which they live.

BOX 7

Lifespan = maximum age at death. From the end of the Civil War until the late 20th Century, lifespan increased rapidly in the United States, a tremendous public health

triumph brought about by a more dependable food supply, improved sanitation, and advances in medical care.

BOX 8

The epidemic of obesity started in the late 1970s and at about the same time the trend of increased life expectancy began to slow down, leading some people to predict that life expectancy (how long one is expected to live) would decline in the United States by the mid-21st century. Preliminary data from the Centers for Diseases Control and Prevention provide new evidence in support of this prediction.

BOX 9

Aging is the greatest risk factor for nearly every major cause of mortality in developed nations.

BOX 10

This study clearly showed that in non-obese subjects CR leads to improvements of human survival and disease risk factors and suggests potential benefits for aging-related outcomes.

BOX 11

Studies showed that CR had many positive effects and no negative effects in quality of life. So, the conclusion should be eat less. Cut the number of calories by 25% and make sure that such a diet is not deficient in essential nutrients. It will be necessary to consult your physician along with a dietitian who will define a CR diet without deficiencies for you. This is a type of personalized nutrition.

BOX 12

Biological age is defined by how rapidly a person's body is aging, regardless of his or her chronological age. Telomere length is a marker of biological aging that may provide a cellular memory of exposures to oxidative stress and inflammation. Telomere length at birth has been related to life expectancy.

BOX 13

Of interest is the fact that in animal studies the loss of telomere length can be prevented by supplementing the animal's diet with EPA and DHA. Of course, it is well known from both animal and human studies that both EPA and DHA have a positive effect. Therefore, improvements in air quality and dietary EPA and DHA supplementation may promote longevity from birth on. The shorter telomeres occurred during mid pregnancy.

BOX 14

Among health risks, poor diet quality is very prominent, followed by physical activity levels, which are quite low. Although time spent on leisure activities increases with age, most leisure time among older adults is spent watching television, so old age is characterized by poor diet quality and a sedentary lifestyle.

BOX 15

In 2013 the average American life expectancy was 77 years, but the average American “healthy life expectancy” was estimated at only 67 years. Of course, healthy aging begins from the moment of conception. Mother’s diet during pregnancy and even before pregnancy influences both survival and the development of chronic diseases later on in life.

BOX 16

Studies in The Gambia also show that maternal diet can influence the methylation of genes in the newborn. DNA methylation and inflammation and oxidative stress influence the expression of genes, which lead to aging-related metabolic diseases.

BOX 17

People and their doctors are looking for biomarkers for healthy aging. There are a number of ongoing studies. An early determinant of an inappropriate aging process is inflammation, which is associated with an inflammatory diet (high omega-6/omega-3 ratio), obesity and its comorbidities. Improving diet and weight loss lower inflammation and restore health. However, personalized markers based on individuals’ perceptions of their own healthy aging must always be taken into consideration. One of the most important markers of successful aging is being proud of how old you are.

BOX 18

Proper nutrition influences health throughout the human life cycle from conception to death. Diet or nutrients sustain life and allow growth, repair, and reproduction. Adequate dietary intake and physical activity influence health and survival and delay the aging process or may prevent the occurrence or progression of chronic diseases.

BOX 19

These studies support the fact that CR preserves more youthful functions by improving several markers of health, including lower body weight, metabolic rate, oxidative damage, lower incidence of CVD and cancer and decreased activity of the insulin-Akt-FOXO signaling pathway. However, there is a lack of clinical data showing consistent effects of caloric restriction in older populations and lack of

complete understanding of the age-specific effects of these interventions such as bone thinning (osteoporosis) and lack of reserve in fighting infections.

BOX 20

Overall, these studies show that both the amount of time spent eating during each day and the time at which food is eaten relative to circadian rhythm are critically important to the effects of diet on health and longevity.

BOX 21

From an evolutionary perspective, fasting is a natural phenomenon to which both animals and humans were regularly exposed. Even today animals in the wild are exposed to periods of famine, since food is not available to them at all times. Humans have evolved over time when they had to hunt for their food, which was not available at all times. Therefore, periods of fasting were a natural phenomenon, whereas today food is easily available practically at all times. Several short-term clinical trials have shown that alternate-day fasting can deliver benefits similar to caloric restriction in terms of weight loss and cardiometabolic health, improved lipid profiles, lower blood pressure, and increase insulin sensitivity.

BOX 22

Changes in meal size (caloric intake) or frequency of meals (by controlling the time of feeding and fasting) have been an important research area and has led to the decrease or improvement of many age-related diseases, such as cardiovascular disease, diabetes, cancer, and dementia. The answer to the question “Can we delay the Aging Process?” is yes, and eat less.

Part IV

Chapter 10. Evolutionary Aspects of Exercise

1. Exercise and the Brain
2. Regular Physical Activity Cuts Risk for Severe COVID-19
3. Proof That Exercise is Medicine

Humans have existed as a genus for about 2 million years. As a species, human physical capabilities and limitations are a result of our species-specific anatomical and physiological characteristics, which in turn are defined by our genetic composition [1]. Through evolution, bodyweight increased and resting metabolic rate (RMR) increased proportionately. Total energy expenditure was increased, as a result of environmental pressures. Prolonged drying periods caused the tropical forest to give way to more open woodland and savanna [2]. Food resources were less abundant and more scattered. Therefore, survival for the early members of the genus *Homo sapiens* had to depend on the ability to perform vigorous exercise. Increased physical activity and overall energy expenditure in order to obtain food and to escape from predators and other dangers became necessary for survival. All hominids occupied the hunter-gatherer niche, and regular daily activity utilizing both endurance and strength was essential. The mean estimated ratio of total energy expenditure (TEE) to resting metabolic rate (TEE/RMR) was 1.80 for hominids since the appearance of full-sized humans (*Homo erectus*), but for the modern sedentary office worker it is only 1.18. The data suggest that the high level of physical activity of the human species is genetically adapted and is normal both in evolutionary and physiological terms. The present low level of physical activity has not been encountered previously in our species, and it is clearly not in harmony with our genetic adaptation [2–4].

Since the appearance of truly modern human beings, *Homo sapiens*, about 40,000 years ago, the human genetic constitution has changed relatively little; even the development of agriculture 10,000 years ago has apparently had a minimal influence on our genes. Furthermore, modern industrial revolution and agriculture have occurred too recently to have had any evolutionary effect at all. Relative to susceptibility to chronic degenerative diseases, our current gene pool is hardly changed from that of Stone Age humans. As a result, chronic physical inactivity—which is our current lifestyle—is an abnormal condition to which humans have not genetically adapted. It is only in the past 100 years that the economic developmental changes in living conditions, technological advances, and food abundance have led to a sedentary lifestyle and low levels of physical activity. Less physical effort is now required for daily living. In fact, less physical effort has become a distinct feature of developed societies and the affluent population of developing countries. What is of great concern in terms of health as well as chronic diseases is that our current sedentary lifestyle has been thought of as a normal state and exercise as an intervention. As a result, physical inactivity (exercise deficiency) has caused two types of harmful effects on human health: (1) the development of diseases that are largely attributed to exercise deficiency; and (2) the development of disuse atrophies and loss of functional capacities. Many of the chronic diseases (the so called “diseases of civilization”), obesity, diabetes, hypertension, CHD,

arthritis, and some types of cancer, result from interaction of genes with exercise deficiency. Increased levels of physical activity/exercise have been shown to reduce the severity, outcomes, and risk factors of chronic diseases; reverse the abnormalities resulting from being sedentary; and stimulate adaptations that compensate for some of the deterioration induced by the aging process through its effects on human physiological, metabolic, immunological, and endocrine effects [5]. Physical activity positively impacts virtually all chronic diseases including, but not limited to, stroke, peripheral artery disease, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, some forms of cancer, obesity, hyperlipidemia, etc. [6]. Studies have shown that the normal day-to-day activities of hunter-gatherers produce high levels of endurance capacity, whereas modern men have one-half as much endurance or degree of fitness as measured by VO_2 max, which is a function of maximal cardiac output and arteriovenous differences. VO_2 max decreases with physical inactivity and increases in response to aerobic exercise training [7]. Factors that affect VO_2 max include the development of diseases, especially atherosclerotic heart disease, weight gain, advancing age, and trained individuals who stop training (athletes). The VO_2 max declines approximately 10% per decade. Some of the decline in VO_2 max with advancing age is due to the decline in physical activity, which is aging plus exercise deficiency.

Human beings evolved to be very active, particularly in comparison to today's energy expenditure. Because of the sedentary nature of industrialized societies, exercise is usually viewed as an activity (jogging, walking, swimming, bicycle riding, aerobics, weightlifting, etc.) separate from daily activities, performed during leisure time to improve fitness or strength. Furthermore, the most popular sports, football, soccer, and basketball, are "spectator" sports in which the audience participates only through "cheering" encouragement or "booing". In contrast, in living hunter-gatherers, exercise results from the daily muscular activity needed to adequately function within the hunter-gatherer niche. Food and water procurement, social interaction, escape from predators, and homeostatic maintenance evoke obligatory movements, and these movements needed to carry out life's functions represent the genetically established exercise patterns of man prior to agricultural revolution of 10,000 years ago. Although human lifestyles have changed almost inconceivably since the advent of the agricultural revolution and the more recent industrial revolution, our exercise capabilities, limitations, and requirements remain the same as those selected by natural selection for our stone age ancestors. Deviation from these intrinsic exercise patterns established long ago inevitably results in dysfunction and disease.

It follows then, that the current sedentary activities as a result of mechanization in travel, work, and everyday life have been shown to increase the risk of obesity, diabetes, CVD, arthritis, and some forms of cancer. More recent studies show

that being physically active contributes to weight loss, improves insulin resistance, lowers the risk for CVD and some forms of cancer, and improves overall mood and wellbeing. Physically active people have a lower risk of dementia, including Alzheimer's Disease.

1. Exercise and the Brain

In the US today, cognitive decline is a serious concern. One in three senior citizens dies with Alzheimer's disease or another form of dementia and the number of cases is rising, according to the Alzheimer's Association. The costs of caring for people with Alzheimer's are expected to reach approximately USD 1 trillion by 2050. The area of the brain that is the "seat" of memory is called hippocampus. Studies using magnetic resonance imaging (fMRI) have found that the fMRI patterns predict memory and that there is an indirect connection between fitness and memory performance. A growth hormone called brain-derived neurotrophic factor (BDNF) appears to connect fitness and memory. There is a greater memory accuracy with greater levels of BDNF in more fit individuals. BDNF is known to play a role in the growth of new neurons in the brain, which may account for the relationship between fitness and good memory. In the hippocampus is where neurogenesis occurs, in a subregion called the dentate gyrus. Animal studies show that the dentate gyrus is enlarged by exercise. Similarly, another part of the brain, the entorhinal cortex, is bigger in people with higher fitness levels. Animal studies suggest that these two regions of the brain, the dentate gyrus and the entorhinal cortex, malfunction first in Alzheimer's disease. The question is, what kind of exercise makes the most difference? Studies are ongoing in which the participants are given an individualized exercise prescription, either an aerobic fitness routine or a resistance training routine to follow three times a week for 12 weeks. Since animal studies show that cardiorespiratory fitness is the key to improved memory, the control group in this study is the resistance-training group. Whatever the results, this type of research is not so much whether exercise will make a difference but rather what kind of exercise makes the most difference and how much is needed. This type of research, in the future, will lead doctors to prescribe an exercise program rather than a drug, just as stated by Hippocrates in the Concept of Positive Health in the 5th Century BC: "there must also be exercise, the type and amount must likewise be known". Obviously, we have not come very far but we are beginning, and as the Ancient Greeks used to say, "the beginning is fifty percent of the whole "effort".

2. Regular Physical Activity Cuts Risk for Severe COVID-19

Among adults infected with COVID-19, those who consistently meet the physical activity guidelines have significantly reduced their risk of severe COVID-19 outcomes compared with inactive individuals [8]. Another study compared

hospitalization rates, Intensive Care Unit (ICU) admissions, and mortality for patients with COVID-19 based on self-reported physical activity. The researchers [8] found that patients with COVID-19 who were consistently inactive (0–10 min/week) had more admissions to the ICU versus patients who were consistently meeting the Physical Activity Guidelines (150+ min/week) [9,10]. Similar findings were seen when comparing patients who were consistently inactive to patients with some physical activity (11 to 149 min/week), including a greater risk for COVID-19, related hospitalizations relative to admissions to the ICU, and deaths. It is obvious that the promotion of physical activity should be promoted by the Public Health Agencies, and physical activity should be included on a daily basis in all schools K–12, the same way the school lunch program is made available. Better yet, physical activity should be incorporated into routine medical care.

The study by Sallis et al. [8] is the very first study to show that patients whose physical activity met the Physical Activity Guidelines before getting COVID-19 had reduced odds for hospitalization, ICU admissions, and death. These patients were enrolled in a large integrated healthcare system Kaiser Permanente, which is one of the few (and largest) healthcare systems that collect physical activity data at every outpatient encounter with a healthcare provider. The study clearly showed that physical activity is an important and modifiable risk factor for severe COVID-19 outcomes. The magnitude of risk for all outcomes associated with being consistently inactive was higher than the odds associated with smoking and virtually all the chronic diseases studied in the analyses of this research paper, indicating that physical inactivity may play a critical role as a risk factor for severe COVID-19 outcomes. When inactive patients are compared to those in some activity category, the physically active had lower odds for hospitalization and death, suggesting that any amount of physical activity may have benefit. Physical inactivity is associated with higher BMI and greater risk of diabetes. Both are associated with severe COVID-19 outcomes. Physical activity may be the most important modifiable risk factor for severe COVID-19. During the COVID-19 lockdown a study in the UK found that adults with chronic conditions were most likely to report reduction in their physical activity levels [9]. Therefore, promoting physical activity is especially important for those with chronic diseases. The US Physical Activity Guidelines established a goal of 150 min per week of moderate to vigorous physical activity to maximize health benefits [10], which is like a “brisk walk”. This amount can be obtained in small units, making achievement of the guidelines within reach for nearly all people. Other studies have shown that on average, Americans have at least 4–6 h of each day of leisure times, the majority of which is devoted to sedentary activities, particularly electronic media [11]. Exercise is essential in healthy weight-loss maintenance in patients with obesity. The combination of physical activity with liraglutide improved healthy weight-loss maintenance more than either treatment alone [12].

Walking and structured aerobic exercise programs increase energy expenditure and cardiorespiratory fitness while reducing fat mass and preserving or increasing lean mass [13–15].

3. Proof That Exercise Is Medicine

Hippocrates emphasized that “If there is deficiency in food or exercise the body will fall sick.” Food as medicine is a well-defined concept. Even the National Institutes of Health (NIH) referred to “food as medicine” in a recent paper about precision nutrition [16]. Recent studies now show that exercise works like a drug, so it is medicine. Hippocrates said “The type and amount of exercise must be known” so the doctor of the future will have to learn to write prescriptions on exercise, and students in school have to be taught to understand the physiological changes that take place in the various forms and duration of physical activity. The effects of exercise in slowing aging, improving stress, putting people in a better mood, less chronic pain, and stronger vision can be measured and therefore should be able to convince people and motivate them to include exercise in their daily activities. In the 1900s with the rise in modern surgery, drugs, X-rays, etc., medicine shifted its focus from the prevention of disease to its treatment. The funny thing is that just as the modern Olympics swelled in popularity and colleges began building campus stadiums, physicians began to de-emphasize exercise. Of interest is the fact that a paper [17] published in a 1905 issue of the *Journal of the American Medical Association* (JAMA) mourned how many people were losing sight of the health benefits of exercise. “The men on the teams are the very ones whom Nature has endowed superabundantly with physical capacity, but on them the physical director bends most of his energies,” they wrote, “while the average student is left to get his physical development by yelling from the bleachers.” This physical activity was no longer the medicine of the masses but the privilege of the elite athletes. When scientists studied exercise, it was to figure out how athletes could improve their peak performance, not how mere mortals could improve their health day to day. This gap persists. At a time when boutique (expensive) fitness studies are more popular than ever, fewer people are getting the minimum recommended amount of exercise.

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BOX 1

The data suggest that the high level of physical activity of the human species is genetically adapted and is normal both in evolutionary and physiological terms. The present low level of physical activity has not been encountered previously in our species, and it is clearly not in harmony with our genetic adaptation.

BOX 2

As a result, chronic physical inactivity—which is our current lifestyle—is an abnormal condition to which humans have not genetically adapted. It is only in the past 100 years that the economic developmental changes in living conditions, technological advances, and food abundance have led to a sedentary lifestyle and low levels of physical activity.

BOX 3

What is of great concern in terms of health as well as chronic diseases is our current sedentary lifestyle has been thought of as a normal state and exercise as an intervention.

BOX 4

Increased levels of physical activity/exercise have been shown to reduce the severity, outcomes, and risk factors of chronic diseases; reverse the abnormalities resulting from being sedentary; and stimulate adaptations that compensate for some of the deterioration induced by the aging process through its effects on human physiological, metabolic, immunological, and endocrine effects.

BOX 5

The VO_2 max declines approximately 10% per decade. Some of the decline in VO_2 max with advancing age is due to the decline in physical activity, which is aging plus exercise deficiency.

BOX 6

The current sedentary activities as a result of mechanization in travel, work, and everyday life have been shown to increase the risk of obesity, diabetes, CVD, arthritis, and some forms of cancer. More recent studies show that being physically active contributes to weight loss, improves insulin resistance, lowers the risk for CVD and some forms of cancer, and improves overall mood and wellbeing. Physically active people have a lower risk for dementia, including Alzheimer's Disease.

BOX 7

There is a greater memory accuracy with greater levels of BDNF in more fit

individuals. BDNF is known to play a role in the growth of new neurons in the brain, which may account for the relationship between fitness and good memory.

BOX 8

Whatever the results, this type of research is not so much about whether exercise will make a difference but rather what kind of exercise makes the most difference and how much is needed.

BOX 9

Among adults infected with COVID-19, those who consistently meet the physical activity guidelines have significantly reduced their risk for severe COVID-19 outcomes compared with inactive individuals.

BOX 10

It is obvious that the promotion of physical activity should be promoted by the Public Health Agencies, and physical activity should be included on a daily basis in all schools K–12, the same way the school lunch program is made available. Better yet, physical activity should be incorporated into routine medical care.

BOX 11

The study clearly showed that physical activity is an important and modifiable risk factor for severe COVID-19 outcomes.

BOX 12

When inactive patients are compared to those in some activity category, the physically active had lower odds for hospitalization and death, suggesting that any amount of physical activity may have benefits.

BOX 13

The US Physical Activity Guidelines established a goal of 150 min per week of moderate to vigorous physical activity to maximize health benefits, which is like a “brisk walk”. This amount can be obtained in small units, making achievement of the guidelines within reach for nearly all people.

BOX 14

Exercise is essential in healthy weight-loss maintenance in patients with obesity. The combination of physical activity with liraglutide improved healthy weight-loss maintenance more than either treatment alone. Walking and structured aerobic exercise programs increase energy expenditure and cardiorespiratory fitness while reducing fat mass and preserving or increasing lean mass.

BOX 15

So the doctor of the future will have to learn to write prescriptions on exercise, and the students in school have to be taught to understand the physiological changes that take place in the various forms and duration of physical activity.

Chapter 11. The Diet of Crete: The Healthiest Diet

1. The Diet Heart Hypothesis and the Seven Countries Study
2. Studies on Defining the Composition of the Diet of Crete
3. The Lyon Heart Study
4. The Greek Orthodox Church and Fasting
5. Implementation of the Diet of Crete
6. Conclusions

1. The Diet Heart Hypothesis and the Seven Countries Study

In the early 1930s, scientists in Europe and in the United States had noticed that in the island of Crete, in Greece, people lived the longest and had less heart disease and cancer than the people in other parts of Western Europe and in the United States. Therefore, the scientists recognized that there was a need to find out the factors that contributed to the long life and good health of the people in Crete. Plans were made to carry out studies in some populations in Europe, the United States and Japan. However, Nazi Germany started World War II by invading Poland in 1939 and plans for the study were put on hold. Meanwhile, interest focused on the diet and scientists became interested in the “Diet-Heart Hypothesis”, which put emphasis on dietary cholesterol and saturated fat as a “cause” of heart disease. They believed that saturated fat raised cholesterol in the blood, which led to atherosclerosis (hardening of the arteries), and early death. There were many proponents of the “Diet-Heart Hypothesis”. Most vocal among them was Ancel Keys, from the University of Minnesota. Keys was not a physician; he was a physiologist/epidemiologist who did not believe in the essential fatty acids—namely the omega-6 and omega-3 fats. Therefore, he ignored them and did not include them in the Seven Countries Study protocol. In fact, from 1954–1956 there was correspondence in *The Lancet* (a British Medical Journal) back and forth between Keys and Hugh Sinclair from Oxford on those issues. Keys was convinced that high saturated fat and cholesterol in the Western Diet (the US, Canada, the UK, and Western Europe in general) caused heart disease and believed that omega-6 fatty acids from vegetable oils (corn, sunflower, safflower, cottonseed, and soybean oils), because they lowered cholesterol, would prevent heart disease.

In England in 1957, John Yudkin identified added sugars as the primary agent in the development of heart disease, while Ancel Keys continued to press his views that total saturated fat and dietary cholesterol played a significant role in the development of CHD. A review in the *New England Journal of Medicine* (NEJM) by McGandy, Hegsted, and Fred Stare from the Harvard School of Public Health in 1967 was commissioned by the Sugar Research Foundation. The title was “Dietary fats, carbohydrates and atherosclerotic vascular disease” and it appeared in two parts [1,2]. This review was instrumental in removing all doubts that added sugar is a primary factor for the development of CHD and the theory of Keys became the standard in research for the control of CHD. A recent analysis of the issues involved in the development of the review concluded that in the period between 1950–1960 the Sugar Research Foundation made every effort to exonerate added sugars and promote the view of Ancel Keys, and the “Diet-Heart Hypothesis” became the primary focus [3,4]. By the 1980s, few scientists believed that added sugars played a significant role in CHD, and the first 1980 dietary guidelines for Americans focused on reducing total fat, saturated fat, and dietary cholesterol for CHD prevention.

In 1946, after the Second World War was over, the Rockefeller Foundation funded a study to investigate the health status of the population of Crete and compared it to the population of the US in terms of heart disease. It is very interesting to read the report [5], which stated “Although Greece and the Mediterranean countries are usually considered to be areas of medium-high death rates (14.0–18.0 per 1000 inhabitants), death rates on the island of Crete have been below this level continuously since before 1930 [5]. No other area in the Mediterranean basin has had as low a death rate as Crete, according to data compiled by the United Nations in their Demographic Yearbook for 1948. It was 11.3–13.7 per 1000 inhabitants before World War II and ~10.6 in 1946–1948. Cancer and heart disease caused almost three times as many deaths proportionally in the United States as in Crete [5].”

The Rockefeller Foundation Report was influential in setting up the Seven Countries Study in 1956, funded by a grant from the US Public Health Service that came to be known as the “Seven Countries Study” [6]. Ancel Keys was the principal investigator who actually carried the banner of the “Diet-Heart Hypothesis”. At first a number of countries were recruited for the study, but Keys “dropped some of them because they did not fit his theory”. Yet data were available from 22 countries. Keys and his associates omitted countries such as France, where consumption of total and saturated fat was very high, but the risk of heart disease remains low. Even before the publication of the Seven Countries study, the American Heart Association (AHA) in 1965 took up the cause, recommending that Americans reduce dietary fat and substitute corn or soybean oil for butter. Soon, margarine with large amounts of trans fats became the “Heart Healthy” alternative to butter. Eggs were also assigned to unhealthy eating patterns, and low-fat diets high in omega-6 fatty acids became the answer to the soaring rates of CHD. In fact, the AHA continues to promote a low-fat diet to date, which is high in omega-6 fatty acids, despite all evidence to the contrary that omega-6 fatty acids increased the risk of CHD [7–9]. The dietary recommendations updated on 12 August 2015 continue to recommend “low-fat dairy products” and “if you choose to eat meat, look for the leanest cuts available” [10]. There are a number of papers in the medical literature that deal with this issue over the past 60 years. The final list of the countries that were included in the Seven Countries Study were Crete and Corfu (Greece), the then Yugoslavia (that included the Dalmatia Coast, Croatia), Italy, Holland, Finland, Japan, and the United States (Table 11.1).

Table 11.1. Countries participating in The Seven Countries Study.

Greece	(Crete and Corfu)	37% fat
Yugoslavia	(Adriatic Sea, Croatia)	
Italy		
Holland		
Finland		
U.S.		
Japan		10% fat

The study included medical examinations, laboratory measurements of fats and cholesterol, and dietary histories. The results showed that the population of Crete had the lowest rate of heart disease, followed by the populations of Japan, Italy, Yugoslavia, Holland and the US. The country with the worst results was Finland, which in addition to high saturated fat intake also had the highest frequency of ApoE4 (24%) (a genetic variant) than all other European populations.

Persons with ApoE4 absorb more saturated fat. However, Keys et al. [6] ignored the genetics of the populations, despite the fact that it was known that Northern Europe had a higher frequency of ApoE4 than Southern Europe (Greeks, Italians, Yugoslavians). The investigators of the Seven Countries Study led by Keys concluded that they had “proof” that low saturated fat and a high amount of olive oil in the diet of the populations of Greece, Yugoslavia, and Italy accounted for the lower rate of heart disease in these countries. Olive oil being high in monounsaturated fat was considered responsible for the beneficial effects of the “Mediterranean Diet” as Keys labeled all diets of the countries bordering the Mediterranean Sea. The fact that the population of Crete had the lowest rate of heart disease, followed by the Japanese, was not considered by Keys or the other investigators is surprising. They were absolutely convinced that saturated fat and cholesterol in the diet led to heart disease and refused to include the data that did not fit their theory.

So, a major political decision was made to use polyunsaturated oils high in omega-6 fatty acids, such as corn oil, sunflower, safflower, cottonseed, and soybean for cooking instead of lard and butter in the US, because the US did not produce olive oil (Table 11.2) [9].

Table 11.2. Content of ω -6 LA and ω -3 α LNA in commercially available edible oils.

Cooking Oil	LA (per 100 g of Cooking Oil)	α LNA (g per 100 g of Cooking Oil)
Vegetable oil *	Depends on specific oil	Depends on specific oil
Safflower †	74.6	0.0
Sunflower †	65.7	0.0
Cottonseed	53.5	0.0
Corn	51.5	0.2
Soybean	50.3	7.0
Canola	18.6	9.1
Olive	9.8	0.8
Butter oil	2.3	1.4
Coconut	1.8	0.0

ω -6 LA = omega-6 linoleic acid; ω -3 α LNA = omega-3 α linolenic acid. Fatty acid contents of oils vary to some extent by season, latitude, and other conditions. USDA National Nutrient Database numbers: safflower 04510, sunflower 04510, cottonseed 04502, com 04518, soybean 04669, canola 04582, olive 04053, butter 01003, coconut 04047. * Food items labeled vegetable oil may contain one or more of the above oils. † Varieties of safflower and sunflower oils with lower LA content are commercially available. Source: Source: [9].

Almost overnight, an experiment for the whole US population was started and omega-6 vegetable oils were substituted for butter and other saturated fats. To add insult to injury, these high omega-6 oils were later hydrogenated to make margarine to replace butter and became trans fats, which are worse than butter for raising cholesterol. Trans fats also increase both the number and size of fat cells leading to obesity. Without carrying out studies to show that trans fats were safe or better than butter, major companies started advertising the benefits of corn oil that included advertisements in newspapers, magazines (including the National Geographic), radio, etc. (Figure 11.1) [11].

So, there was a major experiment involving the whole country. This was unprecedented in the history of science, but it shows how a few people and marketing folks can influence the composition of the Food Supply and Food and Nutrition Policy. Almost overnight a whole processed food industry grew and corn oil as well as the other high omega-6 oils (sunflower, safflower, soybean) flooded the US. food supply and then Canada, UK, Western Europe and today practically the whole world. I do not think you can find a country today in which high amounts of oils high in omega-6 fatty acids have not taken over all other oils, including the Mediterranean countries where olive oil is so abundant. To promote corn oil and other high omega-6 oils, marketers presented them as “light” and “odorless” and totally undermined olive oil in the 1960s and 1970s. Today of course most people know that olive oil extracted from the fruit of the olive tree is high in antioxidants, polyphenols, and other substances, as well as low in omega-6 and high in monounsaturates, making it the healthiest oil.

Tonight's the night Mrs. Ed Flynn starts Polyunsaturating her husband

...with a big assist from Mazola.

For years, millions of Americans have been eating a diet that is supposedly balanced in terms of fats. Mrs. Flynn is no exception.

Today, however, she's doing what medical authorities are suggesting. She's serving her hubby a balanced diet one which includes cutting down on total calories and fat calories, and replacing solid fats with the more highly polyunsaturated vegetable oils.

Her choice of oil is Mazola® 100% Corn Oil—because it is highest in polyunsaturates of all leading national brands. She finds it ideal for mixing her salads into a particularly important part of the better-balanced diet. Mazola is the logical choice for you, too, for all your cooking and salad-making needs.

No matter how many there are in your family, there's one thing you can all enjoy doing together—

Polyunsaturating!

P.S. She uses Mazola's Margarine, too. It's made with liquid Mazola Corn Oil.



Figure 11.1. Campaign for vegetable oil. Source: Reprinted from: [11].

The use of vegetable oils high in omega-6 fatty acids increased in the 1960s, 1970s, and the 1980s, as a result of the very aggressive campaigns to lower cholesterol in the blood. These campaigns were supported by the food and the pharmaceutical industries. The food marketers also developed all kinds of low-fat, low-saturated foods because the pharmaceutical industry at the time could only develop drugs that lowered the “bad cholesterol”. As you can see it was a time that benefited both the food industry, and the pharmaceutical industry, but not the population. Many scientists objected but their voices were not heard. Fred Kummerow’s research on trans fatty acids was ignored before it was eventually accepted 25 years later. Similarly, Drs. Robert Olson and Alfred Harper worked hard to maintain the scientific basis of nutrition, but like a swollen river that overflows and floods the terrain, food

industry and all kinds of food advocates in control at the America Heart Association (AHA) and elsewhere actively promoted the low-fat products. In fact, the AHA and Food and Drug Administration (FDA) were carrying the torch. FDA still carries the statement “Diets low in saturated fat and cholesterol, and as low as possible in *trans* fat, may reduce the risk of heart disease.” Today FDA is in the process of removing trans fats from the food supply but does not distinguish between omega-6 and omega-3 fatty acids on the food label. The FDA continues to list them together as polyunsaturated fatty acids (PUFAs). Here, we need a health policy change. We cannot have a Regulatory Agency that is supposed to safeguard the health of the public be 20 years behind the scientific evidence, and this is occurring in the most advanced, most powerful country on earth: the United States of America.

The fixation on cholesterol as causing heart disease became the dominant factor. Since corn oil and other omega-6 oils lowered cholesterol slightly, it was thought that cholesterol must be lowered both by diet and drugs. The pharmaceutical industry developed drugs to lower the bad, low-density lipoprotein (LDL) cholesterol. The cholesterol in the blood is only one factor linked to heart disease. Other factors are even more important, such as low omega-3 fatty acids, low antioxidants, and high levels of homocysteine in Western diets and conditions such as obesity, diabetes, the metabolic syndrome, and chronic low-grade inflammation, but they were ignored and in fact obscured for many years. In the 1970s and continuing into the 1980s and 1990s, and even up to a few years ago in the 21st century, the “ideal heart diet” appeared to be one that was low in saturated fat and high in omega-6 oils, and thousands of volunteers in the US and Europe participated in clinical trials and other studies that were designed to test this concept of the “ideal heart diet”. Most of these studies were short term, designed to detect changes in cholesterol levels, so whether the diets actually saved lives was anybody’s guess, and those studies that lasted long enough to have adequate data that produced valid mortality statistics led to data that did not show benefit. One study carried out in England in 1965 using corn oil [12] actually increased the risk of dying from heart disease. Their conclusion was “under the circumstances of this trial, corn oil (high in omega-6 fatty acids) cannot be recommended as a treatment for heart disease. It is most unlikely to be beneficial and it is possibly harmful” [12]. However, this study and other publications in medical journals were not picked up by the popular press [8,9]. This lack of public awareness, coupled with permissible economic policies, allowed food manufacturers to develop and sell whatever oils they wished. It was to their financial interest to sell more omega-6 oils, because at the time these oils were little used by-products of the animal feed and cotton industries. Now they could be sold to the public as “heart healthy” foods. Between the enormous marketing of the omega-6 oils by companies and the aggressive increased availability, the uninformed public was persuaded, and practically overnight millions of people

began switching from butter to margarine high in trans fats from corn oil, which later was shown to be worse than saturated fats; and from lard to all vegetable oils; from shortening and from bacon grease to PAM. A 1972 survey showed that 9 out of 10 people chose to eat more vegetable oil as a result of commercial advertising or the media “not on the advice of, or even with the knowledge of, their personal physician” [13]. Since the 1960s the consumption of omega-6 fatty acids has increased enormously—more than double (Figure 11.2)—especially in the US, making Americans the world’s second-largest-consuming population of omega-6 fatty acids after the Israeli population [14].

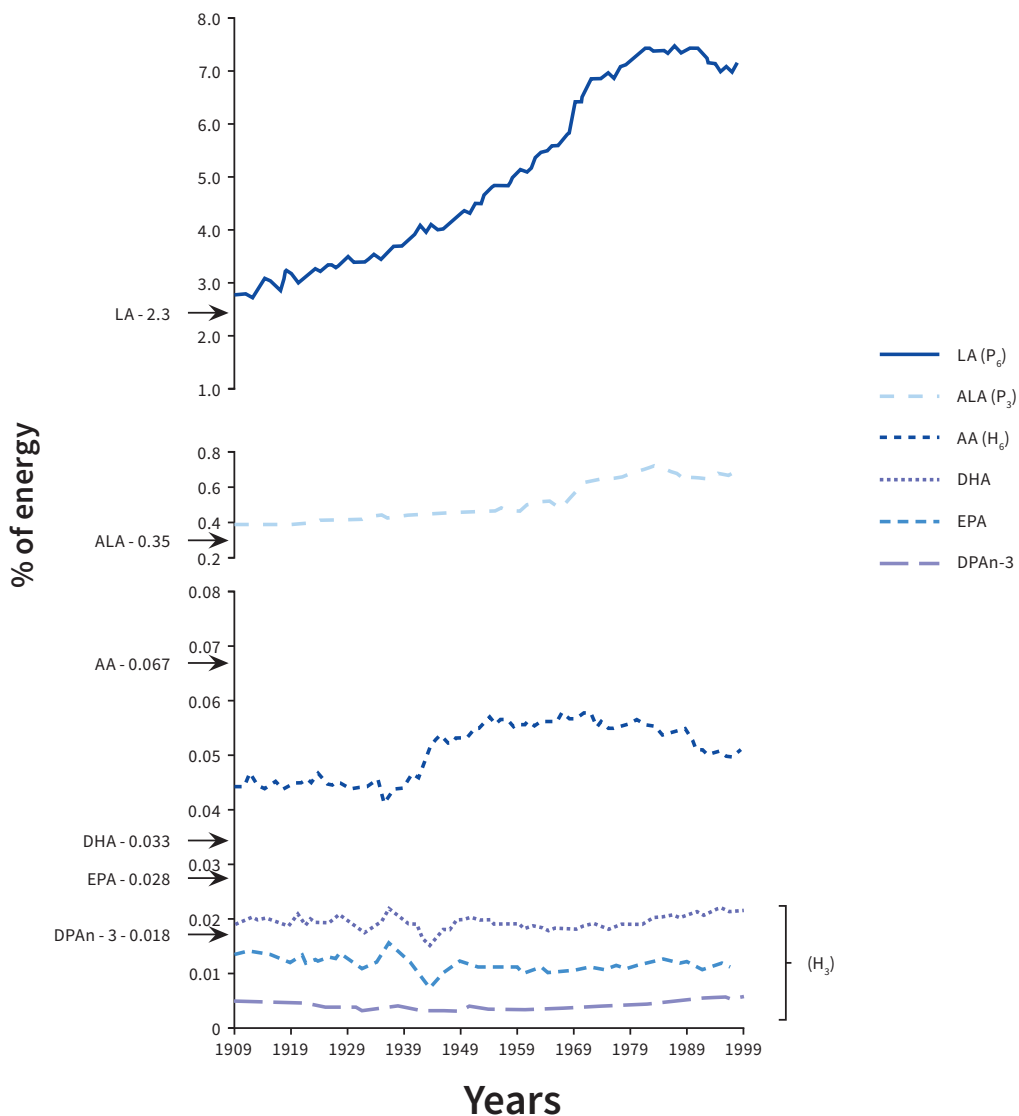


Figure 11.2. Essential Fatty Acid intake in the 20th Century. Availability of essential fatty acids from 1909 to 1999. 1909-Table 2. 23% of energy), ALA (0.35% of energy), arachidonic acid (AA) (0.67% of energy), docosahexaenoic acid (DHA) (0.033% of energy), eicosapentaenoic acid (EPA) (0.028% of energy), and docosapentaenoic acid (DPAn23) (0.018% of energy). Source: [14].

2. Studies on Defining the Composition of the Diet of Crete

Because of the results of the Multiple Risk Factor Intervention Trial (MRFIT) showing that the advice to lower cholesterol did not decrease death from coronary heart disease (CHD), I decided to thoroughly review the data from The Seven Countries Study [6] and began my research on the diet of Crete, the results of which were published in 2001 in *World Review of Nutrition and Dietetics* with the title “What is so Special about the diet of Crete: The Scientific Evidence” [15]. A persistent thought in my mind was the question of what was the common link between the diet of the people in Crete and the people of Japan? Remember, the Seven Countries Study showed that the people in Crete had the lowest rate of heart disease, followed by the diet of the Japanese—and not the other two Mediterranean Countries, Yugoslavia and Italy. It certainly could not be only the olive oil. The Japanese did not consume any olive oil and had the lowest saturated fat in their diet, while the people in Crete had moderate amounts of saturated fat: about 8–10% of energy. In going over the Seven Countries Study data [6], I discovered that fish intake was considered low in the diet of Crete because the way the food frequency questionnaire had been translated into Greek; the word in Greek for fish “psari”—means fresh fish, which was low in the Cretan diet because only the people on the coast ate fish that was fresh, due to lack of refrigeration in the 1960s. However, the people in Crete ate preserved sardines, olives with olive oil, and bread practically on a daily basis, except on Fridays when they ate smoked herring instead of sardines. Both sardines and herring are high in omega-3 fatty acids. I then began very extensive research into the composition of the diet of Crete in terms of its composition of fatty acids, antioxidants, vitamins, minerals, and other compounds. I was determined to precisely define the traditional diet of Crete prior to 1960 and also to discover the common link between the diets of Crete and Japan that decreased the risk of heart disease in those two populations located in two different continents and thousands of miles apart. I embarked on a series of studies to first determine the composition of wild plants and then that of eggs from chickens that fetched their own food and were not fed corn, as were the chickens in the US [16]. I found out that wild plants in general had higher amounts of alpha-linolenic acid (ALA) which is the land-based parent fatty acid of the omega-3 family. In fact, purslane (either wild or cultivated) had the highest amount of ALA compared to any other green leafy vegetable (Figure 11.3) [17,18].

Wild and cultivated Purslane was the first plant I studied. I suppose you could say it was beginner’s luck; regardless, I am glad about it because it stimulated me to study wild plants popular in the diet of Crete and Greece in general. Some of these studies were carried out in the lab at the NIH, directed by Dr. Norman Salem; others at the Beltsville Center in Maryland (USDA) where Dr. Helen Norman worked; and some at the Agronomic Institute at Chania, Crete, where I taught nutrition to Master’s degree students for a period of 3 years. The people of Crete, as well as

the rest of the people in Greece, like wild plants. In fact, wild plants are part of practically every meal throughout the year, either fresh or cooked or in pies wrapped in filo with olive oil, herbs, and feta cheese. You can order them in Greek restaurants under their common Greek name, HORTA, and they can be either wild or cultivated. In fact, the word “Horta” comes from the word “horticulture”—meaning the study of plants in Greek (horticulture is the scientific name of the discipline that studies plants). They are high in antioxidants, glutathione, melatonin, Vitamin C and E, and have more omega-3s than omega-6 fatty acids. One serving of 100 gm (three ounces) of purslane contains 300–400 mg of alpha-linolenic acid (ALA) [17,18] (Table 11.3).

Recently, we measured the melatonin content of purslane and it is significantly higher than most commonly eaten fruits and vegetables. Melatonin is a potent anti-carcinogenic agent.



Figure 11.3. Wild purslane. Photo by Artemis P. Simopoulos, MD.

Table 11.3. Fatty acid content of plants.

Fatty Acid	Purslane	Spinach	Mustard	Red Leaf Lettuce	Buttercrunch Lettuce
14:0	0.16	0.03	0.02	0.03	0.01
16:0	0.81	0.16	0.13	0.10	0.07
18:0	0.20	0.01	0.02	0.01	0.02
18:1 ω 9	0.43	0.04	0.01	0.01	0.03
18:2 ω 6 (LA)	0.89	0.14	0.12	0.12	0.10
18:3 ω 3 (LNA)	4.05	0.89	0.48	0.31	0.26
20:5 ω 3 (EPA)	0.01	0.00	0.00	0.00	0.00
22:6 ω 3 (DHA)	0.00	0.00	0.001	0.002	0.001
Other	1.95	0.43	0.32	0.12	0.11
Total fatty acid content	8.50	1.70	1.101	0.702	0.60

Values are expressed as mg/g of wet weight. Source: Modified from: [18].

Prior to 1960 the people in Crete ate the meat of animals and birds in the wild and the meat of domesticated animals (goats, sheep, pork, veal) that grazed instead of being grain fed. Their meat contained both omega-6 and omega-3 fatty acids, whereas the meats of animals that are grain fed as is in Western diets contain only omega-6 fatty acids in the form of LA and arachidonic acid (ARA). Because grain-fed animals are fed corn and corn is high in LA, Western diets are high in both forms of omega-6 fatty acids. LA from oils and seeds, and ARA from animals (meat, eggs, and dairy) (Table 11.4) [19].

Table 11.4. Fatty acid content and the omega-6/omega-3 ratio in various meats and salmon.

g/100 g of Meat	Total Fat, g	Saturated Fat, g	Ratio of Omega-6 to Omega-3 Poly-Unsaturated Fats
Grass-fed beef	1.87	0.80	1.54
Grain-fed beef	3.65	1.58	5.01
Chicken breast, skinless	1.10	0.39	16.25
Chicken thigh	7.20	2.09	17.64
Pork chop	3.38	1.22	27.45
Salmon, farm raised	7.52	1.41	0.80

Source: Modified from: [19].

You may be surprised at the numbers for grass-fed beef. The fat profile is closer to that of salmon than grain-fed beef. Grass-fed beef also has less than half the saturated fat of dark-meat chicken and a far better ratio of omega-6 to omega-3 polyunsaturated fats (the ideal ratio is less than four).

When we examined the composition of the egg from chickens that are not grain fed, as was the situation in Crete prior to 1960, their eggs had equal amounts of omega-6 and omega-3 fatty acids, whereas the eggs from the supermarkets in the US, from grain-fed chickens, had about twenty times the amount of omega-6 vs. omega-3 and a ratio of 20/1 omega-6/omega-3, whereas the Greek egg under complete natural conditions was balanced in the omega-6 and omega-3 fatty acids with a ratio of about one (Table 11.5) [16].

The balanced omega-6 and omega-3 fatty acids in the food of the people of Crete were found in every meal they ate. They were in the eggs and in the milk, and all the dairy products, and in the noodles and pasta that are traditionally made with eggs and milk. Such noodles and pasta are very different from the pasta you buy at the supermarket in a box, made with refined flour and water. Supermarket pasta in a box increases the blood sugar and has a high glycemic index, whereas Greek noodles do not increase the blood sugar and their glycemic index is lower.

Table 11.5. Fatty acid levels in chicken egg yolk *.

FATTY ACID	GREEK EGG	SUPERMARKET EGG
	<i>milligrams of fatty acid</i> †	
Saturated fats		
14:0	1.10	0.70
15:0	—	0.07
16:0	77.60	56.66
17:0	0.66	0.34
18:0	21.30	22.88
<i>Total</i>	<i>100.66</i>	<i>80.65</i>
Monounsaturated fats		
16:1n – 7	21.70	4.67
18:1 –	120.50	109.97
20:1n – 9	0.58	0.68
22:1n – 9	—	—
24:1n – 9	—	0.04
<i>Total</i>	<i>142.78</i>	<i>115.36</i>
n-6 fatty acids		
18:2n – 6	16.00	26.14
18:3n – 6	—	0.25
20:2n – 6	0.17	0.36
20:3n – 6	0.46	0.47
20:4n – 6	5.40	5.02
22:4n – 6	0.70	0.37
22:5n – 6	0.29	1.20
<i>Total</i>	<i>23.02</i>	<i>33.81</i>
n-3 fatty acids		
18:3n – 3	6.90	0.52
20:3n – 3	0.16	0.03
20:5n – 3	1.20	—
22:5n – 3	2.80	0.09
22:6n – 3	6.60	1.09
<i>Total</i>	<i>17.66</i>	<i>1.73</i>
Ratio of fatty acids to saturated fats	0.4	0.44
Ratio of n-6 to n-3	1.3	19.4

* The eggs were hard-boiled, and their fatty acid composition and lipid content were assessed.

† Per gram of egg yolk. Source: Simopoulos, A.P.; Salem, N., Jr. n-3 fatty acids in eggs from range-fed Greek chickens. *N. Engl. J. Med.* 1989, 321, 1412 [16].

In the Greek Orthodox Church, there are many days throughout the year on which is recommended to abstain from meat, eggs, and dairy (animal products in general). These “fast days” account for about 200 days per year. Fish and escargots are permitted during some days of fasting. Fish usually in the form of sardines or herring are high in EPA and DHA, the fatty acids found in fish or made in the body from ALA. Of interest is the fact that when Serge Renaud compared the fatty acids of escargot from Crete and the Peloponnese (Greece) to those of Bordeaux France,

where he had a summer home, the escargots from Greece had higher amounts of ALA and other omega-3 fatty acids than those of Bordeaux, suggesting that the grass in Greece had higher amounts of ALA than the grass in France. While we were performing all these studies, a paper was published by Sandker et al. [20] containing data from the Seven Countries Study, which Keys et al. had chosen to ignore. In one table the cholesterol esters in the blood of the people from Crete were listed along with those of the population of Zutphen, Holland. The data in the table were confirming what we had originally suspected. The ALA in the cholesterol esters in the blood of the people in Crete was three times higher than that of the population of Zutphen (Table 11.6) and the LA (omega-6) was lower.

Table 11.6. Mean fatty acid composition of cholesteryl esters in serum of 92 elderly men from Crete and 97 elderly men from Zutphen.

	Crete (n = 92)	Zutphen (n = 97)	Significance
16:0	11.1 ± 0.1	11.9 ± 0.1	<i>p</i> < 0.001
18:0	0.7 ± 0.0	1.1 ± 0.0	<i>p</i> < 0.001
18:1 ω9	31.0 ± 0.3	21.4 ± 0.4	<i>p</i> < 0.001
18:2 ω6	41.9 ± 0.4	53.1 ± 0.7	<i>p</i> < 0.001
18:3 ω3	0.9 ± 0.1	0.3 ± 0.0	<i>p</i> < 0.001

Fatty acid composition of serum cholesterol esters (Percent, X ± SD). Source: Adapted from [20].

How exciting; we had just finished showing the reason for that. It was the high ALA in the diet of Crete from wild plants and escargots, along with high EPA and DHA from sardines, herring, and fresh fish that might be the common link between the diet of the people in Crete and Japan. The Japanese eat more fish than other populations and have high amounts of EPA and DHA in their blood. Thus, what accounted for the lower rate of heart disease in the Japanese than that of the Italians and the Yugoslavians could be the high fish intake of their diet.

3. The Lyon Heart Study

Serge Renaud had performed extensive studies on the effect of ALA in platelets and their effects on thrombosis [21]. Thrombosis is a condition in which the blood clots easily and forms small lumps, usually called thrombi. Many times, they dislodge from the blood vessels of the heart and cause a heart attack or stroke. After we had published our results on the diet of Crete and the importance of ALA plus EPA and DHA [15–17,22], Serge came to Washington to visit me to discuss the composition of the diet of Crete. He was already planning the now famous Lyon Heart Study [23] with his associate Michel de Lorgeril and was interested in the concept of the omega-6/omega-3 ratio and the need to balance it. Our data showed that the traditional diet of Greece, which was the diet prior to 1960, was very similar

to the Paleolithic diet in terms of the omega-6/omega-3 ratio, which is the diet we humans evolved on, and our genetic profile was established (Table 11.7) and that our genes were programmed to respond to [24].

Table 11.7. ω -6/ ω -3 ratios in various population.

Population	ω -6: ω -3
Paleolithic	0.79 ^{a,b}
Greece prior to 1960	1.00–2.00
Current United States	16.74
United Kingdom and northern Europe	15.00
Japan	4.00
India rural	5–6.1
India urban	38–50

^a Data from Eaton et al. (1998) *World Rev Nutr Diet*. ^b Assuming an energy intake of 35:65 of animal: plant sources. Source: Adapted from [24].

That ratio is 1–2/1 omega-6/omega-3. I suggested to Serge that the ratio of LA/ALA in the experimental group in the Lyon Heart Study should not be more than 4:1 LA/ALA. In 1995, Serge Renaud published the results of the Lyon Heart Study in the supplement to the *American Journal of Clinical Nutrition* under the title “Cretan Mediterranean diet for prevention of coronary heart disease” [25]. Serge understood the importance of a balanced ratio in making the diet of Crete the healthiest diet and wanted to distinguish the diet of Crete from other Mediterranean diets being characterized by a balanced omega-6/omega-3 ratio. In 1994 a year earlier, Serge’s Associate Dr. Michel de Lorgeril published the results of the Lyon Heart Study under the title “Mediterranean alpha-linolenic acid-rich diet in the secondary prevention of coronary heart disease” [23]. Serge knew that omega-3s made the difference in the results, that people in Crete lived longer and had less heart disease and cancer. Thus, both scientists distinguished the Cretan Mediterranean diet from other Mediterranean diets. It is not just any Mediterranean diet [26,27].

Renaud recognized that the traditional diet of Greece was different than the Key’s interpretation of olive oil and the term of “Mediterranean diet” for all Mediterranean diets is incorrect. Renaud set up The Lyon Heart Study [23,25] in which he compared the experimental diet group on the diet of Crete to the group on the American Heart Association Diet or prudent diet, which was based on high omega-6 fatty acids, low cholesterol, and low saturated fat. All subjects in the study have had one episode of heart attack already and were kept on their medications. They were divided into two groups: the experimental group on the diet of Crete as defined by me at a ratio of 4:1 omega-6/omega-3, and the group on the American Heart Association’s prudent diet. Six months into the study, differences were already noted. The experimental group on the diet of Crete had fewer total deaths. By the

end of the second year the study was interrupted, because the experimental group in the diet of Crete had no sudden deaths and 70% less deaths overall (Figure 11.4).

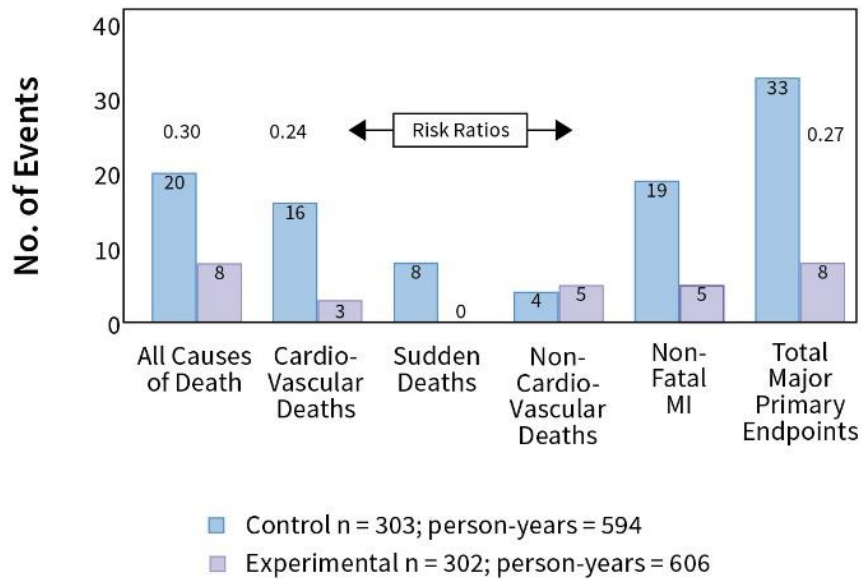


Figure 11.4. Mediterranean α -linolenic acid rich diet in secondary prevention of CHD: End points (27 months mean follow up). Source: Based on data from [23].

There was no need to continue the study further. The data were very clear. The diet of Crete decreased total deaths more so than any other diet or drug, and the AHA-prudent diet had failed. Despite these excellent results, the AHA continues to date to recommend an increase of vegetable oils high in omega-6 fatty acids to patients with heart disease [28].

The Lyon Heart study and our extensive studies proved that the healthiest diet in the Seven Countries Study was the traditional diet of Crete prior to 1960. The major characteristic was that the diet had not changed much since 3500 to 4000 years ago. In essence it was the diet of the Minoan period in terms of composition. First and foremost, the diet of Crete was balanced in the omega-6 and omega-3 fatty acids, was high in fruits and green leafy vegetables, grains such as wheat and barley to make bread and paximathia (doubly baked bread), nuts, fish, and meat from animals that grazed, and cooked with vegetables and, of course, eggs balanced in omega-6/omega-3 fatty acids (Table 11.8) [29].

Table 11.8. Foods eaten for every meal in Crete in 1960s.

	Breakfast	Mid-Morning	Lunch	Mid-Afternoon	Dinner
Monday Diet	Ksinohontros rusk, orange	Pear	Broad beans, onion, salad (cucumber, tomato, purslane, olives, olive oil), whole-wheat bread, apple, red wine	Walnuts, dry figs	Boiled vegetables, potatoes, olive oil, boiled egg, melon, red wine
Tuesday Diet	Rusk, cheese, apple	Orange	Snails , potatoes and vegetables, salad (tomato, cucumber, onion, olive oil), whole-wheat bread, red wine, longan	Halva (homemade)	Rice with spinach, yogurt, whole-wheat bread, longan
Wednesday Diet	Doughnuts (homemade) with honey, apple, herbal tea	Pear	Chickpeas, herring , salad (tomato, cucumber, olives, olive oil), whole-wheat bread, cherries, red wine	Walnuts, figs, raki	Stuffed tomatoes, whole-wheat bread, salad (tomato, cucumber, onion), melon
Thursday Diet	Fresh whole milk boiled with ground wheat	Melon	Fish , broad beans (puree), oil, lemon juice, whole-wheat rusk, salad (tomato, cucumber, olives, olive oil, onion), pear, red wine	Halva (homemade)	Lentils, salad (tomato, cucumber, olives, olive oil, onion), apple, red wine, cheese, whole-wheat bread
Friday Diet	Rusk, olives, herbal tea, apple	Apple	Beans, potatoes, whole-wheat bread, olives, orange	Walnuts, figs, raki	Broad beans, artichoke, olive oil, olives, whole-wheat bread, pear
Saturday Diet	Milk and whole wheat, melon	Apple	Chicken , okra, potatoes, salad (lettuce, cucumber, olives, olive oil)	Homemade cheese, pie, honey, coffee	Boiled vegetables with olive oil, rusk, red wine, melon
Sunday Diet	Homemade cheese pie with honey, melon		Rabbit , pasta, salad (tomato, cucumber, olives, olive oil, onion), rusk wine, orange	Coffee, halvas	Fish, fish soup with vegetables, rusk, red wine, apple

Source: Adapted from [29].

Excavations of cemeteries in Crete and also in Mycenae (Figure 11.5) clearly show that meat was cooked with vegetables, and studies from human bones showed that the deceased person's bones contained protein from marine sources, and in general men who ate more fish (protein) lived longer than those who did not, based on data from the analysis of the marine source protein found in the bone fragments from the excavated graves (16th Century B.C.) [30].

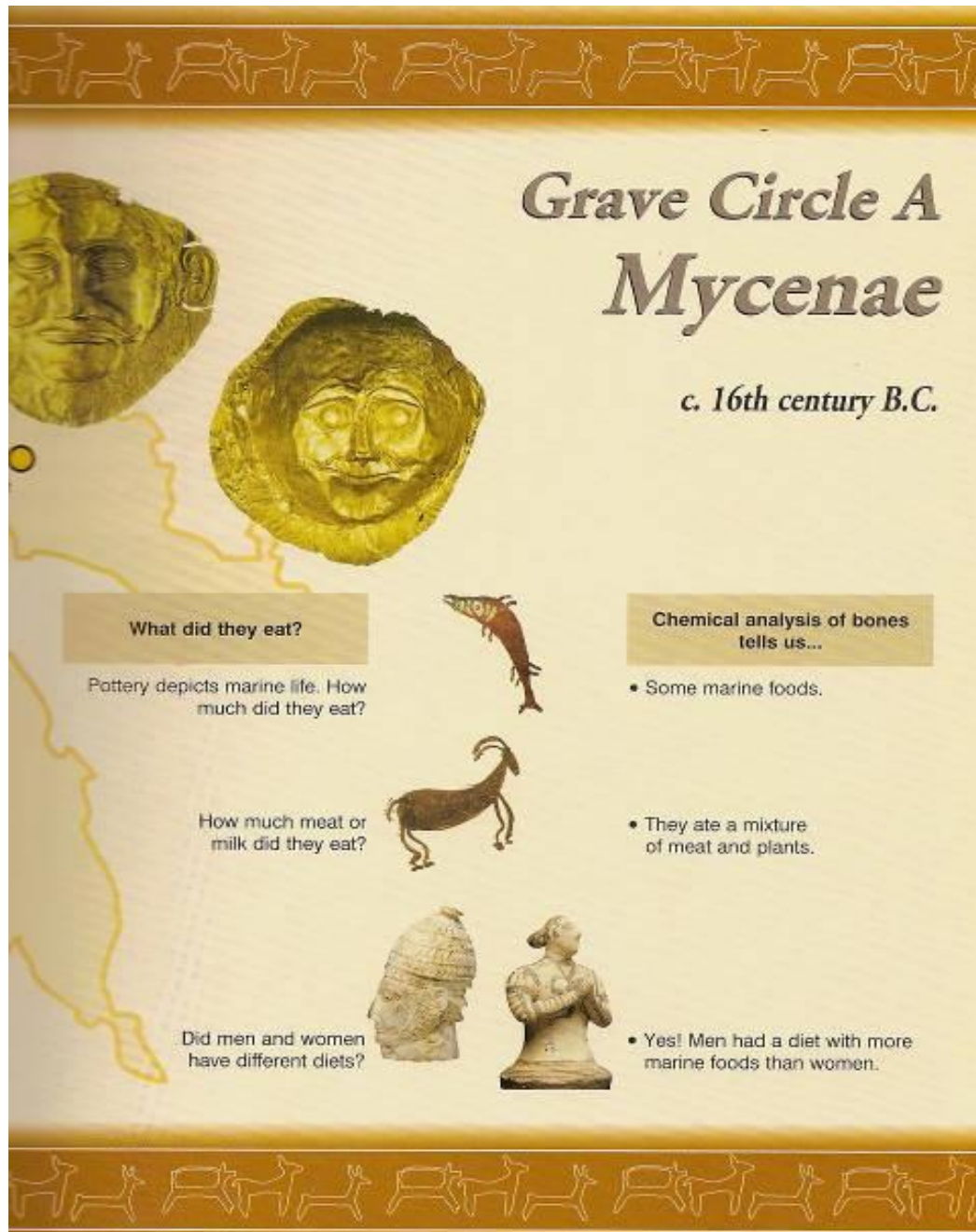


Figure 11.5. Minoans and Mycenaenans: Flavours of their time. Source: Reprinted from [30].

Keys and his collaborators were so convinced that saturated fat and cholesterol were the villains in increasing the risk for heart disease. However, they did not carry complete dietary studies, did not consider the importance of the evolutionary aspects of diet, and totally ignored the opposing functions of omega-6 and omega-3 fatty acids in human metabolism, despite the fact that their own data showed higher omega-3 fatty acids in the blood of the people in Crete [20]. I often wonder why they ignored their own data. Scientific data should never be ignored, and every effort should be made to try to understand and explain their function.

In 1977 I worked as a Clinical Research Associate in the Intramural Program of the National Institutes of Health (NIH) at the Clinical Center, in the section of Endocrinology and Metabolism at the National Heart, Lung and Blood Institute (NHLBI). The Director was Dr. Fred Barter, who had been trained by Dr. Fuller Allbright (the father of endocrinology) at Harvard (Mass General Hospital). So, Dr. Barter followed the teachings of Dr. Allbright and insisted that we “must explain every single datum” (note that datum is the singular for data). So, not only did Keys and company ignore their own data, but they led the US and the rest of the world down the wrong path, supporting concepts that not only were wrong but also interfered with health and led to chronic diseases.

More recently, Ramsden et al. [31] at the NIH revisited the harmful effects of high amounts of omega-6 fatty acids, especially LA in the diet. He re-evaluated the data from studies in Australia and the Minnesota Study. Both studies showed that the investigators did not distinguish between the two polyunsaturated fatty acid (PUFA) families in terms of LA and ALA and many of the beneficial effects were due to ALA. Yet despite all these studies showing that LA from vegetable oils (originally recommended by Keys et al.) is not fit for human consumption at such high amounts in the food supply, it still continues to be recommended by the Harvard School of Public Health and other epidemiologists. Furthermore, the AHA in 2009 recommended increasing the LA intake up to 10% of energy [28]. Yet there are published studies showing that women who carry certain genes double their risk for breast cancer as the LA in the diet increases above 17 g/day [32]. An increase to 10% of energy of LA as recommended by the AHA is equivalent to 22 g of LA on a 2000-calorie diet. Clearly something needs to be done both at the level of FDA to (1) distinguish omega-6 and omega-3 fatty acids on the label, and (2) AHA must carefully examine their statements so that it will not lead to an increase in breast cancer risk in women with special genetic profile.

Most of the emphasis on diet has been on studies in decreasing the risk for coronary heart disease, and many studies have shown the importance of the balance of omega-6 and omega-3 fats for health worldwide. The term “Mediterranean Diet” has been taken over by the marketers and as a result it is being defined not by its composition, but by dietary patterns, which are scientifically inadequate

and very wrong. Truly the only diet that has been extensively studied in terms of food composition is the traditional diet of Crete prior to 1960. Current so-called Mediterranean diets bear little resemblance to the traditional diet of Crete (Greece). Today, Mediterranean diets have high amounts of omega-6 fatty acids with a high (omega-6/omega-3 = 10–15/1) because of lower fish intake, and higher saturated fat and omega-6 fatty acids, and the diets are lower in omega-3 fatty acids, fish legumes, fruits, vegetables, and grains, and higher in refined flour and processed meat than the Mediterranean diets of the early 1960s when the Seven Countries Study was carried out. Even though today's Mediterranean Diets might include fish, most of it is farmed and as such contain less omega-3 and more saturated fat and omega-6 fatty acids than fish in the wild. This is because the composition of the food supply has changed even in the Mediterranean countries in which sunflower oil and soybean oil predominate over olive oil because olive oil is more expensive and chefs on TV keep on emphasizing "not to fry with olive oil" because it spatters! The chefs of today obviously do not know that their mothers and grandmothers in Southern Europe used olive oil in frying vegetables and other foods such as fish, liver and other types of meat from animals either domesticated or in the wild. Current Western diets consist of ultra-processed foods high in omega-6 fatty acids, salt, and added sugars, especially fructose, all of which lead to overeating (See Chapter on Ultra-processed and Imitation Foods).

My studies on the composition of the traditional diet of Greece (the diet prior to 1960) and the results of the Lyon Heart Study, and the more recent studies by Ramsden were very important in understanding and interpreting the results of the Seven Countries Study. It became obvious that the diet of Crete very closely resembled the Paleolithic diet in composition, especially in the intake of omega-6 and omega-3 fatty acids and antioxidants. As mentioned earlier in the diet of Crete prior to 1960, the omega-3 fatty acids were found in practically all meals. This is a very important finding because the fact that the essential fatty acids omega-6 and omega-3 were present in equal amounts it differentiated the diet of Crete from other Mediterranean diets, as well as diets from other parts of the world. This balance of omega-6/omega-3 fatty acids led to the diet of Crete being the most anti-inflammatory diet and the healthiest diet in comparison to other diets and especially the current Western diet.

4. The Greek Orthodox Church and Fasting

Fasting by avoiding meat, dairy products, eggs and occasionally fish was part of the tradition of the Greek Orthodox Church. It was followed by the Greek population for almost 2000 years, until about the 1960s when the diet began to change (Table 8) [29]. Fasting is still practiced by many people who live in the villages and small towns, especially the elders, and less by the young and those living in the cities.

Fasting is practiced 40 days before Easter, 40 days before Christmas, the first 15 days of August, every Wednesday and Friday, and an additional 15–20 days during the celebration of Patron Saints throughout the year. The total number of fasting days for most people is between 190–200 days, which is about half the number of days in a year. As a result, most days the people ate predominantly a vegetarian diet rich in all kinds of legumes, sourdough bread, snails, olive oil, olives, nuts, and a large variety of fruits and vegetables. These foods give the diet a good vegetarian base that was rich in antioxidants, vitamins, and minerals. You may be surprised that the fasting diet of Crete is rich in snails. Snails are not considered meat nor fish, and therefore are eaten throughout the year. Snails feed on grass that is rich in alpha-linolenic fatty acid. As a result, the snails in Crete are rich in omega-3 fatty acids, ALA, EPA, and DHA. Cretan snails are a perfect food rich in protein and omega-3 fatty acids and low in saturated fat. Monks and nuns living in the Greek monasteries keep fasting days faithfully, even today. The monks at Mount Athos have the strictest fasting traditions and a number of studies have documented their fasting and health. In addition to cultural and religious aspects of fasting, an important beneficial effect is the decreased caloric intake which decreases the risk of obesity and its comorbidities. When I was first married, I visited our parents' summer home, which is about 20 km South of Kalamata in Mani. The people of Mani were never occupied by Turkey, were independent, and had very similar habits to the people of Crete, including diet. My husband was surprised at how fit the men looked sitting at the coffee shops after the Sunday service. When I told him that they were above 85 years old and two of them had just had their 100th birthday, he was very surprised. Another characteristic is that overeating is considered bad manners, and obesity is considered a sign of lack of discipline or loss of self-control, both of which are condemned by the Greek culture. In this type of culture, fasting the way it is practiced by the Greek Orthodox Church combines caloric restriction and intermittent fasting (see the chapter on healthy aging).

5. Implementation of the Diet of Crete

The Lyon Heart Study clearly showed that the diet of Crete can be adhered to over a period of 5 years [21]. Figure 11.6 is the Greek Column Food Guide based on the diet of Crete [33].

GREEK COLUMN FOOD GUIDE



Genetics

Principles

Moderation

Variety

Proportionality

Energy intake =

Energy expenditure

Figure 11.6. Greek column food guide. Source: Figure by Alexandra I. Pinkerson.

The visualization of this food guide in the form of a Greek column includes the concepts of genetic variation and nutrition and balanced energy intake and energy expenditure; it is based on foods, not food groups. Although it excludes certain foods made with hydrogenated oils, it does not restrict the intake of naturally occurring foods. It also takes into consideration moderation, variety, and proportionality. The seven dietary guidelines modified from the Omega Diet [34] provide further information on how to implement the diet of Crete:

1. Eat foods rich in omega-3 fatty acids such as fatty fish (salmon, tuna, trout, herring, and mackerel), walnuts, canola oil, flaxseeds, and green leafy vegetables. Or, if you prefer, take omega-3 supplements.
2. Use monounsaturated oils such as olive oil, canola oil, hazelnut oil, and avocado oil as your primary fat.
3. Eat seven or more servings of fruits and vegetables every day.
4. Eat more vegetable protein in its natural form, including peas, beans, and nuts, not plant-protein-based imitation meat, chicken, and fish.
5. Decrease your intake of saturated fat by choosing lean meat over fatty meat and eat less butter by combining butter with olive oil as a spread and in cooking.
6. Avoid oils that are high in omega-6 fatty acids, including corn, safflower, sunflower, soybean, and cottonseed oils.
7. Reduce your intake of ultra-processed foods and trans fatty acids by cutting back on margarine, vegetable shortening, commercial pastries, deep-fat fried

food, and most prepared snacks, mixes, and convenience foods that come in a box.

6. Conclusions

In conclusion, studies on the Paleolithic and Mediterranean diets suggest that omega-3 fatty acids were present in practically all foods that humans ate and in equal amounts with omega-6 fatty acids. The depletion of the omega-3 fatty acids in Western diets is the result of agribusiness, modern agriculture, and aquaculture. The high ratio of omega-6 to omega-3 fatty acids (16–20/1 instead of 1/1–4/1) is the result of excessive production of vegetable oils and the indiscriminate recommendation to substitute saturated fat and butter with oils high in omega-6 fatty acids to lower serum cholesterol levels without taking into consideration their adverse effects on overall human metabolism. The results of the Seven Countries Studies and the Lyon Heart Study based on a modified diet of Crete indicate that a Paleolithic and Mediterranean type diet such as the traditional Greek diet of Crete balanced in omega-6 and omega-3 fatty acids and rich in vitamins C and E (fruits and vegetables) is associated with decreased rates of heart disease and cancer, more so than any other diet or drug intervention. What appears to be so special about the Greek diet of Crete relative to the other Mediterranean diets is the content of bioprotective nutrients, specifically the following: (1) a more balanced intake of EFAs from vegetable, animal and marine sources; a ratio of omega-6 to omega-3 fatty acids of 2/1 instead of the 15/1 in Western and Northern Europe and 16–20/1 in the USA; and (2) a diet rich in antioxidants, i.e., high amounts of vitamin C, vitamin E, b-carotene, glutathione, resveratrol, selenium, phytoestrogens, folate, melatonin, and other phytochemicals from green leafy vegetables; phenolic compounds from wine and olive oil; high intakes of tomatoes, onions, garlic, and herbs, especially oregano, mint, rosemary, parsley and dill, which contain lycopene, allyl thiosulfinates, salicylates, carotenoids, indoles, monoterpenes, polyphenols, flavonoids and other phytochemicals used in cooking vegetables, lean meat and fish. The diet of Crete consists of whole foods. Ultra-processed foods that make up 54–60% of foods in Western diets are not part of the traditional diet of Crete.

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BOX 1

I was able to precisely define the traditional diet of Crete prior to 1960 and also to discover the common link between the diets of Crete and Japan that decreased the risk of heart disease in those two populations located in two different continents and thousands of miles apart.

BOX 2

Prior to 1960, the people in Crete ate the meat of animals and birds in the wild and the meat of domesticated animals (goats, sheep, pork, veal) that grazed instead of being grain fed.

BOX 3

Their meat contained both omega-6 and omega-3 fatty acids, whereas the meats of animals that are grain fed as is in Western diets contain only omega-6 fatty acids in the form of LA and arachidonic acid (ARA). Because grain fed animals are fed corn and corn is high in LA, Western diets are high in both forms of omega-6 fatty acids. LA from oils and seeds, and ARA from animals (meat, eggs, and dairy).

BOX 4

The balanced omega-6 and omega-3s in the food of the people of Crete was found in every meal they ate. It was in the eggs and in the milk, and all the dairy products, and in the noodles and pasta that are traditionally made with eggs and milk. Such noodles and pasta are very different from the pasta you buy at the supermarket in a box, made with refined flour and water.

BOX 5

It was the high ALA in the diet of Crete from wild plants and escargots, along with high EPA and DHA from sardines, herring, and fresh fish that might be the common link between the diet of the people in Crete and Japan. The Japanese eat more fish than other populations and have high amounts of EPA and DHA in their blood. Thus, what accounted for the lower rate of heart disease in Japanese, than that of the Italians and the Yugoslavians, could be the high fish intake of their diet.

BOX 6

Our data showed that the traditional diet of Greece, which is the diet prior to 1960, was very similar to the Paleolithic diet in terms of the omega-6/omega-3 ratio, which is the diet which humans evolved on and on which our genetic profile was established and our genes programmed to respond to.

BOX 7

They were divided into two groups, the experimental group on the diet of Crete as

defined by me at a ratio of 4:1 omega-6/omega-3, and the group on the American Heart Association's prudent diet. Six months into the study, differences were already noted. The experimental group on the diet of Crete had fewer total deaths. By the end of the second year the study was interrupted, because the experimental group in the diet of Crete had no sudden deaths and 70% less deaths overall.

BOX 8

The diet of Crete decreased total deaths more so than any other diet or drug, and the AHA-prudent diet had failed. Despite these excellent results, the AHA continues to date to recommend an increase of vegetable oils high in omega-6 fatty acids to patients with heart disease.

BOX 9

The Lyon Heart study and our extensive studies proved that the healthiest diet in the Seven Countries Study was the traditional diet of Crete prior to 1960. The major characteristic was that the diet had not changed much since 3500 to 4000 years ago. In essence it was the diet of the Minoan period in terms of composition.

BOX 10

First and foremost, the diet of Crete was balanced in the omega-6 and omega-3 fatty acids, and was high in fruits and green leafy vegetables, grains such as wheat and barley to make bread and paximathia (doubly baked bread), nuts, fish and meat from animals that grazed and cooked with vegetables and of course eggs balanced in omega-6/omega-3 fatty acids.

BOX 11

Keys and his collaborators were so convinced that saturated fat and cholesterol were the villains in increasing the risk of heart disease that they did not carry complete dietary studies and totally ignored the opposing functions of omega-6 and omega-3 fatty acids in human metabolism, despite the fact that their own data showed higher omega-3 fatty acids in the blood of the people in Crete. I often wonder why they ignored their own data. Scientific data should never be ignored, and every effort should be made to try to understand and explain their function.

BOX 12

So, not only did Keys and company ignore their own data, but they led the US and the rest of the world down the wrong path, supporting concepts that not only were wrong but also interfered with health and led to chronic diseases.

BOX 13

Yet there are published studies showing that women who carry certain genes double

their risk for breast cancer as the LA in the diet increases above 17 g/day. An increase to 10% of energy of LA as recommended by the AHA is equivalent to 22 grams of LA on a 2000 calorie diet. Clearly something needs to be done both at the level of FDA to (1) distinguish omega-6 and omega-3 on the label, and (2) AHA must carefully examine their statements so that it will not lead to an increase in breast cancer risk in women with a special genetic profile.

BOX 14

The high ratio of omega-6 to omega-3 fatty acids (16.74/1 instead of 1/1–4/1) is the result of excessive production of vegetable oils and the indiscriminate recommendation to substitute saturated fat and butter with oils high in omega-6 fatty acids to lower serum cholesterol levels without taking into consideration their adverse effects on overall human metabolism.

BOX 15

The results of the Seven Countries Studies and the Lyon Heart Study based on a modified diet of Crete indicate that a Paleolithic- and Mediterranean-type diet such as the traditional Greek diet of Crete balanced in omega-6 and omega-3 fatty acids and rich in vitamins C and E (fruits and vegetables) is associated with decreased rates of heart disease and cancer, more so than any other diet or drug intervention.

BOX 16

The diet of Crete consists of whole foods. Ultra-processed foods that make up 54–60% of calories in Western diets are not part of the traditional diet of Crete.

Chapter 12. Dietary Guidelines for Americans

1. Politics, Congress and the McGovern Committee: Dietary Guidelines Instead of Dietary Goals
2. The 2015 and 2020 Dietary Guidelines for Americans

In 1976 I was the Executive Secretary of the Division of Medical Sciences at the National Academy of Sciences (NAS)-National Research Council (NRC). I had just completed the Asilomar Conference at the Asilomar in California on Recombinant DNA technology. Philip Handler was the President of the NAS and was vitally interested in bringing the NAS-NRC functions to the 20th Century. To do so, Handler began to set up a series of Visiting Committees to evaluate various Boards that operated out of the NRC for many years. One of those Boards was the Food and Nutrition Board (FNB), which was established in 1940 and had been in existence for over 35 years. Since the FNB had been transferred to the Division of Medical Sciences, I received the Visiting Committee's Recommendations. The Visiting Committee recommended the establishment of a Commission on Food and Nutrition to coordinate and manage all the NRC food-related activities, and a considerable shift in the emphasis of activities, in view of the changes taking place in available foods, and food habits and customs in the US. Today the old FNB operates out of the National Academy of Medicine (NAM) and develops the Dietary Guidelines for Americans every 5 years in accordance with laws passed by Congress.

1. Politics, Congress, and the McGovern Committee: Dietary Guidelines Instead of Dietary Goals

In 1978 I was appointed Chair of the Nutrition Coordinating Committee at the National Institutes of Health (NIH). It was the time of Senator McGovern's Committee on Nutrition and Human Needs. The Committee's name was the US Senate Select Committee on Nutrition and Human Needs and it was established in 1977. That Committee took it upon itself to tell Americans what to eat and considered everyone to be susceptible to chronic diseases to the same degree.

Their approach was based on the interpretation of the findings of The Seven Countries Study by Keys [1]. NIH was being pushed even more on that philosophy which was not based on science. The Committee was focused on dietary status—what people ate—not on nutritional status—what happens to food when eaten. They were not concerned about differences of individuals in their metabolism and developed the same dietary goals for everybody. A major part of my job was to review the NIH portfolio on Nutrition Research and coordinate our activities with the Department of Agriculture. As is customary, Senator McGovern transmitted his Committee's Report to the NIH for comment. As Chair of the Nutrition Coordinating Committee, I was responsible for drafting the NIH response, which later appeared in the paper I wrote in 1979 on "The scientific basis of the Goals: What can be done now?" [2]. In response to the McGovern Committee's report I pointed out that,

"The Committee's efforts in setting out dietary goals should be commended, even though universal dietary goals for the general public cannot be formulated or implemented.

Rather, dietary guidelines for specific groups of people to prevent certain conditions could be entertained. Based on that premise, certain dietary guidelines could be recommended now. We should endeavor to provide enough food to eliminate starvation, improve the nutritional status of hospitalized patients, reduce food intake in general and increase exercise to avoid overweight and obesity, increase the number of women who breast feed their babies, decrease the number of pregnant women who ingest alcohol, and reduce the frequency of sugar consumption, thereby focusing attention on avoiding sugar- rich snack foods between meals, in order to decrease dental caries. These guidelines could all be implemented through a well-structured program in nutrition education as part of health education that includes human biology, genetics, physical activity—that is, energy expenditure, and an understanding of probability and risk factors. Should increased emphasis on prevention of disease and the promotion of good health ever become more than pious hope, analysis of each genotype will be an essential prelude to guidance toward and away from particular conditions known to enhance or to threaten the individual's adaptive state. The genetic view, which predicts that not everyone is equally susceptible to all threats, suggests that non-susceptible persons should be spared the fearful anticipation of events that never materialize and the requirement to abide by rules that are, for them, irrelevant.” [2]

Thus, I coined the term of “Dietary guidelines” instead of “Dietary Goals” and the term “Dietary guidelines” continues to be in use today. Eventually the McGovern Committee accepted the National Institutes of Health (NIH) definition of Nutrition Research that included any research study in which a nutrient is a variable, including genetic variation and the role of nutrients in gene expression. The United States Department of Agriculture (USDA) and the staffers in McGovern’s Committee objected vigorously. I think it was because they did not understand Molecular Nutrition and genetic methods, and secondly because USDA did not support such research at that time. My Committee at the NIH worked very hard to develop the Human Nutrition Research Information Management System or (HNRIM) which was in use until six years ago (2016) and which was very successful because at a glance one could retrieve the number of grants in many categories funded not only by NIH and USDA, the two major Agencies of the Federal Government for the Support of Nutrition Research and Training, but also the US Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), the Department of Commerce (Fisheries), the Department of Defense (military nutrition), and the State Department (Agency for International Development—AID). All these agencies had representatives on the Joint Sub Committee for Human Nutrition Research and Training that operated in the Office of Science and Technology Policy (OSTP—The White House). The Committee was co-chaired by me and the USDA representative Mark Hegsted, a political appointee from the Harvard School of

Public Health, one of the coauthors of the two reviews in the NEJM on “Dietary fats, carbohydrates and atherosclerotic vascular disease” [3,4] paid by the Sugar Foundation that exonerated the effects of sugar intake and put all the blame on saturated fat and cholesterol in causing coronary heart disease (CHD). Hegsted had a lot of influence on the work of the McGovern Committee because one of his students (Chris Hitt) was on the staff of the McGovern Committee. However, my office of the NIH-Nutrition Coordinating Committee was responsible for the Executive Secretariat. This overall system gave NIH “control” of the scientific basis of nutrition, and in the coordination of nutrition research, which threatened both USDA and the food industry. The food industry certainly did not want any nutrition research funded by the Federal Government. They knew it all and they had been masters of marketing and controlled Food Production. In 1980, shortly after Mr. Reagan’s inauguration, the Multiple Risk Factor Intervention Trial (MRFIT) was completed. To the disappointment of the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI), the data did not show the expected difference in cholesterol lowering in decreasing the risk for CHD. In fact [5], it showed that there was an increase in mortality from cancer that related to the linoleic acid (LA) intake—the omega-6 fatty acid in vegetable oils. The higher the LA intake from vegetable oils, the higher the risk for cancer. The data from MRFIT showed that most certainly omega-6 fatty acids did not prevent heart disease, just as the 1965 study in England had found, which also showed that it might increase the risk for CHD [6,7].

2. The 2015 and 2020 Dietary Guidelines for Americans

In 1979, Congress passed a bill requiring the US government to establish a Dietary Guidelines Advisory Committee to develop dietary guidelines that would be updated every five years. The first such guidelines were developed in 1980 and the last ones were published in June 2020. The preliminary report, released in February 2015, had generated considerable media attention by reversing decades of dogma with the statement that “cholesterol is not a nutrient of concern for overconsumption,” but in the final 2015 report, this statement had been removed and instead suggested that “individuals should eat as little dietary cholesterol as possible” [8]. So, here are two different versions. Which one should people believe or follow?

A number of individuals and organizations have commented on the 2015–2020 Dietary Guidelines without any of them suggesting that the guidelines are based entirely on scientific evidence. In the *Annals of Internal Medicine*, which is the official journal of the American College of Physicians—the powerhouse of American Medicine—Dr. Steven E. Nissen provides a comprehensive critique in his article [9] “U.S. Dietary Guidelines: An Evidence-Free Zone”. He questions, “Which version should we believe? How can the same committee arrive at diametrically opposite

conclusions? Now that the final report is available, it is prudent to examine how, for decades, the US. medical establishment has erroneously advised the population to severely limit cholesterol intake and to consider whether other conventional dietary advice will eventually prove faulty.” How strong is the scientific evidence supporting the current guidelines? Most of the recommendations are similar to previous guidelines, advising the population to limit their intake of sodium, saturated fat (substituting with unsaturated fats), and simple sugars, and to increase consumption of fruits, vegetables, and nuts. Dr. Nissen questions the current 2015 Dietary Guidelines, as previous guidelines since the first ones in 1980 were not based on high-quality randomized, controlled clinical trials (RCTs). RCTs are needed to obtain meaningful clinical outcomes for dietary interventions. Dr. Nissen states, “The report repeatedly makes recommendations based on observational studies, and surrogate end points, failing to distinguish between recommendations based on expert consensus rather than high-quality RCTs. Unfortunately, the current and past US. dietary guidelines represent a nearly evidence-free zone.”

The lack of high-quality RCTs has left dietary advice to cult-like advocates, often with opposite recommendations. One group advises virtually complete elimination of carbohydrates from the diet, whereas others promote a virtually fat-free diet and others write books about “detoxification diets”. A search of online bookstores and websites reveals an unlimited choice of diets, all with extraordinary claims for incredible weight loss and health benefits.

The peer-reviewed medical literature has also created a great deal of misinformation. One observational study, the Nurses’ Health Study (NHS), has generated a plethora of questionable dietary claims. One NHS report claims that eating one ounce of nuts twice per week reduces the risk for pancreatic cancer by 35% [10] and another claims a 33% reduction in the risk for chronic obstructive pulmonary disease for the top quintile of consumption of whole grains, polyunsaturated fatty acids, nuts, and long-chain ω -3 fats and low intakes of red processed meats, refined grains, and sugar-sweetened drinks [11]. This is the group that promotes high intakes of omega-6 fatty acids. Yet another NHS report claims that daily consumption of more than two servings of artificially sweetened soda is independently associated with doubling the risk for a 30% or greater decline in renal function [12].

Dr. Nissen states “These types of poorly controlled observational studies based on food frequency questionnaires and self-reported heights and weights would be difficult to publish in the peer-reviewed literature in any other field of medical science, but they are often reported with dramatic headlines by “respected news” (news that fits to print!) organizations. Findings that suggest harm are particularly attractive to the media, such as a published study that claimed aspartame consumption doubles the risk for multiple myeloma [13]. Such outrageous claims strain thoughtful

scientists, but have little difficulty finding a journal that will publish them and less difficulty finding media outlets that will bring this “science” to public attention. Typically, dietary studies rely on a similar and flawed method, use of periodic dietary questionnaires to ascertain the eating patterns of participants. Recall bias and residual confounding plague such methods. There would be less interest in cult diets and poor-quality studies if nutritional research included properly designed and executed RCTs, but few exist.” [9]

In commenting on the 2015 Dietary Guidelines, DiNicolantonio [14] singled out four areas that lacked sound scientific evidence. These include:

1. “Allowing approximately half of all grains to be refined;
2. The continued recommendations for fat-free or low-fat dairy and limitation of saturated fat intake to <10% of calories;
3. Sodium intake <2300 mg/day; and
4. Consumption of up to 27 g/day of “oils” (high in polyunsaturated fat or monounsaturated fat). These types of recommendations may increase the incidence of cardiometabolic disease, diabetes, obesity, dyslipidemia, cardiovascular disease, and possibly cancer. Dr. DiNicolantonio makes the point that once again the DGA have once more missed the opportunity to develop a simple memorable effective dietary message to Americans: eat natural food and avoid processed food, which would have been a better message.”

The concern expressed by many scientists in the lack of a scientific base on the development of Dietary Guidelines, as well as the selection process of the Committee Members who developed the 2015 Dietary Guidelines, attracted the attention and concern of Congress, which mandated, in the Consolidated Appropriations Act of 2018, two reports from the National Academy of Sciences (NAS), National Academy of Engineering (NAE), and the National Academy of Medicine (NAM). The first report was released in February 2017 and suggested changes to be made in the selection process of members of the Dietary Guidelines Advisory Committee (DGAC). The second report was published in 2017 by the same groups, NAS, NAE, and NAM. In this second report, the DGAC is called the DGSAC to stand for the Dietary Guidelines Scientific Advisory Committee. This second report focuses on a process redesign in developing and updating the guidelines, beyond just the selection of members for the DGSAC. In response to the congressional request, the National Academies set up a committee which was specifically asked to evaluate the process, but not to evaluate the content, recommendations, or scientific justifications used in the current 2015 or past editions of the Dietary Guidelines for Americans (DGA).

Over time the role of DGA has become two-fold. (1) It provides the public with science- based dietary advice on eating patterns that can help reduce the risk of developing a chronic disease and (2) it provides food base guidance (types and composition of foods to be used) in federal nutrition programs, such as the National

School Lunch Program; the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); and many others.

Despite the huge amount of effort that goes into establishing the DGA, fewer than 10 percent of Americans actually follow the guidelines. Congress has suggested that the low level of adherence could be the result of a lack of confidence, in part because of how DGA have been developed and hence a low level of trust in the ultimate recommendations. Therefore, Congress directed USDA to engage the National Academies (NAS, NAE, NAM) to establish an ad hoc Committee to conduct a comprehensive evaluation of the process used to establish the DGA. The report states:

“The adoption and widespread translation of the DGA requires that they be universally viewed as valid, evidence-based, and free of bias and conflicts of interest to the extent possible. This has not routinely been the case. The DGA have been challenged, with critics questioning the validity of the evidence assessments. This has raised concerns in Congress about the trustworthiness of DGA. This second report recommends changes to the DGA process to reduce and manage sources of bias and conflicts of interest, improve timely opportunities for engagement by all interested parties, enhance transparency, and strengthen science in the process.”

In December 2020, the USDA and US Health and Human Services (HHS) Department, issued the 2020–2025 Dietary Guidelines for Americans. Yet like the previous DGA, the 2020–2025 DGA do not reflect the best available evidence, and the recommended intakes for food groups are not optimally healthy or environmentally sustainable. A number of scientists have commented on these issues [15].

The 2020 Dietary Guidelines for Americans were met with a great till of criticism about their scientific base. Over 38,000 public comments were received. In their paper “Food for Thought: A natural language processing analysis of the 2020 Dietary Guidelines public comments”, Lindquist et al. concluded that “public comments were diverse, held conflicting viewpoints, and often based comments on personal anecdotes or opinions without citing scientific evidence. Because the volume of public comments has grown dramatically, natural language processing (NLP) has promised to assist in objective analysis of public comment input” [16]. The 2010 Dietary Guidelines Scientific Report received 2000 comments, the 2015 report received more than 29,000 comments and the 2020 report received 38,368 comments [16]. After publication of the 2015 DGA, significant questions arose about the underlying process for developing the guidelines, including questions about public input and transparency. One reason for these questions was the sheer volume of public comments on the scientific report that supported the final guidelines. On the basis of the number of public comments, the US Congress requested a consensus

report from the National Academies of Sciences, Engineering, and Medicine on making the process for producing the 2020 report more transparent, inclusive, and science driven. Despite this, the report did not address transparency involving the analysis of the public comments.

As in previous editions of DGA, i.e., the 2015 DGA, the 2020–2025, some key recommendations of the current DGA are not based on the best available evidence, and the recommended intakes of food groups are not optimally healthy or environmentally sustainable. The DGA set up an upper limit for sugar at 10% rather than at 6% as recommended by the 2020 US Dietary Guidelines Advisory Committee (DGAC). Drinking one 20 ounce soda is about 240 calories from sugar, which is above the 10% limit for added sugars for most people.

Again, the 2020–2025 DGA support a predominant animal-based diet as the previous DGA. Although DGA acknowledge the healthfulness of the Mediterranean dietary pattern, they do not mention olive oil or the need to balance the omega-6/omega-3 fatty acid ratio. No mention is made to the fact that Mediterranean and vegetarian dietary patterns have a lower environmental impact than current Western diets, which are high in foods from animal sources. The DGA need to focus on promoting the availability, accessibility, and affordability of nutritious whole foods and regulatory reforms requiring the use of processing aids to be declared on food labels. Brazil and Israel have translated the science into national food-based dietary guidelines and recommendations to avoid ultra-processed foods.

Although the DGA acknowledge the healthfulness of the Mediterranean and vegetarian dietary pattern, the recommended intakes of specific foods across the life cycle exclude these dietary patterns, as the recommendations support a heavily US-based style pattern and do not mention olive oil. The traditional diet of Crete described in the Chapter “The Diet of Crete” is the healthiest diet. The Mediterranean dietary pattern, which emphasizes plant foods and low intakes of red meat and dairy foods, is associated with lower risks of many health outcomes, including cardiovascular disease, cancer, type 2 diabetes, neurodegenerative disease, and total mortality. A healthy dietary pattern consists of nuts, seeds, legumes, fish, and lots of fruits and vegetables, olive oil, or other monounsaturated oils, and a balanced omega-6/omega-3 ratio 1–2/1 or up to 4/1 with moderate amounts of meat and meat products. Food should be prepared by boiling, sauteing or in the form of salads or soups, and frying should be used sparingly. Major key issues such as a high omega-6/omega-3 ratio and the pro-inflammatory status of current American diets are not dealt with by DGA. The importance of genetic variation in interacting with various dietary components that increase susceptibility in certain populations must be considered. Ultra-processed foods and imitation foods must be avoided since they have a high omega-6/omega-3 ratio of 11.1/5.1. All scientific evidence points to the fact that we urgently must change the foods we eat and how we produce them. This

urgency has been heightened by the COVID-19 pandemic, the outcomes of which are made worse by a high omega-6/omega-3 ratio and obesity, both of which are associated with inflammation.

The problem of providing effective leadership in the US is greatly complicated by the absence of a “Lead Agency”. Nutrition Activities and concerns are dispersed throughout the government and private sector. No agency has been chosen to establish, or assigned, or has assumed leadership in establishing National Nutrition Policies.

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Part V

Chapter 13. So How Can You Have the Healthiest Diet Today?

Hippocrates defined “diet for Health” as including food, physical activity, the environment, and family (genetics). In determining nutrition and food needs, it is essential to consider two very important aspects.

1. The effects of food production on the environment and;
2. The food composition of foods, which must be consistent with the evolutionary aspects of diet and exercise, and the frequency of genetic variants in the population.

The Mediterranean diet has been well characterized scientifically. It is also recognized as a healthier dietary pattern, and it is appreciated for its lower environmental impact. The Mediterranean diet has been selected by the Food and Agriculture Organization (FAO) and the International Centre for Advanced Mediterranean Agronomic Studies (CIHEAM) for the assessment of diet sustainability models. However, despite the well-documented health and environmental benefits of the Mediterranean Diet, current data show a decline in adherence to the Mediterranean Diet pattern in the Mediterranean area.

Sustainable diets are the diets with low environmental impacts, which contribute to food and nutrition security, and to healthy life for present and future generations. Sustainable diets are protective and respectful of biodiversity and ecosystems, and are eventually acceptable, accessible, economically fair and affordable, nutritionally adequate, safe and healthy, while optimizing natural and human resources (FAO/Biodiversity, 2010) (Figure 13.1) [1].




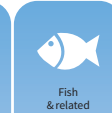
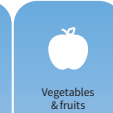
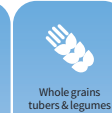



	 Dietary diversity	 Food energy intake/expenditure	 Animal products	 Fish & related	 Vegetables & fruits	 Whole grains tubers & legumes	 Processed foods	 Food losses & waste	 Cooking fuels
Healthier & more sustainable diets	High	Balanced	Low (all parts eaten)	Low to moderate (sustainable)	High (minimally processed)	High	Avoided	Low	Efficient
Diets of the healthy wealthy	High	Balanced	Moderate to high (lean meats)	High	High	Low to high	Avoided	High (consumer)	Heavy use
Western-type diets (global)	Low	Excessive	High	Low to high (unsustainable)	Low	Low	Avoided	High	Inefficient
Diet of the poor in poor countries	Low	Insufficient	Low	Low	Low	High (legumes often low)	Low (but growing)	High (spoilage) Low (consumer)	Inefficient

Figure 13.1. Health and environmental impacts of different diets. Source: Reprinted with permission, from [1].

This figure compares “win-win” diets that are both healthy and have a low environmental impact with other dietary patterns seen around the world today.

The typical Western diet, which is both unsustainable and unhealthy, is growing in prevalence around the world [1].

Germany and Sweden are just two of only four countries in the world that include sustainability criteria in their dietary guidelines. Nearly all governments have failed to promote sustainable diets. The government recommendations do not go far enough to meet targets relating to carbon reduction.

Characteristics of diet with low environmental impacts include:

- (1) Moderate consumption of meat;
- (2) Very limited consumptions of foods high in salt, fat, and sugar;
- (3) Small quantities of sustainably sourced fish;
- (4) More fruits and vegetables.

All four are consistent with good health.

The diet of Crete described in this book is the healthiest and most sustainable diet (Figure 13.2).

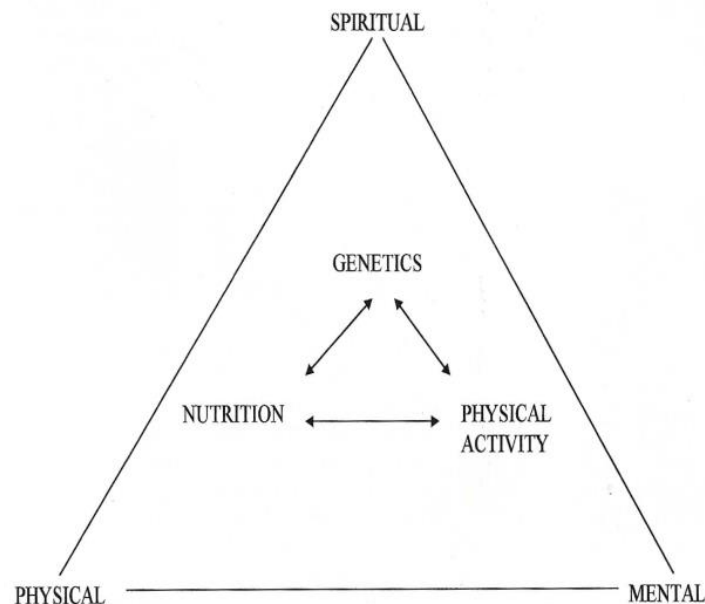


Figure 13.2. The interaction of genetics, nutrition, and physical activity influences the spiritual, mental, and physical aspects of health. Source: Figure by Artemis P. Simopoulos, MD.

A healthy diet is defined as being consistent with increased amounts of fruit, nuts, vegetables, whole grains, fish, dairy products, moderate amount of meat and reduced in refined grains, processed meat, ultra-processed red meat, sugar sweetened beverages (SSBs), trans fats and sodium, and a balanced omega-6/omega-3 fatty acid ratio. By now you should be well informed of the components of a healthy diet for you.

I. As a first measure you must change the cooking oils. Do not use any of the oils high in omega-6 oils such as:

- Safflower (77% omega-6);
- Sunflower (77% omega-6);
- Corn oil (63% omega-6);
- Cottonseed (50% omega-6);
- Soybean (37% omega-6).

II. Use instead:

- Extra-virgin olive oil for salads (less than 6–10% ω -6);
- Regular olive oil for cooking (less than 6–10% ω -6);
- Mix olive oil with canola for cooking to increase omega-3 fatty acid (ALA) content of food;
- Preferably cold press organic canola oil (20% ω -6, 10% ω -3 6/3 = 2/1);
- Try monounsaturate oils (macadamia nut oil, hazelnut, and avocado oil);

III. -Eat fresh fish 2–3 times/week (preferably wild caught); -Eat sardines and herring that are high in EPA and DHA; either fresh or canned in olive oil are cheap and healthy;

IV. The following oils can be mixed with olive oil for making bread, muffins, and cakes.

Oils	ω -6/ ω -3 Ratios
Canola Oil –	2/1
Perilla Oil –	1/1
Flaxseed Oil –	1/1
Chia Oil –	1/1

V. Eat eggs from chickens that are grass-fed, or their feeds contain flaxseeds and/or fish meal. Such feeds lead to the production of eggs enriched with omega-3 fatty acids almost similar to the Greek egg obtained naturally from chickens that fetch their own food and are not fed corn and have a ratio of ω -6/ ω -3 equal to 1.

VI. Dairy Products. Under normal conditions of pasture feeding, grass-fed animal meat, milk, and dairy will contain omega-3 fatty acids. Cheese and yogurt without added sugar may be consumed daily. Full fat—no need to select low-fat dairy products. Imitation milks made from seeds or nuts are not recommended because they are ultra-processed foods.

VII. Remember in the diet of Crete, the omega-6 and omega-3 fatty acids were present in every meal. This is quite different from eating fish 2–3 times/week. Consider daily fish oil supplements in order to have a diet similar to the diet of Crete (Greece) relative to a balanced omega-6/omega-3 fatty acid ratio,

in which the omega-3 fatty acids were present in every meal the people of Crete ate.

- VIII. Meats. Grass fed meat is the best. Agriculture needs to cut down the enormous meat production, which is not healthy in its present form, neither for people nor the environment. Agriculture must move more towards grass fed animal production.
- IX. Increase the amounts of legumes in your diet. Eat them daily. Learn to use them in soups, salads, and spreads with crudités (vegetables) instead of cream cheese and potato chips. Hummus made with chickpeas or any bean spread with yogurt, lemon juice, and olive oil are a healthy spread alternative to those made with mayonnaise and sour cream, which should be used sparingly.
- X. Eat salad at least once/day. Learn to start your meals with a salad made with olive oil or a mix of olive oil and canola oil, lemon or vinegar dressing.
- XI. Green leafy vegetables such as spinach, any kind of lettuce, arugula, watercress, or the cruciferous, vegetables such as broccoli, cabbage, Brussels sprouts and cauliflower (either cooked or raw) could be part of every meal. Learn to cook them lightly and serve them with olive oil/lemon juice dressing or oil vinegar dressing.
- XII. Bread—sourdough, whole wheat or multigrain
- XIII. Restrict refined flour, sugar, omega-6 oils and salt (sodium).
- XIV. Restrict sugar-sweetened beverages. Drink tea, coffee, and plenty of water.
- XV. Restrict alcohol.
- XVI. Avoid smoking.
- XVII. Walking is the easiest form of exercise. Exercise is essential for health. Exercise daily by walking, biking, weightlifting, dancing, and whatever activity you prefer.

Snacks should consist of some kind of fresh or dry fruit or nuts. One of my favorite snacks in the winter are dry figs (Kalamata) stuffed with almonds or walnuts. Figs are high in fiber, calcium, magnesium, and their little yellow seeds are full of ALA. They are also high in phenolic compounds. When you stuff figs with almonds you increase the protein content of the snack, and when you stuff figs with walnuts you increase the omega-3 content of the snack as well. Just compare the composition of stuffed figs versus chocolate chip cookies. These are both snacks, but vary so much in composition. One is healthy (figs) and the other is unhealthy (cookies). That is

why dietary patterns are misleading but studies on food composition provide the right information for you to decide.

Industry and its supporters use terms such as “Mediterranean Pantry.” There is no such thing as a Mediterranean pantry or diet. The term “Mediterranean” is a geographic term, not a scientific one. North African countries such as Egypt, Libya, Algeria and Morocco, and parts of the Middle East are all bordering the Mediterranean Sea, but differ from Southern Europe in culture, food preparation (they use less olive oil), types of meats, and wine (they do not eat pork or drink wine) because their religion (Islam) does not permit pork or alcoholic drinks. Some people insist in using the term “Mediterranean Diet” for various reasons, none of which are scientific. I and others have looked at how the Med Score compares to the omega-6/omega-3 ratio [2]. In today’s definitions, Mediterranean Diets are described as being high in fruits, vegetables, nuts, fish, olive oil, and low in meat. Such a diet provides a score that is used in epidemiologic studies. The higher the score, the healthier the diet and the lower the omega-6/omega-3 ratio. The diet of Crete has a high Mediterranean score and a balanced omega-6/omega-3 fatty acid ratio. Today, the diets of Greece and that of Italy and Spain have 10–15 times the amount of omega-6 fatty acids and a very unbalanced ratio of omega-6/omega-3 15/1 than prior to 1960. This is because olive oil is expensive, and the EU has flooded these countries with cheap sunflower oil, farmed fish, and meat from animals that are grain fed and do not contain omega-3s in their flesh. The Greeks of today and anyone interested in staying healthy and living longer should eat less meat, more legumes, fruits and vegetables, and wild-caught fish, and slowly return to their traditional diet prior to 1960. So, for that matter, so should the rest of the world. Practically all traditional diets before the onslaught of Western diets with high amounts of ultra-processed foods high in omega-6 oils (soybean, sunflower, corn, safflower, cottonseed) and high-fructose drinks had a composition similar to the diet of Crete prior to 1960.

There is no question that, worldwide, today’s diets are depleted of their omega-3 fatty acid content and flooded with omega-6 and high amounts of fructose (from high-fructose corn syrup) and sugar in beverages, and processed food high in sodium, which is ultra-processed and leads to overeating and weight gain. Although the high amounts of omega-6 in the food supply were the results of the misinterpretation of the data from the Seven Countries Study by Keys et al in the 1960s, the messages to increase linoleic acid have been continuing into the 1970s, 1980s, 1990s, and beyond in 2020 to this day by the food industry, pharmaceutical companies, the American Heart Association (AHA), the Food and Drug Administration (FDA), and more recently by the EAT Commission [3].

The use of high-fructose corn syrup and its incorporation in processed foods and beverages have spread worldwide because fructose is very sweet and very cheap, along with the fact that fructose does not increase the level of blood sugar, as sucrose

does, because fructose goes directly into the liver and becomes fat. In the past, industry began to advertise this fact as being good for diabetics! However, fructose in the liver makes triglycerides and leads to fatty liver known as hepatic steatosis or non-alcoholic fatty liver disease. In animal experiments the combination of high fructose and very low omega-3 fatty acids leads to metabolic disease of the brain, which can be prevented by omega-3 fatty acids [4]. More recent studies showed that these effects occur as a result of expression of genes by fructose that are detrimental to the brain metabolism and can be reversed by omega-3 fatty acids such as DHA.

Obesity risk increases by a high omega-6 fatty acid intake and low omega-3 [5]. Of course, today food is high in omega-6 fatty acids and that leads to an increase in the number and size of fat cells in white adipose tissue, whereas omega-3 fatty acids increase browning of white adipose tissue, which produces heat and leads to weight loss. Equal amounts of omega-6/omega-3 fatty acids have opposing effects on human metabolism. Therefore, a calorie of omega-6 does not have the same effect as a calorie from omega-3 on human metabolism. Although obesity may be the end result of excessive food intake relative to expenditure, foods high in fructose stimulate the appetite center and the brain demands more food, whereas glucose does not increase appetite. Therefore, a calorie from fructose is very different metabolically from a calorie obtained from consumption of glucose. Yet despite all this evidence, governments continue to ignore the enormous intake of vegetable oils high in omega-6 and the high fructose in processed foods. These two factors, high fructose and omega-6, but low or depleted omega-3s, account for the persistent increase and regain of weight loss in the US and elsewhere. No government has been able to reduce obesity. It is not a matter of counting calories, but the unnatural composition of the food supply that has created this situation since 1945.

Knowing your family history [6] might encourage you to make dietary changes that I have recommended to you. Genetic testing for certain diseases could provide more specific information. The combination of knowledge from (1) family history and (2) from genetic testing will lead to personalized nutrition and personalized medicine. Genetic information could tell you that there is an increase in risk for developing a disease; people pay more attention to the advice given based on such tests. Genetic testing should be performed in specialized centers by physicians with competence in ordering, interpreting, and managing the results. Genetic testing in all circumstances requires careful consideration of the clinical context. I believe that it is essential that your personal physician should order genetic tests as needed and along with a genetic counselor and dietitian discuss the:

- (1) Results of the genetic tests and provide advice to you.
- (2) Make sure that you understand the advice given to you about the risk.
- (3) The team (your physician, genetic counselor and dietitian) should provide advice on dietary and other lifestyle changes, such as physical activity and the

use of drugs as needed to compliment dietary treatment and lifestyle changes for your health.

Following steps 1, 2, and 3 will provide you personalized nutrition information, which is dietary advice specifically tailored to you. The National Institutes of Health (NIH) have inaugurated a new research program called Precision Nutrition [7] that is based on information about genetics, diet, physical activity, environmental factors, etc. This program is meant to collaborate with the program ‘All of Us’ that started in 2018 [8]. These two programs will be instrumental in developing advice based on personalized nutrition and medicine.

In the meantime, each one of us must become knowledgeable about the unhealthy aspects of ultra-processed foods and industrial oils high in omega-6 fatty acids and avoid them. I believe that this book provides the scientific evidence for you to avoid current Western diets and follow a diet that is consistent with the diet we evolved, and to which our genes were programmed to respond, which is the diet of Crete described in this book illustrated in Figure 13.3.

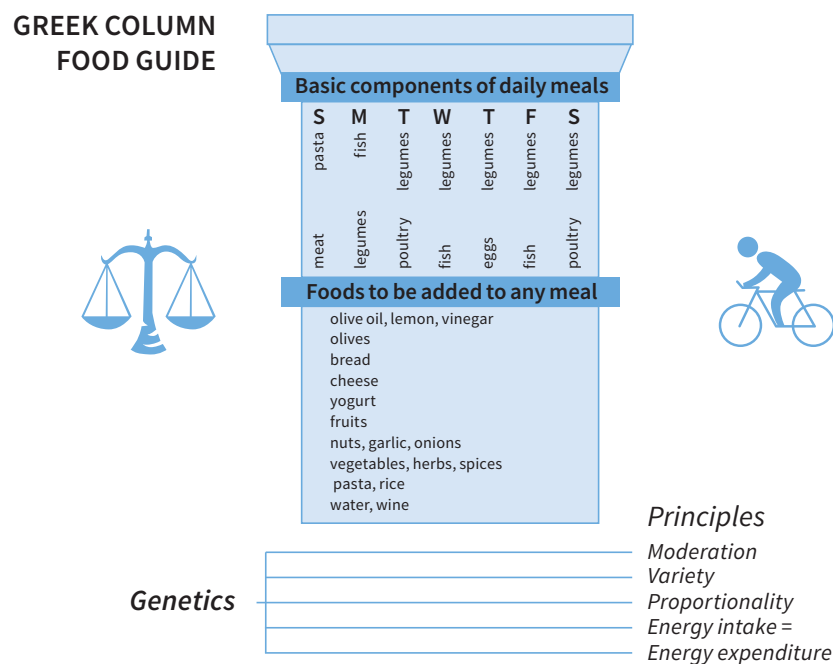


Figure 13.3. Greek column food guide. Source: Figure by Alexandra I. Pinkerson.

The current dietary guidelines (2020–2025 and 2015) are not based entirely on scientific evidence and are not necessarily applicable to the individual (meaning you).

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