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**Cultural, Genetic
and Metabolic Aspects**

Editor
A.P. Simopoulos



WILEY

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Nutrition and Fitness: Cultural, Genetic and Metabolic Aspects

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Shanghai, November 30 to December 2, 2006

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Nutrition and Fitness: Cultural, Genetic and Metabolic Aspects

Volume Editor

Artemis P. Simopoulos

The Center for Genetics, Nutrition and Health, Washington, D.C., USA

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Artemis P. Simopoulos

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Dedication

The proceedings of the conference are dedicated to the concept of positive health as enunciated by the Hippocratic physicians (5th century BC).

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.

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Olympian Shanghai Ode

Olympians and Taoists
both philosophize,
look inward and discover
higher states of mind.

When ancient days were new,
both cultures had a clue:
control diet and exercise!
In two thousand and six
the first conference was fixed
for fitness and food in Shanghai.

China welcomes Greece and their
Concept of Positive Health,
applauding the relation
to the way the Chinese felt.

In two thousand and eight
the Olympians create
a reason for China to celebrate.
The way Greece plays her part
in sports, science and art
has won deep respect from the Chinese heart.

Lee Pinkerson, 2007
www.leepinkerson.com

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Preface

The papers in this volume of *World Review of Nutrition and Dietetics* consist of selected papers presented at the Nutrition and Fitness Conference in Shanghai, China, in November 2006. The conference was under the auspices of the World Council on Nutrition, Fitness and Health (WCNFH). Since 1988, the International Conferences on Nutrition and Fitness (ICNF) have been held every 4 years in Greece, prior to the Olympic Summer Games, either at Ancient Olympia or in Athens. The ICNF are dedicated to the concept of 'Positive Health' as stated by Hippocrates in the 5th century BC. The first conference took place at Ancient Olympia in 1988. At that time, the concept of combining 'Nutrition' and 'Fitness' in a scientific conference was a 'new' one. These two disciplines or fields have moved closer since then and today the 'Nutrition and Fitness' concept has been incorporated in the World Health Organization (WHO) program under the title 'Global Strategy on Diet, Physical Activity and Health' (May 2004).

Similarly, the concept of Positive Health, based on the triad of Genetics, Nutrition and Physical Activity, is attracting many scientists in the areas of Nutrigenetics and Nutrigenomics. The establishment of the new International Society of Nutrigenetics/Nutrigenomics (ISNN – www.isnn.info) and the very successful 1st Congress of ISNN bear evidence to the fact that 'old concepts' are now not only being accepted but their importance is recognized worldwide and rapid progress is taking place. Because of the rapid advances in Genetics, Nutrition and Fitness, it was felt that the meetings should be held every 2 years instead of only every 4 years only prior to the Olympic Summer Games. It was thus agreed by the WCNFH that the ICNF will be held every 2 years as follows.

The country that is holding the Olympic Summer Games will hold a Nutrition and Fitness conference 2 years prior to the games and in the Olympic year, the ICNF will always be held at Ancient Olympia or in Athens.

This volume begins with the keynote presentation 'Nutrition and Fitness from the First Olympiad in 776 BC to the 21st Century and the Concept of Positive Health' by Artemis P. Simopoulos. The paper is a rather extensive overview of the concepts of Olympism, which are unique to Greek thought and the Concept of Positive Health. In fact, the first evidence of the importance of food and exercise in health appears in the Hippocratic corpus in the 5th century BC. Diet did not refer simply to food, but to the whole lifestyle, including nutrition and exercise. Among the Greeks, the concept of Positive Health was important and occupied much of their thinking. Those who had the means and leisure applied themselves to maintaining positive health. Today the need for proper diet and exercise for health and well-being is well recognized and major recommendations to that effect have been made by many national and international organizations. The traditional diet of Greece as exemplified by the diet of Crete was shown by the Seven Countries Study to be the healthiest. In the paper, Dr. Simopoulos gives a detailed description of the components of the traditional diet of Greece and shows that the Greek diet is very similar to the Paleolithic diet on which humans evolved. A major characteristic of such a diet is that it is balanced in the ω -6 and ω -3 essential fatty acids, which is unique to the diet of Greece and not to the other Mediterranean diets. In fact, in the paper which follows, 'Omega-3 Fatty Acids, Exercise, Physical Activity and Athletics', Dr. Simopoulos provides evidence for the metabolic and physiologic aspects of the ω -6/ ω -3 ratio and its beneficial effects in many conditions. Of great interest is the evidence that endurance exercise increases the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content of muscle cell membrane phospholipids, which may account for the beneficial effects of ω -3 fatty acids in increasing sensitivity to insulin and lead to decreased risk in the development of metabolic syndrome.

Obesity is a major risk factor for cardiovascular disease (CVD), hypertension, diabetes, arthritis, and some forms of cancer. Research on the prevention of obesity, its management, the role of diet and exercise has contributed enormously to our understanding in the development of obesity. Dr. Gérard Aihaud and his group have contributed the most on the obesogenic aspects of ω -6 fatty acids. In his paper, 'Omega-6 Fatty Acids and Excessive Adipose Tissue Development', Dr. Ailhaud presents evidence showing that excess of adipose tissue at an early age is associated with subsequent overweight and obesity in adulthood. Polyunsaturated fatty acids (PUFAs) of the ω -6 and ω -3 series have been shown in rodents not to be equipotent in promoting adipogenesis in vitro and adipose tissue development in vivo (ω -6 PUFAs \gg ω -3 PUFAs) with ω -3 PUFAs counteracting the adipogenic effects of ω -6 PUFAs. The biochemical

mechanisms underlying ω -6 PUFA effects have been demonstrated. Since the 1960s, the increasing prevalence of overweight and obesity in humans has been associated with a positive energy balance. In the meantime, however, and consistent with animal data, consumption of ω -6 linoleic acid (LA) and arachidonic acid (AA) has increased dramatically and is accompanied by a major increase of the ω -6/ ω -3 ratio in breast milk, formula milk and most consumed foods. Dr. Ailhaud concludes that, 'Whether prevention appears as the key issue, owing to the continuous presence of adipose precursor cells throughout life and to the slow turnover of fat cells once formed, the status of lipids from the very beginning of the food chain deserves a re-evaluation.'

Despite numerous advances made in identifying the genes for rare, mendelian forms of CVD, relatively little is known about the common, complex forms at the genetic level. Moreover, most genes that have been associated with CVD, whether they are single gene forms or more common forms of the disease, have primarily been involved in biochemical pathways related to what are considered 'conventional' risk factors. However, recent genetic studies have begun to identify genes and pathways associated with CVD that would not be considered to underlie conventional risk factors. Dr. Hooman Allayee, in his paper 'Non-Conventional Genetic Risk Factors for Cardiovascular Disease', presents the evidence for this latter notion based on genetic studies in humans. The author presents evidence of how a combination of mouse and human genetics led to identification of the 5-lipoxygenase pathway for CVD with potentially important implications for its treatment and diagnosis. Increased dietary AA significantly enhanced the apparent atherogenic effect of genotype, whereas increased dietary intake of ω -3 fatty acids EPA and DHA blunted this effect. Lastly, the prospects for identifying CVD genes in the future and for potentially developing more effective therapeutic strategies are discussed.

The genetics of apolipoprotein E (ApoE) polymorphism is one of the most extensively studied over the past 30 years. There are three common allelic variants (ϵ_2 , ϵ_3 , ϵ_4) producing three protein polymorphisms: E2, E3, E4. ApoE3 is the most common or 'wild type'. Drs. Angelopoulos and Lowndes, in their paper on 'ApoE Genotype: Impact on Health, Fitness and Nutrition', provide an extensive review and conclude that ApoE genotype is associated with plasma lipids and inflammation. ApoE2 isoform is usually associated with lower total cholesterol and low-density lipoprotein (LDL) cholesterol, whereas ApoE4 isoform has higher levels of both. Therefore, the ApoE4 isoform has an overall disease-promoting effect on cardiac health. The effect of regular physical activity on serum total cholesterol, LDL cholesterol, the LDL/high-density lipoprotein (HDL) ratio and LDL particle size may vary with ApoE genotype. ApoE2 and ApoE3 individuals are more responsive and show more favorable lipid changes following exercise interventions.

The importance of nutrition has been extensively studied and accepted worldwide as an essential factor in health maintenance and in the prevention and management of chronic disease. In developing countries, the problem is sometimes referred to as double burden of disease, where malnutrition exists in the company of growing rates of lifestyle-related diseases such as obesity, diabetes and CVD. The frontiers of science have brought forth new understanding of the links between early undernutrition and the later development of chronic lifestyle-related disease, challenging the nutrition scientist and practitioner to evaluate practice to better support health throughout the life course. Dr. Linda Tapsell, in her paper on 'Nutrition in the Prevention of Chronic Disease', emphasizes the impact of birth size on later nutritional challenges and the importance of maternal nutrition, not only in pregnancy but perhaps also in the pre-pregnancy period, and the significance of subsequent nutritional practices at critical times in growth and development. Underpinning this understanding is the role of genetic background on nutritional requirements (nutrigenetics) and the effect of nutrients and food bioactives on genetic expression (nutrigenomics). This whole new enterprise has significant implications for the development of the food supply and of dietary advice to support health. An appreciation of the biological significance of whole foods also becomes a necessary parallel activity to that of consuming food in a way that matches and supports human health. Epigenetics suggest that maternal health, and especially nutrition prior to pregnancy and during fetal life, influence the development of chronic diseases in the offspring. This thinking questions many of the true relationships between diet and health in epidemiologic studies that have not considered the factors that may operate prior to conception and fetal life.

Dr. Konstantinos Pavlou, in his paper 'Exercise and Obesity: Lifestyle Modification as a Means in Prevention and Treatment', presents a thorough review of the evidence that diet by itself is not adequate to maintain weight loss. Physical activity is essential for weight loss maintenance. Dr. Pavlou discusses the physiologic and metabolic changes that occur by the addition of physical activity, especially in 'driving up' the metabolic rate, preserving lean muscle tissue, increasing oxygen uptake, reducing calorie absorption, and suppressing appetite. Dr. Pavlou discusses the evidence that exercise is effective in decreasing the symptoms of depression and anxiety in overweight and obese individuals as well as in hospitalized, manic-depressive patients and in non-hospitalized college students. The author makes the point that 'Fitness' needs to be more precisely defined. There is a need to promote diet and fitness and not focus on diet and fatness. It is better to be fit and lean. However, if one cannot be lean, then it is preferable and safer to be 'fit and fat' rather than unfit and fat.

Although several lines of investigation, including studies of migrant populations, indicate that diet is a major contributor to the etiology of cancer, establishing

specific nutritional relationships has proven to be elusive. The Multiethnic Cohort Study was established in 1993–1996 to further research on diet, other lifestyle factors, and cancer, and to explore the interactions between environmental exposures and genetic susceptibility in determining cancer risk. Dr. Laurence Kolonel in his paper ‘Nutritional Risk Factors for Gastrointestinal Cancers: The Multiethnic Cohort Study’ describes the study. The cohort consists of 215,000 participants, all of whom completed a self-administered baseline questionnaire that included an extensive quantitative food frequency questionnaire. Recent findings related to gastrointestinal cancers are discussed, including strong inverse associations between colorectal cancer and intake of dietary fiber in men, and intake of total calcium in both men and women. An interaction between intake of folate and alcohol and the C677T polymorphism in the methylenetetrahydrofolate reductase gene is also discussed in the context of diet-gene interactions. Recent results related to pancreatic cancer show a positive association with red meat intake and an inverse association with dark green vegetable intake among smokers. Contrasting findings regarding the effect of obesity ($\text{BMI} \geq 30$) on pancreatic cancer in men and women are discussed in relation to chronic inflammation and insulin resistance as possible mechanisms. These analyses demonstrate the value of such an ethnically diverse cohort for research on diet, nutrition and cancer.

Dr. Federico Leighton et al. in their paper ‘Mediterranean Diets, Global Resource for the Control of Metabolic Syndrome and Chronic Diseases’ indicate that climate is a key driver in the development of civilization. The Mediterranean ecosystems in the world are associated with characteristic agricultural products that have marked repercussions on the health of the population making use of those products. The relationship among food and health in some Mediterranean Sea basin countries was characterized by Ancel Keys and collaborators, leading to the present view of Mediterranean alimentation patterns as paradigms of healthy diets. Artemis P. Simopoulos expanded on Key’s concepts and pointed out that a balanced $\omega-6/\omega-3$ essential fatty acid ratio and antioxidants are major characteristics of both the diet of Crete and the Paleolithic diet. Other Mediterranean ecosystems in the world share similar characteristics and constitute a global net of healthy scenarios.

Epidemiological and intervention studies such as the Lyon Heart Study by Michel de Lorgeril et al., and the GISSI study by Marchioli et al. have corroborated the close link among Mediterranean diet and health, particularly with regard to mortality from chronic diseases and characteristic risk factors.

Dr. Leighton et al. state that in Chile, health indicators suggest that some specific factors explain the good ranking of the country with regard to longevity and CVD. They have proposed that the relatively high Mediterranean score of the Chilean diet is a main factor to explain the healthier conditions in

the country. In order to evaluate the role of diet ‘mediterrization’ on the level of chronic disease risk, Leighton et al. have assumed ‘that the Chilean diet is susceptible of further mediterrization, a situation that should lead to favorable changes in chronic disease risk factors.’ Metabolic Syndrome is a condition of high risk, which should respond to environmental changes, leading to a decrease in chronic diseases. Consequently, they have evaluated ‘Food at Work’ as a strategy of diet mediterrization for adults. In an intervention study performed for 12 months, indeed they were able to ‘change alimentation habits with a statistically significant reduction in the prevalence of Metabolic Syndrome’. In addition to the Mediterranean Sea basin countries and Chile, there is evidence linking local diet and better health in other Mediterranean Ecosystems recognized in the world. Dr. Leighton et al. conclude, ‘that the world faces today a global challenge of a sharp increase in chronic diseases on which, apparently, we have not been successful in implementing control measures. Diet mediterrization in adult populations, and obviously also in young people, seems to be a necessary and urgent action to be approached by countries and global health organizations. Therefore, we propose the candidacy of the Mediterranean Diet(s) to be included on the Representative List of the Intangible Cultural Heritage of Humanity of the UNESCO.’

Dr. Peter Bourne in his paper ‘The Role of Government in Nutrition and Fitness’ states that the role of government in enhancing the health of the population is vital. How large a role the government should play is open to vigorous debate based on economic factors, concerns about intrusions in the rights of individuals to make decisions about their own lives, politics and practical administrative matters that can make implementing policy decisions difficult. As a result, the role of government varies widely from one country to another. Dr. Bourne illustrates his views with historical and current examples in public health and emphasizes the need for multinational corporations to be convinced that it is in their best interest to expand their research in nutrition and be responsive to the knowledge and demands of an increasingly sophisticated public.

Dr. William Clay in his paper ‘Balancing the Scales: A Common-Sense Look at Global Nutrition Problems and What Can be Done about Them’ shares Food and Agriculture Organization (FAO) of the United Nations’ insight into the nature and extent of some of the nutritional problems around the world and reflects on some of the factors affecting the changing nature of nutrition and fitness problems, and challenges some commonly held perceptions. Dr. Clay points out some of the policy and program considerations that could help guide the development of more rational and balanced approaches for addressing the multiple burdens of malnutrition seen throughout the world.

In Appendix I, Dr. Charles M. Tipton presents an excellent review on ‘Historical Perspective and Commentary: The Antiquity of Exercise, Exercise

Physiology and the Exercise Prescription for Health'. The review clearly shows that the importance of exercise for health and for management of disease was recognized eons ago by civilizations emerging from the banks of the Nile, Euphrates and Tigris rivers and many others. It is indeed fascinating that in the transition from a hunter-gatherer group to an agrarian society in disparate civilizations, that exercise and its physiology evolved more for health reasons than for enhancing athletic performance. In approximately two millennia since the death of Galen, the US Surgeon General, the Institute of Medicine in Washington, D.C., and numerous professional organizations, including the American College of Sports Medicine and the American Heart Association, have published official documents advocating the health benefits of habitual exercise for individuals. The review by Dr. Tipton ends with the death of Galen, since according to medical historian Baas, antiquity for medical history 'closes with Galen'. For exercise, exercise physiology and the exercise prescription, the era is the same but their history is inextricably linked to evolving concepts that pertained to the causes of disease and the attainment of health, the history of physiology and the emergence of rational medicine with Hippocrates in the 5th century BC.

Following Dr. Tipton's paper, in Appendix II, are the ten points of the '1996 Declaration of Olympia on Nutrition and Fitness' printed in the Olympic languages of English, Chinese, Greek, French, Spanish and Russian. This is the first time that they have been published all together and it seemed an appropriate time. They were originally translated and printed by Mars Incorporated, a supporter of the ICNF, for distribution at the Atlanta Summer Olympic Games.

I would like to acknowledge the following organizations for supporting the Shanghai conference and proceedings. Most importantly, we would like to thank the Stavros S. Niarchos Foundation, which has supported most of our ICNF and their proceedings. I would also like to thank Nutrilite/Access Business Group and Dr. Sam Rehnborg for his personal donation, Minami Nutrition (Belgium) and the Columbus Paradigm Institute (Belgium) for supporting the World Council on Nutrition, Fitness and Health.

These proceedings will be of interest to geneticists, nutritionists and dietitians, exercise physiologists, cultural anthropologists, historians, pediatricians, internists, general practitioners, healthcare providers, scientists in industry and government, policymakers, and national and international governmental organizations.

Artemis P. Simopoulos, MD

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Nutrition and Fitness from the First Olympiad in 776 BC to the 21st Century and the Concept of Positive Health

Artemis P. Simopoulos

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Olympism, Fitness and Sports

All parts of the body which have a function, if used in moderation and exercised in labors in which each is accustomed, become thereby healthy, well developed, and age more slowly, but if unused and left idle they become liable to disease, defective in growth, and age quickly.

Hippocrates

Greek civilization is credited with giving the world the idea of excellence, or ‘arête’. Greek men were expected to demonstrate excellence in a number of venues: on the battlefield, in politics, and in sports. Your position in Greek society was determined by what other people thought of you. It was a very competitive world. The Olympic games were an opportunity to demonstrate excellence in public, not only for personal glory, but to please the Gods, in this case, Zeus. As part of a major religious celebration, the games took place in the Altis, the sacred grove of Zeus, and featured the sacrifice of 100 oxen on the middle day of the Festival. Since the earliest times, athletics have been an integral part of man’s life and culture. Originally a part of the basic requirements for survival either for gathering food or protecting oneself and family, eventually athletics developed into contests of speed, strength and skill. With further passage of time, these contests were transformed into more complicated forms of exercise because of a lessening of the need for basic survival skills, the advent of more leisure time, and the ingenuity of man himself.

Fig. 1. Bronze statuette of a young girl (Laconian, middle of the 6th century BC). This statuette of a young, bare-thighed Spartan girl has a muscular, athletic body. She wears a short, sleeved tunic belted at the waist and lifts the hem with her left hand in order to run more easily. Evidently she is participating in one of the women's races in accordance with the Spartan ideal.



In antiquity many of the activities that we would today regard as sports were an intimate aspect of religious and cultic festivities. For example, in the Heraen Games, women raced in honor of the goddess Hera, the acrobatic gymnastics of the Egyptian girls are believed to have cultic significance, and, of course, dance was an integral and essential aspect of religious rites and women played a great role in these. In societies where the status of women was relatively high, such as the Egyptian, the Minoan and the Spartan societies, we see women participating extensively in a variety of physical activities (fig. 1). In classical Athens and in Mesopotamia the status of women was low and their participatory role was similarly low. The role of women in sport was discussed in antiquity. In the chapter entitled 'The Equality of Women' in Plato's *Republic*, Socrates raises the question of whether 'females should guard the flock and hunt with males and take a share in all they do, or be kept within doors as fit for no more than bearing and feeding their children while all the hard work is left to the males.' Socrates' brother Glaucon agreed that 'women are expected to take their full share, except that we must treat them as not quite so strong.' They were concerned that both men and women ought to receive the same upbringing and education. Such a system, Socrates remarked, would at first appear revolutionary, but he reminded his friends that, 'It is not so long since the Greeks thought it ridiculous as well as shameful for men to be seen naked in the gymnasium. When gymnastic exercises were first introduced in Crete and later in Sparta, the cynics had their chance to make fun of them.' However, he observed, 'A new attitude was soon adapted and it will be the same once women are given equal access to physical

education.’ Women today are actively participating in sports. In fact, women have an extraordinary capacity for marathons and long distance running. Women can derive their energy from fat more than men. Plato was concerned with the education of an elite, a selected group of leaders of proven excellence of character, mind, and body. Thus, he argued logically that once the principle of selection is recognized and the wide scope of individual differences among men as well as women is accepted, a distinction between the educational systems for boys and girls is no longer justified.

Many of the sports known to us today are mentioned by Homer in both the *Illiad* and the *Odyssey*. In the *Illiad*, Homer describes chariot races, wrestling matches, food races, discus and javlin throwing, and archery using a live target, a poor pigeon tied to a mast. In the *Odyssey*, Homer refers to Ulysses as swimming, throwing the discus, boxing and shooting an arrow. When Ulysses arrives in the land of Phaeacians, Nausica, the daughter of the king, plays a kind of handball – another evidence of women in sports – and young boys compete against one another in footraces, wrestling, jumps, boxing, and discus throwing. In fact, in his chapter ‘Olympism and Literature’, Banciulescu [1] considers Homer the patron of sports journalists and states, ‘The XXIII song of the *Illiad* describes with artistic mastery sports competitions held at a time which historians still find it difficult to reconstruct. Under the walls of Troy, which were still burning, the hero Achilles organized funeral games in honor of his dead friend Patroclus. These games were in fact magnificent sports competitions. Their description, forceful and colorful, willed with picturesque elements and inventiveness, numerous details on the technique of events, the subtleties and rules used, by far exceeds the best Olympic report presented by our “special correspondents” today!’

Additional information about sports is obtained from archaeological artifacts, illustrations in coins, shields, ornaments, vases, sculptures, and bas reliefs (fig. 2). Many of the sports we participate in today had their beginnings in the Greek culture and were closely associated with the arts (table 1).

From ancient times, sport in its most competitive form – that of the Olympic games – has been regarded and practiced as a kind of art and has affected art in a special way. Sports, as noble emulation, stimulating continuous improvement of oneself and aiming at the best performance of the competing athlete beyond his limits, had inevitably an artistic aspect and inspired both the plastic arts, sculpture and painting, as well as poetry, music, and literature, which is artistic in itself. This aspect of sport is inevitable when practiced in the Olympic spirit, which does not concern only bodily movement and perfection but also and principally the whole of the human being as psychosomatic unit. Pierre de Coubertin, the founder of the modern Olympic Games in 1896, attributed the inestimable prestige the games had enjoyed for so long to the fact that in ancient times writers and artists gathered together at Olympia to celebrate the games.



Fig. 2. Square marble relief base for a statue. The relief on the front is of an ancient ball court where six youths are playing a game, something like our modern hockey, with a ball and curved sticks, a unique representation in Greek art.

Table 1. Partial list of sports popular today that originated in Greece

Gymnastics	The word itself is derived from the ancient Greek term for athletic or disciplinary exercises
Archery	The ancient Greeks used a bow made of wood, horn, and sinew. Unstrung, it took the form of the letter C. It was a bow of this type that Ulysses used to shoot down his wife's admirers
Bowling	In the <i>Odyssey</i> , Homer mentions a party, held to celebrate Odysseus' return home, at which the guests 'pushed stones'. Many think this was the earliest version of the game we now know as bowling
Boxing	This sport has been credited to Theseus, who around 900 BC entertained spectators with his fists
Bullfighting	Bull fighting is supposed to have originated not in Spain but in Crete, the land of the Minotaur
Football	Football was known to the ancient Greeks. The Greeks of 500 BC called it <i>follios</i>
Hockey	The Greeks of about 500 BC played a game similar to what we know as field hockey
Horseshoe pitching	A Greek coin, now in the British Museum, proved that the Greeks shod horses as early as 200 BC. Cavalry soldiers made a game of pitching horseshoes at stakes
Lawn tennis	Walter C. Wingfield, a British army officer who invented tennis in 1872, admitted that his game was patterned on one played by the ancient Greeks
Tug-of-war	The Greeks are said to have invented the tug-of-war to develop soldier's muscles
Olympic games	Incontestably Greek in origin, the ancient Olympic Games date back to 776 BC. They were patterned after regular ceremonial contests that took place in Greece as far back as 1453 BC

The fundamental principle of Olympism is excellence, i.e., the athlete has to excel over others and over his own capacities as realized to date. This basic principle thoroughly influenced the concept of beauty as being the essential element in esthetics. The ancient Greeks had no term directly expressing the beautiful as such. The word *kalos* used in this instance signifies beauty with goodness, as a handsome and virtuous person. This is why it was used together

with *agathos* to denote the perfect human being as a whole, uniting within himself both esthetics and bodily existence. The athlete became one of the main sources of inspiration for the artists. The sculptors did not give individual characteristics to the statues but the athletic ideal, which was *kalos-agathos* (handsome and kind).

Prominent authors of the stature of Homer, Pindar, Bacchylides, Simonides, Epictetus, Plato, Xenophon, Euripides, Plutarch, Theocritus, Virgil, Horace, Lucian, and so many others wrote about sports and fitness. They of course lived within a society and an environment where physical culture through exercise, or what we call sport today in general terms, was an important fundamental aspect of their lives. Physical education with all its apparent forms of play and Greek agonistics were part of the mentality of the time and had their place in the spirituality of the ancient city belonging to the intimate structure of man.

Basic Dietary Patterns

Information about prehistoric people's diets is based on archaeological evidence from remains of food, skeletal remains (teeth being the most important pointer to nature of diet), surviving artifacts (involved in food processing), and painted or sculptured representations of activities (milling, baking, and cooking).

Excavation of graves and studies on cooking utensils along with food that accompanied the dead are indeed remarkable [2]. The people buried at Armenoi, located in the middle of the Island of Crete during the Minoan period (1390–1190 BC), had an active lifestyle indicated by the 15 individuals who suffered from traumatic arthritis, usually an occupationally related condition. Pottery in the graves depicts marine life. The question is how much and what did they eat? Apparently there were not any differences in the diets of rich and poor. However, there were differences between men and women. Men ate more meat or milk in their diets. In the 16th century BC, excavations of graves at Mycenae in the Peloponnese revealed a different picture. The population ate marine foods, a mixture of meats and plants, and the men had a diet with more marine foods than the women. Furthermore, the men who ate more marine foods lived the longest.

The basic diet of both Greeks and Romans was strongly, though not exclusively, vegetarian, comprising a variety of cereals, vegetables (green and dried), and fruit (fresh and dried) with wine (diluted with various proportions of water) as the only drink apart from water. In Greece the commonest meat was that of goats; in Italy it was that of pigs in the form of pork or bacon. Beef might be eaten occasionally after a sacrifice but the cow, like the ox, was a working animal and milk was normally obtained from sheep and goats. Olive oil took the place

Table 2. Some ancient Greek contributions to cooking

Name	Culinary invention
Orion	Invented white sauce
Lampriades	Discovered brown sauce
Nereuse of Corinth	Prepared the conger eel into a dish ‘fit for the gods’
Agres of Rhodes	First thought of filleting fish
Atlantus	Invented the perfect restorative
Euthymus	Is remembered for his creation of exquisite vegetables dishes
Artemidorus	Commented on and made a collection of all the words and recipes used in the kitchens of his time
Timachidas from Rhodes	Was a famous cook and poet who composed an epic poem about his art

of butter and soap and was the major source of domestic lighting. Fish (both fresh and salted) and poultry also were featured in the diet of both peoples.

By the end of the 4th century BC, wheat had achieved the dominant position among grains used for human food. Bread was a logical advance on porridge as an energy-producing cereal because bread is characterized by easy handling, transport, and durability. However, the arrival of bread did not cause porridges and pulses to disappear.

In the earliest writings of ancient Greece, food and cooking are frequently mentioned. There were many famous men who were quite proud of their culinary talent in those days: Thimbron of Athens and Soteriades practiced ‘fad cooking’ – different foods for different moods! The philosopher Archestratus was the author of *Gastrology*, which was considered a culinary masterpiece. He wrote for immortal Greece, presented his concepts with the zeal of a legislator, and traveled extensively to seek out new recipes and new treats to grace his table. The only thing that distressed him was the fact that he could not eat all the foods he liked all the months of the year. He would be very happy if he lived today because modern agriculture, refrigeration, and rapid transportation facilities have eliminated these limitations. He therefore consoled himself by talking about all these delightful dishes all the year round. Many of his recipes, which are probably the oldest in the world (his writing took place around 350 BC), are reportedly still in use in Greece today. The entire Western world actually owes much to Greek cooking for the Greeks gave us the art of dining. As can be seen in table 2, many of the sauces in use today were developed by the Greeks.

When Greece was conquered by Rome, the Greek culture and culinary arts still triumphed in Rome. There are accounts of peacocks from Samos, crabs

from Chios, cranes from Melos, and turkeys from Phrygia. Yet, although the Romans inherited all the luxury of Greece, they never erected as the Greeks did a temple to Addephagia, the Goddess of Good Cheer. Spices and herbs were used for health and medicinal purposes. Hippocrates used over 400 different herbs in his cures and, of these, 200 are still in use today. Tansy was one: the name comes from the Greek word *athanasia*, which means immortality. White thyme, another herb, was known as a symbol of courage. Dill has been used for centuries. The Greeks would chew dill seeds during the never-ending political speeches and throughout long plays to keep themselves awake. The ancient Greeks believed that herbs improved one's mind and, therefore, included them in almost all their dishes.

The Greeks have always been fond of fish and it is a part of their staple diet. Greeks discovered the oyster as an edible fish. Legend has it that one day many centuries ago, a young Athenian boy was wandering along the beach in search of shells. Suddenly he saw an oyster in the act of yawning. Curiosity getting the better of him, he picked up the half-open shellfish and put his finger inside the shell. The oyster at once snapped the shell together, causing the boy to give a sharp cry of pain and to quickly withdraw the injured finger, which he at once popped into his mouth. The flavor was so delicious, however, that he broke open the shell and swallowed the unfortunate oyster. Since that fatal day the oyster has been a much harassed shellfish.

Vegetables have always held an important place in Greek cooking. In the days of Achilles and Ulysses, most conspicuous dishes at state banquets were often those consisting of vegetables. Alexander the Great was extremely fond of vegetables for he was always finding new kinds, bringing them back to Greece. He found onions in Egypt, tasted them, and decided they were just the thing for increasing the zeal of his warriors. It was Alexander who discovered the haricot bean for Europe, which the Greeks have cultivated extensively. Both the Greeks and the Romans used cabbage as a remedy against drunkenness. Leeks were also popular and considered a remedy for many diseases. Other vegetables used in ancient times that are also in use today include beetroot, artichokes, turnips, radishes, etc.

In *The Deipnosophistae*, a 2nd century BC cookbook written by Athenaeus of Naucratis, we find many references to the sweet creations of that period. It seems that one of the most popular desserts was none other than cheesecake. Forty-seven types of differently named cheesecakes are described: cheesecakes made of cheese and cheesecakes made of everything but cheese, cheesecakes boiled in oil and dipped in honey, cheesecakes devoted to Olympian goddesses surrounded with figures of lighted torches and wedding cheesecakes baked over an open fire and drenched with honey, which were given by the bride to the bridegroom to be eaten by the bridegroom's friends.

The Diet of the Athlete

Trainers of athletes occupied an important place in Greek society. They prepared their charges both physically and psychologically, taught skills, and supervised exercise and diet. In early days there was a simple regimen of porridge, cheese, figs, and meal cakes. Meat was only eaten occasionally. Towards the middle of the 5th century BC, a meat diet was introduced by Stymphalos, an ex-athlete who had won two Olympic victories in the long distance race. According to legend the philosopher Pythagoras of Croton was the instigator of the meat diet consumed by Eurymenes of Samos, an athlete he is said to have trained. Some athletes are reported to have consumed enormous quantities of meat. Milo of Croton (a town famous for its athletes), who is reputed to have consumed 9 kg of meat, 9 kg of bread, and 8.5 liters of wine in a day, was the most renowned of all the Greek wrestlers. Milo won five successive Olympic crowns from 536 to 520 BC. In addition to these victories he won many others at Delphi, Corinth, and Nemea.

At the original Olympic Games held in Olympia, Greece for over 1,000 years, the victorious athletes received more than meals. They were rewarded with pieces of ravani, spicy sweet cakes that are still eaten today. Honey, flour, and fruit were offered to the gods and are early indications of the traditional custom of Greek hospitality. It is of great interest indeed that the award or prize of the first six Olympic Games was the golden apple. Was it supposed to signify the nutritional importance or was it simply the golden apple that was given by Paris, the Prince of Troy, to the goddess Aphrodite? In any event, this golden apple award was replaced by a wreath from a branch of the sacred olive tree (fig. 3) at the recommendation of the Delphic Oracle and became a moral reward devoid of any material value.

The Concept of Positive Health

The history of Greek medical thought and practice is an important part of the general history of science. Within the Greek achievement, medicine is second only to mathematics, and the Hippocratic writings have strong links with Ionian nature philosophers. These philosophers developed concepts of a pre-Aristotelian biology, which Democritus (5th century BC) outlined as a forerunner of Aristotle. Anaxagoras of Clazomenae (500–428 BC) in Ionia developed a cosmological theory which has an important bearing on his view of physiology, particularly of nutrition: how out of bread or other foods so different from the tissues of the body, the body tissues could nonetheless be built up or replenished.

Fig. 3. Olive wreath. The prize for the Olympic winner, a wreath of wild olive. The branch is always cut from the same tree – ‘the wreath-bearer.’



It was indeed no accident that scientific medicine among the Greeks began in the age of the nature philosophers who swept away the magic and superstition that hindered its growth in other societies. Nature philosophy was for the Hippocratics and others what general science is today for modern medicine. The beginnings of professional medicine and the Hippocratic Corpus were established in the 5th century BC. A physician of that period wrote that medicine is mainly a matter of regimen, particularly of diet (diet here means lifestyle: not just food but includes nutrition and exercise), discovered by man under stress of necessity and continually improved. Cooking has contributed much to the advance of man from a brutish condition in which he lived insecurely on strong and indigestible foods to a state of civilization in which cooking was one of the necessary arts. Medicine of that time understood man in relation to what he ate and drank.

The first evidence of the importance of food and exercise in health appears in the Hippocratic Corpus in the description about fever. The physicians of that period considered fever as a form of disease that was associated with other diseases. They believed that in individuals fever could arise from an excessive amount of food without exercise.

Among the Greeks, the concept of positive health was important and occupied much of their thinking. Those who had the means and the leisure applied themselves to maintaining positive health, which they often conceived esthetically, and to this end put themselves into the hands of trainers who subjected them to regimen. Training for war and athletic competition was of course well known among them. Health was an excellence in its own right, the physical counterpart and condition of mental activation. The details of regimen practiced for health were an important part of Greek medicine.

Hippocrates in *Regimen I* said that positive health requires a knowledge of man's primary constitution (what today we would call genetics) and of the powers of various foods, both those natural to them and those resulting from human skill (today's processed food). However, 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. This advice of 2,500 years ago is consistent with today's knowledge about genetics, nutrition, and physical fitness and their contribution to health.

Hippocratic medicine was rational medicine and lived side by side with the cult of Asclepius that was faith healing. There was no rivalry or controversy between the two such as there has been in more recent times between science and religion but the two existed in a form of honorable rivalry, not intolerance.

Herodotus (5th century BC) remarked on the Egyptian habit of purging for 3 days every month. He said that the Egyptians pursued health by purges and emetics and believed that all human disease arises from food. Perhaps the most important Egyptian notion found in the papyri was that disease was due to putrefying residues of food carried in the bowels and giving off gases that permeated the body. Hence the continual use of purges in Egypt, a practice that the Greeks followed.

Plutarch's (46–120 AD) view on emetics and cathartics appears to be opposed to the current thinking of his time or at least to current practice. He believed that emetics and cathartics ought not to be introduced (into the regimen) except under pressure of great necessity. He used to say that most people fill up their bodies for the sake of emptying them and then empty them for the sake of filling them up again, thus running counter to nature's principles. He was particularly severe in condemning emetics as promoting an insatiable greed in the patient. Plutarch's statements are applicable today for patients with anorexia and bulimia. He had definite views on how to keep in good health. Plutarch emphasized the importance of good dietary habits when one is well and recommended avoiding overeating at parties. He felt that by remaining hungry one gets more enjoyment from food and advised appetite control and avoidance of lavish recipes.

Plutarch offered a list of nourishing foods. These included meat, cheese, dried figs, and boiled eggs. He recommended sticking to light, thin foods like garden produce, birds, and fish with little fat. He believed that this type of diet gratified the appetite without burdening the digestion. He recommended avoiding meat on top of other foods and that milk to be taken not as a beverage (i.e. as an accompaniment to other food) but as a food possessing solid powers of

nourishment. Plutarch's list of nourishing foods is indeed a forerunner to what are now called 'superfoods.' There are articles in popular magazines on 10 of the healthiest foods and books on 150 health foods. In reviewing them, I still come back to Plutarch's lists and statements. Plutarch's recommendations are indeed scientifically much more accurate than the 'superfoods' of today and their significance for health.

The history of physical education shows sports and medicine to have a long-standing and close relationship from antiquity to today. Indeed if one takes into account the participation of doctors of medicine in national teams and the sporting reputations of some hospitals and medical facilities, a sympathy for sport seems to be almost a tradition of the medical profession. All we need to do is to insist that today's medicine emphasizes the concept of positive health, and look forward to the day when physicians write 'exercise prescriptions' along with specific dietary advice and finally drugs only as needed.

The concept of positive health developed by the physicians of the Hippocratic era is unique to Greek medicine. In most cultures medicine was and is still considered today by most people in a negative way – as a profession that is here to handle sick people through techniques, drugs, and other kinds of remedies. Even the terms prevention and preventive medicine have negative overtones. The concept of positive health is not population dependent but is specific to the individual. The Hippocratic physicians distinguished among the various regimens (which they called diet) to achieve health. As indicated earlier, diet did not refer simply to food but to the whole lifestyle including nutrition and exercise. Their concept of positive health depended on knowledge of man's primary constitution (genetics), food, and exercise. The combination of food and exercise constituted regimen. In developing a regimen they distinguished regimens for laymen from those for professional athletes and paid particular attention to changing regimens for different seasons. Furthermore, the regimens differed in accordance with the physique of the individual. They believed that special physiques needed special diets.

Hippocrates was first to note the association of obesity with reduced life expectancy and said, 'Sudden death is more common in those who are naturally fat than in the lean' [3]. It is rather interesting to read the Hippocratic physicians' recommendations about weight loss: 'Fat people wishing to grow thin should always take exertion on an empty stomach: they should take their food while they are panting and before they are cooled (they must have known about increased metabolic rate), their meat should be rich so that they will be satisfied with a minimum (they must have known the importance of fat in inducing satiety), and they should have only one square meal a day. Thin people wishing to be fat should do the opposite of these things, particularly avoiding exertion on an empty stomach' [4]. Of particular interest is the observation that athletes run

a serious risk of diarrhea in training, an observation well known today. They had noticed that untrained people suffer from fatigue and recommended that the pains must be reduced by vapor baths and by hot baths and gentle walks.

Exercise – Physical Activity

The Olympic games represent the summit of athletic achievement. Few of us will approach these levels of performance in our physical endeavors. But, there is no need to scale Olympian heights to achieve significant health benefits. One can improve his or her quality of life through a lifelong practice of moderate amounts of regular physical activity of moderate or vigorous intensity. An active lifestyle should be available to all. There is plenty of scientific evidence linking physical activity to numerous health improvements. Most significantly, regular physical activity greatly reduces the risk of dying from coronary heart disease; developing diabetes, hypertension and colon cancer; enhances mental health; fosters healthy muscles, bones and joints, and helps maintain function and preserve independence in older adults [5–13].

Although the scientific evidence of the beneficial aspects of exercise are well known, the evidence about what helps people incorporate physical activity into their lives is less clear. Effective strategies and policies have taken place in settings as diverse as physical education classes in schools, health promotion programs at work sites, and one-on-one counseling by healthcare providers. However, more needs to be learned about what helps individuals change their physical activities, habits, and how changes in the community, environment, policies, and social norms might support that process. Few occupations today require significant physical activity, and most people use motorized transportation to get to work and to perform routine errands and tasks. Even leisure time is increasingly filled with sedentary behaviors, such as watching television, ‘surfing’ the internet, and playing video games. Increasing physical activity is a formidable public health challenge that must be met.

The benefits of physical activity have been extolled throughout Western history, but it was not until the second half of the 20th century that scientific evidence began to accumulate on the beneficial aspects of exercise in growth and development, and in the prevention of chronic diseases. By the 1970s, enough information was available about the beneficial effects of vigorous exercise on cardiorespiratory fitness that many organizations, such as the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) [14–16], the Centers for Disease Control (CDC) [17, 18], the National Institutes of Health (NIH) and others developed recommendations for physical activity. Recommendations for physical activity are also now included in the

US Dietary Guidelines [19]. In May 2004, the 57th World Health Assembly (WHA) endorsed the World Health Organization's (WHO) Global Strategy on Diet, Physical Activity and Health. The Strategy was developed through a wide-ranging series of consultations with all concerned stakeholders in response to a request from Member States at World Health Assembly 2002 (Resolution WHA55–23) [20].

The body responds to physical activity in ways that have important positive effects on musculoskeletal, cardiovascular, respiratory, and endocrine systems. Regular participation in physical activity also appears to reduce depression and anxiety, improve mood, and enhance ability to perform daily tasks throughout the life span. In addition to the beneficial effects of physical activity to health, there are also risks involved. The most common health problems that have been associated with physical activity are musculoskeletal injuries, which can occur with excessive amounts of activity or with suddenly beginning an activity for which the body is not conditioned. Much more serious associated health problems (i.e. myocardial infarction, sudden death) are also much rarer, occurring primarily among sedentary people with advanced atherosclerotic disease who engage in strenuous activity to which they are unaccustomed. Sedentary people, especially those with preexisting health conditions, who wish to increase their physical activity, should gradually build up to the desired level of activity. Even among people who are regularly active, the risk of myocardial infarction or sudden death is somewhat increased during physical exertion, but their overall risk of these outcomes is lower than that among people who are sedentary. It remains to be determined how the interrelated characteristics of amount, intensity, duration, frequency, type and patterns of physical activity are related to specific health or disease outcomes.

Physical activity is important for metabolic health in children. To prevent clustering of cardiovascular risk factors, physical activity levels should be higher than the current international guidelines of at least 1 hour per day of physical activity of at least moderate intensity [21, 22]. Achieving 90 min of daily activity might be necessary for children and adolescents to prevent insulin resistance, which seems to be the central feature for clustering of cardiovascular disease risk factors [23]. Therefore, it will be necessary to focus on childhood fitness, not just fatness [24]. To that end, the establishment and the work of the world Council on Nutrition, Fitness and Health is of enormous importance.

The Traditional Diet of Greece

Although Greece and the Mediterranean countries are usually considered to be areas of medium-high death rates (14.0–18.0 per 1,000 inhabitants), death

Table 3. ω -6: ω -3 ratios in various populations

Population	ω -6/ ω -3	Reference
Paleolithic	0.79	28
Greece prior to 1960	1.00–2.00	29
Current Japan	4.00	30
Current India, rural	5–6.1	31
Current United Kingdom and Northern Europe	15.00	32
Current USA	16.74	29
Current India, urban	38–50	31

rates on the island of Crete have been below this level continuously since before 1930 [25]. 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 1,000 inhabitants before World War II and \sim 10.6 in 1946–1948 [25]. Cancer and heart disease caused almost three times as many deaths proportionally in the USA as in Crete [25]. The diet of Crete represents the traditional diet of Greece prior to 1960.

The Seven Countries Study was the first to establish credible data on cardiovascular disease prevalence rates in contrasting populations (USA, Finland, The Netherlands, Italy, former Yugoslavia, Japan and Greece), with differences found on the order of 5- to 10-fold in coronary heart disease [26]. In 1958, the fieldwork started in Dalmatia in the former Yugoslavia. From the inception of the research program, an important focus was on the diet, especially the type of fat, and its possible relationship to the etiology of coronary heart disease. The 5-year follow-up found favorable all-cause death rates in Greece, Japan and Italy compared with the other areas, as well as a lower incidence rate of coronary disease [26].

The diet of Crete, or the traditional diet of Greece, resembles the Paleolithic diet in terms of fiber content, antioxidants, saturated fat, monounsaturated fat and the ratio of ω -6 to ω -3 fatty acids (table 3) [27–32]. The Lyon Heart Study [33–37] and subsequently the study of Singh and colleagues [38, 39] support the importance of having a diet consistent with human evolution. Western diets today deviate from the Paleolithic diet and are associated with high rates of cardiovascular disease, diabetes, obesity and cancer.

The results of the Seven Countries Study are interesting because they show that the population of Crete had the lowest rates of cardiovascular disease and cancer, followed by the population of Japan [26]. The investigators concluded

that the reason for these low rates must be the high olive oil intake and the low saturated fat intake of the Mediterranean diet. The fact that Crete had a high fat diet (37% of energy from fat) and Japan had a low fat diet (11% of energy from fat) was not discussed extensively nor were any other fatty acids considered despite the fact that the people of Crete ate 30 times more fish than did the US population. Furthermore, the people of Crete ate a large amount of vegetables (including wild plants), fruits, nuts and legumes, all rich sources of folate, calcium, glutathione, antioxidants, vitamins E and C and minerals. Melatonin [40], a potent antioxidant and anticarcinogenic agent is found in purslane (*Portulaca oleracea*) [41] and in extra virgin olive oil but not in olive oil extracted under high temperature and pressure [42]. In addition, because the meat came from animals that grazed rather than being grain-fed, it contained ω -3 polyunsaturated fatty acids (PUFA) as did the milk and milk products, such as cheese [29]. The population of Crete eats snails during Lent and throughout the year. Serge Renaud (INSERM, Bordeaux, France; pers. commun.) has shown that the snails of Crete and Greece contain more ω -3 fatty acids and less ω -6 fatty acids than do the snails of France.

The traditional Greek diet, including the diet of Crete, includes wild plants. Wild plants are rich sources of ω -3 fatty acids and antioxidants [43–50]. Purslane, a commonly eaten plant, is rich in α -linolenic acid (LNA, 18:3 ω -3; 400 mg/100 g) as well as in vitamin E (12 mg/100 g), vitamin C (27 mg/100 g), glutathione (15–20 mg/100 g) [44] and melatonin (19,000 pg/g wet weight) [41]. In Crete and Greece, purslane is eaten fresh in salads, soups and omelets or cooked with poultry; during the winter months, dried purslane is used in soups and vegetable pies and as a tea for sore throat and earache. It is highly recommended for pregnant and lactating women and for patients with diabetes.

The purslane study was just the beginning of our involvement in a series of studies that investigated the ω -3 fatty acids in the Greek diet under conditions similar to those before 1960 [50]. In the Greek countryside, chickens wander on farms, eat grass, purslane, insects, worms and dried figs, all good sources of ω -3 fatty acids. The Ampelistra (Greek) egg [51, 52] has a ratio of ω -6 to ω -3 of 1.3 whereas the US Department of Agriculture (USDA) egg has a ratio of 19.4. As a result, noodles made with milk and eggs in Greece also contain ω -3 fatty acids.

Thus a pattern began to unfold. The diet of Greece, including Crete, before 1960 contained ω -3 fatty acids in every meal – breakfast, lunch, dinner and snacks. Figs stuffed with walnuts are a favorite snack. Both figs and walnuts contain α -linolenic acid (ALA, ω -3). Contrast this snack with a chocolate chip cookie that contains *trans* fatty acids and ω -6 fatty acids from the partially hydrogenated oils used in preparation [53]. Although these studies were carried out between 1984 and 1986, further analyses of blood specimens from the

Table 4. Mean fatty acid composition of cholesteryl esters in serum of 92 elderly men from Crete and 97 elderly men from Zutphen¹ [modified from 54]

Fatty acid	% Methyl esters	
	Crete	Zutphen
16:0	11.1 ± 1.0	11.9 ± 1.3
16:1	3.2 ± 1.1	2.9 ± 1.6
18:0	0.7 ± 0.3	1.1 ± 0.5
18:1	31.0 ± 2.7	21.4 ± 3.9
18:2 ω -6	41.9 ± 3.7	53.1 ± 6.5
18:3 ω -3	0.9 ± 0.5	0.3 ± 0.4
Ratio 18:2/18:1	1.37 ± 0.20	2.60 ± 0.75

¹Results are expressed as mean % (by weight) methyl esters ± SD.

Seven Countries Study were published in 1993 by Sandker et al. [54], indicating that the serum cholesteryl esters of the population in Crete had 3-fold more LNA than did the population of Zutphen (table 4). Similar data indicated that the Japanese population also had higher concentrations of ω -3 fatty acids than did the population of Zutphen. Here then was the missing link. It was the higher concentrations of ω -3 fatty acids that added protection against cardiovascular disease, not only the olive oil, wine, fruits and vegetables of the ‘typical’ Mediterranean diet.

The two populations with the lowest coronary heart disease in the Seven Countries Study had a higher intake of ALA. The Japanese obtained it from perilla oil and soybean oil and the population of Crete obtained it from purslane, other wild plants, grape leaves, walnuts and figs. Additional studies showed that the population of Crete not only had higher serum cholesteryl ester levels of LNA but also lower linoleic acid [LA, 18:2 ω -6] (table 4) [54].

Renaud et al. [55] had been working with ALA and had shown that it decreases platelet aggregation. Everything seemed to fall into place in terms of defining the characteristics of the diet of the population of Crete. Their diet was very similar to the Paleolithic diet in composition (table 3). The diet was low in saturated fat, balanced in the essential fatty acids (EFA; ω -6 and ω -3), very low in *trans* fatty acids and high in vitamins E and C, glutathione and melatonin. This diet formed the basis of the diet used by de Lorgeril and Renaud in their now famous Lyon Heart Study [33–37]. The Lyon Heart Study was a prospective

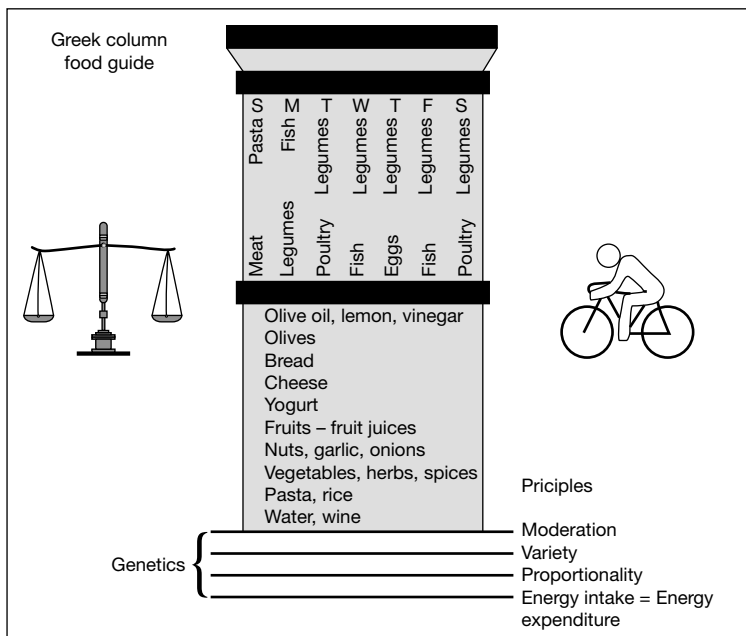


Fig. 4. The Greek column food guide. The guide is based on genetic individuality; the principals of moderation, variety, proportionality, and equality of energy intake with energy expenditure [56].

randomized, single-blind secondary prevention trial that compared the effects of a modified Crete diet enriched with LNA with those of a Step I American Heart Association diet. The study showed a decrease in death rate by 70% in the experimental group and clearly showed that a modified Crete diet low in butter and meats such as deli products but high in fish and fruits and vegetables and enriched with LNA is more efficient than the American Heart Association or similar prudent diets recommended for the secondary prevention of coronary events and total deaths [33]. The same subjects were followed for 5 years. At 4 years of follow-up, de Lorgeril et al. [35] reported that the reduction of risk in the experimental subjects compared with control subjects was 56% ($p = 0.03$) for total deaths and 61% ($p = 0.05$) for cancers, indicating that a modified diet of Crete was associated with lower risk for coronary heart disease and cancer.

The Lyon Heart Study clearly showed that the diet of Crete can be adhered to over a period of 5 years [33, 35]. Figure 4 is the Greek Column Food Guide based on the diet of Crete [56]. The visualization of this food guide in the form

Table 5. The seven dietary guidelines of The Omega Diet [from 27]

-
- 1 Eat foods rich in ω -3 fatty acids such as fatty fish (salmon, tuna, trout, herring, mackerel), walnuts, canola oil, flaxseeds, and green leafy vegetables. Or, if you prefer, take ω -3 supplements
 - 2 Use monounsaturated oils such as olive oil and canola oil as your primary fat
 - 3 Eat seven or more servings of fruits and vegetables every day
 - 4 Eat more vegetable protein, including peas, beans, and nuts
 - 5 Avoid saturated fat by choosing lean meat over fatty meat (if you eat meat) and low-fat over full-fat milk products
 - 6 Avoid oils that are high in ω -6 fatty acids, including corn, safflower, sunflower, soybean, and cottonseed oils
 - 7 Reduce your intake of *trans* fatty acids by cutting back on margarine, vegetable shortening, commercial pastries, deep-fat fried food, and most prepared snacks, mixes, and convenience food
-

of a Greek column includes the concepts of genetic variation and nutrition and a 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 dietary guidelines shown in table 5 provide further information on how to implement the diet of Crete [27].

In conclusion, studies on the Paleolithic diet suggest that ω -3 fatty acids were present in practically all foods that humans ate and in equal amounts with ω -6 fatty acids. The depletion of the ω -3 fatty acids in Western diets is the result of agribusiness, modern agriculture and aquaculture. The high ratio of ω -6 to ω -3 fatty acids (16.74:1 instead of 1:1) is the result of excessive production of vegetable oils and the indiscriminate recommendation to substitute saturated fat and butter with oils high in ω -6 fatty acids to lower serum cholesterol levels without taking into consideration their adverse effect 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-type diet such as the traditional Greek diet balanced in ω -6 and ω -3 fatty acids and rich in vitamins C and E, glutathione and melatonin (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 relative to the other Mediterranean diets is the content of bioprotective nutrients, specifically the following: (1) a more balanced intake of EFA from vegetable, animal and marine sources; a ratio of ω -6 to ω -3 fatty acids of 2:1 instead of the 15:1 in Western and Northern Europe and 16.74:1 in the USA, and (2) a diet rich in antioxidants, i.e.,

high amounts of vitamin C, vitamin E, β -carotene, glutathione, melatonin, resveratrol, selenium, phytoestrogens, folate, 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 thiosulfates, salicylates, carotenoids, indoles, monoterpenes, polyphenols, flavonoids and other phytochemicals used in cooking vegetables, meat and fish [57].

Such a dietary pattern has been shown to be beneficial for health because it is associated with a reduced risk of cardiovascular disease and cancer and increased life expectancy. The time has come for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.

Conclusions

Today, at the first decade of the 21st century, scientists have deciphered the human genome and some animal and plant genomes, which will lead to the definition of the genetic profile of individuals, and by means of recombinant DNA technology and biotechnology we are changing the genetics of plants and animals for the production of better food for man. Medical science will identify the individual at risk for developing illness or disease. This is the time to put into practice the concepts of positive health and develop regimens suited to the individual, taking into consideration the season of the year, whether the individual is a layperson or an athlete, and the individual's physique. In the near future, research will enable us to write prescriptions specifying the type and quantity of exercise and the type of food on the basis of the genetic profile, the physique, and the type of work of the individual and environment and season of the year. We should aim to develop a world where *kalos-agathos* describe human beings in all cultures and where artists, writers, and philosophers write, sing, and praise the concepts of positive health.

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Omega–3 Fatty Acids, Exercise, Physical Activity and Athletics

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Introduction

The health of the individual and population is determined by the interaction between (their) genetic endowment and a number of environmental factors [1–3]. Diet and exercise are two environmental factors of major importance. A number of anthropological, nutritional and genetic studies indicate that human's overall diet, including energy intake and energy expenditure, has changed over the past 10,000–15,000 years with major changes occurring during the past 150 years in the type and amount of fat and in physical activity (fig. 1) [4–11]. Whereas major changes have taken place in terms of diet and physical activity in many populations, the genetic profile has changed very little, if any, in the past 10,000–15,000 years [7]. Both ω -3 fatty acids and physical activity influence gene expression and in turn, genetic variation influences dietary response and the response to exercise [12]. Western societies are characterized by sedentary lifestyles, and obesity has reached epidemic proportions at all ages. Today, industrialized societies are characterized by: (1) an increase in energy intake and decrease in energy expenditure; (2) an increase in saturated fat, ω -6 fatty acids and *trans* fatty acids, and a decrease in ω -3 fatty acid intake; (3) a decrease in complex carbohydrates and fiber; (4) an increase in cereal grains and a decrease in fruits and vegetables, and (5) a decrease in protein, antioxidants, vitamin D, and calcium intake [5–14]. Genetically speaking, humans today live in a nutritional environment, and have adopted sedentary lifestyles that differ from that for which our genetic constitution was selected. It has been estimated that the present Western diet is 'deficient' in ω -3 fatty acids with a ratio of ω -6/ ω -3 fatty acids of 10–20/1 instead of 1/1 as is the case with wild animals [15–17] and presumably human

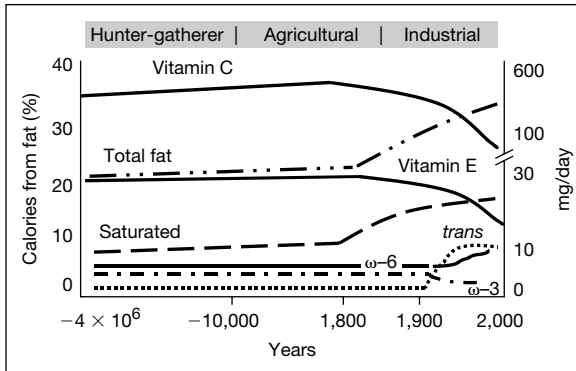


Fig. 1. Hypothetical scheme of fat, fatty acid ($\omega-6$, $\omega-3$, *trans* and total) intake (as percent of calories from fat) and intake of vitamins E and C (mg/day). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years [6].

beings [4–11]. Human beings evolved on a diet where there was a balance between the $\omega-6$ and $\omega-3$ fatty acids, which is a more physiologic state since both $\omega-6$ and $\omega-3$ polyunsaturated fatty acids (PUFA) influence cellular metabolism and gene expression.

Over the past 25 years, many studies and clinical investigations have been carried out on the physiology, metabolism, and gene expression of $\omega-6$ and $\omega-3$ fatty acids. Today we know that $\omega-3$ fatty acids are essential for normal growth and development; play an important role in the prevention and management of coronary heart disease [18–24], and are beneficial in the management of hypertension, diabetes, arthritis and other autoimmune disorders, and cancer [25–30]. Diet and exercise are essential components for health. This paper will focus on biological effects of $\omega-6$ and $\omega-3$ fatty acids, and their effects on exercise, physical activity and athletics; the interplay of physical activity, $\omega-3$ fatty acids and mental health; the effect of exercise training on the $\omega-6/\omega-3$ muscle membrane phospholipid composition in humans, especially the effects of $\omega-3$ fatty acids and myocardial oxygen consumption during prolonged exercise; brachial artery dilation and blood flow during forearm contraction; effect of endurance training and/or fish oil supplemented diet on cytoplasmic fatty acid binding protein in rat skeletal muscles and heart, and finally evidence that fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes.

Biological Effects of ω -6 and ω -3 Fatty Acids and the ω -6/ ω -3 Ratio

Linoleic acid (LA; 18:2 ω -6) and α -linolenic acid (ALA; 18:3 ω -3) and their long-chain derivatives are important components of animal and plant cell membranes. When humans ingest fish or fish oil, the ingested eicosapentaenoic acid (EPA; 20:5 ω -3) and docosahexaenoic acid (DHA; 22:6 ω -3) partially replace the ω -6 fatty acids (especially arachidonic acid (AA; 20:4 ω -6)) in cell membranes, especially those of platelets, erythrocytes, neutrophils, monocytes and liver cells [reviewed in 5]. As a result, ingestion of EPA and DHA from fish or fish oil in eicosanoid metabolism leads to: (1) decreased production of prostaglandin E₂ metabolites; (2) decreased concentrations of thromboxane A₂, a potent platelet aggregator and vasoconstrictor; (3) decreased formation of leukotriene B₄, an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence; (4) increased concentrations of thromboxane A₃, a weak platelet aggregator and vasoconstrictor; (5) increased concentrations of prostacyclin PGI₃, leading to an overall increase in total prostacyclin by increasing PGI₃ without decreasing PGI₂ (both PGI₂ and PGI₃ are active vasodilators and inhibitors of platelet aggregation), and (6) increased concentrations of leukotriene B₅, a weak inducer of inflammation and chemotactic agent (fig. 2) [31, 32].

Because of the increased amounts of ω -6 fatty acids in the Western diet, the eicosanoid metabolic products from AA, specifically prostaglandins, thromboxanes, leukotrienes, hydroxy fatty acids, and lipoxins, are formed in larger quantities than those formed from ω -3 fatty acids, specifically EPA. The eicosanoids from AA are biologically active in small quantities and if they are formed in large amounts, they contribute to the formation of thrombi and atheromas; the development of allergic and inflammatory disorders, particularly in susceptible people, and cell proliferation. Thus, a diet rich in ω -6 fatty acids shifts the physiologic state to one that is prothrombotic and proaggregatory, with increases in blood viscosity, vasospasm, and vasoconstriction and decreases in bleeding time. Bleeding time is shorter in groups of patients with hypercholesterolemia [33], hyperlipoproteinemia [34], myocardial infarction, other forms of atherosclerotic disease, type 2 diabetes, obesity, and hypertriglyceridemia. Atherosclerosis is a major complication of type 2 diabetes patients. Bleeding time is longer in women than in men and in younger than in older persons. There are ethnic differences in bleeding time that appear to be related to diet. As shown in table 1, the higher the ratio of ω -6 to ω -3 fatty acids in platelet phospholipids, the higher is the death rate from cardiovascular disease [35]. As the ratio of ω -6 to ω -3 fatty acids increases, the prevalence of type 2 diabetes also increases (fig. 3) [36].

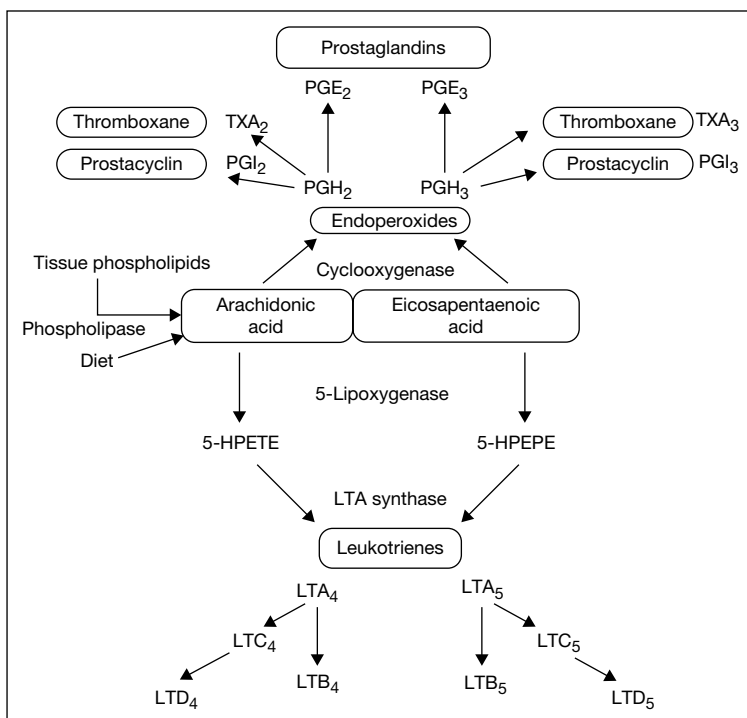


Fig. 2. Oxidative metabolism of arachidonic acid and eicosapentaenoic acid by the cyclooxygenase and 5-lipoxygenase pathways. 5-HPETE = 5-Hydroperoxyeicosatetraenoic acid; 5-HPEPE = 5-hydroxyeicosapentaenoic acid.

The hypolipidemic, antithrombotic, and anti-inflammatory effects of ω -3 fatty acids have been studied extensively in animal models, tissue cultures, and cells (table 2) [37]. As expected, earlier studies focused on mechanisms that involve eicosanoid metabolites. More recently, however, the effects of fatty acids on gene expression have been investigated and this focus of interest has led to studies at the molecular level (tables 3, 4) [38–51]. Previous studies have shown that fatty acids, whether released from membrane phospholipids by cellular phospholipases or made available to the cell from the diet or other aspects of the extracellular environment, are important cell-signaling molecules. They can act as second messengers or substitute for the classic second messengers of the inositide phospholipid and cyclic AMP signal transduction pathways [52]. They can also act as modulator molecules mediating responses of the cell to extracellular signals [52]. It has been shown that fatty acids rapidly and directly alter the transcription of specific genes [53].

Table 1. Ethnic differences in fatty acid concentrations in thrombocyte phospholipids and percentage of all deaths from cardiovascular disease [data modified from 35]

	Europe + USA	Japan	Greenland Eskimos
Arachidonic acid (20:4 ω -6)	26	21	8.3
Eicosapentaenoic acid (20:5 ω -3)	0.5	1.6	8.0
ω -6/ ω -3 ratio	50	12	1
Mortality from cardiovascular disease	45	12	7

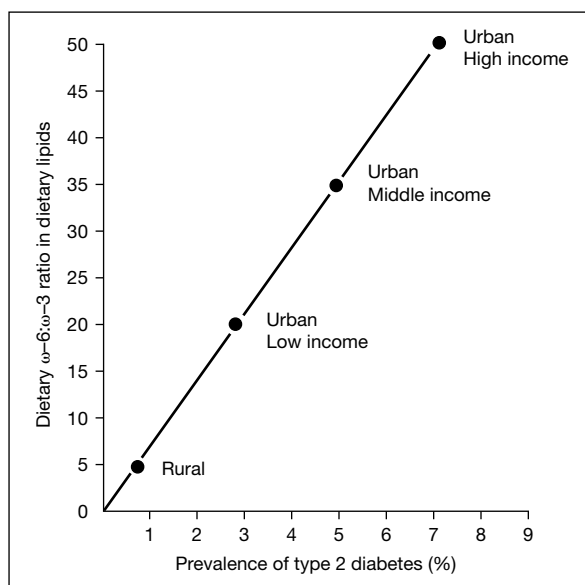


Fig. 3. Relation between the ratio of ω -6 to ω -3 fatty acids in dietary lipids in the Indian diet and the prevalence of type 2 diabetes [36].

Effects of Dietary ALA Compared with Long-Chain ω -3 Fatty Acid Derivatives on Physiologic Indexes

Several clinical and epidemiologic studies have been conducted to determine the effects of long-chain ω -3 PUFA on various physiologic indexes [54]. Whereas the earlier studies were conducted with large doses of fish or fish-oil

Table 2. Effects of ω -3 fatty acids on factors involved in the pathophysiology of atherosclerosis and inflammation [updated and modified from 37]

Factor	Function	Effect of ω -3 fatty acid
Arachidonic acid	Eicosanoid precursor; aggregates platelets; stimulates white blood cells	↓
Thromboxane A ₂	Platelet aggregation; vasoconstriction; increase of intracellular Ca ²⁺	↓
Prostacyclin (PGI _{2/3})	Prevents platelet aggregation; vasodilation; increases cAMP	↑
Leukotriene (LTB ₄)	Neutrophil chemoattractant; increase of intracellular Ca ²⁺	↓
Fibrinogen	A member of the acute phase response and a blood clotting factor	↓
Tissue plasminogen activator	Increases endogenous fibrinolysis	↑
Platelet-activating factor (PAF)	Activates platelets and white blood cells	↓
Platelet-derived growth factor (PDGF)	Chemoattractant and mitogen for smooth muscles and macrophages	↓
Oxygen free radicals	Cellular damage; enhance LDL uptake via scavenger pathway; stimulate arachidonic acid metabolism	↓
Lipid hydroperoxides	Stimulate eicosanoid formation	↓
Interleukin-1 and tumor necrosis factor	Stimulate neutrophil O ₂ free radical formation; stimulate lymphocyte proliferation; stimulate PAF; express intercellular adhesion molecule-1 on endothelial cells; inhibit plasminogen activator, thus procoagulants	↓
Interleukin-6	Stimulates the synthesis of all acute phase proteins involved in the inflammatory response: C-reactive protein; serum amyloid A; fibrinogen; α_1 -chymotrypsin, and haptoglobin	↓
C-reactive protein (CRP)	An acute phase reactant and an independent risk factor for cardiovascular disease	↓
Endothelial-derived relaxation factor	Reduces arterial vasoconstrictor response	↑
Insulin function		Increases sensitivity to insulin

Table 2. (continued)

Factor	Function	Effect of ω -3 fatty acid
VLDL	Related to LDL and HDL level	↓
HDL	Decreases the risk for coronary heart disease	↑
Lp(a)	Lipoprotein(a) is a genetically determined protein that has atherogenic and thrombogenic properties	↓
Triglycerides and chylomicrons	Contribute to post-prandial lipemia	↓

Table 3. Effects of PUFA on several genes encoding enzyme proteins involved in lipogenesis, glycolysis, and glucose transport

Function and gene	Ref.	Linoleic acid	α -Linolenic acid	Arachidonic acid	Eicosapentaenoic acid	Docosahexaenoic acid
<i>Hepatic cells</i>						
Lipogenesis						
FAS	39–42	↓	↓	↓	↓	↓
S14	39–42	↓	↓	↓	↓	↓
SCD1	43	↓	↓	↓	↓	↓
SCD2	44	↓	↓	↓	↓	↓
ACC	42	↓	↓	↓	↓	↓
ME	42	↓	↓	↓	↓	↓
Glycolysis						
G6PD	45	↓				
GK	45	↓	↓	↓	↓	↓
PK	46	–	↓	↓	↓	↓
<i>Mature adiposites</i>						
Glucose transport						
GLUT4	47	–	–	↓	↓	–
GLUT1	47	–	–	↑	↑	–

concentrates, more recent studies have used lower doses [55]. ALA, the precursor of ω -3 fatty acids, can be converted to long-chain ω -3 PUFA and can therefore be substituted for fish oils in vegetarians. The minimum intake of long-chain ω -3 PUFA needed for beneficial effects depends on the intake of other fatty acids. Dietary amounts of LA as well as the ratio of LA to ALA

Table 4. Effects of polyunsaturated fatty acids on several genes encoding enzyme proteins involved in cell growth, early gene expression, adhesion molecules, inflammation, β -oxidation, and growth factors¹

Function and gene	Ref.	Linoleic acid	α -Linolenic acid	Arachidonic acid	Eicosapentaenoic acid	Docosahexaenoic acid
Cell growth and early gene expression						
c-fos	48	–	–	↑	↓	↓
Egr-1	48	–	–	↑	↓	↓
Adhesion molecules						
VCAM-1 mRNA ²	49	–	–	↓	– ³	↓
Inflammation						
IL-1	50	–	–	↑	↓	↓
β -Oxidation						
Acyl-CoA oxidase ⁴	42	↑	↑	↑	↑↑	↑
Growth factors						
PDGF	51	–	–	↑	↓	↓

¹VCAM = vascular cell adhesion molecule; IL = interleukin; PDGF = platelet-derived growth factor.
↓ = Suppresses or decreases; ↑ = induces or increases.

²Monounsaturated fatty acids (MONOs) also suppress VCAM-1 mRNA, but to a lesser degree than does DHA.
AA also suppresses to a lesser extent than DHA.

³Eicosapentaenoic acid has no effect by itself but enhances the effect of docosahexaenoic acid (DHA).

⁴MONOs also induce acyl-CoA oxidase mRNA.

appear to be important for the metabolism of ALA to long-chain ω -3 PUFA. Indu and Ghafoorunissa [55] showed while keeping the amount of dietary LA constant, 3.7 g ALA appears to have biological effects similar to those of 0.3 g long-chain ω -3 PUFA with conversion of 11 g ALA to 1 g long-chain ω -3 PUFA (EPA). Thus a ratio of 4 (15 g LA:3.7 g ALA) is appropriate for conversion. In human studies, Emken et al. [56] showed that the conversion of deuterated ALA to longer-chain metabolites was reduced by ~50% when dietary intake of LA was increased from 4.7 to 9.3% of energy as a result of the known competition between ω -6 and ω -3 fatty acids for desaturation.

Indu and Ghafoorunissa [55] further indicated that increasing dietary ALA increases EPA concentrations in plasma phospholipids after both 3 and 6 weeks of intervention. Dihomo- γ -linolenic acid (20:3 ω -6) concentrations were reduced but AA concentrations were not altered. The reduction in the ratio of long-chain ω -6 PUFA to long-chain ω -3 PUFA was greater after 6 weeks than after 3 weeks. Indu and Ghafoorunissa were able to show antithrombotic effects by reducing the

ratio of ω -6 to ω -3 fatty acids with ALA-rich vegetable oil. After ALA supplementation there was an increase in long-chain ω -3 PUFA in plasma and platelet phospholipids and a decrease in platelet aggregation. ALA supplementation did not alter triacylglycerol concentrations. As shown by others, only long-chain ω -3 PUFA (EPA + DHA) have triacylglycerol-lowering effects [57].

In Australian studies, ventricular fibrillation in rats was reduced with canola oil as much or even more efficiently than with fish oil, an effect attributable to ALA [58]. Further studies should be able to show whether this result is a direct effect of ALA per se or occurs as a result of its desaturation and elongation to EPA.

The diets of Western countries have contained increasingly larger amounts of LA, which has been promoted for its cholesterol-lowering effect. It is now recognized that dietary LA favors oxidative modification of LDL cholesterol [59, 60], increases platelet response to aggregation [61], and suppresses the immune system [62]. In contrast, ALA intake is associated with inhibitory effects on the clotting activity of platelets, on their response to thrombin [63, 64], and on the regulation of AA metabolism [65]. In clinical studies, ALA contributed to lowering of blood pressure [66, 67]. In a prospective study, Ascherio et al. [68] showed that ALA is inversely related to the risk of coronary heart disease in men.

ALA is not equivalent in its biological effects to the long-chain ω -3 fatty acids found in marine oils. EPA and DHA are more rapidly incorporated into plasma and membrane lipids and produce more rapid effects than does ALA. Relatively large reserves of LA in body fat, as are found in vegans or in the diet of omnivores in Western societies, would tend to slow down the formation for long-chain fatty acids from ALA. Therefore, the role of ALA in human nutrition becomes important in terms of long-term dietary intake. One advantage of the consumption of ALA over ω -3 fatty acids from fish is the problem of insufficient vitamin E intake does not exist with high intake of ALA from plant sources.

Exercise, Physical Activity and Athletics

Exercise or physical activity and athletics have been known to be associated with lower risk for cardiovascular disease, hypertension, obesity and diabetes [69–77]. Exercise lowers blood pressure and decreases the overall risk for coronary heart disease by lowering triglycerides, raising high-density lipoprotein (HDL) and decreasing low-density lipoprotein (LDL) cholesterol. Table 5 shows some of the effects of ω -3 fatty acids and physical activity to be similar and to be opposite of those of the effects of the aging process. Therefore, in the athletic setting, the ω -3 fatty acids are essential for overall health of the athlete.

Table 5. Comparison of the effects of ω -3 fatty acids and exercise on risk factors for chronic diseases and aging

Risk factors	ω -3 Fatty acids	Exercise	Aging
Depression	↓	↓	↑
Heart rate variability	↑	↑	↓
Bleeding time	↑	↑	↓
Fibrinogen	↓	↓	↑
Platelet aggregation	↓	↓	↑
Plasma viscosity	↓	↓	↑
Arrhythmias	↓	↓	↑
Red cell deformability	↑	↑	↓
Nitric oxide production	↑	↑	↓
Triglycerides	↓	↓	↑
High-density lipoprotein cholesterol (HDL)	↑	↑	↓
Brachial artery dilation and blood flow	↑	↑	↓
Exercise-induced bronchoconstriction in elite athletes	↓	↑	?
Inflammation and inflammatory markers	↓	↑	↑
Blood pressure	↓	↓	↑
Basal metabolic rate	↑	↑	↓
Insulin sensitivity	↑	↑	↓
Fat mass	↓	↓	↑
Risk of metabolic syndrome	↓	↓	↑
Fatty acid oxidation	↑	↑	?
Fatty acid binding protein	↑	↑	?
ω -6: ω -3 ratio in phospholipids	↓	↓	?

↑ = Increases; ↓ = decreases; ? = uncertain of effect.

Both ω -3 fatty acids and exercise increase fatty acid oxidation. ω -3 fatty acids increase the production of endogenous antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase.

Both exercise and ω -3 fatty acids increase sensitivity to insulin and prevent hyperglycemia. ω -3 fatty acids increase O_2 delivery to the heart muscle so

that the heart does not have to work as hard to get the O_2 it needs for work [78]. Many of the health benefits of exercise are due to increased fat utilization associated with exercise and with endurance training. Exercise has an important role in body weight regulation. The increasing incidence of obesity is more closely related to measures of inactivity than overconsumption of food. This was shown by Dr. Nahla Hwalla in her presentation at the 5th International Conference on Nutrition and Fitness, held June 9–12, 2004, in Athens, Greece [76, 77] and in their paper published in the conference proceedings on ‘Adolescent Obesity and Physical Activity’ which describes the study carried out in Lebanon [79]. The results of this first national population-based study show that adolescent obesity is largely caused by lack of physical activity, and that boys fair worse than the girls. The authors recommend multicomponent intervention strategies at the societal and individual levels for weight control that include health professionals, families, schools, businesses, and healthcare organizations, in order to increase programs and opportunities for physical activity.

During moderate to severe exercise, as in skiing and in elite athletes, there is an increase in the generation of superoxide radical (O_2^-) in the lipid bilayers of muscle mitochondria and trauma to the muscles. Mild to moderate physical activity increases prostacyclin PGI_2 in vascular endothelium and decreases thromboxane A_2 in platelets [80]. These effects are similar to the effects of EPA and DHA. Physical activity increases HDL_2 while it decreases HDL_3 and LDL. It is speculated that the increase in HDL_2 brought on by exercise leads to increased production of PGI_2 . Aerobic exercise seems to be associated with increases in vasodilatory prostaglandins in the circulation [81], but exercise and exhaustive physical exercise promote the increase in thromboxane A_2 [82–84]. Therefore, there is a need to increase EPA and DHA intake during aerobic and/or exhausting exercise.

Excessive radical formation and trauma during high-intensity exercise leads to a state of inflammation which is made worse by the increased amounts of ω -6 fatty acids found in the Western diet. Fish oil concentrates rich in EPA and DHA have been used to counteract the effects of the inflammatory state [85]. For the majority of athletes, especially at the leisure level, general guidelines could include fish oils EPA and DHA of about 1–2 g/day at a ratio of EPA:DHA of 2:1 [86]. A more individualized approach with exercise stress testing is needed and the background diet should be balanced in ω -6 and ω -3 fatty acids by lowering ω -6-rich oils such as corn oil, sunflower, safflower, cottonseed and soybean oils and substitute olive oil and canola. Changes and improvements in the background diet and an additional 1–2 g of EPA + DHA per day should prevent the inflammation in muscles and joints. For the elite athlete, the above prophylactic measures are essential. In fact, higher doses have been recommended as follows: at the leisure sort activity level – EPA + DHA = 1–2 g; regular physical training

Table 6. Defining physical activity

-
1. Non-labor daily physical activities
 - Feeding
 - Bodily functions (e.g. temperature regulation, heart rate, breathing rate)
 - All daily non-labor minimum physical activities necessary for life maintenance
 2. Labor physical activities
 - Industrial
 - Agriculture
 - Carpentry
 - Homecare, etc.
 3. Leisure-recreational (exercise), low-to-moderate intensity of physical activities
 - Walking
 - Dancing
 - Hiking
 - Bowling
 - Cycling
 - Golf, etc.
-

and team sport activities – EPA + DHA = 2–4 g; elite endurance athletes – EPA + DHA = 6–8 g [86] at a ratio of EPA:DHA of 2:1. Table 6 lists the types of physical activity with some examples. The higher the proficiency level, the higher the demand for ω -3 fatty acids. ω -3 fatty acids are needed for structural purposes and for the formation of the preformed eicosanoids, namely the less inflammatory LTB₅ and TX₃ and PGI₃.

It appears that when athletes eat a well-balanced diet, which is made up of a wide range of foods in sufficient quantity to cover energy needs, there is no need for vitamin and mineral supplementation. The fact is that Western diets are imbalanced in the essential fatty acids ω -6 and ω -3. The diet is high in ω -6 and low in ω -3. Therefore, there is a need to lower the ω -6 fatty acid intake and increase the ω -3 fatty acid intake.

ω -3 Fatty Acids, Exercise and Obesity

Both ω -3 fatty acids and exercise have antiobesity effects. Obesity is typically due to an increase in adipocyte size and number. The formation of adipocytes is a critical event, as mature adipocytes do not divide in vivo and do not undergo significant turnover under physiological conditions [87].

The long-term relationship between the fatty acid composition of dietary fats and the development of adipose tissue in humans is difficult to assess in contrast to animals. Mother rats were fed a high-fat diet rich in LA or saturated fat. Suckling pups at 17 days of age exhibited hyperplasia or hypertrophy of white adipose tissue respectively [88]. But fish oil rich in EPA and DHA prevents obesity in rats [89, 90], as well as feeding rats after weaning with dietary fats rich in ALA, the precursor of EPA and DHA, prevents excessive growth of adipose tissue. AA and prostacyclin signaling promote adipose tissue development. The increases in the dietary ω -6/ ω -3 over the past 50 years have led to increases in obesity in sedentary populations. DHA has been shown to decrease body fat and fat accumulation in rodents. DHA may exert its antiobesity effect by inhibiting differentiation to adipocytes, inducing apoptosis in post-confluent adipocytes and promoting lipolysis.

Interplay of Physical Activity, ω -3 Fatty Acids and Mental Health

It is generally accepted that the degree of fitness, amount of exercise, and psychological well-being are related in humans. This effect is seen at all ages, but is more pronounced in sedentary and older adults. Exercise improves creative thinking, independent of the effects on mood [91].

In studies carried out in rodents and human beings, the effects of chronic stress can be mitigated by exercise [92, 93]. Excessive exercise or overtraining may produce negative mood states as well as fatigue, sleep disturbances, frequent infections, injuries and reduced performance. No single identifying performance marker exists. Acute running in animal experiments increases brain serotonin levels, which would support the serotonin deficiency of depression, nonetheless, measurements of metabolic markers of serotonin metabolism have produced conflicting results.

The beneficial effects of ω -3 fatty acids have been studied on the central nervous system, psychiatric behavior and mental health, specifically in depression and possibly in the prevention of Alzheimer's, attention deficit disorders, bipolar disorder and possibly schizophrenia [94–103]. The data are best for depression and schizophrenia.

An important role for the ω -3 fatty acids in mood disorders (bipolar disorder and unipolar major depression) is now supported by a substantial body of indirect and direct evidence. There is compelling epidemiologic data linking low ω -3 fatty acid intake and high rates of major depression, furthermore, uncontrolled open label clinical studies of the efficacy of ω -3 fatty acids in patients with unipolar depression have shown EPA and DHA to prevent or decrease relapse and increase the remission rate [104]. There is a strong

antidepressant effect of the ω -3 fatty acids in patients with bipolar depression [98, 104]. In addition to depression, other brain disorders that are associated with low ω -3 fatty acid intake include schizophrenia, dementia, attention deficit disorder, alcoholism, tardive dyskinesia and violence [105–107]. Furthermore, low ω -3 fatty acids are associated both with depression and cardiovascular disease [108]. In fact, depression precedes cardiovascular disease. Depressed people are more likely to develop cardiovascular disease and to die of it [109–111].

Effect of Exercise Training on the ω -6/ ω -3 Muscle Membrane Phospholipid Composition in Humans

Dietary fatty acid profile plays an important role for the incorporation of fatty acids into the muscle membrane in humans [112–114]. In addition to the effect of diet, there is some evidence that physical activity per se could also be a possible moderator of membrane phospholipid fatty acid composition. Andersson et al. [115] demonstrated that 6 weeks of low-intensity exercise training resulted in significant changes in muscle phospholipid fatty acid composition with a significant increase in oleic acid (18:1 ω -9) and a decrease in AA (20:4 ω -6). Although great care was taken to attempt to control dietary fatty acid profile, the subjects were free living. Helge et al. [116] investigated the effects of regular exercise training on skeletal muscle phospholipid fatty acid composition in humans applying a one-leg training model in which the other leg serves as a reference. In doing so, dietary fatty acid composition initial level of training and other relevant variables were perfectly controlled. Their working hypothesis was that regular training, primarily through its effect on substrate flux and substrate storage, induces an adaptive response in muscle membrane phospholipid fatty acid composition. Training improves insulin sensitivity, which in turn may affect performance by modulation of fuel availability. Insulin action, in turn, has been linked to specific patterns of muscle structural lipids in skeletal muscle. Helge et al. [116] investigated whether regular exercise training exerts an effect on the muscle membrane phospholipid fatty acid composition in humans. Seven male subjects performed endurance training of the knee extensors of one leg for 4 weeks. The other leg served as a control. Muscle biopsies were obtained from the vastus lateralis before, after 4 days, and after 4 weeks. After 4 weeks, the phospholipid fatty acid contents of oleic acid (18:1 ω -9) and DHA (22:6 ω -3) were significantly higher in the trained (10.9 ± 0.5 and $3.2 \pm 0.4\%$ of total fatty acids, respectively) than the untrained leg (8.8 ± 0.5 and $2.6 \pm 0.4\%$, $p < 0.05$). The ratio between ω -6 and ω -3 fatty acids was significantly lower in the trained (11.1 ± 0.9) than the untrained leg (13.1 ± 1.2 ,

$p < 0.05$). Exercise training modulates fatty acid composition of muscle phospholipids in humans and lowers the $\omega-6/\omega-3$ fatty acid ratio in muscle cell membrane phospholipids. In contrast, training did not affect muscle triacylglycerol fatty acid composition. Citrate synthase activity was increased by 17% in the trained compared with the untrained leg ($p < 0.05$). In this model, diet plays a minimal role, as the influence of dietary intake is similar in both legs. Regular exercise training per se influences the phospholipid fatty acid composition of muscle membranes but has no effect on the composition of fatty acids stored in triacylglycerols within the muscle.

In the study by Helge et al. [116], a 4-week regular exercise training induced changes in the muscle membrane phospholipid fatty acid profile; therefore, exercise training should be considered as a modulator of muscle phospholipid fatty acid composition. The ratio of 18:1 $\omega-9$ to 16:0 was significantly higher after training, suggesting an increase in the Δ^9 -desaturase activities induced by training. A lower AA was not found by Helge et al. [116] but it was found in the Andersson study [115]. Muscle triacylglycerol fatty acid composition was unaltered by regular exercise training, indicating that the effect of regular exercise training on muscle phospholipid fatty acid composition is not directly linked to changes in the muscle triacylglycerol fatty acid composition. The fraction of oleic acid in muscle triacylglycerol was significantly increased by exercise training, indicating a preferential recruitment and uptake of oleic acid during and after exercise.

There is good evidence that endurance training increases insulin sensitivity [117–119]. There is some evidence that prolonged adaptation to regular exercise training will lead to increased muscle membrane phospholipid content in humans [120] and rats [121]. In humans, the 16% increase in phospholipid content was almost completely due to an increased phosphatidylcholine content. It may be that some correlate of physical activity rather than the activity itself is responsible for the changes in phospholipid fatty acid composition. Gudbjarnason [122] showed that catecholamine stress by repeated administration of epinephrine can alter the fatty acid composition of cardiac phospholipids. In that study, catecholamine stress caused an increase in AA and DHA content and a decrease in LA – changes that were not detected in the study of Helge et al. [116]. However, the increase in % of DHA was consistent between the Helge et al. [116] and Gudbjarnason [122] studies as was the decreased $\omega-6/\omega-3$ ratio. Exercise performed in the one-leg exercise model at submaximal levels only results in moderate increases in circulating catecholamine levels [123].

There is evidence that insulin sensitivity is related to muscle phospholipid fatty acid composition [113, 114, 124]. An inverse relationship between the muscle membrane content of palmitic acid (16:0) and insulin sensitivity has

been demonstrated [124]. Also, there is evidence that an increased unsaturation and a decreased ratio of ω -6 to ω -3 fatty acids in the muscle membrane are compatible with an increased membrane fluidity, findings that have been linked to the presence of an increased number of insulin receptors and an increased insulin binding [125–127]. In the study by Helge et al. [116] the increased ratio of oleic to palmitic acid (18:1 ω -9/16:0), the increased unsaturation, and the decrease of ω -6/ ω -3 ratio after exercise training may act to enhance insulin sensitivity through an effect of the membrane fatty acid composition. Also, insulin receptor number might increase with long-term training.

ω -3 Fatty Acids and Myocardial Oxygen Consumption during Prolonged Exercise

Fish, fish oil, and the ω -3 fatty acids they contain are gradually being recognized as important nutritional components for preventing many aspects of cardiovascular disease. ω -3 fatty acids deliver most of their benefit through incorporation into cell membranes with consequent modulation of signaling and cell function. This is particularly important in the heart where animal studies demonstrate marked antiarrhythmic effects of ω -3 incorporation, and clinical studies show reduced incidence of sudden arrhythmic death associated with regular consumption of fish or fish oils [128, 129]. Studies using isolated hearts from healthy cats have shown that prior dietary supplementation with fish oil can increase cardiac oxygen efficiency. But, what about the effects of fish or fish oils on normal hearts during exercise? McLennan and colleagues [78] studied whether fish oil feeding might improve cardiac oxygen consumption and increase time to fatigue of trained athletes during prolonged exercise bouts. They carried out a double-blind parallel design study where they evaluated the effects of fish oil supplementation in highly trained endurance road cyclists. Subjects were randomly assigned to receive 1-gram capsules containing either fish oil (325 mg DHA, 65 mg EPA) (FO group) or olive oil (Control group). Cyclists consumed 8 capsules/day (3.120 mg/day) for 8 weeks. Cardiac performance was taken as indirect measurement of myocardial oxygen consumption. Endurance performance was assessed initially and then after 8 weeks of supplementation using the electronically braked cycle ergometer. No difference in peak oxygen consumption (ml/kg/min) (Control: pre 66.8 ± 2.4 , post 67.2 ± 2.3 ; FO: pre 68.3 ± 1.4 , post 67.2 ± 1.2), peak workload (watts) (Control: pre 475 ± 19 , post 470 ± 19 ; FO: pre 437 ± 12 , post 436 ± 9), ventilatory threshold (% of peak workload) (Control: pre 81.2 ± 0.02 , post 81.4 ± 0.05 ; FO: pre 83.7 ± 0.03 , post 83.3 ± 0.02), blood lactate concentration at the point of ventilatory threshold (mmol/l) (Control: pre 5.6 ± 0.6 , post

5.0 ± 0.7; FO: pre 6.4 ± 0.4, post 6.0 ± 0.3), time to fatigue in minutes at workloads of 55% of the peak workload (Control: pre 105 ± 10, post 103 ± 12; FO: pre 106 ± 10, post 99 ± 10) or systolic blood pressure could be attributed to fish oil supplementation. However, within the FO group, heart rate during both incremental ($p < 0.001$) and endurance performance ($p < 0.001$) was lower for any given submaximal workload after supplementation. Additionally, a significant decrease in peak heart rate (HR_{peak}) occurred within the FO group ($p < 0.05$). Consequently, rate pressure product, indirectly estimating myocardial oxygen consumption, during the endurance performance trial significantly decreased ($p < 0.01$). Interestingly, within the fish oil group there was also a significant decrease in the ratings of perceived exertion reported for chest ($p < 0.05$) and whole body ($p < 0.05$) throughout the endurance performance trial. This study indicates that fish oil fatty acids may act directly in the healthy heart to reduce heart rate and rate pressure product, both indirect indicators of reduced myocardial oxygen consumption. In addition to this enhanced cardiovascular fitness there was a corresponding and significant decrease in the ratings of perceived exertion during prolonged endurance. However, none of these effects were reflected in a significant change of exercise performance, recorded as time to fatigue.

Supplementation with ω -3 PUFA Augments Brachial Artery Dilation and Blood Flow during Forearm Contraction

ω -3 fatty acids enhance exercise-induced increases in brachial artery diameter and blood flow during rhythmic exercise, whereas safflower oil had no effect [130]. Results indicate that treatment with 5 g (2 g DHA and 3 g EPA) per day of ω -3 fatty acids enhances brachial artery blood flow and conductance during exercise. These findings may have implications for individuals with cardiovascular disease and exercise intolerance (e.g. heart failure).

Effect of Endurance Training and/or Fish Oil Supplemented Diet on Cytoplasmic Fatty Acid Binding Protein in Rat Skeletal Muscles and Heart

Endurance training and supplementation with ω -3 fatty acids (EPA + DHA) affect cytoplasmic fatty acid binding protein (FABP_c) content in rat skeletal muscle and heart [131]. After 8 weeks of swimming, trained rats exhibited higher FABP_c content in the extensor digitorum longus (EDL) and in the gastrocnemius than did control rats (30%). The FABP_c increase was associated

with an increase of citrate synthase activity (85 and 93%, respectively, in the two muscles), whereas lactate dehydrogenase activity decreased significantly. In contrast, in the soleus and in the heart, no effect of exercise was observed either on FABP_c or on the metabolic profile. Therefore, increasing oxidative capacities of muscle by exercise resulted in a concomitant increase of the FABP_c content. Giving a PUFA (ω -3) supplemented diet for 8 weeks induced a large rise of the FABP_c in EDL (300%), gastrocnemius (250%), soleus (50%) and heart (15%) without a concurrent accumulation of intramuscular triglycerides or modification of the citrate synthase activity, suggesting that PUFA may increase FABP_c content by up-regulating fatty acid metabolism genes via peroxisome proliferator-activated receptor- α activation. Endurance trained rats fed with an ω -3 diet had similar FABP_c content in the gastrocnemius muscle when compared to sedentary ω -3 fed rats, whereas an additive effect of exercise and diet was observed in the EDL. The FABP_c in the soleus and in the heart of rats fed with ω -3 supplements remained constant whether rats performed exercise or not. As a result, both exercise and ω -3-enriched diet influence FABP_c content in muscle. These two physiological treatments presumably acted on FABP_c content by increasing fatty acid flux within the cell.

During exercise, the two main fuels available for providing energy to the working muscle are fats and carbohydrates. The relative contribution of these substrates to the total energy production depends mainly on exercise intensity, duration and dietary status prior to exercise. At rest and during moderate exercise, long-chain fatty acids remain the major substrate sustaining ATP production in muscle [132]. The oxidative potential of muscle and more specifically fat oxidation can be enhanced by endurance exercise training. This adaptive response involves several regulatory steps: (1) increases in the activities of the enzymes of β -oxidation; (2) the tricarboxylic acid cycle, and (3) the electron transport system [123]. Consequently, the shift toward a greater use of fat reduces the rate of glycogen depletion and delays the appearance of fatigue. Substrate availability seems to play an important role in the capacity of muscles to oxidize fatty acids. The enhancement of exercise-induced fatty acid oxidation is mediated by the availability of the fatty acid and the transport process.

Fatty acids and fatty acyl coenzyme-A (CoA) are the primary ligands of FABP_c and are generally considered not only as intermediates in fat metabolism, but also as important messenger molecules with intrinsic activities. Among fatty acids, ω -3 PUFA are of special interest because of their hypolipidemic effect. The ω -3 PUFA have a role in membrane structure, metabolism, signal transduction, control of adipogenesis and also in the control of the genetic expression of many enzymes involved in lipid and carbohydrate metabolism [5, 26, 41, 43, 45, 87, 133].

ω -3 fatty acids stimulate key enzymes involved in the fatty acid metabolism via peroxisome proliferator-activated receptor- α activation and possibly indirectly affect FABP_c. Therefore, in the study of Clavel et al. [131], the ω -3 fatty acid supplemented diet could provoke a rise in FABP_c by enhancing fatty acid flux within the cell. Fatty acids in the cell are metabolized rapidly. Exercise did not further increase FABP_c, which had risen following ω -3 fatty acid supplementation. Therefore, there was no additive effect.

Fish Oil Supplementation Reduces Severity of Exercise-Induced Bronchoconstriction in Elite Athletes

Long-term heavy exertion has been linked to changes in the immune system. Many components of the immune system exhibit adverse change after prolonged heavy exertion. These changes occur in skin, upper respiratory mucosal tissue, lung, blood, and muscle. Although still open to interpretation, most exercise immunologists believe that during this 'open window' of impaired immunity (which may last between 3 and 72 h depending on the immune measure) viruses and bacteria may gain a foothold increasing the risk of subclinical and clinical infection.

Dietary fish oil supplementation has a markedly protective effect in suppressing exercise-induced bronchoconstriction (EIB) in elite athletes, and this is most likely attributed to their anti-inflammatory properties. EIB is a condition characterized by transient narrowing of the airway during or after exercise, which results in decreased pulmonary function following exercise. EIB is more prevalent in elite athletes compared with non-elite athletes and the general population. In the elite athlete, a high prevalence of EIB and asthma-like symptoms such as wheezing, chest tightness, abnormal breathlessness, cough, and sputum production have been noted [134–140]. The relatively high incidence of EIB in elite athletes may be due to exercise hyperventilation, prolonged exposure to allergens and bronchial irritants, and excessive inhalation of cold, dry air [137, 141].

Whereas the mechanisms responsible for bronchial hyperactivity after exercise in asthmatics have been extensively investigated [142, 143], EIB in elite athletes is less understood and most likely involves many mechanisms. It has been suggested that transient dehydration of the airways activates the release of inflammatory mediators, such as histamine, neuropeptides, and AA metabolites, leukotrienes and prostaglandins from airway cells, resulting in bronchial smooth muscle contraction. Repetitive high-intensity exercise itself may contribute to the development of EIB by the release of inflammatory cytokines [144]. Recent evidence of airway remodeling in cross-country skiers [145–147], and the fact that EIB does not respond to pharmacologic agents prophylactically [146], strongly

suggests that EIB pathologically is quite different from asthma. Whether dietary modification through supplementation with 3.2 g of EPA and 2.2 g of DHA could decrease the EIB was studied by Mickleborough et al. [148] in a randomized, double-blind crossover study. The diet had no effect on pre-exercise pulmonary function in either group or on post-exercise pulmonary function in the control group, but in the subjects with EIB, the ω -3 fatty acid diet improved post-exercise pulmonary function compared to the normal and placebo diets. Similarly, leukotriene E_4 (LTE_4), $9\alpha,11\beta$ -prostaglandin F_2 , LTB_4 , tumor necrosis factor- α , and interleukin- 1β , all significantly decreased on the ω -3 PUFA diet compared with normal and placebo diets and after the exercise challenge. Thus, this small study of 10 elite athletes with EIB and 10 normal elite athletes (without EIB) suggests that fish oil supplementation has a significant protective effect in suppressing EIB in elite athletes, most likely due to the anti-inflammatory properties of the ω -3 fatty acids.

Conclusions and Recommendations

Western diets are deficient in ω -3 fatty acids with a higher ω -6/ ω -3 ratio 10–20/1, whereas during evolution the ω -6/ ω -3 ratio was balanced 1–2/1. Similarly, today Western societies are sedentary due to the mechanization that has taken place at home and at work. ω -3 fatty acid intake leads to increases in muscle cell membrane phospholipids and a decrease in the ω -6/ ω -3 ratio. Similarly, exercise leads to increases in DHA muscle cell membrane phospholipids and decreases in the ω -6/ ω -3 ratio. Both ω -3 fatty acid supplementation and endurance training in rodents increase fatty acid binding protein, most likely by increasing fatty acid flux within the cell.

ω -3 fatty acids are essential for normal growth and development and in the prevention and management of chronic diseases and conditions. ω -3 fatty acids have anti-inflammatory, antithrombotic, hypolipidemic, and antiarrhythmic properties. Similarly, exercise and physical activity and athletics are associated with a lower risk for cardiovascular disease, hypertension, obesity and diabetes. In fact, both ω -3 fatty acids and physical activity influence gene expression and have many beneficial effects that lower the risk for chronic diseases and may delay the aging process.

Low ω -3 fatty acid intake is associated both with depression and cardiovascular disease; in fact, depression precedes cardiovascular disease. An important role for ω -3 fatty acids in mood disorders (bipolar disorder and unipolar major depression) is supported by a substantial body of direct and indirect evidence. Studies in rodents and human beings show that the effects of chronic stress can be mitigated by exercise. Also, excessive exercise or overtraining may

produce negative mood states as well as fatigue, sleep disturbances, frequent infection, injuries and reduced performance. ω -3 fatty acids have been shown to improve these adverse effects of excessive exercise. In exercise-induced bronchoconstriction in elite athletes, the ω -3 fatty acids reduce the severity of the condition.

A wealth of scientific reports points to the inescapable conclusion that human fitness and health improve when sedentary individuals begin to exercise. Although low physical activity levels most frequently occur in more industrialized affluent nations, this behavior is becoming increasingly common in developing countries as well. Because mechanization and industrialization have reduced occupational physical activity levels, a need exists to supplement with additional daily physical activities designed to improve health and fitness. A wide variety of fitness parameters, including aerobic capacity, muscular strength and endurance, coordination, flexibility and body composition, improve with increases in activity levels. Perhaps more importantly, indices of human health also improve.

Three of the most common chronic degenerative diseases of westernized nations (hypertension, coronary heart disease, and non-insulin-dependent diabetes mellitus) are increasingly being recognized as diseases of insulin resistance. In all three cases, physical activity clearly has been shown to reduce the severity, and outcome of these diseases. Physical activity also has a well-known role in preventing and reducing obesity and also exerts a beneficial influence upon insulin metabolism. Furthermore, increased levels of physical activity positively impact virtually all chronic diseases, including, but not limited to stroke, peripheral artery disease, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, and some forms of cancer.

Previously sedentary individuals, even non-taxing physical activities such as walking, gardening, bicycling, and swimming can elicit improved health, and reduce all causes of morbidity and mortality. Sports training physical activities should include daily training programs in preparation for competition. Health-promoting physical activities aim at promoting growth, improving body functions and protecting from illness. Exercise prescription (regimen) as a means of treating or reversing various diseases should be considered as an essential therapeutic component.

Excessive radical formation and trauma during high-intensity exercise leads to an inflammatory state that is made worse by the increased amounts of ω -6 fatty acids found in Western diets. EPA and DHA have been used to counteract the inflammatory state. Therefore, EPA and DHA of 1–2 g/day at a ratio of EPA/DHA of 2/1 is recommended for leisure sport activity; 2–4 g/day for regular physical training and team sports activities, and 6–8 g/day for elite endurance athletes.

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Omega–6 Fatty Acids and Excessive Adipose Tissue Development

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Introduction

Adipose tissue development takes place in utero mainly during the third trimester of pregnancy and more extensively after birth, emphasizing the importance of adipose tissue development at early age. Whether excess of adipose tissue at that age is predictive of subsequent overweight and obesity is supported by studies showing that (i) body mass index (BMI) exhibits the best correlation between childhood at 1 year of age to adulthood at 16 years of age, and that the relative risk of becoming fat adults is 2-fold higher for fat than for lean babies [1], (ii) BMI of children at 8 years of age is positively predicted by their BMI at 2 years of age [2], and (iii) infants who are at the highest end of the distribution curve or who grow rapidly during infancy are at increasing risk of subsequent obesity [3]. Consistent with these observations, adipocyte size and even more so adipocyte number, as determined from biopsies of subcutaneous adipose tissue of adult obese patients, depend on the age of obesity onset [4]. As mature adipocytes do not divide, this result underlines the importance of overproliferation of adipose precursor cells, which is a ‘silent weightless’ phenomenon, as a function of development and in response to diets. In this respect, adult obesity correlates *negatively* with the milk fat content [5]. At first sight this result is surprising and may be due to the high protein content of milk and most consumed foods at early age which would lead to high levels of insulin-growth factors favoring in turn overproliferation of adipose precursor cells able later in life to become fat cells [6]. In other words, hyperplasia appears distinct from adipocyte differentiation and subsequent fat cell hypertrophy. Another important developmental issue is whether adipose tissue has the ability to expand at any given age. Contrary to widespread opinion, high-fat diets are known to

induce in adult rodents a large increase in the weight of various adipose depots by hypertrophy often accompanied by hyperplasia [6]. In this respect, the role of dietary fat as a major player in human obesity has remained a controversial issue because the prevalence of overweight and obesity in the last decades had taken place despite no recent major change in the amount of ingested fats. As we shall see, this conclusion deserves some caution. Moreover, the importance of qualitative changes in the fatty acid (FA) composition of fats has been largely disregarded despite a dramatic alteration over decades in the balance of essential polyunsaturated fatty acids (PUFAs). Both absolute and relative changes of the ω -6/ ω -3 ratio in most foods have occurred in the last century, raising the ω -6/ ω -3 ratio during evolution from ~ 1 to 15–20 [7]. The importance of these dramatic changes in various chronic diseases has been well described [8]. Since the 1960s, indiscriminate recommendations have been made to substitute vegetable oils, high in ω -6 PUFAs and low in ω -3 PUFAs, for saturated fats. As a result, the ω -6/ ω -3 ratio of breast milk, formula milk and most consumed foods has increased dramatically [9]; as an example, these changes have been accompanied by a significant increase in the supply of dietary arachidonic acid (AA). Equally important, the minimal requirement for linoleic acid (LA) for growth and development as a precursor of AA and its metabolites has been significantly overestimated [10] whereas the recommendations to reduce ω -6 PUFAs even as the ω -3 PUFAs are increased have not been followed [11].

White Adipose Tissue Development in Early Life

Evidence from animal and human studies discussed below favors the possibility that changes in the balance of essential PUFAs have been altering the early stages of adipose tissue development, i.e. during fetal life and infancy but also at the adult age during which adipose precursor cells remain present and are potentially able to differentiate into adipocytes [12]. The size and self-renewal of the adipose precursor pools in various depots as a function of age or in response to diets is presently unknown in humans. This point is important as subpopulations of precursor cells have recently been characterized in the stromal-vascular fraction of human adipose tissue where they likely represent the true potential of white adipose tissue development [13]. Of note, adipocyte turnover is low, if any, and apoptosis has only been observed under drastic conditions, making questionable its quantitative importance under physiological conditions. Altogether, these observations emphasize the fact that adipocyte formation (adipogenesis) is *de facto* an irreversible process and that *prevention* of this phenomenon should represent a key issue from a health perspective.

Adipogenesis and Non-Equivalence of Fatty Acids as Adipogenic Hormones

Knowledge of adipogenesis has increased dramatically over the last two decades with the use of clonal and non-clonal adipose precursor cells from rodents and humans. Adipogenesis is a sequential process in which glucocorticoids, insulin and IGF-I have been identified as the major adipogenic hormones [6]. Long-chain fatty acids (LCFAs) act also at the precursor stage and enhance the formation of adipocytes. The first line of evidence that FAs are involved has been obtained in vitro after purification of the main adipogenic component of fetal bovine serum which was characterized as AA; it is strongly adipogenic and plays in preadipocytes the role of prostacyclin precursor [14–16]. In contrast, the ω -3 isomer of AA (only present at trace amounts in nature) and two major metabolites of the α -linolenic acid (ALA) elongation and desaturation pathway (i.e. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), which are not metabolized to prostacyclin, are less potent than AA. The adipogenic effect of AA is partially blocked by cyclooxygenase inhibitors and antiprostacyclin antibodies added externally, and it is mimicked by carbacyclin, a stable analogue of prostacyclin [14–17]. This strongly suggests an adipogenic role of prostacyclin through the cell surface prostacyclin receptor IP by an autocrine/ paracrine mechanism. Among all natural FAs (saturated, mono- and polyunsaturated FA), only AA triggers cAMP production and activates, through the IP/prostacyclin system, the protein kinase A pathway. Interestingly, EPA and to a lesser extent DHA, while being inactive as cAMP-elevating agents, inhibit the stimulatory effect of AA on cAMP production [18, 19]. Prostacyclin synthesis ceases in adipocytes in which the cell surface prostacyclin receptor IP (IP-R) is no longer functional [16, 20, 21]. In other words, ligand production and IP-R activity represent *transient* events of adipogenesis. The second line of evidence that all LCFAs are regulators of adipogenesis was shown when it was observed that LCFAs also act as transcriptional regulators of some lipid-related genes [22, 23]. In contrast to AA, the metabolism of these LCFAs is not required to bring an adipogenic effect [24]. The intracellular sensors of LCFA have been identified as nuclear receptors of the family of peroxisome proliferator-activated receptors (PPARs) [25]. Interestingly, AA and some of its metabolites generated through cyclooxygenase and lipoxygenase activities have also been reported to be activators/ligands of PPARs. Taken together, these various observations emphasize that among LCFAs, AA is the most potent adipogenic effector.

Based upon the above data, nutritional experiments have been performed to investigate whether a LA-enriched diet modulates fat mass through an increased flux of LA metabolites, e.g. AA and its metabolites, and whether ALA counteracts this effect. Under *isoenergetic* conditions, comparative experiments

have been performed with wild-type mice and mice invalidated for the cell surface prostacyclin receptor (*ip*^{-/-} mice). These studies have shown that (i) pups from wild-type mothers fed LA diet are 40% heavier 1 week after weaning than those from mothers fed LA/ALA diet, (ii) the weight difference between mice fed LA and those fed LA/ALA diets is maintained at the adult age, and (iii) the LA-induced enhancement of fat mass is abolished in *ip*^{-/-} mice, demonstrating the critical role of AA and that of prostacyclin receptor in excessive adipose tissue development [19]. These studies show that PUFAs of the ω-6 and ω-3 series are *not* equipotent in promoting adipogenesis in vitro and adipose tissue development in vivo. Consistent with the adipogenic role played by LA and the antiadipogenic role played by ALA, similar observations have been reported by other investigators in rats [26] and mice [27], whereas in 5-day-old piglets, 0.5% AA supplementation in the diet leads to a 27% increase in body weight with no change in body length [28]. Importantly, in full-term infants receiving as formula milk 16% LA, inclusion from 0.4 to 3.2% ALA lowered AA and increased DHA levels, and this was accompanied by a significant *lower* body weight at 4 months of age [29]. The most striking effect of LA supplementation on body weight was shown a few decades ago: in elderly institutionalized men (mean age of 66 years) fed for 5 years a diet in which the major modification was to substitute saturated FAs (conventional diet) by LA (experimental diet), the mean body weight of control subjects (389 men) decreased by 2% whereas that of the experimental group (393 men) increased by 3%, strongly suggesting an increase in body fat content even at a late age upon LA supplementation. Moreover, when comparing the FA composition of dietary fat with that of adipose tissue lipids, it was found that the rate of LA equilibration in LA-supplemented subjects was positively associated with weight gain [30].

Relevance of Childhood and Adult Obesity

The key question to be addressed in humans is whether the balance of PUFAs has changed over decades such as it could favor excessive adipose tissue development. With respect to childhood, comparative US data between the National Health and Nutrition Survey II (1976–1980) and the NHANES III (1988–1994) indicate for 6- to 11-month-old infants above the 95th percentile of the weight-for-length reference curve has increased 1.9- and 1.7-fold for boys and girls, respectively [31]. These data appear to exclude at that age sedentarity as a cause of increased adiposity but rather suggest that qualitative nutrient changes have occurred during gestation and/or lactation, and are consistent with changes in the FA composition of mature breast milk and infant formulas

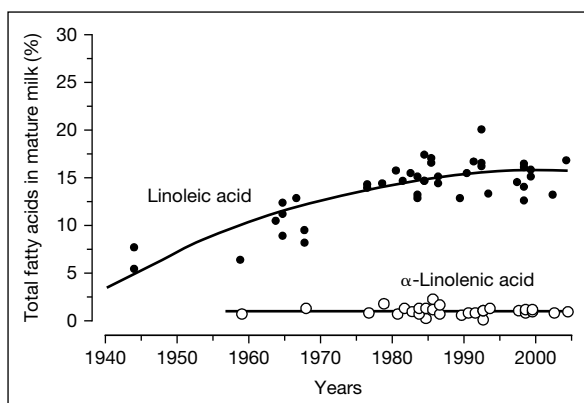


Fig. 1. Linoleic acid and α -linolenic acid content in mature breast milk of US women from 1944 to 2005 [adapted from 9].

over the last decades (fig. 1). Indeed, a time increase of LA content has been systematically reported in breast milk of women living in major industrialized countries of the Western world, which leads to an increase in the LA/ALA ratio. Importantly, AA and DHA content of breast milk are more closely related on a long-term basis to dietary intake rather than to the LA and ALA intakes. Mainly associated to a decrease in DHA intake, the AA/DHA ratio has increased significantly in the last 25 years in North America, Europe and Australia, the highest values being found in the USA [9]. Regarding formula milks, manufacturers have limited since 1995 the LA content and have changed that of ALA in order to match the ratio found in human milk to date. However, the LA content in formulas is still high and greatly variable, ranging between 10 and 30%, i.e. between the adequate level and the highest level reported in breast milks [9]. In any case, considering that LA requirements have likely been overestimated [10], the LA content of infant formulas should be reconsidered according to previous recommendations of nutrition committees [11].

Later in life, the situation for infants, adolescents and adults appears rather worrisome with respect to LA and ALA content of most consumed foods. Between 1960 and 2000, the daily FA intake in France has increased by 40% whereas in the meantime the prevalence of overweight and obesity has ‘exploded’ in a way similar to that of most industrialized and urbanized countries. Importantly, between 1960 and 2000, changes in the intake of ω -6 and ω -3 PUFAs, with a striking increase in the LA/ALA ratio, have also been observed with a disproportionate increase in the consumption of LA (2.5-fold)

Table 1. Main changes in FA consumption in France between 1960 and 2000 [adapted from 9]

	Current intake g/day/adult (in 2000)	40 years' evolution (fold increase)	Plant lipid- related increase g/day	Animal lipid- related increase g/day
Total FAs	104	1.4	+18.8	+10.1
Palmitic acid (C16:0)	22	1.4	+1.3	+5.0
Oleic acid (C18:1)	33	1.2	+2.3	+2.2
Linoleic acid (C18:2 n-6)	21	2.5	+11.9	+1.0
Arachidonic acid (C20:4 n-6)	0.5	2.3		+0.3
Total n-6 PUFAs	22	2.5	+11.9	+1.3
α -Linolenic acid (C18:3 n-3)	0.9	0.6	+0.3	0.9
n-6/n-3 PUFAs	12	2.9		
LA/LNA	23	4.2		

and AA (2.3-fold). During the same period, the consumption of ALA has decreased by 40%, leading to a 2.9- and 4.2-fold increase in the ratios of ω -6/ ω -3 PUFAs and LA/ALA, respectively (table 1). These profound alterations can be traced in the food chain and appear to be due to changes in human food habits as well as in the feeding pattern of breeding stock [9].

Modulation of the ω -6/ ω -3 Ratio by Genetic and Nutritional Approaches

Major changes have taken place in our diet for several few centuries. Modern agriculture using corn and soybean grains, associated with hydrogenated vegetable fats and processed foods, has dramatically altered the PUFA profile. The ω -6/ ω -3 ratio is presently around 15–20:1 instead of \sim 1:1 in the ancient days before agribusiness and modern agriculture expanded [7], and the detrimental effects of such changes have been thoroughly discussed [8]. Two major approaches to ‘normalize’ the PUFA status in modern foods are of considerable interest, as discussed below.

Genetic Approach

By using a viral strategy, an ω -3 FA desaturase (fat-1) gene from *Caenorhabditis elegans* has been transferred into mouse cells. This enzyme is able to convert ω -6 FAs to the corresponding ω -3 FAs, i.e. LA to ALA, and therefore shifts the ω -6/ ω -3 ratio from 15:1 to 1:1. In the meantime, the AA

levels are significantly reduced in these transgenic animals [32]. Most interestingly, compared to wild-type animals, transgenic mice expressing fat-1 are protected from colitis [33] and are less prone to tumor formation [34], demonstrating the physiological importance of an adequate ω -6/ ω -3 ratio. Using the same approach, cloned transgenic pigs rich in ω -3 FAs have been generated [35]. Clearly, transgenic animals are of great interest to delineate the various metabolic roles of ω -3 FAs by eliminating confounding factors arising from the diets and the feeding procedures. However, the technique is still cumbersome and the ω -6/ ω -3 ratio will depend on the uncontrolled number of functional copies of the fat-1 gene inserted at random into the genome, as illustrated in piglets for instance [35]. Moreover, consuming meat from genetically-modified animal species may not be so appealing for worldwide consumers.

Nutritional Approaches

The first strategy has been to increase ALA and its very long-chain derivatives, i.e. long-chain polyunsaturated fatty acids (LC-PUFAs, e.g. EPA and DHA) by either flaxseed oil or EPA/DHA supplementation. The second and more recent strategy has been to intervene at the beginning of the food chain, i.e. at the animal feed level. Dietary supplementation with flaxseed oil [36], flaxseed consumed as either raw flour or incorporated into bread for 4 weeks [37], or flaxseed oil capsules given to obese patients for 26 weeks [38] raised the plasma level of LNA and that of LC-PUFAs of the ω -3 series. Alternatively, foods and ingredients selected to increase the dietary content of ω -3 FAs and to decrease that of ω -6 FAs in educated patients led to a similar increase in ALA and LC-PUFA levels whereas AA levels and eicosanoid production (thromboxane B₂ and PGE₂) were reduced [39, 40]. Altogether, these studies demonstrate that the ω -6/ ω -3 ratio can be nutritionally modulated in adult subjects. In these experiments, no relationship between the decrease in the ω -6/ ω -3 ratio and a decrease in body weight could be observed, as either a slight increase (associated with enhanced protein intake) [40] or no change [38] were reported. However, it cannot be ruled out that the short duration of the assays (4–26 weeks), associated with large range of age (24–50 years), could be responsible for this observation as compared to increased body weight observed in elderly people fed LA-enriched foods for 5 years (see above) [30].

The method of introducing linseed into livestock diet has been recently implemented. The percentages of extruded linseed in ingested dry matter were 2.5, 3.5, 5 and 10% for pig, broiled chicken, dairy cow, and laying hens, respectively, whereas the corresponding LA/ALA ratio decreased from 7.1 to 1.7, 5 to 1.7, 13 to 1.2 and 11 to 1 [41]. Interestingly, the hedonic tests were in favor of linseed-fed animal products (milk, egg, pork, chicken, ham, butter). A double-blind, randomized, cross-over trial involving 50 healthy adult subjects (BMI

25.4 \pm 13; age 34.6 \pm 2 years, range 25–45) was next performed [42]. In order to maintain their regular eating habits, after an 18-day washout period, the subjects were given food allocations for two meals per day of linseed-fed animal products or usual linseed-free diets. No fish consumption was permitted and olive oil was exclusively used for seasoning. Under these conditions, the FA composition of regimens exhibited a 2.3-fold increase of LC-PUFAs of the ω -3 series and a 30% decrease of AA, the LA/ALA ratio being shifted from 14.9 to 6.8. After 3 months of both regimens, the blood lipid levels of ALA and LC-PUFAs were increased 2.1- and 1.3-fold respectively, whereas that of rumenic acid (C18:2 *cis*-9 *trans*-11), originating from ingested butter, raised 1.5-fold. In another study carried out with a population of 44 patients suffering from obesity (BMI \sim 32) and type 2 diabetes, the results showed after 105 days a significant decrease in HOMA index, and this improved insulin sensitivity appeared significantly associated with increased blood lipid levels of ALA and/or rumenic acid [42]. Additional studies are underway and the results are still pending [P. Weill, pers. commun.].

Therefore, despite the statement that ‘the most predictable way to increase a specific LC-PUFA in plasma, tissues or human milk is to supplement with the FA of interest’ [43], these results demonstrate that such changes can take place without changing eating habits of consumers. This nutritional approach is operational in France where various ω -3 FA-enriched foods are sold in bakeries and supermarkets. Clearly, this approach is at odds with those favoring the use of oil capsules or ω -3 FA-enriched dietary supplements, and lies at the core of different eating habits between countries and continents.

In conclusion, owing to the continuous presence of adipose precursor cells throughout life and to the fact that adipocytes once formed exhibit little or no turnover in the body [6], these quantitative and qualitative changes observed in ingested lipids, associated with increased sedentary lifestyles, have in our view led to a stimulation of fat cell formation and to an increase in the prevalence of overweight and obese subjects, leading in turn to physiological dysfunctions. Thus it appears that prevention of obesity represents the critical issue to avoid difficult, if not insurmountable, health problems to solve in the future. If so, the status of lipids should be re-evaluated from the very beginning of the food chain in which the intricacy of the agricultural and food industry policies is now becoming quite obvious.

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Non-Conventional Genetic Risk Factors for Cardiovascular Disease

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Introduction

Cardiovascular disease (CVD), defined broadly as the spectrum of disease states including myocardial infarction (MI), coronary artery disease (CAD), stroke, and surrogate markers of atherosclerosis such as carotid intima-media thickness (IMT) and coronary artery calcification (CAC), is the leading cause of death in Western societies and is becoming increasingly common in other less developed countries as well. The tremendous burden that CVD poses on healthcare costs and patients' quality of life necessitates the development of novel and better treatments that can be used either as alternative medications or in conjunction with already existing drugs.

Atherosclerosis, the most common cause of CVD, is a progressive disease characterized by the accumulation of lipids and fibrous elements in large arteries [1]. It is a complex process involving numerous factors and mediators and is based on the dynamic exchange of signals between resident cells, such as endothelial cells, smooth muscle cells, and infiltrating monocyte/macrophages and lymphocytes. The atherogenic process is initiated by the accumulation of low density lipoprotein (LDL) particles in the subendothelial layer of the artery wall, where they are oxidized by cell-derived reactive oxygen species (fig. 1, step I). The resulting production of adhesion molecules, chemokines, and growth factors by endothelial cells causes inflammatory cells, comprised predominantly of monocytes, to adhere to the vessel wall and migrate into the subendothelial space. In this microenvironment, the activated monocytes proliferate and differentiate into macrophages, which begin to engulf the oxidized LDL particles and subsequently transform into foam cells (fig. 1, step II). Accompanied by a progressive increase in extracellular lipids and intimal

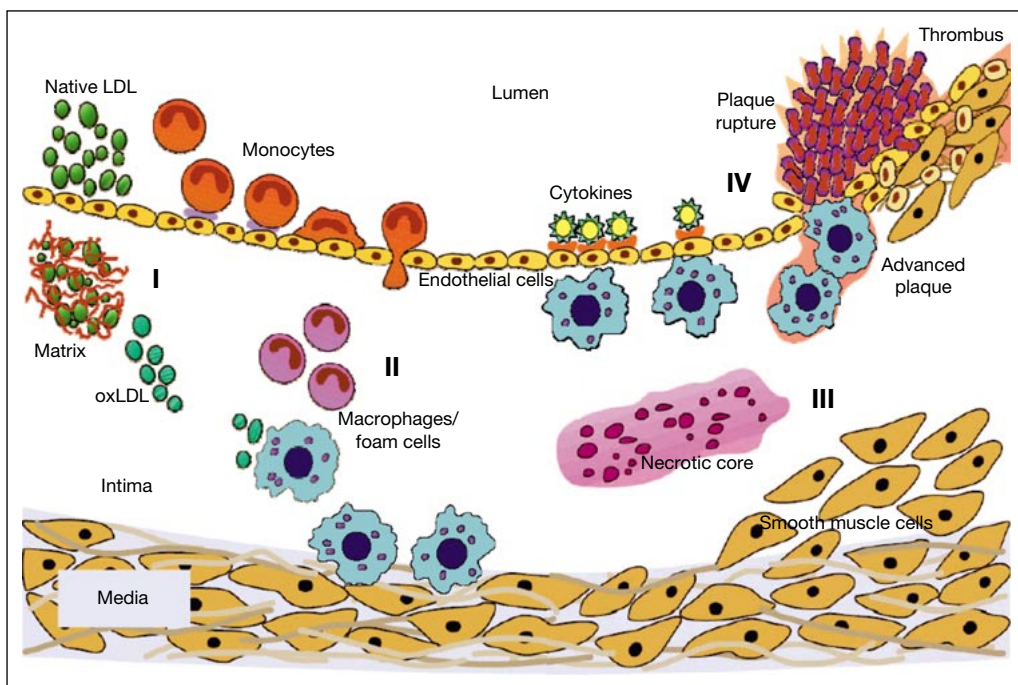


Fig. 1. Steps in the progression of atherosclerosis in the artery wall. (I) LDL particles accumulate in the subendothelial cell layer and become trapped within matrix proteins, where they are oxidized (oxLDL) by cell-derived reactive oxygen species. (II) Chemotactic and growth factors stimulate monocytes to transmigrate across the endothelial cell layer and differentiate into macrophages. Macrophages begin to engulf the oxLDL, leading to foam cell formation. (III) The foam cells produce a variety of mediators and eventually undergo apoptosis or necrosis, contributing their contents to a growing core of cellular debris and cholesterol. This process is accompanied by the migration of smooth muscle cells into the intima from the media and the formation of a fibrotic cap. (IV) As the advanced lesion continues to grow, it becomes increasingly unstable and prone to rupture, which can result in a thrombus or clinical event such as MI or stroke.

smooth muscle cells that have migrated through the media, the resulting 'fatty streaks' develop into advanced lesions as the lipid-laden macrophages undergo apoptosis to form a necrotic core (fig. 1, step III). Proinflammatory cytokines that are also expressed in the lesion cause the smooth muscle cells to proliferate and secrete collagen and other extracellular matrix proteins, resulting in the formation of a fibrotic cap. Such advanced lesions become increasingly complex with calcification, ulceration at the luminal surface, and hemorrhage from

small vessels that grow into the lesion from the media, rendering them unstable and prone to rupture (fig. 1, step IV). Ultimately, plaque erosion and rupture can lead to clinical events such as MI or stroke.

Over the past half century, epidemiological studies have revealed numerous risk factors for atherosclerosis [2]. These are, in large part, controlled by traits with genetic components, including gender, age, hypertension, hyperlipidemia, obesity, and diabetes. Collectively, these have come to be known as 'conventional' risk factors. In addition, environmental risk factors, such as stress, a high fat diet, lack of exercise, and smoking, are also important contributors to CVD. The importance of genetics and environment in CVD has been examined in many family and twin studies. Within a population, the observed heritability of atherosclerosis has been large in most studies, frequently exceeding 50%. With the exception of Lp(a) levels, which are determined almost entirely by common variations of the LPA gene, each of the genetic risk factors involves multiple genes. This complexity can be clearly observed in genetic crosses with animals maintained under similar environmental conditions, which have revealed dozens of loci contributing to atherosclerosis, lipoprotein levels, body fat, and other risk factors [3]. Another level of complexity involves the interactions between genes themselves and the environment, including nutritional and behavioral factors. Thus, common forms of CVD result from the interplay between susceptibility genes and lifestyle.

While the role of conventional risk factors in CVD is generally accepted, it is also likely that there are genetic contributions to CVD that are independent of known risk factors. For example, certain individuals develop premature heart disease but do not exhibit high cholesterol or hypertension. This may, in part, be due to genetic influences that act at the level of vessel wall metabolism, which lead to variations in cellular function or inflammatory responses among individuals. As discussed below, several recent studies support this concept and emphasize the need for identifying new genes and pathways for CVD.

Family-Based Linkage Studies

Since the year 2000, over 10 genomewide linkage scans have been carried out in families to identify chromosomal regions segregating with CVD-related traits. Numerous loci have been reported, some of which exhibit coincident linkage with conventional risk factors such as HDL levels or metabolic syndrome traits. However, recent studies have also identified loci with major genetic effects that do not exhibit coincident linkage with known risk factors. Presumably, these regions harbor susceptibility genes that could reflect novel pathways for CVD.

In the last 2 years, two important genomewide linkage analyses for MI and/or CAD have been published. The first was by Wang et al. [4] who studied 428 US Caucasian families with at least 2 members affected by premature CAD or MI before the age of 45 in males and 55 in females. Of note, this study used more restrictive criteria for ascertaining families by excluding patients with hypercholesterolemia, diabetes, or childhood hypertension, and therefore specifically selected for genetic forms of MI and CAD that are not associated with known risk factors. A locus for MI was identified on chromosome 1p34-36 with a remarkably high LOD score of 11.7. Such a level of significance is very rarely observed for complex diseases and is more typical of linkage results for single gene disorders. This may be due, in part, to the stringent MI phenotype under study and the exclusion of potentially confounding covariates. Interestingly, no significant results were obtained for CAD, suggesting that CAD and MI do not necessarily share the same genetic determinants. Connexin 37 (CX37), a potential candidate gene that resides in the region, is a gap junction protein expressed in arterial endothelium and has previously been associated with MI in a Japanese population [5]. It remains to be determined whether this is the causal gene for MI in these families.

The second genomewide linkage study by Hauser et al. [6] studied 438 Caucasian families from the USA and Europe in which at least 2 siblings were affected by premature CAD. The authors further defined three additional phenotypic stratifications of the families including (i) MI or unstable angina in 2 or more siblings; (ii) the absence of diabetes in any affected family member, and (iii) dyslipidemia in at least 1 member of a nuclear family. Although several linked chromosomal regions were identified in the entire dataset as well as the stratified subsets, most of the loci overlapped with regions where lipid and metabolic traits had previously been mapped. However, one locus on the distal arm of chromosome 5 exhibited nominal evidence for linkage to CAD (LOD = 1.4), which was derived predominantly from the families excluded for diabetes. Similar to the results described above, this locus may represent a gene contributing to CVD independent of known risk factors.

As is true for other complex diseases, understanding mendelian forms of CVD can be a powerful approach for identifying novel susceptibility genes. Recently, Wang et al. [7] conducted a genome scan of a single family with an autosomal dominant pattern of CVD consisting of 13 individuals affected by CAD or MI. A putative locus was mapped to chromosome 15q26 with a significant LOD score of 4.2. This region contained 93 genes, including the myocyte-enhancing factor 2A gene (MEF2A) which was evaluated as a possible candidate given its role in vasculogenesis. All 10 living affected members of this family were found to carry an in-frame deletion of seven amino acids. Functional analysis demonstrated that the mutation acts in a dominant negative

fashion and disrupts localization of MEF2A to the nucleus. Although the molecular mechanism for increased susceptibility to CAD/MI is unknown, the authors speculate that abnormal MEF2A activity affects endothelial cell function, rendering the coronary vessels more susceptible to inflammation and thrombosis [8]. In addition, screening of 207 independent CAD/MI cases for mutations in the MEF2A gene by the same group identified three rare amino acid substitutions whereas none were identified in controls [8]. The significance of these findings have come under debate recently from a study by another group that screened the MEF2A gene in 300 individuals with premature CAD and 300 elderly controls and identified only one amino acid substitution unique to cases [9]. Moreover, this latter study did not observe co-segregation of the 7 amino acid deletion with CAD/MI in one family where the proband was a carrier of the mutation [9]. Thus, the contribution of MEF2A mutations to CAD and MI still remains to be conclusively determined.

In total, genome scans in multiple study populations have mapped over 10 loci for CVD traits. With few exceptions, there is minimal overlap between these loci which could be due to differences in the populations, the phenotypes measured, or the statistical methods used for analysis. For example, although MI and CAD are correlated, these phenotypes could represent distinct pathophysiological processes that are controlled by different genetic factors. Moreover, while the loci described above do not exhibit linkage with known risk factors, it is still possible that the causative genes in these regions could be related to pathways involving lipid metabolism, blood pressure, or obesity. Nonetheless, identification of the genes could also provide novel genetic mechanisms leading to CVD.

Candidate Gene and Whole Genome Association Studies

While family-based linkage studies have identified numerous loci for CVD and other related traits, the identity of the underlying genes, with rare exception, has remained elusive. Another approach for identifying genes for CVD has been to conduct association studies with candidate genes or, more recently, through a whole genome analysis. Association studies in general provide greater statistical power than linkage analyses for detecting genetic effects and dozens of studies have examined a variety of candidate genes for association with CVD traits. Most of these have focused on genes involved in lipid, blood pressure, or obesity-related pathways. By comparison, fewer studies have examined genes involved in other processes traditionally not considered to be risk factors. Studies in the last few years however have reported and

Table 1. Non-conventional risk factor genes with consistent evidence of association to CVD traits

Gene	Type of study/phenotype	Potential mechanism	Ref.
Myocyte enhancer factor 2A (MEF2A)	family-based; case-control/MI, CAD	vascular endothelium function (?)	7–9
Phosphodiesterase 4D (PDE ₄ D)	family-based, case-control/stroke	cAMP degradation, cell proliferation (?)	39, 45
Lymphotoxin- α (LTA)	case-control, cohort study/MI, coronary atherosclerosis	inflammatory response	10–14
Galectin 2 (LGALS2)	case-control/MI	regulation of LTA secretion and inflammatory response	15
Toll-like receptor 4 (TLR4)	cohort study, case-control/carotid IMT, MI	receptor signaling and innate immunity	16–19
Thrombospondin gene family (THBS-1, -2, -4)	case-control/MI	endothelial cell function	20–22
Connexin 37 (CX37)	case-control/CAD, MI	endothelial cell function	5, 23, 46
Matrix metalloproteinase gene family (MMP)	case-control, cohort study/coronary artery aneurysm, MI, carotid IMT	proteolysis and plaque rupture	24–26
Arachidonate 5-lipoxygenase (ALOX5)	cohort study/carotid IMT	LT biosynthesis and inflammatory response	36
Arachidonate 5-lipoxygenase activating protein (ALOX5AP/FLAP)	family-based; case-control/MI and stroke	LT biosynthesis and inflammatory response	37–39
Leukotriene A ₄ hydrolase (LTA ₄ H)	case-control/MI and CAD	LTB ₄ synthesis and inflammatory response	40

MI = Myocardial infarction; CAD = coronary artery disease; IMT = intima-media thickness; LT = leukotriene.

confirmed genes that are part of pathways, such as inflammation, endothelial cell function, and plaque stability that are associated with CVD traits. Although not an exhaustive list, several genes and pathways for which there is consistent evidence of association with CVD are highlighted in table 1 and discussed below.

Inflammatory Processes

Using a whole-genome association study design, Ozaki et al. [10] reported association of the lymphotoxin- α LTA gene (LTA) with MI in a Japanese population. Specifically, the frequencies of an intronic single nucleotide polymorphism (SNP) and an amino acid altering substitution were significantly higher in cases vs. controls, even after adjustment for diabetes, hypertension and hyperlipidemia. Both SNPs occur on the same haplotype and individually result in either increased expression of LTA or its activity. Given its role as a cytokine, these results provide a functional mechanism by which common SNPs of the LTA gene in the human population could lead to increased inflammation in the artery wall, and subsequently MI. Other studies have replicated the association of LTA with CVD traits, including another Japanese population [11–13]. Interestingly, the effect of LTA was not observed in a third Japanese population [14]. Such discrepancies are commonly observed in the genetics of complex diseases and demonstrate the difficulties in carrying out these studies. More recently, the same investigators who first identified LTA used an *Escherichia coli* two-hybrid system to identify galectin 2 as a protein that interacts with LTA and potentially regulates its secretion from macrophages and smooth muscle cells. In a case-control analysis, the T allele of an intronic SNP (C3279T) in the LGALS2 gene was shown to occur at higher frequency in the control group and thus protective against MI. Additionally, the T allele had 50% decreased transcriptional activity in vitro, which would presumably lead to less LTA secretion and inflammation [15].

Another immune response gene recently associated with CVD is toll-like receptor 4 (TLR4). Using a cohort of 810 individuals, Keichl et al. [16] demonstrated that carriers of an Asp299Gly substitution in TLR4 had decreased carotid atherosclerosis and plasma biomarkers of inflammation whereas they were more susceptible to severe bacterial infections. Similarly, other investigators have replicated these results with more clinically relevant phenotypes such as MI [17–19]. Taken together, these studies provide convincing evidence for the genetic contribution of the LTA and TLR4 genes to CVD and are consistent with the hypothesis that immune responses are an important part of atherogenesis.

Vascular Endothelium Function

As described above, endothelial cells can play an important part in the atherogenic process. Recent studies support this concept and suggest that variation in endothelial cell function can be under genetic control. For example, Topol et al. [20] carried out a large case-control study with 62 vascular biology candidate genes and obtained the strongest evidence of association of familial premature CAD or MI with 3 members of the thrombospondin (THBS) gene family (THBS-1, THBS-2, and THBS-4). The association between THBS-2 and

THBS-4 variants with CAD/MI has since been replicated in several studies [21, 22]. Interestingly, variation in the THBS-2 gene confers protection against CVD whereas SNPs in the THBS-1 and THBS-4 genes lead to increased risk. While the exact mechanism by which the THBS proteins modulate artery wall metabolism remains to be elucidated, there is functional evidence to suggest that they are involved in endothelial cell function [22].

Given the role of CX37 as a gap junction protein involved in the growth, regeneration after injury, and aging of endothelial cells, several association studies have examined the CX37 gene in humans. In a large Japanese case-control study with 112 SNPs in 71 candidate genes, a C1019T substitution in CX37 was one of only three variants associated with MI. This association has also been observed in an Italian population from Sicily [23], but the mechanism by which this variant alters CX37 functional is still unknown.

Plaque Instability and Rupture

Plaque instability and rupture is very important from a clinical standpoint since it can lead to MI or stroke. The matrix metalloproteinases (MMPs) are a family of over 25 enzymes that degrade extracellular matrix proteins such as collagen, elastin, and proteoglycans. Several of these enzymes, such as MMP-1, are expressed in the vulnerable shoulder regions of atherosclerotic lesions where they could contribute to plaque rupture. Accordingly, the genes for these enzymes have also been examined in association studies [24]. In particular, polymorphisms of the MMP-1, MMP-3, and MMP-9 genes have shown associations across several studies with various CVD traits, including coronary artery aneurysms and MI [24–26]. Interestingly, certain variants of the MMP-1 and MMP-3 genes increase transcription of the enzymes but are associated with smaller lesions. A plausible explanation for this apparent paradox is that these alleles lead to less extracellular matrix accumulation and, thus smaller plaques, but these plaques are more prone to rupture. Although other MMPs have also been investigated in genetic studies, the evidence for their contribution is not as consistent. Nonetheless, the results are in agreement with the notion that genetic-mediated increased proteolysis in the arterial wall may act as a susceptibility factor for CVD, and MI in particular.

Based on the association studies outlined above, there is convincing evidence for genetic factors that affect atherosclerosis development at the level of the artery wall. As a recent study suggests, CVD can also be associated with completely novel mechanisms for which a pathophysiological link is unclear or not obvious. In a gene-centric genome association study, Shiffman et al. [27] demonstrated that four genes encoding a cytoskeletal protein, a receptor tyrosine kinase, and two G protein-coupled receptors are associated with MI. These genes would most likely never have been selected in candidate gene studies and

demonstrate the importance of unbiased study designs, such as whole genome association, to identify genes. Numerous other genes have also been examined but the initial results are very often not replicated in subsequent studies. These discrepancies can be attributed to confounding factors such as genetic heterogeneity, population stratification, the extent of linkage disequilibrium, and varying statistical methodologies. Such difficulties inherent in human studies underscore the need for appropriately designed and sufficiently powered studies.

A Combined Approach Identifies a Novel Pathway for CVD

With the ability to perform fine mapping, the power to map genes for complex traits, and the ability to genetically manipulate their genome, mice provide a number of advantages for gene discovery. In this regard, numerous knockout and transgenic mice have been generated with varying effects on atherosclerosis [28]. Although common forms of CVD in humans are not due to the complete inactivation of a single gene, the ability to genetically modify genes in mice, either through overexpression or inactivation, has provided an invaluable tool for carrying out experiments that would simply not be feasible or ethical in humans. In addition, linkage mapping studies in mice have identified over 20 unique loci for atherosclerosis, a subset of which show conserved synteny with regions of the human genome where CVD traits have also been mapped [3, 29]. Importantly, many of the loci identified in mice do not exhibit linkage with traits such as lipid levels and metabolic phenotypes, consistent with the observations in humans. This further supports the existence of genetic factors that may act at the cellular level, perhaps influencing the function of vascular endothelium or leukocytes that infiltrate the vessel wall. Thus, it is possible that the genes segregating with atherosclerosis in mouse crosses represent unknown pathways for atherosclerosis, which can be examined in human populations once the genes have been identified in mice.

A series of recent studies have elegantly illustrated this combined approach and led to the identification of a novel pathway for CVD with important therapeutic implications. Initially, an atherosclerosis susceptibility locus, *Artles*, was mapped in an F2 intercross between two inbred mouse strains [30]. Among the candidate genes in the linkage interval was the gene encoding 5-lipoxygenase (5-LO; ALOX5), the rate-limiting enzyme in the production of leukotrienes (LTs), which are a class of inflammatory molecules derived from arachidonic acid. 5-LO is expressed primarily in leukocytes and has been studied mainly in the context of acute, not chronic, inflammation, particularly that associated with asthma [30]. Two types of LTs are generated through the 5-LO pathway (fig. 2). The first, LTB₄, is generated from LTA₄ through the enzyme

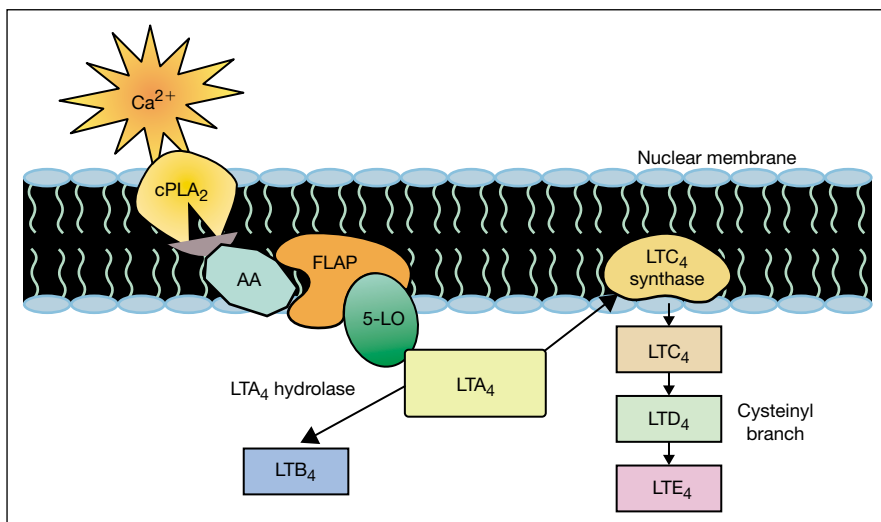


Fig. 2. The leukotriene biosynthetic pathway. Cellular activation by calcium causes cytosolic phospholipase A_2 (cPLA_2) and 5-LO to be rapidly transported to the nuclear envelope, in close proximity to FLAP. FLAP is found only in the nuclear membrane and is required for transferring the arachidonic acid that is liberated from the nuclear membrane by cPLA_2 to 5-LO. 5-LO subsequently oxidizes arachidonic acid to produce LTA_4 , which can further be hydrolyzed to LTB_4 or metabolized through conjugation with glutathione to produce the cysteinyl LTs. LTC_4 and its metabolites mediate bronchoconstriction and SMC contraction whereas LTB_4 is more generally involved in stimulating leukocyte (in particular monocyte) chemotaxis and adhesion to vascular endothelium.

LTA_4 hydrolase (LTA_4H). Alternatively, LTA_4 can be shunted into the cysteinyl branch and converted to LTC_4 . While LTB_4 is predominantly involved in monocyte chemotaxis and inflammatory signaling, the cysteinyl LTs promote bronchoconstriction and smooth muscle cell contraction.

To evaluate 5-LO as a positional candidate gene, Mehrabian et al. [31] crossed 5-LO knockout mice onto a genetically hyperlipidemic background and observed a profound reduction in aortic lesion formation despite cholesterol levels in excess of 500 mg/dl. These studies were one of the first to demonstrate the importance of 5-LO in atherosclerosis. Other studies with 5-LO-deficient mice have suggested the involvement of 5-LO in atherosclerosis-related phenotypes as well [32], and most recently, 5-LO has been implicated in metabolic traits, such as adiposity and bone density [33]. Furthermore, deficiency of the LTB_4 receptors (BLTR-1 and BLTR-2) or their pharmacologic antagonism

reduces lipid accumulation and monocyte infiltration into the artery wall, and, consequently, aortic lesion formation [34, 35].

By extending these findings to genetic studies in humans, an important role for 5-LO pathway genes in CVD has also been observed (table 1). For example, in a cohort study of healthy individuals, certain alleles of a 5-LO promoter polymorphism, consisting of a variable number of Sp1 transcription factor binding sites, were associated with significantly increased carotid IMT and plasma biomarkers of inflammation [36]. This study also demonstrated a gene-dietary interaction where the effect of the proatherogenic alleles was exacerbated in individuals who consumed high levels of arachidonic acid, the substrate for 5-LO. However, this effect was blunted in those individuals who consumed high levels of ω -3 fatty acids, substrates that competitively bind to 5-LO and prevent the binding of arachidonic acid. These latter observations could have important implications for the newly emerging field of 'nutrigenomics'.

In a subsequent study, Helgadottir et al. [37] performed a genomewide linkage analysis of 296 Icelandic families and reported linkage of MI to chromosome 13q12-13. Using fine mapping to narrow the locus, a four-SNP haplotype of the 5-LO activating protein gene (FLAP; ALOX5AP) was found to occur at significantly higher frequency in MI and stroke cases compared to controls. Stimulated neutrophils from male MI cases carrying this 'Icelandic' haplotype also produced higher levels of LTB₄, consistent with a proatherogenic role for this at-risk allele. In contrast, a different haplotype was associated with MI in patients from the UK, suggesting the existence of multiple susceptibility alleles in the population. Importantly, association of the FLAP gene and CVD has been observed in other cohorts as well, replicating the initial results and lending further support for the role of the 5-LO pathway in CVD [38, 39].

Very recently, SNP variants of LTA₄H have also been associated with MI in case-control cohorts from Iceland and the USA [40]. Interestingly, the effect of the LTA₄H haplotype on MI was much stronger in African-Americans, suggesting the existence of interactions with other genes in individuals of African ancestry. While this latter study implicates the LTB₄ branch of the pathway in atherogenesis, it is still not clear whether the cysteinyl LTs are also involved. Thus, additional studies with the other 5-LO pathway genes will be required to genetically dissect the mechanism by which LTs contribute to CVD.

From a clinical standpoint, these findings may have a major impact on the development of novel treatments for CVD. Knowledge that 5-LO and LTs are involved in asthma previously led to the development of drugs targeting different parts of the pathway, such as zileuton, montelukast, and zafirlukast. This raises the exciting possibility of administering existing drugs, or newly developed ones, to target the 5-LO pathway for heart disease patients. Indeed, a

recent report has demonstrated the efficacy of a FLAP inhibitor for reducing inflammatory biomarkers associated with atherosclerosis [41].

With respect to the broader population at risk for CVD, a major question that remains to be answered is which branch of the 5-LO pathway is important for atherogenic-related processes. While mouse and human studies have provided evidence for the role of 5-LO, FLAP, LTA₄H, and the LTB₄ receptor genes in atherosclerosis and CVD [31, 32, 34–38, 40, 42], suggesting that the LTB₄ branch is important, there is less evidence for the role of the cysteinyl branch. However, a recent study demonstrated that administration of montelukast to hyperlipidemic mouse models significantly reduced atherosclerosis, although not to the same extent as a FLAP inhibitor [43]. Thus, both branches of the 5-LO pathway appear to be proinflammatory with respect to atherosclerosis suggesting that therapeutic strategies should focus on targeting 5-LO or FLAP, which are upstream of the bifurcation of LTA₄ to LTB₄ and the cysteinyl LTs. Alternatively, it is possible that the effects of montelukast are due to both blocking cysteinyl LTs as well as direct inhibition of 5-LO itself, as demonstrated recently by Ramires et al. [44]. Even though the therapeutic applications of the 5-LO studies can be considered somewhat serendipitous, these studies illustrate how identification of non-conventional genetic factors for CVD can lead to potentially new strategies for pharmacological and nutritional interventions.

Conclusions

For the more common forms of CVD, a large number of association studies with candidate genes have been performed but few have been convincingly confirmed. Those that have been confirmed explain only a very small fraction of genetic susceptibility in humans. Over the last few years, new evidence has emerged suggesting that genes, which would otherwise not be considered good candidates based on their roles in pathways unrelated to known risk factors, can play an important role in the development of CVD as well. Given the difficulty of dissecting complex traits in humans, mouse models can also become increasingly important in the identification of novel genes, as exemplified by identification of the 5-LO pathway for CVD. Given the genetic complexity of CVD, it is likely that there are important gene-gene interactions, particularly between genes in the same pathway, which have yet to be uncovered. The ability to explore such hypotheses will require large sample sizes and more sophisticated analytic methodology. Newly developed genomic, statistical, and bioinformatics tools, such as the sequences of the mouse and human genomes, microarrays, and high-throughput genotyping technologies, should facilitate the search for CVD genes and may lead to more effective diagnosis, risk assessment, and treatments.

Acknowledgements

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ApoE Genotype: Impact on Health, Fitness and Nutrition

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Introduction

Apolipoprotein E (ApoE) is a constituent protein of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, high-density lipoprotein (HDL) and chylomicron remnants [1, 2]. ApoE plays a central role in atherosclerosis by regulating hepatic uptake of remnant lipoproteins, by facilitating cholesterol efflux and by modifying inflammatory responses [2].

The pathogenesis and progression of atherosclerosis depends on the interacting effects of genetic and environmental factors. Gene-environment interaction refers to the differential phenotypic effects of different environments on individuals with the same genotype, or the differential effects of the same environment on individuals with different genotypes.

Interest in the genetics of ApoE began with the discovery of genetically determined structural variations in ApoE. ApoE displays genetic polymorphism. There are three common allelic variants (ϵ_2 , ϵ_3 , ϵ_4) producing three protein polymorphisms: E₂, E₃, E₄. ApoE₃ is the most common or 'wild type' [3, 4].

The role of lifestyle interventions for the prevention and treatment of heart disease has been evaluated by several investigators in longitudinal studies. It is well recognized that lifestyle changes can significantly reduce the risk for heart disease. Furthermore, there is convincing evidence indicating that the responses of lipoprotein levels to different lipid-lowering interventions may be affected by an individual's ApoE genotype [5–7]. In addition, studies have shown that the presence of a particular ApoE genotype may influence the serum cholesterol response to dietary intervention [8, 9]. Finally, ApoE genotype appears to influence inflammatory markers (i.e., C-reactive protein (CRP)) [10, 11], LDL particle size change following regular exercise training [12], as well as an

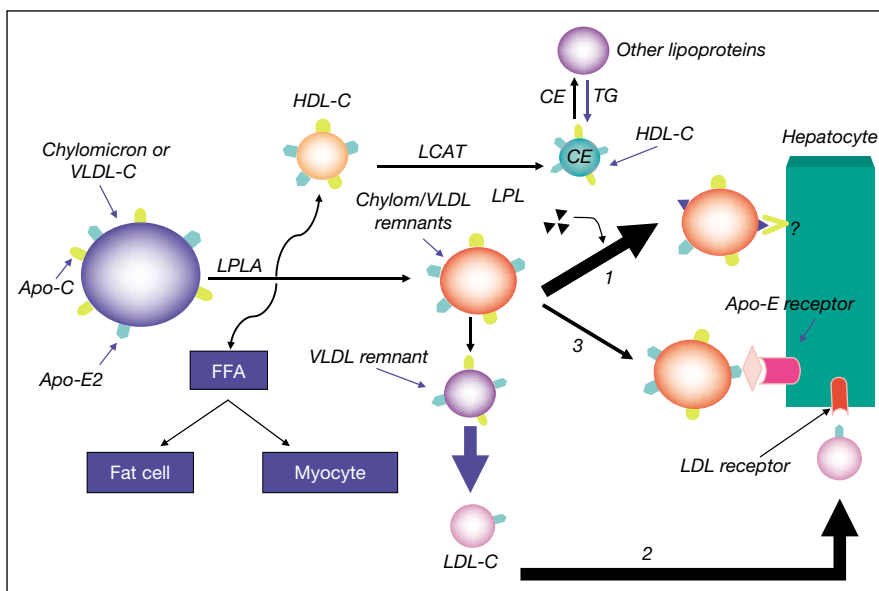


Fig. 1. Role of ApoE in triglyceride metabolism.

individual's response to aerobic training as determined by oxygen uptake ($\text{VO}_{2\text{max}}$) [7].

In this paper the impact of ApoE genotype on lipids, lipid particle size, markers of inflammation, fitness and nutrition will be reviewed.

Effect of ApoE Genotype and Lipids

Epidemiological studies have shown an increase in the risk for atherosclerosis and coronary heart disease (CHD) with increasing serum total cholesterol (TC), LDL cholesterol (LDL-C), triglycerides and decreasing HDL cholesterol (HDL-C) [13]. In atherosclerosis, complex interactions take place between environmental and genetic factors. Variations in candidate genes for lipoprotein metabolism have been linked to dyslipidemias and CHD [14]. The ApoE gene locus has been the subject of several investigations. ApoE plays a pivotal role in triglyceride metabolism because it facilitates the clearance of triglyceride-rich lipoproteins such as VLDL and chylomicrons [15–17] (fig. 1).

ApoE has 299 amino acids with a binding region between amino acids 140 and 160. As mentioned previously, there are three common allelic variants (ϵ_2 , ϵ_3 , ϵ_4)

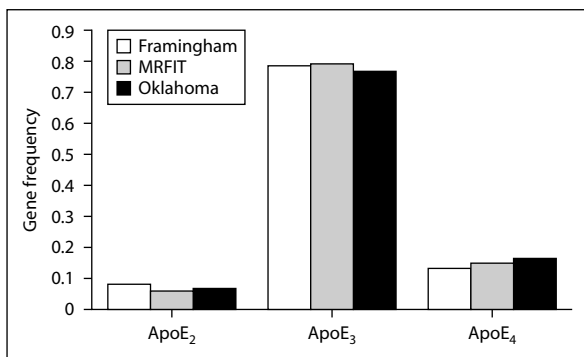


Fig. 2. Distribution of ApoE alleles [data from 18].

producing three isoforms of the protein E₂, E₃, and E₄. ApoE₃ is the most common and contains a cysteine at amino acid 112 and an arginine within the binding region at amino acid 158 [14]. ApoE₄ contains an arginine at the 112 site and has a normal binding capacity [14]. ApoE₂ contains a cysteine substitution within the binding region at amino acid 158 and has only 1–2% of normal binding capacity [14].

Figure 2 provides gene frequencies determined by protein electrophoresis in three studies: (A) Framingham Offspring Study, (B) Multiple Risk Factor Intervention Trial (MRFIT), and (C) Oklahoma Angiography Cohort [18].

The distribution of ApoE genotypes in a meta-analysis of 45 studies from 17 countries ($n = 14,799$) is depicted in figure 3 [19]. These data demonstrate a high prevalence of the E₂/E₃, E₃/E₃ and E₃/E₄ variants in the general population.

The pioneer work of Utermann et al. [3] sparked a lot of interest in the relationship between ApoE genotype and plasma lipids. Population studies have shown that ApoE allelic variation may partly explain the variation in TC and LDL-C observed in the population. Specifically, TC and LDL-C are lower in subjects with the apoE₂ isoform when compared to subjects carrying the apoE₃ or apoE₄. Furthermore, subjects carrying the apoE₄ isoform have the highest plasma concentration of TC and LDL-C [18, 17]. As such, E₄ carriers exhibit higher prevalence of cardiovascular disease when compared to E₂ carriers.

There is importance of CHD risk factors in the pathology of the disease, which is not uniform across the ApoE genotypes. In a Finnish study, BMI was positively associated with the probability of CHD in men with E₃/E₃ genotype, but a protective effect in the E₃/E₄ men was observed [20]. If this finding can be extended to other populations and corroborated medical management of CHD could eventually be significantly dependent upon ApoE genotype. This variable

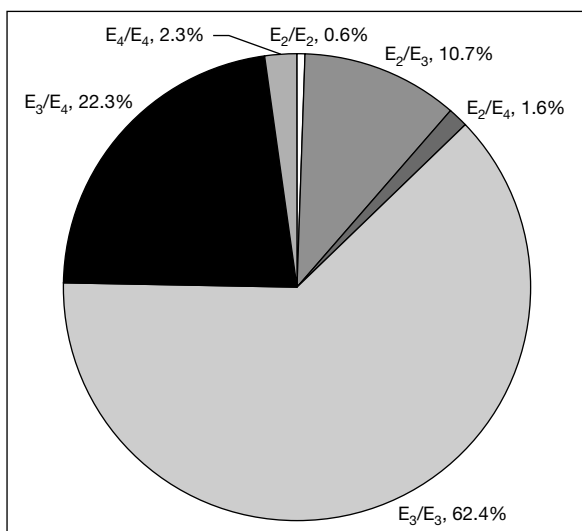


Fig. 3. Distribution of ApoE genotypes.

effect of risk factors may partly explain why despite significantly contributing to the atherogenic lipid profile, ApoE genotype yields poor predictive values when screening for clinically defined atherosclerosis. In two studies evaluating different populations, the ApoE genotype failed to adequately distinguish a person with the presence of angiographically confirmed CHD from a person without [21, 22].

Exercise has been shown as an effective means to positively affect serum lipoproteins thus reducing coronary risk [23, 24]. It has been well documented that lipids and lipoproteins are influenced by heredity [25, 26]. ApoE variants may interact with lifestyle factors (i.e., physical activity) with respect to the levels of cholesterol and LDL-C. Information regarding the familial components for lipid response to exercise may enhance our understanding on a possible interaction between genetics and physical activity in determining responses mediated by training. This interaction may be responsible for the variability in response observed among individuals who participated in similar exercise training protocols. We will briefly examine the interaction between ApoE genotype and physical activity with respect to changes in lipoprotein levels.

ApoE Genotype, Physical Activity and Lipids

Increased levels of physical activity may improve the lipid profile, but is this effect identical across ApoE genotypes? In a cross-sectional study of 1,500

subjects between the ages of 9 and 24, Taimela et al. [5] reported evidence that leisure-time physical activity has a great effect on lipoprotein profiles of ApoE₂ individuals, a lesser effect on ApoE₃ subjects, and no effect on ApoE₄ subjects. St-Amand et al. [27] suggested that ApoE genotype may affect the relationship between lipoprotein and fitness. Specifically, significant relationships were observed between fitness and LDL-C and HDL-C in ApoE₃ individuals.

Data from longitudinal studies, however, may provide more direct evidence of a possible interaction between ApoE polymorphism and exercise training. Hagberg et al. [6] in a well-designed study evaluated the impact of ApoE genotype on plasma lipoproteins response to exercise training in overweight males following 9 months of exercise training. The exercise training included cycle ergometry, walking and jogging. All exercise sessions were supervised by qualified personnel. There was a trend in the data indicating greater reductions for TC and LDL for E₂ and E₃ subjects when compared to E₄ counterparts. Furthermore, ApoE₂ and ApoE₃ experience significant reductions in triglycerides following training while the E₄ subjects did not. It should be noted however that such changes were more dramatic in the E₂ group. Finally, E₂ subjects experienced the highest increase in HDL-C and HDL-2C when compared to E₃ and E₄ subjects.

Leon et al. [28] examined the association of ApoE polymorphisms with blood lipids after exercise training in the HERITAGE Family Study. Participants trained 3 times a week on cycle ergometers under supervision at each clinical center. The duration of the study was 20 weeks. Study participants progressed from a duration of 30–50 min per session for the last 6 weeks of training. Exercise intensity was gradually increased from the heart rate associated with 55% of maximum oxygen uptake (VO₂max) at baseline to that associated with 75% of VO₂max at baseline for the last 8 weeks of training. Racial and gender differences were noted in lipid responses to exercise training across genotypes with greater increase in HDL observed only in white carriers of ApoE_{2/3} and E_{3/3} as compared to E_{4/4} [29].

Bernstein et al. [30] conducted population-based cross-sectional survey study from 1999 to 2000 in 1,708 randomly selected men and women aged 35–74 years. A validated physical activity questionnaire measured, for each participant, the total energy expenditure and its percentage used in high-intensity activities (% high-intensity activity), e.g., brisk walking and sports. Their results revealed that the presence of the E₄ variant negatively affects serum triglycerides and HDL but only in sedentary subjects. As such, no differences were detected in the lipid profiles across ApoE genotypes in more active individuals.

Thompson et al. [7] examined the impact of ApoE genotype on lipoprotein responses to exercise in healthy normolipidemic subjects following 6 months of exercise training. A prospective longitudinal study, conducted at seven centers,

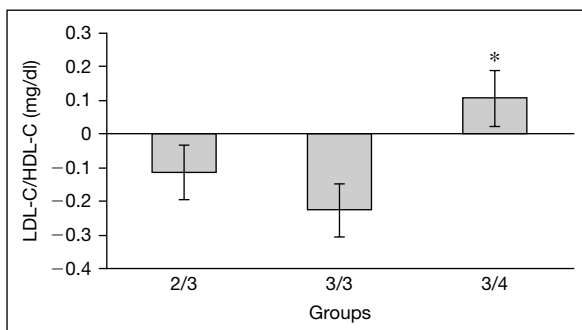


Fig. 4. Change in LDL/HDL after exercise training (n = 113). *Greater than E₃/E₃ p < 0.05.

genetically screened 566 individuals to create three cohorts of healthy adults, equal for gender and the most common ApoE genotypes: E₂/3 (n = 35), E₃/3 (n = 40), and E₃/4 (n = 31). Subjects with BMI ≥ 31 or evidence of dyslipidemia or metabolic disease were excluded. All subjects exercised aerobically under supervision at 75% of maximal heart rate for 40 min, 4 times weekly for 6 months. Fasting lipoprotein subpopulations were measured before and after exercise training using proton nuclear magnetic resonance spectroscopy. The results of this study demonstrated that ApoE polymorphisms affect the lipid response to exercise training. Specifically, reductions in LDL-C/HDL-C and TC/HDL-C ratio were greater in ApoE₃ homozygotes (fig. 4) producing significantly greater reductions with exercise training in common markers of CAD risk.

Although serum lipids for the entire cohort did not change with exercise training, the LDL subpopulation response varied [12]. Small-sized LDL particles decreased only in the ApoE₃ homozygotes whereas medium-sized LDL particles increased only in this group. These changes were directionally different from the responses in the E₂/3 and E₃/4 subjects (p < 0.05). Neither exercise nor ApoE genotype affected overall LDL or HDL size or cholesterol concentration, but exercise decreased VLDL diameter by 3.5 nm (p < 0.001) attributable to decreases in large VLDL in each ApoE genotype group. In conclusion, ApoE genotype influences the serum LDL particle size response to exercise training in normolipidemic subjects. Subjects homozygous for ApoE₃ experienced the most beneficial lipid effects from exercise training.

In summary, allelic variation in ApoE is consistently associated with plasma concentration of TC, LDL-C. TC and LDL-C are lower in subjects with the apoε₂ isoform when compared to subjects carrying the apoε₃ or apoε₄. Furthermore, subjects carrying the apoε₄ isoform have the highest plasma

concentration of TC and LDL-C. Therefore, the apo ϵ_4 isoform has an overall disease-promoting effect on cardiac health.

The effect of regular physical activity on serum TC, LDL-C, LDL/HDL ratio and LDL particle size may vary with ApoE genotype and it can be inferred from the above cited studies that ApoE₂ and ApoE₃ individuals may be more responsive to exercise training thus showing more favorable lipid changes following exercise interventions (table 1).

ApoE and CRP

ApoE has been shown to have anti-inflammatory properties [31], thus providing a further mechanistic explanation beyond the effects on lipid metabolism to the accelerated atherosclerosis seen in ApoE null mice [32, 33]. As plasma ApoE concentrations are genotype-dependent with $E_2 > E_3 > E_4$ [34], it is easy to hypothesize that E_2 carriers would have lower levels of inflammation than E_3 which in turn would have lower levels than E_4 . The observation that plasma ApoE and CRP are negatively related adds weight to this hypothesis [35]. This does not appear to be the case however, in fact the opposite tends to be true in the case of CRP.

Manttari et al. [36] were the first to show the unexpected negative relationship between the ApoE₄ allele and CRP. Most subsequent reports have confirmed this finding [37–42], but not all. Paschos et al. [9] found no association with ApoE genotype in dyslipidemic individuals, but there were very unbalanced sample sizes amongst the groups. Pertovaara et al. [43] found no relationship in a group with primary Sjögren's syndrome and Hubacek et al. [44] suggested that ApoE is merely a genetic marker of CRP and not a functional determinant. Instead, Hubacek et al. proposed the *ApoCI* gene, one that is in strong but incomplete linkage disequilibrium with the ApoE polymorphism to be the functional determinant of CRP levels [44]. However, the majority of evidence, including as yet unpublished work from our laboratory, suggests that CRP is lower in those with an E_4 allele. The reasons for the negative relationship between the ApoE₄ allele and CRP remain unclear, especially considering the anti-inflammatory properties of ApoE and the comparatively low concentration of ApoE in this genotype.

The lower CRP levels in those with E_4 persisted even after adjustment for BMI so it is unlikely to have been mediated by pathology linked to differences in body weight. There were also no differences between the genotypes with regards to insulin resistance as measured by the homeostasis model assessment (HOMA). As such, the genotype effect is unlikely to be due to inherent differences in insulin resistance. One possibility is that the functional variants of

Table 1. Summary of the published studies showing a relationship between ApoE genotype, lipid levels and physical activity or exercise

Population studied	Sample Size	Exercise prescription	Main outcome
Children and young adults [5]	1,498	Cross-sectional association	beneficial relationship between physical activity and lipids (TC and LDL) was modified by ApoE genotype: – $E_2 > E_3 > E_4$
Healthy untrained males and females [27]	129	Cross-sectional association	relationship between VO_2 max and lipids is altered by ApoE genotype: – VO_2 max negatively correlated with TG in E_2 and E_3 – VO_2 max negatively correlated with LDL in female E_3 – VO_2 max positively correlated with HDL only in E_3 homozygotes
Respondents to a general health survey randomly distributed among the Swiss population [30]	1,708	Cross-sectional	in men a higher percentage of physical activity performed at high intensity was associated with greater improvements in: – HDL in E_4 compared to E_2 and E_3 (women – E_4 better response compared to E_2 only) – TG in E_4 compared to E_3
Overweight men [6]	51	– 9 months – 3 supervised sessions per week – 45 min per session – 70–80% VO_2 max	– ApoE ₂ had a greater increase in HDL and HDL-2 than E_3 and E_4 – E_2 and E_3 had greater decrease in TG than E_4
Sedentary men and women [29]	724	– 20 weeks – 3 supervised sessions per week – 30 min progressing to 50 min per session – Heart rate associated with 55% VO_2 max progressing to 75% VO_2 max	A greater increase in HDL only observed in white females with the E_2/E_3 and E_3/E_3 compared to E_3/E_4

Table 1. (continued)

Population studied	Sample Size	Exercise prescription	Main outcome
Sedentary, healthy men and women [7, 12]	120	– 6 months – 4 supervised sessions per week – 15 min progressing to 50 min per session – 60–85% VO ₂ max	– TC/HDL and LDL/HDL decreased in E ₂ /E ₃ and E ₃ /E ₃ , but increased in the E ₃ /E ₄ group – Small-sized LDL particles decreased only in the E ₃ /E ₃ group

ApoE react differently to proinflammatory markers. The difference in the atherosclerotic process is not just mediated by differences in concentration of ApoE, but also by functional differences in lipid metabolism of the ApoE variants. It is possible that the anti-inflammatory properties of the ApoE particle also vary according to the ApoE genotype, which could explain the lower levels of inflammation in E₄ carriers despite the low levels of circulating ApoE. However, there are currently no data on whether ApoE variants differ in the strength of their anti-inflammatory properties.

Lifestyle-Induced Changes in CRP According to ApoE Genotype

Data from the HERITAGE Family Study showed that when a group is classified according baseline CRP levels, those with the highest baseline levels experience a reduction in CRP with aerobic exercise training that is independent of changes in weight loss and insulin resistance [45]. Due to the baseline difference in CRP according to ApoE genotype it is conceivable that the response of CRP to aerobic exercise training might be modified by ApoE genotype. However, there are currently no published studies to substantiate this hypothesis. We recently completed a 6-month aerobic exercise training study in volunteers recruited to create equal cohorts of the most common ApoE genotypes, which are E_{2/3}, E_{3/3}, and E_{3/4} [7]. Both the increase in VO₂max and decrease in the ratio of LDL to HDL varied by ApoE genotype. Our unpublished data showed that ApoE genotype had no effect on how CRP responded to the exercise intervention. It is worth noting that in the entire cohort, changes in body mass and waist circumference were minimal and there was no change in insulin resistance as measured by the HOMA method. As

such, there was no change in CRP in the entire cohort. Whether ApoE has no effect on how CRP responds to aerobic exercise training in a group that lost substantial amounts of weight and significantly improved insulin function remains to be seen.

There is also a real paucity of evidence on how ApoE genotype affects the change in CRP as a result of other lifestyle modifications. Currently the only published work in this area focused on α -linolenic acid supplementation in dyslipidemic men [9]. The effect was a widespread reduction in inflammatory markers in the E_3/E_3 individuals, including CRP, serum amyloid A, and macrophage colony-stimulating factor. A less wide ranging decrease in inflammation was seen in E_3/E_4 with just decreases in serum amyloid A and macrophage colony-stimulating factor being observed. In contrast, no reduction in any inflammatory marker was observed in the E_2/E_3 group.

ApoE and Cardiorespiratory Fitness

The amount of physical activity regularly performed is a well-established predictor of cardiovascular and all-cause mortality [46]. More direct measures of physical fitness, specifically VO_{2max} , is also recognized as a strong predictor of cardiovascular mortality in healthy patients [47] and has been shown to be a stronger predictor of mortality in cardiac patients than established risk factors for cardiovascular disease [48]. Therefore, VO_{2max} is a measurement that has clinical significance.

Exercise performance has been seen to be reduced in ApoE-deficient mice. As ApoE deficiency is also associated with decreased endothelial nitric oxide production and reduced skeletal muscle blood flow, these results are not surprising [49]. The possibility that differences in rates of muscle lipid uptake may be important in determining physical fitness also suggests that ApoE genotype might affect physical fitness. No study to date has shown any relationship between ApoE genotype and VO_{2max} in sedentary individuals [6, 7, 27, 29]. However, whether the ApoE genotype affects the improvement in fitness seen with aerobic exercise training is not clear. At present only three studies have reported such data with little consistency among them. It has been observed that ApoE genotype has no effect [29], that there is an attenuated response in E_3 homozygotes compared to E_2/E_3 and E_3/E_4 (fig. 5) [7], and that E_3 has an intermediate response between E_4 (highest) and E_2 (lowest) [6].

The reasons for these varied results are not clear, but may partly be explained by differences in study design. Hagberg et al. [6] and Leon et al. [29] recruited participants according to the population distribution of the genotypes (see fig. 3) and as such had extremely unbalanced sample sizes amongst the

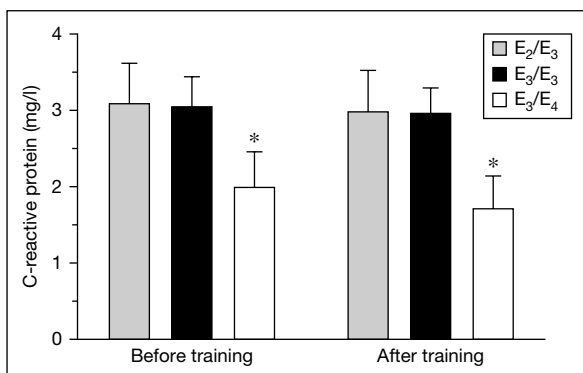


Fig. 5. CRP before and after exercise training. *Lower than E₂/E₃ and E₃/E₃ $p < 0.05$.

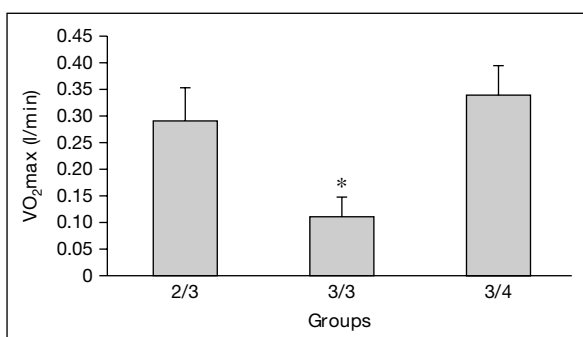


Fig. 6. Change in VO₂max with exercise training (n = 112). *Lower than E₂/E₃ $p < 0.05$ and E₃/E₄ $p < 0.01$.

groups. In contrast, Thompson et al. [7] only included participants from the three common genotypes: E₂/E₃, E₃/E₃ and E₃/E₄ (represents approximately 95% of the population) and with the same number of subjects per genotype (balanced sample) (fig. 6).

ApoE and Diet Interactions

Excess dietary intake of fat and saturated fat have consistently be shown to be associated with a proatherogenic lipid profile [50] and as such the American Heart Association and the National Cholesterol Education Program both

recommend that attempts to maintain adequately low dietary fat intake is a judicious action for heart health [51, 52]. However, changes in dietary fat intake result in variable changes in lipid profile [53]. It is widely accepted that genetic variation partly explains this heterogeneous response and due the role of ApoE genotype on lipid metabolism this particular genotype has been extensively studied. The results of these studies do however not present a clear picture.

In a retrospective study, Loktinov et al. [54] investigated the relationship between ApoE genotype and the effects of a CHD-promoting diet in free-living individuals. When analyzed separately, no relationship between dietary fats and cholesterol levels were observed in the E₂ or E₃ group. In comparison, the presence of the E₄ allele resulted in positive associations between total fat intake and saturated fat intake with TC and LDL-C. This relationship was stronger when expressing fat and saturated fat intake as a percentage of total energy intake compared to absolute amounts. On a positive note for individuals with the E₄ allele it was also suggested that this group may be more responsive to the dietary therapy. Calculations showed that cutting saturated fat consumption in half resulted in a 20% decrease in LDL-C in those with the E₄ allele compared to just a 5% decrease in those without. This speculation is supported by the results of Dreon et al. [55] who found that that LDL-C-lowering effects of a low-fat diet were greater in men with the E₄ allele than those without. However, the fact that this reduction in LDL-C was achieved by an overall reduction in LDL particle size (proatherogenic) questions the overall benefit of this change.

Not all studies have found ApoE genotype to impact the effect of changes in dietary fat intake on blood lipids and cholesterol. Data from the Women's Healthy Lifestyle Project showed that women with the E₄ allele had higher baseline levels of TC and LDL-C [56]. However, after 6 months on a low-fat diet (20% calories from fat with 7% calories from saturated fat), while post-intervention LDL levels were still higher in the E₄ carriers, the magnitude of change in both TC and LDL-C were no different between the ApoE genotypes. Savolainen et al. [57] switched the diet of 44 men and women from a low-fat to a high-fat diet for 4 weeks. While the expected response was observed in the cohort as a whole (increased TC, LDL-C and HDL-C) their magnitude of change was the same regardless of ApoE genotype observed. Interestingly, men were seen to have a more pronounced change in lipid profile than women.

This leads to the speculation that in women, who are generally less responsive to the effects of changes in dietary fat intake, ApoE genotype may not play as important a role in changes in lipids as in men. However, it might be important to consider the effect of menopausal status as data from the Framingham Study showed that the relationship between ApoE genotype and LDL-C was stronger in post- than in premenopausal women [58]. As such, while there was

no effect on TC or LDL-C, the significant effect of ApoE genotype on HDL-C in women observed by Nicklas et al. [59] may be due to the postmenopausal status of the cohort.

As previously mentioned, both the American Heart Association and the National Cholesterol Education Panel advocate low-fat diets for the prevention of atherogenic lipid profiles [51, 52]. However, there is some evidence that in women low HDL-C and high triglycerides carry a greater risk of CHD than high TC and HDL-C [60, 61]. Therefore, whether the benefit of reduced TC and LDL-C as a result of these low-fat recommendations outweigh the negative effects of lower HDL and possibly elevated triglycerides is questionable in women. Nicklas et al. [59] placed obese postmenopausal women on an AHA step I diet (50–55% carbohydrate, 15–20% protein, 20–30 g fiber and <30% of calories from saturated fat) for 10 weeks. While there was an overall decrease in TC and LDL-C, this was unaffected by ApoE genotype. Reductions in HDL-C however were significantly greater in women without an E₄ allele. Therefore, the balance of the benefit from lowering TC and LDL-C versus the negative effect of lower HDL-C with a low-fat diet seem to be more favorable in women with the E₄ allele. This suggests that maybe in the majority of people (without an E₄ allele) the AHA step I diet might not be the most beneficial dietary approach for lowering CHD risk.

On balance it does seem that ApoE genotype does interact with dietary interventions to cause variable changes in lipid profile. However, due to the additional interaction with gender and the possible role of menopause, the exact nature of the gene-diet interaction is still not completely understood. Further work in this area is therefore required to make the picture clearer before the widespread use nutrigenetics becomes practically and clinically useful.

Summary and Conclusions

The effect of a high-fat diet on plasma lipid levels is genotype-dependent. Individuals who have the ApoE₄ variant usually show higher plasma cholesterol and LDL levels whereas those with the ApoE₂ variant have low cholesterol and LDL levels. Although the ApoE₄ polymorphism is indicative of higher risk, whether the individual will develop atherosclerosis cannot be inferred, probably because gene-gene interaction and the polygenic nature of the disease.

Physical activity is associated with lower plasma lipid levels including lower cholesterol, LDL, triglycerides and possibly higher HDL. In the case of the genetic variant of ApoE₄, the effect of exercise is not shown, either because of other genes or because the physical activity (type and amount) cannot overcome the effect of the gene.

Because many chronic diseases are multigenic and multifactorial, future research ought to clarify both the effect of diet and exercise for the prevention and management of these diseases.

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Nutrition in the Prevention of Chronic Diseases

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Introduction

The importance of nutrition in the prevention of chronic disease such as obesity, cardiovascular disease (CVD) and diabetes has been recognized for some time [1]. In 2001, chronic disease contributed to 60% of reported deaths and 46% of the global disease burden, and this latter figure is expected to increase to 57% by the year 2020 [1]. Obesity is of prime concern, not least because of the rate at which the prevalence is increasing, but also because its reach extends across the globe. Since 1980, rates have tripled in areas like North America, Eastern Europe, the Middle East, Australia and China [2]. Likewise, the prevalence of diabetes is increasing, estimated at 2.8% in 2000 (171 million people) to 4.4% in 2030 (366 million people) [3]. Linked to these conditions, CVD is set to become the leading cause of death and disability, with 24 million cases predicted for 2030 [4].

In developing countries, nutrition-related problems are sometimes referred to as a double burden, where obesity, diabetes, and heart disease rest in the company of malnutrition, usually in different locations. For example, a prospective study of schoolchildren in the Gauteng Province of South Africa between 1962 and 1999 saw the percent energy from carbohydrate decrease from 72 to 60% and the fat consumption increase from 17 to 25.8%. The urban children were more likely to change their dietary habits and be overweight, but micronutrient deficiency and stunting were still prevalent [5]. In addition to the nutrition transition phenomenon, variation is also seen in prevalence rates amongst different subgroups within a population. For example, in the USA, ethnicity appears to play a major role in the prevalence of metabolic syndrome [6], a term used to link risk factors associated with overweight, diabetes and heart disease

[www.diabetes-symposium.org]. With these issues in mind, this review considers the role of nutrition in the prevention of chronic diseases, and the implications for the development of the food supply and associated dietary advice.

Origins of Chronic Diseases

By nature, the development of chronic diseases rests in the course of events over time. Food directly contributes to body composition and the processes of the human biological system. With the discovery of the human genome, the complexity of this interrelationship has become more exposed, particularly in view of the interactions between food components and genetic expression. The implications are that diet is important at all points in time, that poor diet is likely to have a deleterious effect if prolonged or occurring at critical points of the development phase, and that modifications in diet may play a pivotal role in managing the disease process.

The mechanisms by which diet influences health are complex. They relate to physiological mechanisms in multiple organs and are linked to regulation at the level of genes, gene expression, proteins and metabolites [7]. Fatty acids, for example, are known to influence gene expression in relation to the development of obesity [8], and this has led to considerations of lifestyle-drug therapies in the management of metabolic syndrome [9]. Overall, the interaction between nutrients and genes is considered to have a central impact on lifespan and disease development [10].

The relationship, however, is not linear, with incremental environmental exposure a critical factor in genetic expression. Perhaps one of the most significant observations here is that early exposure to food components influences long-term health. In a longitudinal study of 4,630 males followed for 12 years in Helsinki, Finland, Barker et al. [11] noted that low birth weight and subsequent poor growth during infancy was related to increased risk of developing lifestyle-related disease reflective of weight gain. A subsequent analysis of 8,760 boys born between 1934 and 1944 found that later development of type 2 diabetes was not related to rate of infant growth following low birth weight (≤ 3.5 kg), but was related following birth weight of >3.5 kg if there was slow growth in length between birth and 3 months. In both groups, rapid gain in BMI after 2 years age was associated with increased risk, and this gain was linked to socioeconomic factors. Thus faltering growth may result in impaired insulin metabolism that cannot meet demands of subsequent increases in BMI [12]. Differences between boys and girls in the pathways for development of coronary heart disease (CHD) were found in a study of 4,130 girls from the same cohort. Girls who developed CHD, rather than thin, were short at birth, compensated for this during infancy then became thin and later

developed a rapid increase in BMI. Girls were seen as less vulnerable to undernutrition in utero and better able to compensate in an adverse postnatal environment [13]. In contrast for boys, poor growth during infancy and small body size at 12 months was a stronger predictor of CHD than low birth weight [14].

The links between early growth and development of later disease have been generally confirmed through studies of cohorts from other parts of the globe. In a study of 356 Guatemalan children, positive associations were found between length at age 2 and fat mass, height and weight, with birth weight directly related to waist-hip ratio in females [15]. Research on persons conceived during the 1944–1945 Dutch famine found an earlier onset of coronary artery disease compared to unexposed persons (hazard ratio adjusted for sex 1.9; 95% CI 1.0–3.8) [16], but a subsequent study could not confirm that this led to increased adult mortality, although the cohort was only studied to 57 years [17]. Thus, while early nutrition may play a role in programming disease, there appears to be opportunity to manage the risk later in life. In the Hertfordshire Cohort Study (37,615 men and women born 1911–1939), lower birth weight was associated with increased risk of mortality from CVD in men and women [18]. Interestingly, a subsequent study of a 59- to 71-year-old subset found that high intakes of total and saturated fat were associated with adverse HDL:total cholesterol ratios in men with low birth weights (≤ 3.2 kg) (interaction effects $p = 0.02$ for total fat and 0.01 for saturated fat, increasing to 0.008 and 0.006 respectively with those taking cholesterol-lowering medications excluded) [19]. This finding could be interpreted as evidence of gene nutrient interactions, whereby the effects of nutrients (is this case fat) are mediated by the genetic profile of the organism.

The initial observations of Barker [20], that low birth weight infants were at greater risk of chronic lifestyle-related diseases, have helped to develop the concept of ‘developmental plasticity’ in humans. It explains how different environmental conditions during development can result in different physiological or morphological states from one genotype. More specifically, it explains how insulin resistance [21] and hypertension [22] may emerge in persons with low birth weight and thinness at 2 years followed by an increase in BMI after 2 years. The implications for growth protection during the first 2 years of life and the prevention of rapid increases in BMI after that age then represent major challenges for nutritional strategies for the health of populations.

If we take the position that the chronic diseases such as obesity, CVD and diabetes have their origins in early development, then it follows that nutrition intervention is important throughout the lifespan, not just at the time where risk factors reach a certain ‘treatable’ point. In any case, with increasing obesity rates, these cut-off points are working their way down from the middle-aged to the young. The term ‘adult onset diabetes’ is now being challenged as obese children emerge with type 2 diabetes mellitus, and the sequence of events leading

to this situation are beginning to unfold. Nutrition practice will need to draw on scientific advances such as that described above where knowledge of a person's nutritional history will form a part of clinical decision-making and personalized nutrition advice will become an imperative.

Demographic Trends

The changes in demographic trends across the globe fuel the need for prevention of morbidities associated with chronic lifestyle-related disease. Life expectancy will increase in all sectors and the percentage of the population aged >65 years is expected to grow substantially by 2025 [23, 24]. While the so-called 'baby boomer' generation is likely to have a significant effect on health-care services in Western societies, the number of people in the age range 20–45 years – those likely to show early signs of lifestyle-related disease – is significant across the globe. In addition, while the percentage of the population below the age of 14 years may be reducing, this will be reflected in the number of children per household who will then gain attention for health and nutrition [23, 24]. The risk is that these children may become overfed and overweight [25], but there is also likely to be a concomitant desire to ensure these children receive optimum nutrition, not just for growth but also for cognition and performance.

These trends are likely to produce demands for better quality food. With increasing knowledge of the impact of nutrition on health and longevity, developments in nutrition research stand to influence the development of the food supply. This represents a challenge for science and food marketing alike, as food standards legislation references the quality of the evidence that substantiates these benefits.

Evidence Base

Establishing evidence for practice has become a significant activity in nutrition, whether this practice relates to dietary guidelines for the general population, clinical practice guidelines for disease management or food standards legislation governing health claims on foods [26–30]. In common is the need for research in humans (preferably experimental but including good quality observational studies), plausible dose responses, explanatory mechanisms and consistency in the evidence base. Levels of evidence tend to be reported as convincing, probable and possible.

In the review of the WHO Technical Report Series 916, Diet, Nutrition and the Prevention of Chronic Diseases [1], convincing evidence was found for

increasing risk of obesity with high intake of energy dense foods, of type 2 diabetes mellitus with the presence of abdominal obesity, overweight and obesity, physical inactivity and maternal diabetes, and of CVD with dietary saturated (myristic and palmitic) and *trans* fatty acid, dietary sodium, high alcohol intakes and the presence of overweight and obesity (table 1). A decreased risk of developing obesity was found with high intakes of non-starch polysaccharides, and of fruits and vegetables and with the practice of regular physical activity. Likewise, decreasing risk of type 2 diabetes mellitus was found with voluntary weight loss and regular physical activity, whereas decreasing risk was found for CVD, with intakes of linoleic acid and fish oils (and of fish itself), and of potassium, fruits and vegetables, with low to moderate alcohol intakes and the practice of regular physical activity. The intake of linoleic acid in CVD, however, continues to be controversial since a balanced ratio of LA to ALA has been shown to decrease the risk of CHD, metabolic syndrome, and hypertension. The high LA intake seen in Western diets increases the risk of all these diseases [see paper by Ailhaud, this volume].

Put together, this evidence base can be seen as a mixture of behaviors relating to physical activity and the consumption of some whole foods and of specific individual nutrients, and the presence of preexisting conditions such as overweight/obesity, which is modifiable, and maternal diabetes, which is not modifiable (from the offspring's perspective, although presumably it can be prevented in the mother prior to the conception of the child). The evidence itself reflects the types of studies that are available for review, and these were not necessarily conducted for the purposes of establishing the evidence base. Nevertheless, from a food/nutrient perspective, there appears to be enough evidence linking patterns of consumption of fatty acids, sodium and potassium, and fruits, vegetables and fish with the development (or not) of chronic lifestyle-related disease. These dietary components could be seen as the first to emerge consistently in a complex picture of diet and health.

Food standards and the drive for health claims related to food may forge an acceleration of this process. Pre-approved health claims in Western societies have also linked reduced risk of CVD with foods such as nuts and those containing whole grains, fiber or soy [29]. There remain challenges, however, in communicating the degree of confidence the evidence base carries with respect to outcomes an individual might expect from including these foods in the diet. On reviewing the PASSCLAIM project outcomes [26] it would seem that the extent of scientific support, in terms of developed methodologies at least, was promising for foods that targeted appetite control and risk factors for lifestyle-related disease, but there was a need for better quality interventions (particularly with respect to background diet and dietary intervention modeling) and for a consideration of genetic factors.

Table 1. Levels of evidence of lifestyle factors for and against conditions of the metabolic syndrome [adapted from 1]

Evidence	Decreases risk	Increases risk
Convincing	<ul style="list-style-type: none"> – Regular physical activity^{a-c} – High intake of non-starch polysaccharides (dietary fiber)^a – Voluntary weight loss^b – Fish and fish oils – Vegetables and fruits – Potassium – Low to moderate alcohol 	<ul style="list-style-type: none"> – Sedentary lifestyle^{a,b} – High intake of micronutrient-poor, energy-dense foods^a – Abdominal obesity^b – Overweight/obesity^{b,c} – Maternal diabetes^b – Palmitic and myristic acids^c – <i>Trans</i> fat intake^c – High intake of sodium^c – Excess alcohol^c
Probable	<ul style="list-style-type: none"> – Environments that support health food choices for children^a – Breastfeeding^{a,b} – Non-starch polysaccharides^{b,c} – α-Linolenic acid^c – Oleic acid^c – Wholegrain cereals^c – Unsalted nuts^c – Plant stanols and sterols^c – Folate^c 	<ul style="list-style-type: none"> – Heavy marketing of fast-food outlets and energy-dense foods^a – Fruit juices and sugar-sweetened drinks^a – Difficult social and economic conditions^a – Saturated fats^b – Intrauterine growth retardation^b – Dietary cholesterol^c – Unfiltered coffee (boiled)^c
Possible	<ul style="list-style-type: none"> – Low glycemic index foods^{a,b} – ω-3 fats^b – Flavonoids^c – Soy products^c 	<ul style="list-style-type: none"> – Large portion sizing^a – A large proportion of foods prepared outside the home^a – Eating patterns such as rigid restraint or periodic disinhibition^a – Fat intake (total)^b – <i>Trans</i> fat intake^b – Lauric acid-rich fats^c – Impaired fetal nutrition^c – β-Carotene supplementation^c
Insufficient	<ul style="list-style-type: none"> – Increased frequency of eating^a – Vitamin E^b – Chromium^b – Magnesium^{b,c} – Moderate alcohol^b – Calcium^c – Vitamin C^c 	<ul style="list-style-type: none"> – Excess alcohol^{a,b} – Carbohydrates^c – Iron^c

Related to: ^aOverweight/obesity, ^bType 2 diabetes mellitus, ^cCardiovascular disease.

Dietary Fat, Food and Lifestyle-Related Disease

Perhaps one of the most extensively studied areas of nutrition in relation to the development of diet-related disease has been that of dietary fat. Extensive mechanistic studies have exposed the relatively positive effects of unsaturated versus saturated fatty acids on insulin action [31]. The related benefits of manipulating dietary fatty acids have been supported with observational and experimental studies in humans [32–35]. To be easily followed though, nutritional advice needs to be given in terms of foods not nutrients. Our team developed research methodologies that targeted whole food sources of unsaturated fatty acids (in this case, walnuts) to produce desired dietary fatty acid profiles [36], which in turn resulted in improved lipid profiles in subjects with type 2 diabetes mellitus [37]. Total antioxidant status improved significantly during the intervention and this was attributed to the antioxidants delivered concomitantly with the walnuts and the recommended 5 serves/day of vegetables and fruits. In another study, the inclusion of walnuts and olive oil in test meals respectively was found to preserve the protective phenotype of endothelial cells through examinations of flow-mediated dilatation, a quasi measure of inflammatory activity following feeding with a high-fat meal [38]. The two studies of whole foods are significant for two reasons. First, inflammation may well become the new target for nutrition strategies in the prevention of chronic disease [39], and positive related effects were observed with the dietary strategies. Secondly, while the delivery of unsaturated fats was a primary focal point of each study, there was recognition of the nutrient or bioactive package that the whole food delivered. Jacobs and Steffen [40] argue that this concept of food synergy is an important consideration in understanding dietary exposure and the development of chronic disease. To convert this knowledge to practice, methodologies are required to differentiate between foods in terms of attributes such as nutrient density [41]. Thus just as the evidence base for risk linking diet with disease has identified certain elements that need to be considered together, the experimental assessment of these elements drives us back to whole foods, and then to whole diets to adequately explain effects and cover all the known bases in disease prevention.

Food-Based Health Strategies

Translating the scientific evidence to policies and strategies for health runs in parallel to advances in nutritional science. There are a number of policies in place that clearly outline the means by which governments and health agencies need to take action. The WHO Global Strategy on diet, physical activity and health outlines the need for leadership, effective communication, functioning

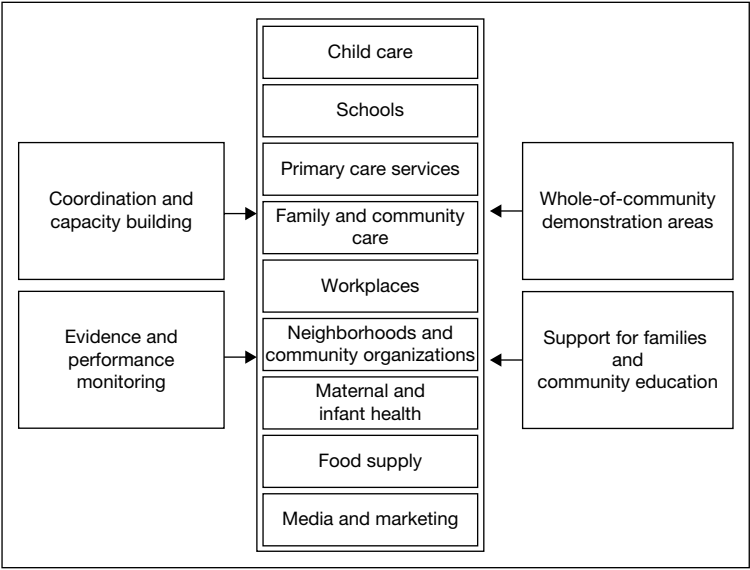


Fig. 1. National and setting-based action strategies for children and young people [adapted from 43].

alliances and partnerships and enabling environments. Strategies relate to surveillance, informed choices, standards and legislation, availability of healthy diets, intersectoral activity and health service provision [42]. In Australia, the national action agenda for children and young people and their families, Healthy Weight 2008 [43], outlines a matrix model of four national strategies (coordination/capacity building, evidence/performance monitoring, whole of community demonstration areas, and support for families/community-wide education) across nine settings strategies (childcare, schools, primary care services, family/community care services, maternal and infant health, neighborhood/community organizations, workplaces, food supply, and media/marketing) (fig. 1).

The components of these policies are reflected in the new paradigm for nutrition proclaimed at the 2005 meeting of the International Union of Nutrition Scientists. In view of the context in which nutrition is likely to have an impact, this new paradigm called for partnerships to solve nutrition problems. These partnerships would see the traditional biological bases for nutrition better integrated with knowledge from the environmental and social sciences [44]. This broadens the potential for problem-solving of nutrition-related problems, but it will be necessary for the nutrition scientist to retain a discipline identity and for advances in the understanding of biological processes to be applied.

An important consideration is the continuing acknowledgement that food lies at the heart of nutrition. The European PASSCLAIM project [26] provides a good example of productive intersectoral engagement targeting an improved food supply. This project integrated knowledge on marketing claims for foods with scientific methodologies and evidence frameworks. The resultant framework provides those working in the field of food and nutrition with direction on the types of measurable effects that can be addressed and thereby identifies targets for the development of healthier food products. The ability to lower cholesterol levels, reduce body weight, improve insulin sensitivity, reduce risk of type 2 diabetes are all tangible targets for food product development in the context of a healthy diet, based on scientific methodologies. ILSI Europe has also produced a review of interventions and programmes targeting the prevention of overweight and obesity in children and adolescents [45], with recommendations relating to outcome measures, participation rates, heterogeneity in intervention groups, tailoring, changes to the physical and/or social environment, sustainability, impact, adverse effects and publications of results. These are all positive steps to improve the scientific quality of interventions to greater public good.

At a policy level, the emergence of evidence frameworks for clinical practice guidelines, and for guidelines for disease prevention and health promotion is another significant development [27, 30]. These developments also demonstrate the need for building our understanding of the way in which food and nutrition translates to health and the means by which we may expose it through scientific practices.

Conclusion

With the increasing prevalence rates of chronic disease related to lifestyle comes a more sophisticated view of food and nutrition. This sees food as a biological system in itself comprising sets of bioactive components that interact with human biology in ways that can only at times be imagined. There is much to be done, however, with the knowledge that is currently at hand. The challenge lies in integrating different forms of knowledge and rigorously testing the evidence that assumptions made actually hold true following changes in diet and physical activity. On a broader scale, policies that govern food and nutrition need to be accommodating of the various sectors' interests and contributions to problem-solving, for example the development of dietary advice and the concomitant development of the food supply. There needs to be synergy in the efforts of academia, government, industry and healthcare providers [46]. The advent of nutrigenomics and nutrigenetics heralds a new era of personalized

nutrition that considers the impact of the nutritional environment on programming nutritional requirements and disease risk later in life. One of the primary platforms for nutrition today and tomorrow will be the prevention of chronic disease through an understanding of the interactions between genes and the nutritional environment [47]. The establishment of the International Society of Nutrigenetics/Nutrigenomics (ISNN) will play an important role in defining the field of gene-nutrient interactions, specifically the role of genetic variation influencing dietary response and the role of nutrients in gene expression [www.isnn.info].

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Exercise and Obesity: Lifestyle Modification as a Means in Prevention and Treatment

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Introduction

The ongoing battle against the obesity epidemic has been fought for almost eight decades. The first attempt to summarize the effectiveness of the treatment methods used by the scientific community during the previous 30 years was by Stunkard [1] in 1958. The failure of the initial efforts to control obesity by dietary manipulations alone was dramatically expressed by the following two sentences expressed by Stunkard, *'Most obese persons will not stay in treatment for obesity. Of those who stay in treatment, most will not lose weight, and of those who do lose weight, most will regain it'* [1, 2]. The discouraging outcomes forced the scientific community to start trying various dietary combinations, thus developing an array of *dietary proposals*, including the reduction of calorie intake in the range of 400–1,500 kcal/day in an effort to meet the individual's daily nutrient and caloric needs on the one hand, and at the same time achieve loss of a considerable amount of fat [3, 4]. To overcome the failure of dietary treatment alone, *behavior modification* was introduced in the 1960s. The addition of this method supplied new arrows to the practitioner's arsenal, but although for quite some time this seemed to produce promising solutions to the problem [5, 6], the final results were not up to expectations. Weight loss, as expressed on the scale, is not the solution to obesity. The objectives of a weight control program are focused, on the one hand, to accelerate fat loss, while at the same time to achieve long-term maintenance after the completion of the treatment. When qualitative assessment of weight loss was taken into consideration, dietary manipulation and behavior modification methods alone, or in combination, did not seem to assure adequate fat loss, protection of the individual's lean tissue during the weight loss phase, and most importantly, maintenance of the

achieved body weight after the completion of the intervention program [7]. Only during the early 1980s, when *exercise treatment* was for the first time introduced alone, but most remarkably in combination with diet and/or behavior modification, did we start to see promising results, not only in fat weight loss but in long-term maintenance as well [8, 9]. The orthologic use of the combination of a nutrient adequate, but energy-deficit diet, increased physical activity, and behavior modification therapy constitutes the so-called *lifestyle intervention* approach, a method which, if appropriately applied, is promising encouraging results in the prevention and treatment of obesity.

Obesity and Health

Obesity and its complications for health and longevity have been documented for some time now [10–12]. Decades of research and scientific documentation indicate that genetics, behavioral, socioeconomic, psychosocial, cultural, and psychological mechanisms are a few of the determinants of body weight.

In addition to all the above-mentioned factors, many others as well influence health status independently. Excess body weight by itself is a risk factor, and is directly related to the level of physical activity, diet, and smoking, just to mention a few [13–15].

Obesity has a strong association with a cascade of cardiovascular risk factors and metabolic abnormalities such as hypertension, higher levels of total cholesterol, lower high-density lipoprotein (HDL)-cholesterol levels, altered lipid profiles, impaired glucose metabolism, higher levels of plasma insulin concentrations and increased insulin resistance, just to mention a few, and has a complex association with smoking [16–21]. In addition, obesity has a strong association with a higher risk of death in both men and women in all racial and ethnic groups and at all ages. The risk among overweight individuals at age 50 years is 20–40% higher than that among individuals who have a body mass index (BMI) of 23.5–24.9 at the same age [22]. It seems that avoidance of obesity and overweight in adult life, with and without coronary heart disease (CHD), may reduce their later risk and total CHD mortality [23].

Lifestyle intervention has now been accepted as the cornerstone of prevention as well as treatment of overweight and obesity [24]. Exercise seems to play a pivotal role in both the prevention and treatment of obesity, as well as in other obesity-related health problems. Physical activity has a strong independent and inverse relation with CHD risk, while at the same time both physical activity and normal weight can reduce the risk of CHD. On the other hand, physical inactivity seems to have an independent effect on CHD risk, whereas obesity increases the risk partly through the modification of other risk factors [25, 26].

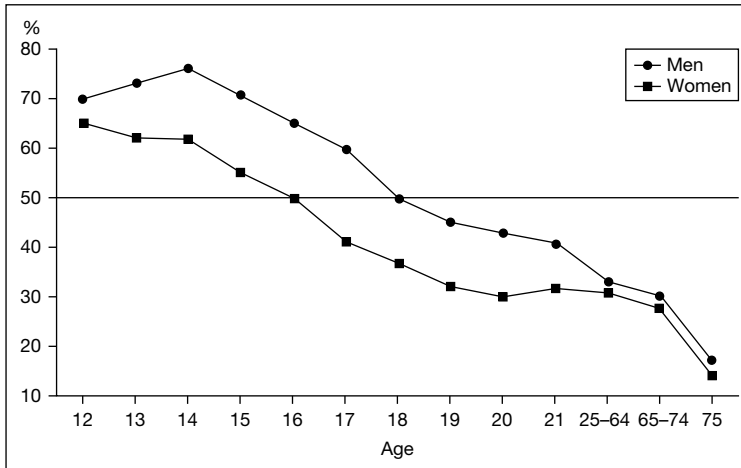


Fig. 1. Physical activity levels of men and women from the ages 12–75 and over.

Sedentary lifestyle is a characteristic phenomenon of both developed and underdeveloped countries. Figure 1 shows how physical activity levels decrease throughout life [27], while energy consumption increases at the same time. Epidemiological studies indicate that low levels of physical activity are both a cause and a consequence of weight gain [25, 28].

The effects of exercise in the prevention and/or treatment of obesity are multidimensional, thus impossible to be covered in this paper. Therefore, I will not go into explaining the beneficial effects of exercise in treating various risk-related parameters associated with obesity, since this constitutes a cumbersome and tedious endeavor. Instead, I will attempt to explore the general and specific contributions of exercise to weight loss, explore the mechanisms involved due to exercise in maximizing fat loss, protection of the various organs involved in metabolism during the weight loss phase, and emphasize the psychological effects, as well as the contribution of exercise in maintaining desirable body weight after the termination of a treatment period. All the above-mentioned positive outcomes are the consequences of the following physiological adaptations, resulting from the addition of a routine habitual physical activity pattern to one’s daily lifestyle.

Drive Up the Metabolic Rate

Many dieters often get discouraged when they find that the rate of weight loss falls off considerably as they continue to diet. They assume that there is

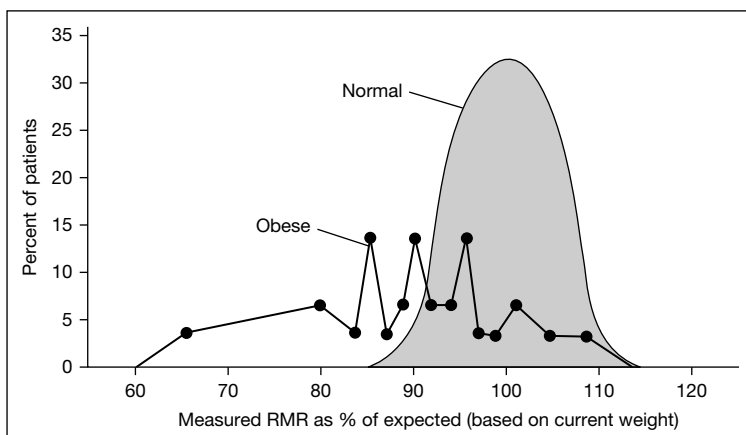


Fig. 2. When the current body weight was used in the calculations, only 64% of the obese patients, as compared to 92% of Boothby's normal, healthy volunteers, had measured resting metabolic rates that were within $\pm 10\%$ of expected values.

something wrong with their metabolism and that weight loss is a hopeless proposition. In fact, and contrary to this notion, they must realize that this observed reduction in the rate of weight loss is a normal physiological response to restricted calorie intake. The metabolic rate decreases with age and is more profound after the age of 40 [29], as well as during a reduced energy intake of 10–15% of calories [9, 30–32]. For dieters needing to achieve a cosmetic 3–5 kg (6–11 lb) of weight loss, this might not be a problem, but for individuals facing a longer dieting term, this drop in metabolic rate can break the dieter's will, since weight loss will begin to level off.

Resting metabolic rate seems to decline with age as a result of sedentary lifestyles, independent of 'free fat' weight and percent of body fat. This decline is related to age-associated reduction in exercise volume and energy intake, and does not occur in individuals who maintain exercise volume and/or energy intake at a level similar to that of young physically active individuals [33, 34]. Metabolic studies have documented that a number of obese individuals have a reduced resting metabolic profile. Figure 2 shows that only 70% of the moderately obese individuals have resting metabolic rates within the expected values [35, 36] and the remaining 30% exhibit impaired resting metabolic rates. By examining the medical history of the subjects involved, it was shown that the obese individuals with 'normal' metabolic rates did not have a past history of unsuccessful weight loss efforts, thus safeguarding their lean body tissue, whereas those with reduced metabolic rate had a history of >3 unsuccessful

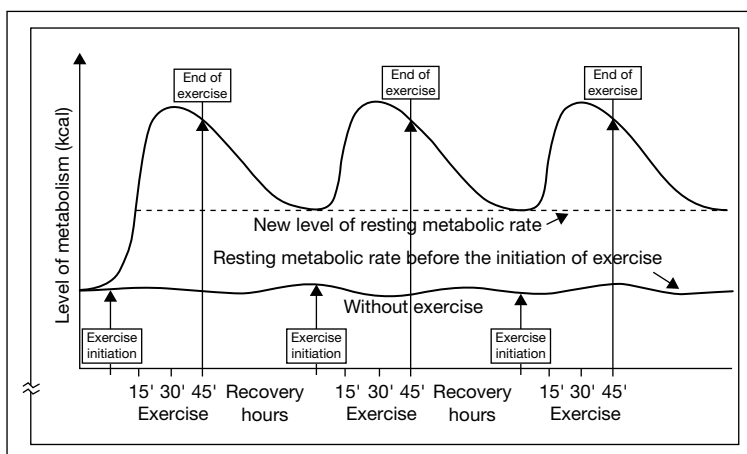


Fig. 3. Metabolic alterations resulting from participation in frequent aerobic exercise (schematic model).

attempts to keep off the weight they lost (>8–10 kg per attempt), demonstrating the classical ‘yo-yo syndrome’.

Although physical activity in general increases the metabolic rate during active participation in exercise, all forms of exercise do not have similar effects. Participation in aerobic activities alone has a negative affect on resting metabolic rate [30–32, 37] due to its adaptive mechanism in calorie expenditure only, and not in triggering the RNA-DNA anabolic mechanism and maintenance of lean body mass. On the other hand, aerobic activity supplemented with strength training during weight loss maintains and/or increases lean body mass and exhibits a parallel increase in resting metabolic rate [37–41].

Until recently, scientists took into account only the time an individual spends in exercise in order to calculate calorie expenditure due to exercise. In this way, they treated metabolism in a similar way to how we treat the electric switch: on and off. However, things are not so bad. The contribution of exercise in energy expenditure has been underestimated. Contrary to this notion, combining, every other day, aerobic and strength training with diet counterbalances the problem by increasing the metabolic rate to a new higher level.

The metabolic rate remains elevated for longer periods of time after exercise has stopped. As can be seen in figure 3, 45 min of exercise creates a wave of increased metabolic rate above and beyond the resting level. At the end of the exercise bout, the metabolic rate does not return immediately to the pre-exercise resting level, but remains elevated for a long period of time, creating a new

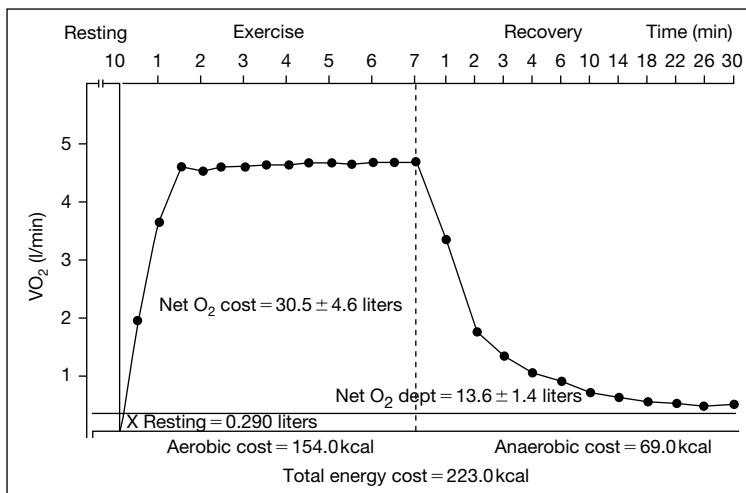


Fig. 4. Metabolic profile during maximal testing and recovery in power.

level of resting metabolic rate. The height at which the metabolic rate will be increased during the exercise session, and its corresponding reduction during recovery, depends on the intensity of the exercise and the body composition of the individual involved.

This observed elevation in metabolic rate immediately at the end of exercise is a well-known and common phenomenon in competitive sport activities, which has been referred to as ‘the oxygen debt’, is considered the anaerobic part of the exercise activity, and is now referred to as ‘post-exercise oxygen consumption’.

It is interesting to note that in competitive rowing [42], a sport event which lasts on average for 7 min of maximum effort, it was determined during the event that 154 kcal were burned. After the completion of the event, the metabolic rate remained elevated and burned an additional 69 kcal during the 30-min observed recovery period. This represents an additional 45% of the energy cost of the activity, burned during the recovery period of only 30 min of observation (fig. 4). Similar phenomena have been reported by many investigators indicating that resting metabolic rate is maintained elevated for at least 12–18 h after the termination of the exercise stimulus [43–45].

If this post-exercise elevation of the metabolic rate is applied to the obese individual, we can see the actual contribution of exercise to fat burning in weight loss programs. The return of the metabolic rate at the pre-exercise level depends upon the duration and the intensity of the exercise program used. This can last

for many hours and even exceed the 24-hour period after the termination of the exercise session. The generally expressed feeling of warmth after the termination of an exercise session, a sense of euphoria due to the maintenance of increased blood circulation and metabolism, is evidenced for some time after exercise.

It has been estimated that for every kcal burned during the exercise session, if the duration of the exercise session exceeds 60 min and the intensity is between 60% and 80% of VO_2max of the individual, the post-exercise recovery period can account, on average, for an additional 0.5 kcal during the following 24 h, thus explaining the discrepancies observed and unaccounted-for-fat-loss in well-controlled studies [9, 46].

Preserving Lean Muscle Tissue

Too often, after weight loss by caloric restriction alone, dieters complain about muscular weakness resulting from losing significant amounts of muscle tissue.

Since lean muscle tissue determines to a great extent the burning power of the body, muscle tissue should be preserved by all means to maintain a high level of metabolic rate throughout the diet. Dietary manipulation by increasing protein consumption is in use in an effort to protect the muscle tissue and vital organs of the body during weight loss phases. However, even these approaches have failed [47, 48]. Fat is a lazy tissue compared to muscle tissue's active ability to mobilize and burn fat. Exercise preserves the existing muscle tissue of the dieter and builds more muscle for a better muscle-to-fat ratio in the body. This insures healthy weight loss over the long term [9, 46, 49–51].

In studies where diet was supplemented 3 times per week with exercise sessions consisting mainly of aerobic and light resistance exercises [46, 49–51], in the non-exercise groups, for every 10 kg of weight lost, 2.9–3.3 kg constituted muscle tissue and the remaining fat loss. On the other hand, the exercise group, during the same period of time, exhibited a total weight loss of 11.8 kg from which 11.2 kg was fat and only 0.6 kg was muscle tissue [46, 49–51]. The addition of exercise to a weight loss program preserves muscle tissue of the body, resulting in maximizing the kcal equivalent per kg loss. The contribution of exercise on the nature of weight loss is better expressed by the fact that the kcal equivalent of the weight loss amounted to 8,000 kcal, achieving maximum value per kg of fat loss, while the non-exercise group had a 5,640 kcal/kg loss, indicating an extensive protein wasting (table 1) [46]. Body composition plays a pivotal role on rates of weight loss. Individuals with intact body composition who did not have 'failed efforts' in weight loss, thus preserving their body muscle tissue intact, exhibit better compliance to diet, stay on the programs for

Table 1. Kilojoule equivalent of weight loss¹

	n	Protein		Fat ²		Total		
		g	kJ	g	kJ	kJ	kJ · kg ⁻¹	kcal · kg ⁻¹
Exercised	31	116 ⁺	2,000	10,000*	392,700	394,700	33,400	8,000
Non-exercised	41	640	11,000	5,300	206,000	217,000	23,600	5,640

¹One gram of protein yields 17.14 kJ and 1 g fat, 38.88 kJ.

²Fat (g) = fat tissue × 0.90.

*p < 0.01; ⁺p < 0.02. Exercised vs. Non-exercised.

longer periods of time and are more successful in losing extra body fat. On the other hand, individuals with an unsuccessful effort history have difficulty in following a weight loss program, are easily discouraged and are prone to failure, and drop out of the weight loss programs. The effectiveness of weight loss contributing to the body composition, and more specifically to the presence of lean muscle tissue, is demonstrated in table 2 [35, 46].

Increasing Oxygen Uptake

Exercise increases the body's capacity to utilize greater amounts of oxygen, which is vital to overall health. At the same time this increase in oxygen utilization is an extra benefit for the dieters, since greater amounts of oxygen allow greater burning of stored fat. A blanket of fat on the body and in the cells inhibits oxygen uptake in obese people, a situation which must be changed for maximum burning of fat.

Studies on obese individuals engaged in aerobic, or in combination of aerobic and strength activities, have demonstrated statistical increases in oxygen consumption in both men [35, 40, 46] and women [32, 38, 50]. It is interesting to note that weight loss programs, using only diet as a treatment method for obesity, demonstrated decreases in maximum oxygen consumption, an indication of impaired capacity to burn fat [37, 50]. Fat can be burned only in the presence of oxygen. Therefore, maintaining and/or increasing oxygen-delivering capacity to the tissues enhances fat catabolism. There is evidence that exercise maintains and/or increases lean muscle tissue during the weight loss phase [46, 49–51]. It has been found that at rest each kg of lean body mass utilizes 28–32 kcal/day [35, 52, 53].

Table 2. Weight loss in two patients

	Patient A (subject 6)		Patient B (subject 30)	
	pRMR ¹	measured	pRMR	measured
Weight, kg		91.5		92.2
Lean body mass, kg		42.5 (46.5%)		64.5 (70%)
kcal/kg · LBM ⁻¹		27.8		28.7
Height, cm		180.0		183.0
Age, years		59.0		53.0
Resting energy expenditure, kJ/day	7,603	4,932	7,511	7,729
	(1,819 kcal)	(1,180 kcal)	(1,797 kcal)	(1,849 kcal)
20% added for daily activity, kJ/day	1,521	986	1,651	1,534
Total kilojoules needed, kJ/day	9,125	5,910	9,012	9,263
Minus 10% metabolic suppression due to diet, kJ/day	911	594	903	928
Actual kilojoules needed, kJ/day	8,176	5,325	8,109	8,335
Minus kilojoule intake, kJ/day	4,180	4,180	4,180	4,180
Daily kilojoule deficit	−4,034	−1,145	−3,929	−3,946
Kilojoule deficit in 7 weeks of treatment	−197,639	−56,121	−192,531	−203,591
	(−47,282 kcal)	(−13,426 kcal)	(−46,060 kcal)	(−48,706 kcal)
Weight loss, kg (kJ ÷ 33,440)	5.9	1.7	5.7	6.1
Comments	Dropped out during week 4 of the treatment without weight loss		Loss of 7.2 kg after 7 weeks of treatment	

¹pRMR = Using current weight in the Harris and Benedict equation [119].

It is not surprising, therefore, that individuals with large tissue muscle exhibit greater resting metabolic rates. The greater the oxygen-delivery capacity of an individual, the easier its capacity to burn off fat, resulting in faster and better weight control. Increased ability to utilize oxygen is an index of cardiorespiratory capacity and fitness, which is a known benefit conferred by aerobic exercise.

Increasing Calorie Expenditure

Movement requires energy [54, 55]. The more movement performed, the more energy is demanded for it. Research indicates that if the intensity and

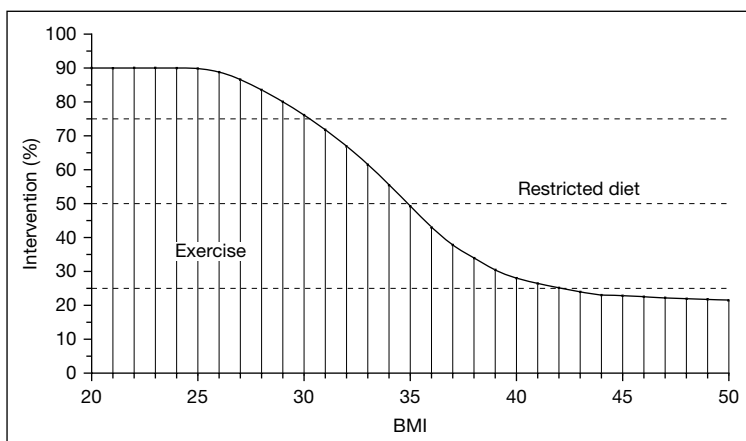


Fig. 5. The impact of exercise and diet at different BMI levels [adapted from 56].

duration of the exercise program is appropriately high and of the needed duration, for every calorie lost through a restricted diet, another half kcal (0.5) is lost through exercise [9, 42]. Dieters too often presume that reducing caloric intake is all that is needed to lose or control body weight, but that is not necessarily the case for obese people with a high percent of body fat. To make calorie output equal to calorie input, overweight individuals could cut calories in half and still gain weight, because their percent of body fat is greater than normal, and lean muscle tissue is minimized, thus undermining their energy-burning capacity. The extra energy demand of exercise can offset this problem, often making the difference between success and failure for a long-term program. Figure 5 demonstrates the possible combined effect of exercise and diet in treating obesity and their relative contribution to control and/or lose fat according to the BMI [56]. As can be seen, when BMI is <30 , exercise is more effective than nutrition and should be aggressively applied. For obese individuals with a BMI >35 , nutrition should be given a priority supplemented by an exercise routine. Again, it is very important to point out that exercise should be included in every weight loss program, and the intensity and duration should be determined on an individual basis, depending on the cardiorespiratory capacity, previous experience in physical activity programs, BMI, and age, just to mention a few parameters. If BMI is >35 , although the intensity and speed of movement is very low, and since the cost of movement is a product of body mass multiplied by the time of movement in minutes, caloric expenditure is increased as a result of a heavy body weight.

Although the obese individual should be encouraged to adapt a more active lifestyle pattern above and beyond the participation in supervised exercise programs, it should be kept in mind that the best long-term results may be achieved when physical activity produces an energy expenditure of about 2,500 kcal/week [57].

For an obese individual with a body weight of 80 kg, this could mean 60 min of exercise every other day, with a caloric equivalent of 400 kcal per exercise session ($400 \times 4 = 1,600$ kcal/week). Adding to that the post-exercise metabolic affect of 750–800 kcal/week, one can estimate a total loss of 300–350 g of body fat as a contribution to participation in exercise. If one combines the weight loss program with a caloric restriction of 500–700 kcal/day ($600 \times 7 = 4,200$ kcal/week), one can easily achieve a total fat loss of 0.8 to 1.0 kg/week (325 g from exercise + 525 g due to diet). This rate of weight loss is safe and acceptable among health professionals and easily tolerated by the average individual. In individuals with a more advanced obesity problem, the above values should be increased.

Coincidentally, this amount of energy spent through exercise is associated with improvement in fitness, and at the same time provides protection from a cascade of health-related problems. It is important to point out that there is a dose-response relation between the amount of exercise performed, from approximately 700 to 2,000 kcal of energy expenditure per week, and all-cause mortality and cardiovascular disease (CVD) mortality in middle-aged and elderly populations [58].

Reducing Calorie Absorption

When an individual lives an active lifestyle and exercises on a regular basis, food passes through the intestinal tract much faster. As a result, a smaller percentage of the day's calories are absorbed. A meal passes through the gastrointestinal tract on the average, during resting conditions, in about 40–60 h [59]. During exercise on a bicycle or on a treadmill for 45–60 min, food transit time is decreased from 51 to 36 h for cycling and 34 h for jogging, and in some instances the transit time has been found to be decreased to <24 h [60–63]. Small bowel absorption of water, electrolytes, and nutrients may be affected by exercise, mediated perhaps by altered motility, decreased blood flow, or neuro-hormonal changes [61]. Although gastric emptying is affected by many factors and constitutes a complex process, light and moderate exercise seem to accelerate the action [62]. In obese people with weak abdominal muscles, and poor physical fitness, this process may take longer than for the lean individual. Well-trained individuals, such as athletes, can complete the digestive cycle in shorter

Table 3. Energy expenditure and intake: means for periods and treatments (kcal/day) (n=6)

	Period			Treatment		
	1	2	3	sedentary	mild	moderate
Expenditure						
Mean	2,475	2,471	2,408	2,221	2,419	2,714
SEM	136	169	30	71	68	119
t-value					5.3*	7.9*
Intake ¹						
Mean	2,233	2,346	2,303	2,233	2,305	2,345
SEM	144	196	165	146	163	196
t-value						
Intake ²						
Mean	2,159	2,308	2,269	2,180	2,267	2,291
SEM	153	200	175	146	179	204
t-value		4.0 ⁺	1.0			

¹Calculated using bomb calorimetry-nitrogen analysis.

²Calculated using McCance-Widdowson food table values.

⁺ANOVA: $p < 0.05$; *ANOVA: $p < 0.001$.

periods of time. The longer the food stays in the intestines, the more calories are absorbed, the greater the chance for food to stagnate, leading to digestive disorders and increasing the risk of bowel cancer. Adopting an active lifestyle might improve abdominal and digestive muscles, and improve transit time, thus reducing the number of calories absorbed on a daily basis.

Appetite Suppression

Most people carry the false notion that exercise increases appetite, but investigators do not agree. A loss of appetite follows strenuous exercise in most people, especially for those who are normally inactive, as are the obese. Woo et al. [64] clearly demonstrated that engaging in low and moderate intensity physical activity did not cause an increase in appetite. They demonstrated a statistical decrease in energy intake over a period of 19 days, while at the same time enhancing fat catabolism (table 3). Additionally, the level of activity has a direct correlation with how many calories a person eats in the first place. There is a biological clock which is turned ‘on or off’ according to the level of

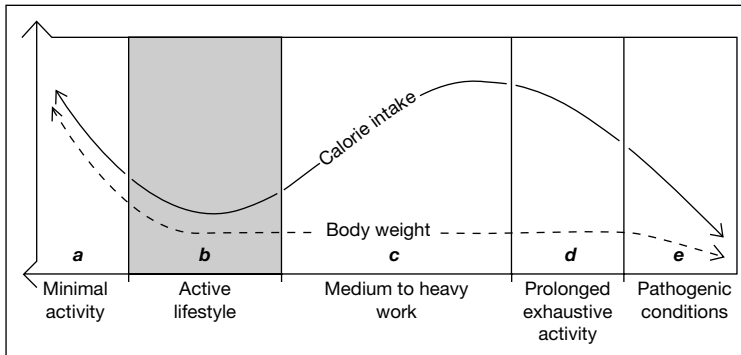


Fig. 6. Calorie intake and body weight in individuals maintaining different activity levels. **a** Those whose activity level is very low, exhibit a parallel increase in calorie consumption and body weight. **b** People who maintain a fairly lifestyle, consume less food while retaining a normal body weight. **c** Individuals who maintain a more active lifestyle, due to workplace demands or voluntary exercising, maintain an ideal body weight, even when they consume more calories. **d** Exhaustive exercise causes a decrease in calorie consumption. **e** In pathogenic conditions, such as the anorectic individual with distorted body image, we notice a decrease in both food intake and body weight.

physical activity [65]. When activity levels are low, studies show that calorie intake increases; the less a person moves, the more the person eats, as is well demonstrated in figure 6. Exercise also releases fat into the bloodstream, which secures blood sugar level. Since a drop in blood sugar stimulates hunger, by maintaining blood sugar levels, exercise helps keep hunger at bay. Studies have revealed a modest decrease in daily calorie intake when aerobic exercise lasts from 45 to 60 min/day. Although this reduction in intake is not great, it can mean the difference between gaining and/or losing weight over the course of a year. The physiological explanation of exercise's ability to suppress appetite is not yet very clear. Investigations show that appetite suppression is mediated by increased concentrations of catecholamines in the blood, decreased levels of insulin, increased body temperature, and the production of certain anorectic (appetite-suppressing) substances found in the blood and urine [66]. Individuals who are engaged in physical activity after the termination of the exercise session tend to concentrate on fluid balance rather than energy intake [67].

It is interesting to note that dehydration, a common phenomenon in exercising individuals, leads to a decrease in ad libitum energy intake [68]. Finally,

it is well established that exercising at an intensity of 60–80% of maximum aerobic capacity results in a negative caloric balance in both men and women [69]. However, overall, it is not clear why initiation of an exercise program does not lead to an increase in food intake sufficient to compensate for the increase in energy expenditure. The fact that it does is good enough to incorporate exercise into weight control-loss-maintenance programs.

Reducing Depression and Anxiety

Anecdotal as well as literature reports indicate that exercise is effective in reducing depression in hospitalized manic-depressive patients, as well as in non-hospitalized college students [70–72]. These reports seem to be in agreement with epidemiological studies showing that exercise is associated with decreased symptoms of depression and anxiety [73, 74].

Overweight and obesity are strongly associated with depression and anxiety [75]. It is not clear as yet whether the presence of depression and anxiety triggers obesity or visa versa. However, participation in physical activity programs has been found to exert a protective effect on depression in older adults [76].

A number of psychological changes occur when a person confronts a challenge and overcomes it. For an obese person who has become sedentary from the burden of weight, that challenge is exercise. Physical conditioning exerts a positive outcome and provides a sense of accomplishment, increased self-esteem, well-being and self-control [77]. These states of mind are associated with the production and release of endorphins, which serve as modulators of pain and mood. By exercising, circulation is increased and glucose availability to the brain is multiplied. With positive feelings of self-esteem and self-worth, the commitment required to stay on diet is easier to find [76, 77]. Weight loss and participation in physical activity programs are strongly associated with mood enhancement [78, 79]. Figure 7 nicely demonstrates the positive effects on depression-mood states in individuals engaging in a supervised aerobic-type physical activity program [72, 80].

Depression and anxiety can lead to overeating, resulting in the accumulation of extra adipose tissue. This in itself can perpetuate the phenomenon, resulting in a never-ending vicious ‘weight gain-depression’ circle, leading to additional anxiety and so on. Exercise has been found to induce an antidepressant effect similar to, or even better than, drug treatment. Participation in physical activity programs has a therapeutic antidepressant effect as well as on emotional and physical functions of the obese. This phenomenon is equally present in individuals with mild as well as high depressive symptomatology [81].

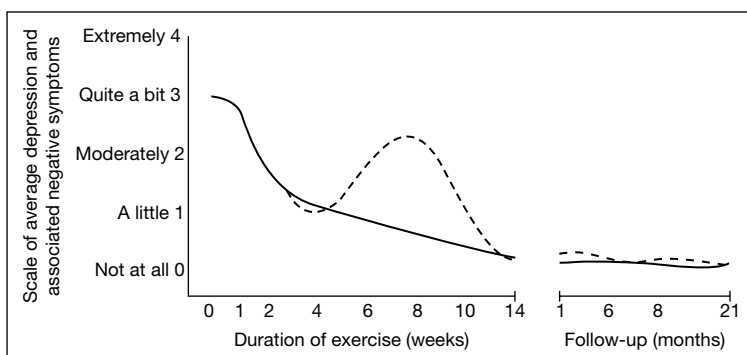


Fig. 7. Changes in depression-mood behavior. For the first 10 weeks, patients walk-run-jog 3 times per week for 30–45 min under supervision. After that, they are encouraged to run 4–6 times per week with infrequent supervision. The dotted line represents mood state of a patient who sustained an injury at week 4 and stopped jogging until week 8, thereafter resuming regular activity [adapted from Greist et al., *Psychiatr Ann* 1979;9:23–33].

An array of meta-analyses studies clearly demonstrates the positive effect of exercise on mood-depression states [82–85].

Prevent Life-Threatening Arrhythmias

Abnormal function of the heart can be a life-threatening situation in an obese person while he/she follows a calorie-restricted diet. The extra accumulated body fat results in an additional strain on the heart. The addition of an exercise regimen, above and beyond the combined stress imposed by dietary restriction and the presence of obesity, if not appropriately calculated and implemented, could be detrimental to the individual [86, 87]. This is not to say that exercise has to be avoided, but rather to stress the importance of a carefully administered diet-exercise regimen with the correct combination, thus achieving provision of all needed nutrients to support the body's vital functions, and at the same time, use exercise to enhance calorie expenditure, support maintenance of muscle tissue and other organs of the body, while at the same time improve all physiological parameters associated with health and well-being [88]. Pavlou et al. [87] have indicated that individuals who follow a very-low-calorie diet exhibit a number of life-threatening abnormalities in their electrocardiograms (EKG), while individuals on the same diet, supplemented by an

exercise and mild strength-training program, seem to develop a protective mechanism.

Improving Maintenance Success

Scientific studies indicate that less than 5% of those who successfully lose weight are capable of maintaining their weight loss at 6–12 months in the post-treatment period. Medically significant weight loss means maintaining that loss for a period of time for more than 2 years after completion of the program. Various methods used in an attempt to succeed in maintaining weight loss by combining self-reporting, internet intervention, clinic reporting, etc., have failed [89]. Successful weight loss maintenance is associated with greater initial weight loss, reaching a self-determined goal weight, and having a physically active lifestyle, a regular meal rhythm including breakfast and healthier eating, control overeating, and self-monitoring of behavior. Weight maintenance is further associated with an internal motivation to lose weight, social support, better coping strategies and an ability to handle life's stresses, self-efficacy, autonomy, assuming responsibility in life, and overall more psychological strength and stability. Factors that may pose a risk for weight regain include a history of weight cycling, uninhibited eating, binge eating, more hunger, eating in response to negative emotions and stress, and more passive reaction to problems [90]. In addition to the above, weight maintenance is determined to a great extent by events pertaining to carbohydrate and fat metabolism and how these two energy-rich macronutrients are related to exercise and/or lifestyle of the individual [91]. When exercise is included as a daily lifestyle choice, the success rates can be improved [8, 91–93]. As a matter of fact, maintenance of weight loss can be extended for at least a period of 3 years. It has been demonstrated that participating in 'aerobic/diet' or 'lifestyle activities/diet' weight loss programs, weight loss can be achieved, but this effort could be undermined by the fact that such programs do not succeed in maintaining lean body mass, a fact necessary to secure long-term maintenance of a high metabolic rate [8]. The addition of a strength-training program to a weight loss regimen has the additional benefit of maintaining the existing muscle tissue, thus enhancing fat loss.

The success story of an appropriately combined diet and well-rounded exercise program in weight loss and weight loss maintenance is demonstrated in figure 8 [8]. However, it should be emphasized that the incorporation of an exercise program on a permanent basis as a lifestyle choice [8, 92, 93] is of utmost importance for successful maintenance of achieved body weight loss, along with a sound dietary program and always remembering that 'a calorie is always a calorie' [94]. Retrospective analysis of weight gain as a function of

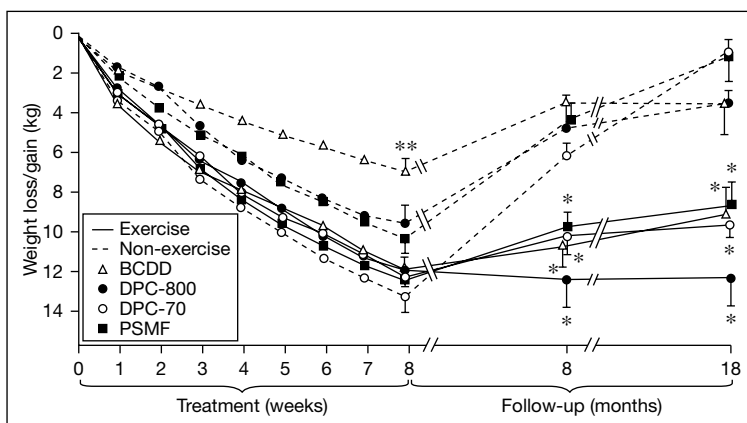


Fig. 8. 18-month follow-up data confirm the effectiveness of exercise intervention in maintenance of weight loss, regardless of the diet involved, during the weight loss phase. BCDD = Balance calorie deficit diet; DPC-800 = 800kcal BCDD liquid diet; DPC-70 = 420kcal protein liquid diet; PSMF = protein-sparing modified diet. * $p < 0.001$ vs. non-exercise; ** $p < 0.005$ vs. all exercise group (—) and DPC-70 group (O—O).

energy expended in physical activity indicates a threshold for weight maintenance of 11.2 kcal/kg of body weight per day, or incorporating into our daily life 60–80 min of moderate activity or 35 min of vigorous physical activity. In combination with well-planned dietary habits, this can be achieved by a modest increase in physical activity, with up to 45–60 min of moderate physical activity per day [95, 96].

The Fit or Fat Question

It is well established that obesity is an independent risk factor for CVD and is associated with an array of health-related disorders [10–12, 96]. On the other hand, weight loss, as expressed by means of fat reduction, has been found to reduce a number of health-related risk factors [24–26, 58, 97]. We know that most of the individuals who are engaged in weight loss programs fail to achieve their desired weight goal [1, 2–7], and although the population trends in ‘leisure-time lifestyle’ physical activity pattern is on the increase [98], energy expenditure and an active lifestyle, as well as the workplace activities, are found to be on the decline, creating an overall positive energy balance leading to obesity. In view of the fact that the majority of the weight loss programs fail to

achieve the desired body weight, the question raised is whether one should consider to be engaged in physical activity or not.

Physical inactivity is a major, if not the primary cause of obesity. It is therefore necessary to accurately balance energy intake and energy expenditure to achieve a fine control of body weight. Epidemiological studies clearly indicate that low physical activity is a strong and independent risk factor for both CVD and all-cause mortality [99–102]. On the other hand, physical activity of moderate and high intensity levels, as well as leisure-time and occupational physical activity, are found to be strongly associated with reduced CVD and all-cause mortality among both sexes [103].

It is worth mentioning that there is a clear dissociation between the adaptation of cardiorespiratory fitness and the improvement in the metabolic risk profile that can be induced by physical training programs. It is evidenced that as long as the increase in energy expenditure is sufficient, low-intensity exercise is likely to produce beneficial metabolic effects [104]. It is therefore important to focus on the improvement of the metabolic profile as well, rather than only on achieving weight loss goals alone.

Taking into consideration the fact that physical activity is associated with a significant reduction in CVD risk, and considering the alarming and increasing prevalence of sedentary lifestyles, we should reinforce the implementation of physical activity programs during weight loss efforts [105].

Several prospective studies have shown that overweight men and women who are active and fit have lower rates of morbidity and mortality than overweight persons who are sedentary and unfit. Therefore, exercise is of benefit to overweight individuals, even if does not make them lean, and should be recommended as an important part of a weight control program, since obesity-related risks are low in ‘fit’ individuals, regardless if they are obese or not [106, 107]. To answer the ‘fit or fat’ question I respond that, if one has a choice, it is preferable to be ‘fit and lean’. However, if one cannot be lean, then it is preferable and safer to be ‘fit and fat’ rather than ‘fat and unfit’.

Lifelong Physical Activity

The inactive lifestyle we adopt today and the consumption of extra calories, slowly but surely, results in the accumulation of extra fat tissue. It is observed that the average individual, over the last decade, is regularly gaining 0.9–1.3 kg of body fat on an annual basis, leading to an uncontrolled overweight and obesity epidemic [108–111]. Studies indicate that the risk of death is increased even among modestly overweight individuals, while this risk persists and increases as age advances [112, 113].

Life is synonymous with movement. When movement ceases so does life. Physical fitness has been found to be strongly associated with the reduction of various risk factors. In the absence of hormonal dysfunction, and assuming a normal body weight at college age, the slow accumulation of body fat at the rate of 1.0 kg/year observed in many studies represents a daily positive calorie accumulation of <22 kcal/day above energy requirements. If one adopts an active lifestyle at college age and maintains a similar daily energy expenditure by incorporating into his/her life an exercise routine of no more than 45 min every other day, this should be sufficient to counterbalance the accumulation of fat and protect one from obesity. This minimum activity pattern is sufficient to maintain musculoskeletal fitness (MSF), a factor crucial in the prevention of overweight and obesity as well as in its treatment. In a prospective study of 20 years' duration, Mason et al. [114] found that MSF was inversely related to weight gain and to BMI at follow-up, suggesting that age-related weight gain may be more pronounced among individuals with low levels of MSF fitness. They observed that individuals with low MSF levels had a 78% increased odd of substantial weight gain (>10 kg) over that period compared with the individuals with high and average MSF. These results provide additional evidence that aerobic and strength training activities throughout life promote MSF levels, thus contributing to health promotion and preventing unhealthy weight gain.

There is evidence that if one incorporates into his/her life daily physical activity, it is easy to maintain healthy body weight. Additionally, women with excess body fat and high MSF are more insulin-sensitive than overweight, sedentary women with equal amounts of body fat [115]. A similar phenomenon is observed in men as well [116]. Low cardiorespiratory fitness is associated with increased risk for impaired fasting glucose and type 2 diabetes. This association is clinically significant; the risk for diabetes is 3.7-fold higher in men in the low-fitness category group than in men in the high-fitness category group. Similarly, aerobic conditioning and strength training significantly increase insulin sensitivity in obese individuals as well, independent of changes in body composition [117]. The exercise intensity necessary to achieve MSF is easily attainable by the average obese individual [118], and the inclusion into the daily lifestyle should not be ignored and/or underestimated [119, 120].

Conclusions

Overweight and obesity are associated with a cascade of life-threatening risk factors which directly or indirectly are associated with the condition known as *metabolic syndrome*, as well as with a number of additional life-threatening conditions such as CVD, hypertension, arthritis, cancer, osteoporosis,

depressed immune system, neuromuscular malfunction and a constellation of other medical conditions. Although it is not as yet clearly understood how all these are interrelated with obesity, it is widely accepted that it is manifested as a result of reduced physical activity and/or improper nutritional habits.

Physical activity or inactivity seems to represent a major player in the prevention and/or treatment of obesity. This could not be a surprise, since movement is associated with life. Hippocrates was very clear in his teachings when he stated that the interaction of genetic factors predisposing to disease, physical activity, proper nutrition, and other environmental factors are intimately interwoven to determine positive health. In this review, I have attempted to explore and describe the outermost layer of the effects of exercise in the prevention and/or treatment of overweight and obesity. The positive effects of exercise on parameters such as resting metabolic rate, building and/or preserving lean muscle tissue, improving musculoskeletal and cardiovascular fitness, improving oxygen delivery and enhancing fat catabolism – thus accelerating fat loss, increasing calorie expenditure and at the same time decreasing calorie absorption and suppressing appetite, reducing depression and anxiety, normalizing through various mechanisms cardiac muscle function during weight loss efforts, and improving the chances of weight loss maintenance – are a few of the positive effects that enhance participation in exercise programs. Answering the ‘fit or fat’ question is only the tip of the iceberg that is called ‘exercise’ and its contribution to protecting and/or treating the epidemic that is called ‘obesity’. These observed physiological adaptations due to exercise described in this article are the minimal steps in understanding the importance and contribution of exercise as a lifestyle modification in safeguarding our population not only from obesity itself, but also from an array of health-threatening conditions.

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Nutritional Risk Factors for Gastrointestinal Cancers: The Multiethnic Cohort Study

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Introduction

Investigations of many kinds, including studies of cancer incidence in migrant populations, analyses of secular trends in cancer rates, and research on basic mechanisms of carcinogenesis all point to a major role of diet and nutrition in the etiology of cancer [1]. Nevertheless, analytic epidemiologic studies, including intervention trials, have been able to establish few specific relationships with certainty. Since the development of cancer is generally a slow process entailing a lengthy latency period, relevant exposures antecede the clinical diagnosis of disease by many years. Unfortunately, reliable biomarkers of long-term exposure to specific constituents of the diet are lacking, so that diet history (recall) methods remain the major source of exposure data.

Early studies of Japanese migrants to Hawaii by our group confirmed that exogenous (environmental) factors were major determinants of cancer risk [2, 3]. For example, we showed dramatic shifts in stomach and breast cancer incidence rates from Japan to first-generation migrants in Hawaii, and further shifts between first- and second-generation migrants in Hawaii (fig. 1). Since those in the latter group were born in Hawaii, they would have had exposure to Western influences throughout their lives, whereas first-generation migrants experienced their formative years in Japan. Thus, more extreme changes in the second-generation migrants were not unexpected. In subsequent research, we sought to identify lifestyle factors underlying these changes, and concluded that diet was a major contributor [4–10]. Although these migrant studies helped establish the dominant role of the environment, other observations, such as higher than

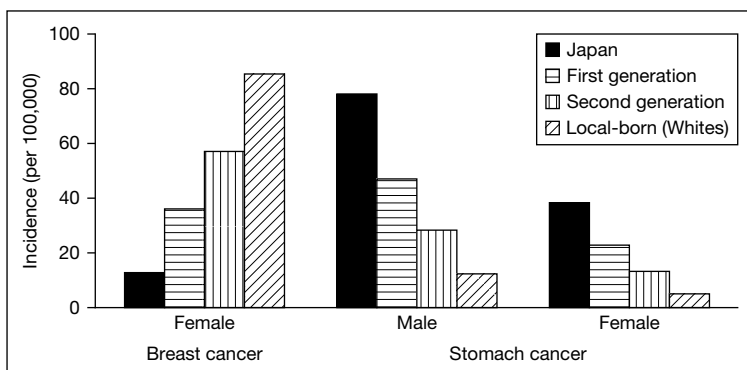


Fig. 1. Cancer Incidence in Japanese migrants and local-born Whites in Hawaii, 1973–1977.

expected colorectal cancer rates in first-generation Japanese migrants and the fact that only a small proportion of heavy cigarette smokers develop lung cancer, indicated that individual susceptibility factors must also play an important role in determining ultimate risks from environmental exposures.

In 1993–1996, we established the Multiethnic Cohort Study (MEC), a large prospective investigation in Hawaii and Los Angeles, to extend our earlier investigations of lifestyle and cancer and to incorporate genetic components into our research [11]. The design of the MEC has several distinct advantages for studies of this type: (1) by including a variety of ethnic populations, we obtained an unusually wide range of exposures to foods and nutrients, thereby facilitating our ability to identify meaningful relationships; (2) by using a population-based study design, we reduced selection bias, so that findings could be generalized more widely, and (3) by collecting biological specimens, we provided a means to investigate genetic susceptibility to cancer and to explore gene-diet interactions [12]. We report here some recent findings related to cancers of the colorectum and pancreas from this large prospective cohort. The incidence of these and selected other cancers in the five main ethnic groups of the MEC at the time the cohort was established illustrates the substantial variation in risks across the different populations (fig. 2) [13]. For example, the incidence of prostate cancer is threefold greater in African-American men than in Native Hawaiian men, while the incidence of breast cancer is nearly twofold higher in White women than in Latino women.

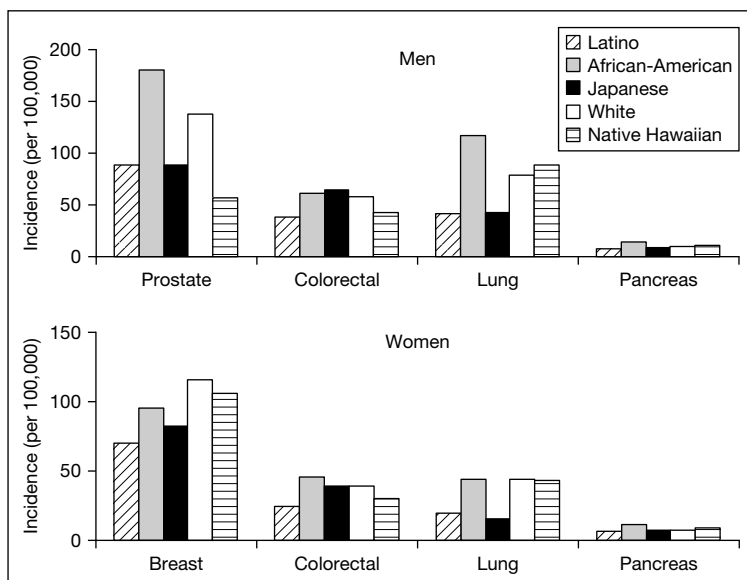


Fig. 2. Incidence (per 100,000)* for some common cancers in the ethnic groups of the multiethnic cohort, 1988–1992. *Age-adjusted to 1970 US standard population [source 13].

Materials and Methods

Study Design

Recruitment procedures, study design and baseline characteristics have been reported elsewhere [11]. In brief, men and women aged 45–75 years when the cohort was created, and primarily from one of five main ethnic groups (African-American, Latino, Japanese-American, Native Hawaiian, and non-Latino White) were enrolled between 1993 and 1996. All study participants initially completed a self-administered comprehensive questionnaire that included a detailed dietary assessment. Other components of the questionnaire included sections on demographic factors, body weight and height, smoking history, physical activity, history of prior medical conditions and use of medications, family history of cancer, and, for women, reproductive history. A biorepository of 67,000 prospectively collected blood and urine specimens was subsequently established between 2001 and 2006. An additional 8,000 post-diagnostic specimens were collected between 1996 and 2006 from cases of breast, prostate and colorectal cancer. Follow-up of the cohort for cancer incidence and mortality is primarily through computerized linkages to population-based cancer registries and death certificate files in Hawaii and California, and to the National Death Index, as well as through active contact with the subjects.

Study Population

At baseline, over 215,000 men and women were recruited to the study. Because the Quantitative Food Frequency Questionnaire (QFFQ) was designed to cover the usual diet of the five ethnic groups of interest, participants not belonging to one of these groups were excluded from the analyses ($n = 13,994$), as were individuals with implausible diets based on energy and macronutrient intakes ($n = 8,265$). To make the latter determination, the top and bottom 10% tails of the log energy distribution were excluded, and a robust standard deviation (RSD) was computed assuming a truncated normal distribution; all energy values out of the range ($\text{mean} \pm 3 \text{ RSD}$) were then excluded. A similar procedure was performed to exclude individuals with extreme fat or protein or carbohydrate intakes (outside the range of $\text{mean} \pm 3.5 \text{ RSD}$). Subjects with a diagnosis of the cancer under study prior to baseline that was either self-reported in the questionnaire or identified by registry linkages, and subjects with missing information at baseline on relevant covariates were also excluded.

Dietary Assessment

Dietary intake was assessed at baseline using a comprehensive questionnaire especially designed and validated for use in this multiethnic population. The development of the self-administered QFFQ has been described elsewhere [14]. In brief, 3-day measured dietary records from about 60 men and women of each ethnic group were used to identify a minimum set of food items that contributed at least 85% of the intake of a specific list of nutrients. Food items that were common in the diet of a particular ethnic group were also included in the QFFQ, irrespective of their nutrient contributions. The QFFQ includes more than 180 food items, and assesses frequency of consumption, as well as portion sizes using photographs and reference to standard serving units. Nutrient analyses used a food composition table developed and maintained at the Cancer Research Center of Hawaii. This table includes a large recipe database and many unique foods consumed by the multiethnic population of the MEC [11, 14].

Identification of Cancer Cases

Incident cancer cases were identified by record linkages to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County and the California State Cancer Registry. All three registries are members of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, and have been operating since 1960, 1972 and 1988, respectively. Case ascertainment was complete through December 31, 2001 or 2002 for the analyses reported here.

Statistical Analysis

We applied Cox proportional hazards models using age as the time metric to calculate relative risks (RR). Person-times were calculated beginning at the date of cohort entry, defined as questionnaire completion or as the date the participant turned 45 for the few individuals younger than 45 when they completed the baseline questionnaire. Person-times ended at the earliest of these dates: date of cancer diagnosis, date of death, or December 31, 2001 or 2002, the closure date for the particular analysis. Tests based on Schoenfeld residuals showed no evidence that the proportional hazards assumption was violated for any analysis. A trend variable, used to test dose-response, was assigned the sex- and ethnic-specific median values for overall quantiles. All statistical tests were two-sided. The likelihood ratio test was used to determine the significance of the interaction between exposures or between

Table 1. Distribution of the multiethnic cohort by sex and ethnicity

Ethnicity	Males	Females	Total
Latino	22,818	24,620	47,438
African-American	12,851	22,256	35,107
Japanese	26,964	29,957	56,921
White	22,857	26,502	49,359
Native Hawaiian	6,120	7,851	13,971
Other	5,200	7,255	12,455
Total	96,810	118,441	215,251

diet and genotype. The test compares a main effects, no interaction model with a fully parameterized model containing all possible interaction terms for the variables of interest.

For most dietary analyses, intakes were expressed as densities, because we [14], like others [15], had found in a validation study that energy-adjusted intakes produced substantially higher correlation coefficients with the reference instrument than did absolute intakes.

Results

The ethnic-sex distribution of the MEC is shown in table 1. The cohort consists of 215,251 participants, the majority of whom belong to one of the five designated ethnic groups.

Colorectal Cancer

Table 2 shows recent findings on fiber intake and colorectal cancer in a multivariate model that adjusts for multiple risk factors that have been associated with this cancer site. Among men, there is a clear inverse trend with increasing fiber intake (seen for both colon and rectal cancer). For the highest quintile of intake (median of 35.6 g/day), the large bowel risk is reduced by 38% in men. Among women, on the other hand, an inverse trend is not seen in this fully adjusted model, whereas in a minimally adjusted model, controlling for age and ethnicity only, an inverse trend similar to that in men was seen (data not shown). For calcium intake (table 3), inverse trends are seen in both sexes for total calcium and for supplements. For foods alone, the inverse trend is seen only in men. These findings were similar for each ethnic group separately (data not shown). One purpose of the MEC, as noted earlier, is to examine gene-diet interactions. In an analysis of a common polymorphism in the methylenetetrahydrofolate

Table 2. Fiber intake and colorectal cancer risk

	Relative risk ¹ (95% CI) by intake quintile					P _{trend}
	1	2	3	4	5	
<i>Men</i>						
Large bowel	1.00	0.75 (0.62–0.91)	0.73 (0.60–0.89)	0.77 (0.62–0.96)	0.62 (0.48–0.79)	0.002
Colon	1.00	0.76 (0.60–0.96)	0.78 (0.61–0.99)	0.88 (0.69–1.14)	0.64 (0.48–0.86)	0.031
Rectum	1.00	0.75 (0.53–1.05)	0.58 (0.39–0.85)	0.47 (0.30–0.73)	0.52 (0.32–0.84)	0.004
<i>Women</i>						
Large bowel	1.00	1.07 (0.86–1.34)	0.84 (0.66–1.07)	0.97 (0.76–1.24)	0.88 (0.67–1.14)	0.245
Colon	1.00	1.16 (0.90–1.50)	0.88 (0.67–1.16)	1.02 (0.77–1.34)	0.92 (0.68–1.25)	0.361
Rectum	1.00	0.85 (0.53–1.37)	0.77 (0.48–1.27)	0.90 (0.55–1.48)	0.82 (0.48–1.43)	0.639

¹Adjusted for age, ethnicity, family history of colorectal cancer, history of polyps, smoking, BMI, physical activity, aspirin use, multivitamin use, calories, alcohol, red meat, folate, vitamin D, calcium, use of HRT (women).

Table 3. Calcium intake and colorectal cancer risk

	Relative risk ¹ (95% CI) by intake quintile					P _{trend}
	1	2	3	4	5	
<i>Men</i>						
Total	1.00	1.02 (0.86, 1.22)	1.08 (0.89, 1.31)	0.85 (0.68, 1.07)	0.70 (0.52, 0.93)	0.006
Foods	1.00	0.98 (0.82, 1.17)	0.95 (0.78, 1.16)	0.91 (0.74, 1.13)	0.76 (0.59, 0.96)	0.02
Supplements	1.00	0.94 (0.81, 1.09)	0.74 (0.60, 0.90)			0.003
<i>Women</i>						
Total	1.00	0.77 (0.60, 0.97)	0.76 (0.60, 0.97)	0.74 (0.57, 0.94)	0.64 (0.50, 0.83)	0.003
Foods	1.00	0.91 (0.72, 1.14)	0.88 (0.69, 1.11)	0.85 (0.66, 1.08)	0.91 (0.72, 1.17)	0.61
Supplements	1.00	1.00 (0.84, 1.20)	0.82 (0.69, 0.98)			0.02

¹Adjusted for age, ethnicity, smoking, family history of CRC, physical activity, NSAID use, history of polyps, BMI, calories, fiber, HRT use (women only).

reductase (*MTHFR*) gene, namely, a C→T substitution at locus 677, we found a significant interaction of dietary folate intake with the homozygous variant form of this gene. As shown in table 4, individuals with intakes of folate at or below the median are at the same risk whether or not they have the variant allele. On the

Table 4. Odds ratio¹ (95% CI) for the combined effect of *MTHFR* C677T polymorphism and folate intake on colorectal cancer risk²

C677T genotype	Folate intake	
	< median	> median
CC or CT	1.0	0.9 (0.7–1.1)
TT	0.9 (0.6–1.3)	0.6 (0.4–0.9)

¹ Adjusted for age at blood draw, sex and race.

² Based on 822 cases, 2,021 controls.

Table 5. Odds ratio¹ (95% CI) for the combined effect of *MTHFR* C677T polymorphism and alcohol intake on colorectal cancer risk²

C677T	Alcohol intake, g/day	
	0.0	>0.01
CC or CT	1.0	1.1 (0.9–1.3)
TT	0.5 (0.3–0.8)	1.1 (0.7–1.6)

¹ Adjusted for age at blood draw, sex and race.

² Based on 822 cases, 2,021 controls.

other hand, individuals whose intake is above the median have a 40% reduction in risk of colorectal cancer. Intake of alcohol shows a similar interaction (table 5); here it is the non-consumers who have the lower risk (by 50%) compared with alcohol users.

Pancreatic Cancer

Table 6 shows findings for animal products and pancreatic cancer risk. Both red and processed meats, but not dairy products, show a positive association with risk. Because both food groups are major sources of total and saturated fat in the American diet, we examined fat intake by food source as well. As seen in table 7, total fat and saturated fat from meat, but not from dairy foods, was associated with pancreatic cancer. When we analyzed vegetable

Table 6. Intake of animal products and pancreatic cancer risk

Food group ¹	Relative risk ² (95% CI) by intake quintile					P _{trend}
	1	2	3	4	5	
Red meat	1.00	1.08 (0.80–1.44)	1.34 (1.01–1.77)	1.03 (0.76–1.40)	1.42 (1.06–1.91)	0.03
Processed meat	1.00	1.68 (1.22–2.31)	1.87 (1.37–2.57)	1.52 (1.10–2.11)	1.66 (1.20–2.30)	0.07
Pork	1.00	1.16 (0.85–1.58)	1.25 (0.92–1.70)	1.46 (1.08–1.98)	1.48 (1.09–2.00)	<0.01
Beef	1.00	1.08 (0.81–1.43)	1.13 (0.86–1.50)	1.06 (0.79–1.42)	1.25 (0.93–1.68)	0.16
Poultry	1.00	1.11 (0.84–1.47)	1.14 (0.86–1.50)	1.21 (0.91–1.60)	0.91 (0.67–1.24)	0.57
Fish	1.00	0.84 (0.63–1.13)	0.85 (0.63–1.14)	0.88 (0.65–1.18)	0.91 (0.68–1.22)	0.85
Dairy products	1.00	1.04 (0.77–1.39)	1.02 (0.76–1.36)	1.33 (1.00–1.76)	1.06 (0.79–1.44)	0.42
Eggs	1.00	0.78 (0.59–1.05)	1.09 (0.84–1.43)	0.84 (0.63–1.12)	0.93 (0.70–1.22)	0.81

¹As grams per 1,000 kcal/day.

²Adjusted for sex, time on study, age, ethnicity, diabetes mellitus, family history of pancreatic cancer, smoking, and energy intake.

Table 7. Intake of fat and cholesterol and pancreatic cancer risk

Nutrient ¹	Relative risk ² (95% CI) by intake quintile					P _{trend}
	1	2	3	4	5	
Fat	1.00	0.84 (0.64–1.11)	1.05 (0.80–1.37)	0.89 (0.67–1.19)	0.94 (0.70–1.26)	0.79
Fat from dairy	1.00	0.90 (0.68–1.19)	1.00 (0.76–1.33)	1.03 (0.76–1.38)	1.02 (0.75–1.39)	0.66
Fat from red meat	1.00	1.48 (1.11–1.98)	1.10 (0.80–1.50)	1.42 (1.05–1.92)	1.47 (1.08–2.00)	<0.05
Saturated fat	1.00	0.91 (0.69–1.21)	1.07 (0.81–1.41)	0.99 (0.74–1.33)	1.03 (0.76–1.40)	0.68
Saturated fat from dairy	1.00	0.88 (0.67–1.17)	1.01 (0.76–1.33)	1.00 (0.74–1.34)	1.03 (0.75–1.40)	0.63
Saturated fat from red meat	1.00	1.52 (1.14–2.03)	1.07 (0.78–1.48)	1.38 (1.02–1.87)	0.51 (1.11–2.04)	0.04
Cholesterol	1.00	1.13 (0.85–1.49)	1.12 (0.85–1.49)	1.04 (0.78–1.40)	1.09 (0.81–1.46)	0.75

¹As % of energy.

²Adjusted for sex, time on study, age, ethnicity, diabetes mellitus, family history of pancreatic cancer, smoking, and energy intake.

intake in the overall cohort, we found no association with pancreatic cancer (data not shown), but when we examined selected subgroups, statistically significant associations were seen. For example, among current and never smokers, but not former smokers, a statistically significant inverse association was

Table 8. Vegetable intake and pancreatic cancer risk by smoking status

Smoking status		Relative risk ¹ (95% CI) by intake quartile				P _{trend}
		1	2	3	4	
Current	Total	1.00	1.10 (0.69–1.76)	0.89 (0.52–1.51)	0.79 (0.44–1.44)	0.35
	Light green	1.00	0.84 (0.52–1.35)	0.72 (0.42–1.23)	0.70 (0.39–1.24)	0.19
	Dark green	1.00	0.77 (0.48–1.24)	0.69 (0.41–1.15)	0.50 (0.27–0.92)	0.03
	Legumes	1.00	1.20 (0.72–2.00)	0.88 (0.50–1.56)	1.46 (0.83–2.55)	0.38
Never	Total	1.00	0.92 (0.62–1.36)	0.96 (0.65–1.41)	0.62 (0.41–0.95)	0.02
	Light green	1.00	0.94 (0.63–1.41)	0.80 (0.53–1.21)	0.80 (0.53–1.20)	0.25
	Dark green	1.00	0.96 (0.64–1.45)	1.20 (0.82–1.76)	0.69 (0.45–1.06)	0.06
	Legumes	1.00	1.31 (0.88–1.95)	1.05 (0.70–1.59)	0.77 (0.49–1.21)	0.05

¹Adjusted for sex, time on study, age, ethnicity, history of diabetes mellitus, family history of pancreatic cancer, red and processed meat intake, energy intake, BMI, and smoking.

found for total or dark green vegetables (table 8). A similar inverse association was seen for cohort members who were obese, but not for those who were normal weight (data not shown). In another analysis, we explored the relationships of body mass index (BMI) and physical activity to pancreatic cancer risk. Obesity, but not moderate overweight, showed opposite relationships in men and women. As seen in table 9, obesity (BMI ≥ 30.0) is associated with an increased risk in men (RR = 1.51), but a reduced risk in women (RR = 0.65). The findings for physical activity, on the other hand, are null in both sexes.

Discussion

The findings from the MEC on colorectal and pancreatic cancers provide additional support for a direct effect of diet on the risk of these cancers.

Diet and Colorectal Cancer

Several dietary constituents, as well as other lifestyle factors, have been associated with colorectal cancer risk, though only a few have been established with certainty [1]. Factors that increase risk include red and processed meat consumption, alcohol and obesity; the only firmly established protective factor is physical activity, though the evidence is substantial for a beneficial effect of calcium, dairy products and vitamin D [16]. The evidence is more inconclusive

Table 9. Obesity and physical activity in relation to pancreatic cancer risk

	Relative risk ¹ (95% CI)	
	men	women
Body mass index		
Normal weight	1.00	1.00
Overweight	0.99 (0.74–1.33)	0.80 (0.59–1.09)
Obese	1.51 (1.02–2.26)	0.65 (0.43–0.99)
P _{trend}	0.09	0.03
Physical activity		
Quartile 1	1.00	1.00
Quartile 2	1.07 (0.74–1.54)	1.02 (0.71–1.46)
Quartile 3	1.06 (0.73–1.54)	0.99 (0.69–1.43)
Quartile 4	1.24 (0.85–1.84)	0.81 (0.55–1.20)
P _{trend}	0.31	0.36

¹Adjusted for time on study, age, ethnicity, history of diabetes mellitus, family history of pancreatic cancer, energy intake, intake of red and processed meat, smoking, and BMI or physical activity, as appropriate.

for fruits and vegetables, and for other micronutrients, including folate and selenium, as protective factors [16]. Perhaps the greatest controversy has centered on the role of dietary fiber, where the findings from epidemiologic studies have been particularly inconsistent [17]. The possibility of a beneficial effect of dietary fiber is supported by several biological mechanisms [18–20]: (1) fiber shortens bowel transit time and increases stool bulk, diluting the effect of carcinogens; (2) fiber binds intraluminal bile salts, which can be tumor promoters; (3) fermentation of fiber in the bowel reduces fecal pH, which has been associated with lower cancer risk, and (4) fiber intake leads to the production of short-chain fatty acids, shown to inhibit growth of colon cancer cell lines.

The data from 13 cohort studies on fiber in relation to colorectal cancer have been pooled [21]. The results of this analysis showed no effect of fiber after adjustment for a variety of other risk factors. In our analysis [22], the initial findings in women became non-significant after full adjustment for confounders, whereas the inverse association in men persisted. The finding in men is consistent with the results of the large multicentered European Prospective Investigation into Cancer and Nutrition (EPIC), which reported statistically

significant findings in both men and women after adjustment for other risk factors [23, 24]. However, the EPIC analysis did not adjust for the full panoply of risk factors that were included in our analysis and in the cohort pooling project. These findings demonstrate the complexity of dietary relationships to colorectal cancer and the importance of carefully controlling for other risk factors. From stepwise regression analysis, we found that it was the combination of hormone replacement therapy (HRT) use with either cigarette smoking or BMI that weakened the inverse association to non-significance. Unraveling these relationships among risk factors should help provide insights into the etiology of this common cancer.

Another nutritional factor that has been studied with regard to colorectal cancer is calcium, which showed a clear inverse association in our data [25]. Findings from cohort studies have been somewhat inconsistent, several showing inverse relationships in men but not women [26–29]. A recent pooled analysis of 10 cohort studies found an inverse association with calcium and milk consumption and colorectal cancer risk [30], but a randomized clinical trial of calcium and vitamin D in the Women's Health Initiative showed no effect of the intervention on colorectal cancer incidence in postmenopausal women [31]. Our findings with regard to vitamin D intake are similar to other studies which also showed inverse associations in men but no, or weaker, associations in women [26, 27, 32]. The basis for this sex difference may be related to hormonal metabolism, since the vitamin D receptor has been linked with the estrogen receptor system [33, 34]. However, studies limited to dietary sources of vitamin D and cancer may be misleading because of the major contribution to vitamin D levels in the body from endogenous production in the skin [35]. Possible mechanisms to explain a beneficial effect of calcium and vitamin D on colorectal carcinogenesis include the binding of long-chain fatty acids and bile acids in the bowel by calcium, thereby protecting colonic epithelial cells from mutagens, growth inhibition and increased cellular differentiation, and stimulation of apoptosis [36, 37].

A third factor that has generated much recent interest in the study of colorectal cancer is folate, a B vitamin. Folate has a central role in biological methylation and nucleotide synthesis. Indeed, folate is the primary methyl donor in cellular metabolism [38]. Low folate intake could increase colorectal cancer risk by disrupting nucleotide synthesis or intracellular methylation. Several cohort studies have examined dietary folate in relation to colorectal cancer, and most reported an inverse association, though it was weak and non-significant in most studies [39]. A meta-analysis of seven cohort studies found a statistically significant inverse association with colorectal cancer risk for folate from foods, but the association for total folate (i.e., including supplement use) was weak and not significant [39].

Genetic Susceptibility, Folate Intake and Colorectal Cancer

The inconclusiveness of the findings regarding folate intake and colorectal cancer may reflect the failure to consider the influence of genetic susceptibility on risk [12]. Genetic susceptibility refers to the fact that many metabolic genes have variant forms (alleles) that result in measurable functional differences in their enzyme products. The most common form of variation is the single nucleotide polymorphism, a site at which two alternative alleles are observed. A central gene in folate metabolism is 5,10-*MTHFR* which has a common polymorphism, C677T. The T variant produces an enzyme product with reduced activity, and individuals with the homozygous TT genotype appear to have a lower risk of colorectal cancer, especially if they have high levels of folate intake. The reason for this risk reduction is not certain, but may reflect greater ease of nucleotide synthesis and genomic DNA methylation in these individuals [40, 41]. Our results on the *MTHFR* polymorphism [42] show that indeed the risk reduction in individuals with the variant genotype depends on an adequate intake of folate, and is consistent with several other studies in the literature [43–47]. The effect of alcohol is opposite, in that low intake is associated with reduced risk among individuals with the variant genotype. High alcohol intake may deplete folate stores and increase cell proliferation within the colon [48].

A public health issue with regard to colorectal cancer has recently arisen with the decision of the US government to mandate fortification of flour and cereal grain products with folate (in the form of folic acid), beginning in 1998. The rationale for this requirement was the dramatic impact of adequate folate intake in reducing the incidence of neural tube defects in the fetuses of pregnant women. The recommended upper limit of intake of folic acid from fortified foods and supplements is 1,000 $\mu\text{g/day}$, and there is concern that many persons may be exceeding this limit, due particularly to the high use of supplements among US adults [49]. Furthermore, in a recent randomized clinical trial to test the efficacy of supplemental folic acid to prevent the incidence of colorectal adenomas (precursor lesions of adenocarcinomas in the large bowel), there was a suggestion that folic acid might actually increase the risk of colorectal neoplasia [50]. Though unexpected, this finding may not be too surprising, since the effects of folate on carcinogenesis are complex, lowering the risk of initial tumor formation, but promoting the growth of existing cancers [49]. The balance of these competing effects is unknown for the general population at the present time.

Diet and Pancreatic Cancer

Pancreatic cancer has a very poor survival rate and little is known of its causes other than cigarette smoking, which is associated with about a twofold increase in risk. Other less-well-established risk factors include a history of

diabetes mellitus, family history of pancreatic cancer, gender (higher risk in men) and ethnicity (higher risk in African-Americans and Native Hawaiians) [51–54]. Few cohorts have reported on pancreatic cancer and diet, and the numbers of cases have not been large. The MEC analysis included 482 cases, the largest sample size to date. Our finding of a positive association with red and processed meat [55] has been seen in some [56, 57] but not all [58–61] prospective studies. Because we did not see an association with dairy products, we concluded that saturated fat was not the responsible component in these meats, since both food groups are high in saturated fat. The formation of carcinogenic compounds during the cooking or preservation of these foods [62, 63], as suggested earlier with regard to colorectal cancer, offers one possible explanation. Heterocyclic amines and polycyclic aromatic hydrocarbons are carcinogenic in animals and may pose a similar risk in humans [64]. Meats preserved with nitrites and nitrates can also be a source of exposure to N-nitroso compounds, another highly carcinogenic group of compounds in animals [65].

A protective effect of vegetables has been reported in two other cohort studies [60, 66], but most such studies reported null results [57, 58, 67–71]. Although we found no overall association with vegetables, when we looked at subgroups within the cohort, including smokers and overweight/obese persons, we did see an inverse association with total vegetables, and with dark green vegetables in particular [72]. We are not aware of other studies with similar findings. Antioxidants, such as carotenoids [73], or other compounds in vegetables, such as isothiocyanates [73, 74], might show a greater effect in smokers who sustain increased oxidative stress.

Obesity and Pancreatic Cancer

We also found a higher BMI to be a risk factor for this cancer in men, though not in women [75]. Some other cohort studies have also found a positive relationship between BMI and pancreatic cancer [58, 76–79], with the finding restricted to men in a few of them [80–82]. BMI is a measure of obesity, and individuals with greater body fat stores, particularly intra-abdominal fat, may develop insulin resistance, in which tissues become less responsive to insulin. To compensate for the reduced tissue sensitivity to insulin, circulating levels of insulin increase in the body. Since insulin stimulates cell proliferation, while also inhibiting apoptosis, this provides a plausible mechanism for the positive association between obesity and pancreatic cancer risk [83–85]. Furthermore, BMI is a stronger indicator of intra-abdominal body fat stores in men than in women, which may explain why we and others found the association only in men.

An alternative explanation for the association of adiposity with pancreatic cancer risk involves inflammation. Obesity produces a state of chronic low-grade inflammation, possibly related to excessive production of storage lipids

and high circulating levels of glucose, thereby creating a pro-inflammatory oxidative environment [86]. Inflammation, in turn, has been associated with an increased risk of cancer, thought to involve enhanced humoral immunity and associated cytokines [87].

Physical Activity and Pancreatic Cancer

Our null finding regarding physical activity and pancreatic cancer is consistent with most other prospective studies [66, 79, 81, 88–93], though a few did report inverse associations [68, 78, 94, 95]. Thus, the evidence for an association is at best weak. A beneficial effect of physical activity on cancer risk is plausible, however, because, contrary to obesity, it has a favorable effect on glucose metabolism and insulin sensitivity [96, 97].

Conclusion

These studies of gastrointestinal cancers in the MEC and their associations with dietary and related lifestyle variables illustrate the value of a large, diverse prospective cohort to investigate such relationships. Our exposure data to date have relied on recall information from questionnaires, which can be subject to measurement error [14, 98, 99]. However, as noted earlier, differential recall bias should not be a factor in this prospective design. Incident cancers are now accruing in the subset of subjects on whom we collected biospecimens between 2001 and 2006. Future analyses will utilize these specimens to conduct studies of nutritional biomarkers that should overcome some of the limitations of the recall methods from the self-administered questionnaires.

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Mediterranean Food and Diets, Global Resource for the Control of Metabolic Syndrome and Chronic Diseases

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In the last 500 years world agriculture has experienced a revolutionary change. The native biota from the various agricultural zones has been displaced by species which originated in distant lands and were successfully domesticated. These species, transported mostly over land and sea, reached agricultural zones often distant, but climatically similar to those of origin. In practice, the regions that today export more foodstuffs, cultivate species that originated abroad.

Mediterranean Ecosystems in the World

The Mediterranean basin, northern California, central Chile, the Western Cape of South Africa and Southwestern Australia share a Mediterranean climate characterized by cool wet winters and hot dry summers. These five regions have similarities in natural vegetation that are being enhanced by the increasing level of biotic exchange between the regions as time passes since European settlement in each region [1]. These are the five terrestrial ecosystems described in the world and constitute the Mediterranean biome.

The Mediterranean ecosystems are climatically controlled and have distinctive vegetation. They represent less than 2% of the emerged land yet they support 20% of the plant species on earth. Mediterranean climate is a dry-summer subtropical type climate as defined by Köppen [2] who recognized the five regions. The Mediterranean ecosystems are localized on the western coasts of

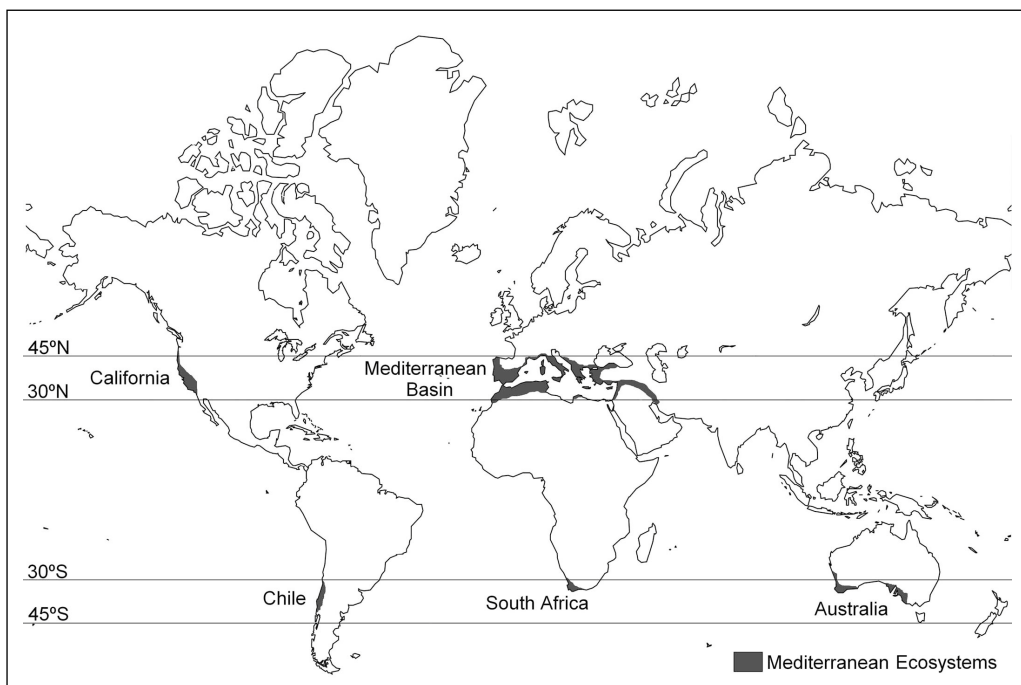


Fig. 1. World Mediterranean ecosystems. The five main ecosystems recognized following Köppen's climate definitions [2].

continental landmasses, at latitudes comprised between 30 and 45°, north or south of the equator (fig. 1).

Mediterranean climate and Mediterranean ecosystems have a restricted distribution and they are also limited in time since the Mediterranean climate developed for the first time in the Pleistocene. The Mediterranean climate depends to a considerable extent on the existence of cold ocean currents; therefore it is dependent on their preservation. If world climatic changes eliminate them, the Mediterranean climate will disappear as a transient episode on a geological scale [3].

In these five areas, the Mediterranean biome is characterized by evergreen or drought deciduous shrublands. The Mediterranean maquis in the old world is the same as the chaparral of southern California, the Chilean matorral, South African fynbos and the Australian mallee scrub communities. Also there is frequently a high degree of endemism in the flora and fauna, due to the limited

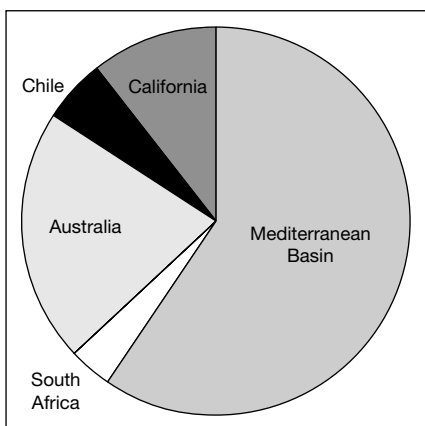


Fig. 2. Proportional distribution of indigenous flora among the five main Mediterranean ecosystems [3].

extent and isolation (almost island-like) of these areas of Mediterranean biome. This isolated condition has some advantage for the agriculture, especially in terms of plague control. The proportional distribution of the Mediterranean indigenous flora among the five ecosystems is shown in figure 2.

The conversion to agricultural production, also recognized as the European invasion, has had great impact in the local flora and fauna of Mediterranean ecosystems.

Agricultural production resorts to a tiny fraction of the existing plant and animal species. Pre-European mammal fauna and native vegetation, in all Mediterranean ecosystems, have been profoundly impacted by agriculture with great loss of diversity.

Mediterranean Agriculture

Origins of Mediterranean Agriculture

Humans created agricultural settlements some 8,500 years BC, in a process that took place in the Fertile Crescent, the land between the Tigris and Euphrates rivers, in Mesopotamia, that also extends to the Mediterranean Sea, in what corresponds to the eastern part of the Mediterranean basin ecosystem. There is evidence that this process also occurred, approximately at the same time or later, in China, in the Highlands of New Guinea, Mexico, the Andes, the southeastern United States, Ethiopia, Africa's, Sahel zone and tropical West Africa. But none of these original agricultural settlements developed inside

Mediterranean ecosystems. These, in fact, would later receive most of its domesticated species from the Mediterranean basin Mediterranean ecosystem.

The process originated in the Fertile Crescent gave birth to Middle Eastern civilization; plant and animal domestication, irrigation and new tools led to the agricultural revolution and the transformation of hunter-gatherers into a more sedentary and socially complex permanent society. Agriculture developed in the narrow swath of hills extending only from southeast Turkey to western Iran. Food production slowly extended westwards reaching the Mediterranean basin in 2,000–3,000 years later. In contrast to native flora and fauna, species domestication concentrated in very few species. There is something like 200,000 species of higher plants and some 4,000 species of wild mammals around the world. Some 150 mammals could be considered candidates for domestication, actually only 14 became valuable domestic animals; of those 14, 13 were species of the Eurasian continent and one, the Llama, the only big animal mammal domesticated in the New World. Around 850 BC, hunter-gatherers of the Fertile Crescent assembled a package of 8 valuable crops, founder crops, providing them with carbohydrate and protein, fat and fiber and they also assembled a package of 4 valuable domestic animals – cows, sheep, goat, pig and later horses – that provided them with meat and hides and leather and milk and traction [4].

The west-east axis of the Eurasian land mass, as well as of the Fertile Crescent, permitted crops, livestock and people to expand at the same latitude without having to adapt to new day lengths, climates and even diseases. In contrast, the north-south orientation in the Americas, Africa and the Indian subcontinent, probably slowed the diffusion of agricultural innovations, accounting for the head start some societies had on others in the march of human history. For example, wheels were invented in Mesoamerica and llamas were domesticated in the central Andes by 3000 BC, yet 5,000 years later the Americas' sole beast of burden and sole wheels had still not encountered each other. In a similar way, iron metallurgy and pottery reached the Sahel zone, north of the equator, at least as early as they reached Western Europe. However, pottery reached the southern tip of Africa around AD 1 and metallurgy arrived there later, from Europe, on ships [4].

Genetic Impact of the Agricultural Revolution in Humans

A general idea, which considers the rate of adaptive mutations in humans, is that in the last 10,000 years the genetic program in humans has not changed very much. In this line of ideas it is assumed that the Neolithic human metabolic capacities have not changed very much, rendering the Paleolithic diet, also referred as hunter-gatherer diet, a model of the diet which our organism can best handle or is better adapted to. However, recent data on the convergent evolution of human lactase persistence in Africa and Europe due to strong

selective pressure resulting from shared cultural traits-animal domestication and adult milk consumption, indicates that apparently man has experienced genetic adaptation to the changing environment in the time that followed the agricultural revolution [5]. A single nucleotide polymorphism in the gene encoding lactase is associated with the ability to digest milk as adult (lactase persistence) in Europeans. In Africans there are identified three single nucleotide polymorphisms that are associated with lactase persistence and that have derived alleles that significantly enhance transcription from the lactase promoter in vitro. All these single nucleotide polymorphisms originated on different haplotype backgrounds. The evidence is consistent with a selective sweep over the past approximately 7,000 years [5–7]. That these changes occur in Central Africa and in Central Europe, allow us to understand why in South American countries genetically linked to Spain, not to Central Europe, lactase deficiency is highly prevalent in adults. If adaptation for milk consumption has been possible, the question now is to know if other adaptive changes have also occurred, thus making the Paleolithic diet a model with limitations.

Some Contemporaneous Characteristic Mediterranean Agricultural Products

Present-day agricultural production in Mediterranean ecosystems is largely indebted to the Fertile Crescent contribution. Yet the contribution from other areas are fundamental like corn from Mexico; tomatoes and potatoes from the Andes; chicken, fruits and rice from China; citrus from South-East Asia; spices from Asia and other places.

Mediterranean agriculture is defined by its products like cereals, vegetables, fruit, olive oil and wine. These products are crucial for the Mediterranean diets, together with marine food. The top ten vegetable foodstuffs in Mediterranean basin are olive, olive oil, garlic, lemon, orange, tomato, chickpeas, eggplant, peppers and fennel. Mediterranean agriculture and geography also determined the type of cattle, principally sheep and goat, leading to a diet low in red meat and butter, but rich in cheese and yogurt.

Olive oil is perhaps the most representative product of Mediterranean agriculture. The world distribution of olive tree plantations shows excellent correlation with the Mediterranean ecosystems. Only 0.5% of the world area of olive trees occurs in countries without Mediterranean climate [8]. Countries from the Mediterranean basin produce 98% of the olive oil in the world, and consume 90%. Spain, Italy, Greece, Tunisia and Turkey are the main Mediterranean olive oil producers (table 1). The production from the other four Mediterranean ecosystems accounts approximately for 0.5% of world production. However, Australia and Chile have increased tenfold their production in the last decade. In Chile olive plantations are growing even faster in the last 2–3 years.

Table 1. World olive oil production by country (1,000 tonnes/year)

Country/region	1996–2000	2006	Change, % 2006/1996–2000
Mediterranean basin	2,319.8	2,532.7	9.2
Spain	891.8	1,108.7	24.3
Italy	527.5	603.0	14.3
Greece	417.6	370.0	–11.4
Tunisia	183.6	170.0	–7.4
Turkey	131.0	160.0	22.1
Others in the Mediterranean basin ¹	168.3	121.0	–28.1
California, USA	0.9	1.0	11.1
Australia	0.7	8.0	1,100.0
Chile	0.2	2.4	1,100.0
South Africa		1.0	
Mediterranean ecosystem total	2,321.5	2,545.1	9.6
World total	2,480.6	2,573.5	3.7
Mediterranean ecosystem/total, %	93.6	98.9	

¹Others in the Mediterranean basin: Morocco, Algeria, Portugal, Palestine, Lebanon, Croatia, France, Israel, Serbia and Montenegro, Slovenia, and Cyprus. From the International Olive Oil Council (IOOC).

The olive was first domesticated somewhere in what is now Syria, Lebanon and Israel, more than 6,000 years ago [9]. From there it traveled to Egypt, Asia Minor and finally Greece; it was found in Crete and the Greek mainland in the fourth millennium BC. It appears that the Phoenicians introduced it to southern Italy and then the entire Mediterranean. By the end of the Roman Empire, olive trees grew and olive oil was made throughout the Mediterranean region. The Spanish introduced the olive to America in 1540. The tree was taken northwards by Jesuit and Franciscan missionaries in the 18th century, and grown in what is now the Baja California region of Mexico and in California in the United States [10]. The tree was recorded in Desert Peru in 1560 and later became established in northern Chile and Argentina, sustained by irrigation in Peru and Argentina [11]. In Chile, olive production extended from the Limarí valley in the north to the Bio-Bio river in the south. In 1952 there were some olive plantations but only in 1990 commercialization strategies started. Now Chile produces only extra virgin olive oil and its present production is approximately 2,400 tonnes per year.

Curiously, olive oil has not become part of the diet in the Latin America in spite of the presence of Spaniards and Portuguese. Possibly olive oil was not an important part of the diet of the early Iberian settlers in their home countries. There is some evidence to suggest that consumption in the past was lower than at present [8]. In Spain the olive industry was neglected especially after the expulsion of the Moriscos in 1609, and experimented expansion only from the 1880s [12].

Although there is abundant evidence of the production and consumption of olive oil in ancient Greece and Rome, there is no evidence on the quantities produced and consumed, and what proportion was used for non-food purposes. Also in the 16th century, Crete estimated production would provide per capita consumption much below present level [13].

Wine is also an emblematic product from Mediterranean agriculture. A world map illustrating the principal wine-producing regions in the world looks remarkably similar to figure 1, the map of the Mediterranean ecosystems, with the addition of some other wine-producing regions in Argentina, in China, eastern USA and others. Mediterranean agricultural products come principally, but not exclusively, from Mediterranean ecosystems.

Almost 75% of the world wine production occurs in the Mediterranean ecosystems. Of this production, three quarters occur in the Mediterranean basin ecosystem and the rest in California, USA, Australia, South Africa and Chile. As shown in table 2, the contribution from Chile and Australia increases rapidly while South Africa and Europe maintain or decrease production. Wine shows, just as olives, that from an agricultural point of view, the Mediterranean ecosystems outside of the Mediterranean basin, experience an active process of modification, increasing the production of Mediterranean agriculture products. For the time being, South Africa appears to be the slowest to adapt.

Some investigators place the discovery of winemaking, or at least its development, in the southern Caucasus. It is also thought that the domestication of wine grape (*Vitis vinifera*) initially occurred within this area. The earliest firm evidence for winemaking to date is from the Neolithic period site called Hajji Firuz Tepe, Iran, where a deposit of sediment preserved in the bottom of an amphora proved to be a mix of tannin and tartrate crystals, familiar to anyone who drinks wine from corked bottles today. Hajji Firuz Tepe has been dated to 5400–5000 BC [14].

Grape growing and winemaking traveled southward from the Caucasus to Palestine, Syria, Egypt, and Mesopotamia. Wine consumption and its socio-religious context, then helped to expand winemaking around the Mediterranean.

European grape vines were introduced to America during Columbus' second voyage, but the first attempts to grow grapevines in the Caribbean region failed, mainly due to climatic problems. In 1519, the higher altitude of Mexico

Table 2. World wine production by country (1,000 hl/year)

Country/region	1996–2000	2005	Change, % 2005/1996–2000
Mediterranean basin	165,165	156,440	–5.3
France	56,271	52,004	–7.6
Italy	54,386	50,556	–7.0
Spain	34,162	34,750	1.7
Portugal	6,828	7,254	6.2
Greece	3,832	4,093	6.8
Hungary (southwest)	4,126	2,900	–29.7
Croatia	2,096	1,900	–9.4
Others in the Mediterranean basin ¹	3,464	2,983	–13.9
California, USA	19,457	26,110	34.2
Australia	7,380	14,000	89.7
South Africa	7,837	8,410	7.3
Chile	5,066	7,890	55.7
Mediterranean ecosystems total	204,905	212,850	3.9
World total	270,826	286,175	5.7
Mediterranean ecosystems/total, %	75.7	74.4	

¹Others in the Mediterranean basin: Macedonia, Slovenia, Morocco, Tunisia, Turkey, Cyprus, Lebanon, Bosnia-Herzegovina, and Israel. From The Wine Institute.

allowed the first successful planting of grapevines in America. In the middle of the 16th century, grapevine reached Cuzco from Mexico or directly from Spain. And then the vines spread to Chile. Chilean wine exports began at the end of colonial period; the first data corresponds to the 5-year period 1784–1789 and the destination was New Spain, as Mexico was known during that period. In 1851, there was a spectacular transformation of the Chilean winemaking industry. Grape growers decided to import from France cuttings of winemaking varieties, Cabernet Sauvignon, Cot, Merlot, Pinot Noir, Sauvignon, Semillon and Riesling. These varieties adapted very well to the Chilean Mediterranean climate and are the only pre-Phloxera clones that exist in the world. Today, Chile is the 10th wine world producer and the 5th wine world exporter [15].

Wine consumption dates to 5,000 years BC. Hippocrates considered the ‘father of medicine’, used wine as medicine 2,500 years ago. Wine was common in classical Greece and Rome. In medieval Europe, the Christian Church was a staunch supporter of wine which was necessary for the celebration of the Catholic mass, whereas wine consumption was forbidden in the Islamic civilization. Strikingly, some Muslim chemists pioneered the distillation of wine,

which was used for other purposes, including cosmetic and medical uses. In Greece, the earliest evidence of winemaking is a stone foot press at Vathipetro, a Minoan villa on Crete, dated to 1600 BC.

Today the highest average consumption of wine per capita and per year is seen in the traditionally producer countries. However these countries, in general, are undergoing a decline in their individual levels of yearly consumption. In 2004, France 55 l/per capita; Italy 49 l/per capita; Portugal 48 l/per capita; Argentina 29 l/per capita; Spain 34 l/per capita; Chile 16 l/per capita; Greece 30 l/per capita, and Romania 26.0 l/per capita. In other countries traditionally producers and consumers of wine, a stabilization or growth in their individual consumption is observed. It is the case for Germany and Austria, stabilized at levels close to 24 and 30 l/per capita; Switzerland close to 42 l/per capita; Hungary with 31 l/per capita, and Croatia with 42 l/per capita. In North America consumption levels have increased more significantly since 2002, to reach 8.2 l/per capita in the USA and 11.4 l/per capita in Canada. In Australia, consumption reached 21.9 l/per capita in 2004 and in South Africa stabilization was observed in 2004 with 7.8 l/per capita. In contrast, countries that are not wine producers show, in general, a growing trend of consumption, as in the United Kingdom, 18.0 l/per capita in 2004 or Norway, Finland and Iceland [16].

On the whole, vegetables and fruits are central to Mediterranean agriculture and Mediterranean diet, yet in contrast to olives and wine, vegetables and fruits are produced in various agricultural ecosystems. The Mediterranean ecosystems accounted for 23% of the world production in 1989–1991 and only 16% in 2004. Production increases more rapidly outside the Mediterranean ecosystems with some remarkable exceptions, such as Chile, Australia, Algeria and Morocco (table 3). Again, as for olives and wine, the Mediterranean ecosystems away from the Mediterranean basin experiment an accelerated growth, clearly exemplified by the growth of production in Chile. The productivity of various countries, expressed as food production per capita, is growing outside the Mediterranean basin, with the exception of Bosnia and Herzegovina and Macedonia, which also exhibit marked growth (table 4). Again the dynamic development of the four extra Mediterranean basin ecosystems can be appreciated.

An Economical Comparison among the Mediterranean Ecosystems

The five Mediterranean ecosystems have a very similar climate, the basis of their definition. When considering their agricultural characteristics, more specifically agribusiness economic parameters that allow estimating their competitiveness, marked differences are apparent. In a preliminary study made by Rojas and Tomic [17] to estimate the competitiveness among the five ecosystems, three factors were considered: salaries, energy price, and land price. The calculations were made specifically for Valencia in Spain, Western Cape in South Africa, Western

Table 3. World fruit and vegetable production by country (1,000 tonnes/year)

Country/region	1989–1991	2004	Change, % 2004/1989–1991
Mediterranean basin	139,295	163,834	17.6
Turkey	27,080	36,046	33.1
Italy	32,004	34,276	7.1
Spain	24,529	29,401	19.9
France	18,189	19,843	9.1
Morocco	5,223	7,810	49.5
Greece	8,076	7,782	–3.6
Algeria	2,900	5,151	77.6
Others in the Mediterranean basin ¹	21,294	23,525	10.5
California, USA	35,387	43,572	23.1
South Africa	5,801	7,769	33.9
Chile	4,539	7,407	63.2
Australia	3,850	5,486	42.5
Mediterranean ecosystem total	188,871	228,069	20.8
World total	812,733	1,383,649	70.2
Mediterranean ecosystem/total, %	23.2	16.5	

¹Others in the Mediterranean basin: Portugal, Hungary, Tunisia, Israel, Lebanon, Yugoslavia, Serbia and Montenegro, Bosnia and Herzegovina, Croatia, Macedonia, Slovenia, Palestine, and Cyprus. From FAO Stat, California Agricultural Resource Directory 2006.

Australia, Central Valley in Chile, and California. The data was normalized and equal weight was given to the three factors. As shown in figure 3, for Mediterranean agriculture agribusiness potential, the leading country is South Africa, followed by Chile. Low salaries sustain South Africa competitiveness and hinder the position for California. The high cost of the land decreases competitiveness in Spain. More sophisticated agribusiness analysis are possible, yet this preliminary calculation stresses the large differences among the various Mediterranean ecosystems, an analysis that can also be extended to the various regions of the Mediterranean basin Mediterranean ecosystems, comparing north and south of the Mediterranean, as well as areas from the western and eastern countries.

Mediterranean Diet and Health, an Epidemiological Theory

For centuries the practice of medicine has considered food as a key determinant of health, a fact recognized by well-known quotes from both occidental

Table 4. Per capita food production

Country	1996	2005	Change, % 2005/1996
Bosnia and Herzegovina	95.77	116.61	21.8
Chile	99.96	113.20	13.2
Macedonia	97.94	104.29	6.5
Hungary	99.51	105.24	5.8
Australia	91.64	96.85	5.7
Israel	99.88	105.49	5.6
South Africa	102.12	105.79	3.6
USA	97.92	100.38	2.5
Turkey	103.33	103.94	0.6
Croatia	90.98	90.39	-0.6
Italy	98.88	97.80	-1.1
Slovenia	104.04	102.42	-1.6
Spain	93.56	90.70	-3.1
Greece	99.01	95.00	-4.1
Morocco	121.41	115.37	-5.0
France	102.03	92.80	-9.0
Portugal	100.69	90.95	-9.7
Tunisia	124.07	104.18	-16.0
Lebanon	117.39	97.96	-16.6
Cyprus	107.59	86.04	-20.0

From FAOSTAT, FAO indices of agricultural production relative to the base period 1999–2001. Disposable production for any use except as seed and feed.

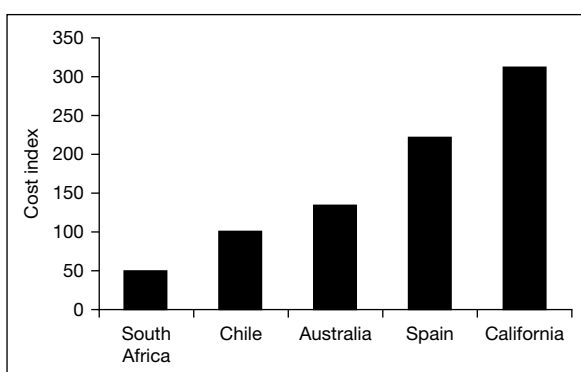


Fig. 3. Mediterranean agriculture agribusiness potential, calculated as a cost index which identifies relative business opportunities for the five different areas [17].

and oriental medicine. The Seven Countries Study constitutes the first nutritional epidemiological investigation that provided solid data for cardiovascular disease rates in different populations, a study designed to investigate the relationship between diet and cardiovascular disease [18]. In this study the results for all-cause death rates in Greece, Japan and Italy were quite favorable compared with the USA, Finland, the Netherlands, and former Yugoslavia; the results also showed a lower incidence of coronary disease after a 5-year follow-up for the same countries that exhibited low mortality. The diet consumed by the Mediterranean cohorts studied was associated with a very low incidence of coronary heart disease, and was called *Mediterranean diet* by Keys [19].

Following the Seven Countries Study, the Mediterranean diet has been singled out as a healthy diet. Scientific evidence increasingly supports this epidemiological theory which defines the relationship among a certain variety of foods and chronic diseases. Additional studies later confirmed the association of Mediterranean diet with decreased incidence and prevalence of chronic diseases, mainly CVD, in countries where it was consumed. There are food peculiarities for the different populations in the Mediterranean basin; however, beyond the apparent differences, there are nutritional characteristics common to all or most of the diets in the Mediterranean region. The Mediterranean diet is characteristically low in saturated and high in monounsaturated fats (olive oil), low in animal protein, rich in carbohydrates, and rich in vegetables and leguminous fiber. People with Mediterranean diet eat a relatively large amount of fish and white meat, abundant fruits and vegetables, and a low amount of red meat; they also drink moderate amounts of red wine [20]. The health benefits of Mediterranean diets have been attributed, at least in part, to the high consumption of antioxidants provided by fruit, vegetables and wine and to the type of fat, rich in monounsaturated and ω -3 fatty acids from vegetables and fish, and especially to a balanced ω -6/ ω -3 fatty acid ratio, as is found in the traditional diet of Greece prior to 1960 [20].

Several studies have used dietary scores as instruments to measure adherence to Mediterranean diet and have reported an inverse association with overall mortality [21–27]. These studies are mostly made on Mediterranean populations. One of these studies, published in 1995, included 182 elderly (>70 years old) residents of three rural Greek villages, followed up for approximately 5 years [28]. Diet was assessed with a validated extensive semiquantitative questionnaire on food intake. The authors used the food groups recommended by Davidson and Passmore [29] to design the score; however, they combined starchy roots with cereals and did not consider sugars and syrups for which, so far, no systemic health implications had been documented over and beyond their contribution to net energy intake. The traditional Mediterranean diet was also defined in terms of these food groups with the addition of moderate intake

of ethanol, and the score was built in terms of eight characteristic components: high monounsaturated/saturated fat ratio; moderate ethanol consumption; high consumption of legumes; high consumption of cereals (including bread and potatoes); high consumption of fruits; high consumption of vegetables; low consumption of meat and meat products, and low consumption of milk and dairy products. They used as cut-off points the corresponding median values specific for each sex. The hypothesis was that an individual diet with more of these components was beneficial whereas a diet with fewer of these components would be less healthy. In the sample studied, 34 subjects (19% of the total) had two or fewer of the eight desirable dietary components, whereas 104 subjects (57%) had four or more of the eight desirable components. The results showed that one unit increase in diet score was associated with a significant 17% reduction in overall mortality.

Another prospective investigation by the same group of authors analyzed a population of 22,043 Greek adults, 20–86 years old, during a median of 44 months of follow-up [21]. In this case, adherence to the traditional Mediterranean diet was assessed by the same scale developed by Trichopoulou et al. [28], but revised to include fish intake. A value of either 0 or 1 was assigned to each of the nine indicated components with the use of the sex-specific median as the cut-off. For each beneficial component (vegetables, legumes, fruits and nuts, cereal, and fish), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1. For each component presumed to be detrimental (meat, poultry, and dairy products which are rarely non-fat or low-fat in Greece), consumption below the median received a value of 1, and for consumption at or above the median, a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g/day and to women who consumed between 5 and 25 g/day. For fat intake, the ratio of monounsaturated lipids to saturated lipids was used. Results showed that a higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality, in deaths due to coronary heart disease and deaths due to cancer. Associations between individual food groups contributing to the Mediterranean diet score and total mortality were generally not significant.

To apply the score to non-Mediterranean populations, Trichopoulou et al. [25] substituted monounsaturated lipid with the sum of monounsaturated and polyunsaturated lipids in the numerator of lipid ratio. These authors investigated the relation of the modified score with overall mortality in a large sample of elderly Europeans participating in EPIC (the European Prospective Investigation into Cancer and Nutrition Study), 74,607 men and women aged 60 or more, from nine European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, UK). The conclusion was that the Mediterranean

diet, measured with a modified score applicable across Europe, was associated with increased survival among older people. In another investigation in elderly Europeans, the HALE Project, that includes 1,507 apparently healthy men and 832 women, aged 70–90 years in 11 European countries, the conclusion was that adherence to a Mediterranean diet and healthful lifestyle is associated with more than 50% lower rate of all-causes and cause-specific mortality [23].

Studies carried out in other parts of the world to evaluate Mediterranean diet adherence, for example in Denmark [30] and Australia [31, 32], also showed that a greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.

Japanese diet also appears to be very healthy in the Seven Countries Study. Japanese are known for their longevity or healthy life expectancy; they consume large amounts of cereals (rice), vegetables and fruits, and fish, but characteristically they have a much lower intake of energy and oils [33]. The Japanese dietary pattern score was also associated with a decreased risk of cardiovascular disease mortality [34]. In fact, in Okinawa, the island of longevity in Japan, the population has a special diet with a low caloric intake, a fact used as an argument to support the calorie restriction longevity hypothesis in humans [35].

The Case of Chile

The Mediterranean characteristics of the Chilean agriculture suggest that the Chilean diet shares characteristics with the Mediterranean diets. In fact, life expectancy for Chile (WHO, 2005) was the highest in Latin America with 77.5 years, followed by Costa Rica and Cuba with 77.3 years. Also the age standardized mortality rate for cardiovascular diseases in Chile is relatively low, 165 (per 100,000 population, WHO 2002) similar to Mexico, higher than France and Spain with 118 and 137, respectively, but lower than the USA which was 188.

A systematic analysis to correlate diet and chronic diseases mortality in Chile is hindered by the lack of national dietary surveys; the last was done in 1974. Using FAO food data, Rozowski and Castillo [36] compared the Chilean and Mediterranean diets (mainly those from Spain, Italy, and Greece). Their conclusion was that although the Chilean diet seems close to the traditional Mediterranean diet of the 1960s, there is concern about changes that are transforming it to a western type one. Characteristic hot dishes like '*charquican*' and '*porotos granados*' contain cooked vegetables, corn and or potatoes, sometimes ground meat, and are prepared on a base that contains onion, oregano, cumin, black pepper, paprika and garlic, sautéed in oil. Traditionally Chilean dishes are

served with fresh parsley and cilantro that are green leafy herbs with antioxidants and some ω -3 fatty acids. Fish may have a similar preparation, like in '*caldillo de congrio*', a soup prepared with conger fish, potatoes, carrots, onions, red and green peppers, garlic, oregano, chili pepper and parsley, a dish that contains a balanced supply of fatty acids. Two frequent salads are tomato with onion and celery with avocado and nut, dressed with oil, salt and lemon juice. *Pebres*, rich antioxidant mixtures, are prepared with onion, garlic, tomato, parsley, chili, and cilantro, all ingredients cut in small pieces, dressed with vinegar, salt and oil; *pebres* are used as dressing and also with bread.

The traditionally Chilean food is undoubtedly a Mediterranean diet, yet, as with other countries, fast food is destroying traditional cuisine and habits. Unfortunately for Chile, carbonated drink consumption in the country is a record, almost 100 liters per person per year, with only 10% mineral water. In contrast, olive oil consumption in Chile is low, but increases very rapidly. Another source of monounsaturated fatty acid and antioxidants which Chileans consume at a growing rate is avocado, presently at 3.5 kg annual per capita consumption, second after Mexico the top avocado consumer with 9 kg. These numbers are still far from the 10–20 kg of olive oil per capita consumption in the top Mediterranean olive oil-producing countries.

The Global Burden of Chronic Diseases and Mediterranean Diet Intervention Studies

Chronic diseases are today in the focus of health protection organizations in the world. Metabolic syndrome, a high-risk condition for chronic diseases, affects 10–30% of the population in the world. More research on its pathogenesis and control is obviously needed. The metabolic syndrome is a cluster of metabolic risk factors associated with a high risk of cardiovascular disease [37]. The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) clinical definition of the metabolic syndrome requires the presence of at least three abnormal risk factors, among a set of five: abdominal obesity, high plasma triacylglycerol, low plasma HDL, high blood pressure, and high fasting plasma glucose. The molecular mechanism responsible for the metabolic syndrome is not known. Since Mediterranean diet is associated with a reduced risk of cardiovascular disease and all-cause mortality, the mechanism for this effect could be related to the pathogenesis of the metabolic syndrome.

The relationship between Mediterranean diet and metabolic syndrome has been investigated in several studies. Some components of this diet have shown a beneficial effect on the development of metabolic syndrome or its component

risk factors. Indeed, fish and ω -3 polyunsaturated fatty acids intake, which are principal components of the Mediterranean diet, have been associated with a lower risk of cardiovascular disease [38]. A large body of scientific evidence has shown that Mediterranean diet improves blood pressure and lipid profile, decreases risk of thrombosis, improves endothelial function, and insulin resistance, and reduces plasma homocysteine concentrations [39–44]. Pitsavos et al. [45] studied the effect of the consumption of the Mediterranean diet on coronary risk, in subjects with the metabolic syndrome. They studied 848 patients with a first event of an acute coronary syndrome and 1,078 people without any evidence of cardiovascular risk, from all Greek areas, and observed that the Mediterranean diet was associated with a 35% reduction of the coronary risk in subjects with metabolic syndrome. Esposito et al. [46] performed an intervention study in patients with the metabolic syndrome, to assess the effect of a Mediterranean diet on endothelial function, vascular inflammatory markers, and persistence of metabolic syndrome risk factors in these patients. They observed that volunteers that consumed a Mediterranean diet had a reduction in the prevalence of the metabolic syndrome and its associated cardiovascular risk. Particularly at the end of the 2-year experimental intervention period only 44% of the patients in the Mediterranean diet group still had three or more risk factors characteristic of the metabolic syndrome, while 87% of the patients in the control group still had metabolic syndrome.

Actually there is an ongoing intervention study in Spain, the PREDIMED (*Prevención con Dieta Mediterránea*). It is a parallel-group, multicenter, randomized, single-blinded trial check aimed at assessing the effects on the risk of major cardiovascular events of two intensive behavioral counseling and nutrition education interventions in comparison with a control group. Both intervention groups are assigned a traditional Mediterranean diet. In one of these two groups the diet is supplemented with extra virgin olive oil (32 g/day) and in other with 30 g/day of nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds). The control group participants do not receive education on the Mediterranean diet and are given advice on how to follow a low-fat diet. 12,150 asymptomatic persons from 55 to 80 years of age at high cardiovascular risk were assigned to these three equal size groups. They will be followed up for clinical outcomes during a median time longer than 4 years, by the primary care physicians who recruited them for the study. The primary endpoint will be a composite outcome of cardiovascular events (cardiovascular death, myocardial infarction, and stroke).

Preliminary results of the PREDIMED study were published recently. These results concern a subgroup of 772 asymptomatic persons, 55–80 years of age, with high cardiovascular risk, who were recruited from October 2003 to March 2004 in Spain [47]. Measurements made were body weight, blood pressure,

lipid profile, glucose levels, and inflammatory molecules. After 3 months of intervention, the results showed that the two variants of Mediterranean diet supplemented either with olive oil or nuts, produced beneficial changes in most outcomes. Compared with the low-fat diet, significant changes were found in the Mediterranean diet with olive oil group and in the Mediterranean diet with nuts group, changes in plasma glucose levels; in blood pressure; in HDL cholesterol and cholesterol/HDL cholesterol ratio. Therefore, Mediterranean diets supplemented with olive oil or nuts are better than a low-fat diet to reduce metabolic syndrome risk factors.

Food at Work and Mediterranean Diet Constitute a Valid Strategy for the Control of Chronic Diseases

Food at Work

The work place could play for adults a role similar to that of the school for children, when nutrition education initiatives are considered. Governments, employers and employees all can benefit from an effective ‘food at work’ policy, yet very often this possibility is not adequately considered. The International Labour Office in Geneva has sponsored the publication of a book that reviews this situation and suggests approaches to improve food at workplaces with the purpose of reducing chronic diseases [48].

Education is a key element for effective food at work interventions and the Mediterranean diets on the whole constitute an objective healthy food pattern, based on scientific evidence. The health protection capability of these diets can be easily illustrated to the workers and, contrary to the often held idea that Mediterranean diets are expensive, history shows that they correspond to the food pattern of economically restricted populations.

In addition to Mediterranean diets as an ideal model of healthy diet – at least for the countries located in and around the five Mediterranean ecosystems – it is also necessary to represent objectively chronic diseases in a more motivating and unified form than simply saying that death is more frequent for cardiovascular, hypertensive, diabetic or obese persons; metabolic syndrome is an alternative. A valid strategy, with emphasis on prevention, is to promote Mediterranean diet for the control of metabolic syndrome, a condition that anticipates chronic diseases and is easily monitored in order to follow the effectiveness of preventive measures [49].

Food at Work Mediterranean Diet Intervention in Chile

In Chile one fifth of the workers, approximately 1,200,000, receive food at the work place, predominantly lunch. With the purpose of evaluating the feasibility

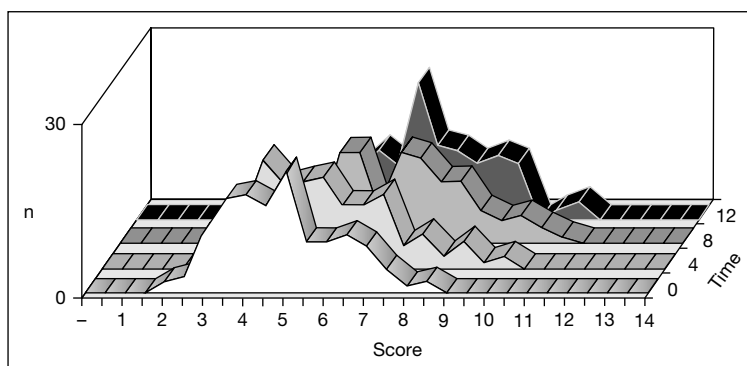


Fig. 4. Evolution of the Mediterranean diet score in volunteer workers that participated in a 12-months ‘food at work’ diet mediterraneanization intervention study. Graphs correspond to score value frequency distribution at 0, 4, 8 and 12 months of the study.

of Mediterranean diet food at work interventions in Chile and in general, we performed a pilot study for which the detailed proceedings and results will be published elsewhere. In summary, this study was made to generate a database that should allow the optimization of future interventions on the basis of scientific evidence and local experience.

A small industry was selected (a heavy machinery maintenance and repair workshop) with approximately 180 workers, 88% men. The industry owners and administrators, the local workers union and the canteen contractor accepted to collaborate for the intervention. The canteen contractor, who received USD 3.75 for each lunch, accepted to modify the food offer, with emphasis on diet mediterraneanization, exceptionally keeping the possibility of the previous diet for those not convinced with the change. The participants were informed about Mediterranean diets and health, and were informed of the relevance of the metabolic syndrome as a risk condition for chronic diseases. All the employees or workers were invited to participate, 90% of them accepted and 68% of these completed all the controls programmed for the 12-month intervention period. At months 0, 4, 8 and 12, clinical, biochemical, anthropometric and nutritional evaluations were performed. A specially designed Mediterranean diet score that evaluates 14 items was applied by nutritionists, giving an overall measure of the evolution of dietary habits, since it covered food at work plus food during the rest of the day and during holidays. As shown in figure 4, there is an apparent continuous improvement in the degree of mediterraneanization of the workers’ diet during the intervention; median score values for months 0, 4, 8 and 12 were

Table 5. Macronutrients consumption, from 3-day food records, in male volunteers

	Month 0	Month 12	p value for difference
Calories	2,251 ± 656	2,091 ± 550	0.046
Carbohydrates, %	54.2	54.3	
Proteins, %	13.8	14.4	
Total fats, %	31.9	31.3	
Fiber, g	19.5 ± 6.2	21.5 ± 7.7	0.011
Fat M/S ratio	1.1 ± 0.3	1.5 ± 0.5	0.0001
Fat ω -6/ ω -3 ratio	23.9 ± 12.0	9.8 ± 6.2	0.0001

4.8, 5.5, 7.0, and 7.0, respectively. Mean score values \pm SD for these time points were 4.8 ± 1.4 , 5.6 ± 1.6 , 6.7 ± 1.9 , and 7.4 ± 1.5 . From 3-day food records, macronutrient intake and other parameters were measured. As shown in table 5, after 12 months there was a slight decrease in caloric intake and significant increases in fiber consumption and in the ratios of monounsaturated/saturated, but a decrease in the ratio of ω -6/ ω -3 fatty acids. This is consistent with the Lyon Heart Study based on a modified diet of Crete and a decrease in the ω -6/ ω -3 fatty acid ratio [50]. Although the various scores to evaluate the Mediterranean dietary pattern have not included the ω -6/ ω -3 fatty acid ratio and its importance in reducing the risk of chronic diseases, especially coronary heart disease, the study by Simopoulos [20], Renaud et al. [50] and Ambring et al. [51], as well as the recent work of Guebre-Egziabher et al. [52], indicate that the dietary ω -6/ ω -3 fatty acid ratio should be evaluated in all studies on Mediterranean diets.

Lunch at the canteen was the opportunity to make objective changes in the food offered to the workers, it was also the opportunity to illustrate the theoretical concepts on healthy diet that were repeatedly explained to them. As shown in table 6, the intervention was successful in modifying habits; fruit and vegetable consumption markedly increased while red meat consumption decreased almost by two thirds; whole meal bread was offered and reached 49% of bread consumption; fish consumption showed a large relative increase, starting from a very small value, and canola plus olive oil were introduced in the diet. The evidence for a change in the alimentary pattern of the workers, a mediterraneanization of their diet, was accompanied by a reduction in the risk factors that define metabolic syndrome. As shown in figure 5, after 12 months of intervention the proportion of workers without any risk factor doubled and those with metabolic

Table 6. Main changes in average daily food consumption (lunch time) in the workers' canteen in 12 months of intervention

Food	Month 0 ¹ g/person/day	Month 12 ¹ g/person/day	Change, %
Vegetables (without potatoes)	174.5	264.2	+51
Fruits	47.2	106.2	+125
Cereals	44.9	61.7	+37
White bread	80.1	34.0	-57
Whole bread	0	32.8	+
Red meat	103.8	38.5	-63
White meat	53.1	68.8	+29
Fish	2.8	21.0	+750
Canola oil	0	21.3	+
Olive oil	0	6.5	+

¹Average daily consumption per person, recorded daily for 4 weeks, during the first and the last month of intervention.

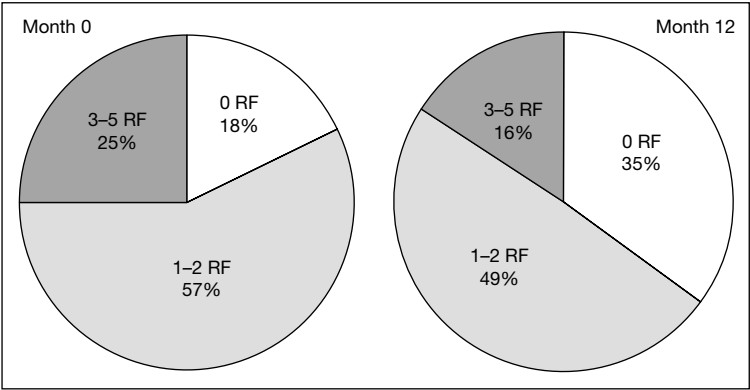


Fig. 5. Metabolic syndrome risk factors in the 99 male volunteer workers that participated for the entire 12 months in the 'food at work' diet mediterraneanization intervention study and were studied at least at time 0 and 12 months. The group includes 5 volunteers under hypertension treatment, which were considered hypertensive regardless of measured blood pressure. Relative distribution, at months 0 and 12, of volunteers without risk factors, volunteers with one or two risk factors, and those with three or more. Metabolic syndrome is recognized by the presence of three or more risk factors, among waist circumference, elevated blood pressure, fasting blood glucose, plasma triacylglycerides, and plasma HDL cholesterol.

syndrome decreased by at least one third or more if those under treatment for hypertension are not considered.

The food at work intervention, made with the purpose of obtaining a mediterraneanization of the worker's diet, was successful. The diet improved at the canteen, also the global diet of the workers improved and the change in diet was accompanied by a marked decrease in the prevalence of cardiovascular risk factors, those that define the metabolic syndrome. Clearly, mediterraneanization of the diet is a feasible objective, and the observed reduction in risk factors supports the hypothesis that it is a powerful tool to reduce chronic diseases in the population. Another very relevant conclusion is that adults are valid targets for chronic disease preventive measures.

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The Role of Government in Nutrition and Fitness

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The role of government in enhancing the health of the population can be vital. How large a role government should play is open to vigorous debate based on economic factors, concerns about intrusions in the rights of individuals to make decisions about their own lives, politics and practical administrative matters that can make implementing policy decisions difficult. As a result the role of government varies widely from one country to another.

The first important intervention may have been in 1854 when John Snow removed the handle of the Broad Street pump in London to prevent the continuing access of the impoverished local people to water contaminated with cholera. This established the precedent for government and public health officials to assume the responsibility of assuring clean water supplies and later adequate sanitation. Thus they made the world safe for big cities. Another 50 years would elapse before governments began to assume responsibility of inspecting food-stuffs to weed out infected or even putrid produce offered for sale. The development of vaccines offered another opportunity for government to intervene to protect people's health. In many countries it remained a voluntary option for parents. In others it was made mandatory, a view that accelerated when the possibility of eradicating diseases such as smallpox and polio were perceived.

Government intervention was justified early on to achieve purely social and health benefits. By the 1960s it became apparent that immense economic savings could be made by mandating certain preventive measures. In the early days of the automobile it had been required that a man carrying a red flag walk in front of all cars to protect pedestrians. There is little data to suggest that it had much impact. However, requiring people to wear seatbelts in cars or helmets while riding motorcycles not only saved tens of thousands of lives but saved vast amounts of money in reducing healthcare costs after accidents.

Sometimes there are complicating factors. Cuba, for instance, felt it could not enforce a requirement that motorcyclists wear helmets as long as such headgear had to be imported and the country lacked sufficient foreign exchange to make them available for all at a reasonable cost.

Perhaps the zenith of government intervention has been over cigarette smoking. Clearly the largest preventable cause of death worldwide the obligation on governments to intervene seems overwhelming despite the powerful economic forces they have to battle. Beginning with the US Surgeon General's Report in 1964 linking smoking to lung cancer, governments started to inch their way into this field. Initially the interventions were purely in the form of education and warnings about the health hazards involved in smoking but overtime more aggressive laws were passed to prevent teenagers from smoking and limiting where adults could smoke. These measures worked savings millions of lives but only where they were vigorously enforced.

The zealotry with which government intervention has been pursued in the name of enhancing people's health and well-being has begun to produce a strong backlash. Nowhere has government intervention been greater than in the European Union where well-intentioned rules have resulted in a barrage of criticism and resistance. In the United Kingdom the Health and Safety Executive has promulgated rules that often restrict people's activities to the point of absurdity. In addition, government involvement in some areas such as HIV/AIDS lacked a clear scientific base and served only to foster political agendas at the expense of those infected or at risk.

The role of government in the field of food and nutrition has been limited in the past for a number of reasons:

- The science of nutrition seemed imprecise and often controversial.
- In developed nations there were vast vested financial interests at stake that governments did not wish to offend.
- In developing countries limited food sources and poverty of the population meant that the struggle for calories transcended all other considerations.
- Although willing to control tightly the drugs people took, the food people ate, while equally involving the ingestion of chemicals that had a significant effect on biochemistry and physiology, was seen as a significantly less important subject for government involvement. The argument was that food did not contain exogenous substances.

With the exception of the discovery by the British Navy that consuming limes prevented scurvy, it was not until World War II that nutrition became a subject of government concern for an entire civilian population. British Prime Minister, Winston Churchill, announced that the war effort should not be allowed to jeopardize the health of the children of Britain. For the first time, nutritional scientists were brought in to advise at the highest level of government. The result

was a carefully constructed rationing program that included free supplemental doses of cod liver oil and orange juice for all children regardless of income. In addition, heavily subsidized feeding centers offered carefully nutritionally balanced meals at minimal cost. Ironically, it created in the country, in the midst of total war, a standard of nutrition among working class children that was substantially superior to that they had enjoyed in peace time or any time previously when the quality of their food was limited by the poverty and ignorance of their parents. Similar, but less comprehensive measures were introduced in the USA.

Following World War II, with vast numbers of displaced starving or malnourished people across Europe and Asia, scientific knowledge about nutrition continued to play an important role in shaping government policy. Restoring the nutritional status not just in the occupied and defeated nations but also in the victorious countries was seen as an integral part of the recovery effort. Even in a country like India a national initiative was started to provide iodinated salt in iodine-deficient areas to reduce the incidence of cretinism.

With the return of plentiful food supplies, especially in the developed nations, people largely returned to their own devices in making decisions that affected their nutritional status. At best, governments were in an advisory role, but in many instances especially in the USA they were in a constant struggle with the food and agricultural industry whose primary interest was in getting people to consume the products they had to sell rather than in improving nutritional status of the population.

In recent years, commensurate with a growing concern among people about their health in general, nutrition has become a topic of enormous commercial and scientific interest. Food supply is controlled by global market forces making it a fierce political issue. The international trade in food is a massive business. The General Agreement on Tariffs and Trade (GATT) and the Common Agricultural Policy of the European Union allow global forces to shape the food supply. International Committees such as Codex Alimentarius which determine food quality and safety standards lack public health representatives while the influence of the food industry is formidable. This is so despite the enormous volume of data now available concerning the relationship of diet to health. More than 100 expert committees have agreed to the dietary goals to prevent chronic disease emphasizing eating more fresh vegetables, fruits and pulses while minimizing animal fat, refined sugars and salt [1].

The World Health Organization (WHO) has urged local, national and international government agencies, non-governmental organizations, and the food industry to ensure that:

- The integration of public health perspectives into the food system to provide affordable and nutritious fresh food for all, especially the most vulnerable.

- Democratic, transparent decision-making and accountability in all food regulation matters with participation by all stakeholders, including consumers.
- Support for sustainable agriculture and food production methods that conserve natural resources and the environment.
- A strong food culture for health, especially through school education, to foster people's knowledge about food and nutrition, cooking skills.
- Growing food and the social value of preparing food and eating together.
- The availability of useful information about food, diet and health especially aimed at children.
- The use of scientifically based nutrient reference values and food-based dietary guidelines to facilitate the development and implementation of policies on food and nutrition [2].

In a broader context, the WHO has focused on the critical relationship between diet and physical exercise. The work of several expert working groups led to the publication in 2004 of the Global Strategy on Diet, Physical Activity and Health [3]. There was, however, considerable difficulty in getting physical activity adequately addressed in the development of the strategy. It was not given sufficient attention especially by the media, overshadowed by prominent issues concerning diet and obesity. A repositioning of physical activity was required for which a special WHO/CDC consultation was held. It examined appropriate ways in which to support the implementation of the WHO physical activity plan [4].

It is easy to pose the issue as a struggle between an agribusiness industry bent on achieving obscene profits and governments seeking to represent the health interest of the populations by reigning in, through regulation, the corporate excesses. In fact the power of government to shape the behavior of corporations is limited, while, in a free market the power of an educated public is immense. Public awareness of the importance of omega-3 fatty acids in the diet has had a dramatic effect on the food industry especially in Europe with corporations seeing their continuing profits as dependent on responding to this new public sophistication. Similarly, fast food chains, Kentucky Fried Chicken, Taco Bell and McDonalds, among others, have seen it very much in their interests to respond to the public concern over *trans*-fatty acids, removing them from their products. In these instances public opinion was quicker and more effective than government might have been. If anything, government has responded belatedly to what has happened in the market. Only after public awareness of the issue was overwhelming apparent did the New York City Health Department announce, with the backing of the City Council, that it will ban the use of *trans*-fatty acids in restaurants beginning in 2008. How significant this will prove in improving the health of New Yorkers is open to question, but the action represents an important new precedent on the part of government in shaping healthier

nutrition for the population. It remains true, however, that local government is more responsive to public pressure than national governments, which are more subject to corporate pressure.

Government's greatest role is probably in sponsoring research, collating studies, disseminating scientifically based factual information, and educating the public on a massive scale.

Foundations have taken great interest in other aspects of health and provided large amounts of funding, but on a relative basis have heretofore largely ignored the area of nutrition, except for such areas as maternal and child health.

Nutrition is a field in which private industry has, despite its detractors, at times, played a vital role. Beginning with the discovery of vitamins an enormous market opened up in populations who believed they had dietary deficiencies or if their diets were adequate that taking supplements would enhance their sense of well-being and their performance. Because of the extraordinary control multinational corporations have over what we eat, their role cannot be dismissed. They must be convinced that ultimately their best interests will be served by expanding their research in nutrition and being responsive to the knowledge of an increasingly sophisticated public.

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Balancing the Scales: A Common-Sense Look at Global Nutrition Problems and What Can Be Done about Them

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Introduction

The Food and Agriculture Organization of the United Nations (FAO) places great importance on the issues of nutrition and health, and is, therefore, particularly pleased to be a co-sponsor of this 2006 International Conference and Exhibition on Nutrition, Fitness and Health, held in Shanghai, China. This conference focuses on one of the most important issues of our day – the nutritional health and well-being of our people – and it is imperative, both from a moral perspective and as an economic investment in human capacity building, that we find the ways and means to put an end to hunger and all forms of malnutrition throughout the world.

However, agreeing how best to promote good nutrition, fitness and health is itself a daunting task. This is due, in part, to the sweeping changes occurring in many of the social and economic areas that affect the production, processing, trade, preparation and consumption of food, along with radical changes in people's lifestyles and activity patterns that tend to accompany economic development. When coupled with the wide range of stakeholders and vested interests – including national and local governments, international agencies, the private sector, academia, special interest groups, and most fundamentally, individual consumers – wanting to participate in the process, agreeing how best to promote nutritional health and well-being among the diverse populations of the world can become very contentious, indeed.

The views and opinions expressed in this paper are those of the author and do not necessarily reflect the opinions of the Food and Agriculture Organization of the United Nations.

Nonetheless, if more effective policies and programs are to be formulated, it is essential that these contentions be overcome. On its part, FAO strongly advocates that the way forward is to ensure that sound science underpins and guides our common understanding and perceptions of diet-health relationships. FAO also stresses the importance of basing local actions on accurate information on the extent and severity of various nutritional problems, and on rational and reasonable assessments of their causes and consequences. Basically, I would like to stress that sound science needs to be surrounded by common sense and real-world experience. We anticipate that some ‘sound science’ and common-sense lessons will arise from the deliberations of this Conference, and look forward to these helping improve our understanding of the best ways to promote nutrition, fitness and health.

What I would like to do today is:

- Share some insight into the nature and extent of some of the nutritional problems seen around the world today;
- Reflect on some of the factors affecting the changing nature of nutrition and fitness problems and challenge some commonly held perceptions, and
- Point out some of the policy and program considerations that could help guide the development of more rational and balanced approaches for addressing the multiple burdens of malnutrition seen throughout the world.

FAO: What It Is and Does

Before proceeding, please allow me to introduce the Food and Agriculture Organization of the United Nations (FAO) to those of you who do not know about it.

The FAO, now headquartered in Rome, was founded in 1945 and still leads international efforts to fight hunger and malnutrition. Serving both developed and developing countries, FAO acts as a neutral forum where all nations meet as equals to negotiate agreements and debate policy. FAO is also a source of knowledge and information. It helps developing countries and countries in transition modernize and improve agriculture, forestry and fisheries practices and ensure good nutrition for all. Since its beginning, it has focused special attention on developing rural areas, home to 70% of the world’s poor and hungry people, but given the increasing rates of urbanizations throughout the world, its efforts now focus on the poor and malnourished wherever they are. FAO’s work encompasses four main areas: serving as a knowledge network that collects, analyses and disseminates data and information that aid development; serving as a meeting place for nations and development partners; sharing policy expertise and providing policy advice to Member Nations, and serving as source of

technical know-how, expertise and resources to aid in both development efforts and recovery from emergencies.

The heart of FAO's mission is to achieve food security for all, that is to ensure that all people have the ability to acquire and utilize a sufficient amount and variety of good quality and safe food needed to lead active, healthy lives. FAO works to give meaning to the commitments and expectations of its Members to create a world without hunger.

Global Overview – Food and Nutrition Situation

So how are the nations of the world doing in their quest to end hunger and malnutrition? It depends on how you look at the situation. For example, never in the history of the world have so many people been able to feed themselves so well. Today there are some 5.5 billion people, about 85% of the total world population, who habitually eat enough to meet their basic energy needs, and increasingly, many eat more than enough; globally between 200 and 300 million people are now classified as obese.

While this is very heartening for the fight against hunger, it also reflects the ongoing tragedy of almost 15% of the world's population, some 854 million people, virtually never getting enough to eat. In addition, there are untold millions more who, at some time during the year, do not have access to enough food to meet their basic energy needs, and hundreds of millions more who cannot eat enough of a variety of foods to meet their vitamin and mineral requirements.

In 1996, FAO convened the World Food Summit in which almost all governments of the world committed themselves to reducing by half the number of chronically undernourished people seen in 1990–1992 by the year 2015. This hunger reduction target was modified somewhat to become part of the first of the Millennium Development Goals, which now calls for halving the proportion of people undernourished at the baseline. In either case, the progress achieved to date is inadequate, and in fact, the total number of chronically undernourished has not diminished at all (fig. 1).

Where are these chronic problems most severe? In relative terms, the problem is greatest in sub-Saharan Africa where 33% – one third – of the entire population is undernourished. This compares to 16% in the Asia-Pacific region; 10% in Latin America and the Caribbean, and 9% in the Near East and North Africa.

However, in absolute terms, the problem is considerably worse in Asia and the Pacific where some 527 million people are chronically undernourished. Of that number, some 300 million are in South Asia alone (India, Pakistan,

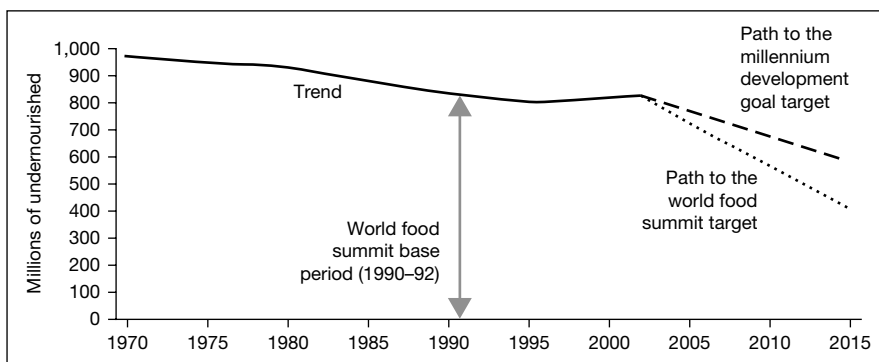


Fig. 1. Number of undernourished people in the developing world. Source FAO State of Food Insecurity (SOFI) [1].

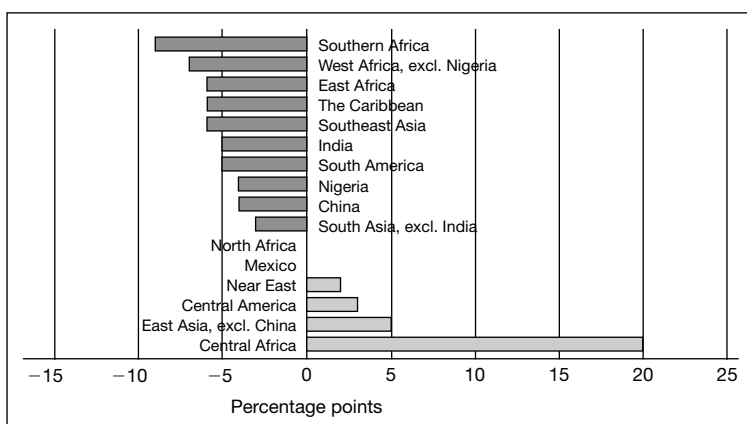


Fig. 2. Changes in proportion of undernourished in subregions from 1990–1992 to 2001–2003. Source FAO SOFI [1].

Bangladesh and Nepal), with another 160 million plus living in East Asia. In sub-Saharan Africa there are 213 million undernourished; 52 million in Latin America and the Caribbean and 37 million in the Near East and North Africa.

But the situation is not all bleak. Figure 2 shows the changes in the proportion of people undernourished – which is the MDG target – in different regions of the world, and it gives the somewhat hopeful picture that progress is being made in many places, even if at a slow pace.

The picture is much different, however, when viewed from the perspective of the actual numbers of hungry people – the WFS goal (fig. 3). While great

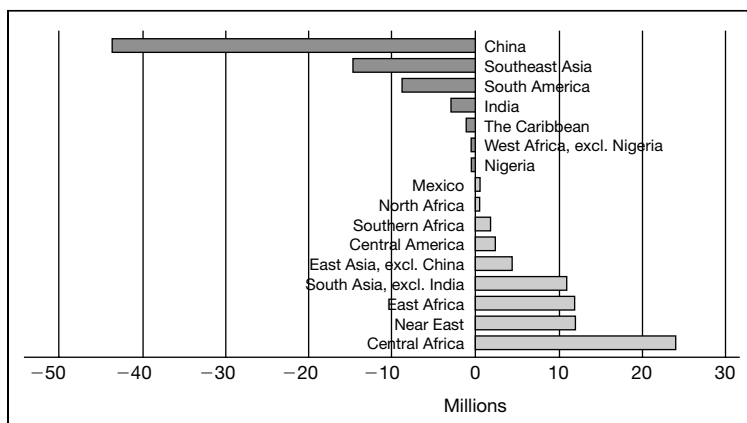


Fig. 3. Changes in number of undernourished in subregions from 1990–1992 to 2001–2003. Source FAO SOFI [1].

strides have been made in reducing the absolute number of undernourished in some countries, particularly China, due to their increased economic development, this is tempered by the lack of progress and even setbacks seen in other parts of the world, especially in much of Africa.

As troubling as they are, these estimates of chronic energy deficiency are not the only indicators of nutritional problems throughout the world. According to UNICEF in *The State of the World's Children, 2005*:

- 30 million infants annually are born with impaired growth due to poor fetal nutrition, which is usually the result of poor maternal nutrition;
- Every year 6 million children die from malnutrition before they reach 5 years of age;
- About 200 million children – one-third of those under 5 years of age in developing countries – are stunted, indicating a life of long-term nutritional deprivation and repeated infections. About the same proportion is underweight;
- The prevalence of stunting and underweight is highest in South Asia, where 44% of the children are stunted and 46% are underweight.

The consequences of fetal and child undernutrition, classically referred to as protein-energy malnutrition (PEM), can be very severe and can include reduced body size, organ development and muscle strength; impaired immune function, and reduced mental capacity and development. PEM consigns a child to a life of struggle – a struggle to learn, to stay healthy, to stay alive.

In addition to PEM, there is also an array of micronutrient deficiencies that retard growth and development and impede the health and productivity of both children and adults [2]:

- 3.5 billion people are affected by or at risk of anemia or iron deficiency;
- 2 billion people are at risk of iodine deficiency disorders, and
- Some 200 million children under 5 years old alone are affected by vitamin A deficiency, with untold millions more older children and adults also affected.

Again, the consequences of these nutritional deficiencies can be severe. Iron deficiency can lead to growth retardation, low resistance to disease, impaired mental and motor development, impaired reproductive functions and to serious lethargy and lack of productivity. Estimates are that iron deficiency is responsible for over 20% of pregnancy-related deaths in the developing world.

Iodine deficiency disorders have a great impact on child development and survival. They can lead to learning disabilities, mental retardation and, when severe, to permanent brain damage. Iodine deficiency leads to goiter and effects overall metabolic function.

The consequences of vitamin A deficiency also include growth retardation, impaired resistance to infections and increased risk of morbidity and mortality among children. Vitamin A deficiency can damage the eyes and impair vision. It is the leading cause of preventable blindness in the world.

In addition to the problems of undernutrition and micronutrient deficiency disorders that continue to afflict hundreds of millions of people, there is now a growing problem of overnutrition and obesity arising in some developing countries. While in general the rates of obesity are low throughout non-industrialized countries – exceptions being made, for example, in the Near East where 30–40% rates are not uncommon, and in South Africa and Mexico with 32 and 24% obese, respectively – the consequences of increasing obesity also have the potential for being severe. Some of the health problems commonly associated with obesity include: cardiovascular diseases, including hypertension, stroke and coronary heart disease; type 2 diabetes; gallbladder disease; musculoskeletal problems; certain cancers, and in some instances, psychosocial problems [3].

An interesting feature of the growing obesity problem is that it often exists alongside continuing problems of undernutrition. This leads developing countries to having to deal with what is often referred to as the double burden of disease or malnutrition that is usually attributed to the effects of a ‘nutrition transition’. In practical terms, labeling the situation in which extensive undernutrition and micronutrient deficiencies coexist along with increasing rates of obesity as a ‘double burden’ can be very misleading and can easily lead to misdirected policies and programs. This will be discussed in more detail below, but no matter how they are labeled, the consequences of all these forms of malnutrition are serious.

For affected individuals and households, malnutrition commonly leads to suffering and poor health, to lost learning potential, to lowered productivity and incomes, and to high household expenses for medical care and associated costs.

There are high costs of malnutrition for communities and nations as well: diminished human resources; increased family and community stress; decreased economic activity and wealth creation, and extensive resource allocation to health and social services. Dealing effectively with nutritional problems must be near the top of everyone's development agenda.

Nutrition Transition and Multiple Burdens of Malnutrition

One of the most talked about issues among the international health and nutrition communities today is the above-mentioned 'nutrition transition' and its impact on health and disease. This transition refers to the situation of populations moving away from their traditional livelihoods, lifestyles and dietary patterns and taking up new ways of earning a living, and adopting more urbanized (often more sedentary) lifestyles and consumption patterns. One of the results of this transition is the emergence of obesity and chronic non-communicable diseases within populations, and their replacement of hunger, deficiency disorders and infectious diseases as the primary causes of disability and death. Where this transition is not yet complete and problems of both communicable and non-communicable are prevalent, the populations are considered to be facing a double burden of disease.

This is a very real situation, and many countries are struggling to cope with changing demographics and new health issues. However, from the very real situation of a double burden of disease, many nutritionists and epidemiologists have made a conceptual leap to an alleged double burden of malnutrition, which juxtaposes problems of hunger and undernutrition with those of overweight and obesity.

This concept was originally intended as a way of calling greater attention to problems of obesity and chronic diet-related diseases without totally dismissing the continuing problems of undernutrition and specific nutritional deficiencies. In practice, however, the use of the concept of the double burden of malnutrition often leads to a considerable de-emphasis of the problems of hunger and undernutrition, and then, rapidly, to diminished efforts to address the basic issues of poverty and social and economic underdevelopment.

The basic problem with promoting such a bipolar orientation to nutritional problems is that it completely confounds the issues of micronutrient deficiencies, dietary balance, nutrient and energy density, physical activity and energy balance, among others things. It also sets up false demarcations within the realms of food supplies, food security, dietary choices, nutrient intakes and nutritional status that inappropriately pit concerns with deprivation and underconsumption against those of excess and overconsumption. It pits the 'hunger

fighters' with their 850 million chronically undernourished against the 'fat fighters' and their 200–300 million obese. This is most damaging, as it obscures attempts to deal with all types of nutritional problems in a comprehensive and complementary manner.

What the global nutrition community needs to do is move away from the polarizing fiction of the *double burden of malnutrition* and to agree to work together to promote wider recognition of the *multiple burdens of malnutrition*. This would help prevent the destructive nature of the debate between the hunger and the fat camps and would permit the development and implementation of more broadly based nutrition intervention programs that aim to overcome the common problems of poverty and household food insecurity, inadequate food supplies, poor food choices, inappropriate care and feeding practices, energy imbalances and micronutrient deficiencies.

However, even finding this much common ground among the various interested parties about how to view global nutrition problems would be a daunting task. Let us look at why this would be so difficult.

Understanding the Transition

It is undeniable that transitions in dietary and disease patterns occur within various population groups. However, one of the more fascinating aspects of such transitions is that the entire process can mean such different things to different people. For example, there are many in the nutritional-epidemiological community who consistently refer to this transition in a pejorative manner. They express great concern about diets and lifestyles becoming 'more Western', which basically translates into concern about greater consumption of 'fast foods', processed foods, snacks and soft drinks, with dietary fats, especially saturated and *trans* fats, sugar and salt being of particular concern. At the extremes, alarmists tend to decry virtually all of these changes and often cast globalization, urbanization, biotechnology, and the existence of transnational corporations as the causes of emergent diet-related chronic disease and death.

From another perspective, one can look at the same transition situation and see a process in which improved diets, sanitation, healthcare and education have combined to reduce morbidity and mortality from infectious disease among the population and, thus, increase their average life span. Given that people are now living longer, an increase in the prevalence in chronic non-communicable diseases would be expected. When coupled with the declining mortality from infections, this results in a dramatic rise in death rates from chronic non-communicable diseases within the population. Accordingly, the rise in morbidity and mortality from non-communicable disease should be seen as a very positive and much sought-after result of the nutrition transition. However, it should go without saying that premature morbidity and mortality are not positive outcomes of this transition, and

in fact, they should be among the priority targets of our efforts to improve nutritional health and well-being.

It should also be noted that the changes that enable people to improve their diets, health, education and general welfare are commonly rooted in social and economic development that fosters the expansion and diversification of food supplies and generates greater income-earning opportunities for the poor. Far from being health risks, readily available and affordable foods and drinks should be seen as major contributors to individual well-being and, ultimately, community and national development. In this context, providing support for creating and strengthening food industries that can produce, process, prepare and sell an expanding array of foods to willing consumers becomes an important instrument of national development planning.

So which is it? Is the *nutrition transition* a good thing or a bad thing? And if that can be answered satisfactorily, we then need to ask, ‘What are the causes and the consequences of this transition, so that we can either prevent or promote them?’

As an illustrative example, table 1 lists some general diet- and lifestyle-related characteristics that could be associated with three groups of people in different stages of socioeconomic development. This clearly points out the nature of the multiple burdens of malnutrition, especially among the groups in transition. It also indicates the importance of designing flexible interventions that combine elements of food security, nutrition and health education, and promotion of physical activity, as needed.

The messages are clear: poor diets – be they too much or too little food – contribute to a range of nutritional disorders, and it is the poor who suffer the most. Accordingly, efforts to overcome problems of undernutrition, overnutrition or micronutrient deficiencies among the poor must be rooted in the same reality: people need year-round access to an adequate amount and variety of affordable foods, and they need the knowledge, time, opportunity and motivation to care for and feed themselves and their families properly. It all comes down to creating the conditions that allow and enable people to make wise and informed choices about their food, their health behaviors and activity patterns.

It is instructive to realize that problem diets may be either very monotonous or highly diversified. They may be too bulky or too energy-dense. They may be too high or too low in fat, or they may have too much of a particular type of fat and not enough of another. They may be nutrient-dense or almost void of nutritious foods. According to whom one listens, the problem may be that food is either too expensive or too cheap. The lesson here is that there is no single characteristic of a poor diet. It is all relative to the problems at hand, and often there are multiple problems at hand at the same time and in the same household. That being the case, there can be no universal prescription for how

Table 1. Common characteristics of the nutrition transition

Low socioeconomic groups	Transition groups	High socioeconomic groups
Food insecure	Mixed food security	Food secure
Physically active	Less physically active	Sedentary
Dietary energy intake: Inadequate	Dietary energy intake: Inadequate Adequate Excessive	Dietary energy intake: Adequate Excessive
Micronutrient intake: Inadequate	Micronutrient intake: Mixed – adequacy and deficiency seen at all levels of energy consumption	Micronutrient intake: Sufficient
Death and disability due to: Acute infections/communicable diseases Deficiency disorders	Death and disability due to: Acute infections/communicable diseases Deficiency disorders Non-communicable diseases	Death and disability due to: Non-communicable diseases

to improve diets, and certainly no scope for narrowly focused, top-down dictates aimed at limiting consumer choice and trying to prevent natural transitions from poor monotonous diets to richer, more varied intakes.

The Simple Truth

At the root of the dietary and nutritional changes inherent in the ‘nutrition transition’ is the simple fact that economic development and its virtually inseparable companion, urbanization, inevitably change the way people acquire and utilize food. In the simplest terms, as people move up the socioeconomic ladder, three trends tend to converge:

- Firstly, due to their improved economic conditions, people have larger incomes and more money to spend on food. Accordingly, they purchase more food, more tasty foods (which often means food higher in fat, salt, sugar and spices), and foods that are convenient and easy to store, prepare and consume (including many processed and preserved foods).
- Secondly, given that economic development is invariably associated with increased urbanization, consumers are placed in more food-rich environments with greater day-to-day access to a range of food items and eating

opportunities, both within and outside the home. One inescapable phenomenon of urbanization is the widespread consumer demand for foods that are tasty, convenient, affordable and safe. This often leads to basic staples and many processed food and beverages being widely available and relatively inexpensive, which in turn, makes the cost of dietary energy correspondingly low.

- Finally, urban populations and higher socioeconomic groups in general tend to engage in less strenuous and physically active work and, overall, adopt much more sedentary lifestyles.

Taken together, these trends lead to the root causes and consequences of the ‘nutrition transition’ and point to the obvious outcomes that result from people moving out of poverty and subsistent/semisubsistent existence into more socioeconomically advanced status and lifestyles:

- People tend to eat more and increase their energy intakes;
- People are less physically active and expend less energy;
- People gain weight, and
- People live longer and ultimately succumb to non-communicable diseases.

In other words, the increases in average population weights and the overall emergence of chronic disease should be attributed to people living longer, to their wanting to live easier lives and eat better foods, and to their having the means to do so. This is a very good thing, and far from being seen with alarm, increased death rates from chronic disease should be seen as a welcome sign of desirable improvements in social and economic development.

As a quick aside, it should be noted that, while economic development and, in general, urbanization are good, clearly not all urbanization is uniformly positive. Obviously, in an ideal society, the transition from poverty to prosperity would be smooth and painless, but reality is often much different. While urban populations on average tend to enjoy much higher standards of living than their rural compatriots, the emergence of widespread, severe poverty in many urban areas of the world is a very worrisome development. In fact, some of the worst living conditions imaginable are to be found in the slums and shantytowns of many major cities, and they present a major challenge for all sectors working to improve nutritional well-being and health. In most instances, the expectation of a better life in an urbanized environment that can provide jobs, food security, education, healthcare and other social services is a valid one for many rural dwellers; however, in all too many other cases, such expectations are just faint hopes kept alive because of just how desperate life is in the rural areas. All too often it is not so much the pull of the city that attracts new immigrants, but the push of a destitute countryside. One of the keys to solving this type of urbanization problem is effective rural development, and that translates into agricultural development and the corresponding development of efficient markets and food systems.

Thinking About Obesity

At the forefront of leading concerns among many in the public health and nutrition communities is the contentious issue of obesity. The debate is complex and, as such, easily reduced to simplistic notions and to being taken over by polemics and positions rather than careful thought and analysis. Part of the controversy surrounds the question of whether obesity, per se, is a serious health problem in its own right or if it is primarily a risk factor for various other pathologies. Fundamental questions also concern: what actually constitutes obesity and how is it to be measured; what causes obesity; how extensive is it among various populations; what are its consequences, and what can be done about it? That is quite a list and, yet, it is only indicative of the type of questions – and controversy – surrounding the issue of obesity.

I will not try to go into each of these, but I will highlight some of the more salient points of the debate. However, if you are interested in exploring the dimensions of obesity issues further, I recommend you seek out a series of discussion papers recently published as a Point-Counterpoint section of volume 35 of the *International Journal of Epidemiology* in which various social and nutritional scientists, researchers, moralists and anti-fat crusaders debate the numbers and their meanings. The lead article is entitled *The Epidemiology of Overweight and Obesity: Public Health Crisis or Moral Panic* by Campos et al. [4], and it sets the stage for the ensuing papers.

At the extremes, there are two opposing views of the changing prevalence of obesity and its importance as a public health problem. One view holds that there is a tidal wave of obesity sweeping the world, which is undermining both individual and national health at an alarming rate. This wave is seen as being propelled by radical changes in food supplies and eating patterns around the world which, in turn, are the result of the inexorable sweep of globalization and the emerging preponderance of ‘Western’ diets and lifestyles. As a result, this camp advocates strong action to improve dietary intakes, including concerted action to remove fat, especially saturated and *trans* fat, sugar and salt from the food supply. This is currently the most widespread and loudly promoted viewpoint.

Another view holds that the purported large increases in prevalence of obesity are, in reality, simply shifts of population averages across the somewhat arbitrary cut-off points of indices that classify people as being overweight or obese. This view holds that in many instances the increased numbers actually reflect relatively minor increases in the actual weights of populations, and therefore often have little bearing on the true health of individuals or populations. This view also stresses the importance of physical activity in both the energy balance equation and overall health; it is somewhat dismissive of the health risks of obesity, per se, and recognizes that small but consistent daily

energy imbalances can, over time, turn into relatively large changes in body weight.

The truth of the situation is likely found between these extremes, but I agree with much of the underlying sentiment of the second viewpoint. There seems to be a good deal of hysteria coming from a vocal and well-funded quarter of the medical-nutritional community who want to see extensive changes in food and agricultural systems and in how food is produced and marketed. It often seems the desire for these changes is based more on philosophical and political persuasion than on science and logic, and one cannot discount the push, as well, of vested interests, which are just as strong in what I call the *obesity industry* (or as they might wish to be called, the *anti-obesity industry*) as in the food industry. While many would have us believe that medical-nutritional researchers and advocates have only the common good at heart, there are many well-known names in the nutrition world who receive significant attention, prestige, invitations and opportunities, not to mention grants, stipends and other types of financial support, from a variety of special interest groups, including pharmaceutical concerns, task forces, institutes and funds. The point is, the *obesity industry* thrives on obesity, and all too often the loudest voices in the debate have the most at stake – and it need not be just a financial stake: visibility and status are powerful motivators, too. Please note, I am neither saying that obesity issues are not a serious health concern nor that many nutritionists, epidemiologists and researchers are not legitimately concerned about these issues – both are true. However, I am pointing out a clear anti-industry, anti-marketing and anti-trade bias that pervades the thinking of many in the health and nutrition field.

Looking Objectively

So, what do we believe? How serious a problem is obesity? Let us look at some figures. From 1976–1980 to 1999–2002 the prevalence of body mass index (BMI) >30 among the US population increased from just under 15 to 30%. Now this can be looked at in two ways. We can say that in just over 20 years the rate of obesity has doubled in the USA, or we can say that in just over 20 years approximately 15% of the US population became obese. Whichever way it is said can give the story a different spin, and this realization points out the pressing need for balance and objective reporting in both the scientific and popular literature. Even so, once we get the statistics and story straight, we are still left wondering what exactly it means in terms of public health.

To answer that, we need to understand four things: the significance of BMI as an indicator of an individual's health; the relevance of 30 as the cut-off point for obesity and poor health; the distribution of the population's BMI status, and

what it takes in terms of weight change for an individual to move up and down the BMI scale. Let us start with the last two. For a person 170 cm tall to move from a BMI of 25 to 30 he or she would need to increase their weight from 72 to 87 kg, i.e. add 15 kg. If their BMI were already at 29, they would need to add only 3 kg to reach 30. So, to evaluate the significance of a proportion of a population moving over the 30 BMI cut-off point, one thing we would want to know is where they were previously. We would want to know if this signifies, say, a 5- or 20-kg increase in weight, and we might also want to know how many people or what proportion of the population gained how much weight. Specifically, we would want to know if this increase in 'obesity' represents massive weight gain among a majority of the population, or if it is the result of more modest gains in weight but at a level that puts people over the 30 BMI cut-off point. This would make a considerable difference in how the problem is viewed and treated, but unfortunately, it seems that this type of more nuanced information gets in the way of the story that many people want to tell.

Another perspective on the 'obesity epidemic' in the USA can be gained from considering that the average increase in weight among adults from 1960 to 2002 was 24 lb or 11 kg. While representing a substantial total amount of weight gained, in fact, it translates into only an excess of fewer than 6 kcal per person per day on average over some 42 years. Recognizing the problem of using averages to describe a population and in this case, with spreading the weight gain evenly across the entire population, let us assume for the sake of argument that only 50% of the population gained this weight. That would mean on average that each person who gained weight put on 48 lb (22 kg), which would correspond to 11 kcal excess dietary energy per day. Let us make another assumption: the majority of the weight was put on only in the last 20, instead of 42 years. This would bring the average daily excess energy intake to just over 23 kcal per caput.

This is fairly consistent with what has occurred recently in China. According to Kim and Popkin [5] in the above-mentioned debate in the *Journal of Epidemiology*, from 1989 to 2000 some 73% of the adult Chinese population gained on average 7.0 and 6.3 kg of weight respectively for men and women. Over 11 years this works out to about 0.6 kg/year which would correspond to fewer than 13 kcal in excess dietary energy per person per day.

This does not necessarily appear to be an alarming situation, especially if much of this weight gain occurred in people who were previously somewhat undernourished. Still, we must be careful not to overplay the statistical game of 'averages equal reality'. Nonetheless, these figures do lead us to conclude that the weight gain seen among much of the US and Chinese populations may be cause for concern, but in neither cases does it constitute a tidal wave of obesity or a tidal wave of overconsumption.

A Balanced View of Energy Balance

An important point to emerge from the above discussion is the realization that small daily imbalances in energy intake and expenditure can, over time, add up to significant changes in body mass. This should not be surprising, but it commonly gets lost in the uproar of the self-appointed guardians of our girth, the *obesity industry*, who would have us believe that the only way obesity can be tackled is through radical changes in global food supplies and in how food is produced and marketed. If the truth that only relatively minor changes in daily energy intake and expenditure are all that are needed to prevent obesity, and only modestly greater changes to reverse its impact, gets out, then they will have lost their platform and their leverage for attacking much of the food and agriculture sector, in general, and the food industry, in particular.

But small changes are all that are needed. A positive average energy imbalance of just over 50 kcal/day will result in a weight gain of 2.5 kg year, which over 5 years translates into an additional 12.5 kg of body weight. And just how difficult would it be to eliminate that daily 50 kcal excess? It could be accomplished, for example, by cutting out any one of the following amounts of food: a spoonful of ice cream, 15 g of pretzels, 5 Pringles potato crisps, 35 g pasta, 2 teaspoons of oil, 30 g of chicken meat, a ½ cup of cappuccino, ½ cup of a soft-drink or ½ glass (65 g) of wine. These are not large amounts of food. It is also possible to reduce the energy imbalance by expending an additional 50 kcal of energy. This could be accomplished by increasing one's physical activity by approximately 12 min of walking, 6 min of bicycling, or 9 min of dancing. The point is that it does not take major changes in daily diet or physical activity to make a real difference in energy balance. We need to keep in mind that, most commonly, it is the small, but regular, imbalance between energy intake and expenditure, arising from the combined effects of easy access to food and lower levels of physical activity, that is driving the so-called obesity epidemic being seen across the world. Preventing excessive weight gain is entirely possible.

To accomplish this, however, we need to move away from both the hysteria that often surrounds the issue of obesity and, especially, the single-minded fixation on high BMIs as the key risk factor for diet-related chronic disease. I believe one of the greatest disservices of the *obesity industry* has been their success in establishing in many people's minds (including, the minds of very many who should know better) the notion that BMIs of 25 and 30 are legitimate cut-off points for overweight and obesity, respectively, and that these levels actually correspond to some degree of increased health risk for individuals. The consequence of this deception is clear: once it becomes accepted that these are the limits set by the experts, policy makers have little choice but to follow.

The problem with this is that the weight and BMI of an individual become the issues and the focus of attention rather than the health of the individual.

Contrary to what we are commonly led to believe, there is little evidence to support the notion that increased weight, per se, leads to poor health and increased mortality, and even less that establishes BMI of 25 and 30 as anything but arbitrary demarcations. Blair and LaMonte [6] state: 'Although it is often purported that mortality risk becomes greater across incremental levels of BMI . . . there is little difference in risk across a very wide range of BMI values', and that there has been an 'uncritical acceptance by many of any claims about the health hazards of obesity' which has led to 'an overemphasis on weight loss as a clinical target'. This agrees with Campos et al. [4], who point out consistent results from studies around the world that show the lowest rates of mortality commonly occur between BMIs of 23 and 29. Data from the USA indicate that more premature deaths are associated with BMI <25 than BMI >25, and that relative risk for premature mortality associated with obesity does not increase appreciably until BMI goes over 35.

There is also compelling evidence from many sources that it is the level of fitness, not fatness, that is the key to health. Improvements in blood pressure, serum lipids and even insulin sensitivity can result from improved diets and exercise independent of changes in weight or body fat, and in some cases, even among individuals who actually gained body fat. Data from the US National Health Interview Survey (1989–1997) also show that people who tried to lose weight (diet and exercise), but failed, achieved the same level of health benefit as did those who lost weight, successfully. It is, however, also true that losing weight can also lead to improvements in health, for example reduction of hypertension, but interestingly, there is no 'dose response' associated with this. In other words, a small loss of weight produces the same benefit as a larger loss; so, getting progressively leaner does not produce progressively greater health benefits. On the contrary, losing weight and especially regaining it, actually increases mortality risk. Finally, Blair and LaMonte [6] report on the conclusions of an extensive expert review of observational data by stating, simply: ' . . . overweight and obese individuals who are active and fit have lower morbidity and mortality risks than their normal weight but inactive peers'.

Clearly, there are associations between obesity and an array of serious health conditions and death; however, there is little, if any, compelling evidence that obesity, itself, is the cause. Even with regard to type 2 diabetes, it is just as likely that obesity is an early symptom of the disease as its cause. The real culprit could be the metabolic syndrome arising from, among other things, poor diet and physical inactivity, that leads to both increased adiposity and insulin resistance.

The significance of this is considerable. By focusing exclusively on weight and BMI as the targets for action, we aim at the wrong things and can miss doing what is really important. The rational promotion of dietary balance, moderation

and variety and of physical activity give way to fad diets, drugs, surgery, eating disorders, weight cycling and recrimination, which feeds the cycle.

The Way Ahead

There is a fundamental choice to be made with regard to public policies needed to address the multiple burdens of malnutrition. Most simply, one can choose to treat the causes or the symptoms. If the symptoms are treated, the focus will be on diseases, risk factors and body weight. If the choice is to treat the causes, then the focus will be on health and on creating the conditions in which people can live and work in healthy environments, can acquire and utilize the foods they need, and can make healthy choices about their diets, their lifestyles and their levels of physical activity.

Creating such conditions requires action across many sectors, and while there is no universal formula for designing appropriate nutrition policies and programs, there are some common guidelines and policy objectives that I would recommend as matters of priority:

- Focus on poverty reduction. In all scenarios the nutrition and health of the poor suffer most and improving their overall welfare and their capacity to care for themselves is of paramount importance;
- Expand and diversify food supplies in poor communities to reduce costs for low-income consumers. In many agrarian societies this will have the added benefit of increasing opportunities for food producers and processors;
- Adopt a holistic approach to improving nutrition and health and give particular attention to creating supportive environments, including:
 - Improving rural and urban infrastructure (transport, marketing and storage),
 - Assuring the quality and safety of food systems,
 - Adopting a sustainable livelihoods approach to development,
 - Strengthening city planning to promote access to goods and services and opportunities for physical activity, and
 - School and work environments.
- Expand nutrition information and education opportunities. Focus on total diets; care and feeding practices, including time constraints and convenience factors, and emphasize dietary balance, variety and moderation in relation to meeting nutritional needs;
- Promote fitness, based on good nutrition, energy balance and physical activity;
- Improve the nutritional status of women of child-bearing age, decrease incidence of low birth weight;
- Promote child growth and monitoring for all forms of malnutrition, not just underweight;

- Establish and strengthen good nutritional habits early in life (day care and school feeding).

Finding the Balance

Progress in combating the multiple burdens of malnutrition can best be realized by embracing a rational and balanced view of food, nutrition and health problems and their causes and the development and implementation of similarly rational and balanced interventions. This balance needs to come in several forms. It needs to come in allowing the various sectors and stakeholders opportunities to have their interests recognized and needs addressed. It needs to come in the form of building equitable partnerships, including in the public and private sectors. It needs to come in the form of fair policies and programs, in reasonable and realistic messages, and in the form of equal participation and benefits for all concerned.

In the mid-1990s, FAO developed a simple set of nutrition education materials, entitled ‘Get the Best from Your Food’ [7], designed to be adapted, as needed, to meet the information needs in various settings. This package provided four broad guidelines with supporting information around which nutrition educators could build more specific messages tailored to local conditions. The key messages are:

- Enjoy a variety of foods;
- Eat to meet your needs;
- Protect the quality and safety of your food, and
- Keep active and stay fit.

I bring these to your attention because I believe they provide a strong framework for building appropriate educational initiatives suitable for addressing the multiple burdens of malnutrition, and because they illustrate well the type of balanced approach required for effective nutrition education in many countries around the world.

We live in an unjust, inequitable world in which the poor suffer much more than most of us could ever imagine. If our hope of a world in which healthy, well-nourished children can grow into healthy, well-fed adults is to be realized, we must also work outside the realms of our professional interests in food, nutrition and fitness. To effectively redress the nutritional imbalances in the lives of so many around the world, we must first seek to balance the scales of social justice and economic opportunity. Sustainable progress in improving the nutritional and health status of the poor can only come by creating opportunity, sharing resources and restoring the dignity and security of the poor and socially disadvantaged so that they can provide for themselves. That is our challenge.

There is an important statement in the Declaration of the 1992 Joint FAO-WHO International Conference on Nutrition that eloquently sums up the reason

and the urgency for attacking all forms of malnutrition. It says: ‘Hunger and malnutrition are unacceptable in a world that has both the knowledge and resources to end this human catastrophe’, and my closing message today is simply to ask that we agree to no longer accept that which is unacceptable. Let us agree to find a common ground on which we can work together to put an end to hunger and to the multiple burdens of malnutrition.

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Historical Perspective: The Antiquity of Exercise, Exercise Physiology and the Exercise Prescription for Health

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Introduction

According to the medical historian Baas [1], antiquity for medical history ‘closes with Galen’. For the topics of exercise, exercise physiology and the exercise prescription for health, the era is the same but their histories are inextricably linked to the evolving concepts concerning disease and health, physiology, and to the practice of rational medicine. For the caved humans of the Neolithic Age (ca. 8000 BC), the ravages of disease were attributed to spirits, demons, and/or to supernatural forces that had to be controlled, appeased, or driven away before cures could occur and health be restored [2, 3]. This process was facilitated in part by ceremonies, incantations, trephining the skull and by kneading the body in the direction of the feet in order for the evil spirits to escape [4]. Explanations for these occurrences and recoveries were sought by ancient civilizations that have arisen from regions served by the Nile, Indus, Euphrates, and Tigris rivers. While not systematic or structured, their evolvement did provide for historical periods that were used by Baas [1] to characterize the evolvement of medicine. As his first edition was published in 1891, his sequence will be followed with the exceptions that (a) the contribution from the Indus civilization will be mentioned after the Egyptians because of the discoveries during the 1920s at Harappa and Mohenjodaro in India [5] and (b), the influences of the Japanese will not be included.

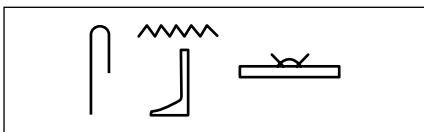


Fig. 1. Ancient Egyptian hieroglyphs for health (= to recover) [from 14, p. 72].

Influences from the Ancient Egyptian and Indus Civilizations

The Egyptian Civilization

Details on the beliefs and practices pertaining to disease, health, and medicine in ancient Egypt have been obtained from select papyri that were written between 1900–1200 BC but contain information that was relevant to the Third Dynasty (ca. 2650–2560 BC) [6–9]. Noted historians of ancient Egyptian medicine [10–13] have indicated the Egyptians considered disease to be the result of hostile spirits or from the anger or displeasure of their gods. Thus the removal of disease or illness from the body was best accomplished by the use of spells, incantations, sorcerers, and prayers that were invoked by priests and magicians [14]. With the exception of the eyes, initially all diseases were treated by priests of the goddess named Sechmet who could inflict plagues, war and death [15]. Subsequently, assistance from multiple gods was sought that included Thoth, Isis, and Horus [15]. Readers should note that Imhotep, a mortal to have been the physician to the Pharaoh Zoser in the Third Dynasty and likely a cult member of the sun god Ra, was not deified as a god of medicine until approximately 800 BC [10]. It is of interest that Breasted [6] suggested Imhotep was the author of the *Edwin Smith Surgical Papyrus*. Priests, priest-physicians, lay physicians and magicians known as *swnw*, were the healers of diseases, illness, pain and discomfort and frequently prescribed pharmacological remedies that were described in the Ebers [7, 9] and Hearst [16] papyri. Like disease during the ancient centuries, health had a supernatural focus that was not identified with the absence of disease while being considered a desirable state and primarily concerned with the recovery process (fig. 1). It is noteworthy that an anonymous author wrote on the back of the Edwin Surgical Papyrus on the possibility of diseases being caused by the wind carrying pests [17]. Although seldom cited, this was an early sign of disease being recognized as occurring from non-supernatural sources and of the evolvement of rational medicine.

Physiological understanding of the functions of the various organs was minimal at best although from the Smith [6] and Ebers [7, 8] papyri, it was apparent that the heart was regarded as the most important organ of the body as it was site for thought, emotion, and intelligence while serving as the ‘center’ of the vascular system and being responsible for the pulse [11, 14]. They understood

blood was associated with the heart but did not recognize its pump functions. To the swnw, air and water were essential for life and believed air, the breath of life, entered the right ear while the breath of death entered the left ear. Functionally, air entered the body through the nose and traveled via the trachea directly to the heart and intestines whereas water entered the heart via the stomach. Both were carried in the blood to the various organs of the body by afferent ducts (blood vessels, nerves, and tendons) which were collectively known as the *metus* [14]. Under normal conditions and when the heart was in its right place [18, p. 128], *‘the Fat of Heart is on the left side. It neither rises upward nor falls downward. It remains soundly in its place’*. In addition the heart could ‘tremble’, become sick, miserable or fatigued while experiencing sadness or disease that required the attention of the swnw. As discussed previously, the large intestine was regarded as an important organ because it contained the undigested food as fecal material that could undergo putrefaction and subsequently lead to disease and a loss in the *‘bodily vigor’* of health [15].

Although health was regarded as a desirable and positive state [15], there was no evidence within the relevant papyri or the cited texts that indicated exercise was ever advocated either for health reasons or to improve performance. However, sports and games were an important component of Egyptian culture and for the preparations of war by Pharaohs that were present during the Old Kingdom (2700–2300 BC) and the Late Period (700–600 BC) [19]. Physical activities for the masses included running, rowing, wrestling, ball games, boxing, jumping, and acrobatic dances. Unknown to most is that all future Pharaohs were expected to excel in the 180 stadia race (33.3 km) [10].

The Indus Valley Civilization

Archeological excavations in the Indus Valley of India, first described by Sir John Marshall [5] included Moenjodaro (in Sind) and Harappa (in Punjab) indicated the existence of an ancient Aryan civilization that select historians [20–23] believe was operational earlier than shown by the upper limit of the carbon dating value of 3300 BC [24]. Detailed descriptions of the excavations by Marshall as well as by Chowdhury and Chawdhury [25] revealed an advanced culture that had a concern for sanitation and public health as demonstrated by their water and sewage draining systems and by their massive public bathing building. Analysis of skeletal remains indicated the residents experienced a wide range of diseases that included metal poisoning, arteriosclerosis, osteomyelitis, cancer, and dental diseases. Like the Neolithic caveman, there were signs of skulls being trephined. Moreover, select skeletons exhibited evidence for infectious diseases. It was the opinion of Bhatia that in the Pre-Vedic Era, disease was regarded as a magical-religious phenomenon caused by supernatural forces which were treated by magic, incantations and related rituals

[26]. Other than the public health practices, their views on health or exercise for health purposes remain unknown. From the positions of recovered statues, they suggest the residents were familiar with the movements of yoga exercises [25].

Influences from the Civilizations in Mesopotamia and Persia

The Sumerians, Babylonians, Assyrians and Chaldeans

Mesopotamia is defined as an ancient country in southwest Asia between the Tigris and Euphrates river that includes a portion of modern Iraq [27]. The early inhabitants were non-Semites known as the Sumerians who were followed by the Babylonians, Assyrians, and the Chaldeans all of whom were Semites [28, 29]. They considered diseases to be demonic in origin that were ‘distributed’ as punishment either for disobedience to the gods or for not following the established practices of the priest who could also function as a healer (an assipu) [29, 30]. After ascertaining the cause for the disease or illness, priests facilitated recovery by leading incantations, encouraging exorcisms, and by requesting the god Marduk to intercede with the god Ea (healing) on behalf of the afflicted. Besides healers (assipu), recovery was aided by physicians (an assu), who used remedies with pharmacological properties that were similar to current prescriptions [14]. From Sumerian clay tablets (ca. 4000 BC), the Babylonian Code and The Statute of Hammurabi (2285–2242 BC), it was known that medical procedures and fees would be ‘regulated’ and that Hammurabi was available to ‘*heal all injuries*’ [31].

Like disease, health was regarded as a cosmic phenomenon and left to supernatural powers to maintain [32]. While there was some concern by the assu for the restoration of health following a disease, there was no evidence that exercise was ever considered to enhance health or to facilitate recovery. The health concerns of the Mesopotamia cultures were focused on hygiene and sanitation that began with the Sumerians who followed practices that were similar to those associated with the Indus Valley civilizations [30].

Physiologically, the liver was the organ of importance because of its role in the production and distribution of blood. It was also considered to be the site of the soul, the center for the vitality of the mind and emotions and the foundation for divination. Besides the Mesopotamia cultures, divination was subsequently practiced by the Greeks and Romans [33].

The Hebrew Influences

The Hebrew practices had components from the Egyptian and Babylonian cultures that existed during the period of Abraham in the Old Testament (2000 BC) to the preparation of the Talmud (200 AD). Unlike their geographical neigh-

bors, the Hebrews believed that one supernatural source was responsible for disease and health. Disease and premature death were regarded as originating from God while illnesses were attributed to previous violations of religious ordinances or as punishment for sins and transgressions [34]. This perspective is demonstrated in the Book of Exodus (15:26) when Moses recalls the conversation with the Lord. He spoke [35, p. 60], '*...and wilt give ear to his commandments and keep all of these statutes. I will put none of these diseases upon thee, which I have brought upon the Egyptians: for I am the lord that healeth thee*'.

The treatment and recovery from a disease was dependent upon a benevolent and divine source that necessitated prayer and repentance while physicians were considered messengers of these powers. The Old Testament gives minimal attention to the restoration of health after an illness but provides extensive and explicit hygienic instructions in the Books of Exodus and Leviticus concerned with cleanliness and the prevention of select diseases [35]. However, there were no indications within the Bible pertaining to whether exercise had importance to the enhancement of health or for the recovery from select illnesses. In II Chronicles (16:12) and during the era of King Asa (915–875 BC), it was noteworthy he requested assistance from a physician, rather than the Lord, to treat a serious foot ailment, because the refusal indicated a separation had begun between medicine, the priesthood and the use of magic [34, 35].

While the physiological information within the Old Testament is meager, blood and the heart were acknowledged in the Book of Leviticus (17:11) when it stated '*For the life of the flesh is in the blood*' [35, p. 49] with the heart being the center of life. After the death of Galen and the publication of the Talmud, there was a marked increase in the amount of physiological information being conveyed.

The Influences from Persia

Geographically, Persia lies between the Tigris and Euphrates rivers on one side with India and Afghanistan on the other side. It is bounded on the south by the Persian Gulf and on north by the Caucasus Mountains, the Caspian Sea, and the steppes of Asiatic Russia [36]. It is the viewpoint of Sigerist [37] that Persia never developed a civilization that was capable of leaving a permanent mark on the course of human culture, except in the area of religion. Hence, its culture contained a myriad of influences from India, Egypt, Assyria, Babylonia and Greece. The period of historical importance was the Achaemenid dynasty (648–330 BC, that occurred after the Persians conquered Babylonia) which highlighted the reigns of Cyrus II and Darius III (who had Egyptians as court physicians) and the destruction of Persepolis in 331 BC by Alexander the Great of Greece [38, 39]. At the time of Darius III death, Persia had conquered and added Egypt, India, and Thrace to its empire [39]. During this period, the religion of Zoroaster was practiced with the holy scriptures being recorded within the various books of the Avesta

(Zend-Avesta or the Bible of Zoroaster) from India with the information devoted to health and medicine being located in the hymns of the Avesta or the Vendidad which translated means 'The law against the demons' [40].

Within the religion of Zoroaster, man is placed in a dualistic universe who is confronted with the powers associated with goodness, light, life, and truth as well as those associated with evil, darkness, destruction, deceit and death [41]. Gods and spirits (daevas) prevailed with health and disease being the '*gifts of gods*' who were capable of sending demons to cause bodily diseases [36]. According to the mythology within the Vendidad of the Avesta and the '*book*' which contained information relevant to health and medicine, the ruffian god named Angra Mainyu created 99,999 diseases to which the supreme god (Ahura Mazda) countered with a holy mathra and a Airyaman or god of healing. It was evident within the mathra [40, p. 222] that Ahura Mazda was responsible for the health of his followers, '*I drive away sickness, I drive away death, I drive away pain and I drive away fever, I drive away the disease, rottenness, and infection which Angra Mainyu has created by his witchcraft against the bodies of mortals. I drive all manner of diseases and deaths.*' Health was bestowed as a reward for obedience to the practices and laws of the gods with the god Ameretat, after Ahura Mazda, being regarded as a protector of health [38, 41, 42].

Because disease was associated with disobedience, displeasure, transgressions, sins or combinations thereof against the gods, religious incantations and ceremonies were included within the treatment process which always included water plus other modalities that had been '*borrowed*' from the Egyptians and Babylonians [34]. The high priests and physicians of Persia attributed numerous disorders, conditions and diseases to the presence of demons. However, they also recognized that cold and heat, stench and dirt, hunger and thirst, old age and anxiety, plus temperance and bad habits were contributing factors [36] indicating not every condition had a supernatural explanation. Medical practice was sufficiently organized in that physicians healed with herbs, the knife, or with the holy word [43]. Interestingly, two subclasses of practitioners existed, the '*Durustpat or Master of Health*' and the '*Tan Beshazak or Healer of the Body*', with the former being concerned with removing the cause of the disease and the later concentrating on the treatment of the disease [39]. As with the sections on health, there was no mention of exercise ever being considered to enhance health or to serve as a therapeutic modality in the management of disease.

Although the Vendidad alluded to a change in humors with sickness, physiology was in a rudimentary stage and limited to the concept that a vital force perished when death occurred. It was uncertain as to whether Persian physicians accepted the humoral theory that evolved from the Indus Valley. While Sigerist [37] and Elgood [39] indicated it was plausible, other scholars were not as positive.

The Indian Influences

The Indian influences began with the Aryan (Indo-European) invasion of the Indus Valley (ca. 2000 BC), which drove the inhabitants into the southernmost regions of the peninsula [21]. Antiquity information concerning the cultural beliefs, health practices, and medical concepts of the emerging culture can be found in the earliest and latest sacred texts of India: namely, *The Rgveda* (Rig-Veda) and *Atharvaveda* (Atharava-Veda) respectively, in the *samhitas* of Susruta (Sushruta) and Caraka (Charaka) and in the *Azurveda*. To the ancient Hindus, veda referred to knowledge and azur meant to prolong life. The authenticity of the *Azurveda* [44] was challenged by Kutumbiah who wrote [45, p. i] *'There was really no veda called Azurveda. Its existence is a myth'*. However, it was the opinion of the Indian scholar Filliozat that the *Azurveda* did incorporate the essential details of the *Atharvaveda* as well as the information found in the writings of both Susruta and Caraka [12].

Insights on how the earliest inhabitants regarded life and perceived matters pertaining to health and disease can be obtained from the *Rgveda* whose date is most frequently cited as 1500 BC but listed by Gordon as early as 4000 BC [21]. Originally written in the Sanskrit language, the *Rgveda* contains 1,028 hymns of which all were directed to one or more mythological deities. While the blessings and benevolence from the gods Agni and Indra were the most frequently sought within the hymns, the attention of numerous god and goddesses were solicited that included heaven and earth [46], dawn [47], the sacred plant soma [48, 49], medicinal plants or herbs [49], waters [50] and the wind [49] which was capable of eliminating disease (*'I drive away thy disease'*). Besides paying reverence to the Aswins as the twin gods of medicine [46], the prevailing belief within the hymns was disease was associated with evil spirits affecting the body that originated from a god, sorcerer, or from an enemy (living or dead) because of sins committed in *'this or in a previous existence'* [26, 47, 49, 51]. Treatment consisted of incantations, rituals and in some situations, the use of herbs [46]. When health was acknowledged, *'that health be enjoyed by bipeds or quadrupeds'* [51], it was not linked to disease or to the recovery from a disease, but was dependent upon the pleasure of the gods. Physiologically, the humoral theory was acknowledged and prayers [52] were directed to the Aswins to *'preserve the well being of the three humors (of the body)'*. In addition, sweating would occur with toil while vigor, strength and speed were needed for combat situations [53].

The *Atharvaveda* (ca. 1000 BC), which consisted of 20 books by numerous authors with 731 hymns, prayers, incantations, or charms, contained detailed information about health and medicine. Diseases continued to be associated with supernatural forces (evil spirits) and regarded as punishments for evil deeds or for sins against the gods by individuals, their parents or because of the intentions of

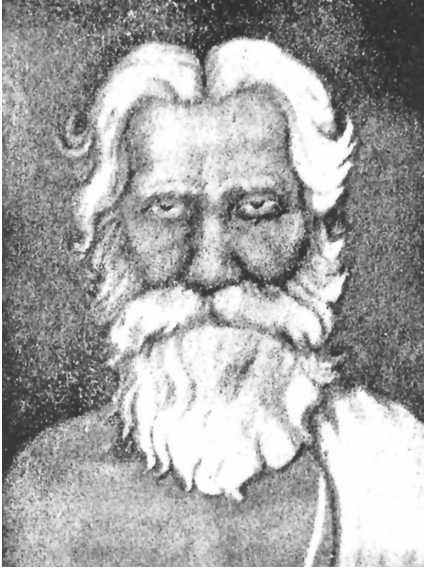


Fig. 2. Susruta of India (ca. 600 BC) who advocated exercise to establish an equilibrium between the dosas [from 63, p. 41, with permission].

their enemies [54]. Malarial fever, for example, was sent by the god Rudra to mortals and incantations were directed to the gods Varuna (sky god) and Dyaus Pita (sky father-god) for relief by medicinal plants. Hymns were focused on a myriad of diseases and conditions that included diabetes and heart disease [54, 55]. The Atharvaveda mentioned physicians used herbs, water, incantations, appeasement and purification rites, penances, and fasting for treatment purposes thus exhibiting early signs of medicine becoming separated from magical-religious doctrines [26, 45]. Like the Rgveda, there was limited information concerning whether exercise was advocated to improve one's health or recovery status.

Sometime during the late Vedic Period (ca. 1500–800 BC) the tridosa (also known as the tridhatu) doctrine [56] was formulated and briefly mentioned within the *Avesta* and the *Rgveda*. It emerged to help explain the phenomena of disease and health as well as life and death [57] and indicated the elements of water, fire, air, earth, and ether were responsible for the formation of the human body. Interacting within the body were three nutrient substances which originally were 'microcosmic representatives' of the wind, sun and moon that, by the time of Susruta (fig. 2) became dosas (humors) that were identified as air, bile, and phlegm [56]. However, Susruta added blood as the fourth humor with the capability of influencing the interactions between the others [57]. The ancient Indians identified the three humors (dosas) as vayu (or vata), pitta, and kapha. Vayu was the vital force responsible for movement, activation of the sympathetic system, maintenance of the vital breath, enhancement of digestion, movement of chyle

and blood through the body, and the maintenance of life. Pitta was responsible for the formation of colored pigments from the liver and spleen, promoting digestion and metabolism, increasing heat production, and aiding fluid movement to and from the heart [56–58]. On the other hand, kapha was to provide mucus substances to the alimentary canal, promote growth, transport body fluids throughout the body, bathe sense organs with fluids, promote body strength and endurance [59] and ‘*contribute to the proper healthy functioning of the body*’ [60, p. 12]. Food was responsible for the supporting structures represented by chyle, blood, flesh, fat, bone marrow and semen while the waste products (malas) were feces, urine and sweat [26]. Indians quickly realized that life was characterized by the first gasp of air by the newborn and death by labored breathing while associating these events with the entrance and passage of the soul [26]. Consequently, the physiology of breathing was of importance to their religious and health beliefs. The circulatory system had 1,000 veins and contained both arterial and venous blood (they had differences in color) that circulated in upward and downward directions [61]. Nerves were described as channels and prana was the nervous energy they carried to the brain, heart and to the lower regions of the body [62]. The occurrence of fatigue with toil was acknowledged as was the need for strength, energy, and vigor for well-being. Aryans enjoyed athletic contests and games, chariot races, hunting and dancing [21]. Whether they had any bearing on Hymn LVII is unknown which contained the words [54, p. 226] ‘*Let it be health and joy to us. Let nothing vex or injure us.*’

Inherent in the tridosa doctrine were the concepts that the vayu, pitta, or kapha humors controlled and regulated all functions of the body [60], and that dosas did not increase or decrease spontaneously. Specifically, they had to be displaced or deranged to produce diseases within the tissues [56, 59]. Besides known diseases, conditions that could displace the dosas were climatic changes, select foods, poisons, fatigue and psychic disturbances. However, the balance, harmony, or equilibrium between the dosas was not restored by natural means; rather, a designated regimen was required that included exercise, diet, and medication [56, 59]. Thus disease was a disturbance of the equilibrium between the three dosas whereas health was the state when the humors were at their normal levels [56, 59]. As emphasized by the physician Caraka (fig. 3) who followed Susruta and wrote [63, p. 39] ‘*the disturbance of the equilibrium of tissue elements is the disease while the maintenance of equilibrium is health*’. Susruta indicated vayu was ‘*deranged*’ by prolonged hard work, carrying heavy loads and by violent movements [60]. Thus the strenuous activities advocated by Caraka (running, swimming, jumping, tumbling and combative sports as wrestling against an opponent with superior strength) would have been considered unhealthy by Susruta [60]. Susruta believed the kapha humor was increased by a sedentary existence (inactivity), sleeping during the day, and by excessive consumption of food and drink.



Fig. 3. Caraka of India (ca. 200 BC–100 AD) who advocated exercise to ‘cure’ diabetes [from 20, p. 17, with permission].

He felt the kapha humor was displaced by sedentary habits (inactivity), sleeping in the day and excessive consumption of foods and liquids [60], hence it was no surprise several centuries later that Caraka [63, p. 152] recommended physical exercise for the ‘*alleviation of dosas (especially kapha)*’.

Susruta defined exercise as ‘*a sense of weariness from bodily activity*’ that should be taken daily [64, p. 485] whereas Caraka [63, p. 151] considered exercise to be ‘*Such a physical action which is desirable and is capable of bringing about bodily stability and strength is known as physical exercise. This has to be practiced in moderation.*’ Susruta favored moderate exercise being performed for durations that were half of what was required to achieve exhaustion and that would be discontinued when breathing became labored [65]. He felt chronic exercise would make individuals stout, strong, firm and compact, promote growth of limbs and muscles, enhance digestion, reduce corpulence, delay fatigue, and improve the appearance of the deformed and aged [64]. Diabetic individuals [66, p. 377], were to perform ‘*regular physical exercise, wrestling, active sports, riding on an elephant, long walks, pedestrian journeys, practicing archery, casting javelins*’, etc. Caraka stated training would inhibit the heart, increase work capacity, result in leanness, and reduce discomfort while enhancing digestion, perspiration and respiration [67]. He recommended daily walking or gymnastic activity for most individuals and considered strenuous exercise to

be a cure for diabetes [68]. Susruta suggested that Indians should exercise in the winter and spring but at an intensity level that was half their capacity (or when perspiration appeared on the body) as death could ensue. Besides his views on humors, he felt diseases [64, p. 486] *'fly from the presence of a person habituated to regular physical activity'* just as small beasts do when seeing a lion. In contrast, excessive exercise would cause coughing, fever, vomiting and weariness while inducing diseases as consumption, tuberculosis, and asthma [64]. Caraka also indicated death could occur from excessive exercise as would dyspnea, heart and gastrointestinal diseases, and bleeding from organs [63].

The Influences from China

Before the designation of Emperors and establishment of dynasties, the health of the ancient Chinese was determined by a world that consisted of gods, demons, devils and spirits. Disease was the result of demons and devils who possessed the body and whose removal required incantations, charms, and offerings. With time, there became one devil for every disease. When cures occurred, they were attributed to supernatural powers [20].

Like the papyri of Egypt and the Rgveda of India, the Ma-wang tui documents of China related to periods that existed before these classical medical documents were written (200 BC–100 AD) [69]. This is an interesting authenticity point because Gordon [70] stated medical gymnastic breathing exercise were practiced in China as early as 2500 BC by Tschì Sung Ti whereas the French missionary, Pere Amiot [71] reported in 1779 and the French physician Gustave Chancereau [72] in 1864 that Taoist monks in Peking were practicing therapeutic medical gymnastic exercises (identified as Cong-Fou) known since the era of Hoang-Ti (ca. 2698 BC). Drawings provided by Amiot show seated monks performing stretching type movements [71]. Since Taoism evolved after the birth of Lao-Tse around 600 BC, it was unclear whether the monks were performing an ancient therapeutic exercise or a current one of their era.

In the Shang Empire, the first Chinese dynasty (ca. 1800–1100 BC) to leave records of importance to this manuscript [69], they recognized the existence of numerous illnesses but few diseases. As with their ancestors, they believed wind spirits were evil and a cause of illness. When disease was present, it was usually associated with a curse from an ancestor [20] or with a punishment for a sin previously committed [69]. Healing required prayers, incantations, divination and herb therapy that were conducted by priests and sorcerers or priest-doctors who also used astrology [20]. While rhythmical breathing exercises with arm movements were advocated for select illnesses with cures expected in several months [70, 73], there were no reports of other types of exercises being practiced (fig. 3).

China is associated with three religions; namely, Taoism, Confucianism, and Buddhism. The first two were founded in China whereas the latter came from India. Tao, 'or the way' in its original form was 'pure philosophy' and closely linked to medicine [74]. The age of philosophy and the golden period of Chinese medicine (ca. 1121 BC–960 AD) followed the demise of the Shang Empire and incorporated the Chou dynasty (1050–256 BC). Although controversial, this time period is associated with *The Yellow Emperor's Classic of Internal Medicine* [74] and the era when the functions of the priest-doctor were separated so that issues related to religion became the responsibility of the priest whereas those pertaining to medicine and medications became the duties of the physician [20].

Emerging during this period were the principles of the Yinyang Doctrine [74]. In accordance with the doctrine, the universe was not created by divine action but by a self-generated process of nature that functioned on the dualistic principles of yin and yang [74, p. 15] which includes, '*The principle of Yin and Yang is the basis of the entire universe. It is the principle of everything in creation. It brings about the transformation to parenthood; it is the root and source of life and death.*' In addition, '*Heaven was created by an accumulation of Yang; the Earth was created by an accumulation of Yin*'. Yang was the active, positive and masculine principle represented by the sun, heaven, day, fire, heat, dryness, light, etc. whereas yin was the inactive, negative and feminine principle identified with the moon, earth, night, water, cold, dampness and darkness [74]. Therefore all animate and inanimate objects as well as circumstances and phenomena were a combination of these principles with the human body consisting of three parts of yin and three parts of yang [74]. Within this dualistic relationship, yang was associated with life and health while death and disease were identified with yin.

A yin disease was associated with internal causes, lower regions of the back, delayed onsets, chills, cardiovascular disorders, and when the patient could not lie on their back, whereas a yang disease was identified with external causes, upper regions of the body, fevers, sudden onsets, respiratory disorders and when the patient was unable to bend forward [20]. Inherent in the doctrine was that both principles had mutual affinities and antagonism toward each other which required a proper balance (equilibrium) before harmony or health could occur. Although acupuncture was used well before the Chou dynasty to remove the demons and evil spirits from the body, it became a specialized treatment requiring knowledge of a complex system of yin and yang anatomical sites to restore the equilibrium between the opposing principles. It also necessitated a detailed understanding of the pulse rate relationship to disease as elaborated by Pien Ch'iao as each part and organ had its own pulse [75]. The physician was required to compare the pulse rate to the rhythm of breathing before making a diagnosis. However to preserve health, it was necessary that individuals not perform excessive exercise [74].

During the Chou dynasty, the doctrine of the five elements was also emphasized. In accordance with this doctrine, the human body consists of a ratio between metal, wood, water, fire and earth whose union produced life while their separation meant death [76]. When their ratio was in 'proper' proportions (in equilibrium), the individual was considered to be healthy. However, any disturbance of this ratio would cause disease(s). As these elements were associated with the spleen, liver, heart, lungs and kidneys, it was possible to identify the 'disturbed' element [20].

In accordance with Nei Ching, as cited by Wong and Lien-Teh [77] and by Gordon [70], the liver formed the heart and ligaments while controlling the lungs. In turn, the heart produced and controlled the blood which circulated continuously within a circle *'that never stopped'* so that in 24 hours it made 50 completions. During inspiration, blood traveled a distance of 3 inches during inspiration and another 3 inches during expiration. The blood contained yin and yang which was distributed through 12 channels with the fluid component (plasma) going to yin areas while the solid constituents (cells) went to yang regions within the body. Besides being responsible for the pulse, the heart formed the spleen, converted fluid into perspiration and regulated the kidneys. The spleen created and nourished the flesh, produced the lungs, converted fluid into saliva, nourished the lips and was responsible for the liver. Both lungs formed skin, hair, and the kidneys, transformed fluid into nasal secretions, maintained the skin while nourishing the fine hairs of the body, and controlled the heart [70, 78]. Lastly, the kidneys produced bone marrow, created the liver, maintained the bones, converted fluids into spittle, nourish the fine hairs, and controlled the spleen [20]. In a document attributed to the Yellow Emperor (*Huang-ti nei-ching*), it was mentioned by Unschuld [69] that circulating vapors were more important than blood and were essential for life.

Huard and Wong [79] noted the Chinese enjoyed dancing, games and performing physical culture activities during the Chou and the Chin's dynasties. During those eras, physical culture consisted of induction, massage, immobility and the Dao being prescribed which consisted of stretching, massaging and breathing procedure to promote energy flow, meditation and harmony with the universe (fig. 4). At the time of Galen's death and during the Han dynasty, the great Chinese surgeon Hua T'o was an enthusiastic proponent of systematic exercise to enhance health. He is reported to have told his disciples [78, p. 54], *'The body needs exercise, only it must not be to the point of exhaustion for exercise expels the bad air in the system, promotes free circulation of the blood, and prevents sickness.'* Apparently he practiced exercises (frolics) which mimicked the actions of deer, tigers, bears, monkeys and birds which strengthened legs, gave a sensation of lightness of the body, increased the appetite, prevented old age and removed diseases while enhancing health. After Galen's death, China 'adopted' Buddhism from India and followed its beliefs and practices which included exercises to improve fitness and to enhance health [20].

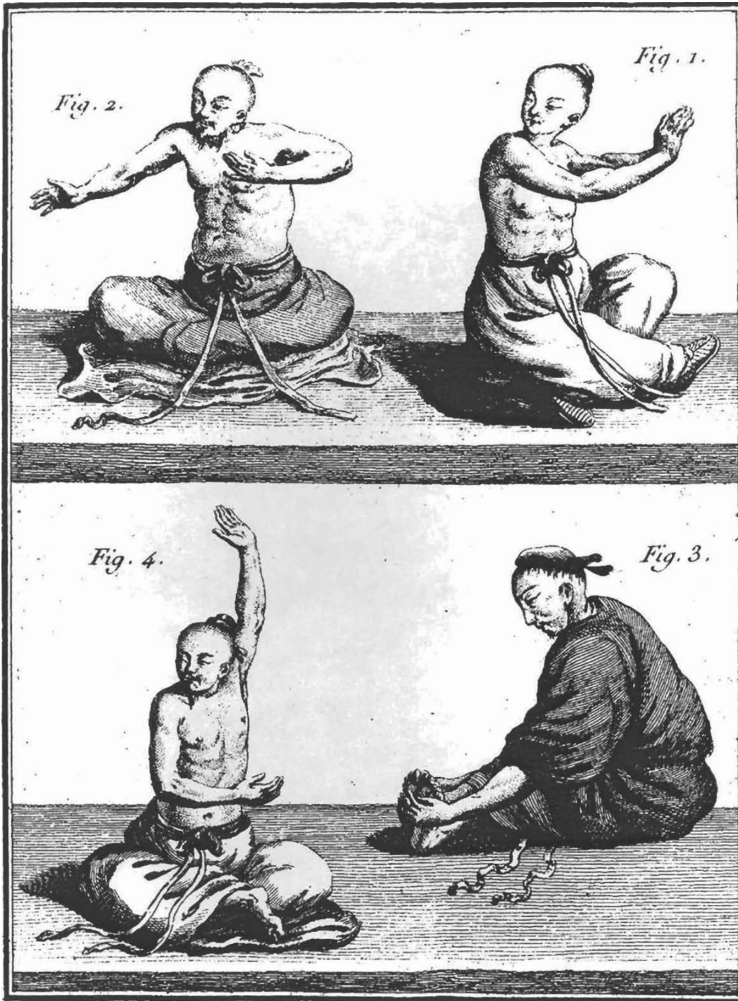


Fig. 4. Ancient Chinese breathing exercises [from 203, p. 451].

Influences from Greece That Include Hippocrates and Erasistratus

Background Information and the Influences from Sparta

Archeological evidence indicated ancient Greece was the site of two ‘great’ civilizations and one Classical period. The civilizations were the Minoan (3000–1100 BC) and the Mycenaeans (1550–1050 BC) with the Classical Period involving the 5th and 4th centuries BC [80]. These inhabitants of the

Balkan peninsular, the islands of the Aegean Sea and the coasts of Asia, were collectively known as the Hellenes and were a composite of various tribes with different dialects and social organizations who colonized the regions by migrations and invasions between 1300 and 1000 BC. The Achaeans were located in northern Peloponnese, Arcadians in the central mountains of Peloponnese, Aeolians in the northern region of the eastern Mediterranean basin (Thessaly), Ionians in the central regions of the basin with the Dorians becoming settled in the southern regions that included Sparta [81].

Like other cultures, the Hellenic priests and physicians attributed disease and illnesses to the actions (punishment) from one or more deities while seeking protection, healing and health from others. For the Hellenes, Zeus was the supreme god who ruled from Olympia; Athena was daughter of Zeus who had various healing functions; Apollo was the son of Zeus and the primary god responsible for inflicting illness while rendering natural deaths to males. His sister Artemis had the same ‘powers’ plus causing natural death to females while Asclepius, who was once a mortal, became a deity as the son of Apollo 1 and subsequently became revered as the physician god of healing. His first daughter was Hygeia who became the goddess of health while the second daughter, Panacea, became the goddess responsible for treatment [82]. If death did not occur from the disease or illness, prayers, sacrifices and/or purification rites were initiated to ‘solicit’ interest of the gods so that recovery could occur, a collective process that was described by Gordon [82] and by Sigerist [83] as religious medicine. Unfortunately, the only written documents to provide insights on Greek culture and medical practices during these early years were the epic poems of Homer (ca. 750 BC) that described conditions predominately associated with the Trojan War (ca. 1250 BC). In the *ILIAD*, Homer [84] indicated Asclepius was a tribal leader who had two sons, Machaon and Podalirius, that became skilled physicians. On the battlefield, warriors as well as physicians treated the wounds of their comrades, and in some instances used drugs. In most situations, diseases were caused by the gods, e.g. a plague was sent by Apollo; however, there were times when the supernatural was not involved. While Egypt was recognized for the training and skill of their physicians, minimal information was provided concerning specific diseases or illnesses, how health was perceived or related to the recovery process. Extensive information was included by Homer on the Greek admiration of athletic skills and warrior abilities as well as the various competitive athletic events scheduled between warriors for the funeral games of Patroclus (chariot racing, boxing, wrestling, running, discus and spear throwing plus archery contests) [84].

Robinson [85] indicated competitive events were scheduled at Olympia as early as 1370–1104 BC and definitely during 776 BC. However, there was little information available before 500 BC on how competitors trained or prepared for

their events. Since exercise can be advocated to improve performance as well as health, it is important, when reading ancient Greek documents, to realize that the general term for exercise was *ascesis* and that an ascete was an individual who exercised his mind and body [86]. Moreover, the individual who exercised only to win a prize (an *athlon*) was classified as an athlete. The Greek word for nude is *gymnos*, hence the term gymnastics was used to describe individuals who exercised in the nude [87]. Thus during the era of Homer, individuals exercised in the nude when performing competitive gymnastic activities. The same was true for the events during the early Olympics that were scheduled after 776 BC.

Dorians conquered the Peloponnese around 1000 BC and subsequently established the state of Laconia and the city of Sparta. They were vastly different than the Ionians who migrated to the region that became Athens [88]. This difference was manifested in the type of governance being established, the philosophy and purposes of education, and in their obedience to the laws of the state. In terms of political power and influence within Greece, Sparta's zenith was during 600 BC when it had become [89, p. 1] the '*strongest single power in the Peloponnese*'. This influence began to decrease during 500 BC when it remained steadfast against the Persian invasion before becoming lost after 400 BC because of a failure to control the states in northern Greece and to defeat Persia [89]. After the '*humiliating King's Peace of 387 BC*', she became reduced to the '*status of a provincial second-rate state*' [89, pp. 1–2].

After establishing an oligarchic form of government with a constitution and an educational system whose primary purpose [90, p. 165] was to '*maintain an army of experts who were ready and able at any moment to suppress sedition within the state or repel invasion from without. The Spartan was a professional soldier and nothing else, and his education directed entirely to two ends-physical fitness and obedience to authority.*'

Like all inhabitants of Greece, the Spartans relied on their gods to protect them from death and diseases. However, death with honor was expected of the male Spartan whether in the flogging ritual at the altar of Artemis Orthia or on the battlefield. Health was focused on being physical fit for the benefit of the state to the extent that babies who were judged to be unhealthy were left to die at the site named *Apothetae*. Healthy males were to become warriors whereas healthy females were to become mothers of warriors. To achieve these goals, fitness and athletics were advocated for both males and females [90]. In fact, only in Sparta and Chios were women allowed to compete against males in wrestling [91].

After the age of seven, children left their homes to live in barracks with others of their age group where they remained until adulthood and marriage. The educational curriculum for both males and females included the arts, music and gymnastics although its focus was preparation for a warrior state. Concerning the education of young males, Wright states [91, p. 68]: '*Of book*

study there was practically none. Hunting, scouting, and foraging for food took up most of the boys' time. Males did not participate in competitive activities in music, dancing, or athletics until they were ten and the emphasis in dancing or athletic events was more for physical than for artistic purposes. The same was true for festival games where endurance and tolerance to pain were expected and intrinsic to the event. While Olympic records indicated Spartans were frequent participants and victors, details of how they 'trained' are missing as are records concerning how they prepared warriors for battle. From the information available on Spartan life, it is safe to assume the frequency of gymnastic or warrior-training bouts was high, intensity ranged from moderate to heavy and the duration was long to very long [88, 90]. Other than their emphasis on fitness, there were no major Spartan contributions to exercise physiology.

The Emergence of Greek Ideals and Practices

The transition from the religious medicine practices of 1000 BC to the rational medical procedures of the Hippocratic era were associated with Hellenic cultural transformations that included the designation of sites (Asclepieia) which led to temples and cults being devoted to the god of medicine. By 600 BC, Asclepius had become a god with healing temples established in Thessaly and Epidaurus [83]. In 420 BC his cult was introduced in Athens and in 295 BC one was established in Rome. The transition also included the 'borrowing' of the alphabet from the Phoenicians and mathematics from the Egyptians with the emergence of schools at Miletus and at Croton which emphasized philosophy and the natural sciences [92].

Interestingly, it was not the priests at the Asclepieia [92, p.85] who were *'the direct founders of Grecian medicine'*, rather it was members of the Asclepiadae or the guilds of purely lay physicians whose membership, including Hippocrates, were from *'descendents'* of Asclepius that assisted the priests at the temples with the rites before leaving to travel the countryside to practice their profession. From the inscriptions found on the walls of their temples, they provided drugs when necessary and advocated bathing, massage, diet and exercise to assist the healing process [93]. Presumed to be gifted and highly intelligent, they increased their education from their conversations with 'celebrated men' during their travels and not from attending established schools [92].

The school at Miletus was founded by Thales (639–544 BC) and several of its graduates provided philosophical insights for various biological concepts that emerged from these times. Thales believed water was the basic element in plant and animal life and the source of earth and air [94]. Anaximander (611–547 BC) extended the view of Thales and felt that all living creatures, including humans, had their beginnings in water. He also proposed the universe existed because of a balance between opposing forces [95]. In contrast,

Anaximenes (610–545 BC) felt that air was divine and responsible for substance, motion, and life whose presence animated the blood and the heart. However with death, it (a psychic force) left the body [95].

Pythagoras (570–490 BC) was invited by the Senate of Croton in Italy to develop a School that emphasized philosophy and science which flourished until the fourth century [96]. He was also responsible for developing a religious cult that followed the mystical practices of Orpheus of which music was an integral component. The philosophical emphasis was on the immortality of the human soul in a universe (that was round and contained a heaven) which encompassed God, time, eternity, and natural phenomena as a commonality. Associated with his philosophical instructions were discussions on astronomy, geometry and music. In his doctrine on numbers, perfection or God was 1, matter was 2, worlds were 3 and the universe was 12. Dividing the universe by its worlds yielded 4 concentric spheres composed of four elements (fire, earth, water, and air) which possessed the four qualities (moisture, dryness, heat, and cold) which subsequently became encompassed into the humoral theory of disease that will be discussed later. While Pythagoras used prayers, offerings and music in his religious practices, he did not believe the gods were the causes for all evil or diseases. Rather, all diseases and bodily sufferings arose from dissolute behavior whereas good health was a state of harmony (equilibrium) between the opposing elements, qualities, or tendencies in the body. To help achieve harmony, careful dietary practices and daily exercise were required. This meant repeated long walks and participating in events as running, wrestling, discus throwing, and boxing [96]. It has been suggested that Pythagoras was an Olympic competitor and a friend of Milo of Croton who was a great Olympic wrestling champion and among the first to practice progressive resistive exercise in training for a competitive bout [97].

A notable graduate of the Pythagorean School was Alcmaeon (ca. 500 BC) who made medicine the study of his philosophy [98]. Physiologically, he had the brain serve as the seat of the soul and responsible for thought, sensation and motion. Nerves functioned as channels for the pneuma (air), odor required the presence of the brain, and taste occurred because of an interaction between humidity, heat, and softness. He believed health represented a harmonious equilibrium between the qualities of wet, dry, hot, bitter, sweet, etc. with disease occurring with the supremacy of any one quality. In addition, diseases occurred with excesses or deficiencies of food, an excess of either heat or cold, phlegm from the head, black and yellow bile from the blood, substances from marrow or water, fatigue and from personal hardships [98, 99]. To cure these diseases, it was necessary to determine what elements were missing and to restore the missing qualities. Alcmaeon views coupled with those of Empedocles (see subsequent material) became the foundation for the humoral theory which is usu-

ally attributed to Hippocrates [100, 101]. Other than noting that fatigue was a contributing factor to disease, little is known about Alcmaenon's interest in exercise or its effects.

Empedocles (504–443 BC) of Agrigento in Sicily was also a disciple of Pythagoras who proclaimed that all matter, including the human body, consisted of the elements (roots) water, earth, fire and air (aether) with transformations being possible without origination or destruction (conservation of matter). Growth was the result of changes in the elements, tissues had equal parts of the four elements, nerves contained two parts water, one part fire and one part earth whereas bones contained one part of earth, four parts fire, two parts water and one part air [102]. Furthermore, human intelligence was influenced by their proportions. He discovered atmospheric air, described the process of inspiration and expiration, felt respiration occurred before birth, considered circulation to be a process of flux and reflux and discussed vision as an in-going and out-going event [103]. Empedocles proclaimed transformations occurred between elements and their qualities in that [103, p. 102]. *'These (elements) are forever themselves, but running through each other they become at times different, yet are forever and ever the same.'* To Garrison [104, p. 77] these changes were as follows:

hot + dry = fire	cold + dry = earth
hot + moist (wet) = air	cold + moist (wet) = water
hot + moist (wet) = blood	cold + moist (wet) = phlegm
hot + dry = yellow bile	cold + dry = black bile.

Inherent with this elemental theory was the premise that diseases would occur with any disturbance of their relationships with health being present when the elements were in equilibrium [105]. Although Empedocles strongly promoted godly means to treat disease, he became a hero to the people of Agrigento by stopping the spread of epidemics by non-godly preventive measures, e.g. draining a swamp and blocking a rift in a hill [106]. Whether he had any views on the role of exercise in either health or disease is unknown.

Gymnasiums were dedicated to Apollo and existed before the Asclepiadae were established [107]. As in Sparta, they (three) were operational in Athens and achieved their prominence during the eras of Hippocrates and Plato. In fact, the most famous was the Academy where Plato taught. It was a public institution, contained stadiums, and provided instruction in music, grammar, literature and gymnastics for affluent and wealthy boys up to the age of 16 years. Attendance was compulsory for 2 years with males (or females in Sparta) when they became 18 years old. Gymnasiums also served as a meeting place for older adults and philosophers and as a training site for gymnastic exercises [107]. Physicians not only served as the director (Gymnasiarch) and subdirector (Gymnast) of the institution, they functioned as Iatroliptes whose duties included preparing prescriptions, performing venesections, and massages, reducing dislocations, and

'advising' trainers on gymnastic exercises [108]. Gymnastic exercise was an extremely important component of the education of the Greek student because of its importance in obtaining a healthy body [109]. They included racing for speed and distances, extended walks, wrestling, boxing, jumping, throwing the javelin and the discus, dancing and playing games with balls [107]. Collectively, the gymnasia physicians were known for favoring exercises over medical treatment to restore health [110]. This was true for Herodicus (480 BC–?) of Selymbria who was considered by Licht [111] to be the *'father of therapeutic gymnastics'*. He apparently recovered from an incurable disease by following his personal exercise regimen. Because his regimens were so complex that a knowledge of geometry was needed to execute the movements, the system was seldom used or advocated [111]. Although Herodicus significantly influenced Hippocrates on the health benefits of exercise, he was criticized by his 'star pupil' for prescribing exercises that were too strenuous for patients [112]. Later, Plato chastised Herodicus for his severe training practices which were unnecessarily prolonging his life span and likely those of others. He wrote [113, p.91], *'But Herodicus, being a trainer, and himself of sickly constitution, by a combination of training and doctoring found out a way of first torturing and chiefly himself, and secondly the rest of the world.'* Plato considered the process as a *'lingering death'*.

The zenith of the Panhellenic games [114] held in the Olympia valley was during 500 BC. Unlike the earlier games, many potential competitors practiced in the stadiums of the gymnasiums and had professional trainers assist them in the process. Authors have identified individuals who provided this service as trainers, paidotribes, alpeipes, and gymnastes. Since paidotribes means *'boy rubber'* and aleiptes meant *'anointer'*, Harris believed these two terms related more to massage duties whereas the coaching responsibilities were best represented by the other two terms [115]. The majority of their advise was devoted to skill acquisitions and to dietary and lifestyle practices with minimal emphasis on training explanations. In fact, their lack of 'scientific' insight and knowledge on such matters raised the ire of both Hippocrates and Galen.

Some trainers did advise athletes to use repeated repetitions, to practice overload to increase strength (bending rods of wrought iron, pulling wagons with yoked animals, lifting animals, boxes and stones, having heavier halters with the jumping exercises, throwing heavier javelin like equipment for height and distance), to chase animals to increase speed, and to run in the sand for long distances to improve endurance for aerobic events [86, 115, 116]. By the time of Galen, many trainers had adopted a tetrad system of training which had similarities to current practices. It was a 4-day system which highlighted preparation, concentration, relaxation and moderation. On the first day the athlete was to perform numerous short-term but intense exercises that would *'prime'* him for the next days activities; the second day was an 'all out' effort to exhaust the

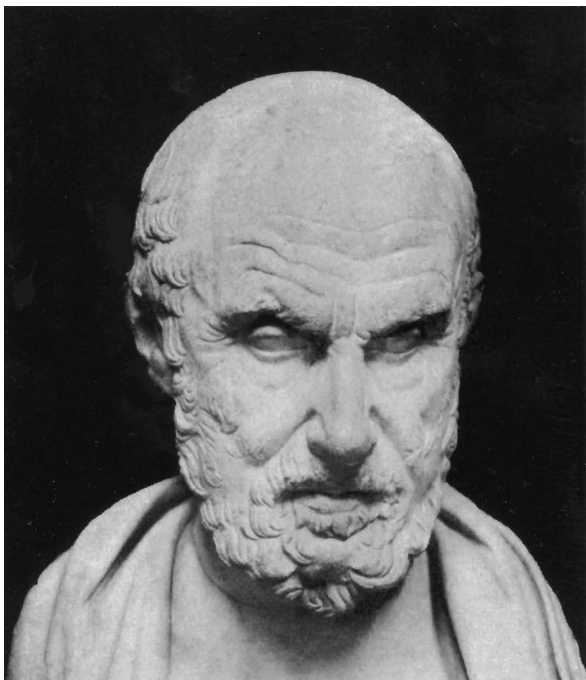


Fig. 5. Hippocrates of Cos (460–370 BC) who is attributed to have separated medicine from philosophy and religion while becoming the father of scientific medicine [from 150, p. 91, with permission].

athlete, the third day was devoted to relaxation and recreation, while the fourth day was one of moderate exertion in skill activities. After the death of Galen, this method of training was severely criticized by Philostratus for its rigidity and lack of consideration for individual differences [116].

The Views of Hippocrates

Prior to the emergence of Hippocrates, Anaxagoras (500–428 BC), a philosopher from Clazomenae in Asia Minor, believed that life arose ‘in the moist’ [117] and proposed that diseases originated from bile before entering the blood vessels, lungs and pleura [92]. Around 440 BC, Philolaus proposed that changes in bile, blood, and phlegm were the causes for diseases [118].

When the views of Hippocrates of Cos (460–370 BC) are discussed (fig. 5), it should be remembered that he may not be the responsible author of the

approximately 76 books on Greek medicine collectively known as the *Corpus Hippocraticum* that have their origins in the 5th and 4th centuries BC [119]. Consequently, one should not be surprised to read ancient texts that are speculative, redundant, contradictory, or confusing. Although in the Hippocratic Oath for Physicians (ca. 400 BC) Hippocrates acknowledged Apollo, his son Asclepius, daughters Hygieia and Panacea, and all the gods and goddesses [120], there was nothing in the oath to indicate disease had a supernatural or religious origin. The Roman Celsus attributed Hippocrates as being responsible for separating medicine from philosophy [118] while historians Garrison [104] and Haggard [121, p. 28] credit Hippocrates as being responsible for separation of medicine from religion and magic and for having '*relieved the gods of their responsibilities for the prevention and treatment of diseases*'. Thus his era was the beginning of rational medicine and the one that established his legacy as the father of scientific medicine [122].

Hippocrates accepted the belief that the human body contained four elements whose four qualities had to be in perfect equilibrium or harmony to prevent the occurrence of disease and for health to exist. He wrote extensively on diseases and classified them into acute, chronic, endemic, and epidemic categories. They were the result of a lack of an equilibrium and were both general and personal in nature [123]. He discussed in *Airs Waters and Places* [124] and in *Breaths* [125] aspects related to air, climate, seasons, water and sanitation that had to be mentioned when causes of disease were considered. In *Aphorisms*, III, Hippocrates stated [126, p. 123], '*It is chiefly the changes of the seasons which produce diseases, and in the seasons the great changes from cold or heat, and so on according to the same rule.*' Diet and exercise were also important considerations for the attainment of health and for the prevention of disease, especially the excessive consumption of food and drink. On this subject he wrote in *Regimen, Book I* [127, pp. 227–229], '*Even when all this is known, the care of a man is not yet complete, because eating alone will not keep a man well, he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health.*' He continued, '*A man must observe the rising and settings of stars, that he may know how to watch for change and excess in food, drink, wind and the whole universe, from which diseases exist among men.*' In *Regimen, III*, he related the topic of food and exercise to the incident of disease and stated [128, p. 367], '*But the discovery that I have made is how to diagnosis what is the overpowering element in the body, whether exercises overpower food or food overpowers exercise; how to cure such excesses, and to insure good health so as to prevent the approach of disease, unless many serious and many blunders be made.*' Besides its relationship with food consumption, Hippocrates believed excessive exercise or the lack of exercise were causes for disease. In *Nature of Man* he wrote [101, p. 25],

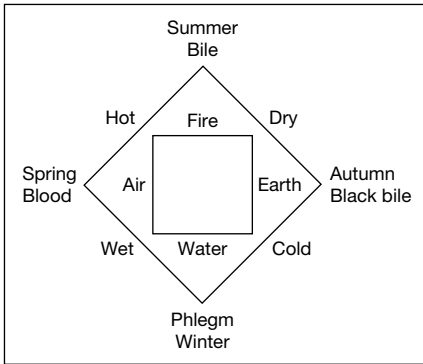


Fig. 6. The humoral theory of Hippocrates [from 129, p. 25, with permission].

‘those due to exercise are cured by rest, and those due to idleness are cured by exercise’.

The idea that disease occurred because of a failure to achieve *‘balance’* among body constituents was best illustrated by the humoral doctrine [100] (fig. 6) that is frequently attributed to Hippocrates although, as noted previously, many historians credit the doctrine to the collective efforts of Alcmaeon, Empedocles, and Philolaus with Empedocles being the most important.

In its elementary form, an equilibrium must exist between blood (from the heart), phlegm (from the head), yellow bile (from the gall bladder to the tissue fluid) and black bile (from the gall bladder to the liver and the mixing with blood) in order for health to be present and disease to be absent [100, 101, 129, 130]. Food and fluids were necessary for their formation and when their combinations were balanced, the condition was known as *crasis* and health prevailed. But whenever an increase or a decrease occurred in one or more of the respective humors, it was the beginning of a diseased condition. Readers should not be alarmed that not all medical historians agree on the identify of the respective humors because, as emphasized by translator Jones [118], different humors were mentioned in *Diseases IV, Ancient Medicine*, and in *Affections I* At the time of Plato (429–347 BC), black bile was associated with a variety of conditions and diseases that ranged from headaches, vertigo, paralysis, spasms, epilepsy, mental illness, and diseases of the kidneys, liver, and spleen [131, 132].

Fundamental to Hippocrates beliefs was that nature (*physis*) would heal disease [130]. The acquisition of health, a state of equilibrium between the humors, provided a rationale for the treatment and management of disease and disorders that, by the time of Hippocrates, became apparent to practicing physicians [133, p. 387] *‘as the only stable good among the changes and vicissitudes of life’*.

To alter the influence of humors, accustomed exercise was recommended to alleviate the fatigue pains caused by unaccustomed exercise. According to Hippocrates [134, p. 363], *'Accustomed should be practiced so that the collected humour may grow warm, become thin, and purge itself away.'*

In *A Regimen in Health* [135] and especially within *Regimen's I, II, and III* [127, 128, 134], the role of exercise in the acquisition of health was discussed. Readers must be cognizant that the Greek word for exercise (ponoi) has also been translated to mean exertion, pain, and labor [136] and recognize the listing and distinction in *Regimen II* [134] between natural exercise (activities of sight, hearing, speech and thought plus walking) and violent exercise (not defined but considered by the translator to mean excessive) are confusing and difficult to relate to 21st century definitions of exercise. For purposes of this article, excessive exercise has been interpreted to mean heavy or maximal exercise [137].

When Hippocrates described exercise, he was referring to walking, running, wrestling, swinging the arms, push-ups, shadow boxing and ball punching [136]. When prescribed, the intensity was usually light or mild at the onset that gradually increased to becoming moderate, but seldom higher. However, in *Regimen, I* [127, p. 283] and in *Regimen, III* [128, p. 411] 'sharp' runs were mentioned, to empty the moisture of the body, which suggested heavy exercise was to be performed. In *Breaths* [125], Hippocrates indicated air (outside the body) and breath (inside the body) were essential for life with breathing being a continuous process of inspiration and expiration that was increased by both exercise and disease [134]. As rapid breathing was one method to cool the *'innate heat of life'* which originated within the heart, it was regarded as a beneficial effect. Temperature changes could alter the equilibrium between humors and affect one's health status; consequently, temperature regulation was an important subject for the Greek physicians that ascribed to Hippocrates beliefs. Interestingly, he recommended warming up with exercise [128, p. 373] because *'the body performs best with warms ups under exercise'* and stated exercise would warm humors and the body while causing the skin to be moist. He indicated *'hot sweat'* could be formed in select conditions but exercise was not one of them. In addition, immoderate exercise by individuals suffering from fatigue pains could cause the flesh (muscle) to become hot, painful, and shivery and result in a *'longish fever'* [134, p. 363]. Running exercise, if not double or long, could cause the flesh to heat, concoct and to dissolve while promoting the digestion of the food. He recommended running in a cloak because the heating process was faster and would make the body [134, p. 355] *'more moist'* while enhancing the loss of excess flesh (*'which they wish to reduce'*) [134, p. 355]. Heat, as noted earlier, would also help to warm, thin, and purge the humors. While changes in the skeletal muscles were frequently mentioned, as muscle pains with fatigue, Hippocrates made no references to exercise induced alterations in the nervous and hematological systems. In *Fractures* [138],

Hippocrates observed muscle atrophy was greater with chronic dislocations of the hip in individuals who failed to exercise than those who were able to ‘practice walking’.

With select diseases, exercise was prescribed [139]. For example, when consumption had been diagnosed regardless if caused by phlegm, bile, or blood in the spinal marrow, long-term treatment consisted of foods, gruels, drinks, medication, vapor-baths, sleep and exercise. After arising from sleep, the patient was to walk for 20 stades (3.70 km). For each subsequent day he was to increase the distance by 5 stades (0.93 km) until a total daily distance of 100 stades (18.5 km) was achieved and maintained until 30 days had elapsed. During the second month he was expected to walk not less than 30 stades (5.50 km) before and 10 stades (1.8 km) after dinner. After 4 months, and on the first day, he was advised to walks 10 stades (1.8 km) which were to be gradually increased until 80 stades (14.6 km) daily was accomplished. This was done by walking 30 stades in the morning, 20 stades after dinner, and 30 stades at other times of the day. Since recovery was expected to occur within a year, Hippocrates advised the patient for the next 7 months to gradually increase his daily walking so that 150 stades (27.5 km) would be covered with 40 stades in the early morning, 20 stades after dinner, and remaining 90 stades throughout the day [139].

It was mentioned that Hippocrates believed diseases could occur with either no exercise, or excessive exercise or if either food or exercise was overpowering. In *Regimen, III* [128] he provided an exercise prescription for both conditions. For example, when symptoms indicated food had overpowered exercise he advocated a 6-day schedule consisting of slow runs, long and gradually increasing early-morning walks, wrestling with an oiled body, and a stroll after dinner. Coupled with the exercise schedule were recommendations concerning food consumption, vomiting, bathing, sexual activity and the use of ointments. On the seventh day, select foods were provided and vomiting was induced. This was followed by a 4-week period of food and exercise adjustments (not specified) resulting in recovery. When exercise overpowered food, rigor was present with the symptoms of chattering teeth, fever, and frequently, delirium. Rigor occurred when the body and head had been drained of their moisture from the cooling down process because the moisture lost was proportionate to the excess of walking, and ‘over the proper amount’ [128, p. 417]. When diagnosed, the exercise program was either terminated or reduced by one-half while the food had to be moist and cool with the fluids being mild and dilute. After 5 days, exercise was increased by one-third, after 10 days, it was elevated by one-half and after 15 days, all exercises were performed, but at a lower intensity level and for shorter durations [128].

Hippocrates associated training with increased bone development and physical stature, improved muscle mass, tone (hardness) and athletic performance.

Because of his low regard and respect for athletes and their trainers, it is speculated he did not advocate maximal chronic exercise to perfect their physical development because perfection did not allow for improvement or change. On this point he stated in Aphorism number III [126, pp. 99–101], *'In athletes a perfect condition that is at its highest pitch is treacherous. Such conditions cannot remain the same or be at rest, and, change for the better being impossible, the only possible change is for the worse.'* Despite his disdain for athletes, he advised athletes in training to wrestle and run in the winter and to 'taper' in the summer with walking and reduced wrestling. In addition, when fatigued, wrestlers should become refreshed by running whereas runners should wrestle.

The Views of Colleagues and Those Who Followed Hippocrates

Plato of Athens (427–347 BC), a younger colleague, was a philosopher, founder of the Academy, stimulated the Dogmatic School of Medicine and was *'one of the keenest intellects of all time'* [140]. He endorsed Empedocles' concept that the human body was composed of the elements' earth, air, fire and water and felt that disease and disorder occurred because of either their excesses, deficiencies or from their transformation into another [141]. If the elements formed the body in a defined order, *'health commonly results'* whereas if process occurred in reverse order causing the cool qualities to become warm, dry qualities to become moist, light qualities to become heavy, or heavy qualities to become light, disease could be expected [141]. Moreover, disease, disorders, inflammations and tumors were expected when the humors, notably phlegm and black bile, were in excess and unable to be transformed, and when the blood was replenished by irregular ways and not by food or drink [141]. In fact, anything that was unhealthy caused diseases. He was among the first to identify mental diseases and emphasized the existence of a soul that consisted of three divisions of which one was rational (reason, located in the brain) whereas two were irrational (spirit, present in the heart, and desire, found in the liver) that could be affected by bodily changes [142, 143].

Plato's concepts of anatomy and physiology were unusual. The heart was an essential organ because it housed the spirit component of the soul, was the origin of blood vessels and received commands from the reason component of the soul. Blood was red because of the action of the element fire. Bodily function was controlled by the head and the brain was responsible for generating semen. The lungs received air and water from the trachea and served to cool the heart. Inspiration and expiration occurred through the pores, mouth and nostrils. Inspiration occurred because of the impossibility of a vacuum. As air was expired, other air must enter to fill the vacancy. Expiration occurred because of

an attraction of similars, namely the entering air became heated and moved outward to seek the place of fire. Bones were present to protect both the brain and spinal marrow while muscles existed to protect the spinal marrow, which existed in triangles, from the heat and cold. The perfection of marrow was the brain which was dominated by the soul and if the two were separated, death would ensue. Besides being the source for lower desires, the liver was the site for divination. The spleen functioned as a storage region for the impurities of the blood while the primary function of the intestines was to prevent the food and from passing rapidly so that the desire (appetite) for food would be decreased while the time to enjoy philosophy and music would be increased [141, 144].

Plato advocated maintaining a *'due proportion'* between the mind (soul) and body to promote health and to prevent disease. However, he was referring to [141, p. 511] the *'greatest of diseases that made the soul, dull, stupid, forgetful, and ignorant.'* To maintain the necessary proportion and to achieve the expected harmony and balance, motion was required which would effectively influence both the body and its soul. For the mathematician, whose thoughts were on mental topics, this meant performing exercise and practicing gymnastics whereas for the gymnast, who was preoccupied with bodily matters, it meant devoting time and effort to music and philosophy. Moreover, to purify and re-unite the body, the best exercises were those associated with gymnastics (dancing, wrestling, walking, running, racing, and track and field events) with sailing being recommended as a *'less good'* activity. If movement occurred because of medicine, then the activity was considered to be *'least good'* [141]. Plato felt, as did Hippocrates, that the purpose of gymnastics should be to improve natural functions and not to increase performance (strength) for competition or to perfect the condition of the body. In the *REPUBLIC* [142, p. 92] he notes *'excessive care of the body'* was detrimental to the management of household, military actions, conduction of civic offices, learning, contemplation, study, and philosophical virtue while creating the impression [142, p. 93] that the individual was in a *'constant anxiety about the state of his body.'* Plato was extremely interested in the functioning of the brain and stated [141, p. 511]: *'We should not move the body without the soul or the soul without the body, and thus they will be on guard against each other, and be healthy and well balanced.'* Jowett highlighted this concept in his marginal notes as *'Mens sana in corpore sana'* which understandably has been credited to Plato [145]. However, Decimus Junius Juvenalis or Juvenal, a Roman satirist during the 1st century AD, wrote in Satire 10 [146, p. 358, line 511] the following,

*'O thou, who see'st the want of human kind
Grant me health of body, health of mind
A soul prepared to meet the frowns of life
And look undaunted on future state'*

Unfortunately for legions of physical educators, these lines have been determined to be the true origin of a '*sound mind in a healthy body*'.

Like Hippocrates, Plato had a low opinion of athletes as he felt they 'sleep away their lives' and were prone to dangerous illnesses if they deviated from their regimens. Since music and gymnastics were necessary for the soul, if athletes trained extensively and excessively (overtrained?), they could harden and brutalized their minds [147]. According to Baas [92], Plato let it be known in *Politics*, Book I, that one of greatest of nuisances was the union between gymnastics and medicine! The best known of Plato's students was Aristotle (384–322 BC) of Athens. Although he was the third generation of his family to be trained as a physician, he never practiced medicine and viewed medical and related issues from the perspective of a philosopher [143]. He promoted the concept of spontaneous generation for lower forms of life, indicated the elements were transformable and included 'spirit' [148] within the element theory which was interpreted by Gordon to mean *pneuma* [143]. Medicine was the knowledge of '*what makes for health in animals and men,*' the science of '*producing health and of dieting*' and said to '*deal with the production of disease and health*' [149, pp. 110b, 141a, 143a]. Health was contrary to disease and represented the balance between the hot and cold elements [4]. He felt the soul was responsible for movement [148]. Gymnastics was acknowledged and trainers had the responsibility to produce vigor, but exercise was never mentioned as having any relationship to either health or to the recovery from disease [148, 149]. On the other hand, he favored gymnastic activities to promote beauty and manliness, felt the activities practiced in Sparta were too harsh, light exercises should be promoted before puberty to facilitate growth and that strenuous (heavy) exercises should be avoided throughout life [133].

Diocles of Carystus (ca. 350 BC) was considered to be the '*Younger Hippocrates*' and his most '*gifted disciple*'. He felt most diseases occurred because of an imbalance of the elements within the body and of the constitution of the air (weather) while writing extensively on pneumonia, pleurisy, dropsy, fevers, apoplexy, epilepsy and diseases of the spleen, liver and the gastrointestinal tract [92, 150, 151]. Although he disagreed with Hippocrates on how fevers alter humors [151], he followed his views pertaining to health. Physiologically, the heart was the site of the soul which functioned as *pneuma* and influenced movement while being renewed by respiration. Diocles was considered to be a '*cooler*' in that he believed that the lungs served to cool the innate heat associated with digestion [152]. The blood, which was formed in the liver, was distributed, along with *pneuma*, to the brain and other parts of the body.

Digestion, which occurred within the stomach, was a form of putrefaction aided by the presence of innate heat. Generated in the left ventricle, this heat was also needed for various secretions [152]. Sweating was an 'unnatural' and

unwanted condition that was to be avoided when ever possible. Like Hippocrates and Plato, he favored moderation and was against the practice of heavy (excessive, violent) gymnastics as advocated by Herodicus of Selmbria [153]. He advocated diet, exercise and baths to promote healthful living and in Regimen for Health, his exercise recommendation take into consideration one's social status, age, time of day, whether food has been eaten, and season. If the individual did not have other responsibilities and had access to a gymnasium, Diocles suggested morning walks before eating commensurate with their strength and physical capacity. Long walks were advised because they made the individual more receptive to nourishment while enhancing digestion. Once food had been consumed, moderate walks were encouraged to promote elimination of a *'digested residue'*. On the other hand, long and rapid walks were discouraged because they *'shakes the body violently'* resulting in indigestion and disturbances within the stomach. For the young that did not take morning walks, a visit to the gymnasium for bodily exercise was advised. If they were old and weak, a trip to a bathing place or to a warm site for anointment was recommended. After lunch and a walk, a brief rest was recommended before going to the gymnasium. During the summer months only walking and mild gymnastic activities were to be performed whereas in the winter season, walking and gymnastic exercises should gradually increase and become more strenuous. Associated with these instructions were a myriad of recommendations concerning hygienic, dietary, bathing, anointment, sleeping and sexual practices [151].

Erasistratus of Chios in Sicily (310–250 BC) was renowned as a teacher at the Medical School in Alexandria and for numerous anatomical and physiological observations [122]. In fact, many medical historians list him as the *'father of physiology.'* He believed the body consisted of atoms that were activated by the presence of the innate heat. In addition, he promoted the corpuscular theory of Strato in that tissue nourishment occurred by a sideways absorption process of the fine pores within the capillary veins which occupied the vacant spaces caused by evacuations and emanations [154]. This theory was related to his concept that disease was caused by plethora (hyperemia) or the flooding of veins with superfluous blood caused by excessive nourishment. The excessive blood then passed into the arterial blood via the capillaries where it was compressed by the pneuma released from the heart causing an inflammatory response leading to fever and disease. Since nourishment was the function of living tissues, starvation or food deprivation was the cure for diseases caused by plethora because the veins [154, p. 117], when emptied, *'will more easily receive back the blood which has invaded the arteries'*.

Physiologically, he supported Herophilus observations of the existence of motor and sensory nerves and extended the concepts that the brain was the *'starting point'* for all nerves and select regions were responsible for intellectual

activity. He minimized the importance of the humoral theory of Hippocrates and ignored the concept that the heart was the center of sensations. To him, the heart functioned as a pump and the actions of the four valves maintained the flow of blood and pneuma in one direction. According to Galen, who wrote extensively on the physiological views of Erasistratus, arteries existed to contain pneuma and blood was a pure nutriment that became consumed to replace the '*wasted tissues*'. Erasistratus knew severed arteries would spurt and lose blood and believed an undetectable pneuma was lost causing a vacuum which attracted blood from adjacent veins [154]. Pneuma was present in atmospheric air as a vapor, was essential for life, entered the body during inspiration, and became distributed via arteries to the body and to the left ventricle of the heart. The primary role of pneuma was to induce physiological and intellectual functions. Although the process was unclear, pneuma in the heart became a '*vital spirit*' whereas in the ventricles of the brain it became transformed into an '*animal spirit*' [144]. One effect of pneuma was the contraction of muscles which was an expansion process associated with fiber shortening [122]. He maintained food was carried from the stomach by internal action (peristalsis) and not by an attraction force within the stomach. Digestion occurred because of the mechanical actions of the stomach causing the nutriment [154] to be '*ground down and dissolved*'. He believed living organisms '*give off*' invisible emanations and reportedly proved his point by conducting an experiment (metabolic) with a weighed bird in a cage (pot) that was provided no food and found the changes in excrement and body weight did not equal the original weight of the animal. According to the writings of Anonymus Londinensis, Erasistratus concluded [155, p. 127] from the great loss of weight that '*perceptible only to reason, a copious emanation has taken place*'. Approximately 1,900 years later, Sortorio Sortorio of Padua conducted human experiments using a calibrated balance chair and found the invisible emanations to be insensible perspiration [122]. In diseases not caused by plethora (ascites and pleurisy) Erasistratus prescribed moderate exercise (walking), dieting, and bathing activities [144]. He accepted the perspective of Alcmaeon that health was present when function had achieved balance and stability [152]. Hence his therapeutic regimen consisted of exercise, gymnastic activities, dieting, and bathing with a minimal use of drugs [108].

The Roman Influences

Select Features of Roman History

Archeological evidence indicates ancient tribes settled the hills of Rome around 950 BC. They believed spirits existed in animate and inanimate objects which became the subject of their worship. Later, they directed their worship to

gods and goddesses and enacted rituals and prayers to seek favors that included being free of diseases because disease [156] was a form of '*divine displeasure*'. Several centuries later, Etruscans moved into the area, became enamored with divination as a means for religious healing, and established a College of Augurs that had a divinity for each disease [157]. The Etruscans also brought their god and goddess which included Jupiter, Apollo, Venus, Mercury and Minerva that were accepted by the Romans. Associated with the Greek establishments in the Mediterranean Sea came acceptance and mostly renaming of many of their gods and goddesses which included Mars (Ares), Neptune (Poseidon), Pluto (Hades) and Salus (Hygeia) [158]. Health was also the responsibility of Aesculapius (Latin for Asclepius, the Greek god of medicine), for whom Rome in 291 BC had a temple constructed on the island of Tiber after the city experienced the ravages of the Great Plaque [158]. A century earlier, a cult dedicated to him was established at Anzio [159].

While Rome began to accept the gods and goddesses of Greece, this was not the case for their medical practices or beliefs. In fact, many centuries before the fall of Corinth (146 BC), individuals who practiced healing were not well respected (many were slaves) and if they were foreigners were only reluctantly tolerated and seldom appreciated. Thus the head of the family household, in accordance with Roman law and custom, fulfilled this responsibility. Pliny the Elder stated [158, p. 3], '*The Roman people for more than 600 years were not without medicine, but they were without physicians.*' As with medicine, instilling and maintaining personal health was also the responsibility of the head of the household. While exercise in the form of games and athletic contests were an important component of Roman culture, it had no importance for the promotion of health or in the recovery and management of disease.

Archagathus of Peloponesia in 219 BC was the first Greek physician to practice in Rome, however he became known as the 'butcher' and subsequently encouraged to leave [158]. More than a century later, Asclepiades of Bithynia (128–56 BC) became prominent in Rome and had a profound influence on Roman medical and health practices until the time of Galen. He and other foreign doctors were permitted to stay when Cicero banned all 'immigrants' from Rome during the plague of 46 BC. He was a graduate of the School at Alexandria, a severe critic of the humoral theory of Hippocrates, a friend to Cicero, a charlatan to Pliny the Elder, and to Galen [160, p. 633], a physician who was '*either mad or entirely unacquainted with the practice of medicine*'. Archagathus was a proponent of the atomic or corpuscular theory of Democritus and promoted the epicurian view that the essence of life was a combination of the soul and the elements. Respiration was responsible for the soul, air for rest, pneuma for motion, heat for vital activity with the undefined fourth element being responsible for all sensory phenomena [153]. To

Asclepiades [92, p. 137], matter consisted of '*extremely small but still divisible, fragile, formless and mutable collection of atoms*'. Their random movements and potential collisions resulted in the formation of particles and different bodies of various dimensions. Once formed, particles left behind empty tubes (poroi) which were occupied by smaller particles which created sensations. Respiration involved air reaching the heart by way of the poroi before entering the blood and being distributed throughout the body. Digestion involved the same process except the food went from the stomach to the heart and blood. Whenever an influx of particles occurred within the poroi, there was a pulse. The same was true to explain animal heat and secretion. On the other hand, hunger and thirst occurred [92] when the pores in the stomach were in different states of '*emptiness*'.

Disease was due to a stagnation of the atoms whereas weak, irregular, or strong motions of the particles were associated with sickness. In addition, the number of atoms per unit of poroi, the size of the atoms influenced the nature and severity of the disease. Disease was also due to the obstruction of the invisible pores located within the abdomen and stomach. Health existed when the particles were moving in a quiet and regular manner. Thus his goal for the restoration of health was to achieve harmony among the particles and to prevent obstructions within the pores [92]. Exercise (usually walking) was included with massage, bathing, dietary changes, riding, and frequent wine, to achieve these purposes. If a patient had dropsy, both walking and running were prescribed provided tissue fluid did not spread to the lower appendages. If edema occurred, exercise was to cease [161]. Besides dropsy, Archagathus recommended walking for patients with consumption or had experienced hemiplegia. Besides exercise effects on pores, it was recommend to aid digestion [97].

Influences from the Army, Gladiators, and the Early Romans

The transformation of the Roman Republic from the overthrow of the monarchy in 510 BC to the Roman Empire of Emperor Marcus Aurelius (161–180 AD) was facilitated by the prowess of the Roman army [162]. Their concern for health and exercise was noted by Vegetitus [163, p. 65] who stated military experts '*considered that daily exercise in arms were more conducive to soldiers health than doctors*'. Army recruits were required to be healthy and to meet specified physical standards. The army expected potential recruits to have a lifestyle that included '*reasonable exercise*', proper sleep and rest and a well-regulated diet [162]. Once in the army, they adhered to a general rule of war which stated '*An army is improved by work, enfeebled by inactivity*' [163]. Recruits were prepared for combat by sessions of marching (32 km in 5 h at the military pace and 38.4 km in 4 h at the full pace), running, charging, long and broad jumping and swimming (summer only) [164]. They performed drills with

wooden swords and wickerwork shields that had twice the weight of their issued items with the intent to strengthen arms [162, 169]. Once within a legion, they [165] were instructed to perform drills with the same intensity as in combat and to complete longer marches to experience fatigue and to *'wear out the stragglers'*. Additionally, they increased the weight of the shaft of the practice spear (javelin) to increase arm strength of throwers. For centuries, they were required to perform drills and exercises daily, however during a war in Spain (ca. 210 AD), Scipio adopted a tetrad system which included the following [165, p. 29], *'He bade them on the first day do a run of nearly four miles in full kit, on the second to rub clean and generally make a close examination of their equipment; on the next day to do nothing, and on the following, some men to fight with wooden swords sheathed in leather with a button at the end, and others to throw javelins similarly fitted with buttons; on the fifth day to revert to marching they had done on the first, and so on.'*

Gladiatorial contests were described [166] as being the *'most successful innovation in the repertory of Roman spectacular entertainment'*. Although such contests began in Paestum, a city south of Naples between 370 and 340 BC, they were officially introduced to Rome in 264 BC with duels involving 6 (3 pairs) gladiators [167]. The public interest in these contests can be assessed by the number of combatants which increased to 640 (320 pairs) during the time of Gaius Julius Caesar (65 BC) to 10,000 with the reign of Augustus (27 BC–14 AD) [167]. Initially the schools performing the training of gladiators were private, but by the first century, had become the responsibility of the state. The staff of each school included physicians, trainers, masseurs, as well as bandage specialists and tailors. Their most renown physician was Galen who served in that capacity in Pergamon and in Rome [110]. The trainers emphasized physical fitness within the strict military guidelines that identified 16 different forms of combat readiness. In addition, gladiators followed many of the procedures listed for Roman Legions such as using heavier weapons and shields to become stronger, practicing at an intensity level required for combat, repeating high intensity periods of running, charging, and jumping, and scheduling longer training sessions to improve endurance. In addition, they used *'warming up'* activities [163].

It was the perspective of Celsus (a chronicler of Roman medical and health practices during the first century after the birth of Christ), that in the 400 years since Hippocrates, medicine had become a composite of dietetics, pharmacology, and surgery [168]. Medicine was the promise of health to the sick while dietetics included exercise, bathing, relaxation, use of select medications and food and drink consumption [168, 169]. Diseases were classified as either acute or chronic with humoral shifts and seasonal changes being contributing causes. Romans were expected to *'manage'* their health problems and

only seek attention when they were ill. Living should include a variety of experiences in the country, town, and around the farm and activities such as resting, sailing, hunting and exercising were encouraged. Exercise included reading aloud, drills, walking, running, and ball activities but only to the point of sweating and never to the degree of fatigue practiced by athletes [168]. Celsus did report gentle (light) exercise (walking) was advocated for diseases as consumption and hemiplegia and that strenuous (heavy) exercise was suitable for dropsy [168].

The Legacy of Galen

Before Claudius Galenus or Galen of Pergamon (129–210 AD) became the court physician to Emperor Marcus Aurelius in Rome during 160 AD (fig. 6), he had been well tutored in philosophy and medicine, attended medical schools in Smyrna, Corinth, and Alexandria, served as the primary physician for the gladiators and was highly respected for his public lectures on anatomy and health [170]. He believed in the power of gods, was a follower of Asclepius and during his youth had been an *'attendant'* at the local temple that honored him. However, Galen was uncertain about his essence or the immortality of his soul [171]. Because of his appointments, personality, knowledge, productivity (434 titles of which more than 350 were authenticated [172]), and devoted followers, Galen's beliefs dominated medical and health practices for more than 1,000 years [173].

Galen accepted the concept that the elements of fire, earth, water and air were the basic constituents of the universe and that living matter was a mixture (crasia) of the elements, their qualities and the four humors whose proportions determined the uniqueness and temperance of individuals while affecting their physiological functions [174]. He advocated the Plato concept of a tripartite soul with distinctive souls being represented in the brain, heart and liver [174]. In the brain, the soul was responsible for reasoning, rational thoughts, directing motion, and interpreting sensations; in the heart it was regarded as *'life's vital force'* and responsible for passion whereas in the liver, the soul was responsible for nutrition, growth and reproduction [170, 174]. A superb anatomist, he considered these organs to be the most important in the body and felt that each was dominated by animal, vital and by natural spirits [170]. He also promoted the concept that each structure within the body existed for the purpose of performing a definite function [175].

To relate to the physiological concepts of Galen (fig. 7), one must understand that digested (concocted) food was used by the liver to form blood which was distributed to the heart and other regions of the body by veins. The liver formed yellow bile from chylus and generated a *'thick, muddy and atrabilious'* humor (black bile) that was taken up by the spleen. Phlegm was formed and secreted by the brain [171]. Both Pioreschi [176] and Scarborough [156] stated

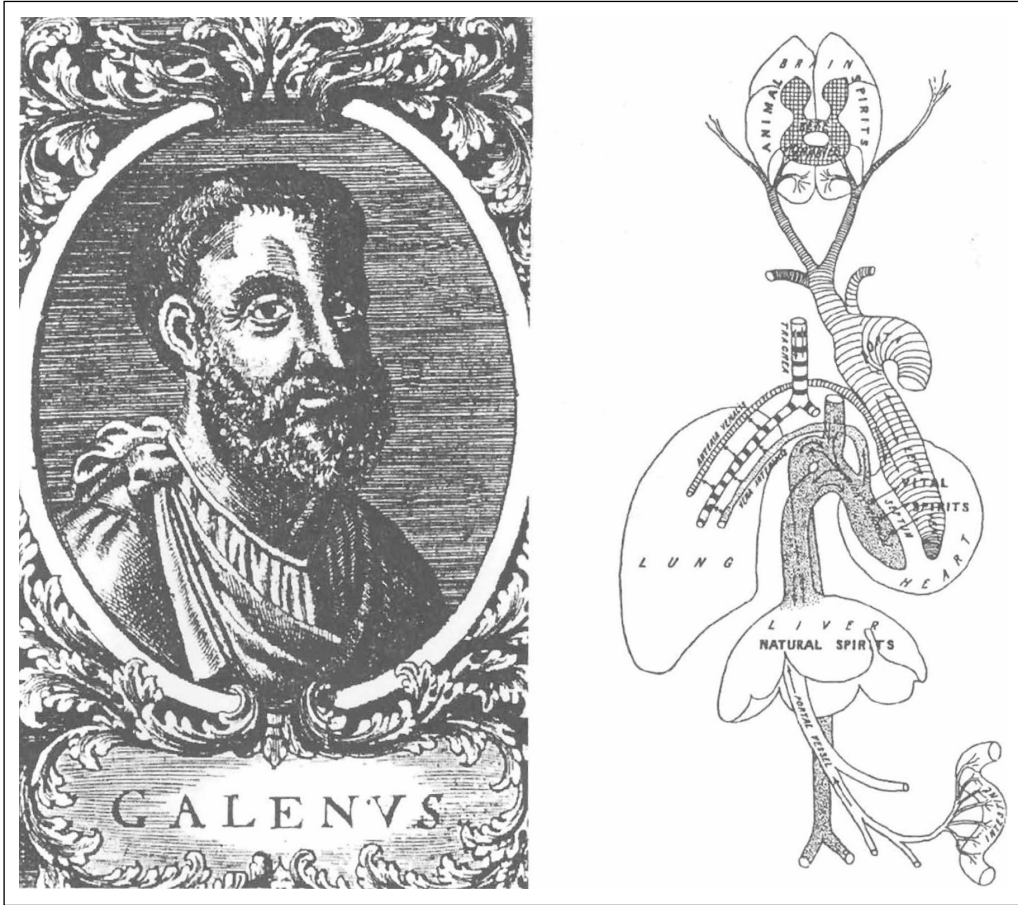


Fig. 7. Claudius Galenus or Galen of Pergamon (129–210 AD) and a representation of his physiological concepts [from 202, pp. 76, 141, with permission].

Galen knew from animal experiments air (oxygen) was essential for fire (life) to continue and believed inspiration allowed the lungs to prepare a pro-pneuma which entered the veins and mixed with blood within the right heart. Subsequently, pro-pneuma and more blood entered the left ventricle by pores in the interventricular septum and became transformed into a vital pneuma. Once in the left heart, which Galen considered to be a muscle, the mixture of pneuma and blood became heated and energized to become a vital spirit which imparted heat and life to other parts of the body via the arteries [177]. Other functions of the respiratory system were to regulate the equivalent of insensible perspiration

(sooty excrement), the innate heat associated with metabolism, and the cooling of the body [176], but not the heart [178]. Fever, an immodulation of heat, was regarded as an abnormality in heat loss that was caused by either an excessive uptake of outside heat or an increase in physical activity and was classified as a thermoregulatory disease of the respiratory system [179].

Galen accepted Erasistratus' view that the arterial and venous systems were linked by invisible capillaries and believed that pulsation of the arteries came from the power generated by the heart to the walls of the arteries [180]. Once the blood carrying the vital spirit interacted with air within the anterior ventricles of the brain, an animal spirit was formed which began to regulate brain and nerve functions while initiating sensations [170, 181]. He recognized two types of nerves and that lesions of motor nerves or of the spinal cord would produce paralysis [182]. As noted earlier, the liver contained the natural spirit and was responsible for nutrition, growth and reproduction [183]. He knew saliva initiated the digestive process of foods that became blood and humors. Once in the stomach, a concoction process occurred which produced chyle and a residue. Both products went to the intestines before going to the liver via the portal vein. Chyle was changed into blood while the heaviest component of the residue went to the spleen, the intermediate component was sent to the kidney while lightest residue was distributed to the gall bladder [176].

Galen promoted the concept that urine was a product of the kidney and was not from the gall bladder. He believed urine was separated from the blood but was uncertain about the process. Because of its yellow color, he speculated urine contained various humors, especially yellow bile. Although he dismissed the idea that filtration was a function of the kidneys, he did indicate that an attraction process was involved and responsible for the specific secretion of serous matter by the kidneys [184].

Health was regarded as an '*unimpaired capacity of function*' (bodily) that occurred because of '*good*' mixtures (eucrasia) and proportions of the elements and their qualities [185]. On the other hand, disease and illness occurred because of '*bad*' mixtures (dyscrasia) and proportions. As defined in '*On Antecedent Causes*' [186, p. 158], '*A disease is a disposition of the body that hinders or prevents the proper activity of one of its parts.*' Thus an excess or a deficiency in the qualities, especially heat and cold or in any of the four humors was considered to be a pathological condition or a disease state [129]. For example, an excess of black bile was associated with cancer whereas an increase in phlegm was identified with rheumatism [175]. Galen believed in the multiplicity of casual factors being responsible for diseases and indicated there were nine possible humoral mixtures or temperaments which served as a predisposition for certain types of disorders [177]. Select causal factors deserving attention were (a) things consumed, (b) things excreted from the body,

(c) things performed (which included exercise), and (d) things happening from within. Galen reinforced causal factors being responsible for both health and disease by introducing the concept of natural conditions (kata physin, or healthy), non-natural conditions (ou kata physin, or hygienic), or contrary to nature's conditions (para physin, or diseased or pathological) [187]. These conditions were collectively related to the evolution of disease and to the preservation of health. Inherent with this concept was that failure to maintain a 'normal' balance between bodily constituents resulted in disease and a loss of health. Within the non-natural conditions were (a) air, (b) motion and rest, (c) sleeping and waking, (d) that which was taken in, (e) that which was secreted, and (f) the emotions or passions [173].

Galen's views on health and disease states were influenced by his personal experiences which included being ill during much of his young life. He wrote [188, p. 188]: *'But after my 28th year from birth, having persuaded myself that there is a certain art of hygiene, I followed its precepts for all my subsequent life, so that I am no longer sick with any disease except an occasional fever.'* Exercise was important to achieve health while lack of exercise or excessive exercise could be associated with illness although Galen did not quantify the relationship. For movement (or gymnastics) to be considered as exercise, it had to be sufficiently intense to elicit a change in breathing (he used the term vigorous but likely meant heavy exercise [137]. Work and exercise were equivalent terms and he considered shadow boxing, leaping, discus throwing, ball activities, and climbing rope to be exercise whereas digging, rowing, plowing, riding, fighting, walking or running could be either exercise or work. Exercise was classified to be either slow or swift, atony or vigorous, gentle or violent [189]. Ball exercises and running were examples of swift exercise [190]; digging, climbing a rope or lifting a heavy weight were vigorous exercises [191] while discus throwing and continuous jumping were classified as violent exercises [189]. Small ball activities were Galen's favorite exercise and he wrote [192, p. 302], *'The form of exercise most deserving of our attention is therefore that which has the capacity to provide health of the body, harmony of the part, and virtue in the soul; and these things are true of the exercise with the small ball.'*

When exercise was recommended for health reasons, moderation was encouraged. Galen and contemporaries during the later portion of his life (Philostratus and Aretaeus) recommended gymnastic and ball exercises (walking, running, jumping, wrestling, boxing, punching bag, track and field events) for weakened individuals recovering from illnesses or for people with arthritis, dropsy, gout, depression, tuberculosis, vertigo and epilepsy [111, 193–195].

Although physiological knowledge was fragmentary, Galen associated acute exercise with an increase in breathing, an acceleration of the pulse rate, an increase in the temperature (warmth, natural heat) of the body, sweating, a readier

metabolism, increased digestion, enhanced elimination of excrement, the sensation of muscular fatigue, an equal distribution of the spirits, opening of the pores, purging the ducts, an increase in the acidity of the fluids and reduced concentrations of phlegm, yellow bile and black bile in the blood [189, 196–199] With chronic exercise or training, Galen believed it would cause ‘*thinning*’ of the body, harden and strengthen muscle, increase flesh (body composition), elevate blood volume and achieve the ‘unqualified good condition’ represented by Milo the wrestler or by either Hercules or Achilles in Homer’s epics [185, 192, 194, 196, 200].

Galen had little respects for trainers of athletes and even less for the professional athlete because of their lack of awareness of the natural good of the soul (intelligence) and because of their daily practices. On this matter he wrote [200, p. 47], *‘Now that athletes have never, even in a dream, enjoyed the goods of the soul is clear to everyone. To begin with, they are unaware they have a soul, so far they are they from understanding its rational nature. Because they are always occupied in the business of amassing flesh and blood, their souls are as if it were extinguished in a heap of mire, unable to contemplate anything clearly, mindless as beasts without reason.’* He felt an athletic state was not a ‘*natural*’ condition and that training had little practical value. In addition, training cultivated disease rather than health. Since athletes were usually in peak physical condition, it was impossible to improve. Consequently, their fate would be to experience deterioration, a viewpoint that was shared by Hippocrates.

Discussion and Summary

Since the Neolithic Age, humans associated with the emerging cultures of Eastern and Western civilizations have sought relief and understanding from supernatural sources for the ravages of disease and disorders. Although select ancient physicians in Egypt, Persia and India had suggested that not all diseases and illnesses were ordained by the gods, it was the early influence of Pythagoras and his disciples combined with the dominating view of Hippocrates and his followers that transformed ‘*religious medicine*’ into the rational form being practiced today. When the leaders of China adopted the principles of the Yinyang Doctrine, they accepted yang being associated with life and health and yin being identified with death and disease.

Excluding the Chinese, health or a healthy state in ancient cultures was considered a pre-ordained state from supernatural sources that at best became transformed into one of being free of disease and assorted illnesses. Exercise in the form of rituals, dances, games and athletic contests were practiced in some form

by all cultures, but with the exception of the ancient Chinese of circa 2700–600 BC, who used breathing exercises in the practice of yoga, they had no relevance to the concept that exercise was being advocated or prescribed for health reasons.

To the inhabitants of India, exercise meant walking, running, jumping, throwing, lifting, climbing and combinations thereof. The Greeks added punching and kicking plus activities as boxing, wrestling, discus and spear throwing and the running broad jump. Romans increased the list with leaping and fighting while including rowing, riding, reaping and tasks associated with work as digging and plowing. To Galen, small ball exercises were the best.

The foundations for exercise being advocated and prescribed for health reasons were (a) the humoral theories mentioned during the Vedic and Hippocratic eras and (b) the identification of elements by ancient Indian authors and by Empedocles that were responsible for the composition of the human body that, to the Indian authors, were originally represented by air, bile and phlegm, whereas to the Greek philosophers, they became phlegm, yellow bile, black bile and blood. For Susruta, blood was a principle that behaved as a humor. Implicit with the humoral theories was that natural physiological functions could occur only when the humors were in equilibrium. Moreover, any displacement or disruption of an established equilibrium would result in illness, disease or an unhealthy state. Thus their existence provided a qualitative definition for the presence or absence of health while providing a medical rationale for the treatment of illness and disease. It was interesting to note the similarities of the Indian humoral theory, the Yinyang Doctrine and the beliefs of Pythagoras in that harmony must prevail among the principles or between the elements for health to be present.

Beginning with Susruta (ca. 600 BC), moderate exercise was advocated to restore the equilibria between the dosas (humors) by decreasing the concentration of the kapha dosa. Moreover, excessive (heavy) exercise was to be avoided because it was disruptive to the vayu dosa and responsible for the occurrence of various diseases. To Hippocrates the humoral theory was a cornerstone for his views on disease and its causes, thus he recommended moderate exercise to dilute, warm and purge humors without specifically identifying which ones were responsible or changing. As health was improved with the restorations of humoral equilibrium, exercise became included within the regimens of Hippocrates and many of his followers. Restoration of humoral equilibrium was also important to Galen and he promoted exercise for this purpose.

Susruta, Pythagoras, Herodicus, Hippocrates, Diocles, Erasistratus, Caraka, Galen, and Asclepiades from either India, Greece or Rome advocated exercise to their ‘patients’ for one or more disease or disorders as arthritis, ascites, consumption, depression, diabetes, epilepsy, gout, hemiplegia, pleurisy, tuberculosis, and vertigo. However, Hippocrates appeared to be the first to

include specific details concerning mode, frequency, intensity, and duration. It was unexpected that the majority of exercise advocates from India, China, Greece, and Rome were against advocating excessive (heavy) exercise because of their concern it would result in assorted diseases and disorders, and in some cases, death. Exceptions were Caraka's advocacy of heavy exercise to 'cure' diabetes and the Romans' use of strenuous exercise for dropsy patients. In the nearly two millennia that have elapsed since the death of Galen, it is understandable that ancient physiological mechanisms have little or no resemblance to current ones and especially when humoralism was rejected by Virchow in 1858 [201]. However, if we consider the proposed humoral mechanisms for disease as antecedents for changes in the functions of the endocrine and immune systems which can lead to subsequent disease states, then these ancient humoral theories become important contributions.

Ancient contributions to exercise physiology include warming up, recognizing that nerves were involved for movement to occur, observing that moderate exercise would increase breathing and pulse rates, fluid shifts (considered as humoral shifts), metabolism, sweating, body temperature, and the sensations associated with muscle pains and fatigue. With chronic exercise or training, they believed that the equilibria among the humors would be restored, bones would become stronger, stature would be enhanced with muscles becoming larger and stronger while having more endurance and work capacity and a greater resistance to fatigue. Sweating and the opening of pores were enhanced, especially in the summer, with digestion and the elimination of excrement being improved. Training increased blood volume, body thinness, and to some, decreased the aging process.

Around 400 BC, athletic trainers were available to instruct competitive athletes or participants at the gymnasium. However, there were few physicians who were qualified or interested in advising them, in part because of the disdain by Hippocrates, and later by Galen for such a role. The most modern of the ancient advice pertained to strength training in that muscles must be 'overloaded' for improvements in strength to occur. This concept was implemented in many different ways for various events and the legend of Milo's daily lifting of a calf until it had become a bull continues to be repeated in exercise physiology textbooks. Although they were unaware of the principle, the specificity of training was practiced in part by ancient athletes and by Roman warriors. Ancient training programs had fragments concerning frequency, intensity, duration, and recovery periods between bouts and after sets of the various activities. The tetrad schedule followed by Greek athletes and the combat training schedule of the Roman legionnaires were examples of this fact.

After examining the collective beliefs and practices of our ancient ancestors, it was concluded they were remarkably modern with their ideas.

Recognition

This manuscript by Professor Tipton was the recipient of the Orr E. Reynolds Award from the American Physiological Society for ‘the best historical article’ submitted in 2007 by a Member of the Society.

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Historical Perspective: The Antiquity of Exercise, Exercise Physiology and the Exercise Prescription for Health

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Introduction

According to the medical historian Baas [1], antiquity for medical history ‘closes with Galen’. For the topics of exercise, exercise physiology and the exercise prescription for health, the era is the same but their histories are inextricably linked to the evolving concepts concerning disease and health, physiology, and to the practice of rational medicine. For the caved humans of the Neolithic Age (ca. 8000 BC), the ravages of disease were attributed to spirits, demons, and/or to supernatural forces that had to be controlled, appeased, or driven away before cures could occur and health be restored [2, 3]. This process was facilitated in part by ceremonies, incantations, trephining the skull and by kneading the body in the direction of the feet in order for the evil spirits to escape [4]. Explanations for these occurrences and recoveries were sought by ancient civilizations that have arisen from regions served by the Nile, Indus, Euphrates, and Tigris rivers. While not systematic or structured, their evolvement did provide for historical periods that were used by Baas [1] to characterize the evolvement of medicine. As his first edition was published in 1891, his sequence will be followed with the exceptions that (a) the contribution from the Indus civilization will be mentioned after the Egyptians because of the discoveries during the 1920s at Harappa and Mohenjodaro in India [5] and (b), the influences of the Japanese will not be included.

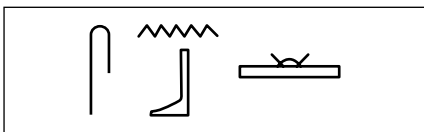


Fig. 1. Ancient Egyptian hieroglyphs for health (= to recover) [from 14, p. 72].

Influences from the Ancient Egyptian and Indus Civilizations

The Egyptian Civilization

Details on the beliefs and practices pertaining to disease, health, and medicine in ancient Egypt have been obtained from select papyri that were written between 1900–1200 BC but contain information that was relevant to the Third Dynasty (ca. 2650–2560 BC) [6–9]. Noted historians of ancient Egyptian medicine [10–13] have indicated the Egyptians considered disease to be the result of hostile spirits or from the anger or displeasure of their gods. Thus the removal of disease or illness from the body was best accomplished by the use of spells, incantations, sorcerers, and prayers that were invoked by priests and magicians [14]. With the exception of the eyes, initially all diseases were treated by priests of the goddess named Sechmet who could inflict plagues, war and death [15]. Subsequently, assistance from multiple gods was sought that included Thoth, Isis, and Horus [15]. Readers should note that Imhotep, a mortal to have been the physician to the Pharaoh Zoser in the Third Dynasty and likely a cult member of the sun god Ra, was not deified as a god of medicine until approximately 800 BC [10]. It is of interest that Breasted [6] suggested Imhotep was the author of the *Edwin Smith Surgical Papyrus*. Priests, priest-physicians, lay physicians and magicians known as *swnw*, were the healers of diseases, illness, pain and discomfort and frequently prescribed pharmacological remedies that were described in the Ebers [7, 9] and Hearst [16] papyri. Like disease during the ancient centuries, health had a supernatural focus that was not identified with the absence of disease while being considered a desirable state and primarily concerned with the recovery process (fig. 1). It is noteworthy that an anonymous author wrote on the back of the Edwin Surgical Papyrus on the possibility of diseases being caused by the wind carrying pests [17]. Although seldom cited, this was an early sign of disease being recognized as occurring from non-supernatural sources and of the evolvement of rational medicine.

Physiological understanding of the functions of the various organs was minimal at best although from the Smith [6] and Ebers [7, 8] papyri, it was apparent that the heart was regarded as the most important organ of the body as it was site for thought, emotion, and intelligence while serving as the ‘center’ of the vascular system and being responsible for the pulse [11, 14]. They understood

blood was associated with the heart but did not recognize its pump functions. To the swnw, air and water were essential for life and believed air, the breath of life, entered the right ear while the breath of death entered the left ear. Functionally, air entered the body through the nose and traveled via the trachea directly to the heart and intestines whereas water entered the heart via the stomach. Both were carried in the blood to the various organs of the body by afferent ducts (blood vessels, nerves, and tendons) which were collectively known as the *metus* [14]. Under normal conditions and when the heart was in its right place [18, p. 128], *‘the Fat of Heart is on the left side. It neither rises upward nor falls downward. It remains soundly in its place’*. In addition the heart could ‘tremble’, become sick, miserable or fatigued while experiencing sadness or disease that required the attention of the swnw. As discussed previously, the large intestine was regarded as an important organ because it contained the undigested food as fecal material that could undergo putrefaction and subsequently lead to disease and a loss in the *‘bodily vigor’* of health [15].

Although health was regarded as a desirable and positive state [15], there was no evidence within the relevant papyri or the cited texts that indicated exercise was ever advocated either for health reasons or to improve performance. However, sports and games were an important component of Egyptian culture and for the preparations of war by Pharaohs that were present during the Old Kingdom (2700–2300 BC) and the Late Period (700–600 BC) [19]. Physical activities for the masses included running, rowing, wrestling, ball games, boxing, jumping, and acrobatic dances. Unknown to most is that all future Pharaohs were expected to excel in the 180 stadia race (33.3 km) [10].

The Indus Valley Civilization

Archeological excavations in the Indus Valley of India, first described by Sir John Marshall [5] included Moenjodaro (in Sind) and Harappa (in Punjab) indicated the existence of an ancient Aryan civilization that select historians [20–23] believe was operational earlier than shown by the upper limit of the carbon dating value of 3300 BC [24]. Detailed descriptions of the excavations by Marshall as well as by Chowdhury and Chawdhury [25] revealed an advanced culture that had a concern for sanitation and public health as demonstrated by their water and sewage draining systems and by their massive public bathing building. Analysis of skeletal remains indicated the residents experienced a wide range of diseases that included metal poisoning, arteriosclerosis, osteomyelitis, cancer, and dental diseases. Like the Neolithic caveman, there were signs of skulls being trephined. Moreover, select skeletons exhibited evidence for infectious diseases. It was the opinion of Bhatia that in the Pre-Vedic Era, disease was regarded as a magical-religious phenomenon caused by supernatural forces which were treated by magic, incantations and related rituals

[26]. Other than the public health practices, their views on health or exercise for health purposes remain unknown. From the positions of recovered statues, they suggest the residents were familiar with the movements of yoga exercises [25].

Influences from the Civilizations in Mesopotamia and Persia

The Sumerians, Babylonians, Assyrians and Chaldeans

Mesopotamia is defined as an ancient country in southwest Asia between the Tigris and Euphrates river that includes a portion of modern Iraq [27]. The early inhabitants were non-Semites known as the Sumerians who were followed by the Babylonians, Assyrians, and the Chaldeans all of whom were Semites [28, 29]. They considered diseases to be demonic in origin that were ‘distributed’ as punishment either for disobedience to the gods or for not following the established practices of the priest who could also function as a healer (an assipu) [29, 30]. After ascertaining the cause for the disease or illness, priests facilitated recovery by leading incantations, encouraging exorcisms, and by requesting the god Marduk to intercede with the god Ea (healing) on behalf of the afflicted. Besides healers (assipu), recovery was aided by physicians (an assu), who used remedies with pharmacological properties that were similar to current prescriptions [14]. From Sumerian clay tablets (ca. 4000 BC), the Babylonian Code and The Statute of Hammurabi (2285–2242 BC), it was known that medical procedures and fees would be ‘regulated’ and that Hammurabi was available to ‘*heal all injuries*’ [31].

Like disease, health was regarded as a cosmic phenomenon and left to supernatural powers to maintain [32]. While there was some concern by the assu for the restoration of health following a disease, there was no evidence that exercise was ever considered to enhance health or to facilitate recovery. The health concerns of the Mesopotamia cultures were focused on hygiene and sanitation that began with the Sumerians who followed practices that were similar to those associated with the Indus Valley civilizations [30].

Physiologically, the liver was the organ of importance because of its role in the production and distribution of blood. It was also considered to be the site of the soul, the center for the vitality of the mind and emotions and the foundation for divination. Besides the Mesopotamia cultures, divination was subsequently practiced by the Greeks and Romans [33].

The Hebrew Influences

The Hebrew practices had components from the Egyptian and Babylonian cultures that existed during the period of Abraham in the Old Testament (2000 BC) to the preparation of the Talmud (200 AD). Unlike their geographical neigh-

bors, the Hebrews believed that one supernatural source was responsible for disease and health. Disease and premature death were regarded as originating from God while illnesses were attributed to previous violations of religious ordinances or as punishment for sins and transgressions [34]. This perspective is demonstrated in the Book of Exodus (15:26) when Moses recalls the conversation with the Lord. He spoke [35, p. 60], '*...and wilt give ear to his commandments and keep all of these statutes. I will put none of these diseases upon then, which I have brought upon the Egyptians: for I am the lord that healeth thee*'.

The treatment and recovery from a disease was dependent upon a benevolent and divine source that necessitated prayer and repentance while physicians were considered messengers of these powers. The Old Testament gives minimal attention to the restoration of health after an illness but provides extensive and explicit hygienic instructions in the Books of Exodus and Leviticus concerned with cleanliness and the prevention of select diseases [35]. However, there were no indications within the Bible pertaining to whether exercise had importance to the enhancement of health or for the recovery from select illnesses. In II Chronicles (16:12) and during the era of King Asa (915–875 BC), it was noteworthy he requested assistance from a physician, rather than the Lord, to treat a serious foot ailment, because the refusal indicated a separation had begun between medicine, the priesthood and the use of magic [34, 35].

While the physiological information within the Old Testament is meager, blood and the heart were acknowledged in the Book of Leviticus (17:11) when it stated '*For the life of the flesh is in the blood*' [35, p. 49] with the heart being the center of life. After the death of Galen and the publication of the Talmud, there was a marked increase in the amount of physiological information being conveyed.

The Influences from Persia

Geographically, Persia lies between the Tigris and Euphrates rivers on one side with India and Afghanistan on the other side. It is bounded on the south by the Persian Gulf and on north by the Caucasus Mountains, the Caspian Sea, and the steppes of Asiatic Russia [36]. It is the viewpoint of Sigerist [37] that Persia never developed a civilization that was capable of leaving a permanent mark on the course of human culture, except in the area of religion. Hence, its culture contained a myriad of influences from India, Egypt, Assyria, Babylonia and Greece. The period of historical importance was the Achaemenid dynasty (648–330 BC, that occurred after the Persians conquered Babylonia) which highlighted the reigns of Cyrus II and Darius III (who had Egyptians as court physicians) and the destruction of Persepolis in 331 BC by Alexander the Great of Greece [38, 39]. At the time of Darius III death, Persia had conquered and added Egypt, India, and Thrace to its empire [39]. During this period, the religion of Zoroaster was practiced with the holy scriptures being recorded within the various books of the Avesta

(Zend-Avesta or the Bible of Zoroaster) from India with the information devoted to health and medicine being located in the hymns of the Avesta or the Vendidad which translated means 'The law against the demons' [40].

Within the religion of Zoroaster, man is placed in a dualistic universe who is confronted with the powers associated with goodness, light, life, and truth as well as those associated with evil, darkness, destruction, deceit and death [41]. Gods and spirits (daevas) prevailed with health and disease being the '*gifts of gods*' who were capable of sending demons to cause bodily diseases [36]. According to the mythology within the Vendidad of the Avesta and the '*book*' which contained information relevant to health and medicine, the ruffian god named Angra Mainyu created 99,999 diseases to which the supreme god (Ahura Mazda) countered with a holy mathra and a Airyaman or god of healing. It was evident within the mathra [40, p. 222] that Ahura Mazda was responsible for the health of his followers, '*I drive away sickness, I drive away death, I drive away pain and I drive away fever, I drive away the disease, rottenness, and infection which Angra Mainyu has created by his witchcraft against the bodies of mortals. I drive all manner of diseases and deaths.*' Health was bestowed as a reward for obedience to the practices and laws of the gods with the god Ameretat, after Ahura Mazda, being regarded as a protector of health [38, 41, 42].

Because disease was associated with disobedience, displeasure, transgressions, sins or combinations thereof against the gods, religious incantations and ceremonies were included within the treatment process which always included water plus other modalities that had been '*borrowed*' from the Egyptians and Babylonians [34]. The high priests and physicians of Persia attributed numerous disorders, conditions and diseases to the presence of demons. However, they also recognized that cold and heat, stench and dirt, hunger and thirst, old age and anxiety, plus temperance and bad habits were contributing factors [36] indicating not every condition had a supernatural explanation. Medical practice was sufficiently organized in that physicians healed with herbs, the knife, or with the holy word [43]. Interestingly, two subclasses of practitioners existed, the '*Durustpat or Master of Health*' and the '*Tan Beshazak or Healer of the Body*', with the former being concerned with removing the cause of the disease and the later concentrating on the treatment of the disease [39]. As with the sections on health, there was no mention of exercise ever being considered to enhance health or to serve as a therapeutic modality in the management of disease.

Although the Vendidad alluded to a change in humors with sickness, physiology was in a rudimentary stage and limited to the concept that a vital force perished when death occurred. It was uncertain as to whether Persian physicians accepted the humoral theory that evolved from the Indus Valley. While Sigerist [37] and Elgood [39] indicated it was plausible, other scholars were not as positive.

The Indian Influences

The Indian influences began with the Aryan (Indo-European) invasion of the Indus Valley (ca. 2000 BC), which drove the inhabitants into the southernmost regions of the peninsula [21]. Antiquity information concerning the cultural beliefs, health practices, and medical concepts of the emerging culture can be found in the earliest and latest sacred texts of India: namely, *The Rgveda* (Rig-Veda) and *Atharvaveda* (Atharava-Veda) respectively, in the *samhitas* of Susruta (Sushruta) and Caraka (Charaka) and in the *Azurveda*. To the ancient Hindus, veda referred to knowledge and azur meant to prolong life. The authenticity of the *Azurveda* [44] was challenged by Kutumbiah who wrote [45, p. i] *'There was really no veda called Azurveda. Its existence is a myth'*. However, it was the opinion of the Indian scholar Filliozat that the *Azurveda* did incorporate the essential details of the *Atharvaveda* as well as the information found in the writings of both Susruta and Caraka [12].

Insights on how the earliest inhabitants regarded life and perceived matters pertaining to health and disease can be obtained from the *Rgveda* whose date is most frequently cited as 1500 BC but listed by Gordon as early as 4000 BC [21]. Originally written in the Sanskrit language, the *Rgveda* contains 1,028 hymns of which all were directed to one or more mythological deities. While the blessings and benevolence from the gods Agni and Indra were the most frequently sought within the hymns, the attention of numerous god and goddesses were solicited that included heaven and earth [46], dawn [47], the sacred plant soma [48, 49], medicinal plants or herbs [49], waters [50] and the wind [49] which was capable of eliminating disease (*'I drive away thy disease'*). Besides paying reverence to the Aswins as the twin gods of medicine [46], the prevailing belief within the hymns was disease was associated with evil spirits affecting the body that originated from a god, sorcerer, or from an enemy (living or dead) because of sins committed in *'this or in a previous existence'* [26, 47, 49, 51]. Treatment consisted of incantations, rituals and in some situations, the use of herbs [46]. When health was acknowledged, *'that health be enjoyed by bipeds or quadrupeds'* [51], it was not linked to disease or to the recovery from a disease, but was dependent upon the pleasure of the gods. Physiologically, the humoral theory was acknowledged and prayers [52] were directed to the Aswins to *'preserve the well being of the three humors (of the body)'*. In addition, sweating would occur with toil while vigor, strength and speed were needed for combat situations [53].

The *Atharvaveda* (ca. 1000 BC), which consisted of 20 books by numerous authors with 731 hymns, prayers, incantations, or charms, contained detailed information about health and medicine. Diseases continued to be associated with supernatural forces (evil spirits) and regarded as punishments for evil deeds or for sins against the gods by individuals, their parents or because of the intentions of

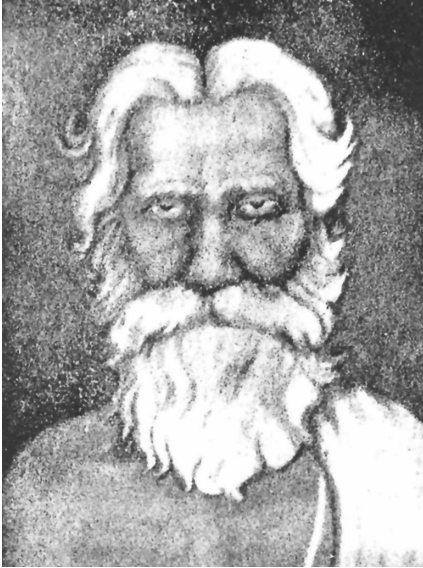


Fig. 2. Susruta of India (ca. 600 BC) who advocated exercise to establish an equilibrium between the dosas [from 63, p. 41, with permission].

their enemies [54]. Malarial fever, for example, was sent by the god Rudra to mortals and incantations were directed to the gods Varuna (sky god) and Dyaus Pita (sky father-god) for relief by medicinal plants. Hymns were focused on a myriad of diseases and conditions that included diabetes and heart disease [54, 55]. The Atharvaveda mentioned physicians used herbs, water, incantations, appeasement and purification rites, penances, and fasting for treatment purposes thus exhibiting early signs of medicine becoming separated from magical-religious doctrines [26, 45]. Like the Rgveda, there was limited information concerning whether exercise was advocated to improve one's health or recovery status.

Sometime during the late Vedic Period (ca. 1500–800 BC) the tridosa (also known as the tridhatu) doctrine [56] was formulated and briefly mentioned within the *Avesta* and the *Rgveda*. It emerged to help explain the phenomena of disease and health as well as life and death [57] and indicated the elements of water, fire, air, earth, and ether were responsible for the formation of the human body. Interacting within the body were three nutrient substances which originally were 'microcosmic representatives' of the wind, sun and moon that, by the time of Susruta (fig. 2) became dosas (humors) that were identified as air, bile, and phlegm [56]. However, Susruta added blood as the fourth humor with the capability of influencing the interactions between the others [57]. The ancient Indians identified the three humors (dosas) as vayu (or vata), pitta, and kapha. Vayu was the vital force responsible for movement, activation of the sympathetic system, maintenance of the vital breath, enhancement of digestion, movement of chyle

and blood through the body, and the maintenance of life. Pitta was responsible for the formation of colored pigments from the liver and spleen, promoting digestion and metabolism, increasing heat production, and aiding fluid movement to and from the heart [56–58]. On the other hand, kapha was to provide mucus substances to the alimentary canal, promote growth, transport body fluids throughout the body, bathe sense organs with fluids, promote body strength and endurance [59] and ‘*contribute to the proper healthy functioning of the body*’ [60, p. 12]. Food was responsible for the supporting structures represented by chyle, blood, flesh, fat, bone marrow and semen while the waste products (malas) were feces, urine and sweat [26]. Indians quickly realized that life was characterized by the first gasp of air by the newborn and death by labored breathing while associating these events with the entrance and passage of the soul [26]. Consequently, the physiology of breathing was of importance to their religious and health beliefs. The circulatory system had 1,000 veins and contained both arterial and venous blood (they had differences in color) that circulated in upward and downward directions [61]. Nerves were described as channels and prana was the nervous energy they carried to the brain, heart and to the lower regions of the body [62]. The occurrence of fatigue with toil was acknowledged as was the need for strength, energy, and vigor for well-being. Aryans enjoyed athletic contests and games, chariot races, hunting and dancing [21]. Whether they had any bearing on Hymn LVII is unknown which contained the words [54, p. 226] ‘*Let it be health and joy to us. Let nothing vex or injure us.*’

Inherent in the tridosa doctrine were the concepts that the vayu, pitta, or kapha humors controlled and regulated all functions of the body [60], and that dosas did not increase or decrease spontaneously. Specifically, they had to be displaced or deranged to produce diseases within the tissues [56, 59]. Besides known diseases, conditions that could displace the dosas were climatic changes, select foods, poisons, fatigue and psychic disturbances. However, the balance, harmony, or equilibrium between the dosas was not restored by natural means; rather, a designated regimen was required that included exercise, diet, and medication [56, 59]. Thus disease was a disturbance of the equilibrium between the three dosas whereas health was the state when the humors were at their normal levels [56, 59]. As emphasized by the physician Caraka (fig. 3) who followed Susruta and wrote [63, p. 39] ‘*the disturbance of the equilibrium of tissue elements is the disease while the maintenance of equilibrium is health*’. Susruta indicated vayu was ‘*deranged*’ by prolonged hard work, carrying heavy loads and by violent movements [60]. Thus the strenuous activities advocated by Caraka (running, swimming, jumping, tumbling and combative sports as wrestling against an opponent with superior strength) would have been considered unhealthy by Susruta [60]. Susruta believed the kapha humor was increased by a sedentary existence (inactivity), sleeping during the day, and by excessive consumption of food and drink.



Fig. 3. Caraka of India (ca. 200 BC–100 AD) who advocated exercise to ‘cure’ diabetes [from 20, p. 17, with permission].

He felt the kapha humor was displaced by sedentary habits (inactivity), sleeping in the day and excessive consumption of foods and liquids [60], hence it was no surprise several centuries later that Caraka [63, p. 152] recommended physical exercise for the ‘*alleviation of dosas (especially kapha)*’.

Susruta defined exercise as ‘*a sense of weariness from bodily activity*’ that should be taken daily [64, p. 485] whereas Caraka [63, p. 151] considered exercise to be ‘*Such a physical action which is desirable and is capable of bringing about bodily stability and strength is known as physical exercise. This has to be practiced in moderation.*’ Susruta favored moderate exercise being performed for durations that were half of what was required to achieve exhaustion and that would be discontinued when breathing became labored [65]. He felt chronic exercise would make individuals stout, strong, firm and compact, promote growth of limbs and muscles, enhance digestion, reduce corpulence, delay fatigue, and improve the appearance of the deformed and aged [64]. Diabetic individuals [66, p. 377], were to perform ‘*regular physical exercise, wrestling, active sports, riding on an elephant, long walks, pedestrian journeys, practicing archery, casting javelins*’, etc. Caraka stated training would inhibit the heart, increase work capacity, result in leanness, and reduce discomfort while enhancing digestion, perspiration and respiration [67]. He recommended daily walking or gymnastic activity for most individuals and considered strenuous exercise to

be a cure for diabetes [68]. Susruta suggested that Indians should exercise in the winter and spring but at an intensity level that was half their capacity (or when perspiration appeared on the body) as death could ensue. Besides his views on humors, he felt diseases [64, p. 486] *'fly from the presence of a person habituated to regular physical activity'* just as small beasts do when seeing a lion. In contrast, excessive exercise would cause coughing, fever, vomiting and weariness while inducing diseases as consumption, tuberculosis, and asthma [64]. Caraka also indicated death could occur from excessive exercise as would dyspnea, heart and gastrointestinal diseases, and bleeding from organs [63].

The Influences from China

Before the designation of Emperors and establishment of dynasties, the health of the ancient Chinese was determined by a world that consisted of gods, demons, devils and spirits. Disease was the result of demons and devils who possessed the body and whose removal required incantations, charms, and offerings. With time, there became one devil for every disease. When cures occurred, they were attributed to supernatural powers [20].

Like the papyri of Egypt and the Rgveda of India, the Ma-wang tui documents of China related to periods that existed before these classical medical documents were written (200 BC–100 AD) [69]. This is an interesting authenticity point because Gordon [70] stated medical gymnastic breathing exercise were practiced in China as early as 2500 BC by Tschì Sung Ti whereas the French missionary, Pere Amiot [71] reported in 1779 and the French physician Gustave Chancere [72] in 1864 that Taoist monks in Peking were practicing therapeutic medical gymnastic exercises (identified as Cong-Fou) known since the era of Hoang-Ti (ca. 2698 BC). Drawings provided by Amiot show seated monks performing stretching type movements [71]. Since Taoism evolved after the birth of Lao-Tse around 600 BC, it was unclear whether the monks were performing an ancient therapeutic exercise or a current one of their era.

In the Shang Empire, the first Chinese dynasty (ca. 1800–1100 BC) to leave records of importance to this manuscript [69], they recognized the existence of numerous illnesses but few diseases. As with their ancestors, they believed wind spirits were evil and a cause of illness. When disease was present, it was usually associated with a curse from an ancestor [20] or with a punishment for a sin previously committed [69]. Healing required prayers, incantations, divination and herb therapy that were conducted by priests and sorcerers or priest-doctors who also used astrology [20]. While rhythmical breathing exercises with arm movements were advocated for select illnesses with cures expected in several months [70, 73], there were no reports of other types of exercises being practiced (fig. 3).

China is associated with three religions; namely, Taoism, Confucianism, and Buddhism. The first two were founded in China whereas the latter came from India. Tao, 'or the way' in its original form was 'pure philosophy' and closely linked to medicine [74]. The age of philosophy and the golden period of Chinese medicine (ca. 1121 BC–960 AD) followed the demise of the Shang Empire and incorporated the Chou dynasty (1050–256 BC). Although controversial, this time period is associated with *The Yellow Emperor's Classic of Internal Medicine* [74] and the era when the functions of the priest-doctor were separated so that issues related to religion became the responsibility of the priest whereas those pertaining to medicine and medications became the duties of the physician [20].

Emerging during this period were the principles of the Yinyang Doctrine [74]. In accordance with the doctrine, the universe was not created by divine action but by a self-generated process of nature that functioned on the dualistic principles of yin and yang [74, p. 15] which includes, '*The principle of Yin and Yang is the basis of the entire universe. It is the principle of everything in creation. It brings about the transformation to parenthood; it is the root and source of life and death.*' In addition, '*Heaven was created by an accumulation of Yang; the Earth was created by an accumulation of Yin*'. Yang was the active, positive and masculine principle represented by the sun, heaven, day, fire, heat, dryness, light, etc. whereas yin was the inactive, negative and feminine principle identified with the moon, earth, night, water, cold, dampness and darkness [74]. Therefore all animate and inanimate objects as well as circumstances and phenomena were a combination of these principles with the human body consisting of three parts of yin and three parts of yang [74]. Within this dualistic relationship, yang was associated with life and health while death and disease were identified with yin.

A yin disease was associated with internal causes, lower regions of the back, delayed onsets, chills, cardiovascular disorders, and when the patient could not lie on their back, whereas a yang disease was identified with external causes, upper regions of the body, fevers, sudden onsets, respiratory disorders and when the patient was unable to bend forward [20]. Inherent in the doctrine was that both principles had mutual affinities and antagonism toward each other which required a proper balance (equilibrium) before harmony or health could occur. Although acupuncture was used well before the Chou dynasty to remove the demons and evil spirits from the body, it became a specialized treatment requiring knowledge of a complex system of yin and yang anatomical sites to restore the equilibrium between the opposing principles. It also necessitated a detailed understanding of the pulse rate relationship to disease as elaborated by Pien Ch'iao as each part and organ had its own pulse [75]. The physician was required to compare the pulse rate to the rhythm of breathing before making a diagnosis. However to preserve health, it was necessary that individuals not perform excessive exercise [74].

During the Chou dynasty, the doctrine of the five elements was also emphasized. In accordance with this doctrine, the human body consists of a ratio between metal, wood, water, fire and earth whose union produced life while their separation meant death [76]. When their ratio was in 'proper' proportions (in equilibrium), the individual was considered to be healthy. However, any disturbance of this ratio would cause disease(s). As these elements were associated with the spleen, liver, heart, lungs and kidneys, it was possible to identify the 'disturbed' element [20].

In accordance with Nei Ching, as cited by Wong and Lien-Teh [77] and by Gordon [70], the liver formed the heart and ligaments while controlling the lungs. In turn, the heart produced and controlled the blood which circulated continuously within a circle *'that never stopped'* so that in 24 hours it made 50 completions. During inspiration, blood traveled a distance of 3 inches during inspiration and another 3 inches during expiration. The blood contained yin and yang which was distributed through 12 channels with the fluid component (plasma) going to yin areas while the solid constituents (cells) went to yang regions within the body. Besides being responsible for the pulse, the heart formed the spleen, converted fluid into perspiration and regulated the kidneys. The spleen created and nourished the flesh, produced the lungs, converted fluid into saliva, nourished the lips and was responsible for the liver. Both lungs formed skin, hair, and the kidneys, transformed fluid into nasal secretions, maintained the skin while nourishing the fine hairs of the body, and controlled the heart [70, 78]. Lastly, the kidneys produced bone marrow, created the liver, maintained the bones, converted fluids into spittle, nourish the fine hairs, and controlled the spleen [20]. In a document attributed to the Yellow Emperor (*Huang-ti nei-ching*), it was mentioned by Unschuld [69] that circulating vapors were more important than blood and were essential for life.

Huard and Wong [79] noted the Chinese enjoyed dancing, games and performing physical culture activities during the Chou and the Chin's dynasties. During those eras, physical culture consisted of induction, massage, immobility and the Dao being prescribed which consisted of stretching, massaging and breathing procedure to promote energy flow, meditation and harmony with the universe (fig. 4). At the time of Galen's death and during the Han dynasty, the great Chinese surgeon Hua T'o was an enthusiastic proponent of systematic exercise to enhance health. He is reported to have told his disciples [78, p. 54], *'The body needs exercise, only it must not be to the point of exhaustion for exercise expels the bad air in the system, promotes free circulation of the blood, and prevents sickness.'* Apparently he practiced exercises (frolics) which mimicked the actions of deer, tigers, bears, monkeys and birds which strengthened legs, gave a sensation of lightness of the body, increased the appetite, prevented old age and removed diseases while enhancing health. After Galen's death, China 'adopted' Buddhism from India and followed its beliefs and practices which included exercises to improve fitness and to enhance health [20].

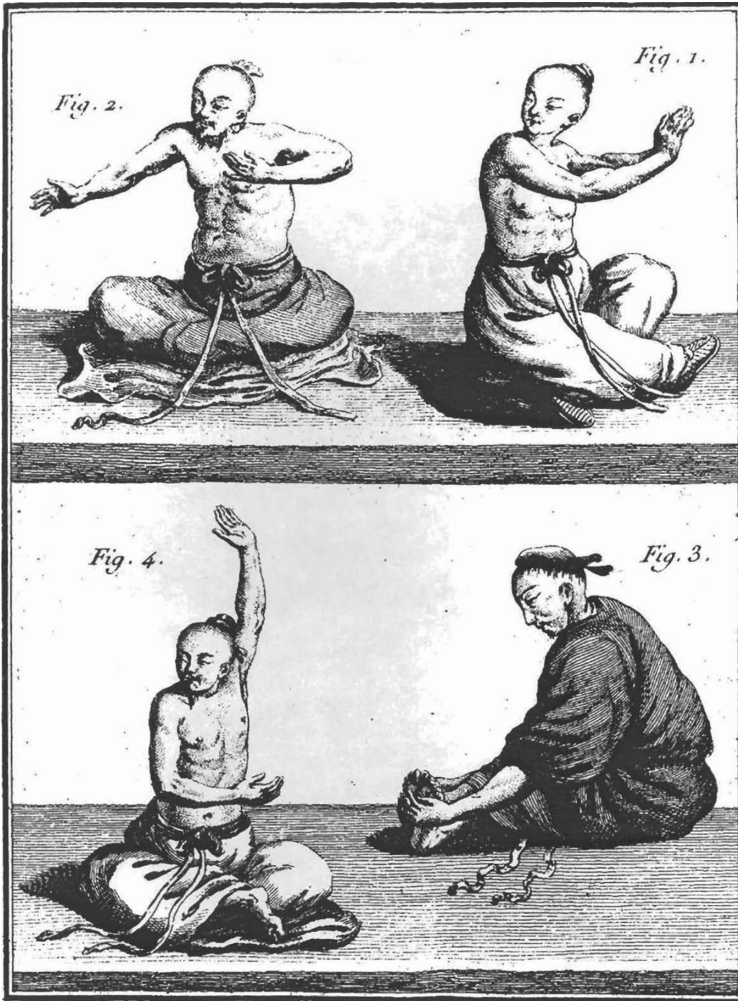


Fig. 4. Ancient Chinese breathing exercises [from 203, p. 451].

Influences from Greece That Include Hippocrates and Erasistratus

Background Information and the Influences from Sparta

Archeological evidence indicated ancient Greece was the site of two 'great' civilizations and one Classical period. The civilizations were the Minoan (3000–1100 BC) and the Mycenaeans (1550–1050 BC) with the Classical Period involving the 5th and 4th centuries BC [80]. These inhabitants of the

Balkan peninsular, the islands of the Aegean Sea and the coasts of Asia, were collectively known as the Hellenes and were a composite of various tribes with different dialects and social organizations who colonized the regions by migrations and invasions between 1300 and 1000 BC. The Achaeans were located in northern Peloponnese, Arcadians in the central mountains of Peloponnese, Aeolians in the northern region of the eastern Mediterranean basin (Thessaly), Ionians in the central regions of the basin with the Dorians becoming settled in the southern regions that included Sparta [81].

Like other cultures, the Hellenic priests and physicians attributed disease and illnesses to the actions (punishment) from one or more deities while seeking protection, healing and health from others. For the Hellenes, Zeus was the supreme god who ruled from Olympia; Athena was daughter of Zeus who had various healing functions; Apollo was the son of Zeus and the primary god responsible for inflicting illness while rendering natural deaths to males. His sister Artemis had the same 'powers' plus causing natural death to females while Asclepius, who was once a mortal, became a deity as the son of Apollo 1 and subsequently became revered as the physician god of healing. His first daughter was Hygeia who became the goddess of health while the second daughter, Panacea, became the goddess responsible for treatment [82]. If death did not occur from the disease or illness, prayers, sacrifices and/or purification rites were initiated to 'solicit' interest of the gods so that recovery could occur, a collective process that was described by Gordon [82] and by Sigerist [83] as religious medicine. Unfortunately, the only written documents to provide insights on Greek culture and medical practices during these early years were the epic poems of Homer (ca. 750 BC) that described conditions predominately associated with the Trojan War (ca. 1250 BC). In the *ILIAD*, Homer [84] indicated Asclepius was a tribal leader who had two sons, Machaon and Podalirius, that became skilled physicians. On the battlefield, warriors as well as physicians treated the wounds of their comrades, and in some instances used drugs. In most situations, diseases were caused by the gods, e.g. a plague was sent by Apollo; however, there were times when the supernatural was not involved. While Egypt was recognized for the training and skill of their physicians, minimal information was provided concerning specific diseases or illnesses, how health was perceived or related to the recovery process. Extensive information was included by Homer on the Greek admiration of athletic skills and warrior abilities as well as the various competitive athletic events scheduled between warriors for the funeral games of Patroclus (chariot racing, boxing, wrestling, running, discus and spear throwing plus archery contests) [84].

Robinson [85] indicated competitive events were scheduled at Olympia as early as 1370–1104 BC and definitely during 776 BC. However, there was little information available before 500 BC on how competitors trained or prepared for

their events. Since exercise can be advocated to improve performance as well as health, it is important, when reading ancient Greek documents, to realize that the general term for exercise was *ascesis* and that an ascete was an individual who exercised his mind and body [86]. Moreover, the individual who exercised only to win a prize (an *athlon*) was classified as an athlete. The Greek word for nude is *gymnos*, hence the term gymnastics was used to describe individuals who exercised in the nude [87]. Thus during the era of Homer, individuals exercised in the nude when performing competitive gymnastic activities. The same was true for the events during the early Olympics that were scheduled after 776 BC.

Dorians conquered the Peloponnese around 1000 BC and subsequently established the state of Laconia and the city of Sparta. They were vastly different than the Ionians who migrated to the region that became Athens [88]. This difference was manifested in the type of governance being established, the philosophy and purposes of education, and in their obedience to the laws of the state. In terms of political power and influence within Greece, Sparta's zenith was during 600 BC when it had become [89, p. 1] the '*strongest single power in the Peloponnese*'. This influence began to decrease during 500 BC when it remained steadfast against the Persian invasion before becoming lost after 400 BC because of a failure to control the states in northern Greece and to defeat Persia [89]. After the '*humiliating King's Peace of 387 BC*', she became reduced to the '*status of a provincial second-rate state*' [89, pp. 1–2].

After establishing an oligarchic form of government with a constitution and an educational system whose primary purpose [90, p. 165] was to '*maintain an army of experts who were ready and able at any moment to suppress sedition within the state or repel invasion from without. The Spartan was a professional soldier and nothing else, and his education directed entirely to two ends-physical fitness and obedience to authority.*'

Like all inhabitants of Greece, the Spartans relied on their gods to protect them from death and diseases. However, death with honor was expected of the male Spartan whether in the flogging ritual at the altar of Artemis Orthia or on the battlefield. Health was focused on being physical fit for the benefit of the state to the extent that babies who were judged to be unhealthy were left to die at the site named *Apothetae*. Healthy males were to become warriors whereas healthy females were to become mothers of warriors. To achieve these goals, fitness and athletics were advocated for both males and females [90]. In fact, only in Sparta and Chios were women allowed to compete against males in wrestling [91].

After the age of seven, children left their homes to live in barracks with others of their age group where they remained until adulthood and marriage. The educational curriculum for both males and females included the arts, music and gymnastics although its focus was preparation for a warrior state. Concerning the education of young males, Wright states [91, p. 68]: '*Of book*

study there was practically none. Hunting, scouting, and foraging for food took up most of the boys' time. Males did not participate in competitive activities in music, dancing, or athletics until they were ten and the emphasis in dancing or athletic events was more for physical than for artistic purposes. The same was true for festival games where endurance and tolerance to pain were expected and intrinsic to the event. While Olympic records indicated Spartans were frequent participants and victors, details of how they 'trained' are missing as are records concerning how they prepared warriors for battle. From the information available on Spartan life, it is safe to assume the frequency of gymnastic or warrior-training bouts was high, intensity ranged from moderate to heavy and the duration was long to very long [88, 90]. Other than their emphasis on fitness, there were no major Spartan contributions to exercise physiology.

The Emergence of Greek Ideals and Practices

The transition from the religious medicine practices of 1000 BC to the rational medical procedures of the Hippocratic era were associated with Hellenic cultural transformations that included the designation of sites (Asclepieia) which led to temples and cults being devoted to the god of medicine. By 600 BC, Asclepius had become a god with healing temples established in Thessaly and Epidaurus [83]. In 420 BC his cult was introduced in Athens and in 295 BC one was established in Rome. The transition also included the 'borrowing' of the alphabet from the Phoenicians and mathematics from the Egyptians with the emergence of schools at Miletus and at Croton which emphasized philosophy and the natural sciences [92].

Interestingly, it was not the priests at the Asclepieia [92, p.85] who were *'the direct founders of Grecian medicine'*, rather it was members of the Asclepiadae or the guilds of purely lay physicians whose membership, including Hippocrates, were from *'descendents'* of Asclepius that assisted the priests at the temples with the rites before leaving to travel the countryside to practice their profession. From the inscriptions found on the walls of their temples, they provided drugs when necessary and advocated bathing, massage, diet and exercise to assist the healing process [93]. Presumed to be gifted and highly intelligent, they increased their education from their conversations with 'celebrated men' during their travels and not from attending established schools [92].

The school at Miletus was founded by Thales (639–544 BC) and several of its graduates provided philosophical insights for various biological concepts that emerged from these times. Thales believed water was the basic element in plant and animal life and the source of earth and air [94]. Anaximander (611–547 BC) extended the view of Thales and felt that all living creatures, including humans, had their beginnings in water. He also proposed the universe existed because of a balance between opposing forces [95]. In contrast,

Anaximenes (610–545 BC) felt that air was divine and responsible for substance, motion, and life whose presence animated the blood and the heart. However with death, it (a psychic force) left the body [95].

Pythagoras (570–490 BC) was invited by the Senate of Croton in Italy to develop a School that emphasized philosophy and science which flourished until the fourth century [96]. He was also responsible for developing a religious cult that followed the mystical practices of Orpheus of which music was an integral component. The philosophical emphasis was on the immortality of the human soul in a universe (that was round and contained a heaven) which encompassed God, time, eternity, and natural phenomena as a commonality. Associated with his philosophical instructions were discussions on astronomy, geometry and music. In his doctrine on numbers, perfection or God was 1, matter was 2, worlds were 3 and the universe was 12. Dividing the universe by its worlds yielded 4 concentric spheres composed of four elements (fire, earth, water, and air) which possessed the four qualities (moisture, dryness, heat, and cold) which subsequently became encompassed into the humoral theory of disease that will be discussed later. While Pythagoras used prayers, offerings and music in his religious practices, he did not believe the gods were the causes for all evil or diseases. Rather, all diseases and bodily sufferings arose from dissolute behavior whereas good health was a state of harmony (equilibrium) between the opposing elements, qualities, or tendencies in the body. To help achieve harmony, careful dietary practices and daily exercise were required. This meant repeated long walks and participating in events as running, wrestling, discus throwing, and boxing [96]. It has been suggested that Pythagoras was an Olympic competitor and a friend of Milo of Croton who was a great Olympic wrestling champion and among the first to practice progressive resistive exercise in training for a competitive bout [97].

A notable graduate of the Pythagorean School was Alcmaeon (ca. 500 BC) who made medicine the study of his philosophy [98]. Physiologically, he had the brain serve as the seat of the soul and responsible for thought, sensation and motion. Nerves functioned as channels for the pneuma (air), odor required the presence of the brain, and taste occurred because of an interaction between humidity, heat, and softness. He believed health represented a harmonious equilibrium between the qualities of wet, dry, hot, bitter, sweet, etc. with disease occurring with the supremacy of any one quality. In addition, diseases occurred with excesses or deficiencies of food, an excess of either heat or cold, phlegm from the head, black and yellow bile from the blood, substances from marrow or water, fatigue and from personal hardships [98, 99]. To cure these diseases, it was necessary to determine what elements were missing and to restore the missing qualities. Alcmaeon views coupled with those of Empedocles (see subsequent material) became the foundation for the humoral theory which is usu-

ally attributed to Hippocrates [100, 101]. Other than noting that fatigue was a contributing factor to disease, little is known about Alcmaenon's interest in exercise or its effects.

Empedocles (504–443 BC) of Agrigento in Sicily was also a disciple of Pythagoras who proclaimed that all matter, including the human body, consisted of the elements (roots) water, earth, fire and air (aether) with transformations being possible without origination or destruction (conservation of matter). Growth was the result of changes in the elements, tissues had equal parts of the four elements, nerves contained two parts water, one part fire and one part earth whereas bones contained one part of earth, four parts fire, two parts water and one part air [102]. Furthermore, human intelligence was influenced by their proportions. He discovered atmospheric air, described the process of inspiration and expiration, felt respiration occurred before birth, considered circulation to be a process of flux and reflux and discussed vision as an in-going and out-going event [103]. Empedocles proclaimed transformations occurred between elements and their qualities in that [103, p. 102]. *'These (elements) are forever themselves, but running through each other they become at times different, yet are forever and ever the same.'* To Garrison [104, p. 77] these changes were as follows:

hot + dry = fire	cold + dry = earth
hot + moist (wet) = air	cold + moist (wet) = water
hot + moist (wet) = blood	cold + moist (wet) = phlegm
hot + dry = yellow bile	cold + dry = black bile.

Inherent with this elemental theory was the premise that diseases would occur with any disturbance of their relationships with health being present when the elements were in equilibrium [105]. Although Empedocles strongly promoted godly means to treat disease, he became a hero to the people of Agrigento by stopping the spread of epidemics by non-godly preventive measures, e.g. draining a swamp and blocking a rift in a hill [106]. Whether he had any views on the role of exercise in either health or disease is unknown.

Gymnasiums were dedicated to Apollo and existed before the Asclepiadae were established [107]. As in Sparta, they (three) were operational in Athens and achieved their prominence during the eras of Hippocrates and Plato. In fact, the most famous was the Academy where Plato taught. It was a public institution, contained stadiums, and provided instruction in music, grammar, literature and gymnastics for affluent and wealthy boys up to the age of 16 years. Attendance was compulsory for 2 years with males (or females in Sparta) when they became 18 years old. Gymnasiums also served as a meeting place for older adults and philosophers and as a training site for gymnastic exercises [107]. Physicians not only served as the director (Gymnasiarch) and subdirector (Gymnast) of the institution, they functioned as Iatroliptes whose duties included preparing prescriptions, performing venesections, and massages, reducing dislocations, and

'advising' trainers on gymnastic exercises [108]. Gymnastic exercise was an extremely important component of the education of the Greek student because of its importance in obtaining a healthy body [109]. They included racing for speed and distances, extended walks, wrestling, boxing, jumping, throwing the javelin and the discus, dancing and playing games with balls [107]. Collectively, the gymnasia physicians were known for favoring exercises over medical treatment to restore health [110]. This was true for Herodicus (480 BC–?) of Selymbria who was considered by Licht [111] to be the *'father of therapeutic gymnastics'*. He apparently recovered from an incurable disease by following his personal exercise regimen. Because his regimens were so complex that a knowledge of geometry was needed to execute the movements, the system was seldom used or advocated [111]. Although Herodicus significantly influenced Hippocrates on the health benefits of exercise, he was criticized by his 'star pupil' for prescribing exercises that were too strenuous for patients [112]. Later, Plato chastised Herodicus for his severe training practices which were unnecessarily prolonging his life span and likely those of others. He wrote [113, p.91], *'But Herodicus, being a trainer, and himself of sickly constitution, by a combination of training and doctoring found out a way of first torturing and chiefly himself, and secondly the rest of the world.'* Plato considered the process as a *'lingering death'*.

The zenith of the Panhellenic games [114] held in the Olympia valley was during 500 BC. Unlike the earlier games, many potential competitors practiced in the stadiums of the gymnasiums and had professional trainers assist them in the process. Authors have identified individuals who provided this service as trainers, paidotribes, alpeipes, and gymnastes. Since paidotribes means *'boy rubber'* and aleiptes meant *'anointer'*, Harris believed these two terms related more to massage duties whereas the coaching responsibilities were best represented by the other two terms [115]. The majority of their advise was devoted to skill acquisitions and to dietary and lifestyle practices with minimal emphasis on training explanations. In fact, their lack of 'scientific' insight and knowledge on such matters raised the ire of both Hippocrates and Galen.

Some trainers did advise athletes to use repeated repetitions, to practice overload to increase strength (bending rods of wrought iron, pulling wagons with yoked animals, lifting animals, boxes and stones, having heavier halters with the jumping exercises, throwing heavier javelin like equipment for height and distance), to chase animals to increase speed, and to run in the sand for long distances to improve endurance for aerobic events [86, 115, 116]. By the time of Galen, many trainers had adopted a tetrad system of training which had similarities to current practices. It was a 4-day system which highlighted preparation, concentration, relaxation and moderation. On the first day the athlete was to perform numerous short-term but intense exercises that would *'prime'* him for the next days activities; the second day was an 'all out' effort to exhaust the

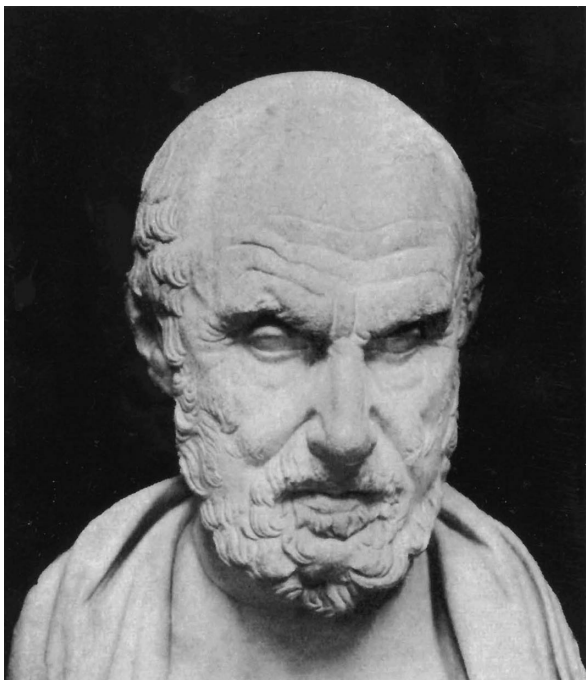


Fig. 5. Hippocrates of Cos (460–370 BC) who is attributed to have separated medicine from philosophy and religion while becoming the father of scientific medicine [from 150, p. 91, with permission].

athlete, the third day was devoted to relaxation and recreation, while the fourth day was one of moderate exertion in skill activities. After the death of Galen, this method of training was severely criticized by Philostratus for its rigidity and lack of consideration for individual differences [116].

The Views of Hippocrates

Prior to the emergence of Hippocrates, Anaxagoras (500–428 BC), a philosopher from Clazomenae in Asia Minor, believed that life arose ‘in the moist’ [117] and proposed that diseases originated from bile before entering the blood vessels, lungs and pleura [92]. Around 440 BC, Philolaus proposed that changes in bile, blood, and phlegm were the causes for diseases [118].

When the views of Hippocrates of Cos (460–370 BC) are discussed (fig. 5), it should be remembered that he may not be the responsible author of the

approximately 76 books on Greek medicine collectively known as the *Corpus Hippocraticum* that have their origins in the 5th and 4th centuries BC [119]. Consequently, one should not be surprised to read ancient texts that are speculative, redundant, contradictory, or confusing. Although in the Hippocratic Oath for Physicians (ca. 400 BC) Hippocrates acknowledged Apollo, his son Asclepius, daughters Hygieia and Panacea, and all the gods and goddesses [120], there was nothing in the oath to indicate disease had a supernatural or religious origin. The Roman Celsus attributed Hippocrates as being responsible for separating medicine from philosophy [118] while historians Garrison [104] and Haggard [121, p. 28] credit Hippocrates as being responsible for separation of medicine from religion and magic and for having '*relieved the gods of their responsibilities for the prevention and treatment of diseases*'. Thus his era was the beginning of rational medicine and the one that established his legacy as the father of scientific medicine [122].

Hippocrates accepted the belief that the human body contained four elements whose four qualities had to be in perfect equilibrium or harmony to prevent the occurrence of disease and for health to exist. He wrote extensively on diseases and classified them into acute, chronic, endemic, and epidemic categories. They were the result of a lack of an equilibrium and were both general and personal in nature [123]. He discussed in *Airs Waters and Places* [124] and in *Breaths* [125] aspects related to air, climate, seasons, water and sanitation that had to be mentioned when causes of disease were considered. In *Aphorisms*, III, Hippocrates stated [126, p. 123], '*It is chiefly the changes of the seasons which produce diseases, and in the seasons the great changes from cold or heat, and so on according to the same rule.*' Diet and exercise were also important considerations for the attainment of health and for the prevention of disease, especially the excessive consumption of food and drink. On this subject he wrote in *Regimen, Book I* [127, pp. 227–229], '*Even when all this is known, the care of a man is not yet complete, because eating alone will not keep a man well, he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health.*' He continued, '*A man must observe the rising and settings of stars, that he may know how to watch for change and excess in food, drink, wind and the whole universe, from which diseases exist among men.*' In *Regimen, III*, he related the topic of food and exercise to the incident of disease and stated [128, p. 367], '*But the discovery that I have made is how to diagnosis what is the overpowering element in the body, whether exercises overpower food or food overpowers exercise; how to cure such excesses, and to insure good health so as to prevent the approach of disease, unless many serious and many blunders be made.*' Besides its relationship with food consumption, Hippocrates believed excessive exercise or the lack of exercise were causes for disease. In *Nature of Man* he wrote [101, p. 25],

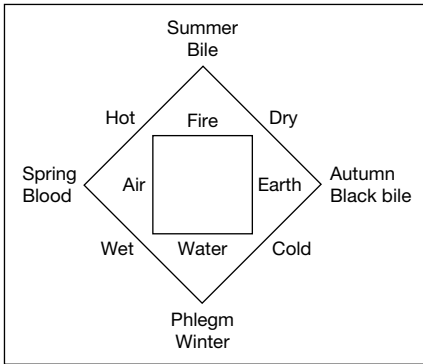


Fig. 6. The humoral theory of Hippocrates [from 129, p. 25, with permission].

‘those due to exercise are cured by rest, and those due to idleness are cured by exercise’.

The idea that disease occurred because of a failure to achieve *‘balance’* among body constituents was best illustrated by the humoral doctrine [100] (fig. 6) that is frequently attributed to Hippocrates although, as noted previously, many historians credit the doctrine to the collective efforts of Alcmaeon, Empedocles, and Philolaus with Empedocles being the most important.

In its elementary form, an equilibrium must exist between blood (from the heart), phlegm (from the head), yellow bile (from the gall bladder to the tissue fluid) and black bile (from the gall bladder to the liver and the mixing with blood) in order for health to be present and disease to be absent [100, 101, 129, 130]. Food and fluids were necessary for their formation and when their combinations were balanced, the condition was known as *crasis* and health prevailed. But whenever an increase or a decrease occurred in one or more of the respective humors, it was the beginning of a diseased condition. Readers should not be alarmed that not all medical historians agree on the identify of the respective humors because, as emphasized by translator Jones [118], different humors were mentioned in *Diseases IV, Ancient Medicine*, and in *Affections I* At the time of Plato (429–347 BC), black bile was associated with a variety of conditions and diseases that ranged from headaches, vertigo, paralysis, spasms, epilepsy, mental illness, and diseases of the kidneys, liver, and spleen [131, 132].

Fundamental to Hippocrates beliefs was that nature (*physis*) would heal disease [130]. The acquisition of health, a state of equilibrium between the humors, provided a rationale for the treatment and management of disease and disorders that, by the time of Hippocrates, became apparent to practicing physicians [133, p. 387] *‘as the only stable good among the changes and vicissitudes of life’*.

To alter the influence of humors, accustomed exercise was recommended to alleviate the fatigue pains caused by unaccustomed exercise. According to Hippocrates [134, p. 363], *'Accustomed should be practiced so that the collected humour may grow warm, become thin, and purge itself away.'*

In *A Regimen in Health* [135] and especially within *Regimen's I, II, and III* [127, 128, 134], the role of exercise in the acquisition of health was discussed. Readers must be cognizant that the Greek word for exercise (ponoi) has also been translated to mean exertion, pain, and labor [136] and recognize the listing and distinction in *Regimen II* [134] between natural exercise (activities of sight, hearing, speech and thought plus walking) and violent exercise (not defined but considered by the translator to mean excessive) are confusing and difficult to relate to 21st century definitions of exercise. For purposes of this article, excessive exercise has been interpreted to mean heavy or maximal exercise [137].

When Hippocrates described exercise, he was referring to walking, running, wrestling, swinging the arms, push-ups, shadow boxing and ball punching [136]. When prescribed, the intensity was usually light or mild at the onset that gradually increased to becoming moderate, but seldom higher. However, in *Regimen, I* [127, p. 283] and in *Regimen, III* [128, p. 411] 'sharp' runs were mentioned, to empty the moisture of the body, which suggested heavy exercise was to be performed. In *Breaths* [125], Hippocrates indicated air (outside the body) and breath (inside the body) were essential for life with breathing being a continuous process of inspiration and expiration that was increased by both exercise and disease [134]. As rapid breathing was one method to cool the *'innate heat of life'* which originated within the heart, it was regarded as a beneficial effect. Temperature changes could alter the equilibrium between humors and affect one's health status; consequently, temperature regulation was an important subject for the Greek physicians that ascribed to Hippocrates beliefs. Interestingly, he recommended warming up with exercise [128, p. 373] because *'the body performs best with warms ups under exercise'* and stated exercise would warm humors and the body while causing the skin to be moist. He indicated *'hot sweat'* could be formed in select conditions but exercise was not one of them. In addition, immoderate exercise by individuals suffering from fatigue pains could cause the flesh (muscle) to become hot, painful, and shivery and result in a *'longish fever'* [134, p. 363]. Running exercise, if not double or long, could cause the flesh to heat, concoct and to dissolve while promoting the digestion of the food. He recommended running in a cloak because the heating process was faster and would make the body [134, p. 355] *'more moist'* while enhancing the loss of excess flesh (*'which they wish to reduce'*) [134, p. 355]. Heat, as noted earlier, would also help to warm, thin, and purge the humors. While changes in the skeletal muscles were frequently mentioned, as muscle pains with fatigue, Hippocrates made no references to exercise induced alterations in the nervous and hematological systems. In *Fractures* [138],

Hippocrates observed muscle atrophy was greater with chronic dislocations of the hip in individuals who failed to exercise than those who were able to ‘practice walking’.

With select diseases, exercise was prescribed [139]. For example, when consumption had been diagnosed regardless if caused by phlegm, bile, or blood in the spinal marrow, long-term treatment consisted of foods, gruels, drinks, medication, vapor-baths, sleep and exercise. After arising from sleep, the patient was to walk for 20 stades (3.70 km). For each subsequent day he was to increase the distance by 5 stades (0.93 km) until a total daily distance of 100 stades (18.5 km) was achieved and maintained until 30 days had elapsed. During the second month he was expected to walk not less than 30 stades (5.50 km) before and 10 stades (1.8 km) after dinner. After 4 months, and on the first day, he was advised to walks 10 stades (1.8 km) which were to be gradually increased until 80 stades (14.6 km) daily was accomplished. This was done by walking 30 stades in the morning, 20 stades after dinner, and 30 stades at other times of the day. Since recovery was expected to occur within a year, Hippocrates advised the patient for the next 7 months to gradually increase his daily walking so that 150 stades (27.5 km) would be covered with 40 stades in the early morning, 20 stades after dinner, and remaining 90 stades throughout the day [139].

It was mentioned that Hippocrates believed diseases could occur with either no exercise, or excessive exercise or if either food or exercise was overpowering. In *Regimen, III* [128] he provided an exercise prescription for both conditions. For example, when symptoms indicated food had overpowered exercise he advocated a 6-day schedule consisting of slow runs, long and gradually increasing early-morning walks, wrestling with an oiled body, and a stroll after dinner. Coupled with the exercise schedule were recommendations concerning food consumption, vomiting, bathing, sexual activity and the use of ointments. On the seventh day, select foods were provided and vomiting was induced. This was followed by a 4-week period of food and exercise adjustments (not specified) resulting in recovery. When exercise overpowered food, rigor was present with the symptoms of chattering teeth, fever, and frequently, delirium. Rigor occurred when the body and head had been drained of their moisture from the cooling down process because the moisture lost was proportionate to the excess of walking, and ‘*over the proper amount*’ [128, p. 417]. When diagnosed, the exercise program was either terminated or reduced by one-half while the food had to be moist and cool with the fluids being mild and dilute. After 5 days, exercise was increased by one-third, after 10 days, it was elevated by one-half and after 15 days, all exercises were performed, but at a lower intensity level and for shorter durations [128].

Hippocrates associated training with increased bone development and physical stature, improved muscle mass, tone (hardness) and athletic performance.

Because of his low regard and respect for athletes and their trainers, it is speculated he did not advocate maximal chronic exercise to perfect their physical development because perfection did not allow for improvement or change. On this point he stated in Aphorism number III [126, pp. 99–101], *'In athletes a perfect condition that is at its highest pitch is treacherous. Such conditions cannot remain the same or be at rest, and, change for the better being impossible, the only possible change is for the worse.'* Despite his disdain for athletes, he advised athletes in training to wrestle and run in the winter and to 'taper' in the summer with walking and reduced wrestling. In addition, when fatigued, wrestlers should become refreshed by running whereas runners should wrestle.

The Views of Colleagues and Those Who Followed Hippocrates

Plato of Athens (427–347 BC), a younger colleague, was a philosopher, founder of the Academy, stimulated the Dogmatic School of Medicine and was *'one of the keenest intellects of all time'* [140]. He endorsed Empedocles' concept that the human body was composed of the elements' earth, air, fire and water and felt that disease and disorder occurred because of either their excesses, deficiencies or from their transformation into another [141]. If the elements formed the body in a defined order, *'health commonly results'* whereas if process occurred in reverse order causing the cool qualities to become warm, dry qualities to become moist, light qualities to become heavy, or heavy qualities to become light, disease could be expected [141]. Moreover, disease, disorders, inflammations and tumors were expected when the humors, notably phlegm and black bile, were in excess and unable to be transformed, and when the blood was replenished by irregular ways and not by food or drink [141]. In fact, anything that was unhealthy caused diseases. He was among the first to identify mental diseases and emphasized the existence of a soul that consisted of three divisions of which one was rational (reason, located in the brain) whereas two were irrational (spirit, present in the heart, and desire, found in the liver) that could be affected by bodily changes [142, 143].

Plato's concepts of anatomy and physiology were unusual. The heart was an essential organ because it housed the spirit component of the soul, was the origin of blood vessels and received commands from the reason component of the soul. Blood was red because of the action of the element fire. Bodily function was controlled by the head and the brain was responsible for generating semen. The lungs received air and water from the trachea and served to cool the heart. Inspiration and expiration occurred through the pores, mouth and nostrils. Inspiration occurred because of the impossibility of a vacuum. As air was expired, other air must enter to fill the vacancy. Expiration occurred because of

an attraction of similars, namely the entering air became heated and moved outward to seek the place of fire. Bones were present to protect both the brain and spinal marrow while muscles existed to protect the spinal marrow, which existed in triangles, from the heat and cold. The perfection of marrow was the brain which was dominated by the soul and if the two were separated, death would ensue. Besides being the source for lower desires, the liver was the site for divination. The spleen functioned as a storage region for the impurities of the blood while the primary function of the intestines was to prevent the food and from passing rapidly so that the desire (appetite) for food would be decreased while the time to enjoy philosophy and music would be increased [141, 144].

Plato advocated maintaining a *'due proportion'* between the mind (soul) and body to promote health and to prevent disease. However, he was referring to [141, p. 511] the *'greatest of diseases that made the soul, dull, stupid, forgetful, and ignorant.'* To maintain the necessary proportion and to achieve the expected harmony and balance, motion was required which would effectively influence both the body and its soul. For the mathematician, whose thoughts were on mental topics, this meant performing exercise and practicing gymnastics whereas for the gymnast, who was preoccupied with bodily matters, it meant devoting time and effort to music and philosophy. Moreover, to purify and re-unite the body, the best exercises were those associated with gymnastics (dancing, wrestling, walking, running, racing, and track and field events) with sailing being recommended as a *'less good'* activity. If movement occurred because of medicine, then the activity was considered to be *'least good'* [141]. Plato felt, as did Hippocrates, that the purpose of gymnastics should be to improve natural functions and not to increase performance (strength) for competition or to perfect the condition of the body. In the *REPUBLIC* [142, p. 92] he notes *'excessive care of the body'* was detrimental to the management of household, military actions, conduction of civic offices, learning, contemplation, study, and philosophical virtue while creating the impression [142, p. 93] that the individual was in a *'constant anxiety about the state of his body.'* Plato was extremely interested in the functioning of the brain and stated [141, p. 511]: *'We should not move the body without the soul or the soul without the body, and thus they will be on guard against each other, and be healthy and well balanced.'* Jowett highlighted this concept in his marginal notes as *'Mens sana in corpore sana'* which understandably has been credited to Plato [145]. However, Decimus Junius Juvenalis or Juvenal, a Roman satirist during the 1st century AD, wrote in Satire 10 [146, p. 358, line 511] the following,

*'O thou, who see'st the want of human kind
Grant me health of body, health of mind
A soul prepared to meet the frowns of life
And look undaunted on future state'*

Unfortunately for legions of physical educators, these lines have been determined to be the true origin of a '*sound mind in a healthy body*'.

Like Hippocrates, Plato had a low opinion of athletes as he felt they 'sleep away their lives' and were prone to dangerous illnesses if they deviated from their regimens. Since music and gymnastics were necessary for the soul, if athletes trained extensively and excessively (overtrained?), they could harden and brutalized their minds [147]. According to Baas [92], Plato let it be known in *Politics*, Book I, that one of greatest of nuisances was the union between gymnastics and medicine! The best known of Plato's students was Aristotle (384–322 BC) of Athens. Although he was the third generation of his family to be trained as a physician, he never practiced medicine and viewed medical and related issues from the perspective of a philosopher [143]. He promoted the concept of spontaneous generation for lower forms of life, indicated the elements were transformable and included 'spirit' [148] within the element theory which was interpreted by Gordon to mean *pneuma* [143]. Medicine was the knowledge of '*what makes for health in animals and men,*' the science of '*producing health and of dieting*' and said to '*deal with the production of disease and health*' [149, pp. 110b, 141a, 143a]. Health was contrary to disease and represented the balance between the hot and cold elements [4]. He felt the soul was responsible for movement [148]. Gymnastics was acknowledged and trainers had the responsibility to produce vigor, but exercise was never mentioned as having any relationship to either health or to the recovery from disease [148, 149]. On the other hand, he favored gymnastic activities to promote beauty and manliness, felt the activities practiced in Sparta were too harsh, light exercises should be promoted before puberty to facilitate growth and that strenuous (heavy) exercises should be avoided throughout life [133].

Diocles of Carystus (ca. 350 BC) was considered to be the '*Younger Hippocrates*' and his most '*gifted disciple*'. He felt most diseases occurred because of an imbalance of the elements within the body and of the constitution of the air (weather) while writing extensively on pneumonia, pleurisy, dropsy, fevers, apoplexy, epilepsy and diseases of the spleen, liver and the gastrointestinal tract [92, 150, 151]. Although he disagreed with Hippocrates on how fevers alter humors [151], he followed his views pertaining to health. Physiologically, the heart was the site of the soul which functioned as *pneuma* and influenced movement while being renewed by respiration. Diocles was considered to be a '*cooler*' in that he believed that the lungs served to cool the innate heat associated with digestion [152]. The blood, which was formed in the liver, was distributed, along with *pneuma*, to the brain and other parts of the body.

Digestion, which occurred within the stomach, was a form of putrefaction aided by the presence of innate heat. Generated in the left ventricle, this heat was also needed for various secretions [152]. Sweating was an 'unnatural' and

unwanted condition that was to be avoided when ever possible. Like Hippocrates and Plato, he favored moderation and was against the practice of heavy (excessive, violent) gymnastics as advocated by Herodicus of Selmbria [153]. He advocated diet, exercise and baths to promote healthful living and in Regimen for Health, his exercise recommendation take into consideration one's social status, age, time of day, whether food has been eaten, and season. If the individual did not have other responsibilities and had access to a gymnasium, Diocles suggested morning walks before eating commensurate with their strength and physical capacity. Long walks were advised because they made the individual more receptive to nourishment while enhancing digestion. Once food had been consumed, moderate walks were encouraged to promote elimination of a *'digested residue'*. On the other hand, long and rapid walks were discouraged because they *'shakes the body violently'* resulting in indigestion and disturbances within the stomach. For the young that did not take morning walks, a visit to the gymnasium for bodily exercise was advised. If they were old and weak, a trip to a bathing place or to a warm site for anointment was recommended. After lunch and a walk, a brief rest was recommended before going to the gymnasium. During the summer months only walking and mild gymnastic activities were to be performed whereas in the winter season, walking and gymnastic exercises should gradually increase and become more strenuous. Associated with these instructions were a myriad of recommendations concerning hygienic, dietary, bathing, anointment, sleeping and sexual practices [151].

Erasistratus of Chios in Sicily (310–250 BC) was renowned as a teacher at the Medical School in Alexandria and for numerous anatomical and physiological observations [122]. In fact, many medical historians list him as the *'father of physiology.'* He believed the body consisted of atoms that were activated by the presence of the innate heat. In addition, he promoted the corpuscular theory of Strato in that tissue nourishment occurred by a sideways absorption process of the fine pores within the capillary veins which occupied the vacant spaces caused by evacuations and emanations [154]. This theory was related to his concept that disease was caused by plethora (hyperemia) or the flooding of veins with superfluous blood caused by excessive nourishment. The excessive blood then passed into the arterial blood via the capillaries where it was compressed by the pneuma released from the heart causing an inflammatory response leading to fever and disease. Since nourishment was the function of living tissues, starvation or food deprivation was the cure for diseases caused by plethora because the veins [154, p. 117], when emptied, *'will more easily receive back the blood which has invaded the arteries'*.

Physiologically, he supported Herophilus observations of the existence of motor and sensory nerves and extended the concepts that the brain was the *'starting point'* for all nerves and select regions were responsible for intellectual

activity. He minimized the importance of the humoral theory of Hippocrates and ignored the concept that the heart was the center of sensations. To him, the heart functioned as a pump and the actions of the four valves maintained the flow of blood and pneuma in one direction. According to Galen, who wrote extensively on the physiological views of Erasistratus, arteries existed to contain pneuma and blood was a pure nutriment that became consumed to replace the '*wasted tissues*'. Erasistratus knew severed arteries would spurt and lose blood and believed an undetectable pneuma was lost causing a vacuum which attracted blood from adjacent veins [154]. Pneuma was present in atmospheric air as a vapor, was essential for life, entered the body during inspiration, and became distributed via arteries to the body and to the left ventricle of the heart. The primary role of pneuma was to induce physiological and intellectual functions. Although the process was unclear, pneuma in the heart became a '*vital spirit*' whereas in the ventricles of the brain it became transformed into an '*animal spirit*' [144]. One effect of pneuma was the contraction of muscles which was an expansion process associated with fiber shortening [122]. He maintained food was carried from the stomach by internal action (peristalsis) and not by an attraction force within the stomach. Digestion occurred because of the mechanical actions of the stomach causing the nutriment [154] to be '*ground down and dissolved*'. He believed living organisms '*give off*' invisible emanations and reportedly proved his point by conducting an experiment (metabolic) with a weighed bird in a cage (pot) that was provided no food and found the changes in excrement and body weight did not equal the original weight of the animal. According to the writings of Anonymus Londinensis, Erasistratus concluded [155, p. 127] from the great loss of weight that '*perceptible only to reason, a copious emanation has taken place*'. Approximately 1,900 years later, Sortorio Sortorio of Padua conducted human experiments using a calibrated balance chair and found the invisible emanations to be insensible perspiration [122]. In diseases not caused by plethora (ascites and pleurisy) Erasistratus prescribed moderate exercise (walking), dieting, and bathing activities [144]. He accepted the perspective of Alcmaeon that health was present when function had achieved balance and stability [152]. Hence his therapeutic regimen consisted of exercise, gymnastic activities, dieting, and bathing with a minimal use of drugs [108].

The Roman Influences

Select Features of Roman History

Archeological evidence indicates ancient tribes settled the hills of Rome around 950 BC. They believed spirits existed in animate and inanimate objects which became the subject of their worship. Later, they directed their worship to

gods and goddesses and enacted rituals and prayers to seek favors that included being free of diseases because disease [156] was a form of '*divine displeasure*'. Several centuries later, Etruscans moved into the area, became enamored with divination as a means for religious healing, and established a College of Augurs that had a divinity for each disease [157]. The Etruscans also brought their god and goddess which included Jupiter, Apollo, Venus, Mercury and Minerva that were accepted by the Romans. Associated with the Greek establishments in the Mediterranean Sea came acceptance and mostly renaming of many of their gods and goddesses which included Mars (Ares), Neptune (Poseidon), Pluto (Hades) and Salus (Hygeia) [158]. Health was also the responsibility of Aesculapius (Latin for Asclepius, the Greek god of medicine), for whom Rome in 291 BC had a temple constructed on the island of Tiber after the city experienced the ravages of the Great Plaque [158]. A century earlier, a cult dedicated to him was established at Anzio [159].

While Rome began to accept the gods and goddesses of Greece, this was not the case for their medical practices or beliefs. In fact, many centuries before the fall of Corinth (146 BC), individuals who practiced healing were not well respected (many were slaves) and if they were foreigners were only reluctantly tolerated and seldom appreciated. Thus the head of the family household, in accordance with Roman law and custom, fulfilled this responsibility. Pliny the Elder stated [158, p. 3], '*The Roman people for more than 600 years were not without medicine, but they were without physicians.*' As with medicine, instilling and maintaining personal health was also the responsibility of the head of the household. While exercise in the form of games and athletic contests were an important component of Roman culture, it had no importance for the promotion of health or in the recovery and management of disease.

Archagathus of Peloponesia in 219 BC was the first Greek physician to practice in Rome, however he became known as the 'butcher' and subsequently encouraged to leave [158]. More than a century later, Asclepiades of Bithynia (128–56 BC) became prominent in Rome and had a profound influence on Roman medical and health practices until the time of Galen. He and other foreign doctors were permitted to stay when Cicero banned all 'immigrants' from Rome during the plague of 46 BC. He was a graduate of the School at Alexandria, a severe critic of the humoral theory of Hippocrates, a friend to Cicero, a charlatan to Pliny the Elder, and to Galen [160, p. 633], a physician who was '*either mad or entirely unacquainted with the practice of medicine*'. Archagathus was a proponent of the atomic or corpuscular theory of Democritus and promoted the epicurian view that the essence of life was a combination of the soul and the elements. Respiration was responsible for the soul, air for rest, pneuma for motion, heat for vital activity with the undefined fourth element being responsible for all sensory phenomena [153]. To

Asclepiades [92, p. 137], matter consisted of '*extremely small but still divisible, fragile, formless and mutable collection of atoms*'. Their random movements and potential collisions resulted in the formation of particles and different bodies of various dimensions. Once formed, particles left behind empty tubes (poroi) which were occupied by smaller particles which created sensations. Respiration involved air reaching the heart by way of the poroi before entering the blood and being distributed throughout the body. Digestion involved the same process except the food went from the stomach to the heart and blood. Whenever an influx of particles occurred within the poroi, there was a pulse. The same was true to explain animal heat and secretion. On the other hand, hunger and thirst occurred [92] when the pores in the stomach were in different states of '*emptiness*'.

Disease was due to a stagnation of the atoms whereas weak, irregular, or strong motions of the particles were associated with sickness. In addition, the number of atoms per unit of poroi, the size of the atoms influenced the nature and severity of the disease. Disease was also due to the obstruction of the invisible pores located within the abdomen and stomach. Health existed when the particles were moving in a quiet and regular manner. Thus his goal for the restoration of health was to achieve harmony among the particles and to prevent obstructions within the pores [92]. Exercise (usually walking) was included with massage, bathing, dietary changes, riding, and frequent wine, to achieve these purposes. If a patient had dropsy, both walking and running were prescribed provided tissue fluid did not spread to the lower appendages. If edema occurred, exercise was to cease [161]. Besides dropsy, Archagathus recommended walking for patients with consumption or had experienced hemiplegia. Besides exercise effects on pores, it was recommend to aid digestion [97].

Influences from the Army, Gladiators, and the Early Romans

The transformation of the Roman Republic from the overthrow of the monarchy in 510 BC to the Roman Empire of Emperor Marcus Aurelius (161–180 AD) was facilitated by the prowess of the Roman army [162]. Their concern for health and exercise was noted by Vegetitus [163, p. 65] who stated military experts '*considered that daily exercise in arms were more conducive to soldiers health than doctors*'. Army recruits were required to be healthy and to meet specified physical standards. The army expected potential recruits to have a lifestyle that included '*reasonable exercise*', proper sleep and rest and a well-regulated diet [162]. Once in the army, they adhered to a general rule of war which stated '*An army is improved by work, enfeebled by inactivity*' [163]. Recruits were prepared for combat by sessions of marching (32 km in 5 h at the military pace and 38.4 km in 4 h at the full pace), running, charging, long and broad jumping and swimming (summer only) [164]. They performed drills with

wooden swords and wickerwork shields that had twice the weight of their issued items with the intent to strengthen arms [162, 169]. Once within a legion, they [165] were instructed to perform drills with the same intensity as in combat and to complete longer marches to experience fatigue and to *'wear out the stragglers'*. Additionally, they increased the weight of the shaft of the practice spear (javelin) to increase arm strength of throwers. For centuries, they were required to perform drills and exercises daily, however during a war in Spain (ca. 210 AD), Scipio adopted a tetrad system which included the following [165, p. 29], *'He bade them on the first day do a run of nearly four miles in full kit, on the second to rub clean and generally make a close examination of their equipment; on the next day to do nothing, and on the following, some men to fight with wooden swords sheathed in leather with a button at the end, and others to throw javelins similarly fitted with buttons; on the fifth day to revert to marching they had done on the first, and so on.'*

Gladiatorial contests were described [166] as being the *'most successful innovation in the repertory of Roman spectacular entertainment'*. Although such contests began in Paestum, a city south of Naples between 370 and 340 BC, they were officially introduced to Rome in 264 BC with duels involving 6 (3 pairs) gladiators [167]. The public interest in these contests can be assessed by the number of combatants which increased to 640 (320 pairs) during the time of Gaius Julius Caesar (65 BC) to 10,000 with the reign of Augustus (27 BC–14 AD) [167]. Initially the schools performing the training of gladiators were private, but by the first century, had become the responsibility of the state. The staff of each school included physicians, trainers, masseurs, as well as bandage specialists and tailors. Their most renown physician was Galen who served in that capacity in Pergamon and in Rome [110]. The trainers emphasized physical fitness within the strict military guidelines that identified 16 different forms of combat readiness. In addition, gladiators followed many of the procedures listed for Roman Legions such as using heavier weapons and shields to become stronger, practicing at an intensity level required for combat, repeating high intensity periods of running, charging, and jumping, and scheduling longer training sessions to improve endurance. In addition, they used *'warming up'* activities [163].

It was the perspective of Celsus (a chronicler of Roman medical and health practices during the first century after the birth of Christ), that in the 400 years since Hippocrates, medicine had become a composite of dietetics, pharmacology, and surgery [168]. Medicine was the promise of health to the sick while dietetics included exercise, bathing, relaxation, use of select medications and food and drink consumption [168, 169]. Diseases were classified as either acute or chronic with humoral shifts and seasonal changes being contributing causes. Romans were expected to *'manage'* their health problems and

only seek attention when they were ill. Living should include a variety of experiences in the country, town, and around the farm and activities such as resting, sailing, hunting and exercising were encouraged. Exercise included reading aloud, drills, walking, running, and ball activities but only to the point of sweating and never to the degree of fatigue practiced by athletes [168]. Celsus did report gentle (light) exercise (walking) was advocated for diseases as consumption and hemiplegia and that strenuous (heavy) exercise was suitable for dropsy [168].

The Legacy of Galen

Before Claudius Galenus or Galen of Pergamon (129–210 AD) became the court physician to Emperor Marcus Aurelius in Rome during 160 AD (fig. 6), he had been well tutored in philosophy and medicine, attended medical schools in Smyrna, Corinth, and Alexandria, served as the primary physician for the gladiators and was highly respected for his public lectures on anatomy and health [170]. He believed in the power of gods, was a follower of Asclepius and during his youth had been an *'attendant'* at the local temple that honored him. However, Galen was uncertain about his essence or the immortality of his soul [171]. Because of his appointments, personality, knowledge, productivity (434 titles of which more than 350 were authenticated [172]), and devoted followers, Galen's beliefs dominated medical and health practices for more than 1,000 years [173].

Galen accepted the concept that the elements of fire, earth, water and air were the basic constituents of the universe and that living matter was a mixture (crasia) of the elements, their qualities and the four humors whose proportions determined the uniqueness and temperance of individuals while affecting their physiological functions [174]. He advocated the Plato concept of a tripartite soul with distinctive souls being represented in the brain, heart and liver [174]. In the brain, the soul was responsible for reasoning, rational thoughts, directing motion, and interpreting sensations; in the heart it was regarded as *'life's vital force'* and responsible for passion whereas in the liver, the soul was responsible for nutrition, growth and reproduction [170, 174]. A superb anatomist, he considered these organs to be the most important in the body and felt that each was dominated by animal, vital and by natural spirits [170]. He also promoted the concept that each structure within the body existed for the purpose of performing a definite function [175].

To relate to the physiological concepts of Galen (fig. 7), one must understand that digested (concocted) food was used by the liver to form blood which was distributed to the heart and other regions of the body by veins. The liver formed yellow bile from chylus and generated a *'thick, muddy and atrabilious'* humor (black bile) that was taken up by the spleen. Phlegm was formed and secreted by the brain [171]. Both Pioreschi [176] and Scarborough [156] stated

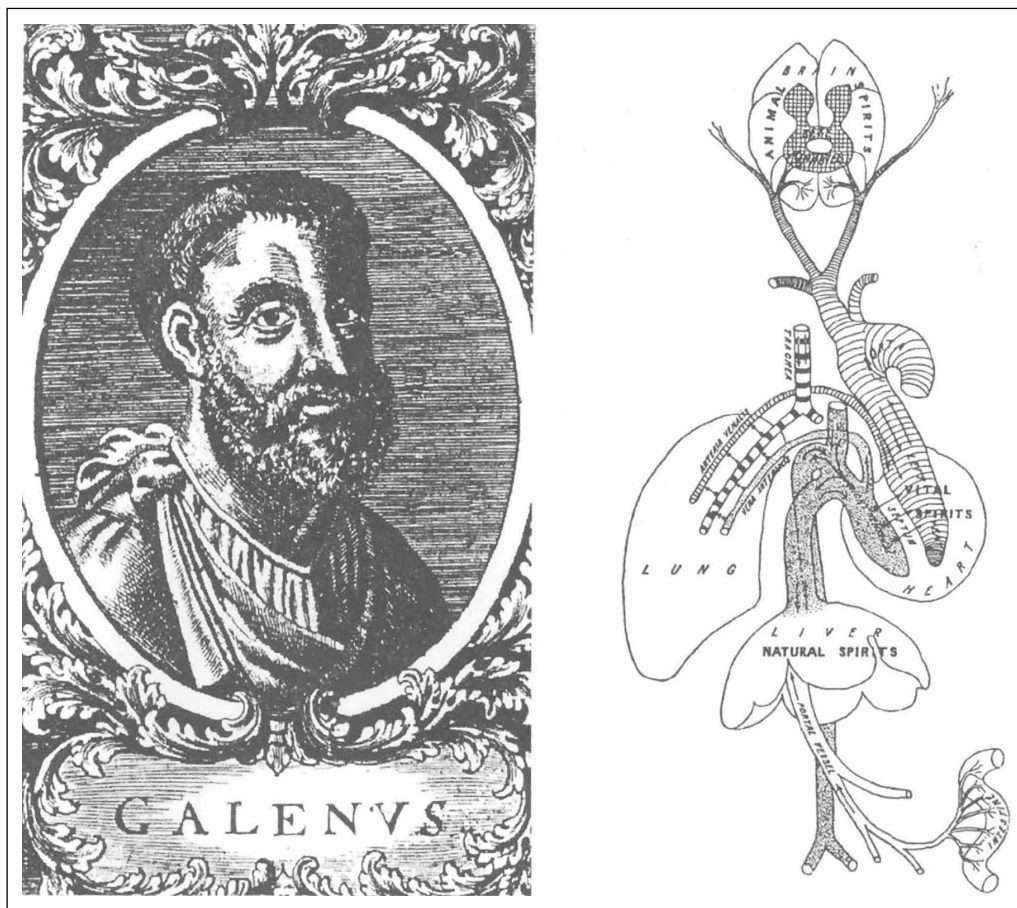


Fig. 7. Claudius Galenus or Galen of Pergamon (129–210 AD) and a representation of his physiological concepts [from 202, pp. 76, 141, with permission].

Galen knew from animal experiments air (oxygen) was essential for fire (life) to continue and believed inspiration allowed the lungs to prepare a pro-pneuma which entered the veins and mixed with blood within the right heart. Subsequently, pro-pneuma and more blood entered the left ventricle by pores in the interventricular septum and became transformed into a vital pneuma. Once in the left heart, which Galen considered to be a muscle, the mixture of pneuma and blood became heated and energized to become a vital spirit which imparted heat and life to other parts of the body via the arteries [177]. Other functions of the respiratory system were to regulate the equivalent of insensible perspiration

(sooty excrement), the innate heat associated with metabolism, and the cooling of the body [176], but not the heart [178]. Fever, an immodulation of heat, was regarded as an abnormality in heat loss that was caused by either an excessive uptake of outside heat or an increase in physical activity and was classified as a thermoregulatory disease of the respiratory system [179].

Galen accepted Erasistratus' view that the arterial and venous systems were linked by invisible capillaries and believed that pulsation of the arteries came from the power generated by the heart to the walls of the arteries [180]. Once the blood carrying the vital spirit interacted with air within the anterior ventricles of the brain, an animal spirit was formed which began to regulate brain and nerve functions while initiating sensations [170, 181]. He recognized two types of nerves and that lesions of motor nerves or of the spinal cord would produce paralysis [182]. As noted earlier, the liver contained the natural spirit and was responsible for nutrition, growth and reproduction [183]. He knew saliva initiated the digestive process of foods that became blood and humors. Once in the stomach, a concoction process occurred which produced chyle and a residue. Both products went to the intestines before going to the liver via the portal vein. Chyle was changed into blood while the heaviest component of the residue went to the spleen, the intermediate component was sent to the kidney while lightest residue was distributed to the gall bladder [176].

Galen promoted the concept that urine was a product of the kidney and was not from the gall bladder. He believed urine was separated from the blood but was uncertain about the process. Because of its yellow color, he speculated urine contained various humors, especially yellow bile. Although he dismissed the idea that filtration was a function of the kidneys, he did indicate that an attraction process was involved and responsible for the specific secretion of serous matter by the kidneys [184].

Health was regarded as an '*unimpaired capacity of function*' (bodily) that occurred because of '*good*' mixtures (eucrasia) and proportions of the elements and their qualities [185]. On the other hand, disease and illness occurred because of '*bad*' mixtures (dyscrasia) and proportions. As defined in '*On Antecedent Causes*' [186, p. 158], '*A disease is a disposition of the body that hinders or prevents the proper activity of one of its parts.*' Thus an excess or a deficiency in the qualities, especially heat and cold or in any of the four humors was considered to be a pathological condition or a disease state [129]. For example, an excess of black bile was associated with cancer whereas an increase in phlegm was identified with rheumatism [175]. Galen believed in the multiplicity of casual factors being responsible for diseases and indicated there were nine possible humoral mixtures or temperaments which served as a predisposition for certain types of disorders [177]. Select causal factors deserving attention were (a) things consumed, (b) things excreted from the body,

(c) things performed (which included exercise), and (d) things happening from within. Galen reinforced causal factors being responsible for both health and disease by introducing the concept of natural conditions (kata physin, or healthy), non-natural conditions (ou kata physin, or hygienic), or contrary to nature's conditions (para physin, or diseased or pathological) [187]. These conditions were collectively related to the evolution of disease and to the preservation of health. Inherent with this concept was that failure to maintain a 'normal' balance between bodily constituents resulted in disease and a loss of health. Within the non-natural conditions were (a) air, (b) motion and rest, (c) sleeping and waking, (d) that which was taken in, (e) that which was secreted, and (f) the emotions or passions [173].

Galen's views on health and disease states were influenced by his personal experiences which included being ill during much of his young life. He wrote [188, p. 188]: *'But after my 28th year from birth, having persuaded myself that there is a certain art of hygiene, I followed its precepts for all my subsequent life, so that I am no longer sick with any disease except an occasional fever.'* Exercise was important to achieve health while lack of exercise or excessive exercise could be associated with illness although Galen did not quantify the relationship. For movement (or gymnastics) to be considered as exercise, it had to be sufficiently intense to elicit a change in breathing (he used the term vigorous but likely meant heavy exercise [137]. Work and exercise were equivalent terms and he considered shadow boxing, leaping, discus throwing, ball activities, and climbing rope to be exercise whereas digging, rowing, plowing, riding, fighting, walking or running could be either exercise or work. Exercise was classified to be either slow or swift, atony or vigorous, gentle or violent [189]. Ball exercises and running were examples of swift exercise [190]; digging, climbing a rope or lifting a heavy weight were vigorous exercises [191] while discus throwing and continuous jumping were classified as violent exercises [189]. Small ball activities were Galen's favorite exercise and he wrote [192, p. 302], *'The form of exercise most deserving of our attention is therefore that which has the capacity to provide health of the body, harmony of the part, and virtue in the soul; and these things are true of the exercise with the small ball.'*

When exercise was recommended for health reasons, moderation was encouraged. Galen and contemporaries during the later portion of his life (Philostratus and Aretaeus) recommended gymnastic and ball exercises (walking, running, jumping, wrestling, boxing, punching bag, track and field events) for weakened individuals recovering from illnesses or for people with arthritis, dropsy, gout, depression, tuberculosis, vertigo and epilepsy [111, 193–195].

Although physiological knowledge was fragmentary, Galen associated acute exercise with an increase in breathing, an acceleration of the pulse rate, an increase in the temperature (warmth, natural heat) of the body, sweating, a readier

metabolism, increased digestion, enhanced elimination of excrement, the sensation of muscular fatigue, an equal distribution of the spirits, opening of the pores, purging the ducts, an increase in the acidity of the fluids and reduced concentrations of phlegm, yellow bile and black bile in the blood [189, 196–199] With chronic exercise or training, Galen believed it would cause ‘*thinning*’ of the body, harden and strengthen muscle, increase flesh (body composition), elevate blood volume and achieve the ‘unqualified good condition’ represented by Milo the wrestler or by either Hercules or Achilles in Homer’s epics [185, 192, 194, 196, 200].

Galen had little respects for trainers of athletes and even less for the professional athlete because of their lack of awareness of the natural good of the soul (intelligence) and because of their daily practices. On this matter he wrote [200, p. 47], *‘Now that athletes have never, even in a dream, enjoyed the goods of the soul is clear to everyone. To begin with, they are unaware they have a soul, so far they are they from understanding its rational nature. Because they are always occupied in the business of amassing flesh and blood, their souls are as if it were extinguished in a heap of mire, unable to contemplate anything clearly, mindless as beasts without reason.’* He felt an athletic state was not a ‘*natural*’ condition and that training had little practical value. In addition, training cultivated disease rather than health. Since athletes were usually in peak physical condition, it was impossible to improve. Consequently, their fate would be to experience deterioration, a viewpoint that was shared by Hippocrates.

Discussion and Summary

Since the Neolithic Age, humans associated with the emerging cultures of Eastern and Western civilizations have sought relief and understanding from supernatural sources for the ravages of disease and disorders. Although select ancient physicians in Egypt, Persia and India had suggested that not all diseases and illnesses were ordained by the gods, it was the early influence of Pythagoras and his disciples combined with the dominating view of Hippocrates and his followers that transformed ‘*religious medicine*’ into the rational form being practiced today. When the leaders of China adopted the principles of the Yinyang Doctrine, they accepted yang being associated with life and health and yin being identified with death and disease.

Excluding the Chinese, health or a healthy state in ancient cultures was considered a pre-ordained state from supernatural sources that at best became transformed into one of being free of disease and assorted illnesses. Exercise in the form of rituals, dances, games and athletic contests were practiced in some form

by all cultures, but with the exception of the ancient Chinese of circa 2700–600 BC, who used breathing exercises in the practice of yoga, they had no relevance to the concept that exercise was being advocated or prescribed for health reasons.

To the inhabitants of India, exercise meant walking, running, jumping, throwing, lifting, climbing and combinations thereof. The Greeks added punching and kicking plus activities as boxing, wrestling, discus and spear throwing and the running broad jump. Romans increased the list with leaping and fighting while including rowing, riding, reaping and tasks associated with work as digging and plowing. To Galen, small ball exercises were the best.

The foundations for exercise being advocated and prescribed for health reasons were (a) the humoral theories mentioned during the Vedic and Hippocratic eras and (b) the identification of elements by ancient Indian authors and by Empedocles that were responsible for the composition of the human body that, to the Indian authors, were originally represented by air, bile and phlegm, whereas to the Greek philosophers, they became phlegm, yellow bile, black bile and blood. For Susruta, blood was a principle that behaved as a humor. Implicit with the humoral theories was that natural physiological functions could occur only when the humors were in equilibrium. Moreover, any displacement or disruption of an established equilibrium would result in illness, disease or an unhealthy state. Thus their existence provided a qualitative definition for the presence or absence of health while providing a medical rationale for the treatment of illness and disease. It was interesting to note the similarities of the Indian humoral theory, the Yinyang Doctrine and the beliefs of Pythagoras in that harmony must prevail among the principles or between the elements for health to be present.

Beginning with Susruta (ca. 600 BC), moderate exercise was advocated to restore the equilibria between the dosas (humors) by decreasing the concentration of the kapha dosa. Moreover, excessive (heavy) exercise was to be avoided because it was disruptive to the vayu dosa and responsible for the occurrence of various diseases. To Hippocrates the humoral theory was a cornerstone for his views on disease and its causes, thus he recommended moderate exercise to dilute, warm and purge humors without specifically identifying which ones were responsible or changing. As health was improved with the restorations of humoral equilibrium, exercise became included within the regimens of Hippocrates and many of his followers. Restoration of humoral equilibrium was also important to Galen and he promoted exercise for this purpose.

Susruta, Pythagoras, Herodicus, Hippocrates, Diocles, Erasistratus, Caraka, Galen, and Asclepiades from either India, Greece or Rome advocated exercise to their 'patients' for one or more disease or disorders as arthritis, ascites, consumption, depression, diabetes, epilepsy, gout, hemiplegia, pleurisy, tuberculosis, and vertigo. However, Hippocrates appeared to be the first to

include specific details concerning mode, frequency, intensity, and duration. It was unexpected that the majority of exercise advocates from India, China, Greece, and Rome were against advocating excessive (heavy) exercise because of their concern it would result in assorted diseases and disorders, and in some cases, death. Exceptions were Caraka's advocacy of heavy exercise to 'cure' diabetes and the Romans' use of strenuous exercise for dropsy patients. In the nearly two millennia that have elapsed since the death of Galen, it is understandable that ancient physiological mechanisms have little or no resemblance to current ones and especially when humoralism was rejected by Virchow in 1858 [201]. However, if we consider the proposed humoral mechanisms for disease as antecedents for changes in the functions of the endocrine and immune systems which can lead to subsequent disease states, then these ancient humoral theories become important contributions.

Ancient contributions to exercise physiology include warming up, recognizing that nerves were involved for movement to occur, observing that moderate exercise would increase breathing and pulse rates, fluid shifts (considered as humoral shifts), metabolism, sweating, body temperature, and the sensations associated with muscle pains and fatigue. With chronic exercise or training, they believed that the equilibria among the humors would be restored, bones would become stronger, stature would be enhanced with muscles becoming larger and stronger while having more endurance and work capacity and a greater resistance to fatigue. Sweating and the opening of pores were enhanced, especially in the summer, with digestion and the elimination of excrement being improved. Training increased blood volume, body thinness, and to some, decreased the aging process.

Around 400 BC, athletic trainers were available to instruct competitive athletes or participants at the gymnasium. However, there were few physicians who were qualified or interested in advising them, in part because of the disdain by Hippocrates, and later by Galen for such a role. The most modern of the ancient advice pertained to strength training in that muscles must be 'overloaded' for improvements in strength to occur. This concept was implemented in many different ways for various events and the legend of Milo's daily lifting of a calf until it had become a bull continues to be repeated in exercise physiology textbooks. Although they were unaware of the principle, the specificity of training was practiced in part by ancient athletes and by Roman warriors. Ancient training programs had fragments concerning frequency, intensity, duration, and recovery periods between bouts and after sets of the various activities. The tetrad schedule followed by Greek athletes and the combat training schedule of the Roman legionnaires were examples of this fact.

After examining the collective beliefs and practices of our ancient ancestors, it was concluded they were remarkably modern with their ideas.

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Appendix II

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奥林匹亚

营养与健康宣言

希腊古奥林匹亚
1996年5月28-29日

在奥林匹克运动100周年之际，重新肯定希波克拉底的健康概念，重新评估和大众健康息息相关的奥林匹克理想，都是非常重要的。如希波克拉底所言，良好健康的概念，是基于遗传、膳食和体力活动之间作用的结果。

- 1** 营养与体力活动相互协调是两个重要因素，个体在遗传赋予的先天基础上，对健康和代谢适应起作用。基因取决于个体健康和疾病易感性的机遇，而环境因素则决定易感个体是否会发展为疾病。因此，为校正微量元素营养缺乏、膳食不平衡和静态生活方式所引起的紊乱，可能需要考虑个体差异。
- 2** 每个儿童和成年人都需要充足的食物和体力活动以显示基因在生长、发育和健康中的潜在能力。如果能量、蛋白质、维生素(尤其维生素A、C、D、E和B复体)和矿物质(尤其是钙、铁和碘、钾与锌)摄取不足，以及体力活动不够，将对全面的健康和骨骼肌肉的功能产生损害。
- 3** 体力活动和满足体能所需营养之间的平衡，可以从热能摄入和消耗观点得到最佳的说明。对于静态生活的人群，必需增加体力活动，对于参加职业性或娱乐性的剧烈体力活动者，应增加食物消耗量以平衡其热能需要。
- 4** 营养成分应尽量与人类遗传进化过程的食物接近，食物的选择应为多样化的膳食，特别是蔬菜和水果，必须营养丰富，并有充足的保护性、抗氧化剂和必需脂肪酸。
- 5** 当前体力活动的运动量应尽量与我们遗传天赋一致。在每日生活中，重新建立一种有规律的体力活动，对体力、智力和精神健康都是必要的。体力活动对年龄性别均应是含有大肌肉群规则和重复的活动，并应有充足的持续时间、频率和强度。对于不同水平竞技运动员的适宜营养应给予特殊的关注。
- 6** 通过能量平衡和良好的体力活动，达到代谢平稳，可以减少许多现代生活方式疾病，如糖尿病、高血压、骨质疏松症、肥胖与心血管紊乱等的危险，并形成治疗计划，维持平稳代谢并改进骨骼肌肉功能的能动性，以及老年人的日常活动。
- 7** 涉及到健康营养和体力活动的教育应尽早开始并坚持一生。营养与体力活动必须纳入到学龄期儿童、教育工作者、营养师和其它从事于健康事业者的日程中。社会与媒介也应帮助和促进建立起一个良好的模式。
- 8** 家庭、社区和社会的各种资源所支持的大部分个人主要行为改变，必须拒绝不健康的生活方式，而接纳一种活跃的生活方式和良好的营养。
- 9** 国家政府和私人机构应协同努力，鼓励人们在一生中保持良好营养和参与体力活动的习惯，从而增加为奥林匹克理想奋斗的后备力量。
- 10** 古希腊人(Hellenes)由于具备良好的营养、经常性体力活动，智力得到充足发展，从而获得高水平的文明，矢志事功臻完美；而现代人同样可通过经常性的体力活动和均衡营养，在为奥林匹克理想的奋斗中变得更快、更高和更强。

此宣言是于1996年5月24-29日，在希腊古奥林匹亚
(继希腊雅典奥林匹克运动中心Spylos Louis举行的第三届国际营养与健康会议后)形成的
2001 S. Street, N. W., Suite 530, Washington D. C. 20009 - Fax:(202)462-5241



Declaration of Olympia on Nutrition and Fitness

Ancient Olympia, Greece
May 28-29, 1996

On the occasion of the 100th anniversary of the Olympic Games, it is important to reaffirm the concepts of positive health postulated by Hippocrates and to reassess their relevance to the Olympic ideal and the health of the world's populations. The concept of positive health, as enunciated by Hippocrates, is based on the interaction of genetics, diet and physical activity.

- 1** Nutrition and physical activity interact in harmony and are the two most important positive factors that contribute to metabolic fitness and health interacting with the genetic endowment of the individual. Genes define opportunities for health and susceptibility to disease, while environmental factors determine which susceptible individuals will develop illness. Therefore, individual variation may need to be considered to achieve optimal health and to correct disorders associated with micronutrient deficiency, dietary imbalance and a sedentary lifestyle.
- 2** Every child and adult needs sufficient food and physical activity to express their genetic potential for growth, development, and health. Insufficient consumption of energy, protein, essential fatty acids, vitamins (particularly vitamins A, C, D, E and the B-complex) and minerals (particularly calcium, iron, iodine, potassium and zinc), and inadequate opportunities for physical activity impair the attainment of overall health and musculoskeletal function.
- 3** Balancing physical activity and good nutrition for fitness is best illustrated by the concept of energy intake and output. For sedentary populations, physical activity must be increased; for populations engaging in intense occupational and/or recreational physical activities, food consumption may need to be increased to balance their energy needs.
- 4** Nutrient intakes should match more closely human evolutionary heritage. The choice of foods should lead to a diverse diet high in fruits and vegetables, and rich in essential nutrients, particularly protective antioxidants and essential fatty acids.
- 5** The current level of physical activity should match more closely our genetic endowment. Reestablishment of regular physical activity into everyday life on a daily basis is essential for physical, mental, and spiritual well-being. For all ages and both genders the physical activity should be appropriately vigorous and of sufficient duration, frequency, and intensity using large muscle groups rhythmically and repetitively. Special attention for adequate nutrition should be given to competitive athletes.
- 6** The attainment of metabolic fitness through energy balance, good nutrition and physical activity, reduces the risk of and forms the treatment framework for many modern lifestyle diseases such as diabetes mellitus, hypertension, osteoporosis, some cancers, obesity, and cardiovascular disorders. Metabolic fitness maintains and improves musculoskeletal function, mobility, and the activities of daily living into old age.
- 7** Education regarding healthy nutrition and physical activity must begin early and continue throughout life. Nutrition and physical activity must be interwoven into the curriculum of school age children and of educators, nutritionists and other health professionals. Positive role models must be developed and promoted by society and the media.
- 8** Major personal behavioral changes supported by the family, the community, and societal resources are necessary to reject unhealthy lifestyles and to embrace an active lifestyle and good nutrition.
- 9** National governments and the private sector must coordinate their efforts to encourage good nutrition and physical activity throughout the life cycle and thus increase the pool of physically fit individuals who emulate the Olympic ideal.
- 10** The ancient Greeks (Hellenes) attained a high level of civilization based on good nutrition, regular physical activity, and intellectual development. They strove for excellence in mind and body. Modern men, women, and children can emulate this Olympic ideal and become swifter, stronger, and fitter through regular physical activity and good nutrition.

The declaration was developed by an International Panel on the occasion of the Third International Conference on Nutrition and Fitness, May 24-29, 1996, in Greece, under the chairmanship of Artemis P. Simopoulos, M.D., President of The Center for Genetics, Nutrition and Health, 2001 S. Street, N.W., Suite 530, Washington D.C. 20009 - Fax: (202) 462-5241



Déclaration d'Olympie sur la nutrition et la santé

les 28-29 mai 1996
Olympie, Grèce

A l'occasion du 100^e anniversaire des Jeux Olympiques, il importe de réaffirmer les concepts de santé énoncés par Hippocrate et de réévaluer leur pertinence au regard de l'idéal olympique et de la santé des populations du monde entier. Le concept de santé d'Hippocrate se fonde sur l'interaction entre la génétique, l'alimentation et l'activité physique.

- 1** La nutrition et l'activité physique doivent entretenir des relations harmonieuses. Ce sont les deux composants principaux de l'équilibre métabolique. Elles interagissent également avec le profil génétique de l'individu. Les gènes définissent les prédispositions à la santé et les sensibilités aux maladies alors que les facteurs d'environnement déterminent qui, parmi les individus prédisposés développera la maladie. Il est ainsi nécessaire de tenir compte des variations individuelles pour la recherche d'une santé optimale et la correction des troubles liés à une carence en micronutriments, à un déséquilibre nutritionnel et à un mode de vie sédentaire.
- 2** Enfants et adultes ont tous besoin d'une quantité suffisante de nourriture et d'activité physique pour exprimer leur potentiel génétique en matière de croissance, de développement et de santé. Un apport insuffisant en énergie, en protéines, en acides gras essentiels, en vitamines (A, C, D, E et B, en particulier) et en minéraux (calcium, fer, iode, potassium et zinc, notamment) ainsi qu'une activité physique insuffisante nuisent à l'acquisition d'une bonne santé en général et aux fonctions musculaires et osseuses en particulier.
- 3** Indispensable à l'obtention d'une bonne condition physique, l'équilibre entre activité physique et alimentation s'illustre parfaitement par le concept de consommation et de dépense d'énergie. Si les populations sédentaires doivent pratiquer davantage d'exercice physique, les populations qui, à travers leur métier ou leurs loisirs, se dépensent intensément auraient intérêt en revanche à augmenter leur apport alimentaire afin de compenser leurs besoins en énergie.
- 4** Il convient d'adapter de manière plus étroite les apports nutritionnels à l'évolution humaine. Le choix des aliments doit aboutir à une alimentation variée, riche en fruits, en légumes et en nutriments essentiels, tels que les anti-oxydants protecteurs et les acides gras essentiels.
- 5** Le niveau d'activité physique devrait être mieux adapté à notre profil génétique. Le rétablissement d'une activité physique régulière pratiquée quotidiennement est essentiel au bien-être physique, mental et spirituel. Tous les individus, hommes et femmes, quel que soit leur âge, devraient pratiquer une activité physique d'intensité appropriée, d'une durée et d'une fréquence suffisantes, faisant travailler de manière harmonieuse et répétitive différents groupes musculaires. Une attention toute particulière doit être accordée à l'alimentation des athlètes de compétition.
- 6** L'acquisition d'un bon métabolisme, par un équilibre énergétique, une alimentation saine associés à une activité physique, réduit le risque et contribue au traitement de certaines maladies typiques de nos modes de vie modernes (diabète sucré, hypertension, ostéoporose, certains cancers, obésité et troubles cardiovasculaires). L'équilibre métabolique maintient et améliore les fonctions musculaires et osseuses, la mobilité et l'indépendance des personnes âgées pour les gestes de la vie quotidienne.
- 7** L'enseignement de la nutrition et la pratique d'une activité physique doivent commencer très tôt et se poursuivre la vie durant. Nutrition et activité physique doivent être intimement mêlées dans les programmes scolaires et faire partie intégrante de la formation des éducateurs, des nutritionnistes et autres professionnels de la santé. Des modèles de comportement doivent être développés et favorisés par la société et les médias.
- 8** Des changements importants des comportements individuels, soutenus par des ressources familiales, communautaires et sociales, sont nécessaires pour rejeter des modes de vie préjudiciables à la santé et adopter un mode de vie sain, englobant activité physique et alimentation équilibrée.
- 9** Les gouvernements et le secteur privé doivent coordonner leurs efforts pour encourager une alimentation saine et la pratique d'une activité physique régulière tout au long de la vie, augmentant ainsi le nombre d'individus en bonne forme physique promouvant l'idéal olympique.
- 10** Les Hellènes (peuple de la Grèce antique) atteignent un niveau de civilisation élevé basé sur une alimentation saine, la pratique régulière d'une activité physique et le développement intellectuel. Ils s'évertuaient à atteindre l'excellence du corps et de l'esprit. Les hommes, les femmes et les enfants des temps modernes peuvent imiter cet idéal olympique et devenir plus actifs, plus forts et en meilleure forme grâce à la pratique régulière d'une activité physique et à l'adoption d'une alimentation saine.

Cette déclaration a été rédigée par un panel d'experts internationaux à l'occasion de la Troisième Conférence Internationale sur la Nutrition et la Santé, du 24 au 29 mai 1996 en Grèce, sous la présidence d'Artemis P. Simopoulos M.D., Président du Center for Genetics, Nutrition and Health, 2001 S. Street, N.W., Suite 530, Washington D.C. 20009 - Fax (202) 462-5241.



Η ΔΙΑΚΗΡΥΞΗ ΤΗΣ ΟΛΥΜΠΙΑΣ ΠΕΡΙ ΔΙΑΤΡΟΦΗΣ, ΑΣΚΗΣΗΣ, ΑΘΛΗΤΙΣΜΟΥ ΚΑΙ ΥΓΕΙΑΣ

28-29 ΜΑΪΟΥ 1996
ΟΛΥΜΠΙΑ, ΕΛΛΑΔΑ

Επί τη ευκαιρία της 100ης επετείου από την αναβίωση των Ολυμπιακών Αγώνων, είναι σημαντικό να επιβεβαιώσουμε τις αρχές της θετικής υγείας, όπως πρώτος τις έθεσε ο Ιπποκράτης και να επανεξετάσουμε τη σχέση τους με τα Ολυμπιακά ιδεώδη και την πορεία της υγείας του πληθυσμού στον πλανήτη μας. Η έννοια της θετικής υγείας, όπως διατυπώθηκε από τον Ιπποκράτη, βασίζεται στην αλληλοεπίδραση των αρχών της γενετικής, της διαίτας και της φυσικής δραστηριότητας.

- 1** Η διατροφή και η φυσική δραστηριότητα αποτελούν καθοριστικούς παράγοντες για τη διατήρηση της καλής υγείας, σε συνδυασμό με το γενετικό κώδικα του ατόμου. Η ποιότητα της ζωής μας είναι αποτέλεσμα της αλληλοεπίδρασης του γενετικού κώδικα και του περιβάλλοντος που ζούμε. Συνεπώς, οι γενικές διαφορές θα πρέπει να λαμβάνονται υπ' όψη για τη διατήρηση της υγείας και για τη θεραπεία ασθενειών που οφείλονται σε έλλειψη θρεπτικών συστατικών, έλλειψη ισορροπημένης διατροφής και καθιστική ζωή.
- 2** Όλοι οι άνθρωποι χρειάζονται επαρκή διατροφή και φυσική δραστηριότητα για την επίτευξη των γενετικά προκαθορισμένων δυνατοτήτων τους, για φυσιολογική ανάπτυξη και καλή υγεία. Ανεπαρκής κατανάλωση ενέργειας (τροφής), πρωτεϊνών, απαραίτητων λιπιδίων, οξέων, βιταμινών (ιδιαίτερα βιταμίνες Α, C, D, Ε και της Β ομάδας) και μετάλλων (ιδιαίτερα ασβέστιο, σίδηρος, ιώδιο, κάλιο και ψευδάργυρος) και ανεπαρκής φυσική δραστηριότητα, εμποδίζουν τη σωστή μυοσκελετική ανάπτυξη και γενικότερα την υγεία του ατόμου.
- 3** Η κατανάλωση ενέργειας (τροφής) και το επίπεδο σωματικής δραστηριότητας θα πρέπει να βρίσκονται σε ισορροπία. Έτσι, άτομα που ζουν καθιστική ζωή θα πρέπει να αυξήσουν το επίπεδο φυσικής δραστηριότητας, ενώ τα άτομα που καθημερινά εμπλέκονται σε έντονες μορφές φυσικής δραστηριότητας θα πρέπει ίσως να αυξήσουν την κατανάλωση ενέργειας για να καλύψουν τις αυξημένες ενεργειακές ανάγκες τους.
- 4** Η διατροφή του σημερινού ανθρώπου δεν θα πρέπει να διαφέρει από τη διαίτα με την οποία ο γενετικός μας κώδικας είχε προγραμματισθεί. Τα χαρακτηριστικά αυτής της διαίτας είναι η μεγάλη ποικιλία τροφών, συμπεριλαμβανομένων πολλών φρούτων και λαχανικών, αντιοξειδωτικών συστατικών και απαραίτητων λιπιδίων οξέων.
- 5** Το επίπεδο φυσικής δραστηριότητας του ατόμου θα πρέπει να προσαρμοστεί ανάλογα με τη γενετική του προδιάθεση. Επαρκής καθημερινή φυσική δραστηριότητα είναι απαραίτητη για τη διατήρηση της σωματικής, διανοητικής και πνευματικής υγείας του ατόμου. Το είδος της φυσικής δραστηριότητας θα πρέπει να προσαρμόζεται ανάλογα με τη φυσική κατάσταση και τα ιδιαίτερα χαρακτηριστικά του ατόμου και θα πρέπει να έχει κατάλληλη διάρκεια, συχνότητα και ένταση. Για την επίτευξη θετικών αποτελεσμάτων θα πρέπει να χρησιμοποιούνται μεγάλες μυϊκές ομάδες και η άσκηση να είναι ρυθμική και επαναλαμβανόμενη. Ειδικά μέριμνα θα πρέπει να ληφθεί έτσι ώστε τα άτομα που απασχολούνται με πρωταθλητισμό σε κάθε επίπεδο να λαμβάνουν επαρκή διατροφή για την κάλυψη των αυξημένων ενεργειακών αναγκών τους.
- 6** Σωστή διατροφή, επαρκής φυσική δραστηριότητα και ενεργειακή ισορροπία μειώνουν τους κινδύνους προσβολής και παράλληλα αποτελούν σημεία αναφοράς για τη θεραπεία πολλών ασθενειών, χαρακτηριστικών του μοντέρνου, δυτικού τύπου τρόπου ζωής, όπως είναι ο διαβήτης, η υπέρταση, η οστεοπόρωση, ορισμένες μορφές καρκίνου, η παχυσαρκία και οι καρδιοαγγειακές παθήσεις. Σωστή διατροφή και επαρκής φυσική δραστηριότητα διατηρούν και προάγουν τη μυοσκελετική ανάπτυξη και ευκινησία και εξασφαλίζουν τη διατήρηση της δυνατότητας αυτοτελούς επιβίωσης μέχρι προχωρημένης ηλικίας.
- 7** Η εκπαίδευση σε θέματα διατροφής και φυσικής δραστηριότητας θα πρέπει να αρχίζει όσο το δυνατόν νωρίτερα και να συνεχίζεται για όλη τη διάρκεια της ζωής του ατόμου. Η σωστή διατροφή και η φυσική δραστηριότητα θα πρέπει να αποτελούν αναπόσπαστο κομμάτι της εκπαίδευσης των παιδιών, των εκπαιδευτικών, των διαιτολόγων και άλλων επαγγελματιών του χώρου της υγείας. Άτομα που αποτελούν παραδείγματα προς μίμηση στους τομείς της διατροφής, φυσικής δραστηριότητας και καλής υγείας θα πρέπει να προωθούνται από την κοινωνία και τα μέσα μαζικής ενημέρωσης.
- 8** Δραστικές αλλαγές στη συμπεριφορά του ατόμου απαιτούνται για την απόρριψη αρνητικών ανθυγιεινών συνθηκών και την αρχή ενός νέου τρόπου ζωής με σωστή διατροφή και επαρκές επίπεδο φυσικής δραστηριότητας. Για να επιτευχθούν οι αλλαγές αυτές, η ολόπλευρη συμπαράσταση της οικογένειας και της κοινωνίας είναι απαραίτητη.
- 9** Οι εθνικές κυβερνήσεις σε συνεργασία με τον ιδιωτικό φορέα θα πρέπει να προωθήσουν τις αρχές της σωστής διατροφής και φυσικής δραστηριότητας έτσι ώστε να αυξάνεται συνεχώς ο αριθμός των υγιών ατόμων που πιστεύουν και κάνουν τρόπο ζωής τα Ολυμπιακά ιδεώδη.
- 10** Η επίτευξη υψηλού επιπέδου πολιτισμού στην Αρχαία Ελλάδα στηρίχθηκε στο συνδυασμό σωστής διατροφής και τακτικής φυσικής δραστηριότητας παράλληλα με την πνευματική-διανοητική καλλιέργεια του ατόμου. Οι αρχαίοι Έλληνες πάσχισαν για την τελειότητα σε όλους τους τομείς. Ο σύγχρονος άνθρωπος θα πρέπει να ακολουθήσει το παράδειγμα αυτό, το Ολυμπιακό ιδεώδες, και να γίνει πιο γοργός, πιο δυνατός και πιο υγιής μέσω τακτικής φυσικής δραστηριότητας και σωστής διατροφής.



Декларация Олимпиады по вопросам питания и физкультуры

Древняя Олимпия, Греция
28-29 мая 1996 г.

В связи с приближающимся столетним юбилеем современных Олимпийских Игр считаем важным напомнить об основных принципах здорового образа жизни, сформулированных Гиппократом, и еще раз отметить их значение для достижения Олимпийского идеала и для здоровья всего населения. Концепция здоровья, провозглашенная Гиппократом, строится на взаимодействии генетики, питания и физической активности.

- 1** Питание и физическая активность гармонично взаимодействуют между собой и являются ключевыми факторами, влияющими на обмен веществ и здоровье на фоне генетической предрасположенности человека. Гены определяют общее здоровье и восприимчивость к тем или иным заболеваниям, в то время как внешние факторы могут способствовать развитию заболевания у предрасположенных к ним лиц. Таким образом, необходимо принимать в расчет индивидуальные особенности человека и в то же время искать пути к достижению оптимального здоровья и коррекции расстройств, связанных с недостатком микроэлементов, пищевым дисбалансом и сидячим образом жизни.
- 2** Для наиболее полной реализации заложенного генетического потенциала роста, развития и здоровья взрослым и детям необходимо получать адекватное количество пищи, белков, важных жирных кислот и витаминов, особенно А, С, D, Е и витаминов В-комплекса, а также минералов (кальций, железо, йод, калий и цинк) в комплексе с малой физической активностью плохо сказываются на общем состоянии здоровья и приводят к нарушению опорно-двигательной функции.
- 3** Равновесие физической активности и правильного питания в целях поддержания хорошей физической формы наилучшим образом можно проиллюстрировать на примере потребления и расхода энергии. Лица, ведущие пассивный образ жизни, должны увеличить свою физическую активность, а те, кто занят тяжелым физическим трудом и (или) интенсивно занимаются спортом, должны увеличить потребление пищи, чтобы сбалансировать потери энергии.
- 4** Используемые в пищу продукты должны больше приближаться к тем, которые традиционно употреблялись человеком в процессе его развития. Рацион должен включать разнообразные фрукты и овощи, богатые основными питательными элементами, в частности, защитными антиоксидантами и важными жирными кислотами.
- 5** Уровень физической активности должен максимально приближаться к генетически заложенному. Регулярные физические упражнения должны вновь войти в нашу жизнь, что значительно повлияет на физическое, умственное и духовное здоровье человека. Людям всех возрастов обоего пола необходимо интенсивно заниматься спортом, регулярно и достаточно продолжительно, давая нагрузку всем основным группам мышц. Особое внимание адекватному питанию следует уделять спортсменам, участвующим в соревнованиях.
- 6** Достижение оптимального уровня метаболизма путем сбалансированного поступления энергии, хорошего питания и достаточной физической нагрузки уменьшает риск возникновения и является частью программы лечения таких болезней, порожденных нашим образом жизни, как сахарный диабет, гипертония, остеопороз, некоторые виды рака, ожирение, сердечно-сосудистые заболевания. Оптимальный метаболизм поможет поддержать скелетно-мышечную функцию и сохранить подвижность до самой старости.
- 7** Обучение здоровому образу жизни и правильному питанию должно начинаться в раннем возрасте и продолжаться всю жизнь. Эти вопросы должны быть внесены в школьную программу и пропагандироваться среди работников образования, диетологов и врачей разных профессий. Позитивное отношение должно также воспитываться обществом и средствами массовой информации.
- 8** При поддержке семьи и общества необходимо произвести смену поведенческой установки человека, направить его на здоровый образ жизни и отказ от вредных привычек. Необходимо сделать упор на активный образ жизни и правильное питание.
- 9** Необходимо скоординировать усилия государственного и частного сектора для приобщения населения к активному образу жизни и правильному питанию на протяжении всей жизни, что позволит увеличить количество здоровых людей, ориентирующихся на Олимпийский идеал.
- 10** Древние греки (эллин) смогли достичь высокого уровня цивилизации, придерживаясь правильного питания, регулярно занимаясь физическими упражнениями и развиваясь интеллектуально. Они искали совершенства тела и духа. Современные мужчины, женщины и дети также могут придерживаться этого Олимпийского идеала и стать быстрее, сильнее, улучшить свое здоровье, идя по пути правильного питания и занимаясь спортом.

Декларация была принята международным президиумом Третьей международной конференции по питанию и здоровому образу жизни, проходившей в Греции 20-24 мая 1996 года под председательством Артемиса Симопулоса, президента Центра по исследованию вопросов генетики, питания и здорового образа жизни.
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Declaración de Olimpia sobre Nutrición y Bienestar Físico

28-29 de Mayo, 1996
Antigua Olimpia, Grecia

Con ocasión del centenario de los Juegos Olímpicos, es importante reafirmar el concepto de « salud positiva » postulado por Hipócrates y valorar de nuevo su relevancia para el ideal Olímpico y la salud de la población mundial. El término « salud positiva », tal como lo enunció Hipócrates, está basado en la interacción de la genética, la dieta y la actividad física.

- 1** Nutrición y actividad física interactúan armoniosamente y son los dos factores positivos más importantes que contribuyen al bienestar metabólico y a la salud, interactuando con la dotación genética del individuo. Los genes definen las oportunidades para la salud y la susceptibilidad a la enfermedad, mientras que los factores ambientales determinan qué individuos predispuestos desarrollarán la enfermedad. Por ello, se deben considerar las diferencias entre los individuos para conseguir una salud óptima y corregir los desórdenes asociados a deficiencias de micronutrientes, desequilibrios dietarios y estilos de vida sedentarios.
- 2** Cada niño y adulto necesita alimentos suficientes y una actividad física adecuada para expresar su potencial genético en cuanto al crecimiento, el desarrollo y la salud. Un consumo escaso de energía, proteínas, ácidos grasos esenciales, vitaminas (en particular las vitaminas A, C, D, E y las del complejo B) y minerales (fundamentalmente calcio, hierro, yodo, potasio y zinc) así como la falta de oportunidades para desarrollar una actividad física adecuada empeoran la salud y la función motora.
- 3** El balance entre la actividad física y el estado nutritivo a fin de alcanzar el bienestar, está mejor definido por el concepto de « consumo y gasto energético ». Para poblaciones sedentarias, la actividad física debe ser mayor; sin embargo en aquellas dedicadas a dicha actividad física de forma intensa, el consumo de alimentos debe ser mayor para compensar las necesidades energéticas.
- 4** El consumo de nutrientes debe ajustarse a la herencia evolutiva. La elección de alimentos debe conducir a dietas variadas con gran cantidad de frutas y verduras ricas en nutrientes esenciales, particularmente antioxidantes protectores y ácidos grasos esenciales.
- 5** El nivel de actividad física debe ajustarse a nuestra dotación genética. Establecer una actividad física regular cada día de la vida es esencial para el bienestar físico, mental y espiritual. Para todas las edades y para ambos sexos, dicha actividad física debe ser lo suficientemente intensa, con la suficiente duración, frecuencia e intensidad, utilizando el mayor número de músculos posibles rítmica y repetitivamente. Una especial atención debe ser prestada a la nutrición adecuada de los atletas de competición a todos los niveles.
- 6** La consecución del bienestar metabólico a través del balance energético, el buen estado nutricional y la actividad física, reduce el riesgo y mejora los tratamientos de muchas enfermedades derivadas de los estilos de vida moderna, como la diabetes melitus, hipertensión, osteoporosis, algunos cánceres, obesidad y las enfermedades cardiovasculares. El bienestar metabólico mantiene y mejora las funciones motoras, la morbilidad y las actividades cotidianas hasta la edad avanzada.
- 7** La educación, en lo que se refiere a la nutrición y a la actividad física, debe comenzar muy pronto y continuar a lo largo de toda la vida. Nutrición y actividad física deben ser impuestas en el « curriculum » de las escuelas infantiles, de los educadores, de los nutricionistas y de otros profesionales de la salud. La sociedad y los medios de comunicación deben promover y desarrollar modelos que fomenten este tema de forma positiva.
- 8** Son necesarios el apoyo familiar y todos los recursos de la comunidad y de la sociedad para inducir cambios en el comportamiento personal encaminados a rechazar estilos de vida poco saludables y a adoptar una vida activa y un buen estado nutricional.
- 9** Los gobiernos de las naciones y el sector privado deben coordinar sus esfuerzos para fomentar una buena nutrición y una actividad física adecuada a lo largo de la vida e incrementar así la adecuación física de los individuos que emulen el ideal olímpico.
- 10** Los antiguos griegos (helenos) consiguieron un alto nivel de civilización basado en una nutrición adecuada, actividad física y desarrollo intelectual. Se esforzaron por la excelencia en espíritu y cuerpo. Los hombres, mujeres y niños de nuestro tiempo deben imitar este ideal olímpico y volver a ser los más rápidos, los más fuertes y los más preparados, a través de una actividad física y una nutrición adecuadas.

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