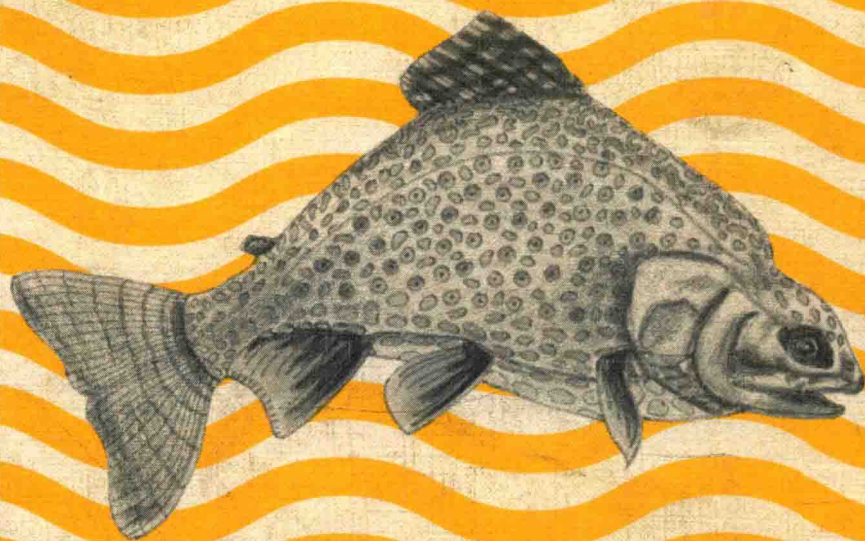


Health Effects of ω 3 Polyunsaturated Fatty Acids in Seafoods

Editors: A.P. Simopoulos, R.R. Kifer, R.E. Martin, S.M. Barlow



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Health Effects of ω 3 Polyunsaturated Fatty Acids in Seafoods

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Health Effects of ω 3 Polyunsaturated Fatty Acids in Seafoods

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Preface

The Proceedings of the II International Conference on the Health Effects of ω 3 Polyunsaturated Fatty Acids in Seafoods contain some exciting and provocative research findings. The conference was under the patronage of the Food and Agricultural Organization of the United Nations and the World Health Organization, and was cosponsored by government agencies, professional societies, international organizations and industry.

The conference goals were to review the latest research data on ω 3 fatty acid metabolism and their relationship to ω 6 and ω 9 fatty acids in relation to: (1) essentiality of ω 3 fatty acids in growth and development, membrane structure and function; and (2) cardiovascular disease, hypertension, diabetes, cancer, arthritis, psoriasis, and other inflammatory and autoimmune diseases.

We feel that the conference goals were fulfilled.

In the short intervening 5-year period from the first conference on the Health Effects of Polyunsaturated Fatty Acids in Seafoods, held from June 24 to 26, 1985 in Washington, D.C., research undertakings and publications increased almost exponentially. This strong indication of worldwide funding and support by medical research institutions has allowed remarkable progress in the exploration of the role of ω 3 fatty acids in: (1) being essential for growth and in developmental processes, (2) membrane structure and function, and (3) control and/or prevention of disease states – cardiovascular disease, hypertension, diabetes, cancer, arthritis, psoriasis, and inflammatory and autoimmune disorders.

The role of ω 3 fatty acids as being essential in growth and development has been expanded over the past 5 years. The scientific evidence is

consistent with the fact that a recommended dietary allowance (RDA) for ω 3 fatty acids for infants be made. A recommendation came from the conference that infant formula should contain 0.7–1.3% of its energy as docosahexaenoic acid (DHA). Speakers at the conference also called on the WHO and FAO to organize a further meeting on recommended daily allowances of fatty acids in order to make some recommendations on ω 3 fatty acids in the light of the considerable knowledge now available.

The role of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in atherosclerosis and hypertension continues to dominate the research support. Several of the factors involved in the development of cardiovascular disease such as prostaglandins, thromboxanes, leukotrienes, plasminogen activating factor, endothelium-derived relaxing factor, platelet-derived growth factor, interleukins and fibrinogen, are modulated by ω 3 fatty acids. In practically all of them ω 3 fatty acids have been shown to have a beneficial effect, which should not be unexpected since ω 3 fatty acids replace ω 6 fatty acids in practically all cell membranes and have also been shown to influence gene expression.

Nowhere else has the progress been so dramatic as in the understanding of the mechanisms of inflammation and autoimmune disorders, particularly in interleukin metabolism. It is therefore not surprising that there are a number of animal and human studies in which ω 3 fatty acids have been shown to affect the course of rheumatoid arthritis, psoriasis, lupus erythematosus, ulcerative colitis, and others.

With respect to cancer, the original findings that ω 3 fatty acids decrease the size and the number of tumors in animal models has been repeatedly confirmed, and human studies are in progress with patients to determine the effects of ω 3 fatty acids in preventing the spread of metastases in patients with breast cancer.

A very exciting and new area of research is uncovering the synergistic effects of olive oil (18:1 ω 9) and linseed oil (18:3 ω 3) in increasing the incorporation of EPA into the cell, whereas ω 6 fatty acids compete with ω 3 fatty acids. This and other findings illustrate the importance of the need to study the various fatty acids and the appropriate proportions to each other in terms of the chain length, saturation, degree of unsaturation and location of the double bonds.

Another most interesting finding is in a new area of research in which ω 3 fatty acids are used as adjuvants to drug therapy. In cardiovascular, inflammatory and autoimmune disorders supplementation with ω 3 fatty acids has been shown to improve or enhance the effects of drug treatment.

In some studies the effect is synergistic. This effect is further strengthened by reduction in energy intake or exercise or both. In other studies, the addition of $\omega 3$ fatty acids appears to reduce the drug dose and thus decrease the toxic effects of drugs.

All these aspects are presented most eloquently in these conference proceedings of the II International Conference of the Health Effects of $\omega 3$ Polyunsaturated Fatty Acids in Seafoods.

These past 5 years of expanded research have not only enhanced our knowledge about $\omega 3$ fatty acids, but also about $\omega 6$, $\omega 9$, and saturated fatty acids. To deal with this expanded research area, it was decided to form an International Society for the Study of Fatty Acids and Lipids. The Society was established in March 1990 at the conclusion of the conference.

The conference consisted of the following panels:

Panel A: Growth and Development in Infants

Panel B: Requirements of Adults and the Elderly

Panel C: Advances in Mechanisms of $\omega 3$ Fatty Acids

Panel D: Cardiovascular I: Cell/Vessel Wall Interactions

Panel E: Cardiovascular II: Heart

Panel F: Cardiovascular III: Circulation – Blood Pressure

Panel G: Rheumatoid Arthritis and Inflammatory Mediators

Panel H: Diabetes

Panel I: Psoriasis

Panel J: Cancer

The conference brought together the pioneers in the field of $\omega 3$ fatty acid research. Drs. Hans Olaf Bang, Ralph Holman, Hugh Sinclair and Maurice Stansby made their presentations on the evening of March 22nd at the conference banquet. Their presentations are in response to the question posed to them, 'what is the most memorable event in your life relative to the $\omega 3$ fatty acids?' The proceedings begin with their presentations.

Without any doubt these four giants kept the interest in $\omega 3$ fatty acids research from being swept away by the storm that overtook western societies with the $\omega 6$ fatty acids, and the cholesterol phobia. The events as recounted by Drs. Bang, Holman and Stansby make it clear that:

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

This, of course, is a quotation from Aristotle. It is this 'quest for/search for truth' that distinguishes science from other endeavors. Dr. Sinclair, an

outstanding researcher and poet, elected to remit his experiences in a poem composed especially for the occasion, thus immortalizing the meeting and the establishment of the International Society for the Study of Fatty Acids and Lipids. The Proceedings of this conference are dedicated to his memory.

These presentations are followed by the Conference Statement, which in turn is followed by summaries by Jørn Dyerberg, chairman of the session summarizing the conference, and the panel chairmen: Norman Salem (Panel A: Growth and Development in Infants); Kristian Bjerve (Panel B: Requirements of Adults and Elderly); Alexander Leaf (Panel D: Cardiovascular I – Cell-Vessel Wall Interactions); Arne Nordoy (Panel E: Cardiovascular II – Heart); Howard Knapp (Panel F: Cardiovascular III – Circulation/Blood Pressure); Dwight Robinson (Panel G: Rheumatoid Arthritis and Inflammatory Mediators); Ritva Butrum (Panel J: Cancer).

Next is the keynote address on ‘ ω 3 Fatty Acids: Research Advances and Support in the Field since June 1985 (Worldwide)’ by Artemis P. Simopoulos, Robert Kifer and Arthur Wykes, followed by the panel presentations. The presentations by the panelists consist of a review paper in the field by one of the cochairmen, followed by papers on mechanisms and new investigations by the other panelists. Each panel cochairman was responsible for initiating discussions and summarizing the panel presentations. It was thought mandatory to provide ample time for discussions in order to discuss future research needs and the appropriate development of protocols, particularly in terms of mechanisms and dosage of ω 3 fatty acids in both animal studies and clinical investigations. There were 86 papers given at the two poster sessions. The abstracts of these papers appear in the appendix.

These proceedings represent the most complete and up-to-date information on the role of ω 3 fatty acids in health and disease. The review papers, research papers, and the summaries by the panel co-chairmen are outstanding and represent clear statements of accomplishments and future research needs. The proceedings should be of interest to all investigators interested in research on fatty acids and lipids, to physicians who take care of patients, to food scientists, dieticians, nutritionists, food producers and policy makers.

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Dedication

Hugh MacDonald Sinclair 1910–1990
Advocate of the Essential Fatty Acids



Hugh MacDonald Sinclair, who has been identified with nutrition and the essential fatty acids throughout his scientific career, died at Oxford June 22, 1990 at the age of 80 years. He was born in Edinburgh February 4, 1910 into a family rich with history, which claimed as ancestors King Woldonius of Finland, the Vikings Nor and Gor, Thorfinn the Skull-Splitter, William Sinclair the Bold, Sir John Sinclair the epidemiologist, and one who discovered North America long before the time of Columbus. Hugh inherited regal bearing and the penchant for discovery.

While a medical student at Oriel College, Oxford, he read the text on vital statistics and learned that life expectancy of a 50 year old man had not changed since 1841. He concluded that medicine could do little more to keep a middle-aged man alive than it could in the middle ages, and that the probable cause was the composition of the dietary fat. This set the direction of his life. He went on to win three prizes while a medical student, including first place in physiology in 1932 when he became demonstrator in biochemistry. In 1937 he was chosen to teach physiology and biochemistry at Magdalen College. He worked with R.A. Peters on thiamine and took his DM in 1939. He remained at Magdalen throughout his life, serving as Fellow, Bursar and Vice President and in later years he became an Emeritus Fellow. Sinclair was a student of Sir Robert McCarrison, an early pioneer in the scientific approach to the study of nutrition and health, and he championed this approach to nutrition all his life, at a time when there were few who would listen. He was content to take quiet pleasure in knowing he was right, and he did not seek the limelight of the establishment.

Sinclair's early work on vitamin B was interrupted by work on chemical warfare, and in 1941 he organized the Oxford Nutrition Survey, the results of which prevented in Britain what had happened in Germany in World War I, and which assured that British wartime food policy was effective. During the war he visited The Royal Canadian Air Force and observed the absence of heart disease in Eskimos, leading him to conclusions about the need for dietary fats which were to give him notoriety and later, fame. With Sir Jack Drummond he led a survey team to Holland, and was in the first allied group to move into the famine-stricken areas of north and west Netherlands. Joining forces with a large group of Dutch scientists, they collected much nutritional information which was published in 1948. Sinclair also took a team to Düsseldorf to survey nutritional conditions in the British Zone. These experiences confirmed his interest in nutrition and gave informational background for his passion for the essential fatty acids. Sinclair was rewarded for his post-war nutritional surveys in Europe by an

appointment as Chevalier of the Order of Orange-Nassau and his Medal of Freedom with Silver Palm from the United States.

Sinclair was a prolific reader, and he lived surrounded by books. His depth and breadth of knowledge became apparent at symposia and conferences around the world, when he was often called upon for information and opinion. He had realized the importance of the essential fatty acids discovered by Burr and Burr in 1929, and by the 40s he developed the concept that deficiency of essential fatty acids was the chief cause of heart disease in Western populations, and that they were necessary for normal health and circulatory function. In 1950 Groen, in the Netherlands, brought evidence to the First International Congress on Nutrition that saturated fats raised plasma cholesterol and that vegetable oils lowered it, concluding that the kind of fat or the fatty acid composition of dietary fat was related to heart disease. At that time he was attacked by an American leader in the field who believed that only the quantity of dietary fat was of importance. Sinclair defended Groen, and in 1956 wrote his classic letter to *Lancet* in which he showed that the essential fatty acids were needed to protect the arteries. In 1985 this paper was chosen a citation classic by *Current Contents*. He also gathered a variety of evidences which indicated that many diseases of man may be explained by low intakes of the essential polyunsaturated fatty acids. His very early recognition of the importance of these nutrients has been amply vindicated by a multitude of laboratory studies in recent decades. Much of the current enthusiasm for essential fatty acids stems from the insights of this man who was ahead of his time.

Sinclair was fearless in the pursuit of ideas, and he was his own guinea pig. In 1976 he conducted an experiment upon himself, in which he consumed most of a deep-frozen seal plus fish as his only food for 100 days. The seal, rich in $\omega 3$ fat, bestowed a distinctive odor on the kitchens at Magdalen College, and induced the longest bleeding times recorded for Western man, except in hemophilia. These hazardous studies upon himself led to his fame as 'the Eskimo Diet Doctor'.

Because of the controversial nature of his favorite subject, he found it difficult to find the necessary support for an adequate research laboratory in the academic world. He persuaded the university to form the Laboratory of Human Nutrition in 1947, and he held the readership in human nutrition from 1951 to 1958 when the university put the laboratory under other leadership. Sinclair stayed on at Magdalen in 'the wilderness', without laboratory, assistant, or adequate salary. Although he had been offered four chairs, he remained loyal to Oxford, and later built an independent Inter-

national Institute of Human Nutrition at Sutton Courtenay 10 miles outside of the city. He never drew a salary and he contributed his large personal library and dedicated his property to this Institute. He served very successfully as Visiting Professor at the University of Reading for many years.

On one occasion Sinclair drove me at breakneck speed through the narrow country lanes of Oxon in his Aston Martin to his estate at Sutton Courtenay for a visit and a revelation of him as a country gentleman. He had made many of the concrete sculptures that graced the pools and paths of the garden, he kept peacocks and exotic birds and sponsored Tibetan students, and he had a life-long collection of rare and old books, including one about the ancestor who had discovered America.

In 1956 Sinclair organized the first international meeting on essential fatty acids, held at Oxford, which attracted all the leaders in this area of nutritional biochemistry. Conferences occurred with increasing frequency in the following decades, and Sinclair was often invited. At one of the early Deuel Conferences on Lipids he composed his first Hiawatha poem about lipids and lipid researchers, and they became popular satires on the scientific scene. They even inspired this writer to attempt them as a form of amusement. At the First International Congress on Essential Fatty Acids and Prostaglandins, held in Minneapolis in 1980, Hugh treated us to a parody on 'To be, or not to be'. At the Second International Conference he was the honored guest and we celebrated his 75th year. At the banquet held at Hatfield House he favored us with a humorous lecture on EFA and a somewhat modified text from King Henry V. Sinclair and that congress inspired the following lines:

Hatfield House! 'Lisbeth's House! What happened there?

We heard a long lecture by Dr. Sinclair.

What was his subject? What did he say?

History, inflation of words, EFA.

Miracles and wonders! What were they about?

Fish oils, the diet, the ague and gout.

What hope didst thou gain for our life and our pain?

Eat oils, make glandins, again and a gain.

At the II International Conference on the Health Effects of ω 3 Polyunsaturated Fatty Acids in Seafoods in 1990, the proceedings of which are summarized in this book, Sinclair was also present, and although gravely

ill, he entertained us with his poetry. Thus did this serious, imposing and tall Scotsman occasionally reveal his lighter side. Only his classic education and wide experience, together with his wide knowledge of the nutritional lipids and the people who worked with them, made it possible.

This past spring Sinclair reached his 80th birthday, and the McCarrison Society, of which he was president in 1983, produced a memoir in his honor. The Biochemical Society held a conference on fatty acids in his honor at Bath in April, at which he gave the introductory talk. Shortly afterward he became so ill that he had to be driven back to Oxford that morning for a corrective operation. His closest friend, Dr. Brian B. Lloyd, wrote of him to Dr. Simopoulos on June 11 that 'he has been an absolute brick in the last weeks, absurdly undemanding, never complaining, very grateful for help, full of beans and 100% on the ball intellectually. He is still trying to meet his last obligations, and is sorry to be sending his manuscript at the last minute'. The 'manuscript' consisting of prose, rhyme and poem appears in these proceedings.

Eleven days later Hugh Sinclair expired, ending a good and productive life. The common man on the street has already benefitted nutritionally from his insights, and Sinclair has grown from 'a voice crying in the wilderness' to a well-known Prophet. Sinclair must have felt gratified many times to know that what he predicted 40 years ago had become reality in his lifetime, that his scientific peers held him in respect and love, that his service has been a benefit to mankind, and that his contributions will be forever.

Ralph T. Holman

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