Metabolism of \( n-6 \) and \( n-3 \) Fatty Acids in Man and Animals

Lipid Group Colloquium in honour of Hugh Sinclair on his 80th birthday. Sponsored by Bio-Oils Ltd, Callanish Ltd, Scotia Pharmaceuticals Ltd and Seven Seas Healthcare Ltd. Organized and Edited by K. W. J. Wahle (Rowett Research Institute, Aberdeen)

Hugh Sinclair died 22 June 1990

Chairman’s opening remarks

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Dr Hugh Macdonald Sinclair, who celebrated his 80th birthday in February 1990, was born in Edinburgh. He is proud of his Scottish ancestry, though he was ‘exiled’ at an early age to be educated at Winchester and Oxford. He graduated in physiology in 1932 (the year of his election to the Biochemical Society) and then in medicine in 1937. Thus were laid the foundations of a distinguished career as a university teacher and as a research worker, beginning with his election in 1937 as a Fellow of Magdalen College, Oxford, and his appointment as Lecturer in Physiology and Biochemistry.

Before he went into residence at Magdalen, Sinclair had spent 3 months in the U.S.A. visiting laboratories, including that of Dr George Burr. Burr, together with his wife, had earlier published a now-classical paper \[1\] which provided convincing evidence that, when young rats were fed on a fat-free diet, they ceased to grow and developed a syndrome of well-defined signs, including scaliness of the tail, dry skin, kidney malfunction and reproduction failure. The condition was reversed by giving the animals small amounts of maize oil or linseed oil and the curative effects of those oils roughly paralleled their content of linoleic and linolenic acids. The term ‘essential fatty acids’ (EFA) thus came into existence. It was against the background of this work and that of others in the 1930s that Sinclair was led to develop his research interests in nutritional aspects of clinical medicine and, in particular, the biochemical and physiological functions of dietary EFA.

Although the advent of war in 1939 curtailed research activities, it provided Sinclair (then working on behalf of the Royal Canadian Air Force) with the opportunity to study the incidence of cholesterol deposition in the eyes (early corneal arcus) of Eskimos and young British pilots. Whereas no arcus could be detected in any Eskimo, young or old, it was present in the eyes of some 10% of the young pilots. In a review \[2\] Sinclair ascribed the findings to dietary differences between the Eskimos, whose diet was rich in EFA, and the pilots, whose diet contained much less EFA.

After the war Sinclair turned his attention to manifestations of EFA deficiency in the rat and, with Ramalingaswami \[3\], described the histological and clinical changes in the skin. He concluded \[4\] that the retardation of growth of EFA-deficient rats was due to an inadequate supply of unsaturated fatty acids required for phospholipid synthesis in cell membranes and went on to show (Bashnayke & Sinclair \[5, 6\]) that, in the skin of such animals, the proportions of dienoic and tetraenoic fatty acids fell as concomitantly the proportions of trienoic acids rose, and that the permeability of the skin to water increased. In 1953, the first International Conference on the Biochemistry of Lipids (ICBL) was held in Belgium, and Hugh Sinclair was one of the founder members. In 1957, he was invited to organize the fourth ICBL (devoted entirely to EFA) in Oxford, and its published proceedings include \[7\] one of the first of Sinclair’s witty parodies of the great poets, in this case, Shakespeare’s Julius Caesar, Act III, Scene 2, beginning ‘Enter Mark Antony contemplating Caesar’s atheromatous aorta!’ The proceedings include, as authors, the names of many of the pioneers in the field, including R. T. Holman, E. Klenk, E. J. Ahrens, L. W. Kinsell and, not least, H. M. Sinclair himself, who, with A. L. Macmillan, presented a paper on the structural functions of EFA \[8\] in which it was reported that erythrocyte fragility was increased in EFA-deficient rats and that the enhanced metabolic rate of the animals was probably associated with structurally defective mitochondria.
Over the years Sinclair became convinced that EFA were of dietary importance for man. It was with considerable prescience that, in 1956, he directed attention [9] to the likely association between the increasing incidence of coronary heart disease in 'Western' countries and the consumption of diets containing hydrogenated oils and ruminant fats, thereby giving rise to a chronic relative deficiency of EFA, especially of dietary importance for man. It was with considerable years some of the recommendations of the Committee on Medical Aspects of Food Policy report on Diet and Cardiovascular Disease [10] and stimulated research into the physiological significance of the eicosanoids (prostaglandins, thromboxanes, prostacyclins and leukotrienes) derived in the body from long-chain polyunsaturated fatty acids.

In the 1950s, soon after it became generally known that cardiovascular (and renal) diseases were very rare among Eskimos, Sinclair compiled a masterly review [11] of their high-fat, high-protein diets and the resulting metabolic consequences. This survey was followed by detailed analyses of samples of the food (seal and fish) eaten by Greenland Eskimos during winter. It was found [12] that the predominant polyunsaturated fatty acids in the diet were those of the \( n = 3 \) family (20:5, 22:5 and 22:6), whereas acids of the \( n = 6 \) family were present in relatively small amount. It was considered that the rarity of heart disease could probably be ascribed, at least in part, to the antithrombotic effects of \( n = 3 \) fatty acids, especially eicosapentaenoic acid (20:5). To study the effects of an 'Eskimo diet' in more detail, Sinclair bravely decided to subject himself to subsist for 100 days on a diet of seal (muscle, blubber and liver) and fish (cooked in mackerel oil), supplemented with \( \alpha \)-tocopherol, and with only water to drink! During that period his 'bleeding time' rose from 3–4 min to > 50 min, which he concluded [13] was probably due to his metabolic processes having 'substituted' 3-series prostaglandins (from 20:5, \( n - 3 \)) for the more usual 1- and 2-series (the latter from 20:4, \( n - 6 \)). Not only that, but his plasma and urinary content of the teratogenic malondialdehyde rose alarmingly, despite the supplementary tocopherol.

It is indeed fitting that this Colloquium has been organized to honour Hugh Sinclair who has charted many of the paths which have led to our current knowledge of the metabolic significance of EFA.


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Essential fatty acids — an historical perspective

HUGH M. SINCLAIR

Introduction

Man's interest in fat probably arose in the Early Pleistocene period, about 100 000 years ago, when he or she invented the manufacture of fire. She will have noticed that when she roasted an animal and its fat fell on the flames, light was produced which helped illuminate her cave in the ice-age. As fat fell on the coals, a black pigment was formed with which she could decorate the walls of the cave. The fat would soothe her chafed skin and chilblains, and would later with water and so remove grease from the skin. When later the wheel was invented, fats were useful to lubricate the axle; and they were also used as cosmetics.

Body fat may have been appreciated quite early. The first representation of man is a small figure of a woman, obese and pregnant and hideous, the Venus of Willendorf. Indeed, though Scheele isolated glycerol from hydrolysed fats in 1779 [2], the main scientific investigation began with the greatest lipid chemist, Michel Eugene Chevreul, whose death probably due to his metabolic processes having 'substituted'

and became so fat he could not ride his horse or even walk, but he cultivated adultery and bigamy; his son, Louis VI, was also obese. Though monks are traditionally lean, the Dominican St. Thomas Aquinas (1225–1274) was very fat. Dietetically, fats were prized. The sound advice about ruminant fats in Leviticus 18, 22, that 'Ye shall eat no manner of fat, of ox, of sheep or of goat' was not commanded because it was unhealthy, but because it was the choicest part and therefore had to be reserved for God. Though Scheele isolated glycerol from hydrolysed fats in 1779 [2], the main scientific investigation began with the greatest lipid chemist, Michel Eugene Chevreul, whose death in Paris at the age of 103 we commemorated last year; he still lectured when aged over 100. A year after he had become Professor of Chemistry at the age of 26, he discovered their true nature in 1814 [3] and isolated cholesterol 2 years later [4]. His magnificent book on the chemistry of fats was published in 1823 [5]. At the same time Prout in England [6] and Magendie in France [7] divided the main constituents of diet. 'the aliments', into protein, fat and carbohydrate. Liebig [8], against the views of the French school, was the first to suggest that fat could arise from dietary carbohydrate. The proof of this came from Lawes & Gilbert in 1877 [9], and it was therefore assumed that dietary fat was not needed. Attempts to raise animals on fat-free diets failed, however, because of retinol deficiency. For instance, in 1909 Stepp [10] found that bread made from milk and wheat flour sustained mice, but not if the mixture was extracted with alcohol. Adding lecithin or cephalin was ineffective. Adding an

Abbreviations used: EFA, essential fatty acids; LT, leukotriene; LDL, low-density lipoprotein.

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