

## Editorial

## Fish oil in asthma

There is considerable interest in the therapeutic potential of fish oils in diseases as varied as atheroma, rheumatoid arthritis, cancer, and multiple sclerosis.<sup>1-6</sup> Several distinct kinds of evidence have supported this interest, including epidemiological studies, clinical trials, and observations of white cell and platelet function in healthy volunteers and of biochemical changes in membrane phospholipids and products derived from fatty acids (including prostaglandins and leukotrienes). The putative role of lipid derived mediators in the airways inflammation and hyper-responsiveness that characterise asthma<sup>7</sup> raised the possibility that dietary supplementation with fish oil could influence the severity of the disease by changing the pattern of such mediators.<sup>8-10</sup> Two papers in this issue of *Thorax* (pp 84 and 93) report studies on the use of fish oils in asthmatic subjects. The conclusions are not therapeutically encouraging, but each study raises intriguing issues regarding the pathophysiology of asthma.

Human tissues do not have specific  $\Delta$ -6 desaturase enzymes, and in individuals consuming a usual Western diet arachidonic acid (C<sub>20</sub>:4, n = 6) is the principal precursor of lipid derived mediators.<sup>11</sup> These include cyclo-oxygenase products (prostaglandins and thromboxanes, sometimes referred to as prostanoids) and lipoxygenase products (including the dihydroxy fatty acid leukotriene B<sub>4</sub> and the peptidoleukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>, which comprise the slow reacting substance of anaphylaxis). These 20 carbon atom fatty acid derivatives are known collectively as eicosanoids.

Arachidonic acid occurs in cell membranes in esterified form, mainly in the 2 position of the glycerol "backbone" of phospholipid. Its dietary origin is either direct from arachidonic acid in meat or from linoleic acid (C<sub>18</sub>:2, n = 6) and  $\gamma$  linolenic acid (C<sub>18</sub>:3, n = 6), which occur in the seeds and leaves of plants and can be converted to arachidonic acid by chain elongation and desaturation.<sup>12</sup> Arachidonate is released from membrane phospholipid in response to various immunological and other stimuli that activate

phospholipases. Liberation of the free fatty acid is the rate limiting step in eicosanoid synthesis.<sup>13</sup> The intracellular concentration of free arachidonate is vanishingly low under resting conditions; the free fatty acid is rapidly re-esterified into the membrane phospholipid if oxidative metabolism does not occur.

Deep sea cold water fish and arctic animals (such as walrus) contain fat that is more highly unsaturated than that of man and animals living in warmer climates. Such animals contain relatively large amounts of eicosapentaenoic acid (C<sub>20</sub>:5, n = 3) and docosahexaenoic acid (C<sub>22</sub>:6, n = 3) instead of arachidonic acid. Sinclair<sup>14</sup> pointed out that this is a necessary adaptation to temperatures at which the fat of animals from a temperate habitat would solidify.<sup>14</sup> Dietary supplementation with cold water oily fish results in an increase in the proportion of eicosapentaenoic acid to arachidonic acid in cell membrane phospholipid.<sup>15,16</sup> Many studies of fish oils (including those of Picado *et al* and Arm *et al* in this issue) have used a commercially available mixture of these called Maxepa. Eicosapentaenoic acid and docosahexaenoic acid are incorporated into tissue phospholipids in place of arachidonic acid when the diet is enriched with fish oil, and can then be liberated instead of arachidonic acid. Docosahexaenoic acid and eicosapentaenoic acid competitively inhibit the conversion of arachidonic acid to prostaglandin (PG) H<sub>2</sub> by cyclo-oxygenase.<sup>17,18</sup> Eicosapentaenoic acid (though not docosahexaenoic acid) also acts as an alternative substrate to arachidonate, and is converted by cyclo-oxygenase to PGH<sub>3</sub> and hence to thromboxane (TX) A<sub>3</sub> and PGI<sub>3</sub>,<sup>17</sup> or by lipoxygenase to leukotriene (LT) A<sub>5</sub> and hence the 5-series leukotrienes.<sup>19</sup> Some of these products differ in potency from their 2-series prostanoid and 4-series leukotriene analogues (cf false transmitters). Thus TXA<sub>3</sub> is relatively inactive while PGI<sub>3</sub> is of similar potency to PGI<sub>2</sub>.<sup>17</sup> LTB<sub>5</sub> has only 1-10% the potency of LTB<sub>4</sub> as regards neutrophil chemotaxis and bradykinin induced vascular permeability,<sup>20-22</sup> in contrast, LTC<sub>5</sub> is equipotent with LTC<sub>4</sub> in contracting guinea pig lung strips.<sup>23</sup>

The net functional result of these changes is difficult to predict. The effect of drugs active on the eicosanoid cascade should provide a basis for interpreting any effect of dietary modification. The drugs available are limited, however, and their actions on asthmatic

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airway function are still imperfectly understood. Glucocorticoids, which are highly effective at improving airway function in asthma, induce synthesis of lipocortin, which inhibits phospholipase A<sub>2</sub>. We do not know, however, whether this accounts for their therapeutic efficacy. Cyclo-oxygenase inhibitors, such as aspirin or other non-steroidal anti-inflammatory drugs, have little or no effect in most patients with asthma, although in a few patients aspirin worsens the clinical state dramatically. Sufficiently potent lipoxigenase inhibitors or receptor antagonists are not yet available to enable us to know what effect selective inhibition of the lipoxigenase pathway has on airway function in asthma. To confound the problem further, functional and biochemical changes do not necessarily proceed *pari passu*: for instance, whereas fish oil supplementation causes changes in the lipid content of platelet membranes and also a prolongation of bleeding time, these changes do not occur over the same time course, suggesting that they may not be causally related.<sup>24</sup> It is therefore essential that measurements of function are performed in parallel with biochemical determinations.

In the study by Arm *et al* of patients with mild asthma, clinical responses, including airways responsiveness to histamine and exercise, as well as subjective measures, were determined in parallel with neutrophil function (chemotaxis), neutrophil phospholipid fatty acid composition, and LTB<sub>4</sub> and LTB<sub>5</sub> generation *ex vivo*. Maxepa caused a greater than 10 fold increase in eicosapentaenoic acid content of neutrophils and 50% inhibition of total LTB synthesis. Neutrophil chemotaxis in response to formyl-methionyl-leucyl-phenylalanine and LTB<sub>4</sub> were significantly suppressed but there was no detectable change in clinical state. In the interesting pilot study on patients with aspirin sensitive asthma by Picado *et al*, Maxepa plus sardine meal had a significant effect on serum fatty acid content and caused a moderate worsening of clinical state. There was no significant change in symptom score but a reduction of roughly 15% in peak expiratory flow rate and a 70% increase in bronchodilator usage. The overall conclusion appears to be that fish oil supplementation has little effect in most patients with mild asthma but may worsen airways obstruction in aspirin sensitive individuals. Fish oil thus behaves in a similar manner to cyclo-oxygenase inhibitors in regard to airways function in asthmatic subjects. This is consistent with evidence that Maxepa has a modest anti-inflammatory effect in patients with rheumatoid arthritis<sup>3,4</sup> and argues against a uniquely important role for LTB<sub>4</sub> or the chemotactic responsiveness of neutrophils (at least as assessed *in vitro*) in the pathogenesis of mild asthma. The findings do not bear on the possible role of the peptidoleukotrienes in asthma, as the 4- and 5-series peptidoleukotrienes

have similar potency in their effect on airways smooth muscle, at least in the guinea pig.<sup>23</sup> The question of whether fish oil supplements may influence arterial occlusive disease and other inflammatory conditions remains to be answered.

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