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**RHEUMATIC
 DISEASES**

Leaders

Fish oil and rheumatoid arthritis: Does a herring a day keep rheumatologists away?

'Eat like an Eskimo' may sound like the title of a recent 'hit song', but some rheumatologists believe it may provide a useful alternative management for inflammatory joint disease. Epidemiological study of the Eskimo has shown a reduced incidence of rheumatoid arthritis (RA), which has been partly attributed to their fishy diet.¹ We all have a healthy respect for the harm as well as the good that drugs can do so the possibility of modifying joint disease by dietary means has aroused considerable interest. Furthermore, adverse publicity surrounding the drugs used to treat RA and growing consumer enthusiasm for alternative medicine have added to this interest.

A fish diet is rich in the omega-3 series long chain polyunsaturated fatty acids, eicosapentaenoic and docosahexaenoic acid. This is important as the production of the inflammatory mediators the prostaglandins and leucotrienes is largely dependent on the type and amount of essential fatty acid precursors in the diet.² A conventional Western diet is rich in arachidonic acid. Arachidonic acid is the precursor of the 2 series prostaglandins—for example prostaglandin E₂, and 4 series leucotrienes—for example, leucotriene B₄. These prostaglandins and leucotrienes have potent proinflammatory effects, with the 2 series prostaglandins contributing significantly to the cardinal signs of inflammation and the 4 series leucotrienes, particularly leucotriene B₄, promoting neutrophil activation. Alteration of the essential fatty acid in a diet can modify these effects, with the omega-3 marine essential fatty acids reported to be less inflammatory than arachidonic acid. Eicosapentaenoic acid provides a substrate for production of the 3 series prostaglandins—for example, prostaglandin I₃, and 5 series leucotrienes—for example leucotriene B₅, some of which differ strikingly in potency from their respective 2 and 4 series analogues. For example, the potency of leucotriene B₅ in inducing polymorphonuclear aggregation is less than 10% of the potency of leucotriene B₄.³ Docosahexaenoic acid, the other major constituent of fish oil, is a strong inhibitor of 2 series prostaglandins biosynthesis. Furthermore, the membrane effects of altering dietary essential fatty acids should also be considered. A diet rich in eicosapentaenoic acid has been shown to stabilise inflammatory cell membranes and decrease neutrophil chemiluminescence,⁴ and this may also contribute to a desired anti-inflammatory effect.

These *in vitro* studies have been extended to animal work and benefits of omega-3 essential fatty acids have been shown in animal models of inflammatory disease.^{5 6} Not all

effects have been beneficial, however, and among these is a report of increased incidence of adjuvant arthritis.⁷ These last studies emphasise the importance of species difference in the study of inflammatory joint disease and reinforce our belief that human studies are more appropriate to this field.

Initial patient work was carried out by Kremer *et al.*^{8 9} Both studies were placebo controlled with Maxepa capsules as the source of eicosapentaenoic acid and docosahexaenoic acid. An improvement in the number of tender joints and morning stiffness was observed, with an anecdotal subjective response by patients. Laboratory markers of disease activity were unchanged. The later crossover study, designed to minimise the effects of background diet, showed evidence of a 'hang over' effect into the placebo phase. It has been suggested that the main positive finding in these studies was a worsening of the disease on withdrawal from the eicosapentaenoic acid treatment.¹⁰ Thus there was a need for further clinical study. A paper in this issue of the *Annals* by van der Tempel *et al* also investigates the effects of fish oil on RA.¹¹ It compares the effect of fish oil with that of inert coconut oil placebo in 16 patients; treatment was for 12 weeks, and the design cross over.¹¹ van der Tempel *et al* reported a decrease in joint swelling and duration of early morning stiffness; results similar to those reported by Kremer *et al.* They also noted a possible subjective benefit of the fish oil but did not formally assess this. Thus this study, although supporting the work of Kremer *et al*, has not extended it. In the papers of both Kremer and van der Tempel 'trends to improvement' have been reported, but these can only adequately be assessed by larger studies. It is disappointing that this latest study did not extend the work of Kremer *et al*^{8 9} and others^{4 12 13} by increasing patient numbers, avoiding a crossover design, and lengthening the treatment period. Twelve weeks' treatment seems short in relation to a disease that may span a lifetime.

What of the future? The three major goals in the effective treatment of RA are (a) to slow progression of the disease; (b) to alleviate the symptoms; and (c) to achieve (a) and (b) without side effects.

Assessment of all published papers does support a real, though modest, effect of fish oil in RA without the production of serious side effects. Most rheumatologists would expect to achieve better relief of symptoms with non-steroidal anti-inflammatory drugs, however. Furthermore, no study has shown a change in any of the measurements conventionally used to assess disease activity and in the

absence of longer term studies there is no evidence to suggest that fish oil treatment will alter the course of RA. Until further work is carried out, therefore, it would seem that fish oil may be best used as an adjunct to conventional treatment in clinical situations where high doses of non-steroidal anti-inflammatory drugs are inappropriate—for example, in patients with peptic ulceration or renal impairment. Whether such long term studies are feasible at the present time is, however, questionable. In our current study of fish oil and RA almost 50% of patients suitable for enrolment in the study are already taking an unprescribed oil supplement with their conventional treatment. Furthermore, we are informed that 200 g of herring (100 g edible portion) provides an equivalent amount of eicosapentaenoic acid to Maxepa treatment.¹⁴ Many of our patients have substantially increased their fish intake in response to this publicity, and thus patient enrolment into future studies may be difficult.

It is well to remember Maurice Ziff who said of diet and arthritis 'Those who follow this path should proceed with exceeding caution, careful controls, and large grants lest their work be in vain'.¹⁵ So, as diet and arthritis is such a contentious subject, van der Tempel and his coworkers are at least to be congratulated for applying a scientific approach to the subject.

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