Deficiencies in the relationships between pharmacists and doctors may be a principal reason for inadequate implementation of formulary policies, and recent recommendations on developing clinical pharmacy services in hospitals point the way forward.[15 16]

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Benefits from oily fish

May help in coronary artery disease and several inflammatory conditions

Greenland Eskimos and the Japanese have a higher intake of fish and a lower incidence of myocardial infarction than Western populations.[1] Within Japan the lowest death rates from coronary artery disease are seen in Okinawa, where fish consumption is about twice as high as on the mainland.[2] Meanwhile, a study from The Netherlands has shown an inverse dose-response relation between fish consumption in 1960 and death from coronary artery disease during the next 20 years.[3] These and other[4] limited epidemiological studies have led to great interest in the possible beneficial effects of oily fish—benefits that seem to extend to conditions other than coronary artery disease.

The fat in fish is rich in the long chain polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid. Oily cold water fish—such as mackerel and herring from the Atlantic—contain the largest amounts of these fatty acids. The acids may be beneficial in coronary artery disease, partly because of their hypolipidaemic effects. In two studies 20-30 g of the acids daily over four weeks reduced serum concentrations of cholesterol, low density lipoproteins, and triglycerides.[5 6] Fish oil may also prevent coronary artery disease by inhibiting the activity of the cyclo-oxygenase pathway,[7 8] which metabolises arachidonic acid to prostaglandins and thromboxane A_2. Eicosapentaenoic acid is both a substrate and an inhibitor of the pathway,[7] whereas docosahexaenoic acid is simply an inhibitor.[8] Thromboxane A_3 derived from eicosapentaenoic acid is less active in aggregating platelets than conventional thromboxane A_2.[9] In contrast, prostaglandin I_3 derived from eicosapentaenoic acid and prostacyclin are equally active in their anticoagulant properties and potency in relaxing vascular smooth muscle.[10] Thus anticoagulant activities are preserved while platelet aggregating properties are reduced by eicosapentaenoic acid, which should inhibit platelet deposition on vascular endothelium. This might explain the prolonged bleeding time and reduced platelet aggregation seen in Greenland Eskimos compared with Danish volunteers.[11]

Not only coronary artery disease but also certain chronic inflammatory and immunological diseases—such as rheumatoid arthritis, psoriasis, and asthma—are less common in Greenland Eskimos than in other Western populations. These observations have led to clinical and laboratory studies of whether eicosapentaenoic acid and docosahexaenoic acid modify inflammatory and immune responses. Eicosapentaenoic acid, it seems, competes with arachidonic acid not only for metabolism by the cyclo-oxygenase pathway but also for metabolism by the lipoxygenase pathway to the leukotrienes.[12] Leukotrienes are a family of molecules that have potent proinflammatory properties.[13] Leukotriene B_4 elicits chemotaxis of neutrophils, whereas leukotrienes C_4, D_4, and E_4 (which comprise what was previously recognised as the slow reacting substance of anaphylaxis) enhance vascular permeability and contract smooth muscle. Eicosapentaenoic acid is metabolised by the lipoxygenase pathway to leukotrienes B_5, C_5, D_5, and E_5.[12] Leukotriene B_5 has only 1-10% of the activities of leukotriene B_4, whereas leukotrienes C_5, D_5, and E_5 are as effective in contracting smooth muscle as leukotrienes C_4, D_4, and E_4.[12] Dietary supplementation with 3 g eicosapentaenoic acid and 2 g docosahexaenoic acid daily for six weeks reduces the capacity of neutrophils and monocytes to produce the inflammatory mediators leukotriene B_4 and platelet activating factor and inhibits both the cells' response in chemotaxis and endothelial cell adherence.[14 15] Dietary supplementation with fish oil lipids may thus have anti-inflammatory effects.

Double blind and placebo controlled trials have now been completed of increasing the eicosapentaenoic acid in the diet to treat rheumatoid arthritis,[16 17] psoriasis,[18 19] atopic dermatitis,[20] and bronchial asthma.[21-23] Eicosapentaenoic acid provides subjective improvement in patients with active rheumatoid arthritis and psoriasis. Significantly fewer tender joints were found in patients with arthritis after 14 weeks of a combination of 2·7 g eicosapentaenoic acid and 1·8 g docosahexaenoic acid, and the time to the first experience of fatigue after arising in the morning was also improved. Patients reduced their consumption of non-steroidal anti-inflammatory drugs. Eicosapentaenoic acid has produced mild to moderate improvement in patients with psoriasis. In patients with atopic dermatitis fish oils led to a mild improvement in cutaneous scaling, itch, and overall subjective assessment of severity.

In patients with asthma fish oil lipids may inhibit the late phase asthmatic response (the inflammatory component of the asthmatic reaction) after inhalation of an allergen.[21] A diet

enriched with eicosapentaenoic acid given to patients with asthma over 10-12 weeks did not, however, lead to any symptomatic improvement or to objective changes in lung function and non-specific bronchial hyperresponsiveness.[22 23] Although dietary fish oil lipids produced no change in most patients with asthma, eicosapentaenoic acid may modulate the disease in a few people. Picado *et al* showed that a diet containing 3 g of eicosapentaenoic acid daily for six weeks worsened airflow obstruction in 10 patients with asthma and aspirin intolerance.[24] These effects were attributed to inhibition of the cyclo-oxygenase pathway.

Thus adding eicosapentaenoic acid to the diet will lead to it being incorporated into membranes and tissues, which may result in important changes in cellular biochemistry and function and may provide some benefit in selected diseases. Coronary artery disease is the condition that is most amenable to this dietary manipulation, but whether the benefit is sufficient to replace or reduce drug treatment in any condition remains to be seen.

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A single seizure

Likely to recur

In 1881 Gowers concluded that when one seizure has occurred others usually follow,[1] but this view has recently come under scrutiny, with some ensuing controversy.[2-5] General practitioners, casualty officers, neurologists, and paediatricians commonly see patients who have had a single seizure. Sometimes it has occurred because of alcohol or drug abuse, acute metabolic disturbance, acute cerebral disease or injury, or (especially in children) fever. More often, however, none of these factors are present and the seizure is regarded as unprovoked, although various reflex mechanisms, changes in sleep pattern, and emotional stress may be overlooked. Recent reports on the prognosis of a single unprovoked attack have seemed to conflict and management remains uncertain. In Britain most patients are not treated after a single seizure on the principle that a single seizure is not epilepsy, though in the United States two thirds of patients are treated, perhaps for medicolegal reasons. Both the British[6] and the American[2] practice have recently been questioned.

In a multicentre study of patients presenting to neurological departments in Britain Hopkins *et al* confirmed that most single seizures (94%) are tonic-clonic attacks.[7] Partial attacks are usually more frequent, may occur in clusters, and initially are often not recognised as seizures; they thus present to doctors as a single event much more rarely. A substantial minority of patients with tonic-clonic attacks also seek advice only after two or more seizures.[8] In patients presenting with a single seizure the rate of recurrence has been reported to vary between 27% and 71% after three years of follow up.[2 9 10] Two recent studies based on children referred to electroencephalography departments found rates of relapse of 59%[11] and 52%.[12] In a retrospective community study based on the records linkage system of the Mayo Clinic Annegers *et al* reported recurrence of seizures in 56% of patients after five years.[13] All the studies agree that relapse occurs most often within the first year of follow up. In 408 adults over 16 the risk of recurrence was greater if the seizure occurred between midnight and 9 am; older patients with a family history of seizures also seemed more likely to have a recurrence, but electroencephalography was of no predictive value.[7] Computed tomography showed tumours in only 3%, and these subjects have a higher rate of relapse.

Some of the variation in the reported rates of relapse may be attributable to differences in the ages of the populations studied, differences in the types and causes of the single seizures, whether the studies were prospective (most were retrospective), and whether some of the patients were treated with antiepileptic drugs. The most important factor, however, is the interval between the seizure and the time of presentation and entry into the study. In patients with established epilepsy the second attack follows the first within one month in one third of patients.[1 14] Therefore if one month elapses before a patient with a seizure is seen in a neurological clinic those with early recurrence will be selected out because they have already developed epilepsy. In the study of patients