Dietary management in multiple sclerosis

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Introduction

There are three current views on the cause of multiple sclerosis (MS): nutrition, viral infection and autoimmune reaction. Interest in nutrition arose from studies on the epidemiology which indicated a high prevalence in countries with relatively high saturated fat intakes; in addition, low levels of essential fatty acids (EFA) were recorded in the blood of MS patients (Swank, 1950; Swank *et al.* 1952; Sinclair, 1956; Agranoff & Goldberg, 1974). The conclusion was drawn that MS might be related to a dietary deficiency of polyunsaturated or EFA (Swank, 1950; Sinclair, 1956; Allison, 1963; Bernsohn & Stephanides, 1967; Dick, 1976). These findings led to a double-blind trial of linoleic acid supplementation in Belfast and London and later in Newcastle (Millar *et al.* 1973; Bates *et al.* 1978), which gave encouraging results. The 'linoleic acid effect' is the reason for the current interest in diet and MS.

The interest in EFA centred principally on linoleic acid. However, Bernsohn & Stephanides (1967) suggested that of the two EFAs, linoleic and α-linolenic acids, the evidence pointed more to dietary deficiency of α-linolenic acid. They called attention to epidemiological information which seemed to indicate that the geographical distribution of MS was inversely related to the intake of foods rich in α-linolenic acid and its derivatives (ω3 fatty acids), such as fish. This proposition arose because of the relatively low incidence of MS found in the Faroe Islands, compared to the Shetlands. The Islanders came from the same Danish genetic backgrounds but the Faroe Islanders remained as fishermen whilst the Shetlanders adopted a British agricultural practice. Similar contrasts were apparent in Scandinavia.

The matter has not been followed up, possibly because of the lack of any supporting evidence that ω3 fatty acids have a nutritional role. However, there is now a substantial amount of analytical information demonstrating the presence of long chain ω3 fatty acids in the central nervous system (Crawford, Casperd *et al.* 1976).

Dick (1976) suggested that the use of cow's milk as a substitute for human milk might be relevant to the aetiology of MS. Two possible mechanisms could be proposed. First, cow's milk is thought to cause allergies (Gerrard *et al.* 1973; Walker & Hong, 1973). Secondly, cow's milk has about three times as much

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protein but a quarter of the EFA content of human milk. There is no hard evidence to link nutrition and MS, but it is not unreasonable to propose that nutritional principles might operate during a vulnerable period of development and modify brain structure in such a way that it becomes more susceptible to attack or spontaneous breakdown in adult life.

It is not, however, the purpose of this paper to discuss the different claims regarding a viral, autoimmune or nutritional aetiology. The evidence to support single hypotheses is not satisfactory and consequently we would in any case like to suggest that an interaction of all three principles may be at work. We would like to focus this paper on the scientific background and the potential role of nutrition in the management of MS patients. It should become apparent that a case for nutritional management can be made independently of any considerations as to the actual cause of MS itself.

Scientific background

Compositional studies. The reason for the focus on lipid nutrition is due to the fact that 60% of the solid matter of the brain and 70% of the myelin sheath is lipid. The essential fatty acid component of the brain has been studied in forty-five different species and is consistently dominated by the long-chain derivatives of linoleic and α-linolenic acids (Crawford, Casperd *et al.* 1976).

Timing. Our studies on the developmental biology of the brain have shown that the period of most active incorporation of the long-chain EFA derivatives is associated with cell division and precedes the accumulation of mature myelin with its long-chain saturated and mono-unsaturated fatty acids (Figs. 1 and 2) (Sinclair & Crawford, 1973). In man, 70% of the adult brain cells and their long-chain EFA derivatives are formed before birth; postnatally, the emphasis shifts to myelination.

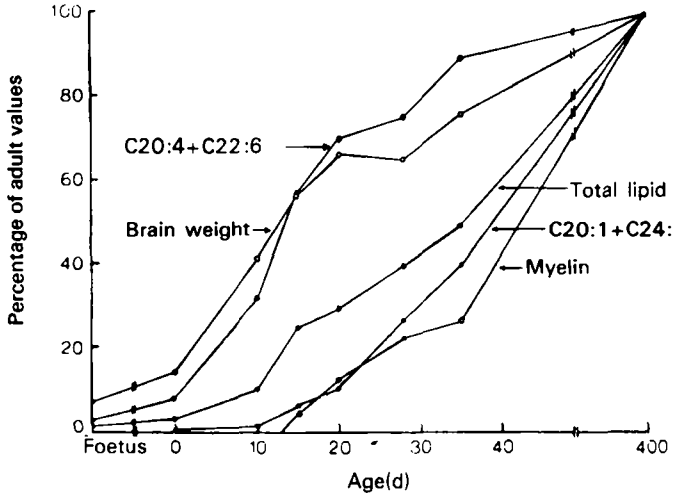

Fig. 1. Some measurements in developing rat brain, expressed as a percentage of adult values.

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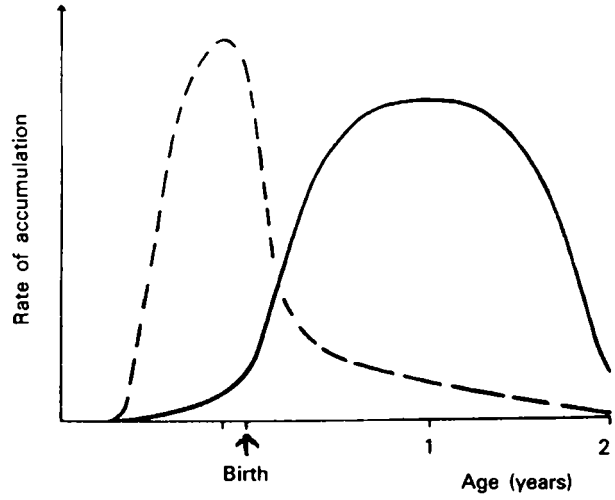

Fig. 2. Accumulation of some long-chain fatty acids (– – –), 20:4+22:6 and (—), 24:0+24:1, in the developing human brain.

Metabolism. Linoleic and α-linolenic acids must first be converted to arachidonic and docosahexaenoic acids, respectively. It used to be thought that these conversions were direct and rapid, but Hassam & Crawford (1976) have shown that this is not the case. The first reaction (Fig. 3), a desaturation step, is rate limiting in all animal species studied and indeed is absent in some (Rivers *et al.* 1975). Consistent with the slow rate of conversion, it has been found that the pre-formed long-chain derivatives are incorporated into CNS membrane lipids many times faster, are oxidized more slowly and are more potent in correcting the symptoms of EFA deficiency than the parent acids (FAO/WHO, 1978; Houtsmuller, 1975). In addition to their function as cell-building units, these long-chain acids act as precursors of prostaglandins (Fig. 4) (Van Dorp *et al.* 1964; Bergstrom *et al.* 1964; Moncada *et al.* 1976).

Linoleic

18:2 (30) → 18:3 (12) → 20:3 (7) → 20:4 (1) → 22:4

α-Linolenic

18:3 (10) → 18:4 – → 20:4 – → 20:5 (7) → 22:5 (3) → 22:6 (1)

Fig. 3. Incorporation of linoleic and α-linolenic acids into long-chain derivatives in the brain of new-born rat pups. The number of precursor molecules required to yield one molecule of 20:4ω6 and 22:6ω3 is also shown in brackets.

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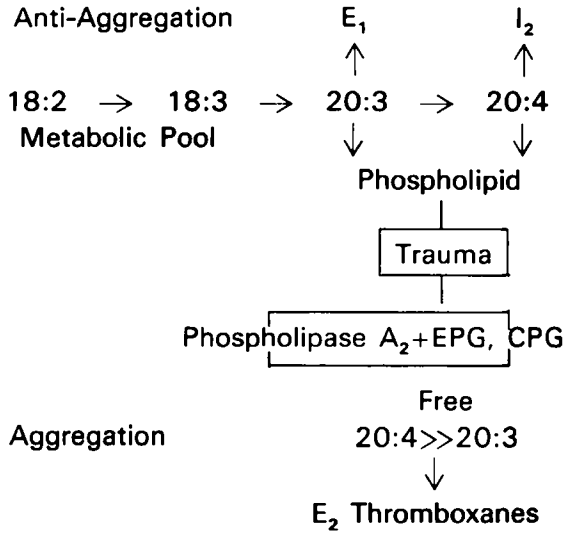

Fig. 4. Essential fatty acids and prostaglandin synthesis.

Dietary dependence. It is obvious that the long-chain EFAs have to be obtained from the food and therefore they are linked with nutrition. The link between diet and prostaglandin (PG) synthesis is not so obvious. However, there is now evidence in man and other animals that PG levels are dependent on dietary linoleic acid (Zöllner *et al.* 1979). It is claimed by some workers that PG synthesis is derived from membrane-bound pools, i.e. from phospholipids. Our results show that this is not necessarily the case (Crawford *et al.* 1978). Studies in the rabbit showed that a reduction of dietary linoleic acid intake did not lead to a decrease of membrane bound phospholipid precursors; yet the production of prostaglandins E1, E2 and F2α was reduced (Tables 1 and 2) (Crawford *et al.* 1978; Hassam *et al.* 1979). This would mean that a direct link between dietary linoleic acid and PGs would result in a quick response to dietary change, which is the case observed where PG-related functions (hypertension, platelet aggregation) are measured.

Two families. Two families of essential fatty acids exist and this fact was ignored in previous attempts to evaluate EFA supplementation in MS. The ratio ω6–ω3 in the body in general is approximately 5:1, and in the brain 1:1.

Conclusions. We can draw some conclusions relevant to the evaluation of nutrition in MS. First, two effects of EFA may need to be considered; immediate PG synthesis; long-term aspects of cell-membrane structure. Also, the desaturation problem implies that: the long-chain derivatives could be more promising as a nutritional supplement than the parent EFA; the different rates of desaturation in different species could mean that genetic differences may also be found within a population. In addition, there is the possibility that a balance of the two families of EFA may be needed.

Table 1. *Effect of fat-free diet on ω6 fatty acid levels in the rabbit*

(Values are means with their standard errors expressed as percentage total fatty acids in phosphatidylethanolamine; four animals/group)

Fatty acid	Liver ethanolamine phosphoglycerides*				Erthorocyte ethanolamine phosphoglycerides†			
	Control		Fat-free		Control		Fat-free	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Linoleic acid (18:2ω6)	20	3·6	12	3·10	30	1·9	17	1·9
Dihomo-1-linolenic acid (20:3ω6)	0·32	0·11	0·27	0·06	0·56	0·22	0·65	0·14
Arachidonic acid (20:4ω6)	8·7	2·2	16	1·6	11	1·2	14	1·3

*Liver is the principal initial site of fatty acid metabolism.
†Erythrocytes provide an index of structural lipids status.

Table 2. *Effect of fat-free diet on prostaglandin (PG) levels (ng PG/g frozen tissue)* in the rabbit*

(Values are means with their standard errors; no. of animals in parentheses)

Tissue	Diet	PGE_1		PGE_2		PGF2α	
		Mean	SE	Mean	SE	Mean	SE
Lung	Control (5)	62	30	210	89	187	105
	Fat-free (4)	16	9	19	5	27	16
Skin	Control (5)	140	13	400	100	111	24
	Fat-free (4)	44	27	48	6	40	26
Eye	Control (5)	137	62	190	48	96	35
	Fat-free (4)	8	1	274	4	13	5

*Allowing for recovery of ^3H tracer.

These points are relevant to understanding the expected small effect in previous trials and provide the material for future work.

Models for brain damage

EFA deficiency. Having established the quantitative state of EFA in brain it is necessary to consider the question: does their presence matter? It has been known for some time that deficiency of EFA in the diet retards brain development (Caldwell & Churchill, 1966; Galli *et al.* 1977; Sinclair & Crawford, 1973), alters synaptic function (Sun *et al.* 1974) and changes the electrical activity of the rods of the retina (Benolken *et al.* 1973). These alterations are dependent on changing the brain lipid EFA content. However, perhaps the most interesting result was the attempt by Alling & Svennerholm (1974) to repeat the EFA deficiency experiment using defatted fish-meal as a protein source. They failed to

alter the EFA content of brain lipids in the new-born rat pups. However, they did alter the sphingolipid characteristic of myelin in the pups born to mothers given the EFA-deficient diet. It is possible that defatting of the fish-meal left sufficient protein-bound phospholipid to maintain the brain EFA. These results are interesting because, in the human situation, we are clearly not dealing with extreme deprivation, as for example in our own studies. On the other hand a physiological stress imposed by minimal supplies could be more interesting. The fact that Alling & Svennerholm (1974) found distortions in myelin lipids rather than cellular lipids under these circumstances could be of relevance to what might be expected to occur in practice.

Experimental allergic encephalomyelitis (*EAE*). It is possible to induce in the guinea-pig a demyelination condition by injecting a basic protein prepared from the brain. The rat was resistant, but Clausen & Møller (1967) demonstrated that if the rat were made deficient in EFA and brain lipids were correspondingly altered, it did then become susceptible. Although these results were clear, they were doubted for some time, until Selivonchick & Johnston (1975) in the USA confirmed Clausen & Møller's work. More recently Mertin & Stackpoole (1978) have been investigating the role of EFA and prostaglandins in the regulation of cell-mediated immunity. EAE can be transferred by living lymphoid cells, but not by serum from actively-sensitized animals, into others that are histocompatible. Feeding linoleic to susceptible (Lewis) rats clearly suppressed the incidence of the disease (Mertin & Stackpoole, 1978). This effect was found to be more pronounced if Naudicelle was used instead of a conventional seed oil. Naudicelle (seed oil of the Evening Primrose) contains γ-linolenic acid (7–8%), as well as linoleic acid. The γ-linolenic acid is beyond the desaturation step and is converted more rapidly to the arachidonic acid (Hassam & Crawford, 1976) used for prostaglandin synthesis. Splenectomy or the use of indomethacin, an inhibitor of prostaglandin synthesis, abolished the effect of EFA administration. These observations suggest that the suppressive effect of EFA on cell-mediated immune reactions is brought about by prostaglandin derivatives of the EFA.

Eylar (1972) suggested that a virus infecting the CNS might behave abnormally and incorporate substantial CNS proteins into its envelope. The possibility exists of a resultant basic protein–virus complex which would be highly immunogenic. Mertin & Meade (1977) suggested that under certain conditions paramyxovirus, for example, may be able to change its behaviour (Compans *et al.* 1972) and altered tissue EFA could thus prepare the ground for such a change. This suggestion brings together the three views on the aetiology of MS (virus, autoimmune reaction and nutrition).

Nutritional encephalomalacia (*NE*). NE is a field disease of growing chicks. The outward signs are loss of balance (ataxia), prostration and death. The cerebellum, but not the large brain, exhibits oedema, haemorrhage and profound degenerative changes including demyelination (Dror *et al.* 1976). The condition can be induced experimentally by feeding a diet deficient in vitamin E but containing linoleic acid (Dam *et al.* 1958; Century & Horwitt, 1959; Machlin & Gordon, 1960). According

to the traditional view, the disease involves cerebellar membranes which are especially rich in the long-chain highly polyunsaturated derivatives of the EFA. Vitamin E is believed to act as a membrane-stabilizing agent and lipid antioxidant, hence it was possible to rationalize NE as due to peroxidation of these highly unsaturated brain membrane lipids (Machlin, 1963). However, Dam *et al.* (1958) have shown that ethyl α-linolenate did not induce NE under conditions in which ethyl linoleate was highly effective; similar findings were reported with tocopherol-stripped linseed oil which is rich in α-linolenic acid (Century & Horwitt, 1959; Machlin & Gordon, 1960). α-linolenic acid is not only more unsaturated than linoleic acid but gives rise to docosahexaenoic acid (22:6ω3) which is the most polyunsaturated component of brain membranes lipids and the most susceptible to peroxidation. Therefore the picture of NE as being due only to oxidative deterioration of brain lipids is an oversimplification.

In view of the suggestion by Bernsohn & Stephanides (1967) concerning an inverse relation between the incidence of MS and the intake of α-linolenate or its derived fatty acids (see p. 373), the failure of linseed oil fatty acids to induce NE was of interest. We have repeated the early experiments, using the methyl esters of the fatty acids separated from various oils (Budowski *et al.* 1979). Table 3 shows the results of a feeding test. When safflower esters, rich in linoleic acid, were supplied as 8% of a vitamin E-deficient diet, eleven out of twelve chicks showed signs of NE, whereas none of fourteen chicks receiving linseed esters was affected. It is also seen that linseed esters exerted a protective effect against NE when added to a diet containing safflower esters, as reported by Century & Horwitt (1959). Cod-liver esters were somewhat less protective than linseed esters. This fish oil is a rich source of long-chain derivatives of α-linolenic acid.

Table 3. *Effect of dietary methyl esters on the incidence of encephalomalacia*

Dietary methyl esters*	Incidence between 10th and 25th d†	Content (% total fatty acids)	
		18:2ω6	18:3ω3
Safflower seed	11/12	75	0·4
Linseed	0/14	15	54
Safflower + Linseed	3/10	45	27
Cod-liver	5/14	2	26‡
Safflower seed + cod-liver	6/10	39	13‡

*Each type of methyl esters was supplied at 80 g/kg diet.

†The incidence of encephalomalacia is expressed as no. of chicks affected/no. of chicks per treatment.

‡Long-chain polyunsaturated ω3 fatty acids.

We have extended these observations by showing that the protective effect of linseed esters was evident from the day the treatment was initiated, i.e. when the safflower diet was replaced by the linseed diet at 15 d of age, when the cumulative incidence curve was steeply ascending, no further cases of NE were found.

We have also found that the fatty acid composition of brain lipids in the chick is profoundly affected by the dietary lipids. However, the protective effect of

α-linolenic acid appears to be too rapid to be ascribed solely to compositional changes of brain lipids. It is plausible that the prostaglandin system is behind the rapid response of the chick to α-linolenic acid and that this system is also involved in the aetiology of NE. For instance, indomethacin tended to exacerbate the disease. In this connexion it is of interest that this compound has also been reported to make MS patients worse (Rudge, personal communication, cited by Mertin & Stackpoole, 1978).

Two points deserve comment in discussing the value of the chicken as a model for human brain studies. In 1930 there was an outbreak of multiple neuritis in the USA claiming thousands of victims. Pathological findings included degeneration of the myelin sheath of peripheral nerves and some central demyelination. The disease was traced to tri-ortho-cresyl phosphate, but when attempts were made to reproduce the disease in animals for toxicity studies and screening purposes, dogs, cats, calves and monkeys were found unsuitable, and the chicken was the only species in which paralysis and neural damage could be reproduced (reviewed by Worden, 1971). Chick NE is a unique model for demonstrating a beneficial effect of α-linolenic acid. It has been stated that if a critical requirement for α-linolenic acid derivatives exists, it is likely to be found in the central nervous system where this family of fatty acids is consistently present in high concentrations (Crawford *et al.* 1973; Lamptey & Walker, 1976). It is plausible to speculate that such a requirement will be exposed under conditions in which brain membranes are made specially vulnerable: vitamin E deficiency coupled with a supply of linoleic acid provides these conditions in the chick, where the cerebellum becomes the target organ. Thus, although the set of circumstances under which NE is induced is unique, the protective effect of α-linolenic acid and its derivatives need not necessarily be restricted to this particular model of brain damage.

Conclusion. Whilst EAE provides a model which exhibits the role of linoleic acid in cell-mediated immune reactions, NE provides a model where α-linolenic acid is clearly acting in a quite different manner to linoleic acid with respect to the brain.

In our view these observations offer evidence that the balance of both families of EFA may need to be taken into account when considering nutrition and the nervous system.

Human results

A shift in the proportion of saturated and unsaturated fatty acids has been recorded in the brains of MS patients. Not unexpectedly, these results are inconsistent. If lipid distortion is a component of MS, it is more likely to result from metabolic or nutritional disturbances in the period of brain growth than in adult life.

It may be relevant that in foetal lipid nutrition, the emphasis is clearly on the long-chain essential polyunsaturates (Crawford, Hall *et al.* 1976), in accordance with the specific demand for cell division. Postnatally, the composition of human milk appears to follow the changing postnatal chemical requirements of brain development, i.e. the proportion of long-chain essential fatty acids used in cell

division diminishes and that of the long-chain mono-unsaturated fatty acids associated with myelin increases (Fig. 5). It is not known if such shift in emphasis from the foetal concentration of long-chain EFA to the postnatal synthesis of myelin-type fatty acids has any physiological significance. However, the point has to be made that this period of early development is one in which the nervous system is most likely to be vulnerable to dietary manipulation. On the other hand it is known from experiments that distortions occurring during this period can be later corrected in terms of chemistry but not necessarily function (Galli *et al.* 1977). This observation would seem to mean that function may be dependent on subtle structural alterations which may develop in response to the biochemical environment but need not necessarily be defineable by chemical analysis. The chemistry of a mineral may be similar to that of a silicon chip but their functions are different.

Other findings on MS patients include increased platelet stickiness (Nathanson & Savitsky, 1952; Caspary *et al.* 1967) which has been confirmed by several workers, including Millar *et al.* (1973) in their double-blind trial. Laszlo (1964) reported increased osmotic fragility of red cells. Certain observations suggest that the handling of essential fatty acids may be disturbed in MS. Field *et al.* (1974) claimed that the degree of inhibition by linoleic acid of the response of the human lymphocyte to antigens is much greater in MS. It has also been claimed that the different behaviour of lymphocytes in an electrophoretic field is specific to MS and can be used as a diagnostic test. Other workers have not been able to reproduce his

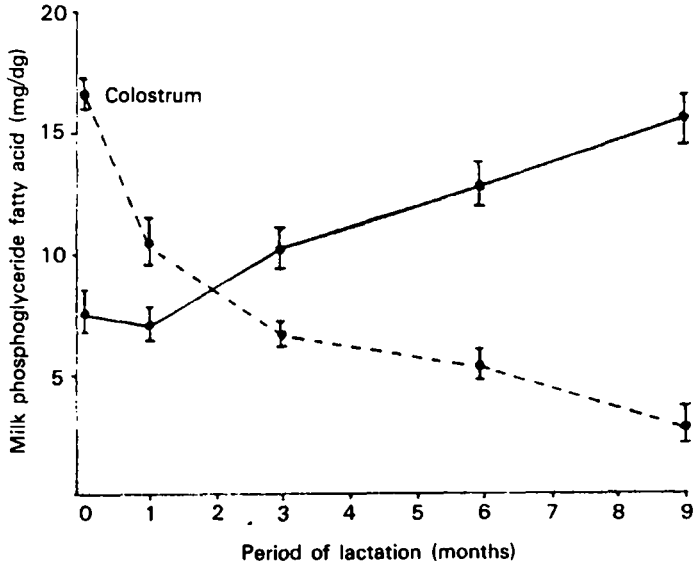

Fig. 5. Alterations of some milk lipids with time in seven lactating European mothers. (– – –), arachidonic acid content in ethanolamine phosphoglycerides (EPG, C20:4ω6) and (—), nervonic acid content in the sphingomyelin fraction (SPG, C24:1). Points are mean values and vertical bars represent the standard derivations.

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results and his suggestions have not received much attention. However, Seaman *et al.* (1979) recently reported that they could reproduce Field's test using a simplified procedure applied to red cells (Table 4). One of the difficulties of Field's test is that oral administration of linoleic acid was reported by Field to correct the abnormality. This observation would indicate that the test would only be reliable if the individuals were eating relatively low amounts of EFA or conversely it might give false negatives if people ate large amounts of EFA (Crawford & Hassam, 1975).

Table 4. *Change in electrophoretic mobility of erythrocytes upon addition of linoleic acid*

Group	no.	Mean change (%) in mobility (±SD)
Multiple sclerosis	65	−7·0±2·5†
Normal controls	27	−0·8±1·2
Other nervous diseases	5	−1·3±0·8

†$P<0.001$ for sixty-five multiple sclerosis patients versus thirty-two controls.

Many unsubstantiated claims have been made for the treatment of MS. ACTH can be beneficial in acute relapses. Two double-blind trials on linoleic acid supplementation have been carried out, the first in Belfast and London and the second in Newcastle, in which there was a significant reduction in the severity and length of relapses in the treated groups (Table 5) (Millar *et al.* 1973; Bates *et al.* 1978). An observation of general nutritional interest has been made by Lange & Shiner (1976); they found abnormalities in the jejunum in biopsies from MS patients. It is interesting to ask if these abnormalities are part of the disease process or reflect some degree of undernutrition.

Table 5. *Multiple sclerosis: number and duration of relapses*

Duration (weeks)	1–5	6–9	10 or more	Total
Belfast series				
Controls	12	23	8	33
Linoleate group	17	4	4	25
London series				
Controls	12	15	2	29
Linoleate group	16	0	0	16

These results are from the results of the Belfast/London double-blind trial (Millar *et al.* 1973) on the supplementation of multiple sclerosis patients with sunflower-seed oil, providing the patients with approximately 23 g linoleic acid.

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Nutrition and blood lipids

The starting point of the linoleic acid supplementation trials was the observation of low levels of plasma EFA in patients with MS. However, there is some inconsistency in the literature about this finding, which in our view is not surprising, as plasma linoleic acid levels are closely connected to diet. Erythrocyte levels, however, tend to reflect longer-term considerations, as one is analysing membranes with life-spans of approximately 120 d. We have repeated the earlier work and examined different phospholipid fractions for long-chain derivatives of linoleic and α-linolenic acids and are basically able to confirm the earlier results on plasma linoleic acid (Table 6).

Table 6. *Long-chain polyunsaturated fatty acid content in the EPG fraction of erythrocytes in multiple sclerosis*

(Values are means with their standard errors; no. of patients in parentheses)

		ω6 family		ω3 family	
		20:4	22:4	22:5	22:6
Normal controls (23)	Mean	25·6	5·09	4·60	9·57
	SE	0·72	0·19	0·27	0.46
Multiple sclerosis patients (16)	Mean	20·5	4·16	3·58	5·90
	SE	1·17	0·39	0·30	0·65
	P	<0·001	<0·025	<0·025	<0·001

However, we could show that nutritional counselling can alter the plasma pattern quickly, but that it takes approximately 9–12 months to change the phospholipid fractions in the erythroyte membrane under the same conditions (Table 7). There is the added complication that the erratic course of the disease also appears to be reflected in a similarly erratic pattern of fatty acids in the blood. Whilst it is common to find low levels of phospholipid EFA in the blood of patients with MS, it is also possible to find high levels of both EFA and long-chain saturated and mono-unsaturated fatty acids typical of myelin (Table 8). These bizarre observations suggested to us that we were probably seeing some evidence of neurological damage, in effect biochemical debris, as these results were usually only obtained in severely affected cases.

It is also of interest that patients will respond readily to ideas on nutrition. This introduces a number of pitfalls for any proposition of using these or other fatty acid-dependent techniques diagnostically. We were studying a group of new patients at the time when much prominence was given in the news media to the results of the Belfast/London sunflower-seed trial. Almost immediately after the publication of the results the blood levels of the patients accurately reflected the increased intake of sunflower-seed oil by those who had read the newspapers (Table 9).

Table 7. *Multiple sclerosis case study following nutrition counselling*•

	Plasma		Erythrocyte ethanolamine phosphoglycerides (% total fatty acids)			
Control	Cholesterol (mg/dl)	Triglyceride (mg/dl)	20:4	22:4	22:5	22:6
			26	5·1	4·6	9·4
Months						
0	173	58	18	3·8	3·1	3·4
3	145	93	19	4·8	3·9	4·6
7	202	141	20	3·3	3·8	5·2
12	172	73	25	5·0	4·1	8·3
36	160	92	24	4·6	4·0	9·7

•The results are taken from a longitudinal follow-up of a multiple sclerosis patient over a period of 3 years. These and similar results on other patients indicate that a change from a habitual diet to one based on the principles outlined in Fig. 7 does not result in a rapid change in erythrocyte membrane fatty acid composition. On the other hand, plasma triglyceride and cholesterol levels respond within a few weeks.

Table 8. *Plasma choline phosphoglycerides (CPG) and sphingomyelin (SPH) abnormalities in seven patients with multiple sclerosis (MS) Kurtzke score 6 or greater (recent relapse)*

	CPG		SPH	
Fatty acid	Normal	MS	Normal	MS
18:2ω6	24	18		
20:4ω6	9·1	10		
22:4ω6	0·6	2·3•		
20:5ω3	0·9	0·4		
22:5ω3	0·8	0·3		
22:6ω3	4·3	6·8•		
24:0	0·3	2·8•	13	18•
24:1	0·7	2·9•	16	21•

•$P<0.01$

Abnormalities of the choline phosphoglycerides (CPG) were encountered in severely affected patients. The relatively high levels of lignoceric (24:0) and nervonic (24:1) acids in the sphingomyelin might reflect disturbed metabolism or, in some way, tissue breakdown.

Table 9. *Mean linoleate content (% total fatty acids) of plasma lipids in normal subjects and patients with multiple sclerosis (MS)*

(Values are means with their standard errors; no. of patients in parentheses)

	Normal		MS1•		MS2†	
	Mean	SE	Mean	SE	Mean	SE
Phospholipids	17·6	1·64 (11)	13·7	1·6 (7)	26·9	1·1 (12)
Triglycerides	11·0	0·8 (14)	7·86	0·71 (6)	26·8	3·1 (12)

•MS1 refers to patients who claimed they were not taking sunflower-seed oil.

†The MS2 group represents those patients who had been taking sunflower-seed oil for at least 1 month (Crawford *et al.* 1973).

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There is further importance attached to the sensitivity of the patients to advice or suggestions. Whilst we were examining the effect of nutrition counselling on patients we found that in some cases the message had been simplified and exaggerated. For example, in one patient the plasma triglyceride level of linoleic acid rose over a period of three weeks from a level of 8% to 47%. The view was taken that if a small amount of sunflower-seed oil was 'good for you' a large amount would be better. This exaggerated action would not have been discovered had it not been for the fact that we were monitoring the blood lipids. Consequently we take the view that any approach to nutrition counselling ought to include some monitoring activity.

We would conclude that the changes seen in the blood of patients with MS are not specific to MS but are in part related to the course of the disease, and that low levels may be the result of a non-specific demand for cell repair (e.g. as in trauma, burns or severe head injury), or simply a function of dietary intake.

Principles of nutrition counselling in MS

This body of evidence suggests that the EFA are involved in MS, but it may be that the changes are secondary to other events such as tissue damage or the demand for cell repair. However, a pragmatic case can be made for nutrition counselling in MS.

We have examined food intakes in seventeen patients by 24 h recall and four others on a weighed-food basis. The results have not been fully analysed because we feel we need more analytical information on dietary lipids and more information on weighed-food intakes. However, two principles seem to emerge; first, food intake of handicapped patients appears to be low. We estimated it to be 6·85±0·84 MJ (1 640±200 calories) (mean ± SE; Fig. 6). If we take an estimate of

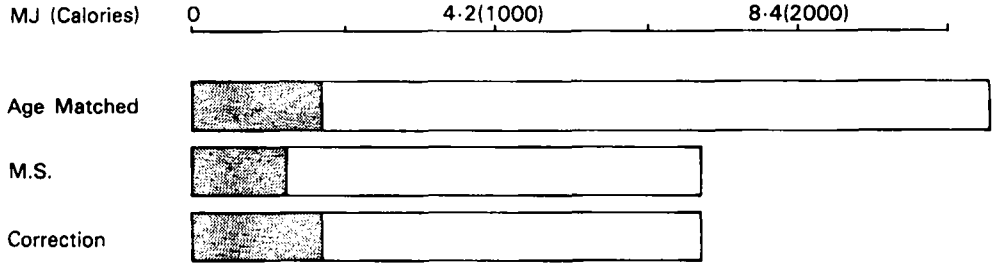

Fig. 6. Impact of multiple sclerosis (MS) on food intake. The estimated (▨) nutrient and (□) energy intakes of MS patients are compared to those of age-matched controls.

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protein intake as representing the general nutrient intake, then the latter was correspondingly low. This observation may mean that the reduction in energy expenditure is matched by a reduction in food intake. On the other hand, one gains the impression that the patients may lose weight and it is difficult to decide to what extent this loss is due to muscle wasting or nutritional weight loss. This view of a low food intake is supported by analysis of blood cholesterol and triglyceride levels which are consistently below those of age-matched controls (Table 10). Clearly, more research needs to be done in food intakes.

Table 10. *Plasma lipid measurements (mg/dl) in multiple sclerosis (MS)*

(Values are means with their standard errors; no. of patients in parentheses)

	Cholesterol	Triglycerides
MS patients (35)	160 (14)	73 (11)
Normal controls, age-matched (29)	204 (27)	138 (21)

The results illustrate that both lipids were found to be significantly lower in the MS patients compared to age-matched controls. The small values of these lipids in the MS patients could reflect lower food intakes or the fact that the patients were generally on low saturated and relatively high polyunsaturated fat intakes or both.

A second point derived from the enquiry was the tendency for handicapped patients to rely on foods that are easy to purchase and prepare. Only two of the seventeen patients ate fish and cooked fresh vegetables more than once a month. There was a heavy reliance on bread, biscuits, cheese, pies and prepared foods. Liver was not used by any of the patients. We recognize the inadequacy of the dietary recall method, but even so the possibility exists that a reduction in food intake by handicapped patients, associated with a simplified pattern of foods used, could reduce the intake of certain nutrients disproportionately. We would suggest that nutrition counselling should be given to MS patients so that the qualitative aspects of the diet could be improved and nutrient intake restored to normal in the interests of the general health of the patient.

If nutrition counselling is to be undertaken, one might ask which qualitative aspects of the diet should be emphasized. In our view it makes sense to emphasize those nutrients that are specifically involved in the central nervous system. A summary of such an approach is shown in Fig. 7.

Linoleic acid-rich foods are recommended as the 'linoleic acid effect' is the only effect demonstrated apart from drug therapy. This means a liberal use of vegetable-seed oils and linoleic acid-rich margarines. This recommendation could include the use of salad dressing made from vegetable oils. The frequent use of green salads with 'French dressing' has the double advantage of providing both linoleic in the oil and α-linolenic acid in the greens.

The basic argument presented here is not only that both EFA families may be involved but also that the preformed long-chain derivatives are used by the brain and should be considered. The rate of conversion of the parent EFA to

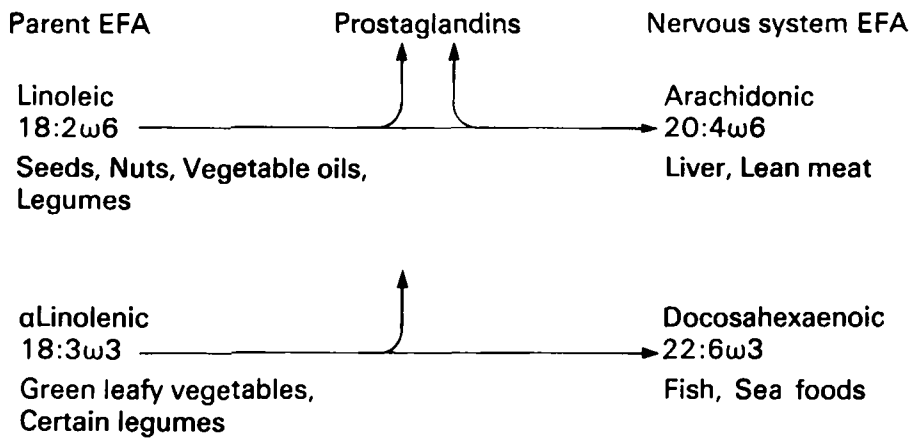

Fig. 7. Essential fatty acid principles in nutrition.

their long-chain products is slow, and the derivatives themselves are physiologically more potent. Direct sources of the long-chain linoleic acid derivatives can be found in liver, kidney and lean meat. The long-chain derivatives of α-linolenic acid are found in fish and other sea foods. They are also conveniently available in cod-liver oil.

In addition to advice on the nature of foods, we recommend, in this context, that attention be given to accessory nutrients. In particular, trace elements such as zinc, copper and iron are components of the desaturase and cyclo-oxygenase systems responsible for the synthesis of long-chain derivatives and prostaglandins. The B vitamins are important for chain elongation reactions and this is an additional reason for the regular use of liver. We would include sources of vitamin E and C as important biological antioxidants and because the role of vitamin E is well-established in NE. Vitamin E can be obtained from the use of wheat germ. It is interesting that one of the beneficial side effects of eating wheat germ and bran, reported by the patients, is the greater ease in passing stools. This result is probably a by-product of the increased oil and fibre content of the diet and is quite important to the patient.

Conclusion

In summary we would suggest that the low levels of EFA found in the blood of MS patients are non-specific, and that they are not indicative of EFA deficiency. This, however, does not mean that nutrition counselling is unimportant. The evidence we have presented, in our view, shows that the case for nutrition advice or supplementation in MS does not depend on the 'cause' of the disease, but rather on the evidence in animals and man, showing that the essential fatty acids and their accessory nutrients are relevant to brain growth and maintenance.

Previous interest in EFA nutrition and MS has been focused on linoleic acid alone. The evidence now tells us that the issue is more complex. If minor benefits can be obtained from the use of linoleic acid alone, then a broader approach might be more successful, i.e. we now know that: it is not linoleic acid but its derivatives that are biologically active; the synthesis of the derivatives is inefficient and likely to be a genetic variant; there is a second family of essential fatty acids which is quantitatively of equal importance in the CNS but has not been considered in trial design.

It seems therefore that there is a case for a new trial designed to test the effect of both families and the long-chain fatty acids actually used in repair and maintenance of the CNS. It is clear from the experimental evidence and indeed from common sense that this case can be made, quite regardless of the aetiology of the disease.

Multiple sclerosis is labelled as an incurable disease. But it follows a course of severe attack, disability and recovery. The remission can be longstanding and permanent. The fact that such remissions do occur suggests that the biological system has a mechanism which is effective against the disease. This means that there ought to be a way to capture that technique, to use it or to encourage its success.

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