Review article

The conditional nature of the dietary need for polyunsaturates: a proposal to reclassify 'essential fatty acids' as 'conditionally-indispensable' or 'conditionally-dispensable' fatty acids

Stephen C. Cunnane*

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto M5S 3E2, Canada

The term essential fatty acid no longer clearly identifies the fatty acids it was originally used to describe. It would be more informative if the concept of essentiality shifted away from the symptoms arising from the lack of *de novo* synthesis of linoleate or α-linolenate and towards the adequacy of the capacity for synthesis and conservation of both the parent and the derived long-chain polyunsaturates. For instance, despite the existence of the pathway for synthesis of docosahexaenoate from α-linolenate, the former would be more correctly classified as 'conditionally indispensable' because the capacity of the pathway appears insufficient during early development, although it may be sufficient later in life in healthy individuals. Similarly, despite the inability to synthesize linoleate *de novo*, abundant linoleate stores and its relatively slow turnover in healthy adults probably makes linoleate 'conditionally dispensable' for long periods. There are two other anomalies with the terms essential and non-essential fatty acids: (1) under several different experimental circumstances, the C-skeleton of essential fatty acids is avidly used in the synthesis of non-essential fatty acids; (2) to function normally, the brain is required to endogenously synthesize several non-essential fatty acids. As with essential amino acids, which have been reclassified as indispensable or conditionally indispensable, such a change in terminology should lead to an improved understanding of the function and metabolism of polyunsaturates in particular, and long-chain fatty acids in general.

Polyunsaturates: Essential fatty acids: Linoleate: α-Linolenate

The aim of the present paper is 2-fold: (1) to review the anomalies and inconsistencies surrounding the term essential fatty acid; (2) to suggest that these problems could be potentially overcome by reclassifying polyunsaturated fatty acids (PUFA) as 'conditionally-indispensable' or 'conditionally-dispensable' fatty acids. I proposed 4 years ago that essential fatty acids could be renamed 'indispensable' or 'conditionally-dispensable' fatty acids (Cunnane, 1996). The experimental basis for this proposal was only beginning to emerge at that time. I would therefore like to take this opportunity not only to reiterate the proposal, but also to change it slightly, because I do not think any single PUFA is truly indispensable, (i.e. must be more or less continuously present in the diet throughout life).

There are several reasons for proposing this change in terminology. First, the traditional definition of essential fatty acids has outlived its usefulness, since this term now encompasses a large number of fatty acids which can be synthesized by mammals if the parent PUFA are present in the diet. Second, the dietary essentiality of the parent or the longer-chain PUFA always appears to be conditional on developmental age, nutritional circumstances, or the presence of diseases that lead to increased fatty acid

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Table 1. n-6 and n-3 polyunsaturated fatty acids (PUFA) that currently qualify as essential fatty acids

n-6 PUFA	n-3 PUFA
Tetradecadienoate (14 : 2n-6)*	Tetradecatrienoate (14 : 3n-3)*
Hexadecadienoate (16 : 2n-6)*	Hexadecatrienoate (16 : 3n-3)*
Linoleate (18 : 2n-6)	α-Linolenate (18 : 3n-3)
γ-Linolenate (18 : 3n-6)	n-3 Eicosatrienoate (20 : 3n-3)
Eicosadienoate (20 : 2n-6)	Octadecatetraenoate (18 : 4n-3)
Dihomo-γ-linolenate (20 : 3n-6)	n-3 Eicosatetraenoate (20 : 4n-3)
Arachidonate (20 : 4n-6)	Eicosapentaenoate (20 : 5n-3)
Adrenate (22 : 4n-6)	n-3 Docosapentaenoate (22 : 5n-3)
n-6 Docosapentaenoate (22 : 5n-6)	Docosahexaenoate (22 : 6n-3)
Tetracosatetraenoate (24 : 4n-6)	n-3 Tetracosapentaenoate (24 : 5n-3)
n-6 Tetracosapentaenoate (24 : 5n-6)	n-3 Tetracosahexaenoate (24 : 6n-3)
C_{26}–C_{36} n-6 PUFA†	Octacosaoctadecaenoate (28 : 8n-3)‡
	C_{26}–C_{36} n-3 PUFA†

* Sprecher (1968), Cunnane et al. (1995).
† Suh et al. (1996).
‡ van Pelt et al. (1999).

β-oxidation. Third, recent research is blurring the traditional distinction between essential and non-essential fatty acids.

Problems with the term essential fatty acids

The term essential fatty acid currently describes two related families of long-chain fatty acids, the n-6 and n-3 PUFA. The best known parent fatty acids in these two families are linoleate (18 : 2n-6) and α-linolenate (18 : 3n-3), which were discovered 70 years ago (Burr & Burr, 1930). Their metabolism and nutritional importance has been widely studied and the sequence of desaturation and chain-elongation steps leading to the derived long-chain PUFA is now well known (Holman, 1971; Brenner, 1974). Several detailed reviews chart the historical development of this field (Aaes-Jorgensen, 1961; Alfin-Slater & Aftergood, 1968; Holman, 1971). Current knowledge concerning the membrane and eicosanoid-based functions of arachidonate (20 : 4n-6) and the other long-chain PUFA is described in detail elsewhere (Spector & Yorek, 1985; Ackman & Cunnane, 1991; Salem et al. 1996).

There are several traditional reasons why n-6 and n-3 PUFA are considered dietarily essential. The primary reason is that mild but distinctive deficiency symptoms are observed when either linoleate or α-linolenate are absent from the diet, but disappear when they are present (Neuringer et al. 1984; Bourre et al. 1989; Cunnane et al. 1998). These symptoms are more severe in classical essential fatty acid deficiency than in specific linoleate deficiency, and in young compared with mature animals.

In addition, there are three secondary reasons for the dietary essentiality of some PUFA: (1) although linoleate and α-linolenate can be synthesized from their C_{16} analogues (Cunnane et al. 1995; see p. 807), in the absence of those analogues they cannot be synthesized de novo in mammals; (2) linoleate and α-linolenate give rise to C_{20} and C_{22} long-chain PUFA which have important membrane functions, are precursors to eicosanoids, and which also cannot be totally synthesized de novo in mammals; (3) tissue levels of the n-6 and n-3 PUFA decline markedly

when the parent PUFA are absent from the diet, but increase after PUFA supplementation. Together, these reasons are valid for designating crucial individual n-6 and n-3 PUFA as 'essential' but which PUFA truly qualify and when?

Although most PUFA are C_{18-22}, C_{24} fatty acids in these two families appear to be required for the synthesis of key membrane PUFA such as docosahexaenoate (22 : 6n-3; Sprecher et al. 1995). Other n-6 and n-3 PUFA up to C_{36} have also been reported (Suh et al. 1996; van Pelt et al. 1999). All these fatty acids are commonly described as essential fatty acids, so this term has gradually become more widely used and is now very loosely applied to at least twenty-three interlinked fatty acids in the n-6 and n-3 PUFA families (Table 1).

There are some important ambiguities and anomalies that arise when an entire interconvertible family of fatty acids is designated as dietarily essential:

1. the longer-chain more-unsaturated PUFA are traditionally thought of as the products, and linoleate and α-linolenate as the precursors. However, the products can be retroconverted to the precursors (Hansen & Jensen, 1986; Sprecher et al. 1995), so there is no longer a clear-cut unidirectional flow associated with this pathway;

2. although linoleate has a well-defined function in the skin that appears to be independent of conversion to long-chain n-6 PUFA, it is unclear whether α-linolenate itself is essential only as a precursor or also in its own right;

3. under certain conditions, particularly in early post-natal development, low tissue levels and symptoms of deficiency of longer-chain PUFA such as docosahexaenoate occur even if relatively high amounts of the parent PUFA (α-linolenate) are present in the diet (Farquharson et al. 1992; Makrides et al. 1994; Gerster, 1997; Birch et al. 1998). Indeed, the parent PUFA may cause substrate inhibition of long-chain PUFA synthesis, i.e. linoleate inhibits synthesis of arachidonate and α-linolenate inhibits synthesis of docosahexaenoate

(Lasserre *et al.* 1985; Ackman & Cunnane, 1991). This factor may contribute to inhibition of weight gain in infants when dietary docosahexaenoate is not present (Jensen *et al.* 1997). Hence, linoleate and α-linolenate cannot always fulfill, and can actually inhibit, their mandate as the essential parent fatty acids.

4. The longer-chain PUFA are frequently termed essential. Like linoleate and α-linolenate, the long-chain PUFA cannot be totally synthesized *de novo*, i.e. in the absence of any dietary or stored linoleate or α-linolenate. However, in the presence of dietary linoleate and α-linolenate, *n*-6 and *n*-3 long-chain PUFA can be synthesized by all mammals that have been studied and, apparently, at all ages from late fetal life to old age. Thus, strictly speaking, they are not essential. The issue revolves around whether there is sufficient capacity to synthesize the long-chain PUFA but the essential–non-essential terminology does not have room for conditional essentiality.

The gradual broadening of the definition of essentiality as more and more of the constituent fatty acids in these two families were discovered has created two problems. The first problem is that the issue of capacity to convert linoleate or α-linolenate to their respective longer-chain PUFA has become of secondary importance relative to the requirement for the longer-chain PUFA, because the whole family, precursors and longer-chain derivatives, are all currently designated as essential. However, capacity and requirement to convert parent to longer-chain PUFA are affected by many nutritional, metabolic and disease processes so the concept of capacity is central to the problem of defining dietary essentiality (see p. 806).

The second problem is that if some fatty acids are essential, by definition, the others become non-essential. Like essential, the term non-essential is widely used but is quite misleading, because both linoleate and α-linolenate are readily β-oxidized and their C-skeletons recycled into non-essential fatty acids. Thus, through *de novo* fatty acid and cholesterol synthesis, C recycling of essential fatty acids occurs in amounts that equal and sometimes markedly exceed their conversion to long-chain PUFA (Sheaff-Greiner *et al.* 1996; Menard *et al.* 1998; Cunnane *et al.* 1999*a*). This process occurs even at extremely deficient intakes of linoleate (Cunnane *et al.* 1998). Non-essential fatty acids such as palmitate rapidly re-accumulate in the body after fasting, but essential fatty acids such as linoleate

continue to be β-oxidized and depleted from body stores (Chen & Cunnane, 1993). Thus, one has the paradoxical situation of essential fatty acids being used as fuels or for the synthesis of non-essential fatty acids, even when the intake and body stores of at least one of the essential fatty acids (linoleate) are totally inadequate and gross symptoms of linoleate deficiency are present.

These problems with the loose definition of essential fatty acids (summarized in Table 2) inhibit a clear understanding of the relationships between their biochemistry, metabolism, nutritional importance and health implications. The intention of classifying fatty acids according to a dietary need is good in principle and works for a variety of other nutrients. The foregoing discussion was intended to illustrate why this principle may now be flawed for long-chain fatty acids with diverse and extensive metabolism.

A good example of the need to achieve a clearer understanding of the relationships between biochemistry, dietary essentiality and health implications of PUFA is the ongoing controversy about whether docosahexaenoate should be added to infant formulas made in the USA. This controversy stems in part from the contradiction of apparent dietary essentiality of a long-chain PUFA (docosahexaenoate) that can be synthesized in human infants and adults. However, if we acknowledge that the dietary essentiality (indispensability) of docosahexaenoate is conditional on developmental age and other variables, the apparent contradiction would largely disappear and the focus could shift towards understanding the conditions, and relating biological function and requirement to tissue levels of PUFA and other long-chain fatty acids in general.

Capacity to synthesize or conserve long-chain polyunsaturates

The variable capacity and need to convert linoleate or α-linolenate to the longer-chain PUFA is a central issue in proposing to change the term, essential fatty acids to conditionally-indispensable or conditionally-dispensable fatty acids. If, according to functional criteria, there was never sufficient capacity to synthesize arachidonate or docosahexaenoate, they would be indispensable (essential) fatty acids. However, if there was always adequate capacity to synthesize or conserve these two fatty acids, they would be dispensable (non-essential) fatty acids. If, under some conditions, there appeared to be a low or negligible risk of having inadequate tissue levels of arachidonate in healthy

Table 2. Summary of the reasons for proposing that essential fatty acids be reclassified as conditionally-dispensable or conditionally-indispensable fatty acids

1.	The term essential fatty acid applies non-specifically to at least twenty-three interconvertible fatty acids
2.	Symptoms of dietary deficiency of PUFA are conditional on age, nutrient intake and/or presence of disease
3.	Convincing but not absolute evidence suggests that α-linolenate alone is not always sufficient as the only dietary source of *n*-3 PUFA. Docosahexaenoate is therefore conditionally indispensable in the diet
4.	In healthy adults linoleate stores are equivalent to the intake for about 1 year. Thus, linoleate is probably conditionally dispensable for periods of weeks if not months
5.	Essential fatty acids are extensively but paradoxically used in the *de novo* synthesis of non-essential lipids (cholesterol and long-chain fatty acids)
6.	It is essential for the brain to endogenously synthesize two non-essential lipids (cholesterol and palmitate)

PUFA, polyunsaturated fatty acids.

adults, arachidonate would be considered to be conditionally-dispensable, because the capacity to synthesize and/or conserve this fatty acid appears sufficient under conditions of normal health or cessation of growth. In the old nomenclature, arachidonate would be non-essential in healthy adults.

Similarly, the wide-ranging benefits of balanced vegetarianism suggest that dietary docosahexaenoate is probably conditionally dispensable in healthy adults. If under some circumstances the capacity to synthesize docosahexaenoate is insufficient to sustain the accumulation of normal levels and results in a functional deficit, then it would be conditionally indispensable. The biochemical ability to make docosahexaenoate might reduce the dietary need for it, but could not make it dispensable if the capacity to synthesize or conserve this fatty acid appears insufficient under specific circumstances. Thus, docosahexaenoate almost certainly appears to be conditionally indispensable in infants under 2 years old who are not provided with dietary docosahexaenoate (Farquharson *et al.* 1992; Agostoni *et al.* 1995; Birch *et al.* 1998; Cunnane *et al.* 2000). Despite widespread scientific support for this concept, an expert committee has recommended continuing to exclude docosahexaenoate from infant formulas made in the USA (Raiten *et al.* 1998).

In this new context the emphasis shifts away from a definition of essentiality based on a fatty acid being derived from another fatty acid that cannot be synthesized *de novo*, towards determining the actual capacity and necessity for conversion, synthesis and/or conservation, as well as the functional outcomes that define deficiency or sufficiency. Unfortunately, and despite the long history of research into nutritional and health aspects of linoleate metabolism, functional outcomes of specific linoleate deficiency have only recently been described (Cunnane *et al.* 1998; see pp. 806–807). Hence, there is a lot of work to be done, starting with the re-evaluation the requirement for linoleate *per se*.

Measuring the capacity to convert parent PUFA to the long-chain PUFA is not easy, especially in man. Isotope studies using ^{13}C or ^{2}H clearly show conversion of the parent PUFA to the long-chain PUFA in infant and adult human subjects (Emken *et al.* 1992; Carnielli *et al.* 1996; Salem *et al.* 1996), but they do not show how much is converted, i.e. they do not show the percentage conversion or capacity of this pathway. Whole-body fatty acid balance studies in animals do provide percentage conversion data for animals (Cunnane & Anderson, 1997*a*). Even in growing animals maintained under controlled experimental conditions the biological variability in percentage conversion of linoleate or α-linolenate is relatively large. Non-invasive or autopsy-based measurement of PUFA balance in human subjects has been attempted in order to estimate their partitioning between storage, oxidation or conversion to long-chain PUFA, but reliable conversion estimates are not yet available (Cunnane *et al.* 1999*b*; Cunnane *et al.* 2000).

Synthesis of linoleate and α-linolenate

In considering the capacity to synthesize and conserve long-chain PUFA, we need to start with the parent PUFA.

Contrary to common belief, linoleate can be synthesized in rats (Sprecher, 1968; Cunnane *et al.* 1995) and man (Demmelmair *et al.*1997) by chain elongation from hexadecadienoate (16 : 2*n*-6). Hexadecadienoate is present at 1–2 % in common edible green vegetables, including broccoli and spinach (*Spinacia oleracea*). In tracer form, it is converted to linoleate in rats at a rate of about 3–4 % per 24 h. This appears to be a modest conversion rate but is equivalent to the rate of conversion of linoleate to longer-chain *n*-6 PUFA (Cunnane & Anderson, 1997*a*). Thus, hexadecadienoate reduces the dietary requirement for linoleate by a modest proportion.

Similarly, chain elongation of hexadecatrienoate (16 : 3*n*-3) contributes to synthesis of α-linolenate in mammals. Considerably more α-linolenate can be made from hexadecatrienoate because the latter is found in common edible green vegetables at up to 14 % total fatty acids (Cunnane *et al.* 1995). Thus, in predominantly vegetarian individuals and in sub-human species, hexadecadienoate and hexadecatrienoate may contribute appreciably to PUFA intake, and would decrease the dietary requirement for linoleate and α-linolenate *per se*.

In fact, tetradecadienoate (14 : 2*n*-6) and tetradecatrienoate (14 : 3*n*-3) are convertible to their respective C_{18-22} PUFA derivatives (Sprecher, 1968), but no known dietary sources of these C_{14} PUFA exist. Furthermore, arachidonate can be retroconverted to linoleate (Hansen & Jensen, 1986), which could also affect the dietary requirement for linoleate *per se*. Functionally, linoleate and α-linolenate remain the principal parent PUFA in the omnivorous human diet, and diets containing hexadecadienoate and hexadecatrienoate or arachidonate also contain linoleate and α-linolenate. Nevertheless, in estimating the conditional dispensability or indispensability of individual PUFA, especially in vegetarian diets, the potential contribution of the C_{16} precursors should not be overlooked.

Deficiency of linoleate *per se*

If the conditional dispensability–indispensability concept is to be more meaningful than the essential–non-essential fatty acid concept, it will be necessary to determine how linoleate utilization and hence, requirement varies with age, disease, and other factors. Unfortunately, the nutritional requirement for linoleate *per se* has never been defined in animals or man. This surprising situation has arisen because the relevant deficiency studies have always used diets deficient in both parent essential fatty acids, i.e. both linoleate and α-linolenate, or even in total fat. Low α-linolenate intake attenuates the symptoms of linoleate deficiency (Hansen & Jensen, 1983; Bourre *et al.* 1990). The absence of α-linolenate from diets deficient in linoleate, i.e. classical essential fatty acid deficiency, exacerbates linoleate deficiency (Cunnane & Anderson, 1997*b*; Table 3). Thus, the actual requirement for linoleate itself remains unknown, and is probably lower than is believed at present.

Essential fatty acid deficiency has always been the model used to study linoleate deficiency (Aaes-Jorgensen, 1961; Holman, 1971). Before our recent report there appears to

Table 3. Effect of classical essential fatty acid (EFA-D) and total dietary fat (FAT-D) deficiencies on growth inhibition and triene: tetraene in the rat; comparison with the effect of specific linoleate deficiency set at a reference value of 100 % (from Trotti, 1998)*

	EFA-D	FAT-D
Growth inhibition	159	176
Triene:tetraene (20 : 3n-9/20 : 4n-6):		
Testes	158	292
Heart	338	238
Liver	144	138
Skin	184	ND
Brain	280	ND

ND, not determined.

* Both growth inhibition and the rise in the triene:tetraene are less severe in specific linoleate deficiency than in either EFA-D or FAT-D, which have been the traditional but non-specific methods of inducing specific linoleate deficiency. Hence, when establishing linoleate requirements EFA-D and FAT-D should not be used as a substitute for specific linoleate deficiency.

have been no previous published work describing the dietary deficiency of linoleate in animals provided with adequate amounts of α-linolenate and oleate. Oleate is of interest because rats cannot synthesize sufficient oleate to maintain 'normal' tissue levels when given an oleate-free diet (Bourre *et al.* 1997). Dietary absence of both oleate and α-linolenate probably increases β-oxidation of linoleate stores in the body because all three fatty acids are relatively easily β-oxidized (Leyton *et al.* 1987; Gavino & Gavino, 1991; Cunnane *et al.* 1999*a*). Furthermore, oleate is the main dietary fatty acid and is present in all diets. As a precaution and to minimize unnecessary differences from 'normal' diets, oleate should always be present in experimental diets.

Diets used to induce essential fatty acid deficiency may contain saturated fat (usually from coconut oil or hydrogenated vegetable oil, or beef tallow), but many diets have also been fat-free. Apart from the fact that a fat-free diet grossly distorts the usual range of macronutrient ratios and hydrogenated fats are poorly absorbed (both of which may affect linoleate metabolism), α-linolenate and linoleate have distinctly different functions, but similar metabolism. Hence, it is inappropriate to study a combined deficiency of linoleate and α-linolenate as a model for determining linoleate requirements. Regrettably, this procedure has been used for 70 years.

The crucial distinction between linoleate deficiency *per se* and combined linoleate and α-linolenate deficiency (essential fatty acid deficiency) appears to be largely one of degree; gross symptoms and changes in fatty acid profiles in specific linoleate deficiency are considerably less severe than those in essential fatty acid deficiency (Cunnane & Anderson, 1997*b*; Table 3). By inference (because the studies have not been carried out yet), if the symptoms of the deficiency are less severe in specific linoleate deficiency, the amount of dietary linoleate needed to correct the deficiency symptoms is also probably less than that needed in the combined deficiency. Hence, the dietary requirement for linoleate is probably lower than is currently believed (2 % energy intake).

Overt *v.* subclinical deficiency of α-linolenate

α-Linolenate cannot be synthesized *de novo* in mammals but, interestingly, it is relatively difficult to induce *n*-3 PUFA deficiency experimentally. Scrupulously low dietary *n*-3 PUFA levels are required over long periods, and even then the symptoms in experimental animals are relatively mild, mainly involving vision, behaviour and cognitive development (Lamptey & Walker, 1976; Neuringer *et al.* 1984; Bourre *et al.* 1989; Weinsinger *et al.* 1996). It has been more difficult to obtain reproducible symptoms of α-linolenate deficiency in human subjects than in experimental animals (Holman *et al.* 1982; Bjerve *et al.* 1988). The difficulty of obtaining consistent results in studies of *n*-3 PUFA deficiency in human subjects probably accounts, at least in part, for the fact that except in Canada and the Nordic countries α-linolenate is not officially recognized as an essential (or even conditionally-indispensable) dietary nutrient.

Despite the difficulties experienced in inducing experimental *n*-3 PUFA deficiency, several studies point to subclinical deficiency of α-linolenate as a significant risk factor for heart disease, cancer and possibly impaired neurological function in infants and adults (Dolecek, 1992; Crawford, 1993; Bougnoux *et al.* 1994; Cunnane, 1995; Hibbeln *et al.* 1997; Horrobin & Bennett, 1999; Hu *et al.* 1999). These studies of disease risk suggest that significant portions of the adult population in North America and Europe are at risk of inadequate α-linolenate intake. The requirement for α-linolenate of adults is thought to be about 1 g α-linolenate/d, which is approximately equal to the dietary intake in North America (Hunter, 1990). Thus, 50 % of the population appear to be getting sufficient α-linolenate, but 50 % are not.

Dietary intake data in North America therefore support the concern about insufficient intake of α-linolenate, but biochemical or molecular mechanisms by which α-linolenate would affect chronic disease risk are still poorly understood. α-Linolenate may act by conversion to eicosapentaenoate, or even to docosahexaenoate, but the rate of conversion (especially to docosahexaenoate) appears to be very slow in adults (Cunnane, 1995; Gerster, 1997). Although there is little agreement between studies (Cunnane, 1995), α-linolenate may have similar efficacy to the long-chain *n*-3 PUFA on variables such as platelet aggregation (Freese & Mutanen, 1997), and therefore may not need to be converted to long-chain *n*-3 PUFA.

Is α-linolenate indispensable? I would say no, for several reasons. First, diets containing sufficient eicosapentaenoate and docosahexaenoate could probably be free of α-linolenate without incurring an increased risk of α-linolenate deficiency or chronic disease risk, i.e. there is little or no evidence to suggest that α-linolenate has unique functions when eicosapentaenoate and docosahexaenoate are present in the diet. Second, eicosapentaenoate and docosahexaenoate can both be retroconverted to α-linolenate (Sprecher *et al.* 1995), and both reduce the increased risk of the chronic diseases associated with low α-linolenate intake (Kromhout *et al.* 1985; de Lorgeril *et al.* 1994). Third, α-linolenate appears to be insufficient to

meet *n*-3 PUFA requirements in infancy (Cunnane *et al.* 2000).

Admittedly, it would be unusual to have a diet that is deficient in α-linolenate but which contains eicosapentaenoate and docosahexaenoate, although not impossible (e.g. diets rich in fish but devoid of green vegetables, soyabean products, nuts and grains). In my view, α-linolenate should be classified as conditionally indispensable because, unlike for linoleate, there are not many realistic conditions that would make it conditionally dispensable. In addition, unlike linoleate, α-linolenate is not extensively stored in body fat.

Making a distinction between essential and conditionally indispensable for a fatty acid such as α-linolenate is not just semantic. Rather, it acknowledges the complexity of the relationship between the biochemical conversions, changing nutritional requirements with age, and health implications of these fatty acids. Being conditionally indispensable instead of indispensable or even essential does not make α-linolenate any less important for health, but it places this importance in the context of the derived long-chain *n*-3 PUFA as well as the extensive β-oxidation and C recycling of α-linolenate.

Can epidemiological and dietary intake data substitute for experimental deficiency in providing a functional outcome on which to base conditional indispensability or dispensability of a fatty acid such as α-linolenate; if so, how does one apply this information on an individual basis? Conversely, if plasma fatty acid profiles appear normal, can one assume that functional variables are going to be normal, or that, conversely, risk of degenerative diseases is minimal? What is the appropriate reference range for 'normal' fatty acid profiles? Do we need 10-year studies of cognitive development, or cancer or cardiac death records as the ultimate functional outcome? These questions are challenging, but we need to try to respond to them if we are to learn the true biological importance of PUFA in mammals. If indeed inadequate intake of a fatty acid such as α-linolenate (or the long-chain *n*-3 PUFA) is fundamentally linked to the risk of chronic degenerative diseases that affect morbidity and mortality, this challenge becomes an opportunity to reduce that risk and improve health accordingly.

Unlike the situation for α-linolenate, there does not appear to be a significant risk of inadequate linoleate intake in most of the population of Westernized countries. An excessive intake of linoleate may actually be a contributing factor to the possible inadequacy of α-linolenate intake (Ackman & Cunnane, 1991; Arbuckle *et al.* 1994). Thus, although both linoleate and α-linolenate are the principal parent PUFA in the diet, it seems more realistic to designate linoleate as conditionally dispensable but α-linolenate as conditionally indispensable.

Functional outcomes or fatty acid profiles

Determining conditions under which fatty acids are conditionally indispensable or conditionally dispensable necessitates valid reproducible functional measures of adequacy or inadequacy. Traditionally, functional measures of overt dietary deficiency of α-linolenate have been

difficult to obtain, and require extreme deficiency over extended periods. Our recent report suggests that functional measures of overt specific linoleate deficiency *per se* develop slowly, even in young growing rats (Cunnane & Anderson, 1997*b*). This slow process takes place despite the fact that young rats have a relatively high dietary requirement for linoleate compared with more mature animals, and when made specifically linoleate-deficient they have markedly depleted tissue levels of *n*-6 PUFA (Cunnane *et al.* 1998).

Using a diet providing no oleate but containing α-linolenate, Bourre *et al.* (1990) demonstrated that 4 g linoleate/kg diet was sufficient for normal growth and reproduction in rats. In this study, a plateau in *n*-6 PUFA profiles in tissues was not reached until 12 g linoleate/kg diet was provided. Growth, skin condition and reproduction are functional outcomes dependent on linoleate adequacy and were widely used in early research into linoleate requirements (Aaes-Jorgensen, 1961; Alfin-Slater & Aftergood, 1968). Which criterion is more appropriate, functional outcomes or a plateau in the relevant fatty acids in tissues?

In my view tissue and plasma fatty acid profiles are a poor indicator of linoleate or α-linolenate adequacy or inadequacy, because there is no implicit reason why a plateau in a specific fatty acid demonstrates that a required fatty acid intake has been achieved. Rather, a plateau in the proportional fatty acid data reflects only the maximum amount of that fatty acid that can be accommodated in that tissue under those conditions. For these reasons, the commonly accepted dietary linoleate requirement of about 10 g linoleate/kg diet (2 % energy intake), which was based more on fatty acid profiles than functional outcomes but also incorporated a flawed dietary design (essential fatty acid deficiency), is probably an overestimate.

In fact, it is quite difficult to induce linoleate deficiency in adult animals or human subjects who are in energy balance. This situation is partly due to the typically slow turnover of linoleate stores relative to the rate of utilization of linoleate or relative to linoleate intake (Hirsch *et al.* 1960), and partly due to the substantial storage capacity for linoleate. In healthy adults linoleate stores are approximately 1500–2000 g, which is equivalent to the average intake for about 1 year (Cunnane *et al.* 1999*b*). Thus, it seems reasonable to suggest that a regular dietary supply of linoleate is not essential in this situation, i.e. that linoleate is conditionally dispensable for periods of weeks, perhaps months, in non-pregnant non-lactating healthy adults in energy balance. Chronic sickness or undernutrition affecting food intake or inducing weight loss would increase linoleate β-oxidation, which could easily exceed linoleate intake (Parsons *et al.* 1988; Chen & Cunnane, 1993; Cunnane & Yang, 1995). These would represent situations in which linoleate would become conditionally indispensable.

Fatty acid profiles of blood or tissues may be useful as biochemical measures of linoleate or α-linolenate deficiencies. These profiles also demonstrate some correlation with functional variables such as insulin action, membrane fluidity and enzyme activity (Spector & Yorek, 1985;

Salem *et al.*1996). Nevertheless, the relationship between fatty acid profiles and functional variables is still poorly understood. This situation makes it experimentally challenging to assess the functional difference between conditional indispensability and conditional dispensability, and the possible transition between these two states. However, this research and the improvement in clarity it will afford are necessary to understand the function of, and requirements for, individual PUFA.

β-Oxidation and carbon recycling into *de novo* lipid synthesis

Recent studies describing the significant degree to which linoleate is β-oxidized and its C-skeleton is recycled into *de novo* lipid synthesis raise another issue about the essentiality of linoleate or α-linolenate; are they essential as precursors to the synthesis of non-essential fatty acids? This question is not as unreasonable as it might seem at first. When consumed at the apparent requirement level for linoleate, rats β-oxidize about 70 % of the linoleate intake under normal growth conditions (Cunnane & Anderson, 1997a; Cunnane *et al.* 1998). In rats and human subjects, the rate of α-linolenate β-oxidation is probably as high, or possibly higher than, that of linoleate (Gavino & Gavino, 1991; U McCloy and SC Cunnane, unpublished results).

Of the linoleate which is β-oxidized, rats recycle a similar percentage (20–30) into *de novo* lipid synthesis to that used to make arachidonate, even during extreme linoleate deficiency (Cunnane *et al.* 1998; Trotti, 1998). Hence, even under conditions in which dietary and body stores of linoleate are severely compromised, a tracer dose of [^{14}C]linoleate is extensively recycled into cholesterol and non-essential fatty acids. These data show that recycling of PUFA-C into non-essential fatty acids is probably obligatory, i.e. it always happens regardless of nutrition or disease status. This situation (making non-essential from essential fatty acids) is a confusing and unnecessarily implausible consequence of these traditional but inaccurate descriptors.

In neonatal rats the amount of tracer α-linolenate used for *de novo* lipid synthesis exceeds that used for synthesis of brain docosahexaenoate by up to 20–40-fold (Menard *et al.* 1998). In fact, about 30 % of the docosahexaenoate itself is recycled into *de novo* lipid synthesis (Sheaff-Greiner *et al.* 1996). In rats that have been fasted and then refed a normal chow diet, linoleate and α-linolenate levels in tissues continue to decline even during refeeding, while body levels of palmitate, stearate and oleate increase because fatty acid synthesis is stimulated under these conditions (Chen & Cunnane, 1993). Clearly, substrates other than linoleate or α-linolenate are used in fatty acid synthesis, but both these PUFA can be avidly used for this purpose. Hence, under a variety of conditions, recycling of essential fatty acids into non-essential fatty acids is a quantitatively significant and apparently obligatory pathway.

It is very difficult to retain the essential–non-essential terminology without asking the paradoxical question: is one of the essential features of essential fatty acids that they be used in some circumstances to make fatty acids that are non-essential? This position is clearly speculative, but data are emerging that support this concept. Whether the animal data can be substantiated in human studies also awaits further study. Nevertheless, by eliminating the essential–non-essential terminology, one pushes the discussion beyond the apparent implausibility of significant conversion of essential to non-essential fatty acids towards asking why recycling of the C skeleton of PUFA occurs, whether some PUFA are excluded, whether this pathway of PUFA metabolism exceeds recycling of saturated and monounsaturated long-chain fatty acids, and what its potential biological relevance may be.

Structural, metabolic or dietary requirement

Essentiality is a concept that, strictly speaking, only applies to compounds that are regularly needed in the diet. However, the essential structural role in membranes of fatty acids that can or cannot be synthesized frequently encroaches on this limited definition. This reason is one that has already been discussed for changing the definition of essential fatty acids. However, there is a further reason for raising this issue. There is no doubt about the metabolic requirement for glucose or the structural requirement in membranes for cholesterol, even though the body readily synthesizes each of these compounds. Indeed, one could argue that the body produces the most essential compounds as needed, thereby avoiding the potential vagaries of the diet.

Cholesterol is interesting in this context because, regardless of the level of cholesterol in the diet, the brain does not import exogenous cholesterol (Edmond *et al.* 1991; Jurevics & Morell, 1995; Turley *et al.* 1996); it is obliged to synthesize its own cholesterol, and has the biochemical capacity to do so. Cholesterol is quantitatively the most important lipid in the brain (Sastry, 1985) and is intimately linked to normal brain development and neurological function (Chiang *et al.* 1996; Porter *et al.* 1996; Salen *et al.* 1996). These functions of cholesterol are as essential to mammalian existence as any functions that are provided by fatty acids that are dietarily essential, yet cholesterol is deemed non-essential and, ironically, dietary cholesterol is inaccessible to the brain. Three non-essential fatty acids are also inaccessible to the brain from the diet (palmitate and stearate and oleate; Edmond *et al.* 1998), but are all present in relatively high proportions in neuronal lipids. As with cholesterol, the brain's capacity to synthesize palmitate, stearate and oleate is sufficient to meet its own needs.

Hence, the presence or absence of cholesterol, palmitate, stearate or oleate in the diet appears irrelevant to the brain, a situation which would make these lipids dietarily non-essential yet, structurally, they are essential to the brain. This apparently unique situation of the brain's lipid requirements being partially independent of dietary sources or hepatic synthesis implies that endogenous synthesis in the brain is needed to control availability of these lipids, and that dietary sources are not sufficiently reliable. This situation is directly opposite to our current definition of essential fatty acids, a paradox that argues against defining essentiality as a dietary attribute alone.

Table 4. Reclassification of some essential polyunsaturated fatty acids (PUFA) as conditionally dispensable and conditionally indispensable at various stages during the lifespan*

Infancy, childhood, pregnancy and lactation		Adulthood (>20 years)	
Conditionally dispensable	Conditionally indispensable	Conditionally dispensable	Conditionally indispensable
Eicosapentaenoate†	Linoleate	Linoleate	α-Linolenate‡
	α-Linolenate	Arachidonate	
	Arachidonate	Eicosapentaenoate†	
	Docosahexaenoate	Docosahexaenoate	

* Since there is much information on the dietary need for PUFA during early development, a distinction is shown between infants and adults. Adolescence is omitted due to lack of sufficient data. Further research is needed to more fully identify the conditions (nutrient deficiencies such as Zn) and diseases (cystic fibrosis, Zellweger syndrome) in which conditionally-dispensable fatty acids become indispensable in the diet.

† Included with eicosapentaenoate are other intermediate PUFA, i.e. γ-linolenate, dihomo-γ-linolenate, n-6 docosapentaenoate n-3 docosapentaenoate, and also $C_{<18}$ PUFA and $C_{>22}$ PUFA.

‡ α-Linolenate is listed as conditionally indispensable in adults due to its role in mitigating risk of chronic killer diseases, even though the specific mechanism is unknown.

Conclusion

The conditionally indispensable–dispensable concept has already been tested and widely accepted in the amino acid field. Amino acids previously termed as essential are now termed as indispensable or conditionally indispensable. This reclassification surrenders no useful information about these amino acids, but helps clarify the transitory nature of the dietary need for some amino acids and the unchanging dietary need for other amino acids.

There are important but conditional reasons for including long-chain PUFA in the diet that depend mostly on a limited capacity for their synthesis and conservation relative to rate of tissue incorporation or utilization. The obvious need for several dietary PUFA in young animals and lower, even questionable, dietary requirement in adults was recognized 40 years ago (Aaes-Jorgensen, 1961). I am aware of no situation in which the absence of any single PUFA from the diet results in reproducible symptoms at all ages, and after a relatively short absence from the diet so I suggest that no PUFA are truly indispensable. As with some amino acids, some long-chain fatty acids such as palmitoleic acid (16 : 1n-7) are probably dispensable, although this possibility has not been fully evaluated experimentally.

Accordingly, the full spectrum of possibilities for long-chain fatty acids would be: dispensable; conditionally dispensable; conditionally indispensable. As argued throughout the present paper, I believe that no essential fatty acids are excluded by the two categories, conditionally dispensable and conditionally indispensable (Table 4). Epidemiological studies on chronic disease risk strongly endorse a dietary need for α-linolenate, but such diets are also usually low in eicosapentaenoate and docosahexaenoate; therefore, while at least one member of the n-3 PUFA family is conditionally indispensable, in terms of chronic disease risk in otherwise healthy adults, this requirement can probably be met by any member of the family.

Other PUFA, particularly arachidonate and docosahexaenoate, serve structural functions in membranes throughout the lifespan. However, vegetarian adults can probably remain healthy without consuming them; therefore, I suggest that arachidonate and docosahexaenoate are conditionally dispensable in adults, but conditionally indispensable throughout pregnancy to adolescence (at least up to 10 years old; Table 4). When dietary energy is not limiting, linoleate is usually abundant and readily stored in the body, especially in healthy adults (>20 years old). As with arachidonate, docosahexaenoate and probably all the other intermediate PUFA, I suggest that linoleate is conditionally dispensable after adolescence. Disease and nutritional deprivation potentially change the conditions and may make some or all these PUFA conditionally indispensable.

The present reclassification serves the purpose of identifying the conditional nature of the dietary essentiality of all PUFA, something that most researchers scientifically involved in the field inherently recognize and understand, but which is not yet reflected in the nomenclature for these fatty acids. Essential fatty acid is a broad and simple term, but I believe it has outlived its usefulness and should be abandoned. Equally broad but more appropriate terms that are suitable for the non-specialist include PUFA, n-6 PUFA or n-3 PUFA. It is often possible to be more specific than PUFA, because 'PUFA-enriched' or 'high polyunsaturated:saturated fatty acid' diets are almost always only enriched in linoleate; this fact can and should be stated more explicitly since it is more correct and more informative.

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