

**BIOCHEMICAL ANOMALIES IN PEOPLE WITH IRLLEN SYNDROME:
OVERLAPPING DIAGNOSTIC CATEGORIES, IMMUNE SYSTEM
DYSFUNCTION AND DIETARY INTERVENTION**

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Visual Processing Problems and Dyslexia

Visual processing problems in people with dyslexia is becoming a more accepted area of research, with most authorities accepting the possibility of at least some degree of visual impairment in large numbers of people with dyslexia (Booth, Perfetti, MacWhinney, & Hunt, 2000; Skottun, 2000; Stein, 2001; Wilkins & Lewis, 1999). One area of investigation has centred upon the proposal by Irlen (1991) of a specific visual-perceptual dysfunction, which has been called Irlen Syndrome (IS) or visual discomfort (Conlon, Lovegrove, Chekaluk, & Pattison, 1999), and is unrelated to skills normally assessed by an optometric examination (Evans, Wilkins, Busby, & Jeanes, 1996; Scott, McWhinnie, Taylor, Stevenson, Irons, Lewis, et al., 2002). Symptoms of IS include a blurring and shadowing of letters and words, a doubling, merging or movement of print, eye strain and fatigue, a restricted span of focus and problems focussing for an extended period of time (Irlen, 1991; Meares, 1980).

There have been a number of explanations of the described symptoms, which relate to retinal malfunction. Grosser and Spafford (1990) identified extra peripheral retinal cones in subjects with dyslexia, which was hypothesised to lead to letter images in peripheral vision competing with letter images in central vision. Irvine and Irvine (1997) suggested a variety of possible retinal abnormalities for people with symptoms of IS, including signal interference between adjacent receptor cells and abnormalities in receptor distribution. Carrol, Mullaney, and Eustace (1994) found an alteration in dark adaptation in subjects with dyslexia in areas away from central retinal area (fovea) although Greatorex, Drasdo, and Dresser (2000) did not find alteration in dark adaptation in a group of adults with dyslexia.

It has also been hypothesised that the identified symptoms could be related to a deficit in the magnocellular visual neurological pathway (Demb, Boynton, Best, & Heeger, 1998; Eden, Van Meter, Rumsey, Maisog, Woods, & Zeffrio, 1996), which may cause an overlapping of visual images between consecutive eye fixations when reading (Boden & Brodeur, 1999; Solman, Cho, & Dain, 1992; Williams & Lovegrove, 1992). Magnocellular activation may be involved in suppressing the potential overlap of images between consecutive eye fixations (which could be related to saccadic suppression), as well as playing an important part in keeping the two eyes steadily fixed on each word (Stein & Talcott, 1999). Stein (2000, 2001) suggests that symptoms are not caused by the superimposing of visual images between successive eye fixations, but by poor motion sensitivity and unstable binocular control. He stated that during eye fixations while reading, the eyes move around by up to one degree of visual angle (4-5 letters) and claimed that in normal readers, the visual magnocellular system detects such unintended motion and this signal is used to help stabilise the eyes. Stein (2000, 2001) describes a series of investigations which indicate that dyslexics have poor visual motion sensitivity, which in turn correlates strongly with their reading ability, spelling ability and visual orthographic skills. Stein and Talcott (1999) further claim that such problems could lead to reports of words moving around the page and appearing to merge, as is reported by people with symptoms of IS (see Irlen, 1991). Evans and colleagues (Evans, Drasdo, & Richards, 1994; Evans, Busby, Jeanes, & Wilkins, 1995; Evans, Patel, Wilkins, Lightstone, Eperjesi, Speedwell, & Duffy, 1999) and Robinson and Foreman (1999a) found a higher incidence of binocular instability and eye movement problems in people with symptoms of IS. Studies have also reported positively on the effect of coloured filters for people with IS who had eye movement problems (Evans et al., 1999; Robinson & Foreman, 1999a; Tyrrell, Holland, Dennis, & Wilkins, 1995). Evans et al. (1999) reported improvement with the use of coloured filters, despite conventional optometric intervention (spectacles, orthoptic exercises). Robinson and Foreman (1999a) and Tyrrell et al. (1995) also reported improved performance in eye movement tasks with the use of coloured filters. Simmers, Gray, and Wilkins (2001) found that accommodation microfluctuations were significantly greater for subjects when they were not wearing their prescribed coloured filters.

There have been a number of investigations which support the magnocellular deficit hypothesis. Some studies have identified a diminished or delayed visual evoked potential for poor readers along the magnocellular pathway in response to moving stimuli (Brannan, Solan, Ficarra, & Ong, 1998; Kubova, Kuba, Peregrin, & Novakova, 1996; Livingstone, Drislane, & Galaburda, 1991). Livingstone et al. (1991) found that magnocellular neurons in the lateral geniculate nucleus of post mortem dyslexic brains were smaller and more disorganised than in control brains. The indications of poor motion sensitivity identified by Stein (2000, 2001) have been supported by functional imaging studies (Eden et al., 1996; Demb, Boynton, & Heeger, 1998). Both of these studies found a reduced activation of the V5/MT area of the visual cortex, which is sensitive to visual motion and is dominated by magnocellular input. Colour filtering is claimed to influence the functioning ability of the magnocellular pathway (Edwards, Hogben, Clark, & Pratt, 1996; Solman, Dain, & Keech, 1991; Williams, LeCluyse, & Littell, 1996), and has been reported to reduce symptoms of IS (Harris & MacRow-Hill, 1999; Robinson & Conway, 2000), improve eye movement (Evans et al., 1999; Robinson & Foreman, 1999b) and lead to changes in visual evoked potentials for people with symptoms of IS (Lewine 1999). Nicholson, Fawcett, Berry, Jenkins, Dean, and Brooks (1999) found dyslexics have decreased activation of the cerebellum during motor learning, including spelling and writing, and the cerebellum receives heavy magnocellular input and itself contains magnocells (Fawcett & Nicholson, 2001). The magnocellular deficit hypothesis, however, has been questioned, with claims that the magnocellular system is suppressed, not activated, during saccadic eye movements (Skottun, 2000; Skottun & Parke, 1999), and thus may not be responsible for saccadic suppression (Evans, 2000). These questions have

been responded to by Stein (see Stein, 2000; Stein, Talcott, & Walsh, 2000), who claims that impairment in the visual magnocellular system is mild and small subject numbers may contribute to inconsistencies in results. Stein further states that magnocellular impairment is not found in every person with dyslexia and as subjects were not screened to identify whether they had visual symptoms in many studies, many may not have had a magnocellular deficit.

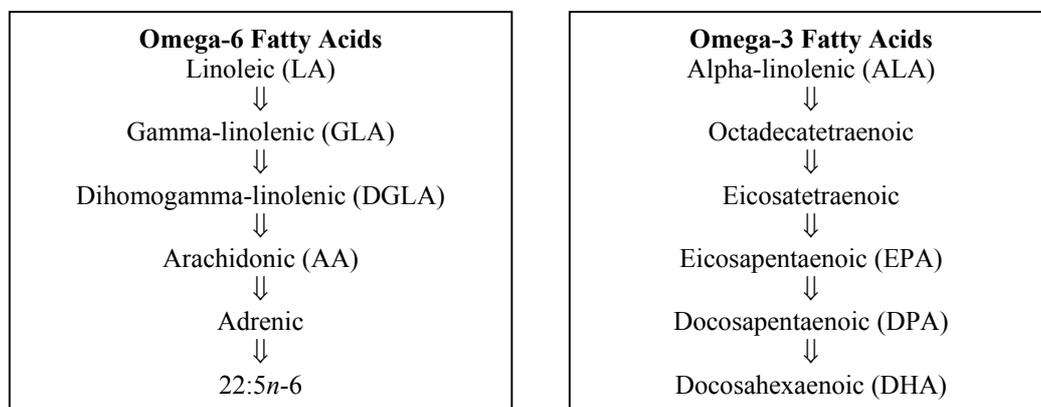
Numerous controlled studies have also reported improvements in reading with the use of coloured filters, although it should be emphasised that reported improvements in print clarity may assist learning to read, but are unlikely to lead to the development of word recognition skills without additional reading tuition (Kyd, Sutherland, & McGettrick, 1992; Robinson & Foreman, 1999b). These studies have reported improvements in reading when using coloured plastic overlays or coloured computer monitors (see Croyle, 1998; Jeanes, Busby, Martin, Lewis, Stevenson, Pointon et al., 1997; Scot et al., 2002; Tyrrell et al., 1995; Wilkins & Lewis, 1999; Wilkins, Lewis, Smith, & Rowland, 2001; Williams, Le Cluyse, & Littell, 1996), as well as improvements in eye strain, headaches and reading when using coloured lenses (see Chronicle & Wilkins, 1991; Evans, Patel, & Wilkins, in press; Good, Taylor, & Mortimer, 1991; Harris & MacRow-Hill, 1999; Irvine & Irvine, 1997; Lightstone, Lightstone, & Wilkins, 1999; Robinson & Conway, 2000; Robinson & Foreman, 1999a, b; Solan, Ficarra, Brannan, & Rucker, 1998). A number of studies have used placebo controls (see Bouldoukian, Wilkins, & Evans, 2002; Jeanes et al., 1997; Robinson & Foreman, 1999a; Wilkins, Evans, Brown, Busby, Wingfield, Jeanes, & Bald, 1994; Wilkins & Lewis, 1999).

While a large number of studies have found improvements in reading when using coloured filters, the causal basis for the described visual symptoms and reasons why coloured filters reduce these symptoms needs to be further investigated. One recent avenue of investigation has been a possible biological basis for the syndrome.

Visual Processing Problems and Fatty Acid Metabolism

A number of studies of abnormal fatty acid metabolism in people with dyslexia suggest that visual processing in particular may be affected. Long-chain highly unsaturated fatty acids (HUFA) are an important structural component of the eye and brain, and are required for normal functioning of the nervous system (Horrobin, 1999). There are two types of unsaturated fatty acids (omega-3 and omega-6), and both can usually be converted from essential fatty acids (EFA) to HUFA from the EFA precursors linoleic and alpha-linolenic acid (Figure 1). Four of these EFAs are particularly important; two in the omega-6 series (Dihomogamma-linolenic acid DGLA and Arachidonic acid AA) and two in the omega-3 series (Eicosapentaenoic EPA and Docosahexaenoic DHA). These four EFAs make up 15% to 30% of the dry weight of neuronal and retinal tissue, with AA and DHA being 80% to 90% of that total (Horrobin, 1999). Essential fatty acids play a primary role in most cell signalling systems in the neurones and are fundamental to neuronal structure, growth, remodelling and function. The key EFAs need to come from diet, either directly or via conversion of Linoleic acid (LA) and Alpha-Linolenic acid (ALA) as humans lack the ability to synthesise these fatty acids (Holman, 1992). If they are not available, they may be replaced by less desirable fatty acids (Horrobin, 1999). There are a variety of factors which may interfere with the conversion of EFA to HUFA, including stress, which reduces the rate of formation of AA and DHA from dietary precursors (Brenner, 1981; Horrobin, 1990), and viral infection, which can also inhibit the formation of AA and DHA (Chandrabose, Cuatrecasas, Pottahil, & Lang, 1981). There are also sex differences, with females converting LA and ALA more rapidly than males (Horrobin, 1999).

Figure 1
Pathways for Synthesis of Omega-3 and Omega-6 Fatty Acids *



* Adapted from Sinclair, H.M. (1990). History of essential fatty acids. In H.M. Sinclair (Ed.), *Omega-6 essential fatty acids: Pathophysiology and roles in clinical medicine*. (pp.1-20). NY: Alan R. Liss Inc.

There is evidence of an association between dyslexia and abnormal fatty acid metabolism (Horrobin, Glen, & Hudson, 1995; MacDonnell, Skinner, Ward, Glen, Glen, McDonald et al., 2000; Rae, Lee, Dixon, Blamire, Thompson, Styles et al., 1998; Richardson, Cox, Sargentoni, & Puri, 1997). The study by Richardson et al. (1997), using ³¹P phosphorous magnetic resonance spectroscopy, identified an irregularity in cerebral lipid membrane turnover in people with dyslexia, suggesting a problem in synthesis of membrane phospholipids. Rae et al. (1998) identified significant metabolic anomalies in males with symptoms of dyslexia in the left temporal lobe and right cerebellum. MacDonnell et al. (2000) found abnormally high levels in people with dyslexia of an enzyme, cytosolic phospholipase A₂ (PLA₂), which is part of a metabolic cycle that strips fatty acids from cell membranes, generating free fatty acids and then reincorporating these fatty acids into cell membranes. This anomaly is consistent with increased fatty acid breakdown and suggests such people may process fatty acids in an unusual way.

There have also been reports that high scores on a scale designed to assess signs of EFA deficiency were related to indications of visual processing problems in dyslexia, in both adults and children (Richardson, Calvin, & Clisby, Schoenheimer, Montgomery, Hall et al. 2000; Richardson, Easton, McDaid, Hall, Montgomery, Clisby, & Puri, 1999; Taylor, Higgins, Calvin, Hall, Easton, McDaid et al., 2000; Wilmer & Richardson, 2001). Richardson et al. (1999) found that high signs of EFA deficiency were significantly correlated with visual symptoms when reading and the checklist used to identify visual symptoms had many indicators of IS, including headaches, eye strain, blurring, movement and pulsation of print, light sensitivity and a haloing effect around words (Irlen, 1991). Richardson et al. (2000) found children with a high level of clinical signs of fatty acid deficiency had significantly poorer reading, and the severity of clinical signs was strongly correlated with visual problems, motor problems and visual symptoms when reading (all of which are reported by subjects with symptoms of IS). Wilmer and Richardson (2001) also identified substantial positive associations between self-reported signs of fatty acid deficiency and a scale assessing typical dyslexic visual and motor symptoms in normal college students. These studies of clinical signs of dyslexia accord well with an earlier single case study by Baker (1985) which identified similar clinical signs, found they were validated by a biochemical analysis of blood, and reported benefits from fatty acid dietary supplementation. Stein (2000, 2001) suggests that efficient magnocellular functioning is dependent upon HUFAs and a deficiency may compromise magnocellular response.

Visual Processing Problems and Fatty Acid Supplementation

There has been some evidence to suggest that supplementation with essential fatty acids may improve retinal and neural function and retinal and neural (magnocellular) dysfunction have been implicated as possible causes of dyslexia (Brannan et al., 1999; Pammer, 2000) and as possible causes of IS (Irvine & Irvine, 1997; Lewine, 1999). The retina contains the highest level of DHA of any organ in the body (Stone, Farnsworth, & Dratz, 1979). Highly unsaturated fatty acids, especially DHA have been found to improve maturation of rod photoreceptor function and visual acuity (Birch, Birch, Hoffman, & Uauy, 1992; Neuringer et al., 1994), as well as influencing neuronal growth cones (Auestad & Inness, 2000). The delivery of DHA is also important for the development of mature synapses (Willatts & Forsythe, 2000), with long chain polyunsaturated acids also showing a significant advantage for visual attention and problem solving (Willatts & Forsythe, 2000). A number of studies have found that DHA is important for normal retinal development in humans (Birch, Hoffman, Uauy, Birch, & Prestidge, 1998; Horrocks & Yeo, 1999). Lee, Jiao, Hetjancik, Kaiser-Kupfer, and Chader (1998) also found that a degenerative retinal disorder, Bietti Crystalline Dystrophy, which involves progressive night blindness and restriction of visual fields, is linked to the lack of a fatty acid binding protein related to omega-3 fatty acids. Taylor and Richardson (2000) hypothesise that a lack of fatty acids may influence foetal neural development, and that a severe deficiency in relevant HUFAs in the mother's diet is likely to starve the foetus of materials needed for development, with the large (magnocellular) neurons more likely to be vulnerable. In particular, DHA was claimed to be more likely to optimise the signalling sensitivity of the neural pathway at the retinal level. Visual evoked potentials in infants in particular may be enhanced by the use of fatty acids (Birch, Garfield, Hoffman, Uauy, & Birch, 2000; Makrides, Neumann, Summer, Pater, & Gibson, 1995), with evidence that the maturation of visual evoked potentials may be faster in infants whose infant formula is supplemented with fatty acids (Faldella, Govoni, Alessandroni, Marchiani, Salvioli, Biagi et al., 1996). Photoreceptors seem to be enriched by DHA and AA (Nourooz-Zadeh & Periera, 1999), with photoreceptor cells in humans having the highest AA and DHA content (Stone, Farnsworth, & Dratz, 1979).

A number of studies have investigated the association between fatty acid supplementation and visual processing problems in dyslexia. Stordy (1995) identified poor dark adaptation among adults and children with dyslexia, as has also been found in subjects with symptoms of IS (Carroll et al., 1994). The dietary essential fatty acid intake of subjects with symptoms of dyslexia was lower than symptom-free family members, and dietary supplementation normalised dark adaptation within one month. Dark adaptation is known to be a function of retinal rods, which require high levels of DHA and AA for normal structure and function (Neuringer, Reisbick, & Janowski, 1994). However, the association between dark adaptation, dyslexia and fatty acid supplementation has been questioned. Greatorex, Drasdo, and Dresser (2000)

assessed dark adaptation in young adults with dyslexia and found they had normal dark adaptation curves, similar scotopic threshold responses and similar suprathreshold responses using an electroretinogram. Aguire, Ackland, Maude, and Anderson (1997) claim that while a deficiency in DHA can occur with rod-cone degeneration, their study found that a diet enriched in DHA failed to correct the degeneration.

Visual Processing Problems and Biochemical Anomalies in Chronic Fatigue Syndrome

Biochemical anomalies have been identified in people with chronic fatigue syndrome (CFS) and the range of symptoms identified for this disability include visual problems and fatigue, which have been reported by subjects with symptoms of IS. McGregor, Dunstan, Zerbes, Butt, Roberts, and Klineberg (1996a, 1996b), and McGregor, Dunstan, Butt, Roberts, Klineberg, and Zerbes (1997) reported that disturbances in urinary metabolite excretion were correlated with physical and psychological symptoms including photophobia, headaches and trouble concentrating, which are common symptoms of IS. Potaznik and Kozol (1992) and Vedelago (1994) also described symptoms in subjects with CFS which are the same as those identified by subjects with IS, including blurring and shadowing of vision, headaches, eye strain, photophobia, decreased span of recognition of words while reading, and difficulty tracking lines of print. He suggested various adjustments to reduce the severity of symptoms, including the use of tinted lenses. Rosenhall, Johansson, and Orndahl (1987, 1996) found abnormal saccades and disturbed smooth pursuit eye movements in large numbers of people with CFS, and similar symptoms have been identified in subjects with IS (Robinson & Foreman, 1999a; Tyrrell et al., 1995).

The evidence and opinion cited above would suggest that biochemical anomalies may play an important role in understanding the aetiology of dyslexia. In particular, fatty acid metabolism has been suggested as a possible causal factor, especially for a visual processing subtype of dyslexia such as IS. One group of studies also suggest an overlap of symptoms between IS and CFS, with biochemical anomalies implicated as a possible causal factor in these symptoms. On the basis of these studies, a more detailed analysis of these associations has been instigated. This more detailed analyses has so far involved three sequential studies, which will be outlined below.

STUDY ONE

Method

The first investigation (Robinson, Roberts, McGregor, Dunstan, & Butt, 1999) involved 143 adults with CFS using the diagnostic criteria outlined by Holmes, Kaplan, Gautz, Komaroff, Shonberger, Strauss et al. (1988). These subjects had been identified on a CFS questionnaire as likely to have some symptoms of IS. A metabolic profile of urine samples using gas chromatography and mass spectrometry (McGregor et al., 1996a) had been collected for all subjects.

The CFS questionnaire, which was used as the basis for identifying subjects likely to have symptoms of IS, consists of 86 items which assess symptoms in a wide variety of areas, including headaches/migraine, body pain or tenderness, stiffness of joints, depression, lack of motivation, nausea and stomach upset, tiredness or fatigue and stress. Items from the CFS questionnaire considered to be indicative of IS and used as the basis for analysis were:

- Item 1: Headaches
- Item 33: Dislike of strong light or photophobia
- Item 55: Trouble concentrating

The urine data (arcsine transformed) and clinical data were analysed using *t*-tests, Pearson product-moment correlations, multivariate and one-way analysis of variance (MANOVA and ANOVA), and forward stepwise discriminant function or multiple regression analysis. Correction for statistical multiplicity occurred where applicable. Group differences were also assessed using Hotelling's T^2 . These data were processed using Access (Ver.1.1, Microsoft), Excel (Ver.4.0, Microsoft), and Statistica (Ver.4.5, Statsoft, Tulsa).

Results

The areas of significant difference in urinary metabolic profiles for subjects who had indications of light sensitivity, headaches and trouble concentrating on the CFS questionnaire are shown in Table 1 below. These results indicate a variety of possible biochemical anomalies, but must be treated with caution as there could be a variety of possible causes for broad descriptive categories such as headaches and lack of concentration.

Table 1
Significant differences in urinary metabolic profiles for subjects with CFS in the specific symptoms area of light sensitivity, headaches and trouble concentrating (N=143)

Chemical	PHOTOPHOBIA		HEADACHES		TROUBLE CONCENTRATING	
	Percentage p	Excretion p	Percentage p	Excretion p	Percentage p	Excretion p
Leucine		<.04				
Asparagine			<.0002	<.0002	<.05	<.04
Succinic Acid			<.004	<.02	<.05	
UM 15b			<.0002	<.007	<.02	
Tyrosine			<.00007	<.05	<.03	
Aspartic Acid			<.02			
Phenylalanine			<.05			<.05
3-Methyl Histidine			<.03		<.003	
Proline				<.05		
Hippuric Acid					<.04	<.04
UM 28					<.04	

Significant anomalies were found in excretion of a number of amino and organic acids, including markers of protein turnover (leucine, proline, 3-methylhistidine) and catecholamine production (tyrosine, phenylalanine). An alteration in the serum phenylalanine: tyrosine ratio has been used to indicate the degree of active tissue turnover (Wannermacher, Klainer, Dinterman, & Beisel, 1976), and has also been linked to impaired contrast sensitivity (Diamond & Herzberg, 1996). The anomalies suggest an alteration in protein and tissue metabolite turnover which may indicate immune system activation and the presence of an infection. Increases in post-viral tissue turnover can result in a dysregulation of fatty acid distribution (Horrobin et al., 1995) and abnormal fatty acid metabolism has been associated with visual symptoms and visual processing problems in dyslexia (Richardson et al., 2000; Stordy, 1995). In particular, HUFAs have been associated with retinal function (Birch et al., 1998; Lee et al., 1998; Neuringer et al., 1994) and magnocellular function (Rae et al., 1998; Taylor & Richardson, 2000), both of which have been implicated as causes of IS.

STUDY TWO

While the results of Study One need to be seen as a very tentative first investigation, they did provide further evidence of the potential association between biochemical anomalies and symptoms in people with CFS, which could be indicative of a visual form of Dyslexia (IS). In particular, the biochemical anomalies identified could be related to immune system dysfunction and may also have implications for fatty acid metabolism, which has been linked to both dyslexia and retinal function. Study Two extended the initial investigation by undertaking a full screening of symptoms of IS in subjects with CFS, as well as an analysis of serum lipids and amino organic acids (see Robinson, McGregor, Roberts, Dunstan, & Butt, 2001).

Method

A total of 61 adults were identified from the University of Newcastle CFS patient database and screened for symptoms of IS using the Scotopic Sensitivity Syndrome Screening Manual (Irlen, 1992). In this study a rating of degree of improvement when using coloured overlays also occurred. These ratings occurred for four areas of symptoms: a) eye strain/fatigue/headaches while reading; b) print distortions/clarity while reading; c) photophobia/light sensitivity while reading, and d) reading speed/errors while reading/duration of reading. The rating sheet used is outlined in Appendix A.

The study subjects all had a metabolic profile of urine and blood samples using gas chromatography and mass spectrometry (GC-MS). All subjects completed a collaborative pain research unit (CPRU) symptom questionnaire. They had previously collected a first morning urine specimen and a blood sample as part of other studies by the method described in McGregor et al. (1996a). Symptom responses and metabolites were compared using Mann-Whitney U-test and Spearman rank-order correlation (non-parametric data), student t-tests and multiple regression and discriminant function analyses (parametric data).

Results

Factor analysis was used to divide the study subjects into two groups according to degree of symptoms of IS, with one group having a high level of symptoms of IS (N=31), and the other group having a low level of symptoms of IS (N=30). There was no difference in age or sex between the high symptom group (Mean age=49.2, sd=16.5 years; females=71.0%) and the low symptom group (Mean age=52.7, sd=11.3 years; females=54.0%).

The two groups identified by factor analysis to have high or low levels of symptoms of IS were assessed for the prevalence of other symptoms using their responses to the 86 items on the CPRU questionnaire. Table 2 shows the odds ratios for the assessment of symptom prevalence difference between the two groups; both for ratings of severity of symptoms of IS and degree of improvement of symptoms using coloured filters. While there were a variety of symptoms in which the two groups were different, of particular note are the recurring indicators of infection (sore or swollen lymph nodes in groin and neck).

Table 2
Odds ratio of difference in prevalence of symptoms of CFS between high and low symptom IS groups according to severity of symptoms and response to colour

Severity of symptoms of IS			
Symptoms of CFS	Odds ratio (95% confidence)	Chi²	p
Sore or swollen lymph nodes in your groin	=7.7	=4.83	<.03
Tinnitus or ringing in your ears	=3.9	=5.15	<.03
Response to coloured filters			
Symptoms of CFS	Odds ratio (95% confidence)	Chi²	p
Sore or swollen lymph nodes in your groin	>30	=11.91	<.0006
Difficulty with words or language	=20	=13.75	<.0003
Unrefreshed or prolonged sleep	=8.5	=5.08	<.03
Poor appetite	=4.3	=5.74	<.02
Sore or swollen lymph nodes in your neck	=4.1	=5.52	<.02
Spells of panic or terror	=4.0	=5.40	<.02
Nausea or upset stomach	=3.7	=4.24	<.04
Abdominal pain or tenderness	=3.5	=4.11	<.05
Hypersensitivity	=3.3	=4.15	<.05
Heart pounding or palpitations	=3.3	=4.06	<.05

The two factor analysis groups with high or low levels of IS symptoms were also assessed for variation in blood lipids and urine amino and organic acids. Table 3 shows the areas of significant difference in lipid and urine components between high and low symptom IS groups according to a) indications of severity of symptoms of IS, and b) assessment of degree of improvement with coloured filters. The mean relative abundance and concentrations are summarised, together with the results of multivariate and univariate analysis.

Table 3
Differences in lipid and urine microbiology between low and high symptom IS groups according to severity of symptoms and response to colour

Severity of symptoms of IS			
Lipid/metabolite	High symptoms	Low symptoms	p
Lipid			
%cis-11, 14, 17 – C20:3	0.12 (0.04)	0.07 (0.04)	<.03
%C17:0	0.24 (0.07)	0.46 (0.41)	<.05
Urine			
%Hydroxyproline	0.58 (0.38)	0.38 (0.25)	<.02
%Proline	1.92 (1.09)	1.40 (0.93)	<.05
Response to coloured filters			
Lipid/metabolite	High symptoms (positive response)	Low symptoms (negative response)	p
Lipid			
Conc. trans-9-C18:1	1910 (680)	1133 (423)	<.003
%trans-9-C18:1	1.23 (0.3)	0.88 (0.3)	<.02
Conc. cis-9-C16:1	5486 (3696)	2369 (1220)	<.005
%cis-9-C16:1	3.30 (1.2)	1.75 (0.5)	<.002
%Lathosterol	0.03 (0.01)	0.05 (0.01)	<.003
%Cholesterol	18.1 (9.0)	26.0 (7.4)	<.04
Urine			
%3-Methylhistidine	1.59 (1.60)	3.03 (2.8)	<.03

There was an increased urinary excretion of the connective tissue amino acids, proline and hydroxyproline, and a decrease in the actin-degradation amino acid, 3-methylhistidine. Similarly the sterols, cholesterol and lathosterol, so important for proper membrane stability and function (Zubay, 1998), were increased in the high symptom IS group. There was also an increase in the long chain polyunsaturated fatty acids CIS 11, 14 and 17-C20:3 and a reduction in the odd chain saturated fatty acid C17:0 (heptadecanoic acid), which has been implicated in impairment of cellular chemistry (Shoemaker, 2001). A spearman-rank correlation analysis of the association between the various serum fatty acid levels and severity of symptoms of IS also identified a significant increase in CIS-9, 12-C18:2 (linoleic acid). In addition the dietary derived fatty acid trans-9-C18:1 or elaidic acid, which has been linked to macular degeneration of the eye (Hammond, Fuld, & Snodderly, 1996), was increased in the subjects with high symptoms of IS, who responded positively to coloured lens use. Importantly, the accumulation of trans-9-C18:1 has been shown to induce an alteration in the very long chain polyunsaturated fatty acids, particularly those between C20:0-C24:0 (Koletzko, 1992). Dietary intakes of trans-9-C18:1 have also been shown to result in an increase in incorporation of cis-9, 12-C18:2 into phospholipids (Abbey & Nestel, 1994). In this study it was found that the levels of trans-9-C18:1 positively correlated with the eye strain/headaches/fatigue when reading. Palmitoleic acid (cis-9-C16:1), which is implicated in the facilitation of neural functioning, was also increased in the high symptom IS subjects who responded positively to coloured lens use.

These anomalies again support the general hypothesis of problems with fatty acid metabolism, which has implications for neural development and visual processing problems (Lee et al., 1998; Richardson et al., 2000; Taylor & Richardson, 2000). The data also supports the suggestion that dietary supplementation with very long chain polyunsaturated fatty acids may benefit visual processing problems in dyslexia (Makrides et al., 1995; Stordy, 1995). It should be noted, however, that the dysregulation of fatty acid characteristics was not the same as noted in other studies of people with dyslexia who have visual processing problems (Makrides et al., 1995; Stevens et al., 1995; Stordy, 1995). The specific association between biochemical anomalies and visual processing in dyslexia, however, is less likely to be apparent in the first two investigations as the study population still had a primary diagnosis of CFS.

STUDY THREE

The two studies described above have identified biochemical anomalies in a population with a primary diagnosis of CFS, which would support the association between metabolic anomalies, neural development and visual processing problems. However, a larger scale study of people who only have symptoms of IS was needed to allow a more detailed analysis of the association between metabolic anomalies and dyslexia. The purpose of Study Three was to investigate subjects who have symptoms of visual processing problems (IS) but not symptoms of CFS. This study also investigated children as well as adults.

Subjects and Measures

The study group involved 51 subjects (mean age=32 years, 1 month) with symptoms of IS, and 54 age- and sex-matched subjects with no symptoms of the syndrome as controls (mean age=29 years, 8 months). The subjects' ages ranged from 10 years to 53 years, with 44% being male. The experimental group were selected from people referred to the Special Education Centre, University of Newcastle for reading and writing problems. The age- and sex-matched control group were recruited primarily from the general public, but also from relatives of subjects with IS.

All subjects were screened for symptoms of IS using the Scotopic Sensitivity Syndrome Screening Manual (Irlen, 1991b). Validity studies of the Irlen Manual by Robinson, Hopkins, and Davies (1995) and Tyrrell et al. (1995) have found significant differences on scores in all sections between reading disabled and normally achieving students. Gray (1999) found significant relationships between scores on the manual and standardised measures of reading achievement, spelling achievement and visual processing. A high test-retest reliability for identification of symptoms and colour choice has also been identified by Jeanes et al. (1997), Robinson and Foreman (1999b), Wilkins (1997), and Wilkins et al., 2001.

Serum Lipid and Urine Specimens and Gas Chromatography/Mass Spectrometry (GC-MS) Identification

The study subjects provided a first of the morning urine sample for analysis using gas chromatography and mass spectrometry (GC-MS) (McGregor et al., 1996a). All subjects had completed a collaborative pain research uni (CPRU) symptom questionnaire completed on the day of their biochemical test. Ten ml of whole blood was also collected from the study subjects by venipuncture into a lithium heparin vacu-tainer (Becton Dickinson) and processed using a Hewlett Packard 5890 series II gas chromatograph and series 5971A Mass Selective Detector (McGregor et al., 1996). The subjects had fasted for 12 hours prior to the blood collection, and were asked to list the drugs and naturopathic remedies they had taken, as well as dietary changes they had made during the preceding four weeks.

Statistical Analysis

Percentage composition lipid and urine data were arcsine transformed before analysis to improve normality. Subject characteristics were assessed using Chi-square analysis. Metabolites were compared using Student's t-test and discriminant function analysis. These data were processed using Access 2000 TM (Microsoft, Redmond, WA, USA) and Statistica TM (Ver. 6, Statsoft, Tulsa, OK, USA).

Results

There were significant differences between experimental and control groups in a number of amino acids and serum lipids as outlined in Tables 4 and 5 below.

Table 4
Significant differences in the relative abundance of excreted amino and organic acids between the Control and IS Groups

Urinary Metabolite	Control (%)	IS (%)	t-test p value
ornithine	1.57	1.22	<0.02
aspartic acid	1.40	1.19	<0.03
tyrosine	2.34	1.89	<0.04

Values are means expressed as percentage of total excreted amino and organic acids. Student's t-test performed on arcsine transformed percentage distribution data.

Table 5
Significant differences in the relative abundance of serum lipids between the Control and IS Groups

Lipid component	Control (%)	IS (%)	t-test p value
heptadecanoic acid (C17:0)	0.21	0.24	<0.02
lathosterol	0.06	0.08	<0.04

Values are means expressed as percentage of total serum lipids. Student's t-test performed on arcsine transformed percentage distribution data.

The significant differences in excretion of tyrosine and aspartic acid have implications for neural functioning. Tyrosine is a precursor for a number of neurotransmitters, including dopamine, norepinephrine and epinephrine, with aspartic acid playing a role in action potentials for neurons (Ekert, 1988). Brain tyrosine levels can significantly affect higher cortical functions (Tam & Roth, 1997) and disturbed tyrosine transport may be a marker for membrane dysfunction in schizophrenia (Bjerkstedt, Edman, & Wiesel, 1999), which has been shown to have similar phospholipid anomalies to those identified in dyslexia (McDonnell et al., 2000). The membrane lipid hypothesis of schizophrenia proposes that dopamine upregulation results from a deficiency in certain EFAs and could be responsible for the visual distortions experienced in this condition (Skinner et al., 1999). A tyrosine difference was also identified in Study One.

The significant difference in the odd chain fatty acid, heptadecanoic acid, is important as odd chain fatty acids are in the coat of certain viruses and may impair proper cellular chemistry (Shoemaker, 2001). These fatty acids are not produced by humans and may be influenced by diet. A similar difference in heptadecanoic acid between experimental and control subjects was found in Study 2. There is increasing evidence of an association between dyslexia and abnormal fatty acid metabolism (Richardson et al, 1997, 2000), especially for visual processing problems (Richardson et al., 2000; Stordy, 1995). Highly unsaturated fatty acids have been associated with retinal malfunction (Birch et al., 1998, Neuringer et al., 1994) as well as magnocellular deficits (Taylor & Richardson, 2000), and both these problems have been hypothesised as causes of IS. The significant difference in lathosterol may indicate increased cholesterol synthesis, which is thought to be associated with a response to viral and bacterial infection (Pfeffer, Kwok, Landsberger, & Tamm, 1985).

The capacity of biochemical profiling to identify people with symptoms of IS was calculated by discriminant function analysis, as shown in Table 6 below.

Table 6
Discriminant function analysis of multivariate differences between serum lipid profiles: Comparison between Control and IS groups

Standard Discriminant Function Analysis			
<u>Model Statistics – Adults</u>			
Wilks' Lambda = 0.195, F(37,24) = 2.670, p<0.007			
<u>Classification accuracy (%)</u>			
Adult Control (n=31) 96.88	Adult IS (n=31) 100	Total 98.39	
<u>Model Statistics – Children</u>			
Wilks' Lambda = 0.137, F(37,4) = 0.683, p<0.076			
<u>Classification accuracy (%)</u>			
Adult Control (n=21) 100.00	Adult IS (n=21) 100.00	Total 100.00	

Values calculated using arcsine transformed percentage data.

A Wilks' Lambda value of 0 is perfect discrimination and a value of 1 is no discrimination. Based on the lipid profiles of adults (18 years and above) and children, the control and IS subjects were correctly predicted between 98% and 100% of the time. It should be noted, however, that the prediction for children was not statistically significant ($p < 0.7$), with a likely reason being low subject numbers. The results of forward stepwise discriminant function analysis identified the primary metabolite in the discrimination between adult IS and Control groups as lathesterol, as well as lignoceric and palmitic acids, which are saturated fatty acids. Lignoceric acid is an odd chain fatty acid associated with viruses and may impair cellular chemistry. The primary metabolite in the discrimination of child IS and Control groups was the odd chain fatty acid heptadecanoic acid, which may also be in the coat of certain viruses and impair cellular chemistry.

The high degree of accuracy in identifying both adults and children through biochemical profiling suggests that this method offers promise as a means of early identification and as a process for establishing the validity of the syndrome. Identification of biochemical "markers" for the specific visual processing symptoms of IS could allow much earlier identification and also contribute to a more accurate identification. Early diagnosis is important for the large numbers of the school population with dyslexia, as lack of early reading success can lead to discouragement, a passive learning style and further failure (Wong, 1986). It has been claimed that many children with a reading disability are not diagnosed until they are about 9 years old (McLesky, 1992). By this age, they may have experienced significant and prolonged failure and are unlikely to bridge and academic gap between them and their peers (Foorman, Francis, Fletcher, Schatschneider, & Mehta, 1998).

The significant differences between experimental and control groups in reported prevalence of medical conditions, as well as in emotional, cognitive and possible neurological symptoms is identified in Tables 7 and 8 below.

Table 7
Significant differences in the medical histories of the Control and IS groups (self-report)

Symptom	Control (%) (n=54)	IS (%) (n=51)	Chi-square p value
Migraine	14.5	31.4	<0.05
Hayfever	14.5	31.4	<0.05
Dairy intolerance	9.1	23.5	<0.05

Table 8
Significant differences in the prevalence of emotional, cognitive and possible neurological symptoms between the Control and IS groups (self-report)

Symptom	Control (%) (n=54)	IS (%) (n=51)	Chi-square p value
Photophobia	17.0	70.6	<0.0000
Headaches	53.4	80.4	<0.004
Forgetfulness	48.1	88.2	<0.0000
Trouble concentrating	55.6	88.2	<0.0003
Difficulty using language	26.4	58.8	0.006
Everything an effort	22.2	58.8	0.001
Mental confusion	35.2	60.	<0.009

The significant differences in photophobia, headaches and migraine between experimental and control groups are important symptom indicators of IS (Irlen, 1991; Tyrrell et al., 1995; Lightstone et al., 1999) and there have been reports of the reduction of headaches and migraine in people with symptoms of IS using coloured filters (Chronicle & Wilkins, 1991; Wilkins, Patel, Adjaman, & Evans, 2001). The significant difference in trouble concentrating, mental confusion and everything requiring effort can also be symptom indicators of IS (Irlen, 1991; Irlen & Robinson, 1996; Whiting, Robinson, & Parrot, 1994). The higher incidence of hayfever among the IS group could suggest an immune system dysfunction, and immunological problems have been suggested as a cause of dyslexia (Galaburda, 1997; Knivsberg, 1997). Immune system

dysfunction was also indicated by suggestions of post-viral tissue turnover in Study One and indications of recurring infection in Study Two. The reactivity to dairy products has been identified in dietary intervention studies in people with autism, which found a diet free of gluten and milk products normalised urine patterns and resulted in a significant improvement in neural, cognitive and communication skills (see Knivsberg, Reichelt, & Nødland, 2001).

DISCUSSION

The differences in lipid and urine biochemistry between experimental and control groups in all three studies supports the hypothesis of an association between metabolic anomalies and various forms of disability, including problems with neural function and retinal malfunction (Richardson & Ross, 2000), and both of these areas have been identified as possible causative factors for IS. Indicators of possible problems with neural function included differences in palmitoleic acid in Study Two and differences in tyrosine and glutamic acid in Studies One and Three. Tyrosine is a precursor for a number of neurotransmitters, while aspartic acid and glutamic acid play a role in action potentials for neurons. Indicators of possible problems with retinal malfunction come from differences in elaidic acid in Study Two. In addition, there were numerous indicators in both Study Two and Study Three of disturbance in fatty acid metabolism, which has been linked to visual processing problems in dyslexia (Stordy, 1995, 1998).

There were also indications from all three studies of alterations to tissue and metabolite turnover, which may indicate the presence of an infective agent. In Study Two in particular, the alteration found in urinary excretion of amino acids, such as hydroxyproline, proline and 3-methylhistidine, along with increases in lymph-node symptoms, support the hypothesis that alterations in protein and tissue turnover may be causally related to an infective agent and activation of the immune system. The significant differences in Studies Two and Three for cholesterol, which is important for membrane stability and function, has been hypothesised to indicate a response to viral infection. Viral infection in turn has been claimed to interfere with fatty acid metabolism. The difference in heptadecanoic acid in Studies Two and Three are also possible indicators of viral infection, as these fatty acids are found in certain viruses and may affect cell structure and function. There were also anecdotal reports from subjects in Study Two of vision improvement following the use of amino acid supplements and/or antibiotic treatment for co-morbid bacterial problems. More investigation, however, is required to establish whether the alterations in excretion of amino acids represent non-normal levels and also to confirm the relationship between identified anomalies and possible immune system dysfunction.

The data from these studies suggest that a complex array of biochemical changes are associated with alteration in vision difficulties in the CFS and IS subjects. The data suggests that these changes may be driven by a pathogen (infective agent). However, the host's response to the pathogen are likely to vary and would be under the control of the host genetics and/or other environmental influences, with genetic control likely because of the high familial incidence of IS (Robinson, Foreman, & Dear, 1996, 2000). These likely variables highlight the complex and multiple interacting factors in causation, with sensory, emotional and motivational factors inseparable from cognition and behaviour. Richardson and Ross (2000), for example, state that fatty acid metabolism can be very complex and influenced by a variety of constitutional and environmental factors.

Overlapping Diagnostic Categories?

These preliminary data represent only the beginning to understanding a wide range of disabilities, which at the moment are subsumed under broad and overlapping diagnostic categories such as dyslexia, specific learning disabilities, ADHD, dyspraxia and CFS. The extent of overlap between these categories is so extensive that the category used for any individual may in some cases be dependent upon the background of the attending professional. Comings (1996) and McCrone (1998), for example, suggest that a variety of biochemical anomalies are likely to be implicated in learning and behaviour problems, and various combinations of these anomalies may cause a variety of overlapping disabilities. It is further claimed (Comings, Wu, Chiu, Ring, Dietz, & Muhleman, 1996) that the underlying cause may be genetic and there may be an additive effect, with a number of genes affecting a range of neurotransmitters. Hardman and Morton (1991) found that 98% of subjects who were chemically dependent (referred to a drug and alcohol rehabilitation centre) also had symptoms of dyslexia, and 89% had symptoms of ADD. Richardson and Ross (2000) hypothesise that abnormalities of fatty acid and membrane phospholipid metabolism may be a factor in a wide range of disorders, including attention deficit/hyperactivity disorder, dyslexia, dyspraxia and autistic spectrum disorder, which they feel could explain the high degree of co-morbidity between these conditions.

Phospholipid abnormalities have also been identified in people with dyslexia similar to those identified in people with schizophrenia (Horrobin et al., 1995; McDonnell et al., 2000). Horrobin et al. (1995) identified one symptom group of schizophrenics to have low levels of AA and DHA. They cite an increased risk of dyslexia in the offspring of people with schizophrenia and a range of clinical features suggestive of

defective phospholipid metabolism. McDonnell et al. (2000) identified similar phospholipid abnormalities in people with schizophrenia and people with dyslexia, with suggestions that the two disabilities may be on a continuum with respect to this abnormality. A number of studies have also identified visual processing anomalies in people with schizophrenia, including problems with smooth pursuit eye movements (Abel, Levin, & Holzman, 1992; Radant & Hommer, 1992), a restricted visual scanning style across faces (Streit, Wolwer, & Gaebel, 1997), and difficulties with forward and backward masking (Skinner et al., 1999). Problems with eye movements and with masking tasks have been identified in people with dyslexia and IS, and are cited as evidence for the magnocellular deficit theory of dyslexia (see Stein, 2001). There is also evidence of poor eye movements in a variety of other disabilities such as Tourette syndrome and Parkinson's disease (Farber, Swerdlow, & Clementz, 1999; Hamilton, 2000; Narita, Shawal, Lask, Taylor, & Harris, 1997). Hamilton (2000) claimed Parkinson's disease was also associated with contrast sensitivity and with impaired processing of the visual magnocellular pathway. Narita et al. (1997) claimed that Tourette syndrome could be associated with reading difficulties, while Farber et al. (1999) claimed that people with Tourette syndrome may also have symptoms of ADD. Evans (2000) claims that poor performance on saccadic eye movement tasks in people with dyslexia could be related to the lack of concentration found in people with ADD.

The analysis of biochemical anomalies could be particularly important in the development of more valid diagnostic categories. It offers the hope that in time we may be able to develop a biochemical profile of each individual. This profile could allow us to effectively identify which individuals are likely to have specific difficulties in certain learning/social situations, and to provide appropriate treatment. The discriminant function analysis of biochemical anomalies in Study Three identified a very high level of prediction of IS. A preliminary multivariate statistical analysis of biochemical profiles of people with symptoms of autism, ADHD and CFS at the Department of Biological Studies, University of Newcastle, Australia also has identified clearly different biochemical profiles for each symptom group. All three groups were also clearly different from a control group with no disabilities.

Biochemical analysis may be particularly important for identifying those symptoms which are the cause of the disorder as distinct from those which are the result of the disorder (Pennington, 1989). It is important that treatment strategies are based on causes rather than on overt behavioural symptoms or responses. With current diagnostic categories, the behavioural symptoms for "non-visible disabilities", such as IS, ADD or CFS, are predominantly treated as the cause, with students being told to "try harder" or "concentrate more", which is likely to have a minimal effect if they cannot concentrate (ADHD), feel fatigued (CFS), or have eye strain and a progressive distortion of print while reading (IS). Biochemical analysis may also help to highlight the fact that overlapping disabilities may mean multiple treatments are required (Hardman & Morton, 1991). Identification and treatment of ADHD, for example, might mean that the possibility of other disabilities and treatments is not considered. Medication for ADHD may lead to improved attention, but academic and reading achievement may still be limited if the student also has a distortion of print while reading (IS).

It is also likely that treatments might cross traditional diagnostic boundaries, such as the possible use of diet to overcome problems with fatty acid metabolism for dyslexia, ADHD and autism. The use of coloured filters may also cross traditional diagnostic boundaries. This treatment has been found to improve reading comprehension in children with reading/spelling disability and ADHD (Iovino, Fletcher, Breitmeyer, & Foorman, 1998). Williams, Littell, Reinoso, and Grieve (1994) also found that colour filters improved the performance of children with ADHD on non-verbal tasks. In addition, there have been positive reports of the use of coloured filters to reduce symptoms of visual perceptual dysfunction in people with autism (see Waterhouse, 1995). A study by Farvel, Bourne, and Iri (1999) also identified a high frequency of night blindness in children with autism and their families, and this disability is frequently reported by people with symptoms of IS, who claim improvement with coloured filters (Irlen, 1991). Altered lighting conditions, in particular the reduction of fluorescent lighting, has been used to assist people with IS and has also been found to reduce maladaptive behaviour of children who are developmentally disabled (Shapiro, 2001).

The development of more effective diagnostic categories through biochemical analysis could also allow a more rational evaluation of the most effective treatment strategies. The broad diagnostic categories currently used are likely to result in a variety of disabilities, or sub-groups of a disability, being present in any one study population (Farmer & Klein, 1995; Torgesen, 1998). As a consequence, when researchers attempt to compare findings, they are frequently conflicting, due to patient group heterogeneity.

Possible Immune System Deficiencies?

It has been claimed that there may be an immunological basis for learning problems. Pennington, Smith, Kimberling, Green and Haith (1987) found elevated levels of antibodies in mothers with dyslexic children, and Lahita (1988) found mothers with a particular immune system disability had a higher than average rate of children with learning disorders. Hugdahl, Synnevag, and Satz (1990) found a higher incidence of asthma,

hayfever, eczema and other immune conditions in dyslexics than controls, while Study Three in this paper found a significantly higher incidence of allergic conditions among subjects with IS than controls. Stein (2000) and Galaburda (1997) also cite evidence that dyslexics and their families have a greater than normal incidence of autoimmune disorders, while Knivsbjerg's (1997) analysis of urine samples found more abnormalities suggestive of immune system dysfunction in the urine patterns of dyslexics. Hardman and Morton (1991) found 82% of a sample of subjects with symptoms of dyslexia and ADD had significant evidence of allergies or immunological problems, as well as a pattern of diseases associated with immune deficiencies and altered biochemistry. Stein (2001) cites preliminary evidence that mothers may develop antibodies to foetal magnocellular neurons, which he claims may in some circumstances cross the blood-brain barrier and damage magnocells. A number of other authors have also reported an association between immune disorders and dyslexia (Armstrong, Seidel, & Swales, 1993; Hugdahl, 1995; Wood & Cooper, 1992). Chronic Fatigue Syndrome has also been associated with a variety of immune system deficiencies (Dykman, Tone, & Dykman, 1997; Ojo-Amaize, Conley, & Peter, 1994), as well as dysregulation of immune cell numbers and cytokine production (Gupta & Vayevigula, 1991).

Further evidence of the association between learning disabilities/visual processing problems and immune system dysfunction comes from studies of the effects of exposure to neurotoxins on visual contrast sensitivity. Contrast sensitivity is considered to be an indication of neurological function between the retina and the cortex (Shoemaker & Hudnell, 2001; Turf, Ingsriswang, Turf, Ball, Stutts, Taylor et al., 1999). Spatial vision is mediated by the parvocellular and magnocellular pathways, and deficits in the magnocellular pathway has been hypothesised as a cause of dyslexia and of IS. These pathways have been found to be vulnerable to neurotoxins (Pasternak, Flood, Eskin, & Merigan, 1985).

A number of studies of watermen and recreational fishermen exposed to *Pfiesteria* infection (which releases toxins that kill fish) have found a significant reduction in visual contrast sensitivity in the mid-range frequencies (Hudnell, House, Schmid, Koltai, Stopford, Wilkins et al., 2001; Shoemaker, 2001; Shoemaker & Hudnell, 2001; Swinker, Koltai, Wilkins, Hudnell, Hall, Darcy et al., 2001; Turf et al., 1999). Hudnell et al. (2001) found the magnitude of deficit increased with increasing hours of contact with fish kills and the deficit was reduced with clinical trials of a medication (cholestramylene), suggesting a neural, not an optical physiological basis for improvement. Shoemaker (2001) concluded that the identified symptoms, including problems with concentration, confusion and short-term memory, overlap with symptoms commonly observed in children diagnosed with learning difficulties. Glasgow, Burkholder, Schmechel, Tester, and Rublee (1995), and Grattan, Oldach, Perl, Lowitt, Matuszak, Dickson et al. (1998) found that cases of exposure to *Pfiesteria* had difficulties in learning new words, reading, spatial orientation, visual speed and accuracy, headaches, blurring, and sensitivity to light, all of which are common symptoms of IS. Both Glasgow et al. (1995) and Shoemaker and Hudnell (2001) further claim that the symptoms seen in some cases suggest the immunological system may be compromised. These symptoms included asthma, chronic colds, respiratory infections and low T-cell counts.

The reduction in contrast sensitivity in mid-range frequencies in people exposed to estuarine infection has also been identified in people chronically exposed to neurotoxic agents, such as solvents and in urban areas of high pollution (Frenette, Mergler, & Bowler, 1991; Hudnell, Otto, & House, 1996; Mergler, 1995; Schreiber, Hudnell, & Parker, 1998). The exposure has been found to affect a range of skills related to learning disabilities, including attention, executive function, visual spatial ability, visual evoked potential and hand-eye coordination tasks (see Dahl, White, Weike, Sorensen, Letz, Hudnell et al., 1996; Feldman, 1999; Swinker et al., 2001).

A possible association between visual/ocular problems and immune system dysfunction was identified in Study Two. The changes in reading ability and response to lens use were associated with indicators of infection as shown by sore or swollen lymph nodes (Table 2), as well as dysregulation of urinary metabolites and fatty acid metabolism, which may be indicative of a reaction to infection (Table 3) (Arao, Soushi, Sato, Moriishi, Audo, Yamada, Padilla, Uno, Nii, & Kurata 1997; Qavi, Xu, Green, Lusso, Pearson, & Ablashi 1996; Robinson et al., 1999; Singh, Lin, & Yang, 1998). The process of forming the highly unsaturated fatty acids AA and DHA from dietary precursors (linoleic acid and alpha-linolenic acid) can also be restricted by viral infection and stress (Horrobin et al., 1995), and AA and DHA have been linked to visual processing problems in dyslexia (Stordy, 1995; Taylor & Richardson, 2000). In Study Three, the odd chain fatty acids heptadecanoic acid and lignoceric acid were significant indicators of symptoms of IS and such acids are in the coat of certain viruses and may impair cellular chemistry. Roberts, Dunstan, Robinson, Cosford, Bull, McGregor, Ellis, and Sparkes (2002) claim that the changes in amino acids and fatty acids identified in the three studies described in this paper may be the consequence of chronic unresolved infection. The body chemistry changes required to fight infection can include using amino acids from other areas of the body, such as muscles, which are a major reservoir of amino acids. This action is called catabolism, and unresolved infection may lead to chronic activation of the immune system and in a chronic catabolic state. This continual activation of the immune system may thus eventually lead to

malnutrition in terms of amino acids and essential fatty acids. The model for this claim was found to apply to multisymptomatic illnesses, including CFS, fibromyalgia, arthritis, Irlen Syndrome and autism.

The high familial incidence of disabilities such as IS (Robinson, Foreman, & Dear, 1996, 2000) suggests that a gene mechanism may influence the probability of immune system dysfunction (see also Stein, 2000, concerning genetic linkage and dyslexia). However, while familial gene traits may influence the probability of familial reading difficulties, the familial transfer of infective agents is also a possibility. While viruses such as Human Herpes-6 (HHV-6) are not transferred across the placenta, children usually contract HHV-6 infections in the first couple of years of life from other family members. This is important as reactivation of HHV-6 has also been implicated in the development of CFS (Ablashi, Roman, Owen, Gupta, Herst, Peterson et al., 2001; Suhadolnik, Reichenbach, Hitzges, Sobow, Peterson, Henry et al., 1994; Suhadolnik, Peterson, O'Brien, Cheney, Herst, Reichenbach et al., 1997). This virus may also play some role in alteration of retinal function. Qavi et al. (1996) showed that HHV-6 was able to infect corneal epithelial cells, whilst Arao et al. (1997) also showed that HHV-6 was able to infect retinal pigment epithelial cells. Significantly, Singh et al. (1998) reported that HHV-6, along with an autoantibody against neuron-axon filament protein, was increased in patients with autism. Thus the alteration in visual processing may be associated with a persistent viral infection by HHV-6.

Dietary Intervention as a Treatment Option?

The identification of a possible dysregulated metabolism in people with symptoms of IS raises the question of dietary manipulation and food supplementation as an addition to the already established treatments of coloured filters and remedial support. Fatty acid metabolism has been implicated as a potential causative mechanism for IS and if the conversion of ALA and LA to the important HUFAs, AA and DHA is impaired (see Figure 1), the only way for the brain to obtain the EFA it requires is through diet (Horrobin, 1999). Dietary intervention for people with dyslexia has been successfully undertaken by Baker (1985), Stordy (1995, 1998) and Makrides et al. (1995) using an essential fatty acid supplementation, while Stordy (2000) found improvements in motor skills for children with dyspraxia using a similar supplementation. Richardson, Taylor, Montgomery, Calum, Schoenheimer, Hall et al. (2001) also reported significant improvements in reading for children with dyslexia who took a HUFA supplement which included EPA, DHA, GLA and AA. The supplementation had a greater effect for children scoring high at baseline in visual symptoms while reading and these visual symptoms include many indicators of IS (blurring, movement and pulsation of print, sensitivity to light and headaches/eye strain while reading). Visual function in infants would also appear to be enhanced by fatty acid supplementation (Birch et al., 1998; Faldella et al., 1996; Uauy, Mena, & Valenzuela, 1999; Willats & Forsythe, 2000). A difference was identified in Study Two and Study Three in heptadecanoic acid, which is not produced by humans and may be acquired by diet.

There have been dietary interventions for people with dyslexia which do not involve fatty acid supplementation. Benton (1997) reported a case study in which a glyconutritional supplement given to a child with dyslexia resulted in claims of a large improvement in reading and writing activities. Hardman, Clay, and Lieberman (1989) found that a diet high in sugar and a provocative challenge in cane sugar, resulted in erratic eye movements (fixations and regressions), and reduced reading efficiency for a group of subjects with dyslexia. De Luca, Foggia, and Chiummariello (1996) found a relationship between central nervous system functioning and food allergens, with changes in diet influencing measures of central nervous system functioning (including handwriting skills).

Dietary intervention has also been shown to have a positive effect for people with ADHD and the clinical overlap between ADHD and dyslexia is 30 to 50% (Richardson, & Ross, 2000), with suggestions that it is even higher for the attention deficit form rather than the hyperactive form of ADHD (Hynd, Lorys, Semrud-Clikeman, Nieves, Huettner, & Lahey, 1991). Children with ADHD have been found to have significantly lower proportions of key essential fatty acids (including AA, DHA, and DGLA) than did controls (Burgess, Stevens, Zhang, & Peck, 2000; Mitchell, Aman, Turbott, & Manku, 1987; Stevens, Zentall, Abate, Watkins, Lipp, & Burgess, 1995; Stevens, Zentall, Abate, Kuczek, & Burgess, 1996). In one study, children with ADHD were found to be breastfed as infants less often than controls (Stevens, Zentall, & Deck, 1995) and breast milk contains adequate EFAs. A more recent double-blind crossover study (Richardson, Higgins, & Puri, 2002) found a significant reduction in attentional difficulties and general behaviour problems with a HUFA supplementation. A wide range of other placebo controlled and blinded studies (Boris & Mandel, 1994; Carter, Urbanowicz, Hemsley, Mantilla, Strobel, Graham, & Taylor, 1993; Egger, Carter, Graham, Gumley, & Soothill, 1985; Egger, Stoller, & McEwen, 1993), as well as a study of peptide abnormalities (Knivsberg, Nødland, Reichelt, & Fosse, 2000) have found improvements in behaviour following diet. In particular, Uhlig, Merckenschlager, Brandmaier, and Egger (1997) found a significant increase in beta brain electrical activity for children with ADHD following the ingestion of previously identified provoking foods. Mitchell et al. (1987), however, claim that it is unlikely a simple deficiency in EFA is the problem, or there would be more signs of ADD in other disease states where DGLA is low, such as cystic fibrosis.

There have also been studies of successful dietary intervention for children with symptoms of autism, with Knivsberg et al. (2001) and Richardson and Ross (2000) suggesting that abnormalities in fatty acid metabolism may play a common role in disabilities such as dyslexia, ADHD and autism spectrum disorder. Bell, Sargent, Tolcher, & Dick (2000) reported a single case study of a person with autism who had reduced HUFA concentrations and evidence of an instability of membrane HUFA which was consistent with the abnormal elevation of PLA₂ found in dyslexia (MacDonnell et al., 2000). Knivsberg, Reichelt, Nødland, & Høien (1995) provided autistic subjects with a diet free of gluten and milk proteins, and there was a normalisation of urine patterns and peptide levels within one year, as well as significant improvements in social, cognitive, and communicative skills in a four year follow-up. Those subjects who stopped the diet regressed. Reichelt, Ekrem, and Scott (1990) also found a normalisation of peptide patterns and improvement in social skills after one year of a similar dietary intervention, while Knivsberg, Reichelt, and Nødland (1999) obtained a similar result over two years of intervention and Cade, Privette, Fregly, Rowland, Sun, Zele et al. (2000) after three months of intervention. Chiang, Misner, and Kemperman (1999) claim that treatment with EFAs would facilitate the connection of the retinoid receptor pathways critical for vision, sensory perception and attention, and abnormal lipid levels in children with autism has been found to be reduced with the use of EPA and DHA (Sporn, Roberts, & Goodman, 1994). Other studies have also found a reduction in symptoms of autism following dietary changes (Knivsberg, Reichelt, Høien, & Nødland, 1998; Whiteley, Rodgers, Savery, & Shattock, 1999). Preliminary investigations at the University of Newcastle, Australia, have identified anomalies in HUFAs, indicative of poor intracellular processing of these lipids. Analyses of faecal bacteria also indicated that important gut bacteria are often lacking, and sometimes almost absent, with treatment to normalise this bacteria having beneficial results.

There have also been a number of studies which found benefits following treatment with omega-3 fatty acids for the management of schizophrenia (see Peet & Horrobin, 2000; Richardson & Ross, 2000; Shah, Ramchand, & Peet, 2000), with Horrobin (1999) postulating that in individuals who develop schizophrenia, there is an accelerated loss of unsaturated fatty acids, especially AA, DHA, EPA and DGLA. Richardson and Puri (1999) also report a single case study of a subject with both schizophrenia and dyslexia, in which there was a reduction in visual symptoms when reading and improvements in reading, spelling and visual motion sensitivity when provided EFA treatment. The measure of impaired motion sensitivity used in the Richardson and Puri study has been associated with magnocellular function and dyslexia (Stein, 2001).

Dietary intervention may also have implications for maternal and early infant nutrition. The normal western diet is relatively deficient in omega-3 HUFAs (see Mahadik, Mulchandani, Hegde, & Ranjekar, 1999), and diet supplements for pregnant women have resulted in increased levels of DHA in newborn infants (Connor, Neuringer, & Reisbick, 1991). In addition, HUFA levels at birth may affect postnatal HUFA levels independent of diet (Foreman-van Drongelen, van Houwelingen, Kester, Hasart, Blanco, & Hornstra, 1995) and adequate amounts of AA and DHA are needed by infants as they cannot adequately convert AA and ALA into other HUFAs.

The success of dietary intervention for visual processing problems, dyslexia, ADHD and autism suggest that a greater understanding of biochemical anomalies may result in dietary intervention being a useful addition to treatment procedures for IS. The identification of specific biochemical anomalies could also allow such intervention to be tailored to specific individual needs. An immediate challenge would be to identify whether changes in diet lead to changes in identified biochemical profiles and to changes in visual symptoms. It would also be interesting to explore whether dietary intervention leads to changes in neural responses, as identified by Uhlig et al. (1997) in relation to dietary changes for children with ADHD. It should be noted, however, that while supplementation based on biochemical anomalies would seem to be an efficient approach to testing a causative relationship, the degree to which supplementation will be effective will depend on the original cause of the anomaly.

CONCLUSION

There is growing evidence of a biochemical basis for a variety of learning and behavioural problems, including a visual processing sub-type of dyslexia (IS), which was the subject of this paper. There are, however, many questions which remain unanswered, and a great deal of further research is clearly needed if we are to determine the place of biochemical anomalies as a method of early identification and as a possible underlying causal mechanism. Learning to read involves many cognitive processes and a breakdown in any of these processes may affect ability to read. Identifying the place of biochemical anomalies in this complex skill is made harder because of the likely interaction between biochemical status and environmental influences. Visual and cognitive development tends to proceed in a sequential and hierarchical fashion and Neuringer et al. (1994) claim that early sensory deficits may lead to a greater vulnerability in later development and thus more vulnerability to the influence of environmental factors such as infection and stress (Horrobin et al., 1995). It is also important to note that changes in biochemistry, such

as fatty acid composition would affect membrane structure and membrane enzymes, as well as many other metabolic processes, and thus a single factor may not explain the whole process of learning affected by fatty acids (Yoshida, Sato, & Okoyama, 1998). It has been further suggested that biochemical anomalies and/or neural malfunction may operate in a reciprocal causation cycle (Farmer & Klein, 1995; Stein & Talcott, 1999), with changes in brain biochemistry leading to alterations in neural functioning, which could lead to further changes in neural functioning. We are only just beginning to be aware of the complexity of causal mechanisms, which may incorporate a multiplicity of chemical and electrical responses.

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Appendix A: Assessment of severity of symptoms/degree of improvement

Name: _____

Date: _____

Scores

0 = not at all

1 = a little bit

2 = moderately

3 = quite a lot

4 = extremely

a. Eye strain/fatigue/headaches while reading

- eyes hurt, burn, itch, feel tired
- become tired while reading
- headaches when reading
- have to make an effort to see words clearly

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

b. Print distortions/clarity while reading

- words move/double/merge
- words go blurry/fuzzy/shadowy
- words come off the page
- have halos around them

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

c. Photophobia/light sensitivity when reading

- fluorescent lighting uncomfortable or too bright
- white patterns and rivers in print
- glare from white page

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

d. Reading speed/errors while reading/duration of reading

- word-by-word reading
- skipping/guessing words
- re-reading
- understand what is read
- duration of reading

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4