I. Fatty Acid Metabolism in Neurodevelopmental and Psychiatric Disorders

Thursday 20th: 9.00-9.10

Alex Richardson
*Imperial College School of Medicine, London; and University of Oxford.*

Introduction to the FAND-2001 workshop – scope and purpose

The first Research Workshop on New Approaches to Neurodevelopmental Disorders was held in Inverness in 1999. This involved researchers from a wide range of different disciplines, addressing as a central theme the biological and metabolic basis of several common and overlapping neurodevelopmental disorders including dyslexia, dyspraxia, ADHD and the autistic spectrum. This event was an outstanding success, and many of the contributions were published in a special issue of *Prostaglandins, Leukotrienes and Essential Fatty Acids* (Vol. 63 (1-2), July 2000). It was agreed that this workshop should be the first of an ongoing series, and central issues noted as reference points for regular review and update included:

- The importance of interdisciplinary approaches when dealing with neurodevelopmental disorders such as dyslexia, dyspraxia, ADHD and autistic spectrum disorders;
- Difficulties in the identification and diagnosis of these developmental disorders, and the need for both early identification and early interventions to minimise the negative impact of these conditions;
- The comorbidity and other associations between these disorders, in contrast with the very separate ways in which they are commonly treated;
- The possibilities that new biochemical approaches can offer in understanding the etiology of neurodevelopmental disorders, and improving identification and diagnosis;
- The potential use of nutritional approaches, and particularly fatty acid supplements, in preventing and managing these conditions.

The current workshop – FAND 2001 - has attracted an extremely impressive range of contributors, and provides a timely update on this rapidly expanding field of research. Oral presentations have been organised into seven themes broadly reflecting the central issues noted above: (1) An overview of fatty acid metabolism in neurodevelopmental and psychiatric disorders, (2) Diagnostic and management issues in dyslexia, dyspraxia, ADHD and the autistic spectrum, (3) and (4) Immunological and other biochemical factors in neurodevelopmental disorders (5) Methods and techniques for investigating fatty acid metabolism (6) Nutrition in neurodevelopment and the role of fatty acids (7) Randomised controlled trials of nutritional treatments in psychiatric and neurodevelopmental disorders.

The eighth and final session is set aside for interactive discussion to review findings from the meeting and identify key issues of consensus or controversy. The aim is to achieve a consensus statement on both current research and future recommendations, as this meeting now seems likely to become an annual event. In this brief introduction to the workshop, some potential key issues will be highlighted for further discussion throughout the meeting.

Dr Alex Richardson is a Senior Research Fellow in Neurosciences at Imperial College School of Medicine, London, member of the Neuropsychiatry Research Group at the MRI Unit, Hammersmith Hospital, and Research Affiliate at the University Lab. of Physiology, Oxford (collaborating with Professor John Stein and Professor Tony Monaco at the Wellcome Trust Centre for Human Geneties). With Professor Stein, Dr Richardson helped found the Dyslexia Research Trust, and she is a co-opted Trustee and scientific advisor for the Dyspraxia Foundation. From a teaching background she became interested in dyslexia, and has spent fifteen years carrying out multi-disciplinary research into neurodevelopmental and psychiatric disorders including dyslexia, dyspraxia, ADHD, schizophrenia and depression, primarily aimed at better preventive, identification and management. Her current research centres on fatty acid metabolism in relation to behavioural and learning difficulties in these conditions, and the broader role of nutrition in brain development and function. This includes controlled trials of the effects of supplementation with highly unsaturated fatty acids in dyslexia, ADHD and dyspraxia.
Thursday 20\textsuperscript{th}: 9.10-9.30

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**Phospholipid Spectrum Disorders – An Overview**

The concept that there exists a range of neuropsychiatric disorders linked to abnormalities in phospholipids with roles in brain development and organisation was proposed on the basis of new understandings of the actions of phospholipids.

Abnormalities in brain function linked to the release, re-uptake and peroxidation of fatty acids have been described in schizophrenia and manic depressive illness and also in dyslexia and autism. The epidemiology of neurodevelopmental disorders shows linkage between all these conditions. A key discovery was that arachidonic acid, a cell signaller, regulated Growth Activating Protein 43 (GAP 43) in neuronal organisation in the brain.

The early discoveries in psychiatry that led to tranquillisers were serendipitous. In contrast, the new phospholipid paradigm has developed from both basic science and clinical observations. This enables the more directed development of new therapeutics and diagnostic techniques.

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After many years in clinical and laboratory research in the MRC, **Dr Iain Glen** founded the Highland Psychiatric Research Group, now the Foundation, in Inverness in 1981. The Foundation is an associate partner of the UHI Millennium Institute and has a spin-off company, Psychiatric Diagnostics Ltd.

After a distinguished career in physiology and in the Canadian MRC, where he proposed a prostaglandin basis for schizophrenia, **Dr David Horrobin** founded Scotia Pharmaceuticals. In order to pursue his work on treatments for neurodevelopmental disorders he founded Laxdale Ltd.
Lipids make up about 60% of the brain’s dry weight, of which phospholipids are a further 60% of this. Phospholipids are a major component of all cell membranes and play key roles in many brain signal transduction mechanisms.

There is now increasing evidence that abnormal phospholipid and related fatty acid metabolism may contribute to neurodevelopmental disorders and illnesses such as schizophrenia, bipolar disorder, depression and attention-deficit hyperactivity disorder (1-3).

This talk will review the main pathways of both EFA and phospholipid metabolism. In addition, the role of phospholipase A2s (PLA2) in signal transduction processes will be described with particular reference to the regulation of human cytoplasmic PLA2 (4).

References

Dr Crispin Bennett joined Scotia Pharmaceuticals in 1996 to work for Dr David Horrobin. In 1998 he joined Laxdale Research Ltd. with Dr Horrobin, specialising in the development of novel treatments for psychiatric and other illnesses. His academic background includes BSc Hons from the University of Reading, PhD from Hannah Research Institute, Ayr, and postdoctoral research at OARDC, Ohio State University studying the expression of foreign proteins by the lactating mammary gland.
On overview of recent findings regarding the role of omega-3 in essential fatty acids in neuropsychiatric illnesses may help to provide a conceptual framework for studying these nutrients in dyspraxia and related disorders. Epidemiological studies may help to define the magnitude of the effect of omega-3 fatty acids in depression and related affective disorders. One cross-national epidemiological study revealed that a 60-fold range of higher annual prevalence rates of major depression were related to lower amounts of seafood consumed in each country (r = -0.85, p<0.005). Seafood is a rich source of omega-3 fatty acids including docosahexaenoic acid (DHA). In a second study, higher prevalence rates of postpartum depression also spaned a 50-fold range across 22 countries and were likewise associated with lower rates of seafood consumption (r = - 0.81, p <0.0001) and the DHA content of mothers milk (r = - 0.84, p<0.000). In a third cross national study, a 30-fold range of prevalence rates of bipolar disorders (but not schizophrenia or anxiety disorders) were associated with lower seafood consumption (e.g. bipolar II disorders r = - 0.89, p <0.004). The antidepressant effects of eicosapentaenoic acid (EPA) and DHA that have been reported in anxiety disorders) were associated with lower seafood consumption (r = - 0.89, p<0.0001) and the DHA content of mothers milk (r = - 0.84, p<0.000). In a second study, higher prevalence rates of postpartum depression also spaned a 50-fold range across 22 countries and were likewise associated with lower rates of seafood consumption (r = - 0.81, p <0.0001) and the DHA content of mothers milk (r = - 0.84, p<0.000). In a third cross national study, a 30-fold range of prevalence rates of bipolar disorders (but not schizophrenia or anxiety disorders) were associated with lower seafood consumption (e.g. bipolar II disorders r = - 0.89, p <0.004). The antidepressant effects of eicosapentaenoic acid (EPA) and DHA that have been reported in randomized, blinded clinical trials among adults are consistent with these epidemiological data.

Unfortunately, these epidemiological and intervention data do not distinguish whether omega-3 insufficiencies are only important in adulthood, or if a life long predisposition to psychiatric illness might result from insufficiencies during early development. In order to partially test this question, we compared 14 infant rhesus monkeys fed standard infant formulas (which are virtually devoid of DHA and arachidonic acid, AA) to 14 infants fed formulas supplemented with 1% DHA and 1% AA. Improvements in motor maturity cluster scores and visual orientation were seen after 5 days of supplementation, but differences were not detectable past 30 days of life.

Contrary to our prediction, supplementation also reduced cerebrospinal fluid concentrations of 5-hydroxyindolacetic acid, a metabolite of serotonin. Serotoninergic dysfunction has been widely implicated as critical mechanism in the pathophysiology of major depression. Finally, we documented improvements in a neurologically driven physiological measure (heart rate variability, HRV) that persisted into adolescence (3.5 y) despite switching infants in both groups to a chow diet rich in DHA and AA after their 6 months of formula feeding. HRV data was collected while the animals were awake and restrained then again after administration of IM ketamine to induce anesthesia.

The magnitude of increase in HRV caused by prior supplementation (3 y ago) was similar to the acute effect of ketamine anesthesia. Reduced HRV is a sensitive measure of sympathetic nervous system reactivity, which predicts future cardiovascular morbidity and mortality. Reduced HRV has also been repeatedly described in subjects with major depression and among violent sociopaths. These preliminary data indicate that further research should be conducted to determine if insufficiencies in DHA and or AA during early development increase lifetime risk for depressive or aggressive disorders.

Dr Joseph Hibbeln is Chief of the Outpatient Clinic at the Lab of Membrane Biophysics and Biochemistry, National Institute on Alcohol Abuse and Alcoholism, NIH. He was recently promoted to Commander within the United States Public Health Service, having received their Outstanding Service Medal in 1999 and Unit Citation Award in 1997. His professional duties include Membership of the Scientific and Institutional Review Boards at NIAAA and the Acute and Ambulatory Care Committee of NIH Clinical Center, and Ad-Hoc Membership of the Board of Scientific Councillors of the National Institute on Aging, and NIMH Study sections. He was Chair and Primary Organizer of the 1998 International Workshop on Omega-3 EFAs and Psychiatric Disorders, Bethesda, MD, and a member of the Scientific Organizing Committee for the meeting in Japan, 2000 of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). He has published widely on the role of fatty acid and lipid metabolism in psychiatric disorder from both epidemiological and experimental perspectives, and is a reviewer for several leading journals in psychiatry and lipid research. He has given more than 30 invited presentations at National and International meetings since 1996, and his research has been covered in more than 250 print media articles, 50 television news programs and 75 radio programs reaching more than 125 million people in the US, Canada, great Britain, Australia, China and Japan.
II. Neurodevelopmental Disorders – Dyslexia, Dyspraxia, ADHD and the Autistic Spectrum: Diagnostic and Management Issues

Thursday 20th: 11.00-11.15

Alex Richardson
Imperial College School of Medicine, London; and University of Oxford.

New perspectives on ‘comorbidity’ in neurodevelopmental Disorders: Dyslexia, Dyspraxia, ADHD and the Autistic Spectrum

Together, dyslexia, dyspraxia, attention-deficit hyperactivity disorder (ADHD) and autistic spectrum disorders (ASD) account for the vast majority of primary school children with special educational needs. Each refers to a specific pattern of behavioural and learning difficulties for which the core defining features are quite different - but in practice the clinical overlap between them is very large. The traits defining each are also dimensional, as milder difficulties with reading and/or spelling, motor-coordination, attention and impulse control, and social and language skills are not uncommon in the general population.

Current definition and diagnosis are problematic, and consider only the behavioural level, while the predisposition to these conditions is clearly biological. The evidence points to shared genetic factors, and the proposal discussed here is that these include mild constitutional abnormalities of lipid metabolism, predisposing to a functional deficiency of certain highly unsaturated fatty acids (HUFA) crucial for normal brain development and function. Expression of such a genetic predisposition will be heavily influenced by nutrition – most critically during prenatal and early development, but also throughout the lifespan. In vulnerable individuals, brain development and function is likely to be more sensitive than usual to the supply of HUFA in the diet.

Certain physical features consistent with HUFA deficiency are associated with all of these conditions. These include mild neurodevelopmental anomalies, an excess of males affected, tendencies for reduced cerebral lateralisation, and an apparent link with autoimmune disorders. Children with dyslexia, ADHD or autism show more soft physical ‘fatty acid deficiency signs’ than matched controls (excessive thirst, frequent urination, rough, dry or bumpy skin, dull hair, flaky scalp and soft or brittle nails). Fatty acid abnormalities could also help to explain many other shared features at the cognitive and behavioural level, notably visual and motor problems, aspects of attentional and language dysfunction, and difficulties with mood, appetite and digestion, temperature regulation and sleep. If HUFA deficiency should contribute to any or all of these features, then dietary supplementation – particularly with omega 3 HUFA, might be able to prevent or ameliorate them.

Formal investigation of these complex neurodevelopmental conditions as ‘fatty acid deficiency syndromes’ still remains limited. ADHD has received most research attention to date, with equivocal results. However, ADHD is arguably the most problematic in terms of definition and diagnosis, and more recently the focus has turned to dyslexia, dyspraxia and the autistic spectrum. Increasing evidence for omega 3 deficiency in psychiatric disorders has provided another important ‘comorbidity’ perspective. Here, the evidence appears strongest for mood disorders, although the schizophrenia spectrum is also implicated. With techniques now available, careful investigation of fatty acid metabolism could help considerably to clarify some of the diagnostic confusion within these overlapping developmental and psychiatric disorders, and may offer important new approaches to their prevention and treatment.

Dr Alex Richardson is a Senior Research Fellow in Neurosciences at Imperial College School of Medicine, London, member of the Neuropsychiatry Research Group at the MRI Unit, Hammersmith Hospital, and Research Affiliate at the University Lab. of Physiology, Oxford.
Thursday 20th: 11.15-11.30

**John Richer**  
*Dept of Clinical Psychology, John Radcliffe Hospital, Oxford*

**Children’s disturbed behaviour – clinical and ethological perspectives on autism and ADHD**

Diagnostically categorising children’s disturbed behaviour is useful and necessary in clinical practice. It helps clinicians think about problems without becoming overwhelmed, it helps parents clarify their child’s problems in their own minds and feel they are not alone, and it helps in communicating with clinicians and others about these issues, thereby improving practice. The categories are “pegs to hang our thoughts on”.

But the categories are simply descriptions of behaviour, often imprecise and subjective, and their implications about underlying mechanisms, causes or treatment are also often vague.

Part of the problem is that the diagnostic categories used to classify children’s behavioural or learning difficulties are not based on solid scientific observation of behaviour in its natural habitat (home, street, school etc). When such an observational approach is adopted, as it is in ethology (a branch of Zoology and defined as the “biological study of behaviour”), subtly different patterns of disturbed behaviour emerge which help clarify treatment options and research directions. Clinicians, faced with the daily reality of the child’s disturbed behaviour and the family’s concerns, are likely to find the descriptions and ideas from this approach map better onto the reality they have to try and deal with, and to find too that parents, usually uncluttered with professional jargon, accept this approach more easily than the standard clinical nomenclature.

These issues are acute with Autism and ADHD, not least because there seems to be an epidemic of both. Autism is said by some to be increasing at an annual rate of 20%, others argue that this increase is due to better detection and a widening of the category. ADHD is also said to be increasing but is notoriously difficult to delineate.

An ethological approach, by studying behaviour in its natural setting and considering both biological and non-biological factors that can shape a child’s behaviour, has a great deal to offer in improving our understanding and management of these complex developmental conditions. Physical factors - including nutritional and other influences - are an obvious starting point for consideration. Assessment also requires a developmental perspective on the child’s behaviour in different contexts, and clinical management may involve a combination of physical, behavioural, cognitive and interpersonal approaches.

**Dr John Richer** is a Consultant Clinical Psychologist in Paediatrics at the John Radcliffe Hospital in Oxford. For many years he has seen young children with a variety of difficulties including autism and attentional problems, and this professional experience combined with an ethological/evolutionary approach has given him some unusual understandings of these and other developmental conditions. He has gained greatly from the many parents who have shared their insights and concerns with him.

He was founder chairman of the British Psychological Society’s Child Clinical Psychology Special Interest Group. Other positions he has held include Honorary Secretary of the Association for Child Psychology and Psychiatry, and Chairman and Secretary of their Oxford Branch. He is on the Editorial board of the Journal of Clinical Child Psychology and Psychiatry and until recently on the editorial board of Ethology and Sociobiology. He has written extensively on the understanding and treatment of autism and other conditions, on attachment, communication and intersubjectivity and consciousness as well as nutritional approaches, but all the time with an ethological/evolutionary approach. He was co-editor of the recently published book “Autism - The Search for Coherence” with Sheila Coates, the Head of Oxfordshire’s LEA Service for Autism. He has appeared many times on television and radio and in the press discussing these and other issues.

Sponsored by The Dyslexia Research Trust, Oxford (Registered Charity No 1052989)  
Contact: Clarice.Davies@physiology.ox.ac.uk
Thursday 20\textsuperscript{th} : 11.30-11.45

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**Perspectives from Educational Psychology: Dyspraxia and Dyslexia**

In educational practice, it is increasingly difficult to identify youngsters who present with symptoms of only one of the developmental disorders - Dyslexia, Dyspraxia, ADHD and Autistic Spectrum disorders. A review of the assessment of more than 600 individuals seen by the Educational Psychology Service in Durham suggests that co-morbidity occurs in more than 60\% of cases.

A sample of 43 dyspraxic primary school children (aged 6 - 11 years) was identified for targeted intervention that included access to motor programmes and perceptual training. These behavioural interventions have been developed over many years and shown to provide an effective method of reducing dyspraxic difficulties in many children. However, nine of these 43 youngsters made little progress following behavioural training in comparison to others in the sample, despite having matched neuropsychometric profiles and baseline levels of attainment.

Further assessment revealed that in seven of these youngsters, signs and symptoms consistent with essential fatty acid deficiency were evident. The outcome of subsequent supplementation with essential fatty acids will be presented in a case study.

**Dr Madeleine Portwood** is a Specialist Senior Educational Psychologist working in Durham. She is also Chairperson of the Education Committee of the Dyspraxia Foundation. Her extensive research into Dyspraxia is internationally accepted as being at the forefront of the work in the field and has formed the basis of several television documentaries on the subject. Her most recently published books – ‘Developmental Dyspraxia – Identification and Intervention (Fulton, London: 1999)’ and ‘Understanding Developmental Dyspraxia (Fulton, London: 2000)’, offer parents and professionals a means of identifying Dyspraxia and provide programmes of intervention, which can be implemented both at home and in the School environment. The focus of her current research is a collaborative intervention study with Dr. Alex Richardson to consider the effects of dietary supplementation with omega-3 and omega-6 fatty acids on a group of primary-age dyspraxic children.
Thursday 20\textsuperscript{th}: 11.45-12.10

**Joseph Biederman**  
*Harvard Medical School, and Massachusetts General & McLean Hospitals, Boston.*

**Common concepts on the neurobiology and pharmacology of ADHD across the lifespan**

There is increasing recognition that attention-deficit / hyperactivity disorder (ADHD), a heterogeneous disorder that carries a high risk of comorbidity, continues past childhood and adolescence into adulthood in many cases and may be under-identified in girls. The etiology of ADHD is unknown, although evidence from family studies of ADHD suggests a genetic origin for some forms of this disorder.

A variety of pharmacologic agents are available in treating ADHD: stimulant medications remain the first-line treatment for non-comorbid ADHD, whereas tricyclic antidepressants and bupropion are recommended for stimulant non-responders and patients with more than one psychiatric disorder. Complex cases of ADHD, however, may require rational use of combined pharmacotherapy.

**Dr Joseph Biederman** is Chief of the Joint Program in Pediatric Psychopharmacology at the Massachusetts General and McLean Hospitals, Chief of the Adult ADHD Program at Massachusetts General Hospital, and Professor of Psychiatry at Harvard Medical School. Dr Biederman is Board Certified in General and Child Psychiatry. He has been the recipient of the American Psychiatric Association Blanche Ittelson Award for Excellence in Child Psychiatric Research and the American Academy of Child and Adolescent Psychiatry Charlotte Norbert Rieger Award for Scientific Achievement. He has been inducted into the CHADD “Hall of Fame”. Dr Biederman has also been selected every year since its inception into the “The Best Doctors in America” compilation of the best physicians in the country. Dr Biederman is mentor to more than 10 junior investigators in the field. He is on the editorial board of multiple journals, a reviewer for most of the Psychiatric journals, and has served as a grant reviewer in the Child Psychopathology and Treatment Review Committee of the NIMH. Dr Biederman is the author and coauthor of close to 300 scientific articles, 50 book chapters and 200 scientific abstracts. During the decade of the 1990s, he was the fourth highest producer of high-impact papers in psychiatry as determined by the Institute for Scientific Information and the highest rank child psychiatrist (Science, 2000, Vol 288, pg959).
III. Immunological factors in Neurodevelopmental Disorders

Thursday 20th: 2.00-2.20

**John Stein**  
*University Lab of Physiology, Oxford*

**Sensory and motor function in developmental disorder - a specific vulnerability of magnocellular systems?**

Reading requires both the visual skill of being able to recognise the visual form of words, their orthography, and the auditory skill of matching letters with the sounds they stand for, phonology. Dyslexics demonstrate mild impairments in the visual magnocellular system that is responsible for detecting visual motion. Paradoxically, this system plays a crucial role in stabilising visual perception. It feeds back to the eye fixation system any visual motion that occurs when unintended movements cause images to move off the fovea (‘retinal slip’) in order to bring the eyes back on target. Thus the weak magnocellular system of dyslexics may destabilise their vision, so that letters may appear to move around and cross over each other, and good magnocellular function appears to be essential for successful development of visual orthographic skill. Likewise precise auditory magnocellular function is required for tracking the changes in sound frequency and amplitude that distinguish phonemes. Most dyslexics also have auditory/phonological problems, and these seem to be associated with mild impairments in the development of their auditory magnocellular neurones. Thus there is good evidence that many of dyslexics’ reading problems may have low level sensorimotor causes.

But why do magnocellular systems fail to develop properly? Reading problems are strongly hereditary. The genetic influence may operate by imped ing the development of magnocells throughout the brain. The best understood genetic linkage with reading difficulties is to the Major Histocompatibility Complex (MHC) Class 1 region on the short arm of Chromosome 6 which helps to control the production of antibodies. Magnocellular development seems also to be under the control of this MHC system. Hence it is possible that in the developing brain of dyslexics antibodies may compromise the development of magnocellular neurones. In addition their high transient sensitivity depends on their channel proteins being able to undergo rapid conformational changes. These require the surrounding cell membrane to be very flexible, which in turn depends on their local environment of flexible polyunsaturated fatty acids. Unfortunately these are becoming rare in modern diets.

In conclusion reading problems may result from impaired development of magnocellular neurones, particularly in the visual and auditory systems; this impedes their acquisition of the orthographic and phonological skills required for reading. The development of magnocells is probably genetically controlled by an immunological mechanism, but their function may also be affected by the availability of flexible polyunsaturated fatty acids.

Professor John Stein trained as a medical doctor at St Thomas's Hospital, London and began specialising in neurology. Since 1970 he has been a Fellow and Tutor in Medicine and Physiological Sciences at Magdalen College, Oxford, becoming Ad Hominem Professor in 1996. He is also a Fellow of the Royal College of Physicians. His research interests centre on the brain mechanisms involved in motor control, vision and hearing and the application of this to neurology and dyslexia. He is particularly interested in the auditory and visual perceptual impairments of dyslexic children as well as their eye movement control, and the effects of these on the multi-sensory processing required for learning to read. In addition to his extensive record of scientific publications on this issue, Professor Stein has also been a pioneer in the development of new treatments to alleviate some of the visual and other difficulties associated with dyslexia.
**Thursday 20**: 2.20-2.40

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A recent study (Corriveau et al., 1998, Neuron 21: 505-520) identified class I MHC, which is critical for antigen recognition in the immune system, as an unexpected candidate mediator of activity-dependent plasticity in the brain. To directly test this possibility, we studied mice genetically deficient for class I MHC signalling. We examined two well-characterised forms of activity-dependent plasticity in the mouse CNS: structural refinement of the developing retinogeniculate projection, and functional long-term potentiation (LTP) and long-term depression (LTD) in the adult hippocampus. These instances of plasticity were chosen since 1) they are known to require neuronal activity and 2) class I MHC is normally expressed in participating neurons.

We found that the development of the retinogeniculate projection is significantly altered in mutant mice genetically deficient for class I MHC signalling relative to that of wild-type mice. The disruption appears to selectively affect activity-dependent refinement of the developing projection, since the gross morphology of the projection, which is established earlier, via molecular cues, is roughly normal in mutant mice.

We also found significant differences in functional plasticity in mutant mice lacking class I MHC signalling. In the hippocampus, tetanic stimulation results in significantly greater potentiation of synaptic transmission in mutants. The enhanced LTP found in mutant mice is mechanistically similar to that seen in wild-types, but differs in magnitude. Furthermore, stimulation which produces LTD in wild-types instead leads to LTP in the mutants. Despite these striking changes in synaptic plasticity, basal synaptic transmission is indistinguishable from wild-type.

Together, these results demonstrate an important role for class I MHC in the activity-dependent remodeling and plasticity of connections in the developing and mature mammalian CNS. Defects in class I MHC signalling disrupt refinement of the retinogeniculate projection, which is essential for later visual processing, as well as LTP and LTD, which are thought to underlie certain forms of learning and memory. Thus genetic defects in class I MHC may represent an etiologic link between neurological and immune disorders, a possibility with important implications for the study of neurodevelopmental disorders such as dyslexia.

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Dr. Lisa Boulanger is a Research Associate in the Department of Neurobiology at Harvard Medical School and a Junior Fellow in the Harvard Society of Fellows. During her graduate work with Dr. Mu-ming Poo at the University of California, San Diego, Dr. Boulanger characterised intracellular signalling pathways that determine the effect of neurotrophic factors on synaptic strength. Recently, Dr. Boulanger and colleagues discovered that members of the class I MHC (major histocompatibility complex), key components of the adaptive immune system, are also expressed by neurons in the mammalian brain. Furthermore, their studies demonstrated that class I MHC is required for normal central nervous system development and synaptic plasticity in the adult. Currently Dr. Boulanger is using electrophysiological, histological, molecular biological and biochemical means to examine the mechanisms and effects of normal and abnormal class I MHC function in neurons, including the unexpected potential role for class I MHC in neurodevelopmental disorders.
Sera from mothers of dyslexic or autistic children contain antibodies to cerebellum

Some cases of neurodevelopmental disorders could be caused by maternal antibodies. Antibodies are molecules in the blood which normally protect us from bacteria and other foreign organisms. However, some conditions are caused by antibodies that attack, instead, the patient’s own tissues causing autoimmune disease. It appears that maternal antibodies which cross the placenta can sometimes affect the fetus. We previously showed antibodies to fetal muscle in sera from women who had had several babies born with a severe muscle developmental disorder. We confirmed the pathogenic role of the antibodies by injecting pregnant mice with the human sera and showing that mouse babies, but not the pregnant mouse, had muscle problems. Here, we have extended this idea to dyslexia and autism. We have selected women who have two or more consecutive children with either dyslexia (Dys-Ms) or Autism (Aut-Ms). We have looked for antibodies in their sera that might interfere with development of the fetal brain, and injected the sera into pregnant mice to look for effects on fetal development.

To see if these sera contained antibodies that bind to cerebellum, we tested six Dys-M sera and three Aut-M sera. We tested for IgG antibodies to neuronal antigens by indirect immunohistochemistry, flow cytometry and immunoblotting of extracts of newborn mouse brain. Three of the Dys-M sera bound to cells at the outer edge of the newborn cerebellar plates, with a distribution similar to an antibody against Purkinje cells; one bound to a neuroblastoma cell line, and two showed strong bands on western blots. One of the Aut-M sera showed strong binding to the Purkinje cells and a band on western blotting. Pregnant mice injected with Dys_m and Aut-M sera gave birth to healthy litters. However, subtle changes in the mouse pups were detected as they developed. These changes were compatible with alterations in the function of the cerebellum.

Cerebellar functional abnormalities have previously been reported in both dyslexia and autism. These preliminary findings suggest that maternal serum antibodies could be involved in the aetiology of some cases of dyslexia and autism.

Professor Angela Vincent is Professor of Neuroimmunology in the Department of Clinical Neurology at the University of Oxford. She heads an internationally recognised, multidisciplinary research group at the Weatherall Institute of Molecular Medicine at the John Radcliffe Hospital. The Group works mainly on autoimmune and genetic disorders of the peripheral nervous system, but is increasingly interested in autoimmune diseases of the central nervous system, such as some forms of epilepsy and sleep disorder, and in the role of maternal antibodies in causing developmental abnormalities.
Thursday 20th: 3.00-3.20

**Kathleen Taylor**  
*University Lab of Physiology, Oxford*

**Does platelet-activating factor (PAF) have a role in developmental dyslexia?**

The FAND-2001 workshop is centred around the claim that fatty acids may be involved in neurodevelopmental disorders, and that the typical Western diet is much more heavily weighted than may be optimal for human health in favour of the omega-6 fatty acids (such as arachidonic acid), relative to the omega-3 variety.

The enzyme PLA2, which releases arachidonic acid from cell membranes, may be raised in dyslexics compared to controls. This suggests that dyslexics are particularly likely to have high levels of arachidonic acid available. Dyslexic brains also appear to have structural microanatomical differences. How might these differences arise?

Proinflammatory cytokines such as platelet-activating factor (PAF), a product of arachidonic acid metabolism, could be involved. PAF is known to be neurotoxic at high concentrations, and is a good candidate to cause the sort of damage observed in dyslexic brains. The question then arises of how PAF could come to be so elevated in dyslexia. It seems that both genetic and environmental factors are involved. A prime candidate for environmental influence is infection during brain development.

The PAF hypothesis is consistent with infection as a cause of damage. Furthermore, it makes specific predictions about the types of infection involved. The hypothesis can explain some puzzling features of dyslexia, and opens up some exciting new avenues for research.

**Dr Kathleen Taylor** is a postdoctoral researcher at Oxford's Physiology Department. She studied physiology and philosophy as an undergraduate (Oxford), then did a research MSc in neuropharmacology (Stirling), before returning to Oxford to do a D. Phil in computational neuroscience. She has presented posters at BNA and FENS meetings and has published letters and articles in a range of journals from the Lancet to the Journal of Consciousness Studies. Her wide-ranging interests include epidemiological and neuroimmunological aspects of dyslexia and schizophrenia, as well as theoretical models of brain function.
Diagnoses such as “Autism”, “Asperger Syndrome”, “Dyslexia” and “Attention Deficit Disorder” rely totally upon descriptions of symptoms exhibited by affected individuals. We believe that they are descriptive of varying manifestations of a common underlying pathology. Our studies suggest that symptoms are consequent upon the passage of peptides with opioid activity from the intestines to the CNS. These opioid peptides constitute the bullets that affect transmission in all major systems of the CNS as well as the development of specific regions. These peptides are predominantly derived from incomplete digestion of gluten and casein but other proteins may be involved.

Any mechanism which results in increased levels of peptides in the intestines or increased permeability of the intestines or blood brain barrier will result in more peptides reaching the CNS. Most of the “alternative” biomedically based therapies are based upon this concept in some way.

Our studies have focused on analyses of urine from subjects with autism. We sought peptides with opioid activity derived from dietary sources. During these investigations, we became aware of one particular component that was present in apparently substantial quantities in some 80% of our subjects. This we later identified as being Indolyl Acryloyl Glycine (IAG). IAG is considered as a minor metabolite of tryptophan. It has been reported in Hartnupp Disease in which dietary tryptophan is not absorbed and so is available for conversion to Indolyl pyruvic and/or propionic acid by intestinal bacteria. There is newer evidence to suggest that this may also occur within the mammalian body. These compounds are then converted to Indolyl Acrylic Acid (IAcrA) which is then metabolised, in the liver, by the addition of Glycine. Our evidence suggests that IAG has little physiological relevance but IAcrA is a flat and very reactive molecule. We hypothesised that it could be incorporated into triglycerides (by replacing a fatty acid during synthesis). These fats form the bulk of membranes such as occur in the intestines and blood brain barrier but also other membranes throughout the body. This would result in increased permeability and encourage passage of peptides from the intestines to the CNS. There is evidence from Sunderland (Lees) and Stirling (Bell) that IAG will affect membrane integrity as described but it is unclear whether or not these effects are of clinical relevance.

We have observed that in the majority of the cases of autism where vaccine damage (particularly combined MMR vaccine) is alleged this IAG is absent. This could be interpreted as evidence that these two elements have a causative role in triggering these syndromes. We have also demonstrated (Anderson) that Organo-Phosphorous (OP) pesticides could inhibit some normal metabolic processes of tryptophan metabolism in such a way that processes are distorted in this direction. We speculate on the role of OP pesticides in the reported increases in the incidence of Autism and related disorders. We believe that the use of appropriate fatty acids is effective in ameliorating some symptoms of these disorders and that they act in accordance with these hypotheses.

Dr Paul Shattock (OBE) is the father of a young man with autism. He is a Pharmacist, Director of the Autism Research Unit at the University of Sunderland, and founding Chairman of Communities for Autistic People (CAP) and European Services for People with Autism (ESPA). He has been a Member of the Executive Committee of the National Autistic Society 1982-1995; Member of Council (1990 to date), Hon. Sec. of Autism-Europe (1991-2000) and Vice President of the World Autism Organisation (2000 to date). He was appointed OBE for his services to people with autism in 1999. His research centres on the biological mechanisms that underlie autism, including biochemical and metabolic pathways that have implications for digestive and immune function as well as the development and function of the brain. His aim is to use this understanding to develop practical strategies for ameliorating some of the problems associated with autistic spectrum disorders.
Autistic spectrum disorder (ASD) was first described by Kanner and, until recently, the incidence was around 5-10 in 10k of the population. Over the last ten years the incidence has increased dramatically and three recent epidemiological studies in England put the incidence between 1 in 500 and 1 in 175 of children under five years. While the reasons for this increase are at present unclear, and likely to be multi-factorial, the potential burden on Health, Education and Welfare budgets will be substantial. Recent figures from the Mental Health Foundation put the lifetime cost at around £3m per patient with a total annual cost to the U.K. economy of over £1 billion. If the recent figure described above is correct this cost could rise to £5 billion per annum.

To date we have analysed the fatty acid compositions of polar lipids from RBC of twelve patients on the autistic spectrum, six with a diagnosis of autism and six with Asperger’s syndrome. Four of the six with autism showed reduced levels of EPA and DHA, compared to control samples analysed simultaneously, and compared to control samples from previous studies. The ARA levels were normal in all but one of these where the level was above control values. In Asperger’s syndrome EPA and DHA were reduced while ARA levels were higher than control values making the ARA/EPA ratio particularly high in this group.

Upon storage at –20°C for 6 weeks, four of the six autistic samples showed dramatic reduction of HUFA (up to 70%), particularly of DHA, EPA and 22:5n-3, but also of ARA and 22:4n-6. The control samples and five of the six Asperger’s syndrome samples showed no, or only slight (up to 10%), reduction of the same HUFA. One of the patients with Asperger’s syndrome also showed an above average loss of HUFA (up to 33%), suggesting that HUFA loss may occur in both forms of ASD or that the diagnosis was wrong. In addition, Dr Alastair Glen’s group, at the Victoria Hospital in Glasgow, have developed an assay to measure the concentration of PLA\textsubscript{2} enzyme (µg PLA\textsubscript{2}/g Hb) in RBC. In four patients with ASD (all with “classical” autism or Asperger’s syndrome) analysed to date all had PLA\textsubscript{2} concentrations above the normal maximum range value of 2.8 µg/g Hb. The mean value of 3.89 ± 0.59 µg/g Hb in patients with ASD was significantly greater than the mean control value (2.58 ± 0.16; P < 0.02). In a very recent sample from a patient with “regressive” autism, which suffered high losses of HUFA on storage at –20°C, the PLA\textsubscript{2} value was 5.4 µg/g Hb. Furthermore, in a recent assessment of children with ASD (n = 43) using a fatty acid deficiency (FAD) questionnaire, > 65% scored greater than 3 compared to 13% attaining the same FAD score among control subjects. Results from the small numbers of blood samples studied to date suggest that patients with ASD have abnormal fatty acid metabolism, resulting in an apparent essential fatty acid deficiency which may, in part, be due to increased concentrations/activity of PLA\textsubscript{2}. Before successful treatment of these phospholipid spectrum disorders can be employed, an in-depth study of the extent of these abnormalities should be undertaken.

**Dr. Gordon Bell** is a project leader in the Nutrition Group Institute of Aquaculture. The Nutrition group has particular expertise in the nutrition and biochemistry of n-3 polyunsaturated fatty acids, fat soluble vitamins and carotenoid pigments. Dr. Gordon Bell is a senior biochemist with particular interest and expertise in lipid nutrition and with more than 80 peer – reviewed publications. While the reputation of the group has been built on the study of nutrition and lipid metabolism in the aquatic environment our knowledge of polyunsaturated fatty acid metabolism coupled with expertise in complex lipid analysis has seen our activities develop in the field of human nutrition and disease, particularly neurological conditions. The Nutrition group has recently undertaken studies on red blood cell abnormalities in patients with schizophrenia, in conjunction with Dr David Horrobin and others in this field. This work has confirmed evidence of a “phospholipid spectrum disorder” in schizophrenia which has been shown to respond to nutritional intervention using essential fatty acid concentrates.
Tryptophan is bound to albumin in the blood: it is the precursor for the neurotransmitter 5-hydroxytryptamine (5-HT), which is involved in fatigue and sleep. An increase in plasma free tryptophan is thus likely to increase the rate of synthesis of brain 5-HT, leading to central fatigue. Central fatigue is involved in overtraining, chronic fatigue syndrome and post-operative fatigue.

Tryptophan competes with the branched chain amino acids (BCAA) for entry into the brain across the blood-brain barrier. The plasma concentration of BCAA was measured in chronic fatigue syndrome patients (CFS) before and after exercise, and in patients undergoing major surgery. In the CFS patients, the pre-exercise concentration of plasma free tryptophan was higher than in controls (p<0.05) but did not change during or after exercise. This might indicate an abnormally high level of brain 5-HT in CFS patients leading to persistent fatigue. In the control group, plasma free tryptophan was increased after maximal exercise (p<0.001), returning towards baseline levels 60 min later. The apparent failure of the CFS patients to change the plasma free tryptophan concentration or the free tryptophan/BCAA ratio during exercise may indicate increased sensitivity of brain 5-HT receptors, as has been demonstrated in other studies.

After major surgery, the plasma free tryptophan concentration and the free tryptophan/BCAA concentration ratio were markedly increased compared with baseline levels. There was a correlation between these parameters and fatigue, as measured by the Profile of Mood States (POMS). Provision of BCAA has improved mental performance in athletes after endurance exercise.

Lindy Castell left school at 16 to embark on a career in farming. A winter spent feeding 200 Landrace pigs in fields knee-deep in mud put paid to that, and she went to work in Human Physiology here as a technician for the late Dan Cunningham and Brian Lloyd. After a chequered educational career which included taking some Open University courses and some graduate courses in the USA (where she worked for 2 years), she was delighted to find that it was not too late for her (as a grandmother) to embark upon a higher degree at Oxford, under the supervision of Eric Newsholme. Since Eric’s retirement she has been running the Cellular Nutrition Research Group.
Thursday 20th: 5.00-5.15

**Caroline Pond**  
*Dept of Biology, the Open University*

**The role of adipose tissue in managing the supply of lipids to other tissues**

Adipose tissue is a major source of fatty acids during lactation, birth, and the many periods of anorexia and undernutrition that are inevitably associated with diseases of infancy and childhood. The fatty acid composition of adipose tissue storage lipids reflects that of the diet ingested weeks or months previously. Since the immune system, the mammary glands and the developing nervous system compete for many of the same precursors, it is important to understand the role of adipose tissue in partitioning dietary and metabolic supplies between the two systems.

Observations on wild animals show that the adipose tissue associated with major lymph nodes does not expand excessively in natural obesity and is selectively conserved even in severe starvation. Studies on laboratory rodents reveal complex internal organisation of adipose depots that contain lymph nodes. Polyunsaturated fatty acids selectively accumulate in the triacylglycerols of adipocytes surrounding lymph nodes. The absolute proportions of the fatty acids can be manipulated by the long-term changes in the diet, but the pattern of site-specific differences in the composition of triacylglycerols in relation to lymph nodes is constant. The existence of this gradient means that single biopsies of subcutaneous adipose tissue do not adequately represent the composition of fatty acids made available to inflamed lymph nodes *in situ*, and perhaps that supplied to other tissues. Lipolysis in adipocytes of node-containing depots can be stimulated via immune activation of the lymph nodes that they enclose. This interaction can be modulated by the fatty acid composition of the diet during the weeks before immune stimulation. The time course and anatomical organisation are consistent with the hypothesis that perinodal adipose tissue is specialised to provision the proliferation and maturation of lymph node lymphoid cells during immune responses, thus emancipating the immune system from competition with other tissues.

These site-specific properties of perinodal adipose tissue may be important for understanding the contribution of undernutrition, fevers and infectious diseases to neurodevelopmental disorders. Lymph node-associated adipose tissue may also be involved in the many known effects of dietary lipids on normal and pathological functioning of the human immune system.

**Dr Caroline Pond** studied Zoology at Oxford University, completing a doctorate in 1971, and taught comparative physiology there for four years. Her interest in adipose tissue began after she moved to USA in 1975, and taught Biology and veterinary anatomy at the University of Pennsylvania in Philadelphia. She came back to Britain in 1979 and is now a reader in Biology at the Open University in Milton Keynes, where she mostly writes textbooks for a wide variety of undergraduate courses. Her research aims to find a functional basis for the distribution of adipose tissue and its role in managing lipid reserves, integrating comparative studies of naturally obese wild animals with laboratory experiments.
V. Methods and Techniques for Investigating Fatty Acid Metabolism

Friday 21st: 9.00-9.20

Iain Glen, Marion Ross, Brian Ross
Highland Psychiatric Research Group, Inverness

Development of new objective diagnostic tests for neurodevelopmental disorders.

The diagnosis of neurodevelopmental disorders such as schizophrenia and autism relies on clinical assessment. These procedures are time consuming and frequently inaccurate, as well as needing experienced and trained personnel. This can result in both misdiagnosis and, especially in childhood disorders, cases being missed.

New tests are being developed which provide simple, objective means to diagnose these disorders. Instead of relying on the expertise of clinical staff, these new tests utilize the changes in body biochemistry that underlie these disorders. The procedures being developed include:

- Visually readable skin tests that examine the functioning of signaling mechanisms.
- Non-invasive analysis of volatile compounds in breath samples for signs of metabolic disturbance.
- Molecular genetic analysis of candidate genes to diagnose and predict occurrence of the disorder.
- Use of microarrays to detect patterns of gene expression unique to the disorder.

Use of any one of these procedures, or more likely a combination, will revolutionize our ability to diagnose, and then treat, a variety of conditions. These procedures will also likely differentiate between the disease subtypes contained within the various ‘spectrum’ disorders, allowing informed treatment options to be chosen.

After many years in clinical and laboratory research in the MRC, Iain Glen founded the Highland Psychiatric Research Group, now the Foundation, in Inverness in 1981. The Foundation is an associate partner of the UHI Millennium Institute and has a spin-off company, Psychiatric Diagnostics Ltd.
There is evidence of co-morbidity in the neurodevelopmental disorders. A potential common trait is linking these conditions is a depletion of polyunsaturated fatty acids (PUFA) from the cell membranes. Although the underlying biochemical cause is unclear, an abnormality of fatty acid metabolism is likely. Decreased PUFA in these disorders may be genetic in origin, however oxidative stress may also contribute.

Lower levels of PUFA may have implications for brain and neural development since the brain is highly rich in AA and especially DHA. Deficiencies in either fatty acid may have deleterious effects upon brain development. Furthermore, reduced availability of fatty acids will also impair production of the eicosanoids.

In addition to dietary abnormalities or increased energetic breakdown, low levels of PUFA as found in autistic and ADHD children may also be the result of increased oxidative stress. Oxidative stress is caused by the body over-producing free radicals in the absence of sufficient protection by antioxidants. The balance between free radicals and antioxidants can be upset by many different factors, which can cause an increase in free radical activity resulting in damage to DNA, proteins and fatty acids.

Studies of lipid peroxidation in neurodevelopmental disorders are however limited, being mainly restricted to schizophrenia in which there is evidence of increased oxidative stress. However, all clinical studies involving oxidative stress must be interpreted carefully due to the presence of confounding factors such as smoking which also results in a reduction of PUFA levels via the inhalation of free radicals in cigarette smoke.

A very straightforward measure of oxidative stress makes use of the fact that hydrocarbon gases are also products of lipid peroxidation, which are excreted in breath. A recent study has found increased levels of the hydrocarbon butane in the breath of patients with schizophrenia and bipolar disorder, compared to that of control subjects. The origins of butane are unclear and may not be related to oxidative stress. There are over 4000 volatiles found in breath, some of these reflect the environment and others, products of metabolism. Therefore non-invasive measures such as breath analysis may have a role in identifying both those at risk and the metabolic abnormality responsible.

Marion Ross (BSc, MSc, CChem. MRSC) trained as an analytical chemist, but her interest in nutrition whilst working in the field of lipoproteins led her to a degree in nutrition and dietetics. She qualified as a dietitian and always being interested in research then went back to the Department of Biochemistry in Aberdeen. This led to an MSc and to further work in the field of antioxidants and lipid peroxidation. She maintained a strong interest in lipids, lipid peroxidation, carotenoids and antioxidant vitamins and has published in this area. She joined Highland Psychiatric Research Foundation in 1998. Her current work includes developing a ‘breath test’ as an aid to diagnosing neurodevelopmental disorders using Gas Chromatography / Mass Spectrometry with ATD.
Friday 21st: 9.40-10.00

**Basant Puri**  
MRI Unit, MRC Clinical Sciences Centre, Hammersmith Hospital, London

**MRS/MRI techniques for the investigation of lipid metabolism**

The following three types of cerebral magnetic resonance scanning techniques will be briefly discussed with respect to the investigation of lipid metabolism in humans: 31-phosphorus magnetic resonance spectroscopy, proton magnetic resonance spectroscopy, and image registration.

The advent of 31-phosphorus magnetic resonance spectroscopy has made it possible to study phospholipid metabolism non-invasively *in vivo* in the human brain. In particular, the phosphomonoester and phosphodiester resonances index cell membrane phospholipid turnover. Proton magnetic resonance spectroscopy can also be used to investigate lipid metabolism.

The techniques of image segmentation, subvoxel registration and quantitation of serially acquired high resolution 3D magnetic resonance images can be used to investigate changes in cerebral structure, which may occur in relation to changes in lipid metabolism.

**Dr Basant K. Puri** is a consultant psychiatrist/senior lecturer at the Robert Steiner Magnetic Resonance Unit, Imaging Sciences Department, Clinical Sciences Centre, Faculty of Medicine, Imperial College, Hammersmith Hospital Campus, London, and honorary consultant in imaging, Department of Radiology, Hammersmith Hospital, London. His recent publications include:


The reasons for analyzing tissue fatty acid compositions in clinical studies for dyspraxia, dyslexia and related disorders should be carefully considered. In clinical intervention trials which compare pre and post treatment status, these measures can be used (1) To determine which subjects have complied with treatment by utilizing preset criteria for change in fatty acid status. (2) To determine resulting tissue compositions. The consumption of the same dose of EPA or DHA may not produce the same tissue changes in each subject. It must be assumed that each subject will enter the study with a different baseline fatty acid status so that subjects who receive the same dose are not likely to end up with the same resulting fatty acid status. For example, a subject with a background diet high in fried food containing soy oils will have a smaller response to EPA and DHA compared to a subject with a background diet containing olive oil. (3) To determine if any resulting clinical improvements are due to increases in the fatty acids prescribed or due to secondary alterations in other fatty acids. For example, prescribing EPA ethyl ester may, or may not, raise DHA levels or alter arachidonic acid levels. Correlational analyses can be used to assess if there is a specificity of response. Great care must be taken in assuming if single time point compositional data can reveal any useful information regarding differences in endogenous metabolism in comparisons of subjects to controls. Consider that the maximal capacity to metabolize linolenic acid to docosahexaenoic acid apparently occurs in newborns who can produce only as much as 500 ug/day. Since several grams of EPA and DHA can be consumed in one meal, the dietary intake of subjects and controls may have to be rigidly controlled for a prolonged period of time in order to make meaningful comparisons regarding differences in endogenous metabolism. Exogenous factors that increase oxidation also need to be controlled. For example, smoking lowers DHA erythrocyte status. In stable isotope tracer studies we have found however that the rate of production of DHA from LNA is increased among smokers compared to controls, but that this increase does not appear to be able to overcome the effects of smoking. Not surprisingly, “products to precursor ratios” have no relationship to rates of metabolism in stable isotope studies in healthy volunteers, smokers or alcoholics and may also be uninformative in the dyspraxic population. Without control of the large number of confounding variables, and the use of stable isotope studies, it will be difficult to make any definitive conclusions regarding abnormal elongation and desaturation of essential fatty acids in these populations.

The choice of tissue to sample and its ability to reflect of brain and peripheral tissue compositional status should also be carefully considered. Plasma, serum or erythrocytes are attractive candidates because of their ease of sampling. Recent studies of animals that have been reared for three generations on omega-3 deficient diets then re-fed EPA and DHA have helped to provide an insight into the time course of restoring brain and peripheral tissue compositions. In brief, plasma and liver become nearly completely restored after 2 weeks, while the brain is nearly restored in its DHA composition after more than 8 weeks. These data suggest that a clinical trial of 8 weeks or more should be conducted if the goal of the treatment is to restore brain DHA composition.

(2) Blood fatty acids in unmedicated patients with schizophrenia

(3) The relation of maternal LC-PUFA status to infant visual and cognitive development
VI. Nutrition in Neurodevelopment – The role of fatty acids

Friday 21st: 11.00-11.35

**Michael Crawford**  
*Institute of Brain Chemistry and Human Nutrition, University of North London*

**The role of essential fatty acids in membrane function and neurodevelopmental disorder: clinical and evolutionary perspectives**

Mortality and morbidity rise as birthweights fall below 2.5Kg providing an important clue to aetiology especially of the neurodevelopmental disorders. The very preterm infant is at high risk to brain damage and several other complications or prematurity. Brain lipids are highly conserved. Compositionally, the signalling membranes date back to their marine origins 600 million years ago.

Arachidonic (AA) and docosahexaenoic (DHA) acids are substrates for the fast growing lipid bi-layers of the cell membranes of the endothelium, retina and brain. The placenta normally doubles their proportions found in maternal plasma for the fetus. Subsequent nutritional methods for very preterm infants do not replicate that placental input. The design for lipid nutrition follows that of the term infant for lipids although for protein, minerals and energy, the practise is to replicate the placental input. Yet this is a time when the vascular system and brain are growing at an extremely rapid rate. Moreover, the requirement for essential lipids is at its height. The brain is a lipid rich organ (60% of structural material). The fetal brain consumes 70% of all the calories fed to the fetus. In addition, several studies have shown that post-natally, the plasma levels of AA and DHA plummet to a third of the levels that the baby would have received had it remained as a fetus.

The consequences of membrane deficits at critical levels, at this time of fast growth demands for lipid membranes, are predictable: namely, leaking cell membranes, rupture, hemorrhage followed by an eicosanoid and cytokine response leading to ischemia and inflammation. In the brain, reperfusion would be followed by peroxynitrite formation, aggressive peroxidation and cell death. Morbidity associated with inadequate provision of brain specific lipids would also be expected in more subtle manners such as restricted mental development or distortion of normal brain growth pattern. Indeed it is thought that the rapid rise in mental ill health in the last two decades, which is following from country to country the previous rise last century of mortality from heart disease, is a consequence of lipid malnutrition affecting the fetus. Perinatal conditions, cardiovascular disease and mental ill health are predicted to be the top 3 in the rank of the global burden of ill health by 2020.

Peter Willatts  
*Dept of Psychology, University of Dundee*

**Long-term effects of LC-PUFA in infancy on cognitive function at 6 years of age.**

Long-chain polyunsaturated fatty acids (LC-PUFA), especially docosahexaenoic acid (DHA) and arachidonic acid (AA), are important for normal visual and cortical development.

Several randomised studies have reported improved performance on a variety of cognitive measures in infants fed a formula containing LC-PUFA, compared to control infants fed a formula with no LC-PUFA. One consistent finding has been shorter duration of looking at visual stimuli in infants who received LC-PUFA compared to infants who received no LC-PUFA.

Shorter look duration has been interpreted by developmental psychologists as indicating faster and more efficient information processing, and shorter look duration in infancy is moderately correlated with better performance on cognitive tests in later childhood. The aim of the present study was to determine whether dietary preformed LC-PUFA in infancy affect efficiency of processing in later childhood.

A total of 237 infants were randomised to formulas containing DHA + AA or no LC-PUFA for a period of four months in four centres (Dundee, Birmingham, Leuven, Milan). Of these children, 147 (62%) were enrolled in the present study (LC-PUFA = 71, control = 76). Children were tested at mean age 5 years 10 months (SD = 3.3 months) on the Matching Familiar Figures Test (MFFT). The MFFT involved choosing the one picture from four alternatives that exactly matched a target. Dependent measures (averaged across 12 problems) included latency to respond, number of errors, efficiency, and impulsivity. Children were also given the Day-Night test (a measure of ability to inhibit interfering information), and the WPPSI IQ test.

Although both groups were equally successful at identifying the correct picture on their first MFFT responses (LC-PUFA = 5.4, Control = 5.5; p = .839), children who received LC-PUFA in infancy were faster at making correct choices (LC-PUFA = 6.2 sec; Control = 7.8 sec; p = .035). MFFT efficiency was also significantly better in the LC-PUFA group than the control group (p = .034). There were no differences between the groups on MFFT impulsivity, Day-Night test scores, and IQ.

These results show that dietary preformed LC-PUFA in infancy enhance more efficient information processing at 6 years of age. This long-term influence of LC-PUFA on children’s cognitive behaviour demonstrates the importance of adding LC-PUFA to infant formula.

Dr Peter Willatts is a Senior Lecturer in Developmental Psychology at the University of Dundee. His main research interest is the development of cognitive abilities in infants and young children, with a special focus on the development of thinking and problem solving. In collaboration with Dr Stewart Forsyth (Institute of Child Health, Dundee), he has investigated the role of long-chain polyunsaturated fatty acids (LC-PUFA) on cognitive development in infants. Together, they have undertaken a series of studies, using novel methods for assessing cognitive function, which have shown that LC-PUFA contribute to the development of attention, memory, and problem solving. They have recently completed two studies showing that dietary LC-PUFA in early infancy have long term effects in later childhood, and maternal LC-PUFA status during pregnancy is related to infant cognitive function.
Stereoacuity at age 3.5y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study

**Background:** Observational studies have suggested that breast-feeding benefits the visual development of pre-term children, which has been attributed to the presence of docosahexaenoic acid (DHA) in breastmilk but not most formula milks. Randomized studies showed that pre-term children require a dietary supply of DHA in the first few weeks of life for optimal visual development, but it is unclear whether full-term children experience similar benefits from breast milk or DHA supplements.

**Objective:** The objective in this study was to compare stereoacuity at age 3.5 years in healthy, full-term children who were breast-fed and in similar children who had not been breast-fed after adjustment for socio-economic status and maternal diet.

**Design:** Prospectively collected data on maternal diet during pregnancy (including intake of oily fish), the child’s diet and the socio-economic status of the family were examined. Stereoacuity at 3.5 years was assessed.

**Results:** Children who had been breast-fed for 4 months were more likely to achieve high grade stereopsis, or depth perception, than were children who had not been breast-fed (adjusted odds ratio 2.77; 95% CI: 1.54, 4.97). The mother’s antenatal blood DHA content was associated with her intake of oily fish (P < 0.001). Children whose mothers ate oily fish during pregnancy were also more likely to achieve high-grade stereopsis than children whose mothers did not eat oily fish (adjusted odds ratio 1.57; 95% CI: 1.00, 2.45).

**Conclusions:** The results of this study suggest that for full-term infants, breast-feeding is associated with enhanced stereopsis at age 3.5 years, as is a maternal DHA-rich antenatal diet, irrespective of later feeding practice.

Dr Cathy Williams and colleagues have been studying visual development in collaboration with the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is a population-based birth cohort study, following children born over a 21-month period from April 1991 to December 1992, in the area that was Avon. Approximately 14,000 children were recruited whilst in utero. Diverse, prospectively collected data are available for these children, including that from physical samples such as blood and DNA. The main areas of her research have been into the effects of pre- and postnatal diet on the developing visual system and the effectiveness of pre-school vision screening. Dr Williams is also a part-time Consultant Paediatric Ophthalmologist at Bristol Eye Hospital, responsible for providing eye-care for children with “special needs” due to a variety of developmental and behavioural problems.
VII. Nutritional Treatment of Neurodevelopmental & Psychiatric Disorders – Randomised Controlled Trials

Friday 21st: 2.00-2.35

Malcolm Peet  
NHS Dept of Psychiatry, Sheffield

Eicosapentaenoic acid (EPA) in the treatment of depression and schizophrenia

Epidemiological and biological studies have provided the rationale for treating depression and schizophrenia with omega-3 polyunsaturated fatty acids (PUFA).

In schizophrenia, initial open-label studies suggested improvement in schizophrenic symptoms and tardive dyskinesia when concentrated fish oil was added to existing antipsychotic treatment. A double-blind, placebo-controlled pilot study indicated that this benefit was related to EPA rather than DHA.

A larger multi-centre double-blind placebo-controlled trial of 1,2 and 4 grams of Ethyl EPA added to existing antipsychotic medication has now been completed. This has shown significant dose-related benefits from adding 2 grams of Ethyl EPA to treatment with Clozapine. The 2g dose of Ethyl EPA produced significant increases in red cell membrane levels of AA and DHA as well as EPA, which was not seen with the lower and higher dosages. Ethyl EPA also reversed the increases in serum triglyceride levels produced by Clozapine.

In a separate study, EPA was given as a sole treatment, and it was found that by the end of the three month study, every patient on placebo required treatment with antipsychotic drugs, whereas in the EPA group half of the patients were maintained on EPA alone and had significantly lower PANSS rating scale scores.

In depression, an initial double-blind pilot study again indicated that EPA, not DHA, may have antidepressant properties. We have now completed a study in which 1,2 or 4 grams per day of Ethyl EPA or placebo were given to patients who had failed to respond to initial antidepressant treatment. The patients on Ethyl EPA showed marked improvement relative to those on placebo. Again this appeared to be dose dependent, with a 1g dose producing the biggest improvement.

Several other independent studies have now been completed in both depression and schizophrenia, and these lend support to the conclusion that EPA may play a role in the treatment of both depression and schizophrenia.

Professor Malcolm Peet is currently working as a Consultant Psychiatrist in the NHS. He was previously Head of the University Department of Psychiatry in Sheffield. He has researched and published extensively on the biology and psychopharmacology of mental illness.
Supplementation with highly unsaturated fatty acids in dyslexia and ADHD

Mounting evidence suggests that mild abnormalities of fatty acid metabolism may contribute to a range of common and overlapping neurodevelopmental disorders including ADHD and dyslexia. This has raised the possibility that nutritional treatments could help to alleviate some of the associated behavioural and learning difficulties. Controlled trials of fatty acid treatment in ADHD have so far yielded only equivocal results, although well-designed studies have been few. In dyslexia, anecdotal evidence and open studies have suggested that fatty acid supplements may be of benefit, but until very recently, this issue has not yet been addressed via randomised controlled trials.

Effects of HUFA supplementation were therefore studied in two controlled trials involving children with specific learning difficulties. (1) Subjects were 41 children aged 8-12 years at a special school with both dyslexia and ADHD-related symptoms, who received random double-blind allocation to either HUFA supplementation or placebo for 12 weeks, followed by one-way crossover (placebo to active) for a further 12 weeks. At each time-point the CPRS-L (1) was used to assess a range of behavioural and learning problems. (2) Subjects were 102 dyslexic children aged 8-12 years referred to a research clinic. In this study, random double-blind allocation to either HUFA supplement or placebo for six months was followed by one-way crossover (placebo to active) for a further six months. Reading progress was re-assessed at 3-month intervals using the British Ability Scales.

Results from study (1) showed significant reductions in ADHD-related symptoms in children treated with HUFA versus placebo after 12 weeks. In study (2), gains in reading age, controlling for initial reading ability, were significantly greater in children treated with HUFA versus placebo, and benefits of HUFA supplementation appeared to be greater in children scoring highly at baseline on simple checklist ratings of either minor physical signs of fatty acid deficiency, or visual symptoms when reading. These results constitute preliminary evidence that HUFA supplementation may help in the management of dyslexia, although further investigations are needed.
Palatable behaviour: Reducing the antisocial behaviour of young adult prisoners with improved dietary intake of micronutrients.

It is widely accepted that young offenders are socially deprived but they also have been found to have inadequate micronutrient status compared to controls, which has lead to suggestions that micronutrient deficits might be one cause of antisocial behaviour.

Research undertaken with the permission of the Home Office provides evidence that inadequate dietary intakes of micronutrients may indeed be an important cause of antisocial behaviour. In a double blind placebo controlled trial with 231 young adult prisoners in a maximum-security Young Offenders Institution in England, it was found that supplementing their diet with vitamins, minerals and essential fatty acids reduced their antisocial behaviour, as assessed by their disciplinary infringements, by an average of 26.3% on an intent to treat basis or an average of 37% for more serious offences committed by those who actually consumed the capsules.

These findings confirm that antisocial behaviour may be significantly reduced by better nourishment; and they have important implications for our understanding and ability to modify such behaviours in the community.

Bernard Gesch is both the Director and Founder of the research charity Natural Justice that seeks to encourage multi-disciplinary research into the multi-factorial causation of offending behaviours. He has twenty years experience of working in the criminal justice system, and was formerly a member of Northampton’s pioneering Delinquency Services Team, a Research Fellow in the Department of Psychology and a Senior Research Fellow in Biomedical and Life Sciences at the University of Surrey. The Minister of State for Prisons has presented his research at the House of Lords. Bernard is now a Senior Research Scientist at Oxford University Laboratory of Physiology, studying diet and antisocial behaviour.