

Engaging with Myalgic Encephalomyelitis (ME):

Towards Understanding, Diagnosis and Treatment

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He married Mary in 1959 and they have three children, John, Paul and Susan, and five grand-daughters.

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DEDICATION

FOR DEREK PETERS AND DR JOHN RICHARDSON AND ALL WHO
SUFFER WITH AND CARE FOR PEOPLE WITH M.E. WHO HAVE
TAUGHT ME SO MUCH ABOUT COURAGE, ENDURANCE AND BEING
FULLY HUMAN.

"Others have laboured and you have entered into their labours."
John Chap 4 vs 38

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In this second printing I have taken the opportunity to correct some minor errors and make some small useful additions.

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INTRODUCTION

In 1997 I joined four Gulf War Veterans, GWVs, in the Autism Research Unit, ARU, at Sunderland to hear their stories and share something of their medical and personal histories. From them I learned for the first time about Gulf War Syndrome, GWS, a hotly debated description of the diverse and chronic illnesses they were experiencing. Since they were all using sticks to walk and were generally overweight- they all seemed to me to be sick with something. Clearly also, they did not have any obvious psychiatric disorder as they told their stories lucidly and calmly. They had visited the ARU at the invitation of its Director, Paul Shattock, to discuss GWS and take the IAG test if they wished. Paul is a longstanding colleague over some 30 years who had engaged with autism following the birth of his son Jamie. I was familiar with the work of the ARU and the development of the IAG test that was increasingly being used to help in the diagnosis of autism spectrum disorders, ASDs. With characteristic perception Paul had recognised that some of the symptoms described by GWVs seemed to have something in common with some of the symptoms of ASDs, particularly those affecting the central nervous system, mood changes, social withdrawal, perception changes, memory problems and irritability. The veterans' IAG tests proved positive.

We discussed some of the routine biochemical test results that the GWVs had brought with them and I was asked if I would help them in the future. I agreed to this and subsequently found myself nominated as their Chief Scientific Advisor and for two Government Committees, the Independent Panel for the assessment of Government Research into the possible Interactions between Vaccines and NAPS tablets, 1997, and the Depleted Uranium Oversight Board, DUOB, 2001. I was also invited to serve on the Gulf Support Group, 1997, organised by the Royal British Legion which includes a variety of people drawn from politics (members of the Commons and Lords), military welfare organisations, representatives of the GWVs, and clinicians and scientists. Since 1997 I have been increasingly involved with the GWVs, both the Gulf Veterans' Association, GVA, and the National Gulf Veterans and Families Association, NGVFA, supporting them in applications and submissions to the War Pensions Agency and Appeals Tribunals. Veterans from other conflicts and campaigns have also contacted me for help including, Falkland, Balkan and Atomic Veterans. There is clearly a great need for independent, soundly-based, scientific and medical advice that will help all veterans to make their cases to the appropriate statutory bodies.

GWS is also called the ME of the Military by some commentators and there is considerable overlap in the extensive and intensive symptoms that they describe. I proposed, therefore, that we test ME sufferers using the IAG test. Almost all the people tested had high to very high levels of IAG. Hence I was drawn into the world of ME to discover new and disturbing areas of suffering, abandonment by conventional medicine, and heroic persistence in mutual support and the search for understanding, diagnosis, treatment, and hope for the future.

Organophosphates and other pesticides were widely used in the Gulf, despite initial and total denial by Government. This led to our testing of sheep farmers and others involved in agriculture. Once again the list of symptoms described by this community had much in common with those of the GWVs and ME sufferers and their IAG tests were nearly all positive. Other pesticide and chemically poisoned people came to know of our work and were also tested. In nearly every case high levels of IAG appeared in their urine.

We had not anticipated the almost universal response to the IAG test from a wide diversity of sick people who presented with bewildering and complex medical conditions associated with very similar constellation of symptoms.

In the search for more understanding I was generously supported in exploring the work and standpoint of the Institute for Functional Medicine, IFM, and attending two of its major international meetings. This opened up the whole field of nutritional and environmental medicine for me. At the same time I met that doyen of ME in the North East, Dr John Richardson, and the interesting and expert people he has brought together over many years in the Newcastle Research Group.

I see myself on a steep learning curve with regard to these many and varied conditions but I have no doubt of their organic origins. I am profoundly aware that a number of eminent investigators have, and are, exploring ME with great commitment and some success. I am mindful that I am a “new boy” in these fields still with much to learn. This booklet is my response to the request, following three sequential meetings of the Northern Ireland ME/C.F.S. Association, that the information I presented might be more readily available to the ME community both in Northern Ireland and elsewhere.

The organisation of this booklet reflects my way into the field of ME. I have not followed the exact format of my lecture presentations but have arranged the same material in a different order to give a greater coherence and a more systematic presentation to that recorded on the video of my last presentation in Belfast.

A. DEFINITIONS

There has been much debate and some deception in the language and definitions given of ME, myalgic encephalomyelitis- Marshall et al, 2001.

(a) The World Health Organisation in its ICD manual (International Classification of Diseases) classifies ME as a neurological disorder, ICD-10, Section G93.3, and earlier volumes. ME was accepted as a distinct entity in 1978 at a symposium held at the Royal Society of Medicine.

In ICD-10 two alternative terms are listed, namely, Chronic Fatigue Syndrome, CFS, and Post-Viral Fatigue Syndrome, PVFS.

(b) In America the term, CFIDS, Chronic Fatigue Immune Dysregulation Syndrome, is widely used.

(c) In the earlier literature a huge list of different names has been used, some purely descriptive, eg. Raggedy Anne syndrome, whilst others are based on presenting symptoms drawn from neurology, neurasthenia (literally- weak nerves); immunology, allergic fatigue, antibody negative lupus, low natural killer cell syndrome; endocrinology, owl-syndrome describing sleep problems, **functional** hypothyroidism with normal routine thyroid test values; cardio-vascular conditions vasculitis, neural hypotension; neurology, neural hypotension, autodynomia, atypical polio. In recognition of the diversity of presentations attempts have been made to rename ME as a neuroendocrine-immune disorder. Many patients are not happy with such a re-assignment and until they are ME is the best name for what has been described as “one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stage”, Peterson, 1997.

B. THE DECEPTION

(a) This is based on Fatigue Syndromes in ICD-10, Section F-48, which come under Mental and Behavioural Disorders. Whilst ME, CFS, and PVFS are specifically excluded from this section there has been a clear attempt to redefine ME in this

category, by psychiatrists at King's College London. This College is one of the WHO collaborating centres and under the WHO logo they attempted to publish a psychiatric definition of ME. This drew condemnation from the international community and the following statement, "It is possible that one of the several WHO Collaborating Centres in the United Kingdom presented a view at variance with the WHO position", Saraceno, 2001.

- (b) The seriousness of this "sleight of hand" is illustrated by the following quotations, "There lies at the heart of CFS not a virus (or) immune disorder, but a distortion of the doctor-patient relationship"

From a doctor at the Mayo Clinic-"the doctor will see that they (ME patients) are neurotic and he will often be disgusted with them", Wessely, 1990.

- (c) What lies behind this attempt to redefine ME seems to be the concerns of the insurance industry in the USA where there is no National Health Service provision. "In the five years from 1989-1993 men's disability claims for CFS increased 360%, whilst women's claims for CFS increased by 557%.

No other disease category surpassed these rates of increase. In order of insurance costs, ME came second in the list of the five most expensive chronic conditions, UNUM, 1994."

Following this remarkable rise in the manifestations of **serious** neuro-immune disease and **profound incapacity** it was asserted that – "the field could change from an epidemiological investigation into a health insurance nightmare", Johnson, 1996.

'Chronic fatigue' and chronic 'fatigue syndromes' do not equate with CFS or with ME.

C. NUMBERS

Estimates of the numbers of people with ME in the UK vary greatly, at least by eight-fold. A widely accepted figure is that there are at least 300,000 sufferers in the UK – 1 in 200. Twenty five percent of these are severely affected and have, in consequence, been excluded from major surveys and any experimental studies. This figure is in line with the data from the USA and represents a huge field of human suffering that places enormous demand on clinical services. Costs have been estimated at between £180 million to £1 billion per annum.

D. SYMPTOMS

Symptoms of ME are seemingly without end. Not only is there remarkable variability in the actual symptoms but even within the same day symptoms can appear and disappear, much to the consternation of both patients and doctors. The most common findings are

- ◆ Extreme post-exertional muscle fatigability- a severe disabling weakness with exhaustion.
- ◆ Accompanied by recurring nausea and incapacitating malaise.
- ◆ Abdominal pain with diarrhoea.
- ◆ Persistent headache with a stiff neck and back with generalised myalgia.
- ◆ Severe pain with muscles tender to palpation and often frequent muscle spasm.
- ◆ Inability to walk unaided or stand unsupported for more than a few minutes.
- ◆ Vertigo, dysequilibrium, dizziness with ataxia and impaired coordination.
- ◆ Fine finger movements are often affected and swallowing and voice production.

Nicolson et al, 1996, provides a list of 33 symptoms that are common to ME and Gulf War Syndrome, GWS/I. A more limited list that shows the common symptoms of seven chronic conditions is given in Table 1.1.

Table 1.1. Common Symptoms shared by Seven different Chronic Illnesses

SYMPTOMS	OPs	GWS/I	MCS	FMS	CFIDS	MS	AIDS
JOINT PAIN	+	+	+	around joint area	+	+	+
FATIGUE	+	+	+	+	+	+	+
HEADACHE	+	+	+	+	+	+	+
MEMORY PROBLEMS	+	+	+	+	+	+	+
SLEEP DISTURBED	+	+	+	+	+	?? due to medicines	+
SKIN PROBLEMS	+	+	+	+	+	burning skin	+
CONCENTR ^N PROBLEMS	+	+	+	+	+	+	+
DEPRESSION	+	+	+	+	+	+	+
MUSCLE PAIN	+	+	+	+	+	+	+
DIZZINESS	+	+	+	+	+	+	+
G.I. - Irr. Bow.	+	+	+	+	+	+	+
PERIPH PARESTHES/ TINGLING	+	+	+	+	+	+	+
CHEM/ENVIR SENSITIVITY	+	+	+	+	+	Reported	-
EYE PROBLEMS	+	+	+	+	+	+	+
ANXIETY	+	+	+	+	+	+	+
TACHY&/OR CHEST PAIN	+	+	+	+	+	+	+
BREATHING PROBLEMS	+	+	+	Reported	+	+	+
LIGHT SENSITIVITY	+/-	+	+	Reported	+	+	-

OP = Organophosphate Poisoning; GWS/I = Gulf War Syndrome/Illness; MCS = Multiple Chemical Sensitivity; FMS = Fibromyalgia Syndrome; CFIDS = Chronic Fatigue Immune Dysregulation Syndrome = ME/CFS; MS = Multiple Sclerosis; AIDS = Acquired Immune Deficiency Syndrome.

+ Literature Reported ie. Anecdotal

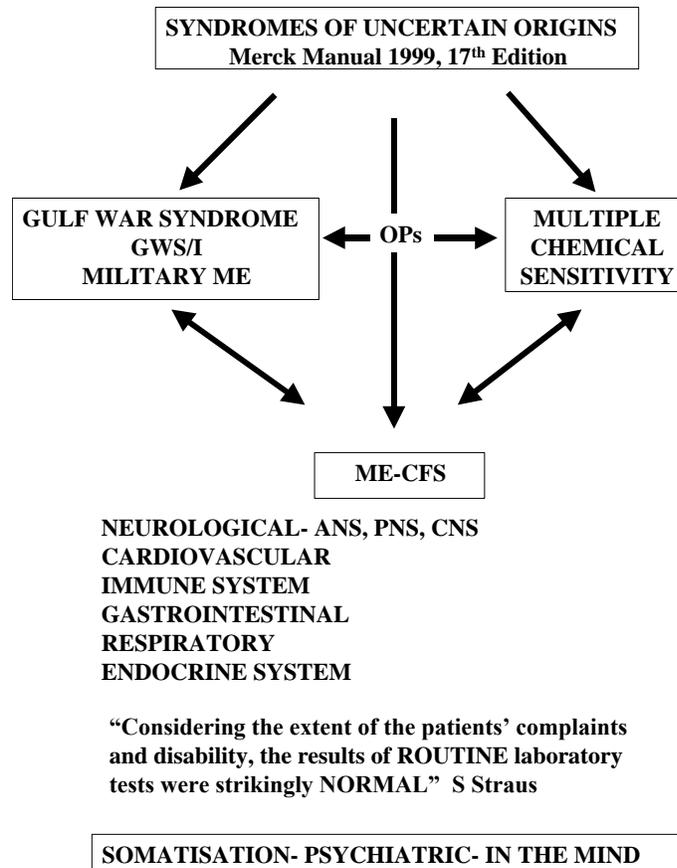
Adapted from Jackie Burkhead

Although AIDS and MS are now both widely recognised and undisputable illnesses the remaining five syndromes continue to be disputed, particularly, in the UK. It is interesting that AIDS, a serious and extensive immunological disorder, and MS, a chronic neurological autoimmune disorder previously attributed to hysteria, reflect the evidence that shows ME to be an illness with extensive neurological and immunological deficits.

E. SYNDROMES OF UNCERTAIN ORIGINS.

These are described in the Merck Manual, 1999, a common medical reference manual. They display a wide variety of syndromes which are complex and puzzling to modern medicine. The pattern of shared symptoms indicates a possible common basis for these illnesses, Table 1.1 and Figure 1.1.

Among these syndromes are Gulf War Syndrome, ME/Chronic Fatigue Syndrome, and Multiple Chemical Sensitivity. I have added organophosphate poisoning which shares many of the symptoms of these other syndromes, Table 1.1.



Key ME= myalgic encephalomyelitis; CFS= chronic fatigue syndrome; FMS= fibromyalgia syndrome; OPs= organophosphate poisoned personnel; GWS/I.

Figure 1.1. Syndromes of Uncertain Origin and the extensive effects on numerous major systems of the body.

F. PSYCHIATRISTS AND SOMATISATION

A bewildering variety of alternative names have been coined to describe syndromes of uncertain origin. These include, signs and symptoms of ill-defined conditions, SSIDCs, much used by the War Pensions Agency (now the Veterans’ Agency), multiple unexplained physical signs, MUPS, and persistent unexplained physical signs, PUPS. The latter terms are

much favoured by the Medical Assessment Panel, MAP, of the Gulf Veterans Illness Unit, Lee et al, 2000 and 2002, and by psychiatrists and others committed to theories of somatisation which seek to demonstrate that GWVs, ME sufferers and others are essentially suffering from psychiatric conditions and not any organic illness, Wessely, 1999. Fortunately, psychiatric explanations are undermined by a recent paper that explicitly declares that GWVs are not suffering from any increases in formal (defined) psychiatric illnesses or from excessive levels of post-traumatic stress disorder, PTSD, Ismail et al, 2002. This paper perversely ignores the obvious corollary that organic causes must therefore underlie GWS/I and retreats into the psychiatric and psychological thickets of somatisation. Using this label they assert that GWVs have illnesses that are driven and derived from disturbances of the psyche, ie are purely psychological. In order to maintain this schizoid attitude they ignore swathes of evidence in support of organic damage from biological and chemical toxins, Hooper 2002a. In the USA any theory of stress or psychiatric disorders has been completely abandoned and apologies offered to the GWVs for the long neglect of their illnesses. A new climate of openness has been created and a new start made on relevant research into the causes of their illness(es), Mackay 2002, Research Advisory Committee, 2002. Despite this the situation in the UK remains one of denial and refusal to face all the evidence now available on GWS/I, Slessor 2002.

ME sufferers and others with related syndromes are similarly affected by the same official attitudes and unwillingness to consider all the evidence that is in the published literature, Hooper et al 2002b, 2003. There is some promise of a new era if the recognition by the BMA, British Medical Association, of the patient as expert is acted on. Undoubtedly, ME patients have, of necessity, gained much information about their condition and in their awareness of their own bodies have an essential contribution to make to any understanding of their illness and its diagnosis and treatment. The widespread existence of ME patients groups and the mutual support they offer one another is another source of information vital to the clinician and the scientist.

G. NATIONAL REPORTS

(a) The CMO's Report

The recent CFS/ME Report to the Chief Medical Officer, 2002, which emerged after much controversy, Eaton, 2002, Lawrence, 2002, and with no endorsement by either the psychiatrists or leading members of the ME community demanded the recognition of ME as a real and significant illness but on the negative side it offered only psychiatric and psychological techniques, pacing, cognitive behavioural therapy (CBT) and graded exercise (GRE) as the preferred treatments. Much evidence was ignored in reaching these conclusions, Hooper et al 2002b, 2003.

(b) Research Advisory Group (RAG) Report

Things did not improve with the publication of the Medical Research Council's Research Advisory Group (RAG) by a supposed independent panel. Here again the emphasis was on pacing, CBT and GRE. An appendix to this report written by a group, including lay representatives, provided an overview that included environmental and other factors that concern many in the ME community. This appendix has not been sent out with the main report-the Whitehall loop in full swing, Slessor 2002.

(c)The Royal Australasian College of Physicians (RACP) guidelines

This report published in 2001 after considerable delay and dispute was even less welcome than the CMO's report by the ME community. Searing comments came from a number of world experts including Abhijit Chaudhuri in the UK, Chaudhuri, 2001, - flawed , biased, inaccurate, based on personal belief and not evidence-based medicine. Similar criticisms came from Dr Eleanor Stein in Canada, Dr Peter Rowe, USA, Dr Peter del Fante, Dr Nicole Phillips and Laurence Budd in Australia. Judy Lovett, President of the ME/CFS Association of Australia, and Frances Sanbach of another national organisation, ACT ME/CFS, could not support the report on behalf of their members. The guidelines were inadequate and potentially damaging, made no mention of nutritional factors and ignored the 25% severely affected, Williams M, 2001.

(d) Canadian report of the Canadian Consensus Panel Criteria for M.E.

This recent report, 2003, provides a comprehensive assessment of the illness and identifies the major common features as

- Post-exertional malaise and fatigue
- Sleep disorders
- Pain
- Neurological/cognitive manifestations
- At least one symptom out of two of the following categories
 - ❑ Autonomic manifestations- orthostatic intolerance (eg. neurally mediated hypotension, NMH, postural orthostatic tachycardia, POTS, delayed postural hypotension, low plasma and/or erythrocyte volume), vertigo, light-headedness,extreme pallor, intestinal or bladder disturbances with irritable bowel syndrome, IBS, or bladder dysfunction, cardiac arrhythmias, vasomotor instability and respiratory irregularities.
 - ❑ Neuroendocrine manifestations – loss of thermostatic stability, heat/cold intolerance, anorexia or abnormal appetite, marked weight change, hypoglycaemia, loss of adaptability and tolerance for stress, worsening of symptoms with stress and slow recovery, and emotional lability.
 - ❑ Immune manifestations – tender lymph nodes, sore throat, flu-like symptoms, general malaise, development of new allergies or changes in status of old ones, and hypersensitivity to medications and/or chemicals.

The only disagreement was whether or not cardiac symptoms should be included in a separate category as they are in the USA.

This comprehensive report has been welcomed and was published after I had completed most of this manuscript. It confirms everything I have advocated here and is fully consistent with the new proposals to rename ME as NDS, neuroendocrineimmune dysfunction syndrome, Section 9B,C.

2. THE IAG TEST

A. THE ASSAY

IAG, *trans*-indol-3-ylacrylglycine is a urinary metabolite of the essential amino acid, tryptophan, that has been unequivocally identified at the University of Sunderland, Anderson et al, 2002. An assay procedure was developed, as an aid to the diagnosis of autism spectrum disorders, ASDs, by the Autism Research Unit at Sunderland, Anderson et al, 2002, Shattock and Savery, 1997, Shattock et al, 1991, Shattock et al, 1998 . To date urine samples from some 5000 ASDs patients, 600-700 ME patients, and around 100 GWVs, and 40-50 organophosphate poisoned patients have been analysed.

The analysis is carried out using high performance (pressure) liquid chromatography, hplc, that involves passing a small volume of urine down a column that separates some of the components that are detected at the end of the column using ultraviolet absorption detectors. The result is a chromatogram, a tracing of the elution of material over time. The eluted material appears as a series of peaks whose intensity is plotted against time, Figure 2.1. The peaks of interest are above 15 minutes with the IAG peak appearing at ~19-20 minutes. The result is positive when the IAG peak is the largest one over 15 minutes.

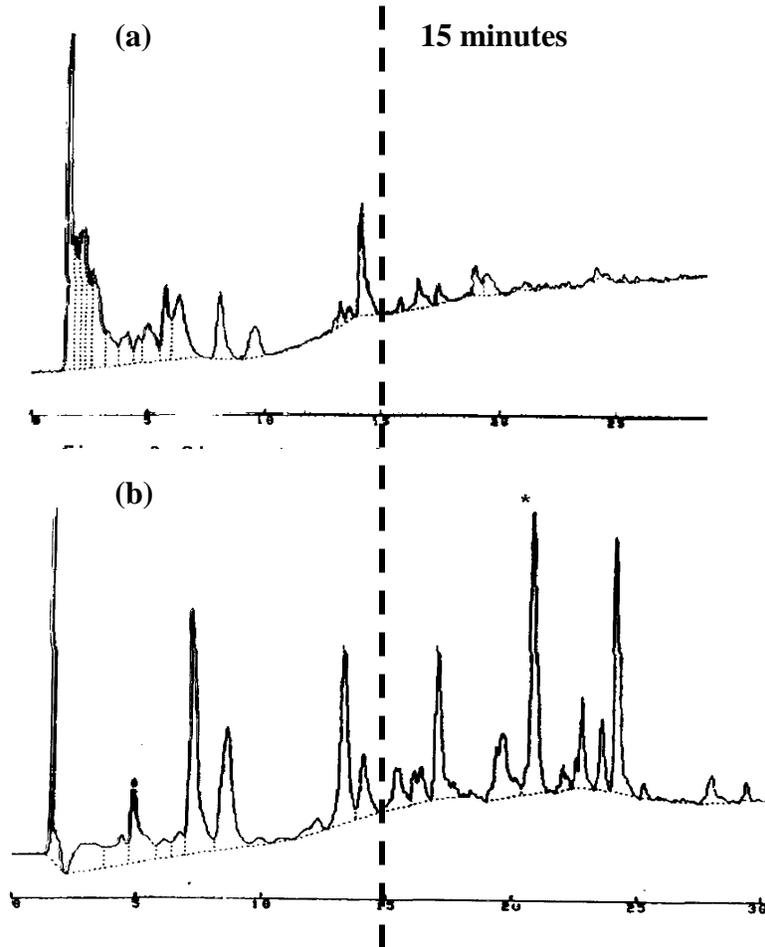


Figure 2.1. Chromatogram (a) Normal and (b) Autistic Person
* marks IAG peak.

The IAG peak varies slightly depending on the nature of the detector and characteristics of the hplc column. An internal check is provided by the comparison of the peaks in the chromatogram determined at 215 nm and 360 nm, Figure 2.2.

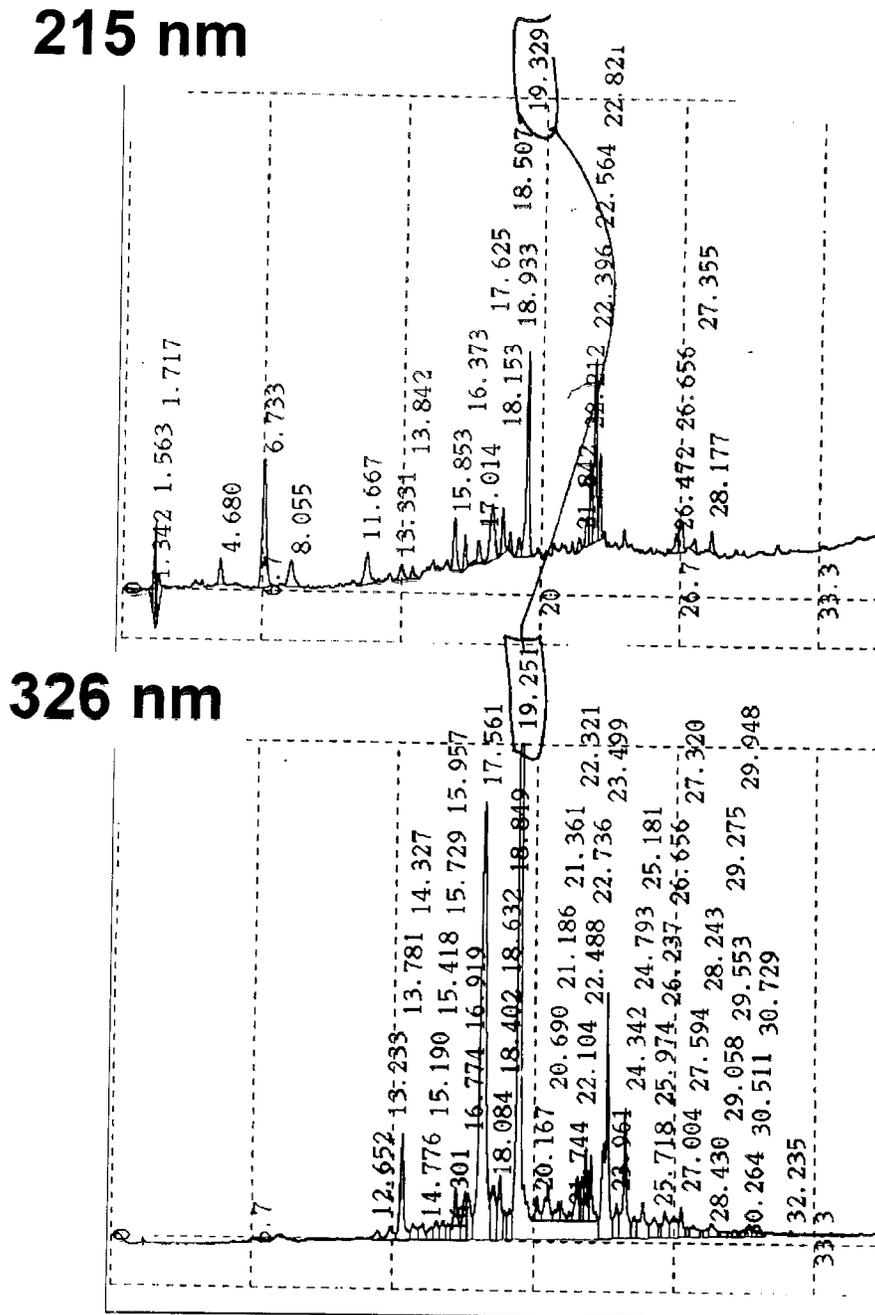


Figure 2.2. Chromatogram from a ME/CFS patient showing identification of IAG using two different detectors.

Note presence of other peaks over 15 minutes.

Although the IAG assay has proved extremely useful to clinicians and scientists it is under extensive development to meet some criticisms that have been levelled at it. The aim is to quantify the amount of IAG under the peak and not simply use the peak height for comparison and also to identify the other peaks that occur above 15 minutes, some of these are associated with opioids derived from milk and gluten proteins, **Section 3** below. A further refinement is to assay creatinine, a common biological reference compound, in the sample at the same time. Despite all these critical comments, the assay in its present form has proved extremely valuable and has been confirmed by independent chemists in the USA at AAL, Antibody Assays Laboratories.

B. THE ORIGINS OF IAG?

IAG is derived from the essential amino acid, tryptophan, that must be obtained from the diet. Although there is some evidence that IAG occurs in small amounts in pigs reared in an aseptic environment, Markolova, 1999, the most likely source, in people with high urinary IAG levels, are microbial sources in a dysfunctional gut, Figure 2.3.

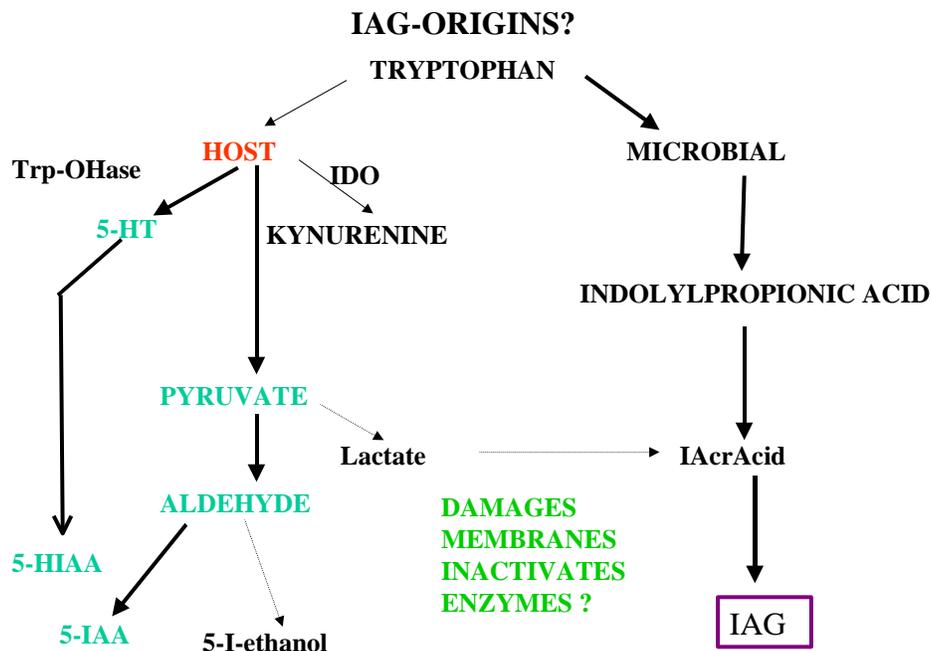


Figure 2.3. Possible Origins of IAG and IAcrAcid .

Tryptophan from the diet is needed for protein synthesis and some for the synthesis of the important neurotransmitter substance 5-hydroxytryptamine, 5-HT which is also known as serotonin. In the host tryptophan is broken down by the enzymic pathway that leads via the pyruvate then the aldehyde intermediates to indol-3-ylacetic acid, IAA. Although the lactate or indol-3-ylethanol, I-ethanol, are possible alternative products they occur only in small amounts or not at all. The lactate could possibly be a source of indol-3-ylacrylic acid,

IACrAcid, which is finally metabolised, probably in the gut wall, Stryer et al, 2002, [p 735] to the glycine conjugate, IAG, which is then excreted in the urine. The much more likely route to IACrAcid and IAG is from indolylpropionic acid, IPA, a product of microbial metabolism in the gut. Dehydrogenase enzymes then metabolise IPA to IACrAcid that is finally converted to IAG. IACrAcid is a reactive compound that is known to damage membranes, Bell, 2001, and has the potential to inhibit some gut enzymes that break down proteins and other components of food in the diet.

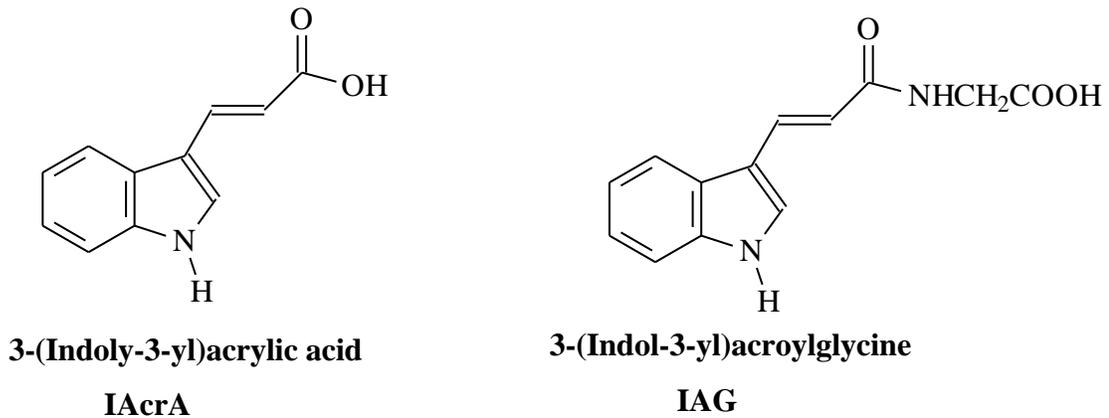


Figure 2.4 Chemical Structures of IAG and Indolylacrylic Acid.

C. THE LEAKY GUT

Although more evidence is needed we believe that IACrAcid is a key factor involved in or indicator of increased permeability of the gut wall, Figure 2.4.

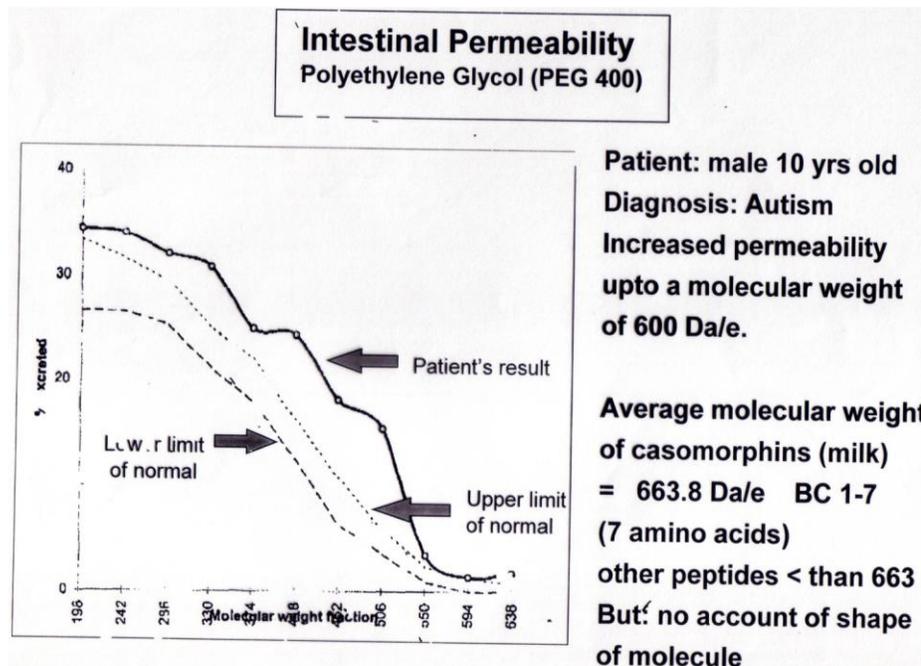


Figure 2.5. Increased permeability of Gut Wall leads to larger Molecular Weight Compounds crossing into the Blood Stream and then into the Urine.

Increased permeability results in larger than normal molecules being absorbed into the bloodstream- the gut is 'leaky'. IAcAcid also reduces the usual metabolic breakdown of molecules in food. The overall effect is to seriously compromise gut structure and function. Normally the cells of important membrane barriers that line the gut, the lungs, and provide the blood-brain barrier have tight cell junctions that prevent many compounds crossing these membranes. However, some chemicals, microbial toxins, eg zodulin and zot (zona occludens toxin), and allergens are all known to open these tight cell junctions and allow free transport of previously excluded compounds into the protected areas.

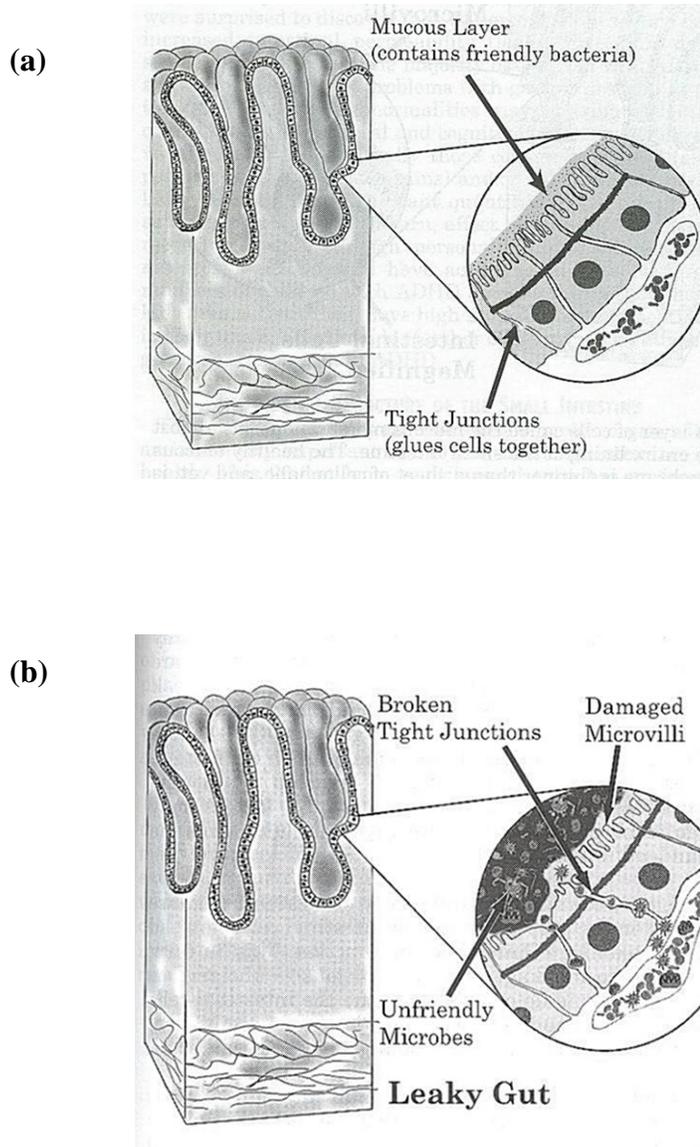
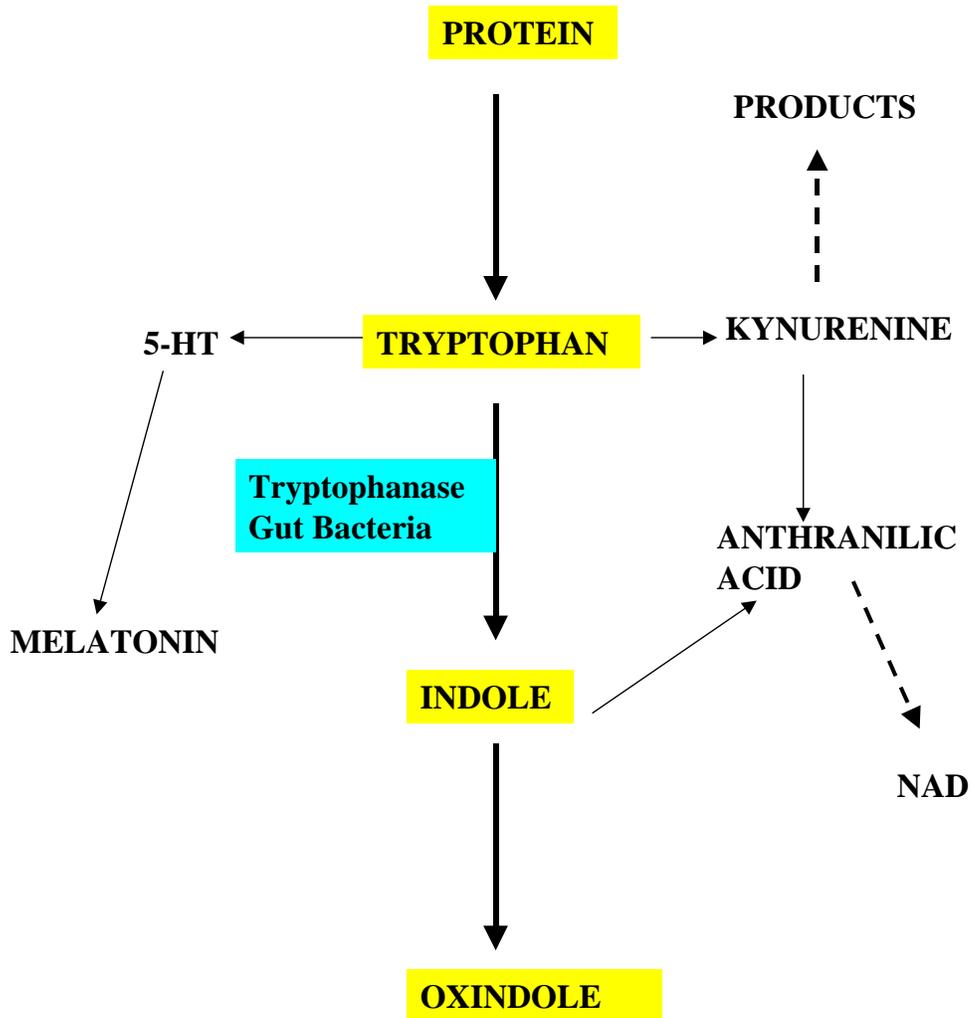


Figure 2.6. Details of (a) Tight Cell Junctions preventing access of materials through the Gut Wall and (b) Open Tight Cell Junctions allowing previously excluded Compounds through the Gut Wall.

The compromised gut also facilitates the development of a gut dysbiosis, **Section 6?**, in which ‘unfriendly’ gut micro-organisms and the toxins are present in excess quantities and access to the bloodstream and thence the brain and other organs across the ‘leaky’ gut wall. The metabolism of tryptophan by some gut organisms can also yield toxic compounds other than IacrAcid, Figure 2.7.



1. NEUROSUPPRESSANT. 2. PLASMA ~nmol levels .

LIVER DAMAGE LEADING TO HEPATIC ENCEPHALOPATHY

Figure 2.7. Metabolism of Tryptophan by Gut Organisms to produce the toxic Oxindole Molecule.

Oxindole will cross the permeable gut wall and cause both liver damage and effects on the brain.

Further metabolic transformations of tryptophan involve the kynurenine pathway and gives rise to compounds some of which are neurotoxic and others neuroprotective, Figure 2.8.

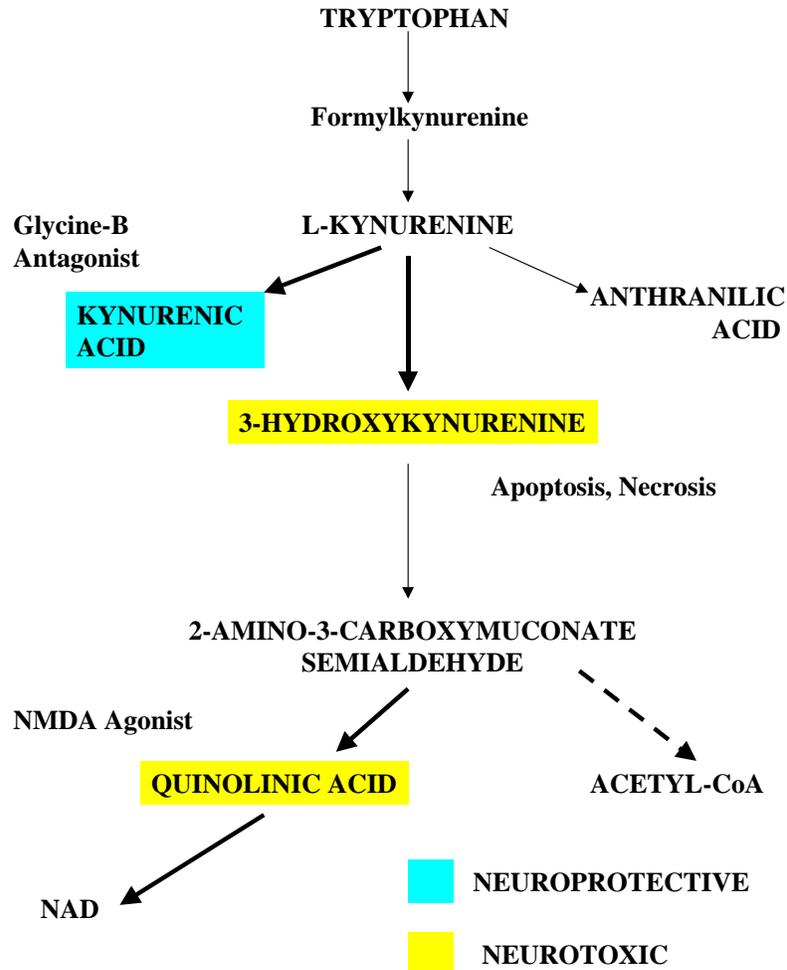


Figure 2.8. The Kynurenine Pathway for the Metabolism of Tryptophan.

The neuroprotective action of kyurenic acid is derived from its antagonistic effects at Glycine-B receptors that are implicated in facilitating excitatory responses at the NMDA (N-Methyl-D-Aspartate) receptor. The neurotoxic action of quinolinic acid results from direct stimulation of the proconvulsant NMDA receptors that also play an important role in cell death. This pathway is one induced by viruses in order to reduce the immunomodulatory properties of tryptophan, Section 6A see also 12G.

Overall the metabolism of tryptophan can produce a wide variety of different compounds that cause a wide variety of, mainly adverse, effects. A ‘leaky’ gut will allow both individual compounds and whole organisms to access the body and exert their different effects.

It is clear that the condition of the gut is critical to good health and that events initiated in and associated with a compromised gut can have far reaching effects.

Increased gut permeability is now known to be associated with at least 36 different clinical conditions, Table 2.2, Lipski, 2000. These diseases/disorders as well as being associated with

the gut include other digestive organs (liver, pancreas), skin, immune disease (HIV, psoriasis, allergies, lupus), infection (giardiasis, endotoxins), neurological diseases (multiple sclerosis, autism, hyperactivity, schizophrenia, ME, inflammatory joint conditions, drug and chemically induced illnesses, and something as non-specific as trauma (accidents, burns etc.).

Table 2.2. Common Clinical Conditions Associated with Increased Intestinal Permeability.

Alcoholism	Inflammatory Joint Disease/Arthritis
Acne	Intestinal Infections
Aging	Irritable Bowel Syndrome
Ankylosing Spondylitis	Liver dysfunction
Autism	Malnutrition
Coeliac disease	Myalgic Encephalomyelitis-CFS
Chemotherapy	Multiple Chemical Sensitivities
Childhood Hyperactivity	Multiple Sclerosis
Crohn's disease	NSAIDS Enteropathy
Cystic Fibrosis	Pancreatic Insufficiency
Eczema	Psoriasis
Endotoxaemia	Reiter's Syndrome
Environmental Illness	Rheumatoid Arthritis
Food Allergies	Schizophrenia
Food Toxicities	Systemic Lupus Erythematosus
Giardiasis	Thermal Injury
Hives	Trauma
HIV-positive	Ulcerative Colitis

D. THE OPIOID THEORY OF AUTISM

This theory, developed by Panksepp, Reichelt and Shattock and their colleagues, is based on the above understanding of the compromised gut.

Loss of digestive capacity leads to reduced breakdown of proteins in the diet that contain amino acid sequences with pronounced pharmacological (opioid) activity. Opioids are small peptides that have been found to possess morphine-like activity and are known to be naturally occurring important transmitter molecules, particularly, in the gut, brain and immune system.

[Note on terminology- amino acids are a group of substances that are linked like beads on a string into very long chains, containing hundreds of amino acids, to form proteins. Proteins, are among the principal foodstuffs in the diet, and are also called large peptides since the bond linking the amino acids together are called peptide bonds. Enzymes in the gut break down the proteins into much smaller fragments, peptides, and even the individual amino acids which are then absorbed from the gut into the bloodstream.]

When digestion is impaired then the larger peptide fragments are not broken down. Among these are opioid peptides that vary from 5–30 peptides in length and are derived from two principal sources, casein in milk (the casomorphins) and gliadin in gluten (the gliadomorphins) which occurs in wheat and related cereal crops.

When the gut wall has increased permeability these opioid peptides, which would normally be excluded, are absorbed and evoke their pharmacological actions both locally, in the gut, and in other organs particularly the brain. The same factors that render the gut permeable also appear to increase the permeability of the blood brain barrier and allow access of these compounds to the brain, Figure 2.9.

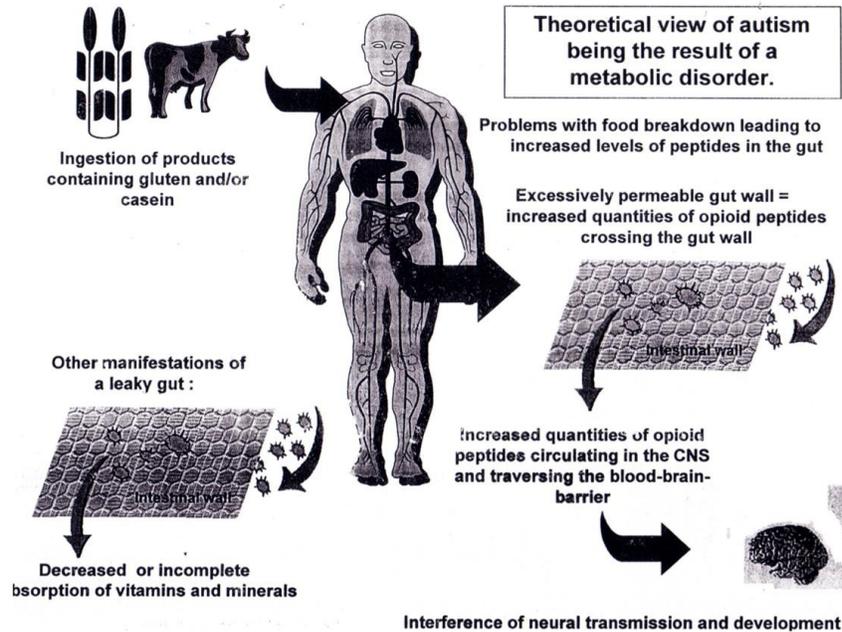


Figure 2.9. An Overview of the Opioid Theory of Autism

Depending on the concentration of opioids in the gut and the permeability of the gut and blood-brain barrier then the over all level of these compounds in the bloodstream and the brain will vary giving rise to variable expressions of symptoms and dysfunction. This is shown schematically in Figure 2.10 –used with permission from Autism as a Metabolic Disorder: Guidelines for a Gluten and Casein-free Dietary Intervention, Shattock, Whiteley and Savery, 2nd edition.

Figure 2.10 (a) represents the situation in a ‘normal’ gut with the stars indicating a single opioid molecule. Some opioid peptides are formed and some, a very few, cross the gut wall with still fewer reaching the brain. In (b) compromised digestion gives rise to a greater number of opioid molecules and if the permeability of the gut is the same as in (a) then more will enter the blood and brain. In (c) the gut wall has increased permeability and many more opioid molecules will pass into the blood but with the blood-brain barrier still intact only a few enter the brain. In (d) when both the gut wall and the blood-brain barrier are permeable then the levels of opioids in the brain are increased.

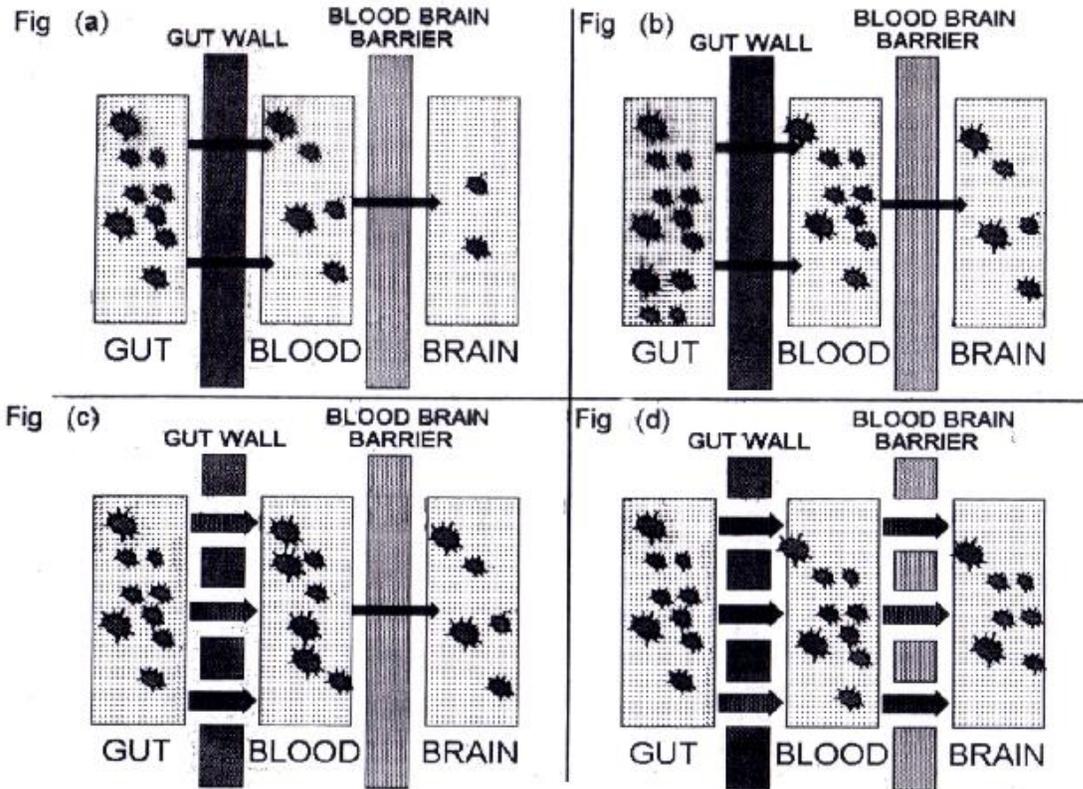


Figure 2.10. Schematic showing movement of Opioid Peptides from Gut to Brain with increasing Permeability of the key Membranes.

This understanding of the IAG test and the natural components of our everyday diets led to the use of dietary intervention in children with autism. Dietary treatment has been effective in many cases in bringing about behavioural changes and increasing socialisation. Autism spectrum disorders are now regarded, at least in part, as a metabolic disorder.

Major features of some autistic children is self-injurious behaviour and the production of very large stools. Both these are consistent with excess levels of opioids.

Another interesting observation is the use of exclusion diets that are frequently recommended in the treatment of a wide variety of disorders, syndromes and diseases. The most common exclusion diets remove dairy and wheat products and often produce some benefits in those concerned. This suggests that such people will have a positive IAG test.

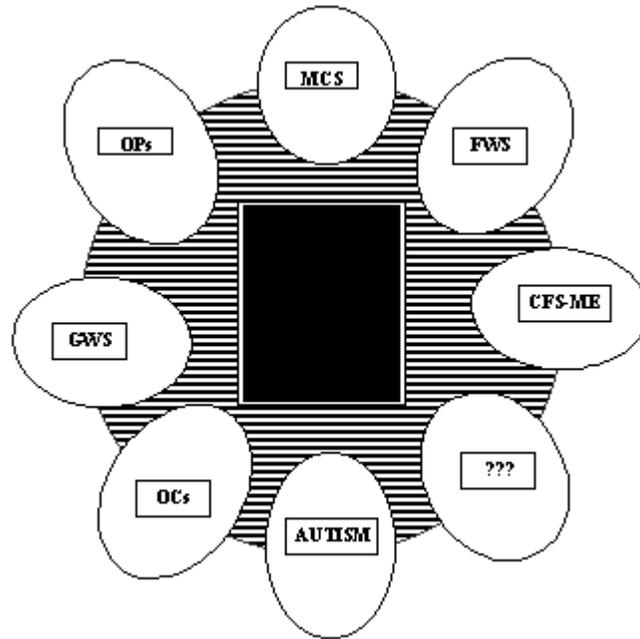
Our understanding of the positive IAG test found in over 90% of ME and fibromyalgia patients, GWVs, and organophosphate poisoned farmers is that opioid excess is playing some part in their symptomology and benefits would be expected from dairy and/or gluten free diets. This is borne out in practice although such dietary changes do not produce a 100% 'cure'. Rather symptoms are ameliorated and there is an improvement in mood, memory, gut behaviour and an increased sense of well being.

IAG, tryptophan metabolism, and opioid excess are only a part of the story.

3. OVERLAPPING SYNDROMES

This is an important part of our understanding of ME and other conditions that provide a positive IAG test. Even at this stage and considering only the IAG test it is possible to speculate that the IAG test points to a common biochemical basis for all those conditions that share a common pattern of symptoms, Table 1.1. Figure 3.1 summarises our present awareness of overlapping syndromes which several other commentators have also recognised from the symptoms displayed.

The shared biochemical deficits extend beyond IAG and these will be discussed later, Section 9.



Key: OCs = organochlorine pesticides; OPs = organophosphate pesticides; FMS = Fibromyalgia Syndrome; ??? = other syndromes eg PPS post polio syndrome

Figure 3.1. Overlapping Syndromes with Common Symptoms and shared biochemical Deficits

4. GUT PROCESSES, BACTERIAL POPULATIONS AND FOOD

A. Gut Processes.

It is worthwhile considering in detail the complex nature of digestion which is largely under the control of the enteric nervous system and carried out independently of the central, peripheral, and autonomic nervous systems. The gut has a brain of its own – The Second Brain, Gershon, 1999. Only the reflexes controlling swallowing and defaecation are under central control, Figure 4.1. Most of the communication between the gut and the brain takes place via the vagal nerve in which 95% of the fibres are afferent ie. carry messages from the gut to the brain. The key neurotransmitter for the vagal nerve is acetylcholine which is modulated by organophosphate pesticides, chemical nerve agents, and pyridostigmine bromide. All these chemicals were used in the Gulf War and together make up the ‘triple whammy’, Hooper, 2000, that is part of the toxic exposure suffered by the GWVs. In the enteric nervous system itself the major transmitter molecule is 5-HT. The control and co-ordination of the activity of the gut to facilitate digestion involves a host of other communicating molecules are involved in the detailed signalling that takes place directly between cells, through transport in the blood, as well as in the nerve plexus surrounding the gut. Opioids act locally on the gut. Another example is secretin that acts in the gut to facilitate the release of bicarbonate from the pancreas that is necessary to reduce the acidity of the stomach contents as they pass into the small intestine. Secretin has been found to have dramatic effects on the conduct of some autistic children and clearly affects areas of the brain associated with autistic behaviour.

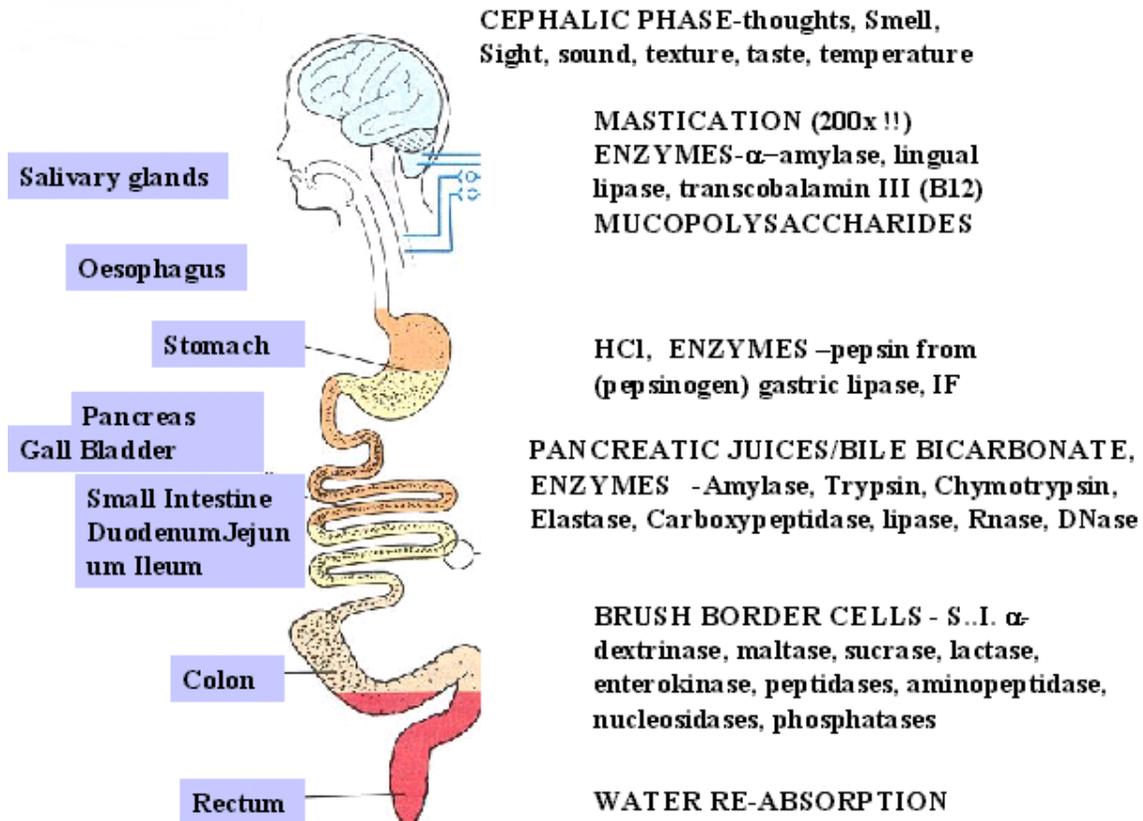


Figure 4.1. Main structural Features and Processes taking place in the Gut.

The enzymes listed degrade various components in the food which is a complex mixture of proteins, starches and sugars, fats, and nucleic acids. Water re-absorption is a major activity of the gut necessary for reducing the demand for large intakes of water. The cephalic phase describes the complex interwoven factors that affect our enjoyment of food- awareness of smell, ambience and activity in the cooking/eating area, and the anticipation of a meal.

B. BACTERIAL POPULATIONS.

The gut has a vast population of micro-organisms, Figure 4.2. Professor Bjorksten of the Karolinska Institute in Sweden states there are 1014 different microbe species in the normal gut. Their numbers are huge and vastly exceed the approximately 1 billion cells of cells in the body. They play a crucial role in maintaining the health of the gut and the body generally. When these populations become seriously unbalance then a dysbiosis ensues that can cause very significant and sometimes chronic damage to health.

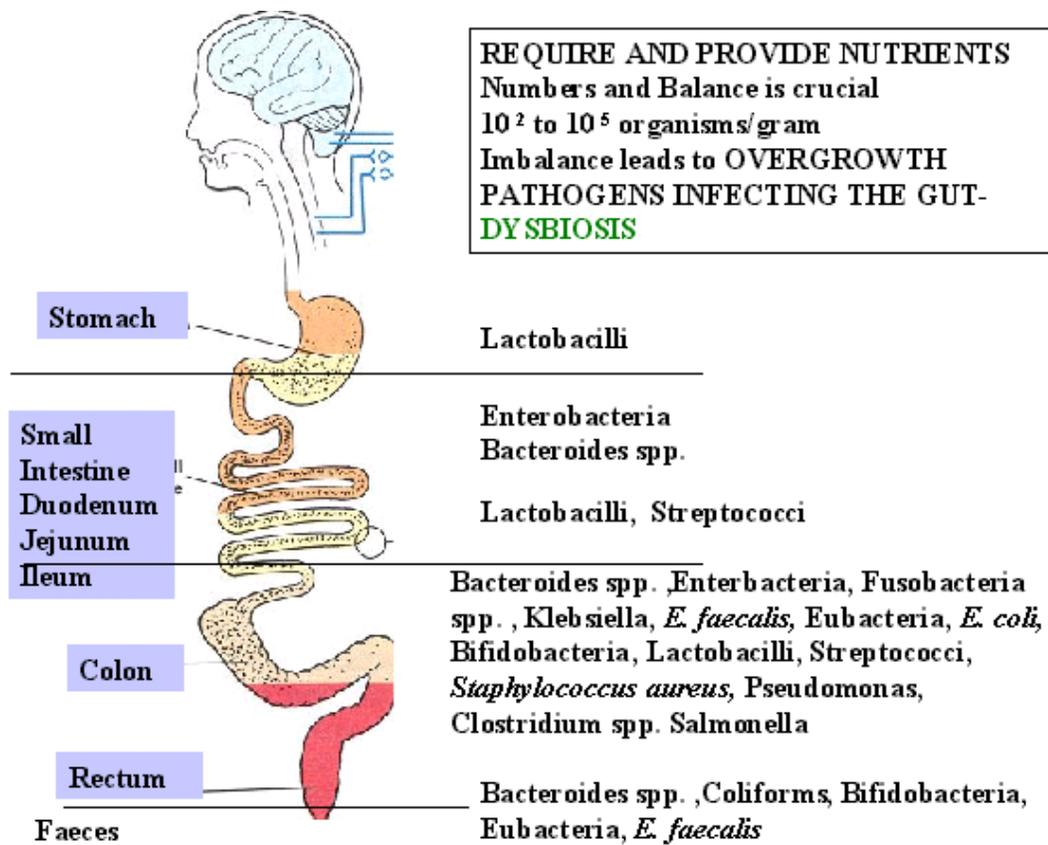


Figure 4.2. Main Bacterial Populations of the Gut

C. BACTERIA IN HEALTH AND DISEASE

The principal bacteria for health are lactobacilli and bifidobacteria whilst the most damaging are staphylococci, pseudomonas, and clostridium species. In small numbers these remain controlled by the competition from other bacteria and micro-organisms. Fungi also occur in the gut but only in small numbers in the healthy gut. The principal ones are candida species.

Candida overgrowth can give rise to major health problems and usually arises when extensive antibiotic treatments are given. Many people on a visit overseas where the water supply and sanitation is inadequate will know about some of the other parasites that give rise to unpleasant and sometimes prolonged illness. Among the most common are giardia, amoebic dysentery, and shigella. A reactive arthritis is not uncommon following infection by some of these organisms. The role of these different organisms is outlined in Figure 4.3.

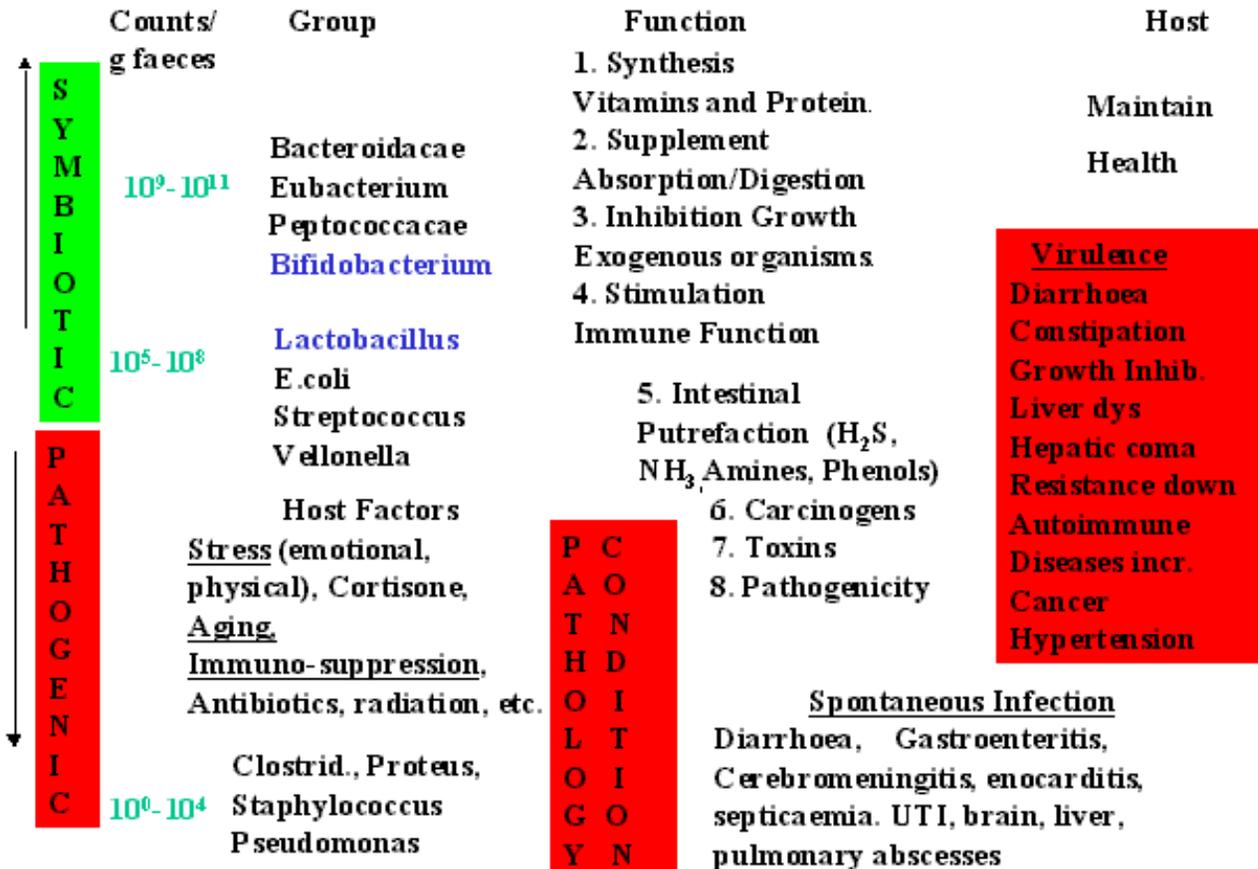


Figure 4.3. Role of Bacteria in Health and Disease.

It is clear that bacteria not only provide essential nutrients such as vitamins but also have important roles in maintaining a healthy immune response from the host. Dysbiosis can give rise to autoimmune diseases, cancers and hypertension. Host factors can also be crucial in affecting the gut population, stress, antibiotics, and radiation all have adverse effects. The neglect of the gut when antibiotics are prescribed can greatly affect the health of the patient. See treatment Section 12B.

D. Food

Obviously the nature of the food we introduce into the gut is important and is increasingly recognised as supporting or damaging health generally. Table 4.1 summarises the results of a study that introduced various foods into bacterial cultures that mimicked the conditions in

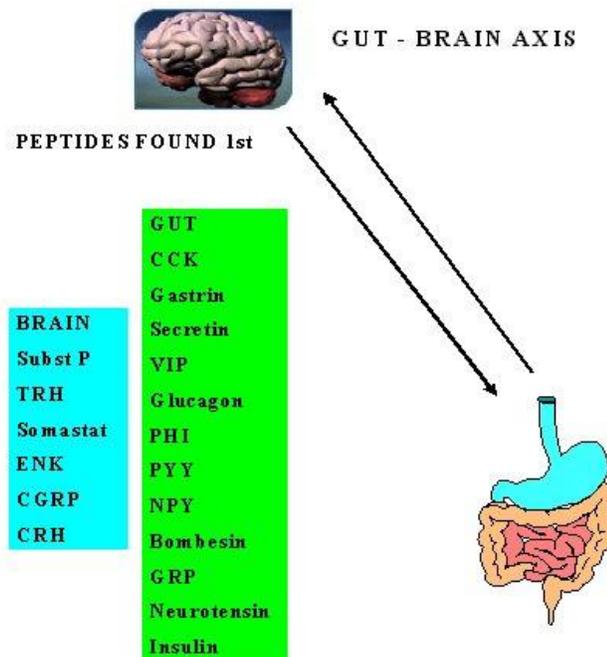
various parts of the gut. Unfortunately, I have not been able to trace the source of this information so it must remain anonymous for the present.

It is clear that rice promotes the growth of the ‘good’ bacteria such as lactobacilli and bifidobacteria. Oats do not support these bacteria anything like as well but there is only minimal growth of the ‘bad’ bacteria, clostridia. Wheat, however, very clearly supports the good bacteria least and encourages the growth of clostridia. The use of rice in a diet will therefore offer the strongest support for the gut flora. Other foods also supply important nutrients for the growth of good bacteria, eg fructooligosaccharides found in leeks and other vegetables, IFM, 1999.

Table 4.2 Effects of different Cereals on the growth of Bacteria in the Gut.

BACTERIA/FOOD	RICE	WHEAT	OATS
Lactobacilli	67	0	0
Bifidobacteria	11	8.3	18
Bacterioides	22	47.2	79.2
Clostridia	0	30.5	0
Coliforms	0	5.5	2.8
Total Aerobes	0	8.5	0

5. THE GUT-BRAIN AXIS.



Key: TRH = throid releasing hormone; ENK = enkephalins (opioids); CGRP = calcitonin gene-related peptide; CRH = corticotrophin releasing hormone; CCK = cholecystokinin; VIP = vasointestinal peptide; PHI = peptide histidine isoleucine; PYY = peptide YY; NPY = neuropeptide Y; GRP = gastrin-related peptide.

Figure 5.1. Peptide Messengers and Hormones found in both the Brain and the Gut (Greenspan and Gardener, 1997).

A. MESSENGER MOLECULES.

There are many important similarities between the major messenger molecules associated with the brain and the gut, Figure 5.1.

In addition to these peptide hormones there are the classical neurotransmitter substances that also transfer messages between nerves and nerves, and, nerves and organs. These too are common to both the brain and gut, Figure 5.2.

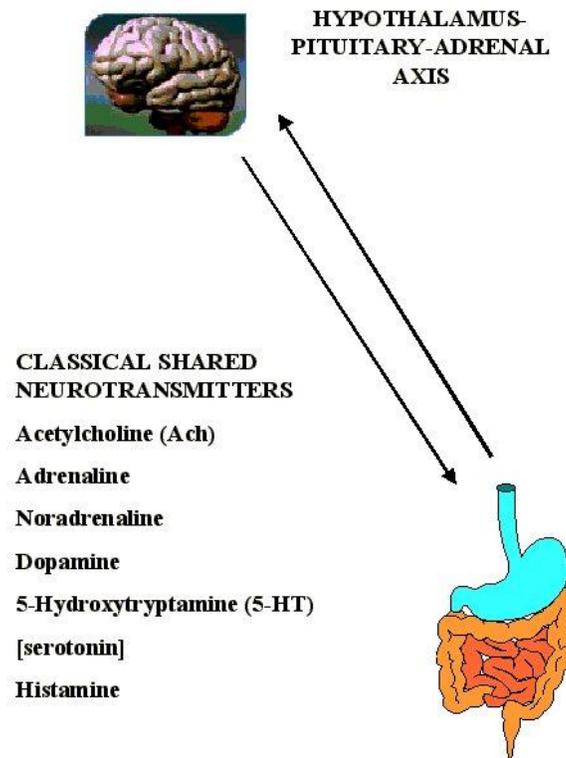


Figure 5.2. Gut–Brain Axis shared Classical Neurotransmitter Substances and the Hypothalamus-Pituitary-Adrenal Axis.

The hypothalamus-pituitary-adrenal, HPA, axis is a complex control system of the body that involves a hormone cascade. Hormones that are released into the blood eventually stimulate different glands in the body, eg. thyroid, adrenal glands, testes and ovaries, and alter libido, development of sperm, ovaries, response to stress etc. The stress response is a typical example. It is initiated by the release of corticotrophic releasing hormone, CRH, in the hypothalamus which, in turn stimulates the release of adrenocorticotrophic hormone, ACTH, from the pituitary, which then travels in the blood and stimulates the production of cortisol by the adrenal glands situated above the kidney. Cortisol then exerts its own immunosuppressant action throughout the body. The real control centre for this modulation of the immune response is therefore found in the brain. We shall return to the HPA axis later, Section 9B,C, when we consider the neuroendocrine-immune paradigm.

The gut contains a wide variety of cells that produce, neurotransmitters, communicating with nerves, endocrine molecules that are released into the blood and carried to the target organs

including the brain, and paracrines which are locally released short-lived molecules that communicate with adjacent cells, Figure 5.3.

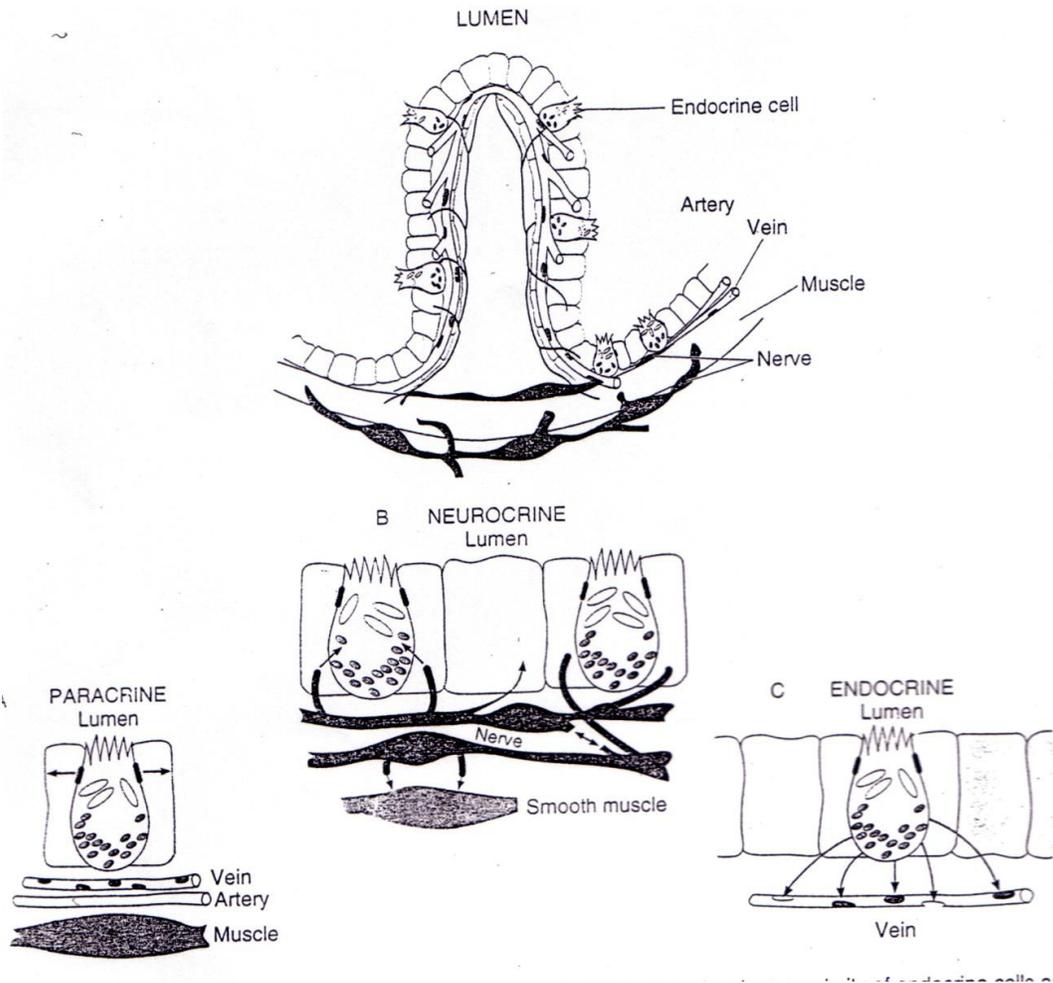


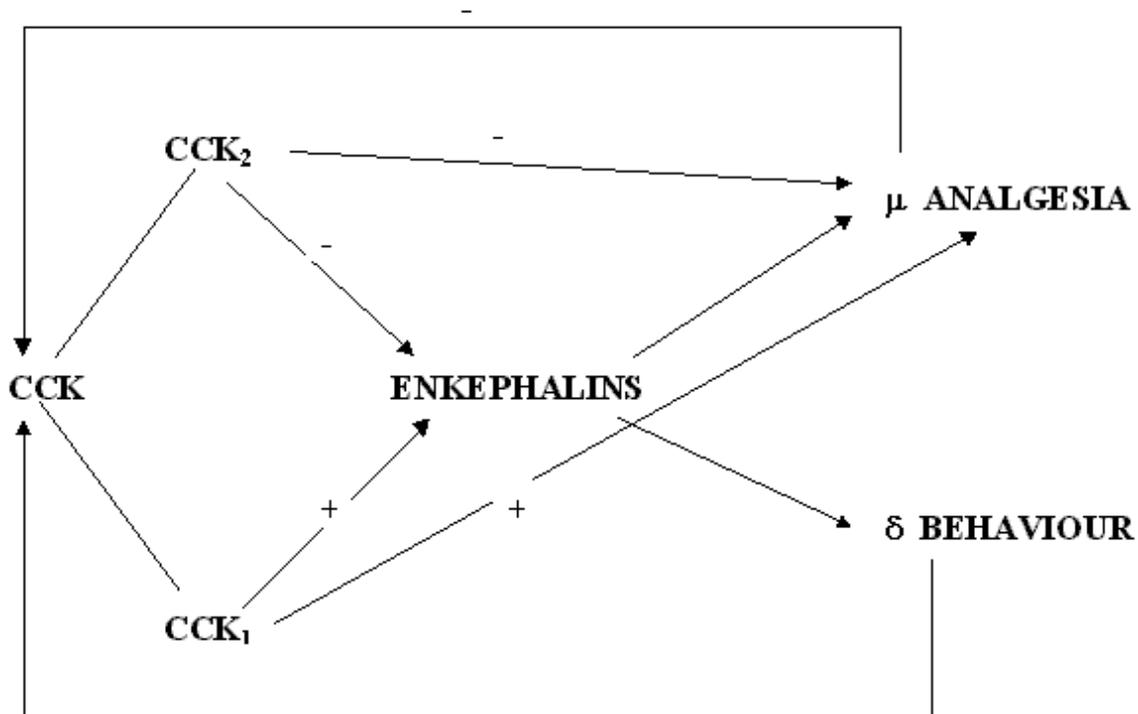
Figure 5.3. The Structure of a Gut Villi showing Cells that produce Neurotransmitters, Endocrines, and Paracrines (Greenspan and Gardner. [The lumen is the space inside the small intestine].

The gut is therefore an exquisite organ in two-way communication with the brain and other parts of the body by a variety of different mechanisms involving nerves, the bloodstream, and local cell-cell interactions.

A. OPIOIDS IN THE BRAIN

The opioid-excess theory suggests a significant role for these compounds in ME. These compounds which include enkephalins and endorphins not only act directly on target organs, see Section 9, NEI, but also modulate the response to other compounds. Cholecystokinin, CCK, is the most abundant neuropeptide in the brain and therefore plays a big part in brain function and control. CCK occurs in a variety of molecular sizes, two common molecules are CCK-58, a 58 amino peptide found largely in the gut and CCK-8 found largely

in the brain. These bind to specialised membrane regions, called receptors. These receptors were called originally CCK-A, A for alimentary (gut) and CCK-B, B for brain, where they were first identified. They have now been relabelled as CCK₁ and CCK₂ respectively. An important feature of the CCK molecules is that the active molecule carries a sulphate group, Section 7. Figure 5.4 shows how opioids interact with the actions of CCK in the brain at the different receptor sites.



Key + = increase - = decrease in levels and effects.

Figure 5.4. Modulation of Pain and Behavioural Responses by interactions between CCK and Enkephalins (Opioids).

CCK plays an important role in depression, anxiety and panic attacks (raised levels/activity) and schizophrenia (low levels/activity). CCK is also important in memory, learning -free recall, and cognition although it is not clear whether opioids are involved in all these activities.

Opioids are known to play key roles in

- Endocrine system, HPA axis.
- Stress where they are released from the adrenal glands.
- Communications from the pineal gland.
- Reward responses.
- Cognition.
- Emotion and aggression probably via the amygdala, part of the brain involved with these expressions and activities.

A key aspect of opioid expression is the critical dependence of receptor binding and expression on the composition of the membranes surrounding the receptors. Of particular importance is the proportion of polyunsaturated fatty acids, PUFAs. These fall into two groups, the n-3 (also omega-3, or ω -3) PUFAs which are found principally in fish oils and flax oil, and the n-6 (also omega-6, or ω -6) which are found in most plant oils such as evening primrose oil, see Section 8.

The dependence of neuropeptide expression on membrane composition is a general feature of neuropeptides in the brain. Neuropeptide Y which also plays a role in modulating behaviour, circadian rhythms, and endocrine responses as well as pancreatic secretion in the gut is known to be greatly affected by changes in the proportion and nature of PUFAs in cell membranes.

Over all opioids and other neuropeptides make up a group of compounds that are shared between the gut and brain and are known to exert significant effects on

- Transmission in the CNS.
- Perception.
- Cognition.
- Behaviour.
- Mood.
- Emotions.

The neurological basis of ME is clearly strongly supported by all the above data. In addition the function and behaviour of the gut is widely affected by these molecules and also, as we shall see, the immune system.

Little wonder then that our awareness of our gut in sickness and in health is so pronounced or that the Authorised version of the Bible speaks of bowels of mercy, eg. Phillipians chapter 2 verse 1 and following. The word used is the Greek word for bowels. Attending to our bowels, the gut, is therefore both scientifically, medically, and humanly, wise and sensible. Modern insights recognise the serious damage done when the main concern was to purge the gut by the use of chemicals, eg. liquid paraffin, and phenolphthalein- both are now banned. Any treatment that ignores the complexity of the gut is likely to do more harm than good. One of the side-effects of oral antibiotic therapy that is so widely used today is the failure to support the gut so that the bacteria responsible for health are not dangerously reduced. The prescription of an oral antibiotic for a lung or bladder infection should not be followed by one to treat the resultant thrush infection that results from an overgrowth of candida.

6. THE IMMUNE SYSTEM.

A. INTRODUCTION

The use of the term CFIDS in the USA as an alternative to ME clearly indicates the importance of immunology in understanding this complex illness. It is not possible to give a full account of the immune system here. Briefly, it is the system that protects the body against invading micro-organisms, bacteria, viruses, fungi, and other parasites. It also carries out a range of functions that maintain the health of the body by removing aberrant cells, such as cancers cells, and recycles some materials such as iron from the haemoglobin in old red blood cells.

There are two types of immune mechanisms that provide

- Humoral immunity.
- Cellular immunity.

A large family of white blood cells are responsible for providing these two basic types of immunity, lymphocytes, monocytes, macrophages, eosinophils, basophils, neutrophils, B and T cells. In addition there is a complex system for the recognition of foreign cells involving large molecules on the surface of cells, the major histocompatibility complexes, class I and class II. These are crucial for distinguishing self tissue from non-self material. The problem of transplant rejection is a consequence of cellular immunity and necessitates the finding of closely matched organ donors and the use of immunosuppressant drugs in maintaining the transplanted organs.

(a) Humoral Immunity

This is due to circulating antibodies that are produced by specialised cells, B cells, supported by other cells called T- helper /inducer cells. After recognising foreign material B-cells multiply rapidly and produce antibodies. Antibodies are immunoglobulins, large proteins, that are produced in large numbers and are usually specific to the infective or foreign agent. The antibodies form complexes with the foreign material and these complexes are then destroyed by other cells, such as macrophages. There are many classes of antibodies labelled Ig, for immunoglobulin, followed by a capital letter and if necessary a number, eg. IgA, IgE, IgG, IgG2, IgM, etc. A particularly important immunoglobulin is secretory IgA, sIgA. Daily production of sIgA is greater than any other immunoglobulin. sIgA is secreted at mucus membranes, gut , lungs etc where it is a major barrier to pathogenic organisms. Humoral immunity is the major defence mechanism against bacterial infections.

There are 4 types of allergic reactions, types I-IV. The first three are mediated by immunoglobulins of which the best known is Type I, IgE-mediated hypersensitivity. Hayfever, asthma, hives, food allergies and eczema are all IgE mediated and usually the cause is readily identified by the sufferer. Skin testing is widely used to identify the substances/foods causing this type of reaction. Type IV is a cell-mediated delayed response and is seen in contact dermatitis, leprosy where the decaying and dead mycobacteria cause the reaction.

(b) Cellular Immunity (Cell-mediated Immunity)

This involves a variety of T-cells that are responsible for protection against viruses, cancer, some disease-causing bacteria such as tuberculosis and leprosy, and tissue graft rejection. T-helper, T_H cells assist B cells in mounting a humoral response and T_C cells are converted into cytotoxic T lymphocytes that actively destroy aberrant cells that are infected or disordered by

a malignant transformation. A further group of cells are natural killer cells, NK cells, which play an important role in counteracting cancer.

The complex interactions between all the B and T cells requires a bewilderingly complex system of signalling molecules usually referred to as cytokines. Some examples are, interleukins, ILs, usually differentiated by numbers with additional Greek letters if needed eg IL-1, IL-2, IL-2 β , IL-3 up to IL-16 and sure to go beyond this, interferons, INF, distinguished from one another by Greek letters, eg INF- α , INF- β , INF- γ , tumour necrosis factor, TNF, differentiated by Greek letters eg THF- β . There are many others.

During an infection both T and B cells multiply rapidly, a process known as cloning. When the infection is over cell numbers return to normal levels but crucially some memory cells remain so that a second infection is more rapidly combated.

(c) The Inflammatory Response

This is a complex response to local injury or trauma and although it is usually acute there are a number of chronic inflammatory diseases that are well known such as rheumatoid arthritis and asthma.

The inflammatory response involves cytokines and several other classes of important bio-active molecules. Chemokines are cytokines that attract different types of leukocytes to the place of an injury. Cell-adhesion molecules, CAMs, facilitate the attachment of cells to vessel walls and cells in the injured area. Selectins are responsible for the initial attachment of leukocytes to the endothelium that lines blood vessels. Mucins are molecules that bind selectins. Integrins enable cell-cell adhesion as well as binding to the endothelium. Leukocyte-adhesion deficiency is a rare genetic disorder where the adhesion process is inadequate, as a result affected individuals have more frequent and more severe bacterial infections.

Blood clotting mechanisms also come under the inflammatory response since almost any injury leads to bleeding that must be stopped quickly as part of the recovery process. Again another family of enzymes and control molecules are involved, eg. complement.

Two further large families of molecules that modulate the inflammatory response are the prostaglandins and leukotrienes. They are derived from PUFAs in cell membranes and will be considered in Section 8E.

B. TRYPTOPHAN

Tryptophan has another surprising property. It is the only immunomodulatory essential amino acid, with the possible exception of cysteine. It controls T-cell cloning that is crucial in maintaining a balance between too many or too few T-cells.

If cloning is excessive then resistance to infection and cancer will be very strong but the risk of the 'over wound' immune system erroneously reacting to 'self' tissue and initiating an autoimmune disease is greatly increased.

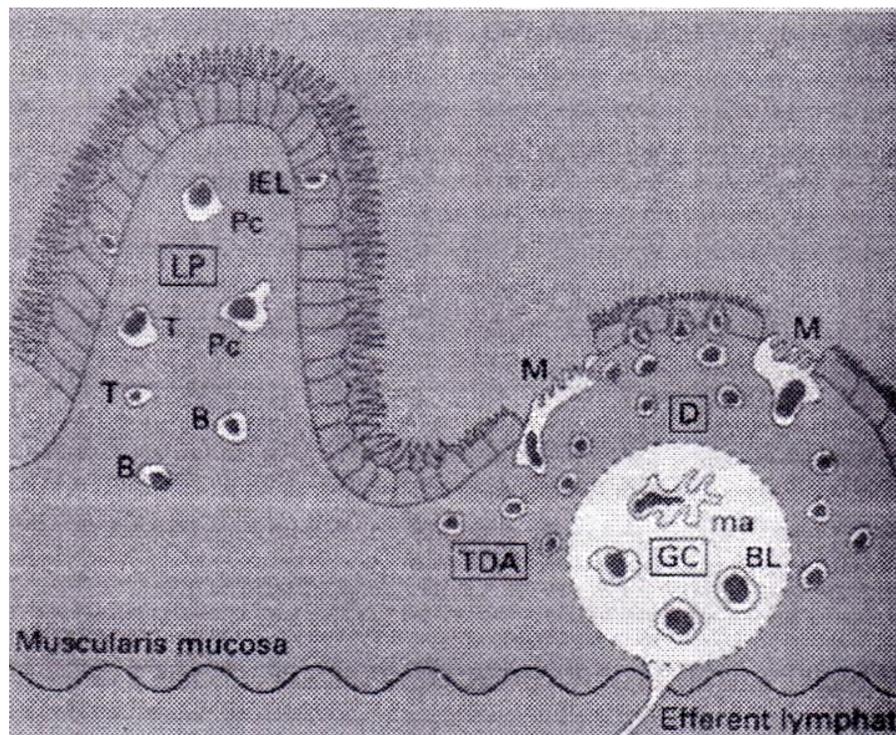
If cloning is reduced then resistance to infection and cancers is reduced.

An interesting example is pregnancy where the embryo, which is only partly 'self' tissue, could be destroyed if T-cell cloning became excessive. However, it is essential that the embryo is supplied with tryptophan in the diet to develop. A very fine control of tryptophan

levels both between and within cells is necessary for a pregnancy to proceed successfully to full term.

C. THE IMMUNE SYSTEM, THE GUT AND THE BRAIN.

The gut contains the largest area of lymphoid tissue in the body. This makes sense as it is the first barrier to infection, foreign material, and other toxins, both natural and man-made. It must therefore be able to exercise a diverse number of functions to maintain the health of the body and its own integrity- no mean task. Lymphoid tissue is spread throughout the gut but occurs in specialised regions such as the tonsils and Peyer's patches of the small intestine, Figure 6.1.



Key: PC= Plasma Cell; IEL= Intraepithelial lymphocyte; Peyer's patch (on right) comprises D=dome; TDA = Thymus Dependent Area; GC= Germinal Centres; T= T-cell; B= B-cell; M= M-cell.

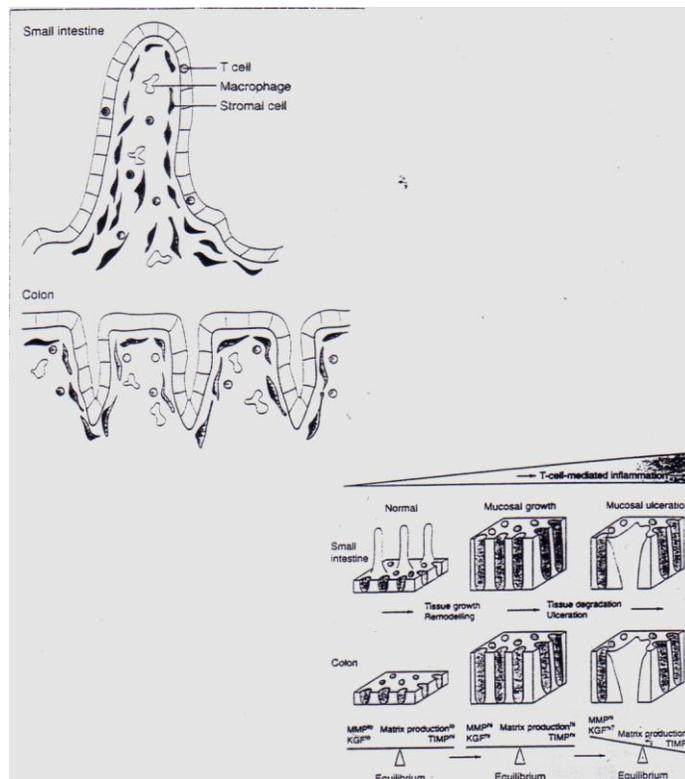
Figure 6.1. Details of Gut Lymphoid System in the Small Intestine.

Some viruses, known as enteroviruses, are known to be particularly important in ME. One such family, the Cocksacchie B group, has been studied extensively by Dr John Richardson over some 50 years. Sadly John died in June 2002 not long after he had completed his important book that describes the role of enteroviruses in ME. There are numerous adverse neurological, immunological, endocrine and cardiovascular effects from such infections if they persist, Richardson 2001. Polio and measles viruses also belong to the enteroviruses. The recent controversy about the role of MMR (measles, mumps, and rubella) being

associated with the development of autism involved the identification of grossly inflamed lymphoid tissue in the lower part of the small intestine, Wakefield et al, 2002.

Inflammation of the gut is common among ME patients and many have been diagnosed with irritable bowel syndrome, inflammatory bowel disease, and even Crohn’s disease. Allergic reactions to food are common including gluten. The best known of these is coeliac disease in which the structure of the small bowel is destroyed and a flattening of the deeply folded villi of the gut wall are lost and with it the capacity to properly absorb many key food components, Figure 6.2. The definitive test for coeliac disease involves the detection of endomysial antibodies which are formed in response to gliadin peptides in gluten. Often a great deal of damage is done before an accurate diagnosis is made but gluten free diets provide a comprehensive improvement in coeliac patients. Generally ME patients do not test positive for coeliac disease.

It is vitally important that coeliac disease should not be confused with the opioid theory of autism. We are NOT dealing with an allergic reaction to milk (casomorphins) and gluten (gliadomorphins) but with pharmacological phenomena arising from increased gut permeability and compromised digestion detected by the IAG test.



Note the distortion of the normal structure by thickening (mucosal) of the gut wall followed by ulceration.

Figure 6.2 Structure of the Small and Large Intestine (Colon) and the consequences of T-cell mediated Inflammation.

A very common bowel disorder in many older people is diverticulitis. This arises from rupture of the underlying muscle in the wall of the gut and leads to small pockets/pouches (diverticuli) where the contents of the gut can remain trapped and lead to a marked inflammatory response. It is due to frequent straining during defaecation and/or the excessive use of laxatives. A good diet will provide all the necessary components for regular and easy bowel action.

The gut and the brain also communicate via messenger molecules of the immune response. There are receptors on brain cells for IL-1 and IL-2, Figure 6.3.

So now we have the gut and the brain communicating with each other and the rest of the body through nerve transmission, endocrine release, and cytokines. This theme will be developed later, Section 9.

Opioids also play a significant role in the immune response through receptors found on cells of the immune system. Generally they suppress the immune response increasing susceptibility to infection.

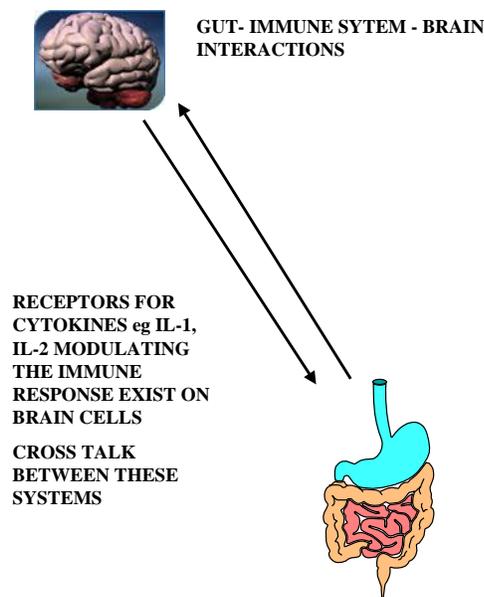


Figure 6.3. Cross talk between the Gut and the Brain via Messenger Molecules of the Immune System.

7. METABOLISM, DETOXIFICATION AND THE SULPHUR CYCLES

A. METABOLISM AND DETOXIFICATION

Metabolism is the “sum of all the chemical and physical changes that take place within the body and enable its continued growth and functioning.” A metabolite is a substance that is produced by metabolic transformation(s) in one or more processes that usually depend upon one or more of the vast array of enzymes (biological catalysts) that enable metabolism to take place.

There are three aspects of metabolism that we need to recognise.

- i. **Catabolism-** this involves the breaking down of complex molecules that occur in food
 - to produce energy that is required for many other processes, eg movement, thinking, fighting infection etc.
 - smaller chemical units eg amino acids from proteins (including casein and gluten) that are used to build up the bodies own specific proteins.
- ii. **Anabolism-** involves the building up of the bodies own complex substances from smaller ones produced by catabolism.
- iii. **Detoxification** – many substances taken into the body in, food and drink, or as medicines need to be removed to avoid a build-up of compounds that might give rise to toxic damage. Among these are many novel chemicals that have been introduced since the chemical revolution that led to the development of pesticides, herbicides, and drugs. This era started in the 1930s and has mushroomed since then. The nature of many of these molecules is often completely novel to the metabolic capacity of the body which means that they can accumulate in the body and produce a wide variety of toxic effects that are difficult to recognise.

A well-known example is the insecticide DDT. This belongs to a group of compounds which have many chlorine atoms present in them – the organochlorine insecticides which also include lindane, dieldrin, aldrin, and hexachlor benzene. The widely used insulating material incorporating polychlorobiphenyls, PBCs, also belong to this chemical grouping. Following Rachel Carson’s groundbreaking studies in the Silent Spring, 1962, there is now a ban on all these compounds in the west. However, DDT is still used, in some countries, to control mosquitoes that carry the malaria parasite.

Organochlorines, which are highly fat-soluble, accumulate in body fat and have a biological half-life of some 50 years. As a rule of thumb it requires 4-5 half-lives for the body load of these compounds to become imperceptible. So once we are contaminated we are contaminated for life. It is a salutary fact that most people in the UK are unfit to eat- and our flesh could not be sold on the open market because of its pesticide load. In the Arctic, Inuit mothers have been advised against breast-feeding their children because of the high levels of organochlorine pesticides that have accumulated in their breast milk. The rupture of this primary human bond by our own self-poisoning of the environment is deeply disturbing. It is particularly so when there has been no spraying of these pesticides in the Arctic- sea and air currents have carried these materials around the globe and up the food chain so that eventually they are concentrated in the food that is consumed by the Inuits and others. The Inuit diet is largely composed of fatty animals, seals, and fish.

Dr John Richardson has described how he identified organochlorine poisoning in patients referred to him with all the symptoms of ME (Richardson 2000). His treatment with a simple mixture of ascorbic acid and choline citrate was effective in increasing the excretion of these compounds and a concomitant reduction in body load and the severity of symptoms.

Successively further novel chemicals have been introduced as alternatives to the organochlorines- these include the organophosphate and pyrethroid insecticides. Unfortunately these too have many toxic effects and are responsible for much ill-health. Over all some 50,000 novel compounds are in common use that have not been toxicologically investigated- pesticides, herbicides, fungicides, food additives and preservatives, flame retardants, anti-fouling paints, insulators, solvents, etc.

Our homes and our food are widely contaminated with a variety of chemical compounds whose chemistry, pharmacology and toxicology have not been studied extensively. A prime example are endocrine disrupters that are now so widespread that we are beginning to see very obvious and peculiar effects among some animals. Many endocrine disrupters have oestrogen-like actions. In some river estuaries fish have become hermaphrodite, having both male and female sex organs, exposure to dioxins following the explosion at Seveso in N. Italy led to a 3:1 ratio of females in the babies born over an 8-year period. Sperm counts in young men are decreasing significantly.

B. METABOLIC TRANSFORMATIONS

The main organ of metabolism is the liver but other parts of the body, especially the gut wall also carry out many metabolic transformations. Usually metabolism is a two-stage involving phase I and phase II transformations. Generally,

- (a) a relatively water insoluble compound is converted into a highly reactive intermediate compound (chemically this is often a free radical or its formation involves free radicals) – phase I. This involves a large family of cytochrome P-450 enzymes that are genetically determined. Sensitivity to certain compounds can arise from low or zero levels of one or more of these enzymes.
- (b) This intermediate then reacts further (commonly referred to as conjugation) with a variety of compounds that confer high water solubility on the original compound- phase II. Some compounds can enter phase II metabolism directly. IacrA is already set-up for conjugation and is metabolised in the gut wall, by conjugation with a glycine molecule, to give IAG which is excreted.
- (c) The now freely water-soluble compound is then excreted in the urine.

A less used pathway involves excretion into the bile that goes into the gut- the entero-hepatic circulation. Metabolites of oestrogen are excreted by this route. An added complication is the ability of gut bacteria to remove the water solubilising group leading to reabsorption of oestrogen. This negates the whole process and maintains high oestrogen levels. This has implications for the development of oestrogen-dependent cancers such as most breast cancers.

Volatile compounds are excreted through the lungs, an example are the ketones produced in diabetics when their sugar load becomes too high. Alcohol and some of its metabolites are also excreted in the breath.

Imbalance between phase I and phase II metabolism can be severely detrimental to health. If there is an accumulation of phase I metabolites, due to increased phase I or decreased phase II activity, then these highly reactive molecules will produce extensive oxidative stress. Scott Rigden, 1999, estimates that 80% of ME-CFS patients have an imbalance between phase I and phase II metabolism. It is relatively easy to measure both phase I and phase II metabolism and to modify the consequences of any imbalance- see Section 11C.

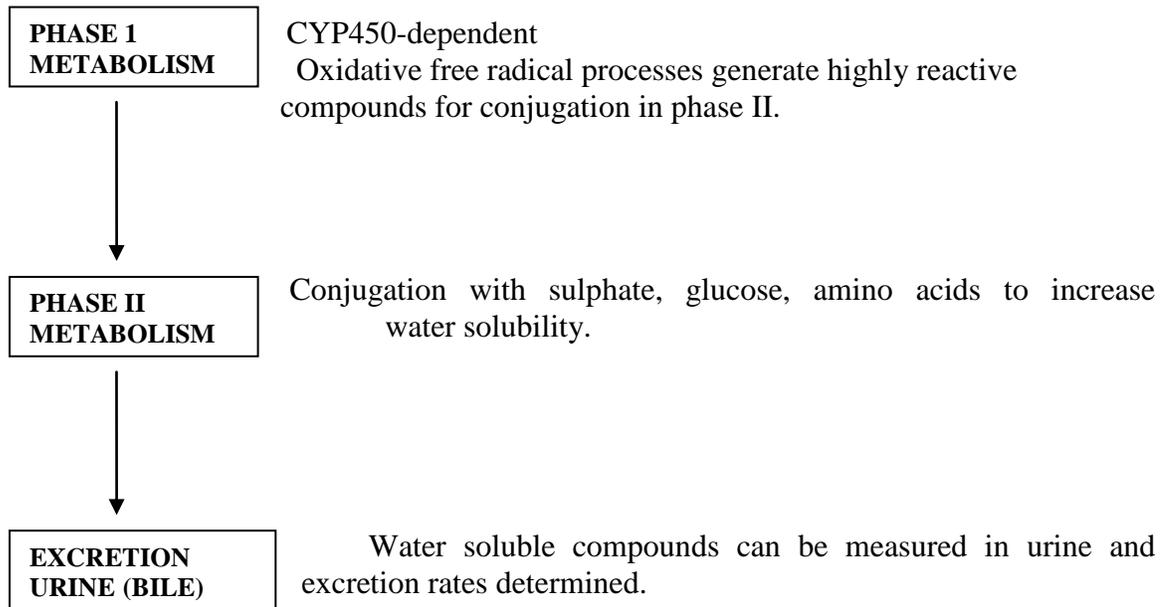


Figure 7.1 Summary of Metabolic Processes for Elimination of Natural and Synthetic Molecules.

C. SULPHUR CYCLES - ANOTHER LINK WITH AUTISM.

Rosemary Waring and her colleagues at the University of Birmingham have made a special study of this complex area of biochemistry, Waring 2000, provides a comprehensive review.

(a) Sulphate, Sulphite and Detoxification.

A very common way of assessing the efficiency of phase II metabolism uses the common analgesic drug, paracetamol. In the body this is conjugated with glucuronic acid, a derivative of glucose, to form a water-soluble glucuronate or with sulphate, to form a water-soluble organic hemi-sulphate.

Waring and her colleagues measured the plasma levels of the sulphate and glucuronate metabolites of paracetamol, and the plasma sulphate levels in children with autism, Table 7.1.

Table 7.1. Sulphate/Glucuronate Ratios and Plasma Sulphate Levels in Autistic Children and a Control Group.

MEAN RATIO OF SULPHATE/GLURONIDE			
	AUTISM	0.87 +/- 0.67	n=46
CONTROL	2.09 +/- 0.65	n= 46	p< 0.005
PLASMA SULPHATE LEVELS			
	AUTISM	1.51 +/- 2.75	
CONTROL	8.30 +/- 5.40		p< 0.001

The more than doubling of the glucuronate/sulphate ratio and the more than fivefold lowering of the sulphate concentration indicates a dramatically reduced capacity for metabolism by the sulphate pathway and low sulphate availability. This would certainly, among other things, indicate an increased susceptibility to paracetamol toxicity and a general loss of metabolic detoxifying capacity.

The pathways involving sulphate metabolism are shown in Figure 7.2.

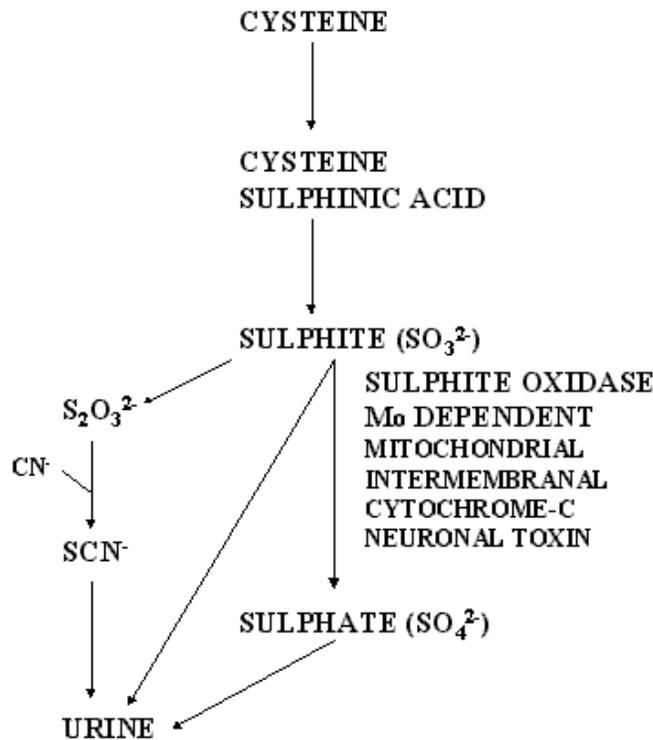


Figure 7.2. The Formation of Sulphate and Other Ions from Cysteine that are Excreted in the Urine.

Although sulphate can be absorbed from the gut or through the skin it is commonly produced within the body from the amino acid, cysteine. Cysteine is metabolised to sulphite, via cysteine sulphinic acid which is then oxidised to sulphate. The particular enzyme involved, sulphite oxidase, contains molybdenum as a vital participant in the oxidation process. Molybdenum is an essential trace metal which plays a key role in several oxidase enzymes, sulphite, nitrite, xanthine, and aldehyde, and formate reductase utilise molybdenum.

Sulphite is a toxic molecule that is known to damage mitochondria, the energy producing organelles in the cell which include cytochrome C as an essential component of the energy pathway. It is also toxic to nerves. Sulphite is widely used as a preservative in tinned fruits and jams. Some people with ME are sensitive to sulphite in these foods and react badly to it. Sulphite serves a useful purpose in removing cyanide from the body as thiocyanate ion by reaction with metabisulphite.

Normally there should be no free sulphite in plasma and therefore none in the urine. When ME patients have been tested for urinary sulphite many prove positive. Treatment is easy and direct with 100 micrograms being given daily for 3 months- see Section 11.

The importance of sulphate extends far beyond detoxification processes. Sulphate plays a crucial role in the function of many different systems in the body, Figure 7.3.

- 1. GLYCOSYLAMINOGLYCANS (GAGs) – maintain the integrity of mucous membranes eg in the gut and lungs.**
- 2. CONTROL SECRETORY PROCESSES –**
- 3. HEPARANS – immunocytokines, cell migration, receptor binding**
- 4. PEPTIDE HORMONES – CCK and Gastrin are both active as sulphated molecules.**
- 5. STEROID HORMONES – DHEA exists largely as the sulphate in equilibrium with the non-sulphated form.**
- 6. DETOXIFICATION – PHENOLS, AMINES**

Figure 7.3. Summary of the Role of Sulphate in Various Biological Systems.

Susan Owen, 1998, has written a comprehensive review of the structure and function of GAGs which describes how these important molecules are dependent on an appropriate supply of sulphate otherwise significant and adverse changes occur some of which have been described in association with disease and malnutrition. Sulphate groups carry a negative charge that confer many vital properties on GAGs in mucous membranes, in particular the ability to hold water molecules, ions and protein layers on the surface of these membranes.

The immune response also depends on the structural of GAGs to a marked extent. Shedding of GAGs is a feature of immune activation of the gut and other lymphoid tissues such as the skin. Lack of sulphate leads to GAGs that cannot protect the cell from infection.

A GAG-rich intracellular matrix makes up 20% of the adult brain and up to 40% of the immature brain- another gut-brain axis.

Heparans play an important role in many biological processes particularly blood coagulation processes. Berg et al, 1999, have identified hypercoagulation processes underlying cardiovascular damage in ME.

CCK and gastrin are important hormones associated with both the gut and the brain. Both are most active in the sulphated form whilst the most abundant steroid hormone DHEA (dehydroepiandrostenone) exists in equilibrium with the sulphated hormone. Any lowering of sulphate levels will potentially cause adverse effects on all the systems affected by these compounds- brain and gut responsiveness, and stress and sex hormones.

Phenols and amines in the body are commonly detoxified via sulphation. Lack of sulphate can lead to a build up of these compounds.

(b) The Methionine Cycle.

Cysteine is the key molecule linking the sulphate cycle, Figure 7.2, and the methionine cycle, Figure 7.4.

The cycle turns clockwise in the direction of the arrow. Successively homocysteine is methylated to methionine, via methylcobalamine. This is a key step that introduces a methyl group into the molecule. This methyl group is passed on to other molecules via the reactive intermediate, Adomet (adenosylmethionine). This is a key step in the synthesis of a neurotransmitter, acetylcholine, various folate molecules, nucleic acids, and modification of membrane structures. The Adohomocysteine remaining is then transformed into homocysteine and the cycle can restart or the homocysteine can lead via cystathione to cysteine.

In turn cysteine may be incorporated into other key molecules particularly, glutathione a key detoxifying molecule that also maintains the redox potential in cells. Taurine has a major role in bile salts as an emulsifying agent and can also act in detoxifying lipid soluble material. Taurine is also an excitatory amino acid. Finally sulphate may be produced, see Figure 7.2.

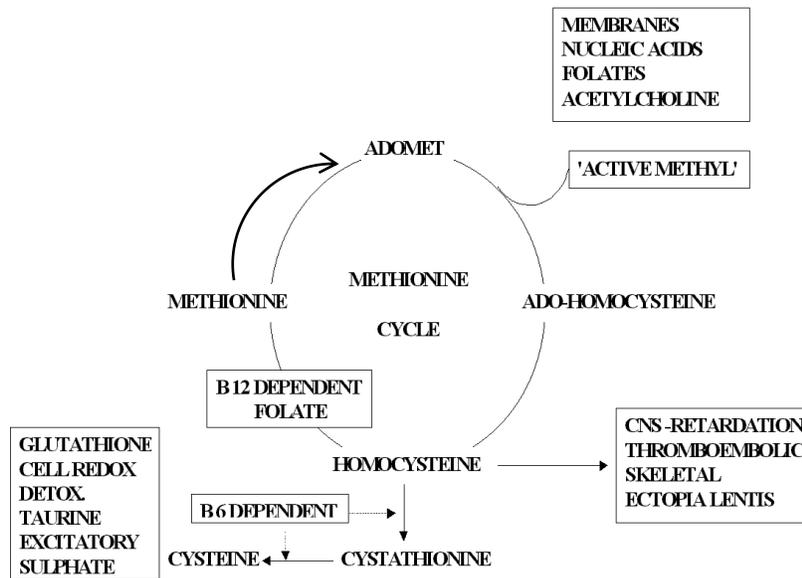


Figure 7.5. The Methionine Cycle

Excess homocysteine is now known to play an important role in several disease states including extensive cardiovascular damage and heart problems, damage to the eye- ectopia lentis is dislocation of the lens of the eye, and skeletal problems involving size and shape of limbs. In Marfan’s syndrome, which involves a genetic deletion of cystathionine synthetase, leads to high levels of homocysteine and its appearance in the urine. Loss of functional B12 and folate capacity and low B6 will also increase homocysteine levels. There are useful tests for B12 and folate functional status and these should be done before these vitamins are supplemented. It is important to give both folates and B12, IFM 1999, if these are indicated. An alternative source of methyl groups is betaine which is a common supplement in some treatment regimens, Section 11.

8. POLYUNSATURATED FATTY ACIDS (PUFAs), MEMBRANES, OXIDATIVE STRESS, EICOSANOIDS.

A. WHAT ARE PUFAs?

(a) Names, Numbers and Structure.

The fatty acids we are considering consist of long straight carbon chains usually having 16 to 22 carbons with zero to 6 double bonds that terminate in a carboxylic acid group. When no double bond is present the carbon chain is described as saturated. Double bonds confer unsaturation on the molecule and the greater the degree of unsaturation the lower the melting point of the compound and the more chemically reactive the molecule. Oxidation leading to rancidity and resinification is a particular problem. Fatty acids are found in oils and fats that are present in plant oils and fish oils and it is these that supply essential nutrients in our diet. The fatty acids in these oils are largely unsaturated having 1 to 6 double bonds. In contrast, saturated fats that mainly occur in animal fats have become a problem for many people since they are now very widely consumed in the diet (animal meats and processed foods) and contribute to the high level of cardiovascular disease that is common in western society. The current labeling of foods so as to indicate the nature of the fat, saturated, unsaturated, reflects the medical concern about the over-consumption of saturated fat in our diet.

Figure 8.1 gives full details of the structure, numbering and naming of DHA and EPA two important PUFAs. Whilst these two molecules are the most complex of the PUFAs they are important among nutritional supplements and are commonly identified in labels on the products sold to supply PUFAs.

The carbon chain is numbered from the carboxylic acid carbon atom, number 1, and the double bonds given the number of the first carbon atom, eg. 4,7,10,3,16,19 in DHA, as shown in black. On historical grounds other systems of numbering continue to be used and can be confusing. The important essential PUFAs fall into two groups that are distinguished by the position of the terminal double bond. In the case of DHA the final double bond, number 19, is three carbon atoms from the terminal carbon atom, number 22 -see red numbering.

Table 8.1 lists the important PUFAs which are commonly assigned to either the n-3 or ω -3 (omega-3) or n-6 (ω -6) group of fatty acids. The use of Greek letters like omega, ω , is sometimes not appreciated and can be outside the capabilities of some labeling systems so, instead of ω , the letter, W or w, is quite commonly used on labels for fish and plant oils supplied from health stores.

Table 8.1 also lists the sources of the different PUFAs and the transformations that take place from the essential precursor compounds, LA and ALA.

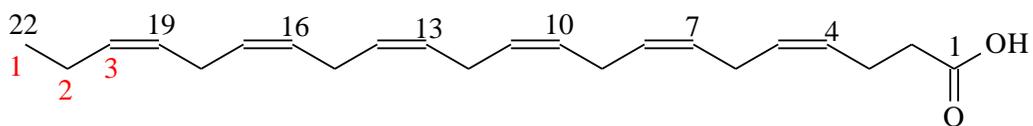
DHA and EPA are ω -3 fatty acids that are found exclusively in fish oils but can be synthesised in the body from less saturated, ALA, found in a few plant oils such as flax, etc.

The ω -6 acid, DPA, is also synthesised in the body from precursor ω -6 oils that are generally found in plants, these include evening primrose oil etc.

The key enzymes, and their essential co-factors, in these pathways are indicated in the central column of Table 8.1. The activity of these enzymes slowly decreases with age and some people recommend supplementation with mixtures of ω -3 and ω -6 oils for every one over sixty years old.

An important factor in determining the balance of the crucial PUFAs, DGLA, AA, and ETA is the preferential metabolism of the ω -3 ETA rather than the ω -6 DGLA by the

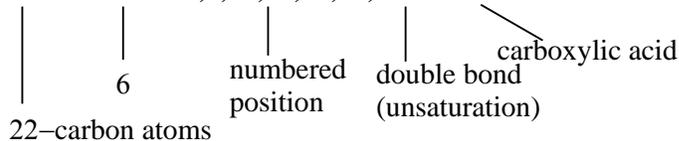
Δ^5 -desaturase enzyme. DGLA and ETA are precursors to anti-inflammatory compounds whilst AA gives rise to pro-inflammatory compounds, Section 8E.



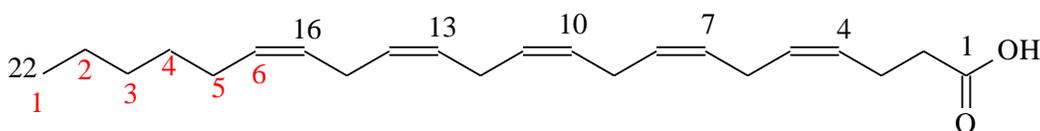
n-3

ω -3

DOCOSAHEXA-4,7,10,13,16,19,22-ENOIC ACID



DHA (22:6 ω 3)



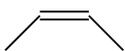
n-6

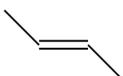
ω -6

DOCOSAPENTA-4,7,10,13,16-ENOIC ACID

DPA (22:5 ω 6)

NOTE- the double bond may have two different spatial arrangements-

cis  side chains attached on the **same** side.

trans  side chains attached on **opposite** sides.

All the unsaturated oils under consideration have the cis configuration.

Figure 8.1. The Structures and Nomenclature of DHA and DPA.

A diet rich in animal fat and deficient in ω -3 PUFAs will result in an increased susceptibility to inflammatory illnesses such as irritable bowel syndrome, rheumatoid arthritis, asthma, and inflammatory skin disorders

Table 8.1. Summary of ω -6 and ω -3 Series of Poly Unsaturated Fatty Acids (after Nutritional Management of Inflammatory Disorders - IFM).

Sources	ω -6	Enzymes	ω -3	Sources
Safflower, sunflower, sesame	LA α -linoleic acid (18:2 ω -6) 9,12 ESSENTIAL		ALA α -linolenic acid (18:3 ω -3) 9,12,15 ESSENTIAL	Flax, soybean, hemp, walnut, pumpkin,
	↓	Δ^6 - Desaturase (B3, B6, C, Zn, Mg)	↓	
Borage, evening primrose, blackcurrant, fungi, human milk	GLA γ -linolenic acid (18:3 ω -6) 6,9,12		SDA Stearidonic acid (18:4 ω -3) 6,9,12,15	Blackcurrant
	↓	Elongase	↓	
Human milk	DGLA γ -dihomo-linolenic acid (20:3 ω -6) 8,11,14		ETA Eicosatetraenoic acid (20:5 ω -3) 8,11,14,17	Fish oils
	↓	Δ^5 - Desaturase (favours ω -3 substrates)	↓	
Beef fat, egg yolk	AA arachidonic acid (20:4 ω -6) 5,8,11,14		EPA Eicosapentaenoic acid (20:5 ω -3) 5,8,11,14,17	Fish oils
	↓	Elongase	↓	
	DTA Docosatetraenoic acid (22:4 ω -6) 7,10,13,16		DPA Docosapentaenoic acid (22:5 ω -3) 7,10,13,16,19	

	↓	Δ^4 - Desaturase	↓	
	DPA Docosapentaenoic Acid (22:5 ω -6) 4,7,10,13,16		DHA Docosahexaenoic acid (22:6 ω -3) 4,7,10,13,16,19	Fish, marine algae oils

B. OILS, FATS, AND PHOSPHOLIPIDS

Strictly speaking oils and fats are lipids (oil soluble natural compounds) that are fatty acid esters of glycerol which can combine with up to three fatty acids to give a true oil or fat. Membranes are composed of phospholipids in which the glycerol molecule usually has two different fatty acids bound to it and another unit that provides a polar group that carries positive and negative charges. Phospholipids thus have an oil soluble part/lipid and a water soluble/charged part- they are amphipathic molecules, Figure 8.2.

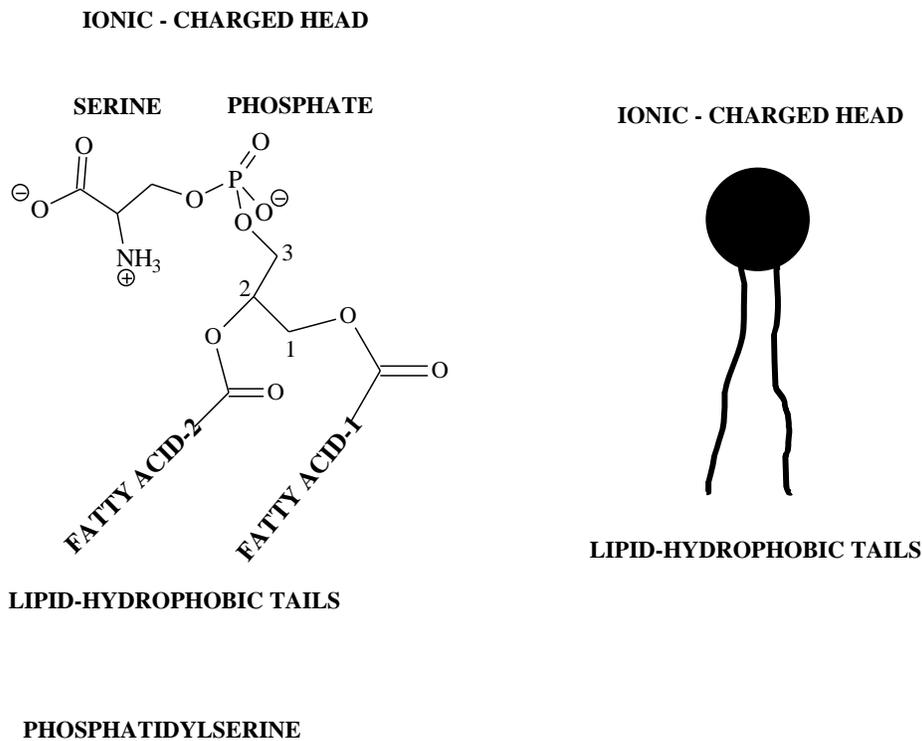


Figure 8.2. The Structure of Phosphatidylserine and its Amphipathic Symbol.

The greater the degree of unsaturation of the PUFAs in the lipid layers the more fluid and flexible the membrane and the greater the availability of precursor molecules for protection against inflammation. We have already seen that the fatty acid composition of membranes is known to affect the efficiency of receptor binding and function, Section 5B.

C. LIPID BILAYERS AND MEMBRANES

Figure 8.3(a) shows how lipid bilayers are formed from the tail to tail coupling of phosphatidyl lipid molecules. These bilayers form the centre of a membrane and have embedded in them various protein molecules that may span the bilayer completely or be embedded on the inner side or outer side of the membrane, Figure 8.3(b1). These proteins are membrane associated macromolecules that function as enzymes, ion channels, and receptors. This early model of cell membranes is usually described as the mosaic model, Figure 8.3(b2).

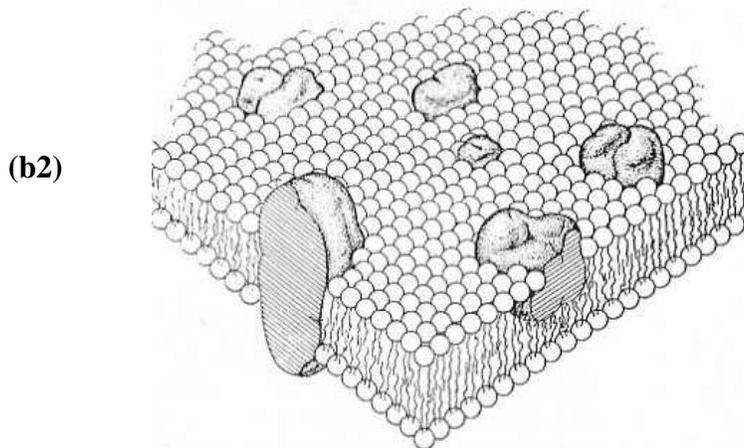
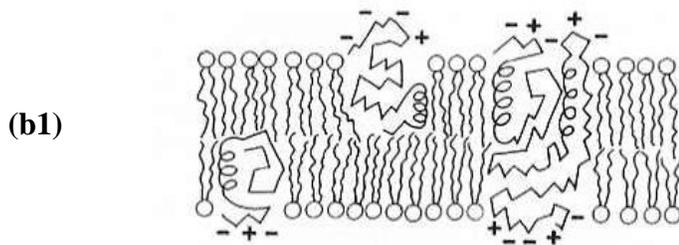
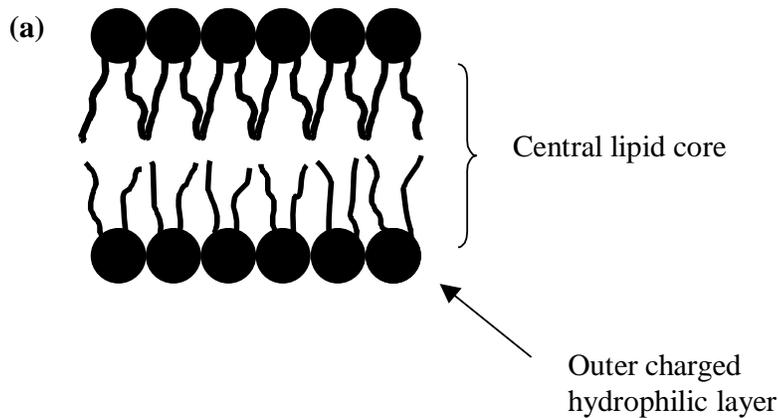


Figure 8.3. Cross Sectional view of (a) Lipid bilayer and (b1) Proteins embedded in the Lipid Bilayer: (b2) Three Dimensional View of Membrane Mosaic.

However membranes are much more complex than simple bilayers and the mosaic model shown in Figure 8.3. A variety of other functional macromolecules are associated with and sometimes bound to both the inner and outer surfaces of the membrane. The overall complexity of membranes is indicated in Figure 8.4. Carbohydrate macromolecules, including GAGs, glycoproteins made up of complex sugars and amino acids, glycolipids composed of proteins and fatty acids are enmeshed with the supporting fibres of the extracellular matrix and the cytoskeleton filaments inside the cell.

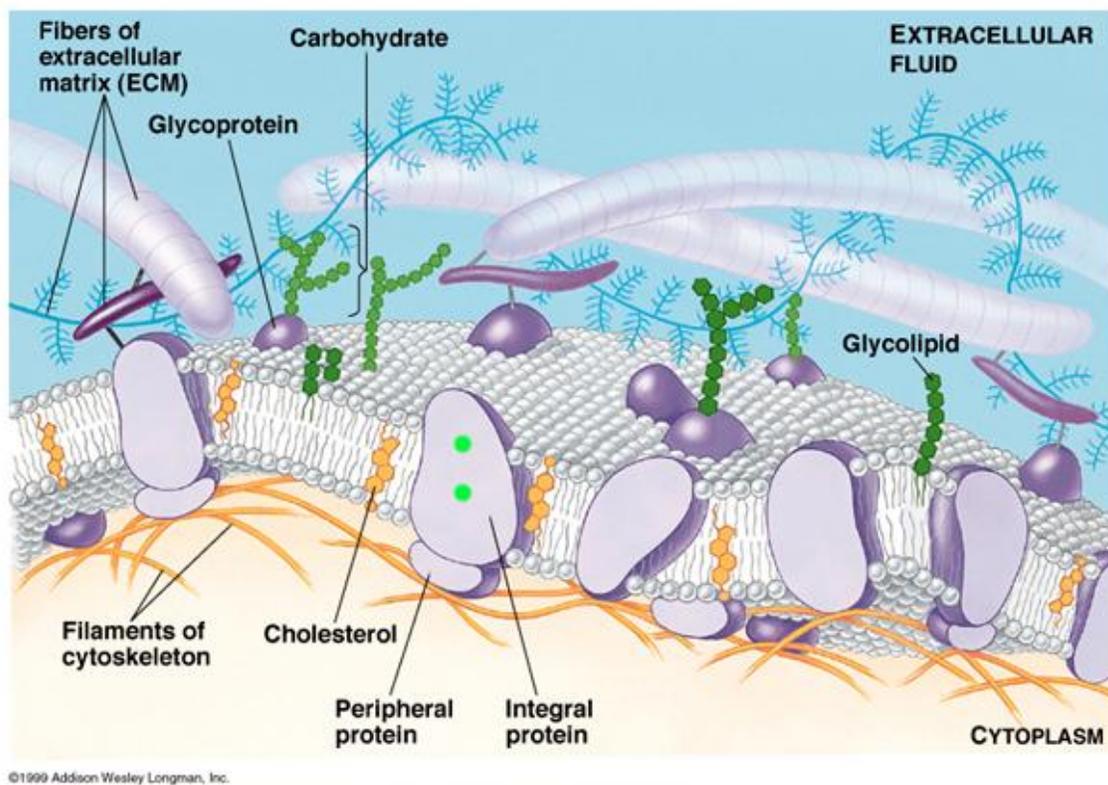


Figure 8.4. The Complex Structure of Cell Membranes incorporating a Lipid Bilayer (download from internet)

D. MEMBRANE COMPOSITION AND OXIDATIVE STRESS. A significant number of people have submitted blood samples for testing by Leslie Simpson, a New Zealand biochemist, who evaluated the functional efficiency of red blood cell (RBCs) membranes by direct inspection of cells that had been freshly collected in a fixing fluid, Figure 8.5.

Simpson, 1989 a,b, and Spurgin 1995, looked for the proportion of RBCs that have aberrant shapes that depart from the characteristic biconcave shape of healthy and fully functioning RBCs. Generally, the most common aberrant shape is a flattened disc and in ME patients up to 80% of cells have this shape. The cup form, Figure 8.5 (c) is often associated with a viral infection.

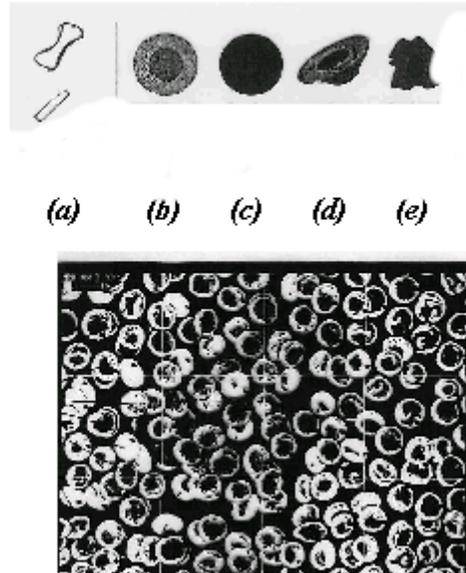


Figure 8.5. Red Blood Cell Shapes (a,b) normal; (c) flat; (d) cup; (e) altered margins.

Simpson regards these aberrant shapes as a result of PUFA deficits and recommends treatment with evening primrose oil. Such a deficit he regards as indicative of loss of fluidity and flexibility of the RBC membrane resulting in reduced access of these cells to the deep capillary beds (RBCs have to fold to pass through small capillaries). Reduced access leads to loss of oxygen supply to these areas giving rise to fatigue. If cup forms are present injections of vitamin B12 (hydroxycobalamine) are helpful.

This procedure requires a trained operative but similar information can be obtained by direct analysis of the fatty acid composition of RBC membranes, Table 8.2.

Table 8.2. Composition of RBC Cell Membranes as a % of Total Fatty Acids

ω -6 Series		Reference Ranges
18:2 LA	8.4	8.10 – 13.5
18:3 GLA	0.27	0.22 – 0.47
20:3 DGLA	1.5	1.40 – 2.20
22:4 AA	9.4	9.00 – 13.8
22:4 DTA	2.2	2.00 – 3.90
22:5 DPA	1.6	0.40 – 0.87
ω -3 Series		

18:3 ALA	0.67	0.60 – 1.15
20:5 EPA	0.68	0.70 – 1.51
22:5 DPA	1.5	1.60 – 2.50
22:6 DHA	2.4	2.70 – 4.50
Other Fatty Acids		
14:0 Myristic	1.6	0.40 – 1.60
16:0 Palmitic	30.4	22.0 – 33.0
16:1 Palmitoleic	3.3	0.60 – 1.10
18:0 Stearic	17.7	13.0 – 18.0
18:1 Oleic	21.5	14.0 – 24.0

The above data show generally low levels of both ω -6 and ω -3 PUFAs with most of the ω -3s being below the reference range. Supplementation with fish oils is recommended. Nonenal, a short nine-carbon fragment is a common product of the oxidative degradation of PUFAs and can be readily detected in urine. It is a useful marker for membrane damage.

E. EICOSANOIDS AND THE INFLAMMATORY RESPONSE

As well as providing the unique structural characteristic features of membranes some PUFAs, DGLA, AA, and EPA, also serve as substrates for the production of three families of compounds directly involved in the inflammatory response, Figure 8.6. Collectively these compounds are called eicosanoids (Greek, eicosa = 20) because they are all derived from PUFAs with twenty carbon atoms in the fatty acid chain. The ω -6 acids, DGLA and AA, give rise to series 1 and 2 prostaglandins, respectively, whilst EPA gives rise to series 3 prostaglandins, cyclooxygenase enzymes are responsible for these transformations. Series 1 and 3 prostaglandins are generally anti-inflammatory and series 2 prostaglandins generally pro-inflammatory. There are, however, exceptions to this general rule which make this a very complex area of biology. Thromboxanes, derived from some prostaglandins, and leukotrienes, produced from lipoxygenase enzymes, broadly have the same kind of anti- or pro-inflammatory effects.

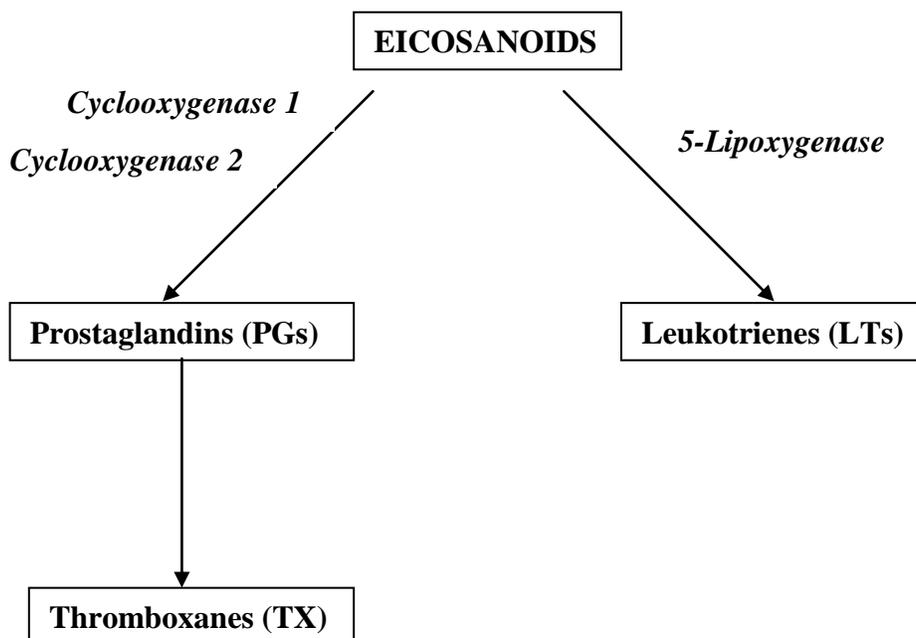


Figure 8.6. Inflammatory Mediators derived from Eicosanoids.

The nomenclature of eicosanoids is complex and not consistent between the different series. Generally, the abbreviation, PG, LT, and TX is followed by another capital letter

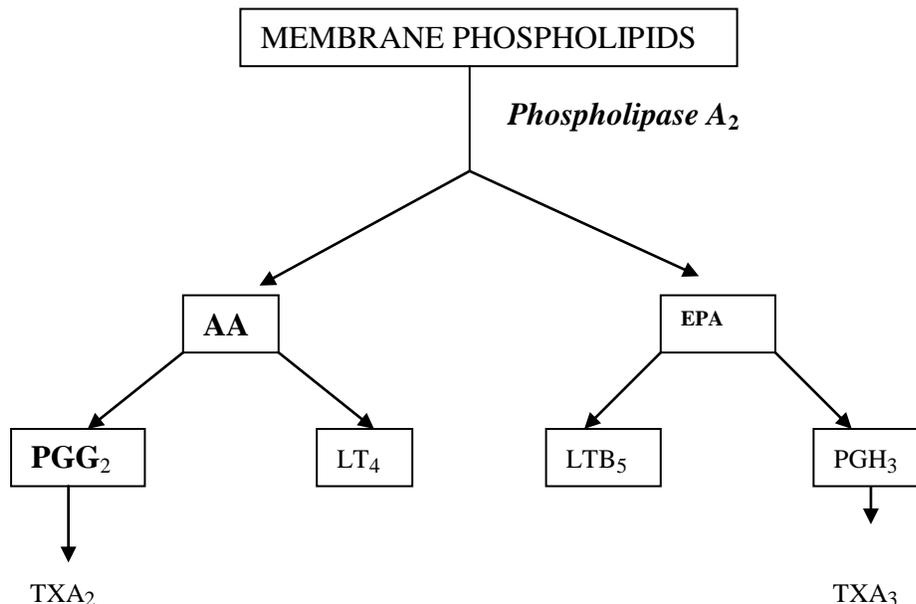


Figure 8.7 Nomenclature of Eicosanoids derived from AA and EPA.

and then a subscript number. For example, AA gives PGG₂ then PGH₂ which in turn gives TXA₂, but 5-lipoxygenase on AA gives LTA₄ etc, Figure 8.7. Note that the membrane phospholipids are broken down by phospholipase A₂ releasing the fatty acids which in turn are converted into PGs and LTs by the action of cyclooxygenases and 5-lipoxygenase respectively.

The arachidonic cascade has been widely studied and is the target for a number of anti-inflammatory drugs. Glucocorticoids were used as potent anti-inflammatory drugs long before it became known that they stabilised lipid membranes and prevented the break down of phospholipids, by phospholipase A₂, with the release of arachidonic acid other PUFAs. The best known anti-inflammatory drug is aspirin (acetylsalicylic acid) which together with the related non-steroidal anti-inflammatory drugs, NSAIDs, such as ibuprofen block the action of cyclooxygenase enzymes. Sulphasalazine, which blocks 5-lipoxygenase, is used to treat Crohn's disease which is a severe inflammatory bowel disease. It is sometimes used in irritable bowel disease. A surprising number of nutritional and botanical products also act on the AA cascade. All these are summarised in Figure 8.8.

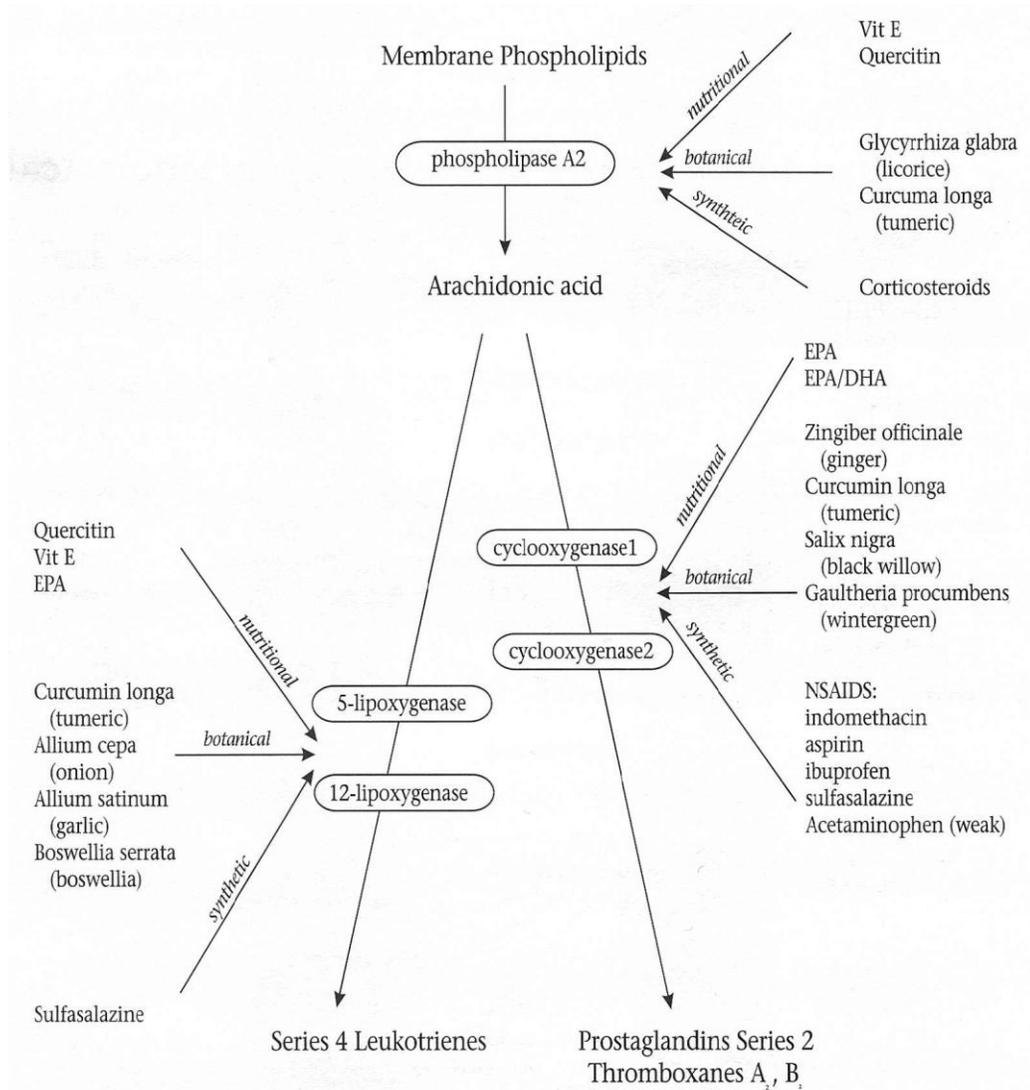


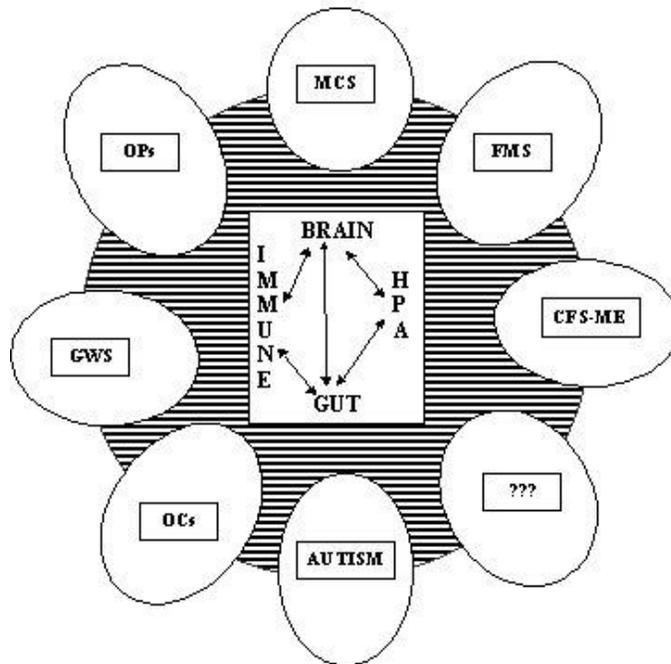
Figure 8.8. The Sites of Action of Anti-inflammatory Drugs, Nutritional and Botanical Products on the Pro-inflammatory Arachidonic Acid Cascade(IFM, 1998).

B. OVERLAPPING SYNDROMES RECONSIDERED.

It is now possible to reconsider the questions around overlapping syndromes, Figure 9.2 contrast Figure 3.1.

The major deficits in ME patients identified above are-

- Disordered tryptophan metabolism
- Disordered gastrointestinal function and structure
- Gut dysbiosis
- Increased gut permeability
- Opioid excess
- Endocrine dysfunctions
- Disturbances of the Central Nervous System
- Immune dysfunction
- Failure of detoxification mechanisms
- Disordered lipid, phospholipid, and fatty acid metabolism
- Unbalanced modulation of inflammatory mediators derived from fatty acids
- loss of cell membrane integrity



OVERLAPPING DYSFUNCTIONAL STATES WITH DISORDERED, GUT FUNCTION/STRUCTURE, TRYPTOPHAN, SULPHATE, AND LIPID METABOLISM

Key see Figure 3.1. HPA = Hypothalamus-Piuitary-Adrenal axis.

Figure 9.2 Overlapping Syndromes with Multiple shared Biochemical Deficits.

In ME it is clear that these biochemical deficits are extensive and a proper study is needed to consolidate this information. It is striking that other research workers have also found evidence of impaired detoxification processes, Rigden 1999, and grossly impaired lipid metabolism, Spence, et al, 2002. The availability of established methods for quantifying key marker molecules, IAG, sulphate levels in serum, functional vitamin tests, and fatty acid levels in marker tissue like RBCs means that objective tests are available as diagnostic aids for clinicians engaging with these syndromes of uncertain origin.

It is important to note that for the overlapping syndromes there are also some objective tests that can uniquely characterise the individual syndromes. Organochlorine poisoning can readily be identified by measuring serum or fat levels of these compounds. FMS can be identified by clinical assessment using the established 18 pain points. Recently, a test unique for ME has been published, Spence et al, 2000. Acute OP poisoning can be readily identified from, cholinesterase levels in serum and RBCs, and from urinary metabolites but there are as yet no useful persistent marker molecules or enzyme systems. Paraoxonase is an important protective enzyme against oxidative stress and is particularly important in atherosclerosis and diabetes, Mackness et al, 1997, 1998, 1999, 2000. Damage to deep brain structures has been identified in Gulf War veterans using magnetic resonance spectroscopy, Haley et al, 1997a,b, 2000 and 2002, which has frequently been applied to ME patients and found excess levels of choline in certain brain areas, Puri et al, 2001. MCS can be assessed using a clean environment and low level challenge by suspect compounds, BSAENM, 2000 .

All these tests can only sensibly be used with the most careful history taking and clinical examination which is absolutely essential for an accurate diagnosis, Richardson, 2001, 2002.

C. NEUROENDOCRINEIMMUNE PARADIGM

The centre panel of Figure 9.2 summarises the extensive interactions between the gut and the neuro-, endocrine, and immune systems, Ader, 1991, sometimes also, but less accurately, described as psychoneuroimmunology, PNI, Watkins, 1997. It is now clear that the cross-talk between these three systems, Figure 9.3, that uses common messenger molecules, neurotransmitters, peptides, hormones, cytokines etc, provides a level of integrated and sophisticated control that affects all the major organs of the body.

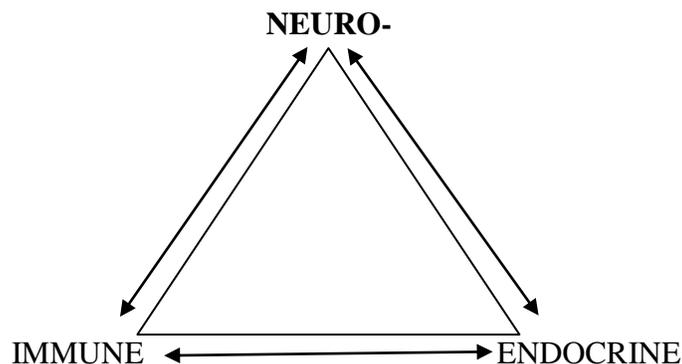
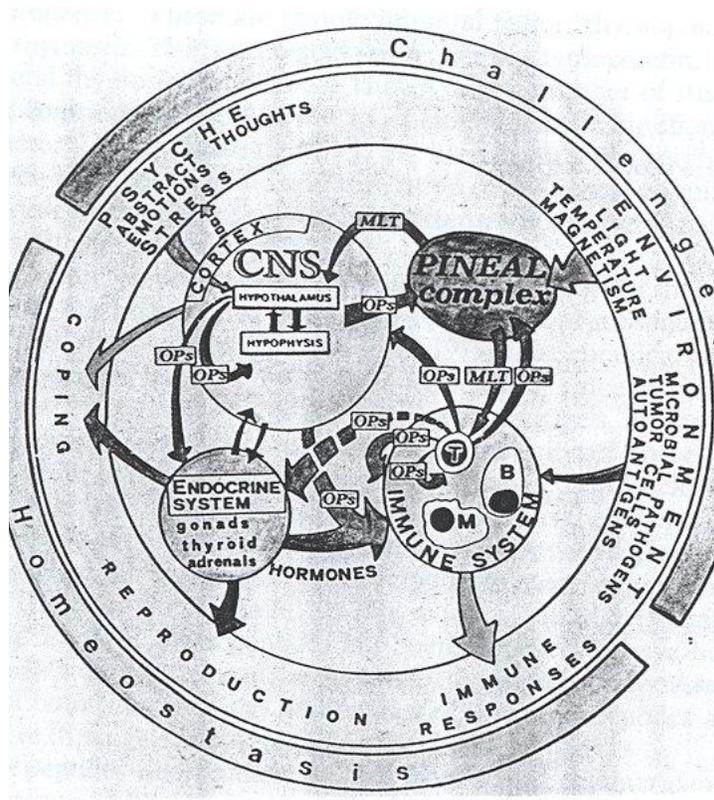


Figure 9.3. Bi-directional Signalling between the Neuro-, Immune, and Endocrine Systems.

Richardson, 2001, 2002, and others, Section 12A, have shown that viral infection is often the precipitating factor in ME. It is clear that immune disturbances brought on by infection can

give rise to extensive disturbance of both the peripheral and central nervous system. This fact has been known for centuries in the common response to an infection involving tiredness, sleep, high temperature, sweating and headaches. 'Go to bed, keep up the fluids and take pain killers until you feel better,' is the usual advice. We now know how many of these effects are produced by the different messenger molecules released in response to an infection. We also know that infecting organisms can release biologically active compounds when they are destroyed in the body, for example, fragments of the cell wall of the TB bacillus are sleep inducing.

Figure 9.4 summarises the complexity of these interactions in a schematic form.



Key: OPs = opioids; MLT = melatonin; Hypophysis = pituitary gland.

Figure 9.4. Schematic of NEI Paradigm showing Interactions between the Central Nervous System, CNS, the Endocrine System and the Immune System. (Ayer 1991)

It is probably easiest to engage with this diagram using compass points to identify the main features. The outer circle of the diagram identifies the general challenges to the whole system

(top- NE) and homeostasis (bottom- SW). Homeostasis is the resting but active equilibrium of the undisturbed system.

Different challenges enter and disturb the whole system and evoke a response that is contained by a coping mechanism that restores the system to its original balance (homeostasis). Most of us are familiar with these different challenges and responses and often take them for granted. **Note the importance of opioids in the communication between the different systems.**

The second circle lists the psyche and environment.

- Psyche (NNW) –the senses play an important role. Simply seeing something pleasant or unpleasant can evoke a whole range of responses from elation to sweating, pallor, fainting, vomiting etc. These responses are mediated by chemical messengers, including opioids, that are well characterised and affect the total system and extend to peripheral organs eg. Lowering of blood pressure, reduction followed by increase in heart rate, etc.

There is no doubt that the psyche is very important for our well being. Meditation (control of blood pressure, heart and breathing rates), prayer, and relaxation techniques (used in asthmatic children) all provide useful ways of modulating our physiological responses. However, these responses are all accompanied by objective changes in marker molecules. Indeed all psychiatric drugs are developed on the basis that they modulate molecules known to be important in psychiatric illness, eg. Selective Serotonin Re-uptake Inhibitors, SSRIs (seroxat, paroxetine) increase the amount of free circulating serotonin (5-hydroxytryptamine) in the brain and other parts of the body, especially the gut.

Stress is associated with increased blood pressure and a lowering of the immune response.

Coping responses (W) involve our responses coordinated through the whole system.

- The physical environment (light, temperature, magnetism and other forms of radiation (NE) may affect and disturb the whole system. Although such challenges are often regarded as unimportant, and some have not been widely studied, they can cause many adverse effects, eg strobe lighting and headaches and seizures, darkness and seasonal affective disorder, SAD, mobile phones and possible brain cancer etc. Radiation and magnetism have both been associated with effective healing of damaged tissue.
- The outer environment includes micro-organisms (E) that are detected by the immune system but the over all response encompasses the whole system.

The inner environment may involve tumour-inducing viruses and autoantibodies. The latter are a arise from an aberrant immune response to a foreign protein that leads to the immune system destroying the body's own tissue, eg rheumatoid arthritis, lupus etc.

- The immune response (S) protects against infection and aberrant cells that may develop into cancers. All the major tissues in contact with the environment are well supplied with lymphoid tissue- the gut, skin, lungs.
- Reproduction involves prolonged major changes to endocrine and immune systems especially. The foetus is partly foreign tissue so the immune system is subtly down regulated to allow its survival and growth. Some diseases such as leprosy may break through during a pregnancy whilst others such as rheumatoid arthritis may improve.

Melatonin is the hormone of the pineal gland which traditionally has been associated with the control of circadian rhythms- one name for it is the sleep hormone. However, it is now

known to have a much wider role and is possibly the major control hormone for the hypothalamus and pituitary gland. It is also a potent anti-oxidant and can exert a protective role in this way.

Figure 9.5, shows the actual location of the different components described in the schematic, Figure 9.4.

The stress system is stimulated by the neurotransmitters, acetylcholine (cholinergic system) and serotonin (serotonergic system) in the brain and inhibited by gammaaminobutyric acid (GABA) which responds to benzodiazepine drugs such as valium. POMC (pro-opiomelanocortin) is a large precursor molecule for several peptides including opioids. Release of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus stimulates the pituitary to release adrenocorticotrophic hormone (corticotropin, ACTH) that stimulates the adrenal gland to release cortisol, a potent immunosuppressant. Arginine vasopressin (AVP) controls water metabolism and also raises blood pressure. The adrenal gland is also a potent source of adrenaline (epinephrine) and noradrenaline (norepinephrine) that activates the whole sympathetic nervous system. Opioids are also secreted by the adrenal gland.

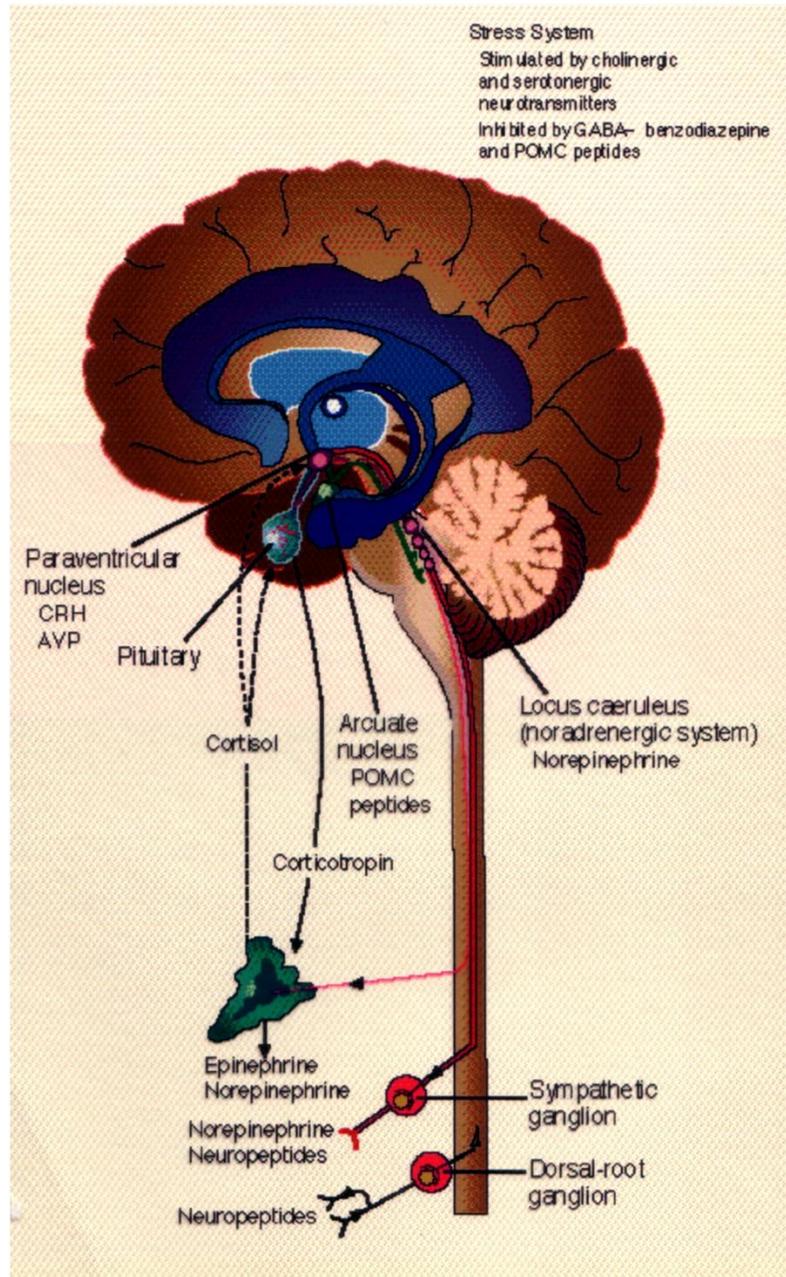


Figure 9.5. The Anatomy of the CNS and HPA Axis (see text for explanation of abbreviations).

10. DIAGNOSIS

From all the above considerations it is possible to list the test data that would be helpful in making a diagnosis of ME and related overlapping syndromes. However, such tests should only be used following a careful clinical history and thorough examination.

The following tests have been validated and are available to clinicians. Some of these may be available through pathology and biochemical laboratories accessed through the NHS but others may require referral to private laboratories such as Biolab Medical (see www.biolab.org). Although Biolab were the first in the field in the UK there are many other laboratories emerging and some well-known laboratories in the USA also can provide testing for clinicians and health professional in the UK, eg. Great Smokies Laboratory and Great Plains Laboratory

- IAG test available at www.osiris.sunderland.ac.uk/autism
- Gut permeability – involving polyethylene glycol or the simpler mannitol/lactulose test that depends on the fact that mannitol passes through the gut wall and is not metabolised but excreted unchanged in the urine. Lactulose, a common laxative, should not pass through the gut wall and should not appear in the urine.
- Serum sulphate
- Urinary sulphite and sulphate
- Glutathione Sulphar transferases and other detoxification enzymes.
- Evaluation of phase I (benzoic acid) and phase II (paracetamol) metabolism
- Serum/urinary homocysteine
- Functional B12 – urinary methylmalonic acid
- Functional folate – urinary formiminoglutamic acid
- Functional B6- RBCs glutamic –oxaloacetic transaminase activity
- RBCs fatty acid profile
- Urinary nonenal and lipid peroxides
- Antioxidant status which involves a battery of tests assessing vitamin E, carotenes, ascorbic acid, selenium, copper, and glutathione peroxidase levels
- Pesticide screens involving blood, fat and urine samples

Specialised tests in neurology, endocrinology and immunology may also be required. A vast range of tests are available either in specialist hospital units, central facilities such as magnetic resonance units, or through external laboratories.

The recent report of the Canadian Clinical Working Case Definition, 2003, insists that both MRI, magnetic resonance imaging and MRS, magnetic resonance spectroscopy are used to assess patients.

Bruno, 2002, has described intense spots on MRI scans that indicate significant damage in parts of the brain, see also Hyde, 1992.

MRS has identified biochemical lesions in the brain (basal ganglia and brain stem) of sick Gulf Veterans, Haley, 2000, 2002. Excessive levels of choline have been found in a different part of the brain (occipital cortex) in ME patients, Puri et al, 2002.

SPECT (single photon emission computed tomography) and PET (positron emission tomography) scans provide important information about blood flow in the brain, Richardson, 2001.

Some further tests that are of major importance are

- Tests for fatigue- some simple but useful tests involve a repeated lifting of a weight (2 pound bag of sugar or something a bit heavier). ME patients can often manage a small number of repeats but performance rapidly falls off and recovery is very slow compared to healthy controls. It is this rapid ‘fatiguability’ and very slow recovery that is characteristic of ME patients. More sophisticated treadmill tests will show the same effect.
- Mineral screens – there is strong anecdotal evidence that magnesium and zinc are often at low levels in many people with ME and other trace metals/elements may also be low eg. selenium, molybdenum, chromium, copper, boron etc. Selenium is particularly important as the UK population generally has low levels of this element due to adverse changes in food and agriculture, Rayman, 2000; Neve, 2000. Selenium is important in the conversion of T4 to T3, see below, and is also essential for effective detoxification by glutathione sulphur transferase enzymes.
- **Thyroid status** – very commonly ME patients are described as biochemically euthyroid (normal) but clinically hypothyroid (excessive and disabling fatigue, low level of alertness, weight gain, dry skin and hair, brittle nails, emergence of autoimmune disorders, etc). This contradictory picture is usually based on the measurement of blood levels of TSH (thyroid stimulating hormone) and T4 (thyroxine). However, the most important and potent thyroid hormone is T3 which is formed in the body from T4 by deiodination by a selenium-dependent enzyme. If this process is faulty then thyroid function will be dangerously compromised. Low levels of free, circulating thyroxine and raised receptor resistance can also contribute to a hypothyroid state. The complex factors involved with hypothyroidism have recently been recognised, Dayan, 2001, Shames and Shames, 2001. All these different steps need to be checked out before normal thyroid function is accepted in an ME patient.
- Other more specialised endocrine tests are, the buspirone-prolactin test in which an exaggerated response occurs, Richardson, 2001, whilst the ACTH-cortisol response test often results in a blunted response, and there is no significant cortisol response to mild stress, Bruno, 2002. Many ME patients have reduced adrenal reserve and ultrasound scans reduced adrenal mass.
- Bell, 1998, has studied the unstable nature of the cardiovascular response in ME patients. Very commonly there are significant and varied changes in blood pressure that occur on changing position, from sitting to standing, or just prolonged standing. Blood pressure and pulse rate measurements under varying conditions are often diagnostic. Tilt table testing provides a more comprehensive and sophisticated assessment. Blood volume is often very low both with regards to RBCs and plasma volume. Low levels of circulating vasopressin (anti-diuretic hormone, ADH) indicate a dysfunction of the posterior lobe of the hypothalamus.
- The Romberg or tandem Romberg tests, involving standing with eyes open then with eyes closed with feet together or one behind the other. A positive Romberg is when the position is maintained with eyes open but not when they are closed. It is a useful test of brain stem function; commonly many ME patients fail these tests.
- Nystagmus, rapid involuntary movement of the eyes- side ways or up and down, is also common in ME.

- Total and differential white blood cell counts can often indicate immunological imbalance whilst antibody tests can identify infection and autoimmune disorders.
- A significant proportion of ME patients develop (multiple) chemical sensitivities. The most common ones are to caffeine, perfume, and alcohol but sometimes the condition can become very extensive and involve most volatile organic materials.

A significant and perplexing aspect of test on ME patients is the variability in test responses that can occur. For example nystagmus may be obvious in the morning but absent in the afternoon. Blood pressure responses can also be very variable.

11. TREATMENT

There are a wide range of treatments and one of the major features of any meeting with ME sufferers is the heart-breaking stories of a number of people who have spent very large sums of money on a whole variety of treatments often involving complementary therapies without any benefit. A confusing number of vitamin, mineral and nutritional supplements have been consumed but without any systematic approach. It is then difficult to know when any particular treatment has been helpful.

Neuropsychiatric drugs of various categories but commonly antidepressants have been found of little value by many people and positively harmful by some sufferers.

What is offered below is a systematic approach that will allow each treatment to be evaluated and built on, or abandoned, depending on the response. What follows corresponds to the main features I have described earlier and summarises the information available. Additional important information will be given at the end.

A. THE GUT

(a) The 4 Rs- recommended by the Institute of Functional Medicine.

This approach provides a comprehensive and systematic treatment plan for the gut in four steps.

- i. **REMOVE-** food related toxins, xenobiotics (foreign materials) that function as allergens, and any pathogenic organisms – bacteria, fungi, other parasites.

In response to a positive IAG test this means remove dairy products and/or wheat and related cereal products. Remember we are not talking about coeliac disease which is a true allergic reaction.

- ii. **REPLACE-** essential components of the gastrointestinal tract. These include gastric acid, gut enzymes derived from pancreas and other sources.

Gastric acid can be either too high or too low. Unfortunately the symptoms of excess or deficit are very similar.

Many modern drugs are available for the lowering of gastric acid levels, eg cimetidine, ranitidine, omeprazole, and some are available over the counter in low dose formulations. The use of these classes of drugs to treat gastric and duodenal ulcers is now known to be only part of the story. Antibiotic therapy in conjunction with gastric acid lowering drugs, and bismuth preparations are now the treatment of choice.

Betaine hydrochloride increases gastric acid levels. It is important to distinguish between betaine hydrochloride and betaine. Betaine supplies methyl groups and provides a useful alternative source of methyl groups in support of the methionine cycle, Figure 7.5. Betaine hydrochloride is source of acid and methyl groups.

Clearly it is important to know whether the acidity of the stomach is too high or too low before commencing treatment.

Various pancreatic enzyme preparations are available under the general name pancreatin and include enzymes that break down proteins, fats, and starches. These preparations can be prescribed by a physician. Bromelain, an enzyme that breaks down proteins and preparations such as ‘serenaid’ are also available from non-prescription sources.

A useful test of gut integrity is available at Biolab and involves swallowing a carefully prepared capsule that degrades gradually in response to the contents of the gut and a mini-transmitter reports the level of acid and key enzymes.

iii. REINOCULATE- probiotics are the organisms associated with the microbial integrity of the normal gut. These are available either in food preparations containing live cultures usually of lactobacilli or as capsules containing organisms freeze-dried including lactobacilli and bifidobacteria. Generally, the capsule preparations supply much larger numbers of organisms and are more effective than the live culture foods that are more appropriate for maintaining the gut that is functioning normally.

The maintenance of a healthy gut also requires prebiotics from dietary sources that support the growth of 'good' bacteria. Bifidobacteria use fructooligosaccharides, FOS, as a major food source. FOS occur widely, in many natural food stuffs, and are found especially in leeks, onions, bananas, and the more exotic Jerusalem artichoke. Encouraging the growth of 'good' bacteria results in crowding out of the harmful bacteria, see Figures 4.2, 4.3 and Table 4.1.

Recently a yeast strain, *Saccharomyces boulardii*, has become very popular as it is effective in countering other yeast infections, particularly, *Candida* species. Sometimes the rapid killing of harmful gut organisms, especially *Candida*, can release large quantities of toxins that need to be removed effectively. Capsules of finely powdered activated charcoal can be very helpful in these circumstances, Baker, 2002.

A neglected area of patient care is the failure to support the gut when antibiotics are given orally. This common practice results in the destruction of many gut bacteria and a profound imbalance of the normal gut organisms. Some people recommend the use of a compound B vitamin preparation (B vitamins are produced by gut bacteria) to replace the loss of the bacterial source. Additional support should be provided by pro- and pre-biotics. This is particularly important when repeated courses of potent antibiotics are used to treat mycoplasma infections that are now known to occur in a significant number of ME patients, Gulf War veterans, and rheumatoid arthritis sufferers, Nicolson et al, 1998,2000; Vojdani and Franco, 1999.

iv.REPAIR- a major requirement for cells in the gut wall is glutamine. This simple supplement is best taken with food and is available as a powder that can be sprinkled on food or mixed with a cold drink. Glutamine is also very important for optimum brain cell function.

Butyric acid generated by bifidobacteria from FOS is another key repair molecule and has cancer protective properties, Clayton 2001.

There is a need for anti-oxidants in the gut to protect against oxidative stress- these include vitamins A, C, E, carotenes, and key minerals, zinc, manganese, selenium, and support for intracellular glutathione synthesis with N-acetylcysteine.

Using this step by step approach any improvement in general health and not just the health of the gut can be registered. Ideally when normal gut function has been established then a properly constructed diet should be all that is necessary to maintain future health. However, this is not as easy as it sounds due to the extensive contamination of our food by residues of toxic chemicals used in the growing, storage and preservation of food. For example it is not

generally known that organophosphate contamination in wheat and other foodstuffs is very widespread because of their use as pesticides and drying agents. The recognition of extensive food contamination is demonstrated in the advice to wash all foods before use and in some cases always to peel some foods, eg. carrots –lindane a persistent organochlorine compound has been found in very high levels in some carrots. It should be a legal requirement for all food retailers to declare the levels of contamination by pesticides and from other treatments in the foods they sell so that consumers can make an informed choice.

Many foods that are pre-prepared and widely consumed have excessive levels of sugar, fat and salt. Under the general heading of ‘junk’ food products with high levels of additives, dyes and colours, as well as sugar, and salt are widely sold in school tuck shops and elsewhere. Undoubtedly these are contributing to social disruption, vandalism, aggression, irritability, and low concentration levels found in many school children, prison populations and young offenders institutions. Providing a diet that is informed by the above principles has been shown to result in extensive improvements in education, social behaviour, and lifestyle, Fullerton 2003.

B. THE SUNDERLAND PROTOCOL (slightly amended)

This has been formulated from the extensive work of the Autism Research Unit, University of Sunderland, which is lead by Paul Shattock. Although derived mainly to support children with autism it is clear from the above consideration of overlapping syndromes that the shared biochemical deficits can be readily addressed using this protocol which is summarised in Table 11.1A-C and D-E. With his characteristic humour and teaching skills Paul Shattock has patterned the protocol on the Good Friday Agreement in Northern Ireland. The protocol is available at <http://osiris.sunderland.ac.uk/autism>

Table 11.1. THE SUNDERLAND PROTOCOL (slightly amended)

A. REMOVE THE BULLETS (MAJOR SOURCES OF OPIOIDS)	
1. CASEIN	- on average benefit appears within 3-6 weeks- if not OK to re-introduce.
2. GLUTEN	- on average takes up to 6-8 months for benefits to appear.
BEWARE - Commonly the patient may feel worse at the beginning of this exclusion diet.	

B. TEST FOR PESTICIDES IN BLOOD/BODY FAT.

C. PRELIMINARY AGREEMENT (SORTING THINGS OUT)	
3. OTHER FOODS -	Keep a food diary for other provocative foods, eg. caffeine, alcohol, corn, soya, tomatoes, aubergines, beef, avocados.
4. TESTING	-Vitamin status- B group- B1, B2,B6, B12, Folates, etc, E, C, etc. -Mineral status- Mg, Mo, Se, Mn, Zn, Cu, Fe. -Amino acid status -Allergy IgE, IgG etc. -Co-vitamins NADH, Co-Q, etc.
5. ANTI-OXIDANT STATUS-	Vitamins C, E, carotenes, Se, Zn, Glutathione
6. PARASITIC ORGANISMS	-Candida and other yeasts -others eg. viruses, VP1 coxsachie spp.,

It is interesting to note that the first step in almost any exclusion diet is to remove dairy and wheat and this often leads to a noticeable improvement in many ME patients. It is now clear why this is so. So a dietary approach to ME is consistent with the IAG test data and is supported by it.

The involvement of opiates is supported by the not uncommon experience that exclusion of dairy and/or wheat gives rise to an increase in unpleasant symptoms that would be expected from withdrawal of opioid compounds.

In view of the known association of common symptoms with organochlorine pesticides and ME, Richardson 2000, a blood test for pesticides will rule out such poisoning and avoid any false diagnosis. Usually the results of such tests are reported as the proportion of people with blood levels of a particular pesticide, eg lindane 5%. This means that 1 in 20 people have this blood level and suggests a need to address this problem. John Richardson has used a combination of ascorbic acid and choline citrate to treat organochlorine poisoning. It is likely that this simple mixture increases the rate of turnover of membrane phospholipids and releases fat-soluble compounds trapped/ dissolved in the membrane.

**Dr. John Richardson's Mixture for the Treatment of Organochlorine Poisoning
and Other Disorders involving Choline and Antioxidants**

Choline Dihydrogen Citrate	500 mg
Ascorbic Acid	250 mg
Distilled/Deionised Water	5 ml

Send 500 ml.

Dose 5 ml three times a day.

Store in a well sealed container in a cool place.

Can be taken in orange juice or flavoured with a suitable fruit extract if necessary.

Any responsible pharmacist should be able to supply this mixture at reasonable cost.

The role of choline in optimising membranal structure and function is now widely recognised and an alternative to the simple mixture of Dr Richardson would be 'citacholine' a complex of cytidine and choline that is the form in which choline is transported into in the body. This has been patented, prior to marketing, by Professor Alan Wurtman of MIT (Massachusetts Institute of Technology, USA), Wurtman, 2000. It is not yet available in this country but John Richardson's mixture may well be adequate if the diet contains enough uridine. Most food contains nucleic acids but seeds and fish roe, liver etc would be good sources. Glutamine would also support the manufacture by the body of nucleic acids.

The Preliminary Agreement is concerned with identifying other possible food intolerances and allergies. These are quite common and may also include more defined chemicals such as caffeine, alcohol and pesticides. Some ME sufferers may have unusual and unexpected responses to less frequent exposures. In our local group a number report a severe reaction to dental injections containing adrenaline. An exaggerated stress response- pounding heart rate, sweating etc. This may be associated with a disturbed HPA stress axis. Any diary should therefore include these kinds of responses as well as food reactions. Obviously when a reaction is identified then the food must be withdrawn. It is important to discuss your diary with a dietician and/or nutritional therapist in order to get the best advice.

General screening test for vitamins, minerals and other key marker compounds are also advisable at some stage. Functional tests should be used wherever possible. The very widespread selenium deficiency, in almost every area of the UK, makes consideration of such a supplement advisable, almost mandatory, Rayman, 1997, 2000; Neve, 2000. A range of products which contain selenium combined with a natural carrier compound such as methionine are available.

Zinc is a major element in resisting viral infections and supplementation is recommended after blood levels have been determined.

Magnesium is often very deficient in many people with ME. Magnesium supports hundreds of enzyme systems and any deficit has extensive adverse consequences.

Potassium levels are often low and improvement has clear advantages, Feng et al 2001.

Parasitic organisms may be found in the blood and specific treatments required to remove them. The 'killer' yeast, *Saccharomyces boulardii*, is gaining widespread acceptance as a useful treatment for candida infections. It is important to seek expert advice in this area of treatment.

Table 11.1 (continued)

<u>D. ACTIVE RECONSTRUCTION</u>	
7. SULPHATION ISSUES -	Epsom Salt (Magnesium sulphate) -internal/external Molybdenum supplementation 100 micrograms for 3 mths. MSM
8. FATTY ACIDS	ω-3 and ω-6 essential fatty acids- fish, evening primrose oils. Cod liver Oil (Vitamin A) Flax Seed Oil (carnitine)
9. L-GLUTAMINE	Intestinal nutrient
10. ENZYME ACTIVITY/SUPPLEMENTS	Betaine hydrochloride - pH modifier, Bromelain, Serenaid
11. PROBIOTICS	Lactobacillus, Bifidobacteria

E. OTHER POSSIBLE FACTORS	
13. TAKE OUT PIGMENTS	
14. SALICYLATE FREE	
15. MEGA DOSE B6, Mg.	
16. DIMETHYLGLYCINE	
17. SECRETIN	

Active Reconstruction addresses the major issue of sulphation described above, Section 7. The use of Epsom salts, magnesium sulphate, addresses both magnesium and sulphate

deficiency. Small oral doses of magnesium sulphate BP (a product that complies with the standards of the British Pharmacopoeia) may be all that is needed. It is best to use a dose of around 600mg (1/3 teaspoonful) in water once or twice a day with food. Alternatively, Epsom salts can be placed in the bath water (couple of handfuls of the cheaper grade of commercial Epsom salts).

Magnesium and sulphate are not readily absorbed orally or through the skin but the above regimen will provide a sufficient supply for most people- others may need intravenous infusions. Larger doses of magnesium sulphate are used as a purgative so if a watery diarrhoea develops then the dose should be reduced or an alternative source of magnesium and sulphate used. Too much magnesium may lead to adverse effects some of which are known to be serious so small doses and regular monitoring is strongly advised. Once normal levels of magnesium and sulphate are reached then no further treatment is necessary. Onion, garlic and broccoli are good food sources of sulphur and green vegetables of magnesium. Other preparations of magnesium salts are available but much more expensive eg. the glycinate. Sulphur can be supplied as MSM (methylsulphonylmethane).

The importance of essential fatty acids is recognised in the protocol and important sources indicated. Cod liver oil has the added advantage of providing vitamin A in addition to the fatty acids.

It is important to ensure that all products containing PUFAs are free from pesticide and mercury contamination and contain a protective anti-oxidant such as vitamin E to prevent the rapid degradation that occurs in air.

The gut supplements, betaine hydrochloride and enzymes, bromelain and 'serenaid', probiotics and glutamine provide support for the compromised gut.

Other Possible Factors include a variety of factors that have been reported by some people with the underlying biochemical deficits of ME and other syndromes. Pigments and salicylates in foods and medicines (ie aspirin) can adversely affect some people and are probably a reflection of compromised detoxification mechanisms since phenolic compounds are metabolised via sulphate conjugation. Dimethylglycine is an alternative to betaine as a source of methyl groups but is less efficient. Mega doses of B12, up to 5000 micrograms daily, and folates are effective for some ME patients, Wehrbach, 2000. Secretin a major gut hormone with activity in the brain has had spectacular success in about 10% of autistic children. It is still being evaluated after the considerable media 'hype'.

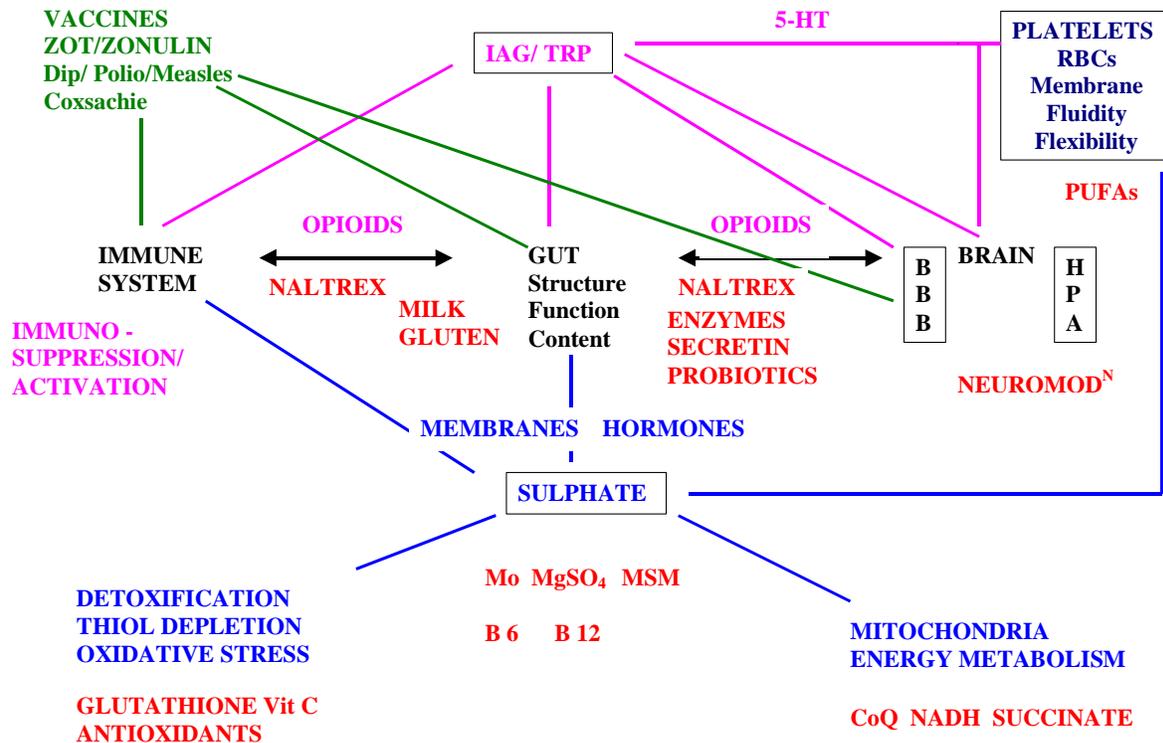


Figure 11.1. Composite of Interactive IAG/TRP-Sulphation/Sulphur and PUFA Systems with Treatment Summary.

Figure 11.1 presents a composite picture of the interactive IAG/Tryptophan (IAG/TRP), sulphation/sulphur, and lipid metabolism systems with treatment options in red type.

Most of the helpful nutritional treatments have been discussed under the Sunderland Protocol. Mitochondrial energy metabolism is adversely affected by sulphite and other toxins. Supporting energy production is helpful in about one-third of ME patients in separate studies of Co-Q, and NADH. Very important studies in rats, recently reported in the Proceedings of the National Academy of Science, Hagen et al, 2002, Liu et al, 2002a,b, have shown that lipoic acid and N-acetylcarnitine supplements, which support lipid and energy metabolism, restore vigour and activity and reduce the effects of aging compared to control animals. Useful general sources of dietary information are 'Health Defence', Clayton, 2001, and IFM, 1999.

Zot and zonulin are part of the numerous products of microbial organisms that open tight cell junctions and cause leakage through important membranes in the gut, brain and lungs. The involvement of viruses in ME is beyond dispute, Richardson, 2001, 2002; DeMeileir, 2000, Section 12G, Among the most likely candidates are large DNA viruses that belong to the herpes family. One possible treatment would be a course (possibly prolonged) of a modern anti-viral agent, acyclovir/ aciclovir, or the newer more potent analogue, famciclovir. Although no advantage resulted from the use of acyclovir, Shepherd, 1999, a later 6-month trial involving continuous treatment valacyclovir was effective against Epstein-Barr virus, EBV, in patients who had CFS for less than 1 year and had no antibodies to cytomegavirus, CMV. Patients with antibodies to both EBV and CMV did not respond to this

treatment, Lerner et al, 2002. This suggests prolonged treatment with a combination of anti-viral drugs is worth exploring further.

Naltrexone is a potent opioid antagonist that has had some success in treating autism. The doses used and time of treatment vary considerably. A long term-high dose study reported significant beneficial changes in autistic children, Cazzullo et al, 1999. Where opioid excess is part of the disordered biochemical/pharmacological profile then naltrexone might be worth considering for short-term relief before the effects of gluten exclusion from the diet become apparent.

C. INSTITUTE OF FUNCTIONAL MEDICINE TREATMENT SCHEMES.

The Institute of Functional Medicine has published a very useful assessment of the clinical features, diagnostic tests and treatment options in ME, Rigden, 1999. Six different clinical profiles are characterised and appropriate laboratory tests and treatment suggested.

(a) Impaired Detoxification

Physical Examination and History

Chronic generalised flu-like symptoms.

Exercise intolerance.

Increased sensitivity to environment (especially chemicals), MCS.

Brain fog.

Fatigue.

Laboratory Tests

Imbalanced detoxification and/or low phase II detoxification activity (low sulphate etc).

Abnormal urinary organic acids.

Treatment Considerations

Modified elimination diet- wheat, dairy, especially but also eggs, chocolate, citrus, peanuts, yeast etc

Diet high in vegetables that stimulate phase II metabolism (broccoli, cabbage (savoy), brussel sprouts, leeks etc)

Glutathione 75-150 mg three times daily

N-acetyl-L-cysteine 1500-3000 mg daily

α -lipoic acid 50-200 mg daily

Avoid toxins in drinks eg aspartame, tartrazine etc

Herbs – silymarin strengthens liver function

Some 80% of ME patients (called CFS in the USA) fall into this category. The urinary organic acids have been investigated extensively by the Australian group headed by Dunstan, McGregor et al- see Section 12. These provide an assessment of dysfunctional energy metabolism associated with mitochondrial damage.

It is clear that there is a close correspondence with the Sunderland Protocol recommendations.

(b) Intestinal Dysfunction

Physical Examination and History

Use of NSAIDS, nicotine (tobacco), caffeine and alcohol.

Irritable bowel syndrome, IBS, excessive gas, bloating, distention, diarrhoea, constipation, exposure to parasites and Candida overgrowth.

Laboratory Tests

Full gastrointestinal analysis- stool analysis

Intestinal permeability, Lactulose/mannitol ratio

Candida and other pathogenic parasite tests.

Gut dysbiosis and/or leaky gut

Treatment

4Rs regimen- see above

Rice-based medical foods

Fatty acids especially GLA- 300-1200 mg per day

Garlic, allicin equivalent to 1 clove per day.

Herbs Goldenseal, echinacea both inhibit gut dysbiosis

Some 50% of ME patients in USA fall in this category which is consistent with the common occurrence of this condition in this country.

(c) Immune/Inflammatory Imbalance

Physical Examination and History

Fever, chills, sweats, recurring respiratory infections. Environmental and food sensitivities.

Laboratory Tests

Up-regulated T-cell ratio, CD4/CD8, decreased NK (natural killer) cell activity,

Abnormal 2'-5' Rnase (see DeMeileir, Sodolnik, Boeuf et al)

IgG/IgE reactivity to specific foods.

Treatment

Avoid or rotate reactive foods (especially dairy and wheat). Modified elimination diet.

Bromelain

Curcumin 1500-3000 mg per day

Vitamin C 1000 mg per day

Herbs – boswellia 200 mg three times daily (tid), echinacea 500 mg tid

(d) Endocrine Imbalance

Physical Examination and History

Low blood pressure, dizziness, lightheaded, (neurally mediated hypotension)

Hypoglycaemic,

Inability to cope with stress

Persistent infections

Laboratory Tests

Positive tilt-table test

ACTH stimulation test- for possible adrenal insufficiency

Decreased DHEA

Hypothyroidism markers, TSH, T4, T3 etc.

Treatment

Increase water and sodium intake (generally sodium intake does not need to be increased but in this situation it needs to be considered to raise blood pressure) with liquorice extract.

Alternatively prescription drug treatment with fludrocortisone

Adrenal cortex extract 200 mg twice daily (bid)

Vitamin B12 1000 micrograms daily

Vitamin B complex 100 mg tid

Pantothenic acid (Vitamin B5) 500 mg daily.

DHEA 10-25 mg daily

Vitamin C 1000 mg daily

(e) Oxidative Stress

Physical Examination and History

Exercise intolerance and post exercise malaise

Laboratory Tests

Low blood reduced glutathione and/or SOD (superoxide dismutase) a key enzyme that destroys superoxide a potent member of the reactive oxygen species (ROS) responsible for causing oxidative damage.

Low glutathioneperoxidases another key group of enzymes that destroy peroxides which are also major ROS.

Elevated lipid peroxides (markers for membrane damage) and/or raised hydroxyl radical levels indicated by increased catechol recovery and elevated 2,3- dihydroxybenzoic acid (also associated with excessive phase I metabolism)

Treatment

Ensure a good supply of key nutritional antioxidants Vitamin C up to 2-6 gm daily, mixed carotenoids 15,000-20,000 IU (international units) per day, mixed tocopherols (vitamin E complex) 400-800 IU per day.

Selenium, 100-200 micrograms daily, to support glutathione peroxidases and other enzymes.

Glutathione precursor N-acetyl-L-cysteine (NAC) 1500-3000 mg per day. It is important to use only the L-cysteine compound as the D-isomer or the racemic mixture may, on theoretical grounds prevent or reduce the uptake of NAC.

Proanthocyanins 50-200 mg daily. There are numerous plant sources of these strong antioxidant compounds that will remove ROS.

α -lipoic acid 50-200 mg daily. This is a major reducing compound involved in energy metabolism.

CoQ10 200 mg daily another key compound in mitochondrial energy metabolism.

L-carnitine 500 mg daily to support energy metabolism by transporting fatty acids into mitochondria for energy production.

EFA's –see below under nutritional deficiencies.

Zinc 15-20 mg daily- it is important to consider copper intake/utilisation since too much zinc can reduce copper uptake.

(f) Nutritional Deficiencies

Physical Examination and History

Fatigue

Musculoskeletal pain

Sleep disorders

Cognitive dysfunction, moodiness, irritability

Dry skin, hair loss

Abnormal thirst

Constipation

Heart palpitations

Restless leg syndrome

Pre-menstrual tension (in women)

Laboratory Tests

PUFA's imbalance by RBC testing

Mineral imbalance by RBC testing

Abnormal amino acid and organic acid analyses

Raised methyl malonic acid and/or homocysteine levels

Treatment

ω -3 PUFA's that include preformed EPA and DHA 1000 mg daily.

ω -6 PUFA's that include preformed GLA 1000 mg daily.

Magnesium 200-400 mg daily

Vitamin B12 - by injection (IM) 5000 microgram twice a week.

B complex vitamins 50 mg tid

Pre-digested protein source with branched chain amino acids (neurotransmitter and Krebs's cycle precursors)

Low fat diet- defects in fat transport

No sugar – defects in carbohydrate utilisation

Clearly these extensive recommendations do not partition into exclusive clinical presentations. Usually there is considerable overlap. It is apparent, for example, that compromised detoxification may be accompanied by gut dysbiosis and both will need to be addressed.

Functional medicine is based on the following tenets

- Biochemical individuality
- Patient not disease centered
- The dynamic balance between the internal and external environments
- Web-like interactions see Figure 11.2. Pulling on any part of the web will affect all other parts. Different approaches will mean that people will vary in how they address a patient with ME but eventually there should be a recognition of the dominant factors for each patient. In this presentation I have chosen to pull first on the gut/GI point of the web

whilst being aware that the factors affecting any response are intimately and interactively connected to the other major points. This is what holistic medicine is all about.

- Health is a positive experience and not just the absence of disease
- Organ reserve is part of a healthy human being

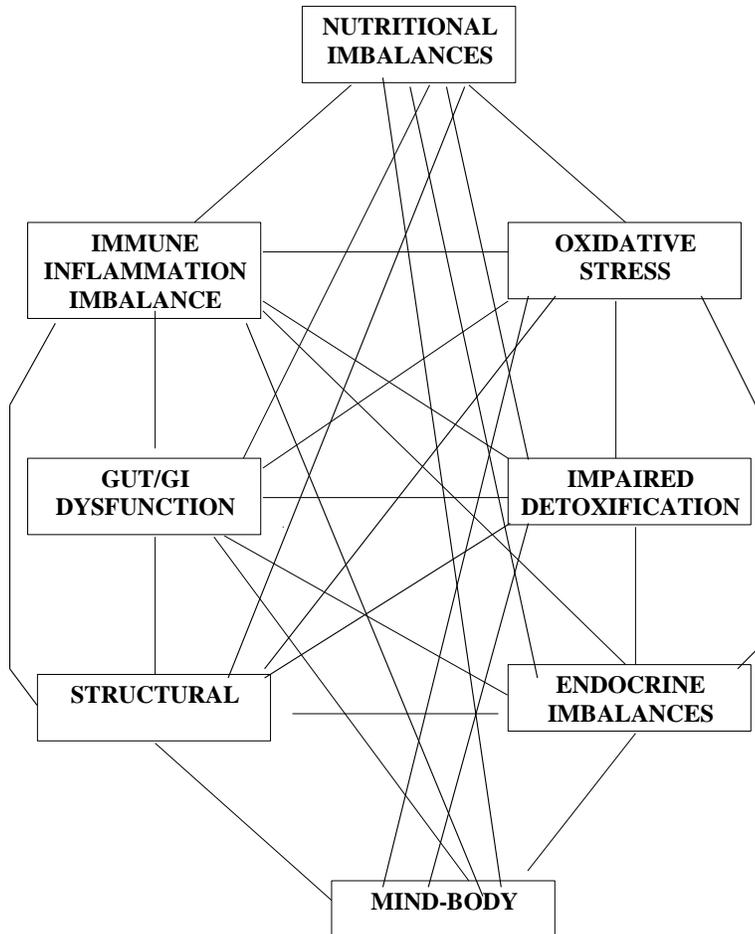


Figure 11.2. The Functional Medicine interactive Web.

D. RECOMMENDATIONS

Readers are free to make their own selections from the above information. My own preference is to do a limited range of tests to find out the status of ME patients with regard to

- Gut function and integrity
- Detoxification status- sulphate levels atc.
- PUFAs deficits
- Trace element and mineral status- especially magnesium, zinc, and selenium and possibly potassium.

The advice and co-operation of qualified clinical nutritional therapists and dieticians is essential together with clinical supervision and assessment. The contribution of ‘the patient as expert’ is essential.

The ability of clinicians to prescribe dairy and gluten free foods and PUFAs is important for the support of many ME patients who are often not well off and able to purchase their own supplements.

12. SOME OTHER MAJOR CONTRIBUTORS

In this section I want to point to the work of other investigators who have, often over many years, made extensive studies of patients with ME. As a ‘new boy’ in the field I have been enormously impressed by the dedication, expertise and humanity of the people who have cared for and supported patients with ME. Some of them suffer from ME themselves, Martin, 2002. Medical and para-medical staff with ME can make a particular contribution in the ongoing debate in this country about the organic nature of the illness and the opposing view of some psychiatrists, Section 1B. Stephen Ralph, a radiographer, has made an immense contribution by posting key information on his web site and providing a forum where the voices of ME patients can be heard. In the present medico-legal climate many of these people have suffered many personal attacks and obloquy from both individuals, the medical establishment and other organisations.

A. JOHN RICHARDSON

Throughout a long career in general practice, spanning 50 years, John Richardson has studied more than 4000 cases of ME often with the involvement of Consultants and research workers in other disciplines. He founded the Newcastle Research Group that was concerned with a deeper understanding of ME. Annually experts in various disciplines from all over the world met to share their research and deepen their understanding of ME. I was fortunate indeed to know John and to be the recipient of his wisdom and knowledge. Sadly John died, aged 87, in June 2002. A wise doctor, informed research worker, compassionate physician, and man of profound Christian faith he has left a legacy that will ensure ME patients cannot be dismissed as suffering from a form of psychiatric illness but have an organic illness that can be identified and treated, at least to some degree.

(a) ME is a consequence of a viral infection

John showed that ME is often initiated by a frequently unremarkable viral illness that continues and usually develops into a chronic and progressively disabling illness. His study of families, both vertically, parents and progeny, and horizontally, siblings, brought him face to face with many of the paradoxes that face clinicians and others engaging with all the conundrums of ME, Richardson 2001.

‘Enteroviral and Toxin Mediated Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Other Organ Pathologies’, published not long before his death summarises much of his life-time’s work. This lengthy title accurately reflects his emphasis on viral infections particularly associated with Coxsackie B viruses but also considering other viruses including, polio viruses, herpes viruses and Epstein-Barr virus that have been found in ME patients. Enteroviruses are associated with the gut. John describes many patient histories, useful clinical and laboratory tests, and possible treatments that he has found useful for ME patients. There are chapters on the damage to major systems in the body.

- The central nervous system
- The cardiovascular system
- The endocrine system
- The immune system- including vaccination

He has wise words on how viruses interact with the host immune system. The newly identified and controversial 'stealth viruses' avoid the body's immune defences in a manner that is akin to known immuno-viruses such as HIV, Martin 2002. John discusses treatment options such as injections of pooled human immunoglobulins that are helpful to many with ME. The emphasis on viral infection suggests that anti-viral drugs such as acyclovir (aciclovir) may have a useful role in treatment especially where herpes and closely related viruses are involved, Section 11. John formulated a choline citrate/ ascorbic acid mixture that has also proved useful to many, see Section 11. He draws on the work of others in addressing the importance of steroid metabolism, particularly DHEA, and essential fatty acids for cell membrane function.

He recognises the close relationship with other puzzling syndromes such fibromyalgia syndrome and how other toxins, particularly organochlorine pesticides, Richardson 2001 and 2002, can mimic the symptoms of ME.

This book is a must for all clinicians and provides a model for clinicians to engage with patients who present with the perplexing constellation of symptoms found in the increasing number of overlapping syndromes that have a common core of biochemical dysfunctions/deficits. I cannot recommend it too strongly.

John recognised from the beginning that my own engagement with Gulf War Syndrome/Illness and his enormous knowledge of ME could be mutually enriching and so it has proved. Very much as a junior partner I have learned so much from him and I owe him a great debt, personal, scientific and clinical.

(b) Dr Betty Dowsett, a longstanding friend of John Richardson and member of the NRG, is a doughty champion and servant of numerous ME patients and also Patron of the Northern Ireland Campaign for ME/CFS Healthcare. She shares John's understanding of ME as primarily a viral illness but regards it principally as a post polio syndrome, PPS, Presentation to Cross Party Group in Scottish Parliament on ME 4th April 2001. Recent advances in post polio syndrome, Dalakas, 1999, may provide a means of distinguishing this illness from ME despite the very close similarities in the shared constellation of symptoms.

(c) Dr Richard Bruno, 2002, is undoubtedly the world authority on PPS which gives rise to all the complex constellation of symptoms found in ME. He describes the primary damage from polio as an encephalitis with or without paralysis from damage to motor nerves originating from the spinal cord. Polio virus travels along myelinated nerves and damages the key deep brain structures, brain stem, basal ganglia, thalamus and hypothalamus. Dopaminergic neurones are especially affected often to a degree that falls short of the frank Parkinsonian symptoms of tremor and rigidity but is nevertheless extensive.

(d) Other members of the Newcastle Research Group include Byron Hyde, who with Jay Goldstein and Paul Levine co-edited the major reference book on ME, 'The Clinical and Scientific Basis of Myalgic Encephalomyelitis-Chronic Fatigue Syndrome', 1992, dedicated to John Richardson. Any reading of this major text will demonstrate, beyond any peradventure, that ME is a major organic illness with widespread effects on all the major systems of the body.

B. AUSTRALIA– THE NEWCASTLE COLLABORATIVE RESEARCH GROUP.

This group, headed by Neil McGregor, Tim Roberts, Hugh Dunstan, and Henry Butt, made a series of major presentations at the Second World Congress on Chronic Fatigue Syndrome, September 1999, and have continued to produce important research studies. Much of their work is described, with useful lecture material and list of publications, at <http://www.newcastle.edu.au/department/bi/birjt/cpruis/> They have a special interest in objective diagnostic tests

- Analysis of a large number of urinary metabolites which they find in ME-CFS patients. They link these test results to various biochemical disorders, for example,
 - ❑ hyperglycinaemia to vitamin B12 (excess methylmalonate), and/or propionyl CoA (co-enzyme A) disorders modulated by bicarbonate levels and acid-base disturbances. These, in turn, point to possible immune related changes that can be investigated by further tests for α -haemolytic streptococci in nose and throat, reduced lymphocyte counts, increased neutrophil counts.
 - ❑ Increased lysine excretion may be associated with increased excretion of tyrosine and point to one kind of muscle breakdown and other immune marker molecules that can be tested for, eg interleukin-1, and tumour necrosis factor, TNF.
 - ❑ Increased citric acid and succinate excretion. Other investigators have noted raised blood levels of citric acid in ME-CFS and FMS patients.
 - ❑ Raised β -alanine excretion which is associated with pain and increased gastrointestinal symptoms.
- Food intolerances that exist co-morbidly with ME-CFS.
- Bacterial toxins especially from certain strains of staphylococcus species in facial pain and latterly with gut dysbiosis.
- Blood lipid tests that identify different sub-groups of patients with different patterns of fatty acid deficits.
- Oxidative stress associated with increased severity of symptoms.
- Pesticides and other environmental toxins with a useful essay by toxicologist Mark Donohoe.
- Some suggestions for treatment are given including amino acid and fatty acid supplements.

This group are carrying out an impressive range of studies that provide a sound basis for investigation of ME and other patients with severe fatigue symptoms. The use of objective and validated biochemical tests underlines the fact that ME is an organic disease that can be understood and addressed by careful testing. The approach is one that is consistent with the NEI paradigm and the insights and understandings of functional medicine presented in this booklet.

C. ABHIJIT CHAUDHURI

Dr Chaudhuri is Senior Clinical Lecturer in the University of Glasgow and also Consultant Neurologist at South Glasgow University Hospitals NHS Trust. He has a long history of involvement with and support for ME patients. He has provided a searing critique of the very inadequate Australian Report on CFS, RACP, 2001. He regards the illness as involving major neurological dysfunctions and having similarities with multiple sclerosis, Parkinsonian disorder, head injury or stroke, Presentation to Cross Party Group on ME in the Scottish

Parliament, 4th April 2001. The dysfunction is associated with loss of ion channel integrity, channelopathies. Ion channels exist in all cell membranes and allow the ingress and egress of ions which would, otherwise, not traverse the lipid membrane. Sodium, potassium and calcium ions play an essential role in the propagation of nerve impulses. Dr Chaudhuri and his collaborators have clearly identified channelopathies that explain loss of neuronal and muscle cell function, Chaudhuri et al, 1997. Recently, he has replicated earlier findings of increased levels of choline in the brain of ME patients, Section 10. Choline is a major part of phospholipids that have a key role in maintaining the function of nerve cell membranes, Section 8. The channelopathies may be a consequence of loss of membrane integrity and not only changes in the structure of the channel proteins themselves. A number of drugs are known that act on the various ion channels. Some of the best known are calcium ion channel blocking drugs that are used to treat blood pressure problems and cardiovascular diseases such as angina.

D. DAVID MASON-BROWN

David is an experienced physician who suffers from ME. He uses nimodipine, a calcium channel blocking drug, to dilate blood vessels in the brain and improve blood flow to the areas like the brain stem where it is known that blood flow is reduced in ME patients. David usually administers very low doses of nimodipine on an individual patient basis. He also sees glutamine supplementation as important for brain function and regards organophosphates as particularly damaging to brain function in some ME patients, see www.cfs-me.com

E. THE DUNDEE GROUP

Professor Jill Belch, and Drs Vance Spence, Faisal Khan, and Gwen Kennedy are part of a major research group that has recently carried out a large research study involving ME patients, organophosphate-poisoned farmers and Gulf War Veterans. Together with Neil Abbot at the recently constituted Scottish charity for ME, MERGE, they provide rigorous clinical and scientific research that addresses the overlapping conditions in their study. Vance Spence, the Scientific Advisor to the NICME, who suffers from ME knows this illness as a patient and research worker.

At the latest meeting of the NRG he gave a lecture which identified very extensive damage to the endothelium that lines all blood vessels. The endothelium was found to be swollen and stiffened as a result of severe damage from reactive oxygen species with high levels of oxidised fatty acids found in the blood. Damage of this kind would compromise the blood supply to the deep capillary beds in all tissues and also to nerve cells. This is a very important and novel finding that provides new insights into the aetiology of ME. These findings are quite distinctive and very different from those found for the toxin-mediated, largely neurological, damage found in GWVs and OP poisoned farmers. They illuminate the common finding of low blood volume, variable blood pressure and heart rate responses emphasised by other investigators, eg Bell, 1998, and point to possible treatments involving a range of anti-oxidants and essential fatty acids as well as more specific drug therapies.

F. DR PAUL CHENEY

Paul Cheney has developed a scheme that involves a three-step progression in the development of ME, Figure 12.1.

Step 1 involves microbial infections, viruses, intracellular bacteria (chlamydia) and other organism like rickettsia and candida, that activate the immune system defence mechanisms, particularly, the RNase- INF-β pathway, see below 12G. Treatment at this stage consists of antibiotics, including antivirals, antibacterials, antifungals and pooled immunoglobulins. Silymarin is a liver protectant with anti-inflammatory and antioxidant activity, and glutathione the major detoxifying and antioxidant intracellular compound.

Step 2 is primarily neurological and can arise from xenobiotic injury associated with pesticide exposures and/or conventional drugs. Treatment may involve known drugs such as GABA antagonists- the benzodiazepines such as valium and librium, or the antidepressants/antipsychotics represented by doxepin. Alternatives to drug therapy involve mitochondrial support from co-enzyme Q, lipoic acid and antioxidants.

Step 3 involves primarily gastrointestinal damage and increased gut permeability, loss of detoxification capacity, and disturbance of the gut-brain axis coupled with endocrine dysfunction. Treatment addresses all these factors with the 4Rs programme, and the endocrine hormones, melatonin, T3, and cortisol.

This extensive understanding agrees with our own insights and provides a useful scheme for understanding the extensive changes underlying the great diversity of symptoms found in ME and other overlapping syndromes. The three steps do not have to be sequential but may occur simultaneously particularly as the major systems involved all interact and communicate with each other.

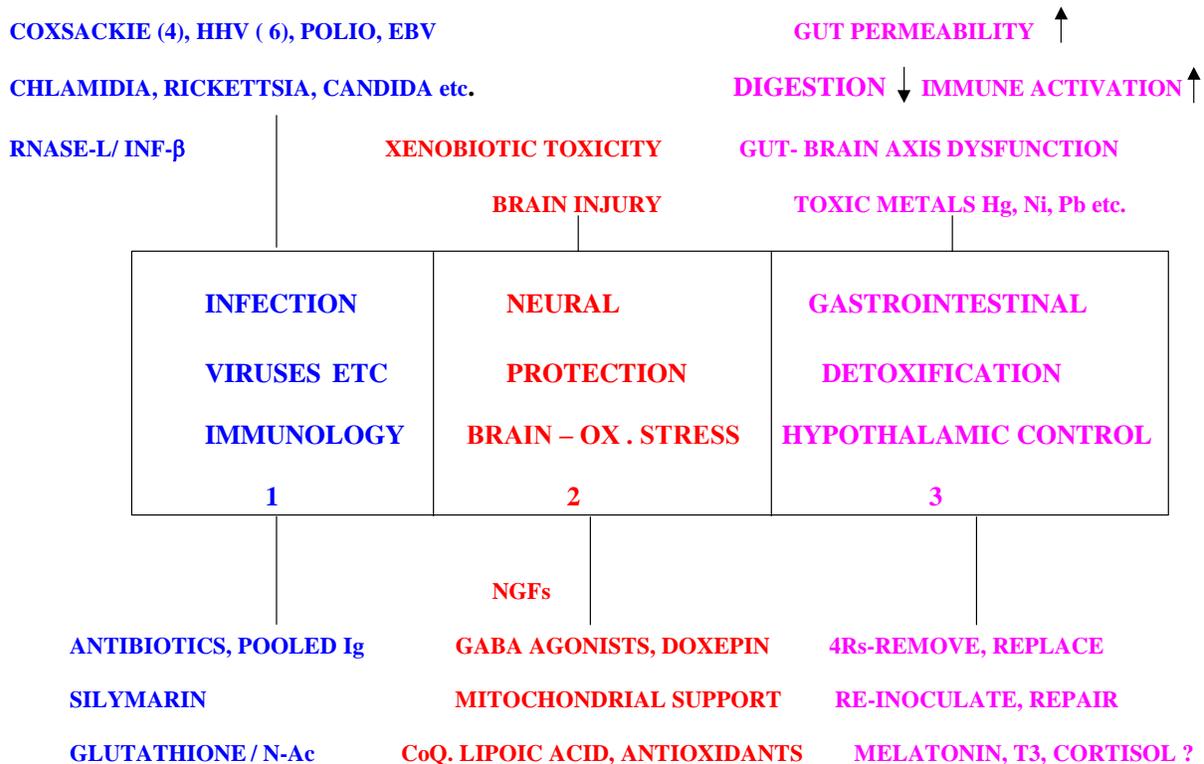


Figure 12.1. The Three Step Progression of ME according to Dr Paul Cheney.

G. THE IMMUNE SYSTEMS AND VIRUSES- RNase and Interferons.

At the Brussels Conference in 1999 two research groups, Lebleu et al, 1999, and Suhadolnik et al, 1999, described, in independent studies using advanced analytical techniques, a distinctive deficit in the interferon pathway that provides a major defence against viruses and other intracellular infections. They identified an aberrant low molecular weight form of the enzyme L-RNase which persists in ME patients and degrades host as well as viral RNAs (ribonucleic acids). This damages all host systems by preventing the synthesis of proteins essential for maintaining the normal function of cells and tissues – patient ‘wipe out’. [RNAs are macromolecules made up of nucleotides which carry the information necessary for the synthesis of proteins. The activity of the cell depends on a whole variety of proteins for normal functions and defence. RNases are enzymes that degrade RNAs. RNase-L is a defence enzyme produced in the cell following the release of an interferon in response to an infection by a virus or intracellular parasite.]

Although the identification and assay of the low molecular weight L-RNase has proved controversial it now seems that this aberrant pathway is a major and distinctive feature in many ME patients and provides a reliable, albeit complex, diagnostic test.

Dr Kenny De Meirleir and his colleagues have used this test system and developed a treatment using the novel drug ampligen. The treatment is expensive and vigorously debated among the ME community, Summers et al, 1999, Behan et al, 2001, Ostrum 1998, De Meirleir and Patacara-Montero, 2000, clinical studies and formal clinical trials are under way in the USA and Belgium,.

Since the RNase-L pathway is activated by viruses generally it is possible that ampligen may prove to have wide anti-viral activity and be useful in major viral diseases such as hepatitis B and C. In the latter case there is no vaccine or effective treatment. Such studies are now under way.

There is little doubt that this new development does provide new insights and possibilities for diagnosis and treatment in ME. This evidence clearly identifies the immunological nature of ME and is consistent with the very common association of the illness with an intracellular microbial infection, most commonly by a virus. Mycoplasma, rickettsia and chlamydia are all intracellular parasites that have been associated with ME, Brussels 1999, Bottero, 1999. The well established links between the immune system and the central nervous system make clear the impact of immunological and inflammatory changes on nerve and endocrine function, Black, 1994.

A new name has been coined by De Meirleir and Petersen, Rnase-L-Enzyme dysfunction disease, R.E.D.D. for the sub-group of patients with this identifiable disorder. A full assessment is at www.mecf.bc.ca/articles/volume14.html with numerous links to various sources of further information.

H. CHILDREN AND ME

The occurrence of this illness in children and young people is especially disturbing and has involved brutal treatment of children and their families in painful legal and medical battles when some clinicians have sought to impose a psychiatric diagnosis. It is now clear that Munchausen’s by proxy is a contrived ideological diagnosis in every case of ME. Dr Nigel

Speight is a UK paediatrician who has studied ME extensively in children and young adults, Speight 2001. He offers a broad approach to diagnosis and treatment in which neuropsychiatric drugs and endocrine modulators are sometimes used, eg. ritalin and melatonin.

Dr Katherine Rowe in Melbourne has shown that ME is driven by immunological disturbances following an infection in adolescents, Rowe, 1999.

I. A NEUROPSYCHIATRIC APPROACH

A recent development in the UK has arisen from close collaboration between John Crichton, an ME patient, and his Consultant Psychiatrist, Dr Douglas Turkington. They constructed a complex combination of various neuropsychiatric drugs including somewhat atypical drugs such as modafanil and mirtazepine. Taken together these drugs affect all the main neurotransmitter systems in the brain. It is imperative that such a drug cocktail is individually tailored and monitored by a Consultant.

13. AN ALL ENCOMPASSING MODEL FOR OVERLAPPING SYNDROMES

In my work with the Gulf War Veterans, the ME community, organophosphate-poisoned farmers and operatives, and multiple chemical sensitivity sufferers I have discerned not only the underlying biochemical deficits described in this booklet but also a common area of damage in the brain. This observation springs from the incisive research of Dr Robert Haley with Gulf War Veterans, Haley, *inter alia* 2000, 2002. He identified cellular damage to the deep (silent) brain structures, the basal ganglia, and the brain stem, Figure 12.2. Using magnetic resonance spectroscopy he found about 25% of cells in these areas of the brain were dead. The basal ganglia located deep in the brain and composed of several different nuclei initiate and control movement sequences, such as walking and other voluntary movements carried out unconsciously. They wrapped round the thalamus that sits at the top of the brain stem. The thalamus is a relay centre for sensory nerves and relays signals coming via the spinal cord and brainstem to the higher areas of the brain. It is particularly involved in pain sensations.

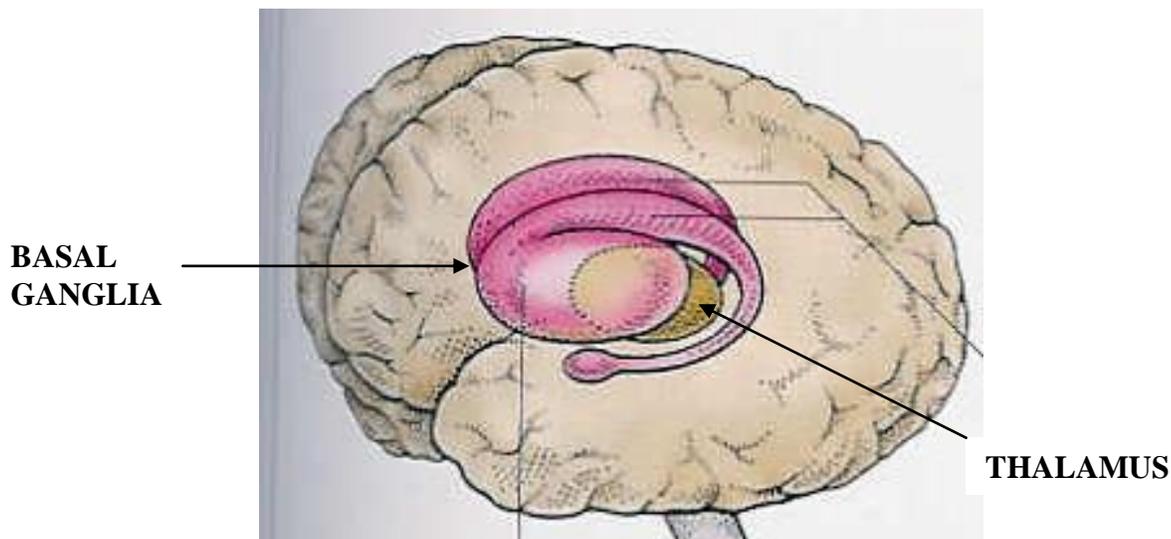


Figure 13.1. Basal Ganglia wrapped round the Thalamus deep in the Brain.

The brain stem is composed of the midbrain, pons, and medulla. The midbrain controls visual and auditory reflexes and damage here would make for photophobia and aversion to noise. The pons is concerned with facial expressions and eye movement- nystagmus is quite commonly found in ME. The medulla regulates heart rate, blood pressure, digestion-swallowing and vomiting, respiration and temperature. Most of these functions are disturbed in ME. Balance and orientation, both noticeably affected in ME, are also effected through the brain stem.

Haley described the symptoms found in GWVs as arising from damage to these parts of the brain that are known to be damaged in Parkinson's disease and other diseases such as, Huntingdon's chorea, Fahr's and Wilsons disease.

The cause of this damage Haley put down to chronic exposure to low levels of nerve agents, particularly sarin gas. Sarin is an organophosphonate that is similar, in structure and biological activity, to organophosphate pesticides that were widely used in the Gulf War 1990-1. Both these groups of chemicals (together with pyridostigmine bromide- NAPS tablets) attack the cholinergic nervous system producing a devastating 'triple whammy', Hooper, 2000. A cholinergic neurone plays a crucial regulating role in controlling the activity of the dopaminergic, glutaminergic and gabaminergic neurones associated with Parkinson's disease, and Huntingdon's chorea, the basal ganglia, Kruk and Pycock, 1991. Cheney and Hyam, 1999, describe ME-CFS as 'cholinergic wipeout'.

When I shared these new developments with Dr John Richardson during the days of his final illness he recognised the accuracy of Haley's diagnosis. In his book John describes a 15-year old boy with frank parkinsonian symptoms following a virus infection. Bruno also describes, in some detail, the damage to dopaminergic neurones in the basal ganglia that is caused by the polio virus.

Goldstein, 1999, describes ME-CFS as a limbic encephalopathy brought about by viral infection. The limbic system is encircles the basal ganglia and is part of the deep (silent) brain structures, Figure 13.2.

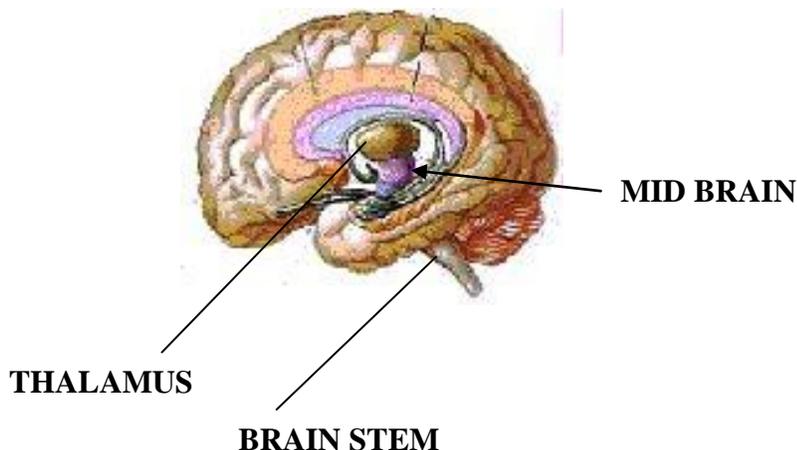


Figure 13.2. The Limbic System encircles the Basal Ganglia (not shown in this cut away) which enclose the Thalamus at the top of the Midbrain, part of the Brain Stem.

The limbic system is also the area of the brain that is affected and damaged in multiple chemical sensitivity, Ashford and Miller, 1998. It is composed of a number of brain regions including the amygdala, particularly associated with aggression, the hippocampus associated with learning, recognition and memory (some GWVs have reduced hippocampal mass), and hypothalamus that drives the pituitary gland and the endocrine system. The activities of the body that are governed by the limbic system are concerned with self-preservation (hunting for food, fighting) preservation of the species (sexual behaviour and rearing of offspring) fear, rage and pleasure and the establishment of memory patterns. Loss, or partial loss, of these functions is common amongst ME sufferers.

An important part of the limbic system is the olfactory bulb, Figure 13.3. It is now known that volatile chemicals and odours are transported intraneuronally into the limbic system. The problems of smells and odours are all too common in ME and the other overlapping syndromes.

Acetylcholine is a major neurotransmitter in the limbic system and it is not surprising that exposure to OPs, and nerve agents used in chemical warfare cause serious deficits in this system.

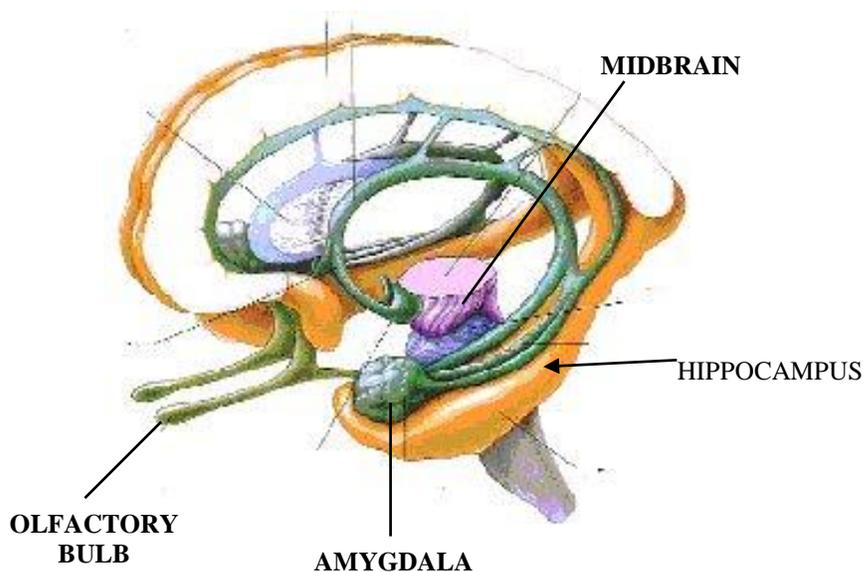


Figure 13.3. A cut away view of the Limbic System

Now we have a basis for the neurological damage produced by a common mechanism but by different insults, biological or chemical, to which those expressing symptoms common to the overlapping syndromes, including ME.

The brain is protected from exposure to chemical or biological toxins by the blood brain barrier, BBB. This barrier is a consequence of the tightly sealed endothelial cells that line the blood vessels serving the brain, see also Section 2C. Water, oxygen, glucose and many other essential molecules have mechanisms for crossing this endothelial barrier. Generally, most

toxins and foreign compounds cannot breach this barrier. However, it is now clear that certain chemicals and biological toxins cause the tight cell junctions to open and allow these toxic materials to enter the brain. The BBB is least efficient round the primitive brain regions, described above, making movement of toxins into these areas of the brain easier. Volatile compounds are transported intraneuronally directly into the deep brain areas via the olfactory bulb, thereby bypassing the BBB. The deep, silent, brain regions are more susceptible to damage from all environmental toxins.

The common symptoms are associated with common pattern of injury to the deep areas of the brain, the brain stem, thalamus, basal ganglia, and the limbic system provide a coherent explanation for all the overlapping syndromes, Figure 1.1, Sections 3 and 9.

- ME may arise from a number of different viral infections. The inflammatory response to viral infections resulting in endothelial damage, Section 12E, provides an indirect but devastating mechanism for damage to the central nervous system. The recent comprehensive model, for ME-CFS, fibromyalgia, multiple chemical sensitivity, post traumatic stress disorder, that involves glutamate receptor sensitisation by excessive release of nitric oxide and its highly destructive derivative, peroxynitrite also fit this scheme, Pall, 2000a,b, 2001, 2002; Pall and Satterlee, 2001. It is noteworthy that nitric oxide has a major role in intestinal inflammation, Kubes and McCafferty, 2001.
- PPS arises from polio virus.
- Organochlorine poisoning from excessive exposure to organochlorine pesticides
- OP poisoning from excessive exposure to this class of pesticides. The role of synergy with other chemicals that occur together in pesticides and mixtures of pesticides is associated with a massive increase in toxicity, Abou-Donia et al, 1996; Abou-Donia, 2001.
- Multiple chemical sensitivity from exposure to toxic chemicals or combinations of toxic chemicals, Ashford and Miller, 1998
- Fibromyalgia is a variant on ME that is associated with excessive pain sensations
- Gut dysbiosis provides an alternative source of toxins, Butt et al 2001.

14. END NOTE

I am conscious that some well-known names are not included in this account but it is not been my intention to provide a complete history of ME, others are far better equipped to do this. A comprehensive history of ME, particularly in North America, is available in the splendid book 'Osler's Web' by Hillary Johnson.

I have simply sought to place the talks I gave in Northern Ireland within the context of the science and medicine of ME as it is at present. I am aware that the many changes currently taking place in the world of ME may well overtake some of the information given here.

I have examined much of the ME literature and am fully persuaded of the organic nature of this illness and the folly and cruelty of attempting to regard it otherwise. What I have offered is intended to provide greater understanding of, more effective treatment for, and more compassionate care for, those with ME and related syndromes.

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