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ME RESEARCH UK

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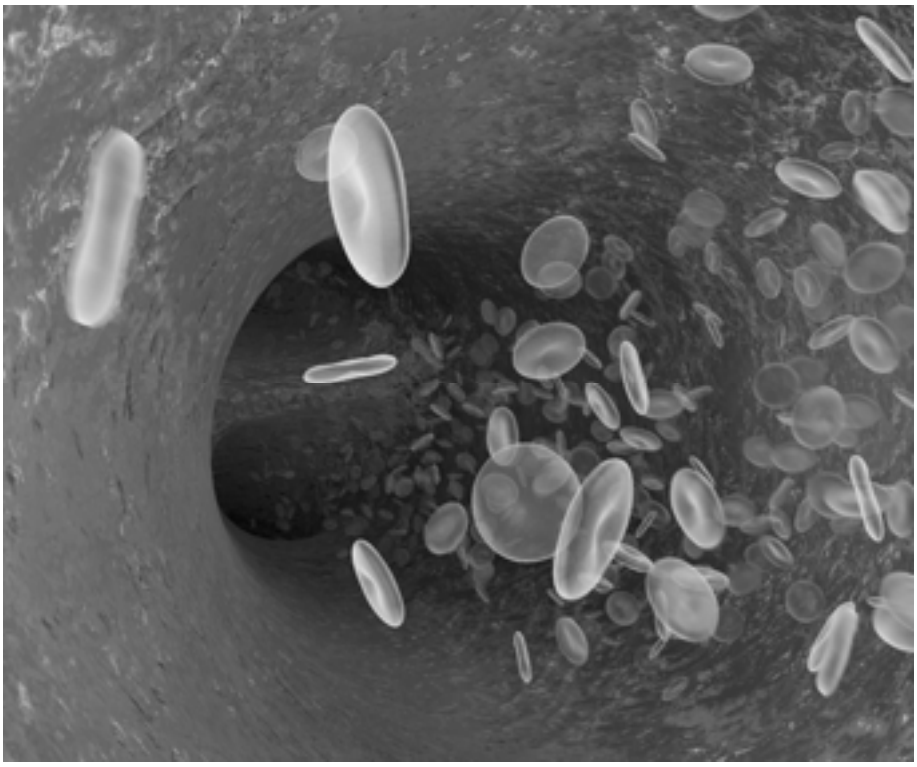


SPRING 2008

Blood vessel stiffness and inflammation

An important characteristic of blood vessels is the flexibility of their walls. This affects how each pulse of blood from the heart is transmitted through the cardiovascular system from the larger to the smaller arteries, and ultimately to the capillaries and back to the heart via the veins. Stiff arteries have been linked to high blood pressure, kidney problems and heart disease, and, surprisingly, may also contribute to the orthostatic hypotension experienced by some ME/CFS patients.

Increased arterial stiffness has been reported in children with ME/CFS, leading Dr Faisel Khan at the Vascular and Inflammatory Diseases Research Unit, University of Dundee, to investigate this in adult patients. His team also looked at the relationship between arterial stiffness, inflammation and oxidation. In an article soon to be published in the leading journal Clinical Science, Dr Khan reports that the arteries of ME/CFS patients were indeed stiffer than those of healthy individuals of the same age. Furthermore, the patients had higher levels of various blood-borne markers of inflammation which correlated with arterial stiffness; i.e., the higher the levels of inflammation, the stiffer the arteries.

This combination of blood vessel stiffness and low-grade inflammation puts ME/CFS patients at a higher risk of developing cardiovascular problems in the future, although longer-term studies will be needed to confirm or refute this. With this work, Dr Khan has highlighted yet another important physical change in ME/CFS that is worthy of more investigation. Read the full story on page 6. ●

Response to exercise

Objective evaluation of post-exertional symptoms

Post-exertional symptoms, including pain and "malaise", are characteristic symptoms of ME, but objective ways of measuring these key symptoms after exercise are lacking. This has consequences for patients since modern medicine likes to "quantify" complaints and tends to devalue or discount those it cannot. Yet, there is an urgent need to have objective, widely accessible tests for ME/CFS, and although physical exertion is difficult for some people, it has been suggested that repeat testing with a graded exercise test might show quantitatively that patients do not recover as quickly from this kind of physical challenge as would be expected.

For example, at the IACFS conference in Florida in 2007, researchers from the University of the Pacific reported pilot results from a small study in which maximum oxygen consumption decreased significantly 24 hours after exercise in patients though not in healthy controls. If these results are reproducible, then "dual graded exercise tests" separated by 24 hours might indeed be a useful element in diagnosing the condition.

A new MERUK-funded investigation, led by Prof. Brian Macintosh (Professor and Associate Dean of Kinesiology at the University of Calgary) and Dr Ellie Stein, will diagnose patients using the Canadian Consensus Criteria for ME/CFS (2003) as well as the standard 1994 CDC criteria, a basic assessment step which ME Research UK is requiring all its prospective grant-holders to undertake when assessing new study patients.

Each person will perform a symptom-limited incremental exercise test on an electronically-braked cycle ergometer, while connected to the metabolic cart through a mouthpiece. Effort in each test will be assessed from blood measurements of peak blood lactate concentration, and performance will be measured by maximum oxygen consumption, V_{O_2} max, and a range of secondary outcomes. The researchers' hypothesis is that the performance of patients with confirmed ME/CFS plus post-exertional symptoms will decrease on a second test conducted 24 hours after the initial test. By contrast, control subjects (matched for age and chronic activity level) will have similar performance on the two tests.

If successful, the pilot data could be an important step to further work to differentiate better the symptoms of patients with ME/CFS from those with other medical conditions on the basis of responses after exercise. ●

WHAT IS V_{O_2} MAX?

V_{O_2} max is the maximum volume of oxygen that the body can consume during intense, whole-body exercise breathing normal air. Because oxygen consumption is related to energy expenditure, it is an indirect way of measuring an individual's maximal capacity to do work.

During exercise, contracting muscle cells consume most oxygen, and measuring the breath (using a combination of ventilation volume-measuring and oxygen/carbon dioxide-sensing equipment) gives a highly accurate estimate of the sum total of oxygen consumed by the billions of cells in the body.

The average person has a V_{O_2} max of about 40 mL/min per kg; a thoroughbred horse, 150 mL/min per kg.

Identifying gene SNPs

The information inherited from our parents (usually in the form of a gene, a sequence of DNA) has to be translated into a product, such as an RNA molecule or a protein, before it can be used by the body, a process called gene expression. In recent years, the number of scientific reports investigating gene expression in ME/CFS has increased steadily, and the genes found to be over or underexpressed seem to be related to "immunity and defence", supporting what is known about the role of the immune system.

Dr Jonathan Kerr's group at St George's Hospital, University of London, has been one of the most active in defining the molecular basis of ME/CFS. Their initial study of gene expression in patients demonstrated marked human gene dysregulation, principally affecting the immune system. And in 2007, the latest in a series of papers was published in the Journal of Clinical Pathology outlining the identification of a putative "gene signature" for the illness consisting of 88 human genes.

As the table below shows, these genes can be subdivided into categories by diseases and disorders, say, or by molecular and cellular functions. The research team says that three of the genes identified are directly linked with mitochondrial metabolism, and a further ten have indirect links with mitochondrial metabolism.

As these 88 genes have been linked directly to the pathogenesis of ME/CFS, the next step is to study the inherited determinants of susceptibility by examining single nucleotide polymorphisms (SNPs) — pronounced "snips" — within these genes. Some SNPs have been linked with features and complications which might be associated with ME/CFS (e.g., IL10RA SNPs are associated with lymphoma, a disease which some have speculated occurs more frequently in ME/CFS).

With funding from ME Research UK, the St George's group will shortly begin the next phase of their work: identifying the key SNPs for each of these 88 genes. As there are hundreds of SNPs within each gene, the team proposes to focus on "determinative" SNPs (i.e., those which are known to predict all or most of the others within one gene); there are typically 3 to 7 per gene. Once these have been identified, the researchers will design and use low density array cards to test genomic DNA samples of 105 patients in the initial sample group. After comparing allele frequencies between the ME/CFS and control groups, the allele frequencies will be related to the gene expression levels.

The results will indicate those genes within the 88-gene "signature" for which inherited determinants exist, and provide a thorough genomic database from which to determine the role that these SNPs may play in the pathogenesis of ME/CFS. ●

Important disorders and functions associated with some of the genes in the putative ME/CFS gene "signature"

Diseases: *Haematological (22 genes), Immunological (14), Cancer (31), Dermatological (3), Endocrine system (9)*

Molecular & cellular function: *Cellular development (26), Cell death (33), Gene expression (31), Cellular growth & proliferation (31), Cellular assembly & organisation (15)*

Physiological system development & function: *Haematological system (22), Nervous, immune & lymphatic system (18), Tissue morphology (18), Survival (17), Immunity (20)*

WHAT ARE SNPs?

SNPs (single nucleotide polymorphisms) are small genetic changes in DNA that vary between individuals. Humans are 99% identical as regards their gene sequences, and the 1% which remains is mostly accounted for by SNPs, of which there are approximately 10 million in the human genome. This makes them very useful. They can serve as helpful landmarks for population genetic maps, but their greatest importance is in biomedical research for comparing specific regions of the genome between groups or individuals with and without a disease.

While most SNPs are silent, some can have important consequences for individual susceptibility to disease and reactions to treatment. For example, the apoE gene is associated with an increased risk of Alzheimer's disease. It is also thought that certain SNP combinations can contribute to a predisposition to developing medical conditions.

At present, an enormous literature exists reporting possible associations between SNPs and a range of diseases; the SNP500Cancer project, for example.

The challenge in ME/CFS is to identify SNPs which will ultimately allow patients to be quickly and simply "diagnosed" from a sample, and possibly assigned to illness subgroups for specific therapies.

TABLE

NICE Clinical Guidance recommendations on the use of CBT for 19 different clinical conditions

Is CBT postulated to be a main intervention for the condition (Clinical Guideline number)?	
Anxiety (22)	YES
Bipolar disorder (38)	YES
Depression (23)	YES
Eating disorders (9)	YES
Obsessive-compulsive disorder (31)	YES
Schizophrenia (1)	YES
Chronic pulmonary disease (12)	NO
Dementia (42)	NO
Dyspepsia (17)	NO
Type 1 diabetes (15)	NO
Hypertension (34)	NO
Lung cancer (24)	NO
Multiple sclerosis (8)	NO
The epilepsies (20)	NO
Parkinson's disease (35)	NO
Familial breast cancer (41)	NO
Tuberculosis (33)	NO
Chronic heart failure (5)	NO
CFS/ME (53)	**YES**

The NICE guideline

What's the problem?

A landmark event of 2007 was the publication of the National Institute for Clinical Excellence (NICE) Clinical Guideline 53: the final word on the diagnosis and management of "CFS/ME". However, the storm of protest from Registered Stakeholders, including ME Research UK, over the initial draft guideline — more than double the usual volume of replies, with a higher than usual proportion coming from patients, according to Dr Fred Nye in a subsequent letter in the Journal of Infection — has not abated with publication of the final document, and it is important to ask why. Is Guideline 53 really so bad?

Like the curate's egg, some parts are palatable. The NICE clinical diagnosis now requires "*post-exertional malaise and/or fatigue… with slow recovery over several days*" to be present. Also, doctors "*should acknowledge the reality and impact of the condition and symptoms*", and should look out for "red flag" signs and symptoms that might be caused by other conditions in both existing and newly diagnosed patients.

But because — to quote the Guideline — "*there is no known pharmacological treatment or cure… symptoms… should be managed as in usual clinical practice*", NICE has been forced to flag up cognitive-behavioural approaches for the specialist management of the illness, approaches generally considered to be non-specific in their effect, and to be non-curative including by Guideline 53 itself (section 6.3.8, p. 252). Moreover, the Guideline has based this decision on randomised controlled trial evidence which is skewed towards a small group of mildly positive cognitive-behavioural clinical trials (see page 9 sidebar of this issue), while devaluing other evidence from basic scientific studies and surveys of patients' experiences.

In most illnesses, cognitive-behavioural approaches are adjuncts to the contemporaneous biomedical research that spearheads the drive towards a cure. Yet, in ME/CFS, they stand centre-stage, with the result that it is the only physical condition for which cognitive behavioural therapy is flagged up as a primary specialist management approach in a NICE guideline (see the sidebar on the left). The table below — from Guideline 53's companion National Costing Report — shows the cost to the country of implementing the guidance in full: £45.2 million over 5 years.

Like almost all patient-based charities and ME support groups in the UK, we think that NICE Guideline 53 is "unfit for purpose" in its final form. So the battle goes on to move basic scientific and clinical research centre-stage, into the spotlight presently occupied by psychosocial models in the minds of opinion formers and healthcare professionals. ●

Cost increase of implementing Guideline 53

Recommendations	*Recurrent annual costs (£m)*	*Non-recurrent costs (£m)*
Cognitive behavioural therapy	*1.03*	*7.30*
Graded exercise therapy	*0.58*	*4.10*
Activity management strategies	*0.92*	*6.46*
Activity management programmes	*1.22*	*8.59*
Total	***3.75***	***26.45***

Brain neuroimaging

Research at Imperial College

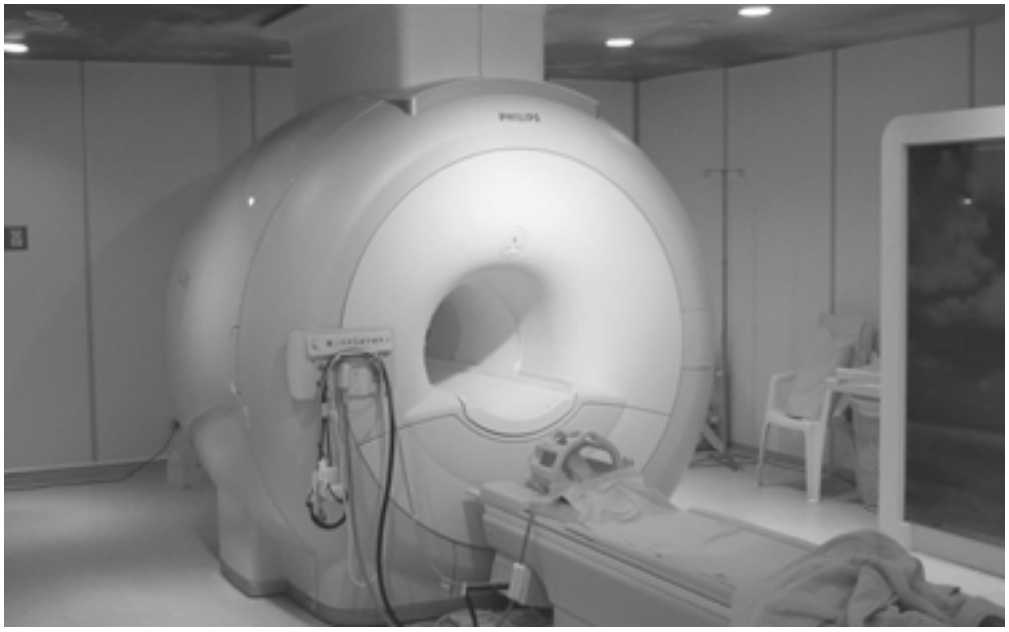
In historical publications on "epidemics" of ME-like illness, symptoms consistent with central nervous system pathology were reported with regularity, and were as characteristic as the post-exercise malaise, myalgia or the range of other symptoms that patients experienced. Fifty years later, "neurological/cognitive manifestations" form a key element of the 2003 Canadian Consensus definition of ME/CFS.

It has not yet been established for certain what causes the prominent cognitive dysfunctions in the illness, but factors which might contribute include vascular insufficiency, metabolic dysregulation or an ongoing infectious process. To date, a variety of structural and functional studies have been undertaken to try to identify physiological changes, and the results have been very interesting though inconclusive. It is entirely possible that well-conducted, objective, structural and functional studies in clearly defined or subgrouped ME/CFS patients might yet be able to provide diagnostic information in place of the present deduction or guesswork about what might be going on in the brain. So, the study which is just beginning at the MRC Clinical Sciences Centre at Imperial College London is particularly welcome.

Funded jointly by the charities ME Research UK and ME Solutions, and by the MRC Clinical Sciences Centre (Imperial College), the lead researcher and grant-holder, Professor Basant Puri of the MRI Unit, Hammersmith Hospital, London, intends to examine 26 patients (fulfilling the CDC 1994 Criteria and the Canadian Consensus Criteria for ME/CFS) and 26 age and sex-matched healthy controls over the course of 18 months. Each person will undergo a full medical history, a full physical examination, and MRI scanning. Generalised linear modelling will be used to analyse the statistical relationship between clinical symptomatology and parameters derived from MRI images.

The main objectives of the investigation are to assess the nature of any cerebral structural, biochemical and cognitive neuropsychological changes in people with the illness, and the relationship of these to clinical symptoms. The combination of brain chemistry measures, MRI assessments of the structure of the brain and white matter pathways, and global functional MRI may reveal underlying anomalies.

The outcome of this research will determine whether or not a much larger study is justified. ●



RECENT PROJECTS

Our primary aim is to fund high quality projects on ME/CFS, and ultimately to develop effective treatments. At present, we fund the work of a growing number of scientists, some listed below (our website lists others).

Autonomic dysfunction and its consequences — a clinical cohort study (clinical fellowship)
Dr Julia Newton, University of Newcastle

Vitamin D Status and its association with cardiovascular function
Dr Faisel Khan, University of Dundee

SNPs within CFS-associated human genes
Dr J Kerr, St George's University of London

Non-invasive structural and functional neuroimaging
Prof. BK Puri, MRC Clinical Sciences Centre, Imperial College London

An investigation into biochemical and blood flow aspects of ME/CFS in children
Dr Gwen Kennedy, University of Dundee

Focal and global endothelial function and their association with arterial stiffness
Dr Faisel Khan, University of Dundee

Post-exertional malaise in ME/CFS: the role of intracellular immunity and sensory processing
Dr Jo Nijs, University College Antwerp

WHAT IS ME/CFS?

Myalgic encephalomyelitis/ encephalopathy (ME) is characterised by a range of neurological symptoms and signs, muscle pain with intense physical or mental exhaustion, relapses, and specific cognitive disabilities.

During the 1990s, the term chronic fatigue syndrome (CFS) came into vogue. Since there was no specific diagnostic test for ME, and since post-exercise 'fatigue' was one of its prominent symptoms, people with ME began to be diagnosed with 'CFS'. At present, efforts are being made to elucidate the diagnostic confusion, and meanwhile the term ME/CFS is used.

ME/CFS affects 120,000 to 240,000 people in the UK, and it is classified by the World Health Organisation as a neurological illness (ICD10: G93.3). Most people with ME/CFS are unable to work to full capacity, and 25% are severely disabled, some house or bed-bound. Little support is available to their families and carers. The cause of the illness is unknown, and no cure or universally effective treatment has yet been found.

A report to the Chief Medical Officer of England in 2002 states, "*ME/CFS is a genuine illness and imposes a substantial burden on the health of the UK population. Improvement of health and social care for people affected by the condition is an urgent challenge.*"

Blood vessel stiffness

An essential characteristic of the blood vessels that deliver blood throughout the body is the flexibility of their walls. This affects how each pulse of blood from the heart is transmitted through the cardiovascular system from the larger to the smaller arteries, and ultimately to the capillaries and back to the heart. Normal, healthy arteries have reasonably flexible (elastic) walls which allow the heart to eject blood into the blood vessels easily and smoothly. If the arteries become stiff, the heart has to work harder and, ultimately, blood pressure becomes higher.

A certain amount of stiffening occurs normally with age, but diseases such as atherosclerosis can worsen this. Stiff arteries have been linked to kidney problems and heart disease, and may also contribute to the orthostatic hypotension (dizziness on standing) experienced by some ME/CFS patients. Furthermore, increased arterial stiffness has also been reported in children with ME/CFS.

With funding from ME Research UK, researchers at the Vascular and Inflammatory Diseases Research Unit, University of Dundee, have uncovered a range of potentially important cardiovascular findings in ME/CFS patients, including increased oxidative stress (causing damage to blood vessels), abnormal metabolism of acetylcholine (an important neurotransmitter and dilator of blood vessels), and increased early death of white blood cells (which may indicate active inflammation). All this has provided accumulating evidence of a compromised cardiovascular system in patients with ME/CFS, and of the potential importance of inflammation in this disease process.

Increased arterial stiffness has previously been associated with inflammation and the risk of cardiovascular problems in other patient groups, but little is known about these relationships in ME/CFS. Accordingly, Dr Faisel Khan in Dundee decided to investigate the presence of arterial stiffness in adult patients with ME/CFS, as well as its relationship with markers of inflammation.

With a grant from ME Research UK, 41 ME/CFS patients and 30 healthy, age-matched volunteers attended the blood flow laboratory at the University of Dundee. Blood samples were obtained from which to measure a number of chemical markers of inflammation and oxidative stress. These included C-reactive protein which increases dramatically in inflammation, as well as isoprostanes and oxidised low-density lipoprotein which are sensitive markers of oxidative stress. Arterial stiffness was measured using a technique called pulse waveform analysis, producing a parameter called the augmentation index (see Box).

Dr Khan found that patients with ME/CFS had significantly stiffer arteries than healthy, age-matched control subjects; their average augmentation index was 22.5%, compared with 13.3% for controls. Patients also had higher levels of C-reactive protein (2.58 versus 1.07 µg/mL) and isoprostanes (470.7 versus 331.1 pg/mL) than controls, indicating significant inflammation and oxidative stress.

Furthermore, the extent of arterial stiffness was significantly correlated with C-reactive protein, isoprostanes, oxidised low-density lipoprotein and blood pressure

and inflammation

levels, suggesting a relationship between arterial stiffness, inflammation and oxidation.

The cause of increased arterial stiffness in ME/CFS is still unknown. While lifestyle characteristics such as smoking, obesity and physical fitness also play a role in its development, the patients in this study were no different to the control subjects in this regard. In addition, reduced physical conditioning has been associated with increased arterial stiffness, and might be involved to some degree. However, the relationship with inflammatory markers found in the current study suggests that long-term inflammation may be a potential cause of arterial stiffness in ME/CFS. Dr Khan is careful to emphasise that this is an association only and that the current results do not prove cause and effect.

Do these results mean that people with ME/CFS are at an increased risk of developing cardiovascular problems such as heart disease? In his paper recently published in the journal Clinical Science, Dr Khan points out that very few long-term follow-up studies have been carried out in ME/CFS patients, and none on the occurrence of other health conditions such as cardiovascular disease. It is therefore not possible to estimate cardiovascular risk in this patient group at present. However, his work does raise the possibility that suppressing inflammation in carefully selected patients may lead to an improvement in arterial stiffness and a reduction in long-term cardiovascular problems, something already achieved in patients with rheumatoid arthritis. However, further research is needed before this can be answered definitively. ●

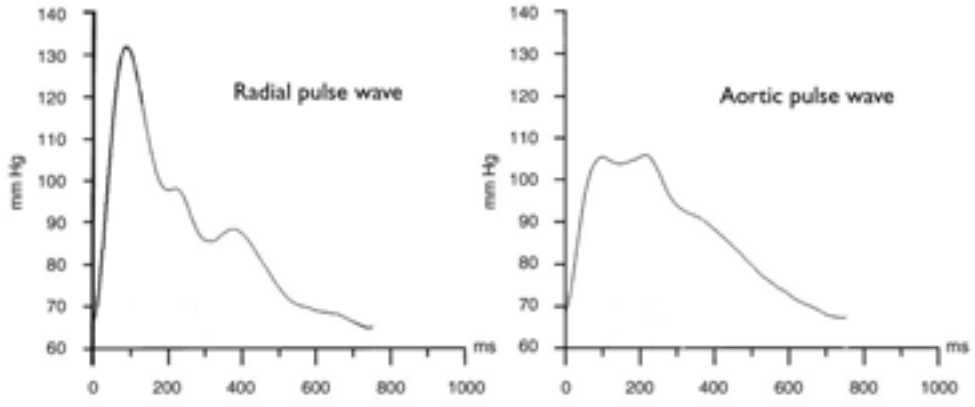
Pulse wave analysis

When you place your fingers on your wrist, you can feel your pulse; that is, the regular increase in pressure as each pulse of blood travels down the radial artery. This pulse can also be detected by a pressure sensor applied to the wrist, and this is the technique used by Dr Khan and his colleagues to determine arterial stiffness.

The sensor produces a continuous recording of the fluctuations in pressure caused by each pulse wave (see Figure below), and their shape is analysed to determine how stiff the artery is.

The pulse pressure wave is composed of a wave generated by the ejection of blood from the heart and a reflected wave from the periphery. As arteries get stiffer, the velocity of both waves increases, causing the reflected wave to arrive earlier in the aorta and augment the size of the pulse.

The augmentation index is therefore related to blood vessel stiffness.



WHAT IS ME Research UK?

ME Research UK is a medical research charity which commissions and funds scientific (biomedical) investigation into the causes and treatment of ME/CFS. We also have a mission to "Energise ME Research", and our in-house team identifies potentially important biomedical research projects, maintains a database of information on ME/CFS, produces high quality professional reports, and hosts scientific conferences.

Recognising that much of the existing research into ME/CFS has concentrated on psychological interventions designed to "manage" the illness, ME Research UK believes that biomedical research is urgently required and is what most patients and carers want to see. For this, researchers with fresh, novel ideas have to be recruited and encouraged to undertake research in this field. This is the most difficult task of all, and ME Research UK sees its role at this leading edge: to give help to biomedical scientists for novel research projects that would otherwise not be funded, and to support research groups to the stage where they can apply to major funding agencies for further support based on their initial data.

With your help — and building on our close working relationships with researchers and other ME/CFS organisations — ME Research UK can be a force for change, and a source of real hope for thousands of people.

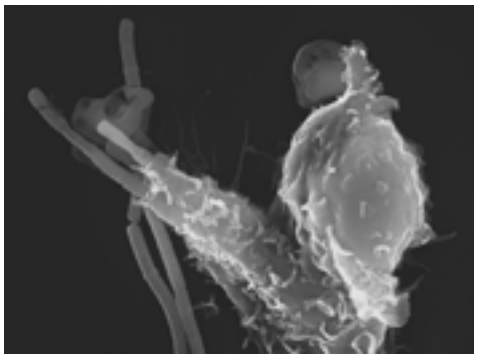
Enterovirus in the stomach

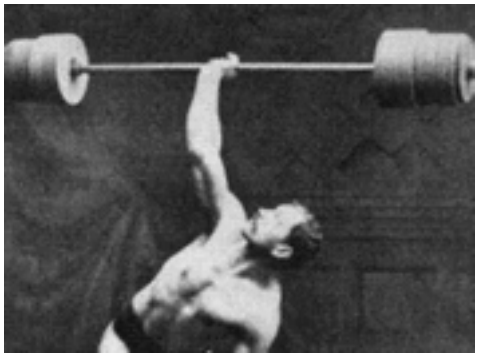
Enterovirus infection is known to be a triggering or perpetuating factor for ME/CFS. Since persistent or intermittent, upper and/or lower gastrointestinal symptoms are a well recognized feature, and since there is a recognised relationship between digestive symptoms and enteroviruses, Drs Andrew and John Chia produced a review of the subject in 2005, and then followed the work up experimentally using upper gastrointestinal endoscopy and antrum biopsy to look for evidence of enterovirus infection in the stomach of ME/CFS patients.

Their study (published in the Journal of Clinical Pathology in 2007), reported that 135 out of 165 (82%) of patients' biopsies stained positive for enterovirus VP1 protein within parietal cells, compared with 7/34 (20%) of the controls ($p<0.001$). In addition, the degree of staining was related to the patients' capacity to do sedentary work. Enterovirus RNA was detected in 9/24 (37%) of paraffin-embedded biopsy samples, but in only 1/21 of the controls.

Clearly, a significant subset of ME/CFS patients examined had "a chronic, disseminated, non-cytolytic form of enteroviral infection, which could be diagnosed by stomach biopsy". As Dr Jonathan Kerr pointed out in an accompanying editorial, the question now is whether this startling result is a general finding, or specific to these patients in California. ●

Recent research from





What's in your urine?

Over the years there have been isolated reports of unusual findings in the blood or the urine of people with ME/CFS. However, the most recent of these, from an Environmental and Pathogenic Microbiology Laboratory in Australia (Experimental Biology and Medicine 2007), is rare because both blood and urine were examined in a large cohort of 100 ME/CFS patients and 82 well-matched control subjects.

Using a case-control design, the authors found that, while blood biochemistry fell within normal laboratory ranges, patients had a significant decrease in red cell distribution width as well as an increase in neutrophil count. Furthermore, in urine samples there were a number of anomalies including a reduction in the rate of urinary metabolite excretion in patients, reflecting significant reductions in excretion of essential branched-chain amino acids.

What does this mean? Well, higher numbers of neutrophils have been shown before and indicate the presence of inflammation and a non-viral, pathogen-like stimulus; and the alterations in red cell shape could be caused by oxidative damage. The reductions in urine amino acid levels indicate disturbance to amino acid and nitrogen metabolism. Interesting stuff, but isn't the core message that blood and urine anomalies can be found in ME/CFS patients if anyone takes the trouble to look for them? ●

Rehabilitation gets a facelift

Everyone knows that people with ME/CFS are physically unable to do certain things, but there is still debate about why. In an excellent paper (published in Clinical Rehabilitation), researchers at University Hospital Gasthuisberg, Belgium, reviewed the literature on motor performance.

They claim it is important to distinguish between such aspects as effort capacity (the ability to generate energy for force and endurance) and effort tolerance (the capacity to tolerate and recover from effort). While the former can be reliably assessed by an exercise test (such as progressive bicycle ergometry), effort tolerance requires systematic monitoring of post-exercise responses.

They arrive at some interesting conclusions. First, although physical deconditioning is not an essential characteristic of the illness, if present it may have a negative influence. Second, the current CDC diagnostic criteria for CFS should be refined to incorporate essential aspects of the patients' post-exertional sickness response. Finally, exercise programmes for CFS should not follow a strict graded exercise format, but should involve an individually tailored exercise protocol modulated by a pacing strategy.

This review is a welcome addition to the literature from researchers who see exercise therapy as a rehabilitation strategy which is useful if appropriate and under well-defined conditions. ●

around the world

Immune dysregulation is key

Current Rheumatology Reports published an overview at the end of 2007, co-authored by Prof. Nancy Klimas and Dr Anne Koneru of the VA Medical Center in Miami, of current biomedical findings in ME/CFS, with specific reference to immune function and neuroendocrine interactions. And what interesting reading it makes!

They explain that investigations into the underlying cause of the illness have advanced the field considerably, and go on to describe some of the results. Gene microarray work has evaluated genetic signatures and suggested biological subgroups and potential targeted treatments such as INF-β. Acute viral infection studies have found that initial infection severity is the single best predictor of persistent fatigue. Genomic studies show that persistent cases express Epstein Barr virus-specific genes and demonstrate abnormalities of mitochondrial function. Studies of immune dysfunction have shown dysfunction of natural killer cytotoxic cells. Other research has focused on a subgroup of patients with reactivated viral infection.

Overall, the preponderance of available research confirms that immune dysregulation is a primary characteristic of CFS, and that research should focus on targeted therapies to impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation in patients. ●

Inflammatory toolbox

Given the increasing evidence (arterial stiffness, isoprostanes, etc.) that inflammation is involved in ME/CFS, it was heartening to read the superb review in Psychoneuroendocrinology on the need for improved recognition and management of inflammation-associated symptoms in medically ill patients. The experts at this multidisciplinary meeting pointed out that medically ill patients present with a high prevalence of non-specific comorbid symptoms, including pain, sleep disorders, fatigue, and cognitive and mood alterations — indeed many of the symptoms experienced by ME/CFS patients!

The experts, however, recognised the danger of psychiatrists ascribing these to "somatisation disorder", an action which "is of little operational value if not misleading"; as they say, the enduring fatigue experienced by the vast majority of breast cancer survivors could be easily labelled as a somatisation disorder when in fact it has an organic basis.

The meeting recommended that there should be a "toolbox" of standard tools for assessing inflammation-associated symptoms, and a minimum set of inflammatory biomarkers which would include acute phase proteins (CRP, sialic acid and haptoglobin), IL-6, and inflammatory mediators (prostaglandins E2 and C3A). Including such a toolbox in the assessment of ME/CFS patients — for example, in the regional clinics in England — would be a great advance. ●

Modest effect of CBT

Meta-analysis is a method of combining results from a range of studies to obtain an overall estimate of the "true" effect of a treatment. Researchers at the University of New England, Australia, have just published a meta-analysis of all relevant clinical trials using cognitive behavioural therapy (CBT) or graded exercise therapy (GET) to manage the symptoms of ME/CFS. Interestingly, the authors made no particular distinction between CBT and GET, preferring to examine both within one overarching framework.

Overall, they found a very mixed bag of 13 clinical trials (representing 1371 patients; 5 trials using the Oxford definition which focuses on unexplained chronic fatigue and does not require additional symptoms), and found a significant difference in post-treatment "fatigue" between "treated" and "control" participants, concluding that overall the interventions "tend to be moderately efficacious". In fact, the magnitude of the effect size is small to moderate by the standards of the famous monograph by Cohen (1988), and similar in magnitude to effect sizes reported for relaxation techniques or meditation.

Could it be that good supportive clinical care combined with self-help strategies (which by definition involve cognitive behavioural elements) might be as effective and less costly, as the Canadian Consensus Document on ME/CFS has already suggested? ●

FRIENDS SCHEME

Our Friends scheme provides the core support needed for our work to continue. There are three categories: **Individual Friends**, **Corporate Friends** and **ME Group Friends**, all sharing our aim of a biomedical breakthrough in ME/CFS, and representing many thousands of patients and carers across the globe.

Individual Friends can give their support in a variety of ways, such as fundraising, regular donation by standing order, taking a collection box, or by just spreading the word — word-of-mouth is one of the most efficient ways of getting our work known.

The **Group Friends** scheme is for local ME support groups, and there are currently 25 groups informally signed-up. The Groups range from Castleford to Solihull & Birmingham, and from Aberdeen to Warwickshire, and the full list can be found on the Friends of MERUK section of our website.

Corporate Friends is designed for larger independent organisations — corporations, larger registered charities, companies, businesses — that share our aims, and the scheme brings collective power to the drive to energise ME research.

With the help of all our Friends, we can continue to be a force for change, and a source of real hope for the thousands of people with this debilitating illness.

Women's Challenge

Thirty thousand people completed the Hydro Active Women's Challenge in London, Birmingham and Liverpool in September 2007, and on the finishing line in Birmingham were Sue Smith and her daughter Danielle. Sue lives in the West Midlands and was diagnosed with ME more than 15 years ago, since when she has had good and bad periods. However, she is currently in a "good" period, and so was persuaded by her daughter to join her in entering the event! Both completed the 5-km course — Danielle speeding over, and Sue limping with a torn ligament — and persuaded many of their friends to support them and ME research.

As Sue said, "Completing the course was a fantastic achievement, for Danielle and also for myself as a person with ME. Crossing the winning line was a marvellous moment, and I hope that others can take courage from the fact that there is light at the end of the tunnel even though at times it flickers!" ●

Coast-to-Coast

In the Summer of 2007, Allan Mason from Caterham, Surrey embarked on a 190-mile walk from Robin Hood's Bay on the east coast of England, across North Yorkshire and the Lake District to St Bees Head in Cumbria, to raise awareness of ME and money for ME Research UK. Allan's daughter Sally has suffered from ME for two years, which led Allan to take up the challenge, despite suffering badly himself from arthritis.

The walk was a variation on the classic Wainwright route and, after fifteen continuous days of walking and carrying all his gear on his back, Allan finally reached St Bees having raised well over £2,000, mostly through his superb Justgiving fundraising website. As Allan says, "Not surprisingly, I had sore feet and plenty of aches and pains in the legs, but all the generous sponsorship from everyone really did focus the mind on plodding on. It was a great experience, despite the many rainy days — trust me to pick

the wettest Summer on record!" Allan's walk was also covered by a number of local papers, such as the Surrey Mirror, helping to raise awareness of the plight of people with the illness. ●

Belfast fundraiser

October 27th 2007 was the date for Antoinette Christie's fundraising night at the Devenish Arms, Belfast, which was attended by over 500 people.

The evening was opened with a song from Andrea Hanaway (pictured centre, with Antionette on the left), followed by a few opening words from Dr Vance Spence, Chairman of ME Research UK, who had come with his wife to support the event and to thank Antoinette and the family. Councillor Bernie Kelly, the Deputy Mayor of Belfast, was one of the distinguished guests.

In her speech Bernie said, "I attended this fundraising event to help raise awareness of ME which has affected Antoinette's son David and stripped his young life of everything he once took for granted. I was saddened to hear about the lack of support for people like David and his family and pledged to help the family access services."

Entertainment was provided by the compere for the evening, Citybeat presenter Robin Elliot, followed by Micheal Persell and Tony Ajir. The revellers spent the remaining hours dancing the night away with DJ Pado. ●

VegEPA for ME

The VegEPA for ME Scheme, through which every pot of VegEPA sold raises 50p for research into the illness, now has several thousand members from over 20 countries across the world, and to date the scheme has contributed £16,200 towards our research projects.

The scheme is organised by Lynne Kersh, who cares for her daughter Daliany (pictured) who has had ME for nearly 10 years. She is delighted to have been able to give several large donations to the ongoing research programme.

As Dr Neil Abbot said, "We warmly welcome Lynne's donation from her scheme. The evidence for EFA supplementation suggests that much more needs to be done to research the possible link between symptoms and supplementation, and ME Research UK would look favourably on applications from established academic researchers to carry out such work. There is evidence that EFAs, particularly omega-3s derived from such things as fish oils and blackcurrant seeds, are good for cognitive function generally, and we need to know if this also applies in ME/CFS. ●

A MESSAGE FROM OUR PATRONS

"ME/CFS is a substantial medical and social problem, yet relatively little research has been conducted into its causes and consequences.

The Countess of Mar

"A recent report to the Chief Medical Officer said that a programme of research on all aspects of the illness is urgently needed, and that improvement of health and social care is an urgent challenge.

Roger Jefcoate, CBE

"Given the recent sea change in the public perception of ME/CFS, and the possibility that patients will now be encouraged and supported rather than derided and scorned, we hope that ME Research UK's scientific and policy research will lead the way towards a treatment and cure. Please help us to make a real difference to the lives of people with ME/CFS."

To allow us to press ahead with our mission to Energise ME Research, please consider responding to our Standing Order appeal.

ME Research UK receives no public money and relies entirely on donations from ordinary people. It is vitally important that all our supporters understand that we are one of the very few charities in the world funding biomedical research into ME/CFS, and raising awareness of the issues in a truly professional manner.

Help us to make the breakthrough that patients need and deserve by completing the standing order form on this page, or by donating through the online giving facility via our website.

Please send this form to:

ME Research UK
The Gateway
North Methven Street
Perth PH1 5PP, UK

Tel: 01738 451234
Email: meruk@pkavs.org.uk
www.meresearch.org.uk

For office use only:

Clydesdale Bank
23 South Methven Street, Perth
(82-67-09) for the credit of ME Research UK, a/c no. 50419466

Bank reference number:

_____

Standing Order Form

1. **Name** _____

   Address _____

   _____

   Postcode _____

   Telephone _____

   E-mail address _____

2. **To the Manager**

   Bank/Building Society _____

   Branch address _____

   _____

   Postcode _____

3. **Name of account holder(s)** _____

   Account number _____

   Branch sort code _____

4. **Please arrange to debit my/our account with the sum of £** _____

   On the _____ **day of each month until further notice**

   Starting on _____

5. **Pay to: Clydesdale Bank, 23 South Methven Street, Perth PH1 5PQ, UK**
   Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

6. If you are a UK taxpayer, under the Government's Gift Aid scheme ME Research UK can reclaim the tax you have already paid on your gift. This means that your donation can increase by nearly a third at no extra cost to you. It doesn't matter what tax rate you pay as long as you pay an amount of income or capital gains tax equal to the tax we reclaim on your donations in that financial year. Please inform us of changes in your tax status. Please indicate below if you would like ME Research UK to reclaim the tax on your gift.

   ○ **Please treat this and any future donations I make to ME Research UK, and all payments I have made since 6th April 2000, as Gift Aid donations.**

7. **Signature** _____ **Date** _____

Thank you for your support