North Methven Street, Perth PH1 5PP, UK

MERGE
breakthrough
News of the ME research YOU are helping to fund

research conference in Washington

2003

MERGE
Energising ME Research

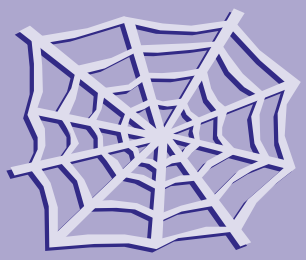
The American Association for Chronic Fatigue Syndrome held its sixth international conference earlier this year in Washington, DC. The range of presentations illustrated aspects of ongoing biomedical investigations into ME/CFS: dysregulation of the 2-5A/RNase L pathway, increased oxidative stress, abnormalities of acetylcholine metabolism, and dysregulation of the nitric oxide/peroxynitrite pathway. In addition, results from gene expression profiling raise the possibility that objective measures of biochemical changes in people with ME/CFS might be provided by microarray technology.

Given this research interest, it seems that attention is turning from the "management" of symptoms towards uncovering the cause of the illness, and identifying the range of different patient groups currently grouped together under the broad term "chronic fatigue syndrome".

However, the volume of biomedical research into the illness is still meagre, especially when compared with some less prevalent, higher profile conditions. Many researchers face difficulty in maintaining financial support for their work, and rely on private benefactors and charities to continue their research.

MERGE was created to try to overcome these funding barriers. It is committed to funding novel biomedical research, encouraging new ideas, and bringing new blood into the field — in short, to energising ME research! ●

ON THE WEB



www.meresearch.org.uk

MERGE's web site has been online since 2002. Its purpose is to be a source of news, education, and information on ME/CFS research and other issues of interest to biomedical researchers, health care professionals, people with the illness and their carers, and the general public.

Our **RESEARCH** pages contain summaries and explanations of MERGE-sponsored projects, reviews of the scientific literature, and details of our funding procedures.

In the **LIBRARY**, you can find our own publications dealing with issues of concern, a collection of literature on ME/CFS and its consequences, and a selection of research papers from work undertaken by our own staff or sponsored by MERGE.

The **SOCIAL CARE** section contains information and advice on accessing social care support for people with ME/CFS.

The web site also keeps you up-to-date with the latest ME/CFS research news, and with recent Friends of MERGE fundraising ventures.

american association for cfs

Research conference contributes towards understanding of ME/CFS

Three members of the MERGE team visited Washington, DC earlier this year, to take part in the sixth international conference of the American Association for Chronic Fatigue Syndrome. The purpose of the meeting was to allow clinicians and researchers to present and discuss their work with other scientists, and delegates got through a broad range of topics over the two days.

There was a clinical day aimed at educating physicians about ME/CFS and the treatments available. Dr Charles Lapp presented an overview of the common symptoms experienced by patients — impaired memory or concentration, sore throat, tender cervical or axillary nodes, muscle pain, headaches, unrefreshing sleep, multi-joint pain, and post-exertional malaise.

He suggested a step-wise approach to the management of the symptoms of chronic fatigue syndrome, consisting of *education*, which includes reassuring the patient that their illness is real and sketching out the prognosis; *activity*, involving a gentle programme of light exercise balanced with frequent rest; recommendations on *nutrition*; and specific *symptomatic therapies* to help treat the symptoms.

Dr Leonard Jason noted that the prevalence of CFS in women in the USA — 522 per 100,000 — is higher than for some other, better publicised disorders, such as women with HIV (125 per 100,000), women with lung cancer (43 per 100,000), and women with breast cancer (26 per 100,000). However, $1.8 billion was spent on AIDS in 1997, $409 million on breast cancer in 1997, and $315 million on Alzheimer's Disease in 1997. In contrast, in the ten years from 1987–97, only $100 million in total was spent on CFS, for research and diagnosis combined.

Presentations on the scientific day included an excellent overview of the biochemistry and genetics of ME/CFS by Dr Robert Suhadolnik. He explored the processes that are altered in the illness, including: oxidative stress (nitric oxide/peroxynitrite), 2-5A synthetase/RNase L, p68 kinase (PKR), apoptosis (programmed cell death), skeletal muscle function, mitochondrial function, and brain metabolism. These abnormalities may come to be useful as biochemical markers for ME/CFS.

> "Progress is possible with good funding, and attention is turning towards uncovering the cause of the illness."

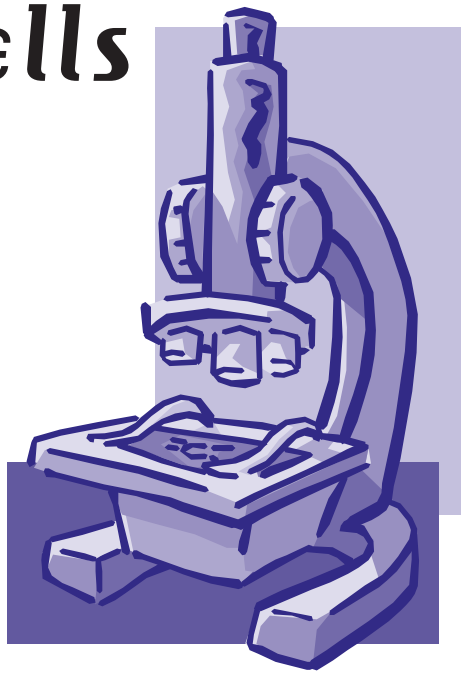
Further talks covered other aspects of biomedical investigation, and the conference illustrates the progress that can be made if researchers have the necessary impetus and funding.

MERGE is committed to helping stimulate the new ideas which are essential if we want biomedical research to move forward (in Churchill's words), "in full flood, inexorable, irresistible, benignant, to broader lands and better days."

You can find MERGE's full conference report, "Broader Lands and Better Days", at the MERGE web site (see sidebar). ●

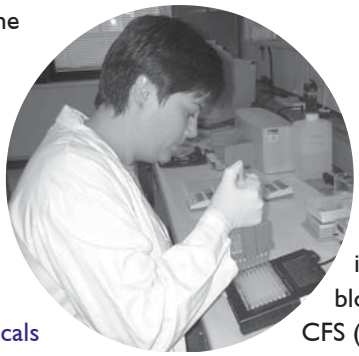
damaged cells

Evidence of oxidative stress in ME/CFS



Oxidative stress has been a hot topic in medical research over the last few years, and it is now clear that it is also an important factor in ME/CFS.

Circulating in our blood are highly reactive molecules, known as free radicals, which can cause damage to our body's cells; a process called oxidative stress. Such damage is implicated in a number of conditions, including cardiovascular disease, most neurological diseases (including Alzheimer's), and the ageing process. Importantly, oxidative stress might also be associated with acute and chronic infections, which many believe to be at the root of ME/CFS.



Gwen Kennedy in the laboratory at the University of Dundee

Several scientific studies have found that there is an excessive number of free radicals in people with the illness, which might well be linked to the generation of their symptoms.

Dr Gwen Kennedy and the team at the University of Dundee's Department of Medicine have been exploring this in more detail. They measured isoprostane levels in the blood of 47 patients with ME/CFS (as defined by the 1994 Centres for Disease Control classification). Isoprostanes are by-products of the oxidative process — specifically, modifications of arachidonic acid — and are particularly nasty, causing blood vessels to constrict and promoting damage to the endothelium (which is the special lining of blood vessels).

Isoprostanes are particularly sensitive and reliable markers of oxidative stress, and Dr Kennedy has found that their levels were raised by as much as 40% in patients compared with healthy volunteers. The source of the free radicals which are leading to this increased lipid peroxidation has yet to be determined, but it could arise from a variety of biological processes such as chronic infections, immune dysfunction, and abnormalities within muscle cells or within the central nervous system. The team in Dundee is engaged in investigating this further. ●

HOW IS IT DONE?

Isoprostanes absorb certain wavelengths (or colours) of light more strongly than others, and this pattern is characteristic of these molecules. By shining light through a blood sample and measuring what comes out, Dr Kennedy and her colleagues are able to determine by how much these wavelengths have been attenuated, and thereby measure the level of isoprostanes in the blood.

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 revise the definitions of both ME and CFS, and meanwhile the term ME/CFS is used.

ME/CFS affects at least 120,000 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 "CFS/ME 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."

FUTURE PROJECTS

MERGE-funded research has raised interesting questions which, coupled with other recent biomedical findings, reveal key areas for further, urgent investigation.

Orthostatic intolerance
A key element in the generation of ME/CFS symptoms is the abnormal cardiovascular response to being upright. We will investigate arterial stiffening, the cardiovascular risk profile, and blood vessel regulation.

Oxidative stress
This has become an important feature of ME/CFS patho-physiology, and we would like to fund projects on the source and role of post-exertional free radical generation in the peroxidation of lipids, and the generation of symptoms.

Endothelial chemistry
Our central hypothesis is that there is endothelial dysfunction in ME/CFS, and we would like to fund a project looking at endothelial chemistry. It is also important to see if children with ME/CFS have the abnormalities in endothelial function and oxidative stress seen in adults.

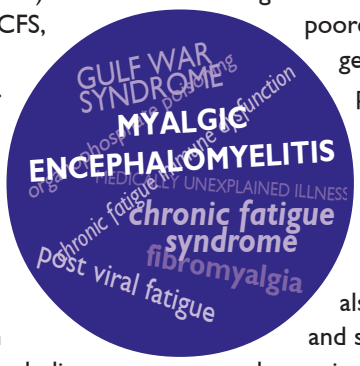
These are some examples from the wish-list of projects we would **LIKE** to fund. As a medical research charity, we support only good quality projects based in established research institutions. MERGE relies entirely on donations for its survival, so we need **YOUR** help, and **YOUR** donations for the work to continue.

what's in a name?

"Chronic fatigue syndrome": successful research needs accurate diagnosis

One of the most animated debates surrounding the diagnosis and treatment of ME concerns the name of the illness and how it is defined. This may seem a trivial side issue, but it is actually very important, both to patients and to clinicians, because it influences the public perception of the condition, how clinical research is carried out, and the treatment options that are offered.

At present, the umbrella term "chronic fatigue syndrome" (CFS) is used. To fulfil the criteria for CFS, according to the Centre for Disease Control (CDC) 1994 definition, a person must have experienced at least 6 months of persistent or relapsing chronic fatigue that is not alleviated by rest, and that causes a substantial reduction in daily activities. In addition, 4 other symptoms, including muscle pain, cognitive problems, and tender lymph nodes, must be present. There is now mounting criticism of this definition which seems to be so broad, so open to bias, and so insensitive to symptom severity that it very likely contains patients with a range of illnesses, including a distinct sub-group with ME, which share common symptoms, but which may have very different causes.



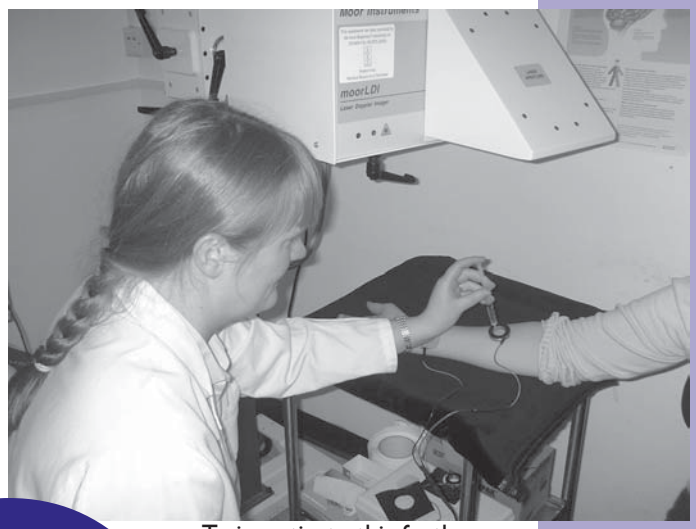
The work of Drs Kennedy, Spence, and Underwood at the Vascular Diseases Research Unit in Dundee has illustrated this issue very well. They examined 97 patients — all fulfilling the CDC criteria for CFS but reporting different causes of their condition. Forty-eight were members of ME self-help groups and reported no consistent cause of their illness (CFS sporadic), 24 had become ill after serving in the first Gulf War (Gulf War syndrome), and 25 had been exposed to organophosphate pesticides.

The researchers found that the 3 patient groups differed considerably in the distribution and severity of their symptoms, though all the participants had significant health problems and much poorer quality of life than the general population. In particular, the patients with Gulf War syndrome had more severe fatigue, muscle pain, and joint pain than the other 2 groups, and their leg muscles were weaker. They also had poorer general health and suffered more from depression. CFS sporadic patients tended to be more severely affected than those exposed to organophosphates, but they had lower anxiety and better mental health. In fact, it is worth noting that these two psychological measures were almost normal in this group.

These findings support the idea that the CDC criteria for CFS is an overarching umbrella term which is too broad to be clinically meaningful, and which contains a number of patient sub-groups. This may help explain why some clinical trials have had inconclusive results. As there is not yet a laboratory test for ME or any other of these conditions, it is still important to take into account what patients report to be the cause of their illness, and the intensity and severity of their individual symptoms. ●

sensitive blood vessels

Cholinergic abnormalities may explain some ME/CFS symptoms



Many of the symptoms associated with ME/CFS, such as fatigue, muscular pain, intestinal problems, and neural disorders, can be linked to abnormalities in the regulation of acetylcholine, or ACh. ACh is an important chemical in the nervous system, but only recently was it discovered to have an entirely separate function in blood vessels, causing them to dilate.

Dr Faisel Khan and his colleagues in the Department of Medicine at Dundee University use ACh regularly to test the reactivity of blood vessels in a wide variety of diseases. A small amount is transferred through the skin, and the resulting change in blood flow can be measured using a special laser (see sidebar).

"Researchers believe patients with ME may have less of an enzyme called cholinesterase in their blood."

Patients with vascular diseases have a smaller blood flow response than normal, but, in a recent study, Dr Khan found that patients with ME/CFS had a higher response than healthy subjects, indicating that their blood vessels are abnormally sensitive to ACh, a most unusual, if not unique, situation.

To dilate an artery, ACh attaches itself to special receptors on the endothelial lining of the vessel wall — these are called ACh-muscarinic receptors. Soon after ACh activates the receptor, an enzyme called cholinesterase removes the molecule, and its dilatory effects then die away very quickly. The Dundee researchers' theory is that patients with ME/CFS have less of this enzyme on their blood vessel walls, or that it is less active, so prolonging and increasing the effects of ACh.

To investigate this further, Dr Khan looked at the blood flow response of patients with ME/CFS to methacholine, which is almost identical to ACh except that it is far less affected by cholinesterase. Healthy people normally have a larger response to methacholine than to ACh, but in the patients there was no difference. This suggests that the blood flow abnormalities in ME/CFS may indeed be a result of problems with endothelial-generated cholinesterase.

Interestingly, many believe that Gulf War syndrome and the illness experienced by people exposed to certain insecticides called organophosphates, both of which have similar symptoms to ME, are caused by chemicals which inhibit cholinesterase. However, in further studies in Dundee, it was clear that patients with Gulf War syndrome and those exposed to insecticides had normal blood flow responses to both chemicals. Although they experience a similar range of symptoms to people with ME/CFS, their illnesses may have an entirely different biological basis. ●

HOW DOES IT WORK?

The laser scanner (pictured above) used by Dr Khan to measure blood flow works on a very well-known principle — the Doppler effect. (This same effect, but on sound waves, is what causes the pitch of an ambulance siren to change as it passes you.)

When light is shone into the skin, it is scattered and reflected off all the microscopic cells it encounters there. When it bounces off a moving particle such as a blood cell, the light changes colour slightly. This colour change (or shift in wavelength) is related to the speed of the blood cell. The change is detected by the scanner and turned into a measurement of blood flow.

SETTING THE AGENDA

MERGE produces reviews of past and current scientific research into ME/CFS, and has responded to public policy issues with widely distributed publications offering constructive analysis and discussion.

Unhelpful Counsel?
MERGE's detailed response to the CMO's report of January 2002. This explores many of the issues — scientific and political — which complicate research and treatment of ME/CFS.

Research into ME/CFS in the UK: Can the National Research Register inform future policy?
MERGE's analysis of ME/CFS research funding sources

Who Cares? A submission on care pathways
MERGE's submission to the Scottish Executive's Short-Life Action Group on CFS/ME.

Shattered — Life with ME
by Lynn Michell. Thorsons, 2003 (HarperCollins, ISBN: 0-00-715503-4)
Dr Michell collaborated closely with MERGE during the writing of this book, which contains a Foreword and Appendix by MERGE.

These documents and more can be found at the MERGE web site. For more details, see the sidebar on page 2.

repairing damaged lives

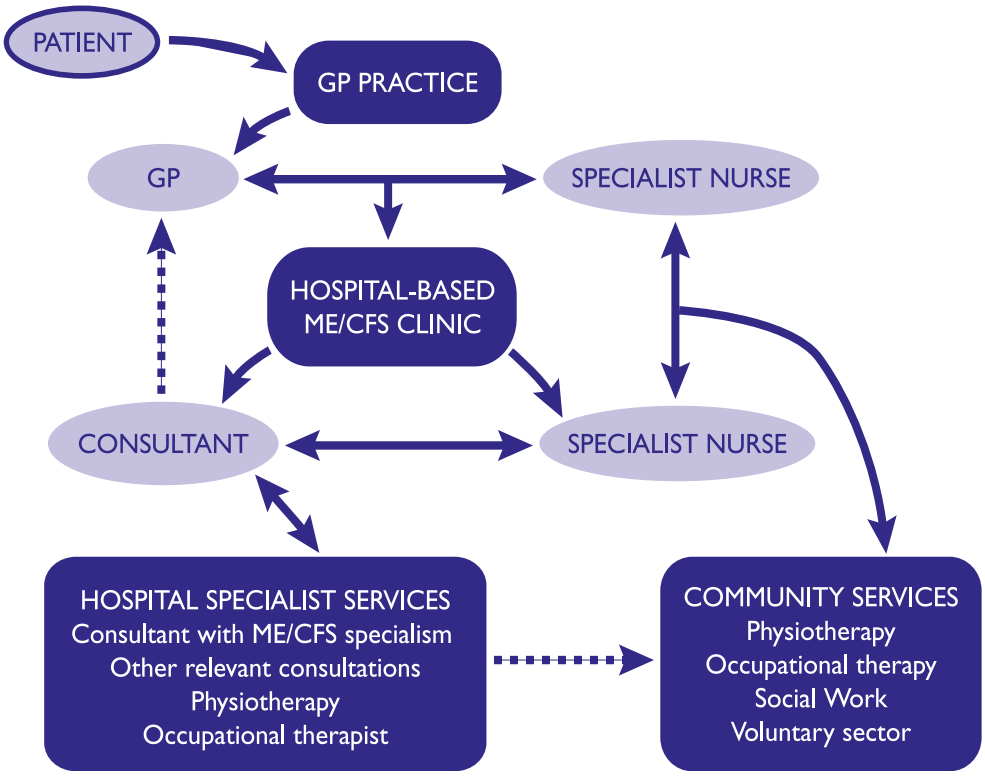
Policy research and social care

Although the main focus of MERGE is biomedical research, other kinds of research can have as direct an impact on the lives of people with ME/CFS.

For example, the 2002 report of the Chief Medical Officer of England stated that improvements in the commissioning and management of care for patients of all ages was an "urgent challenge." So, when the Scottish Executive — the executive arm of the Scottish parliament — called for policy submissions on this topic, MERGE prepared a consultation document.

The conclusions were that action on four fronts could have clear beneficial effects on the provision and delivery of care to people with ME/CFS: the institution of a national health-needs assessment, the creation of skilled multidisciplinary teams to support rehabilitation programmes and adjustment to illness and disability, intervention at the early stages of illness when primary care services can be most effective, and the integration of ME/CFS into a grouping for planning purposes.

One suggested "Care Pathway" for ME/CFS patients is illustrated below. You can read the full version of this document, called "Who Cares?", at the MERGE web site (see page 2). ●



what is merge?

MERGE is the Myalgic Encephalomyelitis Research Group for Education and Support. We are a UK charity with the principal aim of commissioning and funding scientific investigation into the causes, consequences, and treatment of myalgic encephalomyelitis, or ME/CFS. This is a debilitating illness which affects at least 120,000 people in the UK, but which is not well understood nor, in many cases, properly recognised.

MERGE was founded by Dr Vance Spence and Mr Robert McRae, with a mission to further the understanding and recognition of ME/CFS, and to provide support. With Roger Jefcoate CBE as founding patron, and The Countess of Mar and Dr Gordon Parish as patrons, our official opening was in May 2001. We are based at The Gateway in Perth, Scotland.

Though in its early stages, MERGE has already accomplished much with our strong in-house team, advisory panel of professional scientists, and core group of trusted volunteers: the Friends of MERGE. In its first year, MERGE was instrumental in forming a Cross Party Group on ME at the Scottish Parliament, to provide a forum for the concerns of patients and carers. Recently, we have published an extensive response to the Chief Medical Officer's Working Group report on ME/CFS, an overview of ME/CFS research funding sources in the UK, and a document on care pathways which was submitted to the Scottish Executive of the Scottish Parliament. These documents are available from our web site (page 2).

"MERGE is committed to commissioning and funding scientific investigation into the causes of ME."

On the biomedical research front, we have commissioned and funded a number of research projects, some now completed. We have established research links with local ME self-help groups, and have close working relationships with the 25% ME Group and the Irish ME Trust.

Our social care arm aims to progress the social care policy agenda and assist access to social work services.

With your help, MERGE can continue to be a force for change, and a source of real hope for the thousands of people with this debilitating illness. ●








A MESSAGE FROM OUR PATRON

The Countess of Mar

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

"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.

"Given the recent sea change in the public perception of ME, and the possibility that ME patients will now be encouraged and supported rather than derided and scorned, I hope that MERGE's scientific and policy research will lead the way towards a treatment and cure for people with ME.

"Please help us to make a real difference to the lives of people with ME."

friends of merge

Above: The Friends of MERGE gather in Perth for the launch of the scheme (Photo by Nye Stenning, 2003)

The Friends of MERGE scheme was officially launched at a meeting in The Gateway earlier this year. The purpose of this scheme is to harness volunteer support for MERGE, and to secure the core support needed for our biomedical and social care research work to continue.

Through its Executive Committee of committed volunteers, Friends of MERGE will raise funds for the charity through a variety of activities. It is hoped that, in time, there will be branches all over Britain. As well as an individual Friends scheme, there are group and corporate schemes for larger organisations that wish to raise money for ME/CFS research.

Friends can give their support in a variety of ways: By acting as local fund-raisers, volunteering for specific tasks, making a regular donation to MERGE, or just spreading the word. If you would like more information or wish to make a donation, please fill in the form below. ●

If you would like further information about the Friends of MERGE scheme or about the charity's work, or if you would like to make a donation to help MERGE fund research and its other activities, please complete this form and send it to the address below.

We have separate **General**, **Research**, and **Welfare** accounts, so you can specify the area for which your donation is to be used.

To include MERGE in your Will, please ask us for more information, or visit our web site.

Please send this form to:

MERGE Headquarters
The Gateway
North Methven Street
Perth PH1 5PP, UK

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

How to help MERGE

○ Please send me information about the Friends of MERGE scheme

I would like to make a donation to help MERGE make a difference

○ I enclose a cheque or postal order for £ _____ made payable to MERGE

○ Please send me a Standing Order form so I can make regular donations to MERGE

○ Please send me information about leaving a legacy to MERGE in my Will

○ I would like you to reclaim tax on my donation through the Gift Aid scheme

(You must pay an amount of income tax and/or capital gains tax at least equal to the tax the charity reclaims on your donations in the tax year—currently 28p for each £1 you give.)

Name _____

Address _____

_____

Postcode _____

Telephone _____

Email address _____

Date _____