

**UNDERSTANDING**  
**AND**  
**DIAGNOSING**  
**CHRONIC FATIGUE SYNDROME**

BY

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On these pages Dr David Smith shares with you his almost unique experience and knowledge of Chronic Fatigue Syndrome (or Myalgic Encephalomyelitis {M.E.} as it is also known). He has had remarkable success in the management and treatment of the illness, entirely within the NHS, and it is hoped that the pages here will prove helpful, not only to his colleagues in the medical profession but also to those involved in healthcare generally, to schools and also, of course, to sufferers and their carers.

More details and information needed to build an effective and structured Management Programme can be found on the second PDF on this site, entitled **Get Well Guidelines**.

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# **THE BACKGROUND TO MY WORK ON CHRONIC FATIGUE SYNDROME - A TREATABLE AND POTENTIALLY CURABLE DISORDER USING CONVENTIONAL MEDICAL APPROACHES**

I qualified in Medicine in 1969 in Edinburgh and then studied for a B.Sc in Neurophysiology.

I am a mainline organically based clinician who has been looking at the field of Chronic Fatigue Syndrome now for 30 years. I spent 12 years as Medical Adviser to the Myalgic Encephalomyelitis Association based in Stanford-le-Hope, and wrote and published, after peer review, some ten papers based on the concept that this illness was caused, sustained and maintained by a virus of one kind or another.

In 1990, it became quite clear that this illness was simply triggered by a virus and its presence was not pathological. In many cases I was convinced that viruses were not involved. The virus, therefore, if found in the blood became irrelevant. In 1992, it became clear that the fatigue syndrome was purely centrally based and that the problem was that of disturbed brain function and an overactive immune response. With further work it became clear that probably every neurone and all brain function within the central nervous system is affected and neural networks suggest that a diminished brain function would be associated with diminished pan-neurotransmitter regulation. Thus a treatment became apparent and that it would be a neurotransmitter regulator of one kind or another; in other words, the use of antidepressants became axiomatic.

Fortunately seventy percent of neural transmission is made by five neurotransmitters namely 5Hydroxytryptamine, Nor-adrenaline, Adrenaline, Gamma-aminobutyric acid Dopamine and Endorphins etc. There are of course many other neurotransmitters present in very much reduced amounts. By using a tailor made mixture of Tricyclic Antidepressants (TCIs) and/or and SSNRIs like Mirtazapine, at night and stimulating 5HT re-uptake inhibitors (SSRIs) in the morning, this treatment approach began in 1994. Since then, having had a poor treatment outcome previously, the effect upon this illness has been dramatic. All of this, of course at the moment, is anecdotal and can only be proven by peer reviewed published papers. My paper, written with others (Professor Simon Wessely, Prof Trudie Chalder and Dr Maxine Patel), relating to the treatment of children using these medications was published in Archives of Diseases of Childhood in October 2003 and demonstrated that this illness is now effectively curable in children.

I would like to invite you to participate in examining my concept and treatment programme which follows on this Web Site. This is intended to be an information only service - I am afraid that I cannot enter into personal responses.

I hope that you find this interesting, sensible and progressive.

With best wishes

**DR DAVID GEOFFREY SMITH M.B. Ch.B. B.Sc.**

# **INTRODUCTION**

## **CHRONIC FATIGUE SYNDROME (CFS)**

**Otherwise known as Myalgic Encephalomyelitis (M.E.)**

**Post Viral Fatigue Syndrome (P.V.F.S.)**

**American Terminology - Chronic Immune Deficiency Fatigue Syndrome (C.I.F.D.S)**

**Also incorporating Fibrositis Fibromyalgia Syndrome (F.F.S.)**

The 5th October 1996, found the Royal College of Physicians officially recognising the presence of Chronic Fatigue Syndrome and in January of 2002 the Chief Medical Officer of Great Britain stated that the medical profession also recognised this illness. Disliking the terminology M.E. they stated that the illness was not physical, not perpetuated by a virus, not psychological (although recognising that complicating psychological problems were relevant), not stating what they believed it might be but what it was not. This however, is how I have perceived the illness for the last several years, and I will tell you that the illness lies as a biochemical dysfunction of the central nervous system, probably affecting all neuronal tissue and sustained by an immunological dysfunction of heightened immune activity, loss of central regulatory mechanisms and intellectual cognitive processing. Despite popular understanding to the contrary this illness is not only treatable but potentially curable.

Within these pages and fields of this website you will find the description of how these various named disorders came about, definitions of C.F.S. and some of its major subsets. Understanding the generation of the symptoms

experienced by sufferers and the philosophy of what is going wrong in this illness is complex. More importantly, however, you will find details of how to develop the three major stages to recovery. Firstly, the development of a modified activity programme for both physical and mental activity, secondly the use of sedative tricyclic antidepressants to restore and normalise and regulate sleep pattern and thirdly the introduction of antidepressants in the day to try and help the reduction of fatigue and anxiety to help sufferers move forward.

Since 1994 I have been using a combination of Fluoxetine Hydrochloride (Prozac) in the day for its anti-fatigue property and for its increment in cognitive function and also the use other SSRIs for similar reasons but also for their anxiolytic effect and to lift mood. These are medications that are used during the day and at night in various combinations of tricyclic antidepressants to help normalise and restore sleep pattern. Since that time the success rate in treating C.F.S., and more specifically the subset that appears to have been precipitated by an acute virus onset, has risen dramatically.

I hope you find the following pages enlightening but also please remember that I cannot enter into specific answers with patients that I have not seen.

**David Smith**

# **OVERVIEW**

## **CFS AND ITS SUB-GROUPS**

There is no doubt that opinions from countries around the world that have been studying Chronic Fatigue Syndrome (C.F.S.) are drawing to a consensus on a working definition, of what we should all be looking at when we talk about C.F.S. There have been many others. It is however interesting that the countries that appear to be complaining more of this disorder are those of westernised or 'advanced' countries, Australia, New Zealand, South Africa, North America, Canada, Great Britain, Europe. I will draw your attention to the fact that these countries suffer more mental stressor factors than maybe elsewhere. It is a syndrome, which means it probably includes different illness processes with similar symptoms but in all of them the principal complaint is one of persistent chronic fatigue and fatigueability without any other reasonable explanation for its cause. One can see that there must be a number of possibilities for the cause of this type of complaint, but if you have come to this stage I would have assumed that all other medical explanations would have been excluded but you might have been told it's psychological. There seem to be two major types; the slow onset variety and the acute onset variety. Within the latter, and to some lesser extent the former, the major complaint is that of chronic fatigue (and probably many other symptoms) which then would draw the attention to a diagnosis of C.F.S., but often widespread muscle pain appears to be the principal complaint in which case the diagnosis would include that of Fibromyalgia Syndrome (FMS). In all of these conditions I will argue that the predominant pre-morbid factor is that of significant negative mental and other stressor factors.

One of the major sub-groups of C.F.S. is that of acute onset where the fatigue disorder has been apparently precipitated acutely by some kind of infective agent. There are many sorts of infective agents but it appears that the majority are brought on by some kind of 'virus' type infection. The symptoms here would typically be malaise, high temperature, aches and pains, sore throat, headache. Something of the kind that we have all had at some stage in our lives.

I have looked at several thousand cases of C.F.S. over the last thirty years and have seen many patients that appear to have predictable factors that make them worse and that also make them better. By analysing these various markers I have developed strategies for patients to help them feel better. To optimise their chances of recovery by preventing them from making themselves worse you can encourage their ability to make themselves better. The majority of patients realise that by doing too much either mentally or physically they make themselves worse, but what they don't realise is that by making themselves worse they actually perpetuates the illness process itself – chasing rainbows. There are now some proven recognised effective remedies, namely those of Cognitive Behavioural Therapy (C.B.T.) and Graduated Exercise Treatment regimes (G.E.T.). I will also suggest that antidepressants help the recovery as well. This is not universally accepted. I will also suggest that CBT and G.E.T. are not the whole answer.

There are many worldwide centres studying C.F.S. and most have independently adopted various types of management programmes and strategies that have similar treatment styles and they amount to those of management programmes, C.B.T. and G.E.T. I too have found that this type of approach is the most effective treatment presently available. I also make use of antidepressants. These medications are used here as neurotransmitter regulators

to try and help correct the biochemical disturbances within the central nervous system and act as post-synaptic membrane support systems; these medications are not only safe but non-addictive and non habituating. They have problems in their use and side effects, but the prescription is designed and tailor made to treat the patients themselves, and nothing should be taken that makes the symptoms worse or the patient feel unwell. In this situation the patient is in control of their medications. They need to be taken for quite considerable lengths of time, often years, typically two to four years. They are, however, highly efficient not only in relieving the symptoms but I believe in actually treating the illness process itself. Success of this type of regime is high and a **Dr.Smith's Get Well Club** exists to offer group support for my patients with C.F.S., all of whom I am happy to say have a positive and optimistic approach to their illness process, and as they have one source of information the approach is the same. C.F.S. is not only treatable but potentially curable.

I trust that you will find this approach thoughtful and well worked out. I am a middle of the road Clinician and offer evidence based medicine. There is nothing here that would be not recognised by all practising Physicians as being reasonable and acceptable. I hope you find the contents of this website educational, enlightening and an answer to your problem.

## DEVELOPMENTS IN RESEARCH AND UNDERSTANDING.

Within the diagnosis of C.F.S. there are essentially three major sub-groups:

- ✦ **Acute onset C.F.S.**
- ✦ **Slow onset C.F.S.**
- ✦ **Fibrositis Fibromyalgia Syndrome, which is nearly always of slow onset variety.**

I will suggest that all three of these fatigue states are almost invariably associated with long standing negatively directed pre-morbid stressor factors. In my earlier days in the mid and late eighties I believed that these illness processes especially the acute onset variety of C.F.S. were caused and perpetuated by a virus infection.

The reason for my bringing this up now is that a large number of doctors, patients and support groups believe that this is still the case. Whilst I am reviewing this website in the middle of March 2012, just two months ago Dr Charles Shepherd spoke on the Two day (radio 4) programme and said in essence that the ME Association were distressed at the continuing insinuation that there were psychological problems, that research should be concentrated on looking for a virus, an ME virus, or something similar, as the course.

Approximately 6 months ago, in the middle of 2011, in California in the USA, a new retrovirus was found in some 96% of patients with their form of chronic fatigue syndrome referred to as chronic immune fatigue deficiency syndrome and that this virus was only found in 4% of the normal population. If this is the case, that CFS is caused and sustained and maintained by virus infection of any kind, it is incurable as we cannot kill viruses and it is unlikely that for the foreseeable future that this is the situation. Therefore patients with this "virus" cannot get better.

In 1989, I published, with others a paper entitled 'Chronic Enterovirus Infection in Patients with Post-Viral Fatigue Syndrome' in the Lancet, January 23<sup>rd</sup>, pages 146-149 and it demonstrated very clearly that even after a number of years of being ill, we could not only demonstrate the presence of bits of viral protein inside blood samples but we could even recover live infective virus from the gut of patients with this illness. Others, around this time also, were able to demonstrate that these viral particles could be found in muscle biopsies and that physical and physiological abnormalities were demonstrable in muscle tissue. I also wrote papers showing biochemical abnormalities in muscle. This being the case meant that there would be absolutely nothing anybody could do to help a person with C.F.S. if their illness was caused by a virus because, at that time, and indeed to date, we do not have anti-viral medications which can penetrate into cells and kill a persistent virus infection of any kind. So around this time I was seeing patients and telling them that there was essentially nothing I could do to make their illness better but hopefully it would go away in time or they would tend to improve. Statistically that was true, although the statistics at that time were horrendous and ME was seriously bad for your health.

It was also true that a large proportion of patients not only had the acute variety that was not associated with the enteroviruses but they were showing a story suggestive of glandular fever as a start of their illness. Ninety-six percent of the clinical illness of "glandular fever" is associated with the Epstein-Barr virus. In 1989, I approached and started to do some work with Professor Dorothy Crawford. With others we wrote a paper entitled 'Active Epstein-Barr Virus Infection in Post-viral Fatigue Syndrome', (Journal of Infection (1989) 18, 143-150). This showed that approximately 25% of patients with this acute onset variety of ME could be shown to have antibody responses in their blood directed towards the Epstein-Barr virus and that these abnormalities were persistent. However the antibody responses that we found were suggestive that the patient had had a reactivation of the Epstein-Barr virus rather than an acute new infection.

This all led me to write an article summarising the patients that I had been studying, those that were associated with enterovirus and those that were associated with Epstein-Barr virus and to tabulate the various abnormalities that one could find. This was published in The Royal College of General Practitioners Members Reference Book in 1989. Two things then happened that were to change my entire understanding of the illness and which, for a year or so, would leave me with a headache and an internalised dichotomy.

Firstly there was a paper written by Professor Richard Edwards at Liverpool University Hospital, (a Professor of Medicine specialising in muscle disease and a world authority on Duchenne's muscular dystrophy), that suggested that patients with C.F.S. had nothing wrong with their muscles and that there was no fatigue that could be demonstrated anywhere, in

any of the muscles, in any part of the body. I have long since learnt not just to read papers but if anything is really of great significance then one should go and see the author and discuss it and this is exactly what I did. I also took some patients of mine with me and I spent ten days with Professor Edwards studying his techniques and the methodology behind the statement that there was no peripheral fatigue demonstrable. I came away from Liverpool totally convinced that there was no demonstration of any fatigue in skeletal muscles and that, whilst patients often felt worse after exercise or for what was, for them, less than the usual amount of physical activity, the muscles could be made to work normally over long periods of time. This then must, of course, bring into doubt whether there is any pathological process going on inside the skeletal muscles that affects their function. The abnormalities that are demonstrated in electrical activity, or structurally in muscle biopsies, or the presence of virus particles inside the muscle have no demonstrably abnormal impact in the muscles power or work output.

Secondly, and much more importantly from my point of view, was the fact that, by the time I had reached the end of writing this article for The Royal College of Practitioners, I couldn't tell the difference clinically between the patients that were made ill by enteroviruses and those that were made ill by the Epstein-Barr virus; they seemed to me to be totally identical. I went back to one of my previous authors and one of my most important mentors and pointed this out but I am afraid that this did not go down well and caused some acrimony . It was suggested to me that patients with enterovirus infection had much more in the way of muscle pain than those that had Epstein-Barr virus who were complaining mainly of just simple tiredness and fatigue. I had to disagree.

I then came across the Department of Cellular Research at Northwick Park, North London, which at the time was run by Dr Timothy Peters, so I went to see him and told him my story. He admitted to being a C.F.S. sceptic but agreed to admit twelve patients for intense investigation. By the end of this process the patients had been "taken apart" by Physicians, Psychiatrists, Neurologists and Immunologists and the summary was that they all agreed that these patients were ill, that they were not psychologically disturbed, that there appeared to be nothing in the body that was abnormal and the problem had to have a different explanation, as yet unknown. Now, I knew they didn't have any differences, that whilst some of these patients were ill with enterovirus abnormalities in the blood and others were those that had active antibodies to Epstein-Barr virus, none of the experts could tell the difference between them.

If one now stands a little further back from this picture and starts to apply a little bit of lateral thinking, when you have patients that you cannot differentiate between, or tell apart, then they must be the same. They may, however, have different degrees of severity but if all the investigations are normal (apart from the virology) and all of the Physicians looking at them cannot tell the difference, then there is probably and most likely to be only one disease process going on and that process must lie somewhere out with the body and inside the brain. Another statement is that this is likely to be one disease process and not a syndrome. Also it is quite a straightforward step to state that you cannot get one single process within the brain being caused by two or possibly more different viral agents.

Viruses cause one illness. Certainly, the majority do exactly this, although, of course, chicken pox is also associated with later reactivation and causes shingles, but it is the same single virus. The mumps virus

causes mumps, influenza virus causes influenza, Coxsackie's B virus and the other enteroviruses cause some a flu-like illness and Epstein Barr virus causes glandular fever. The herpes viruses generally can come back again, and again, under the mode of reactivation. If you have one illness caused by two, three or even more different viruses (and there are a lot of patients with C.F.S. who associate their illness onset with other types of viruses, generally a non-specific 'flu') then this particular illness can only be triggered by the virus and the virus is not the cause.

If the virus is only the trigger and not the cause, and is not perpetuating the illness and is not pathological then, of course, one has an enormously important statement to make and that is that you do not have to kill the virus to get the patient better. Indeed even if the virus is present in the body, and there is no doubt we could demonstrate this in the two papers that I published, then the presence of these viruses is irrelevant. So now suddenly the virus 'disappears'; it is of no importance!

It then took me a long time to try to clear my head of all the work that I had done previously and put it into my psychological dustbin, although of course at the same time not totally discarding it because there was one unanswered problem and that was the fact that all of the patients that I had studied had a turned on immune system. Their immune system seemed to be fighting a virus on what appeared to be an almost constant basis. What was happening? Why was this occurring? I wasn't the only person who found this particular immunological abnormality. By this time in the very early part of 1990 there were at least one hundred papers demonstrating a non-specific immunological turn on directed mainly and principally towards a viral or anti-viral reaction.

I had by now come to the opinion that this illness had nothing to do with viruses but I wasn't quite sure what it was caused by and, of course, as I was working as Medical Advisor to the M.E. Association, who believed that ME was caused by virus, they quite rightly and properly asked me to leave. I felt a little aggrieved at the time but have long since seen that that was inevitable. It wasn't until much later, I am not quite sure when but I believe probably by 1993, that it became much clearer to me that patients with this illness process invariably had a long story of negative stress.

## **Psychoneuroimmunology**

In the Annals of Medicine 25: 473-479, 1993 was the first article that I read on the basics in Psychoneuroimmunology. This, coupled with a paper entitled the **Psychotropic Treatment of Chronic Fatigue Syndrome and Related Disorders published in the Journal of Clinical Psychiatry Volume 54, Number 1. January 1993**, gave me the understanding of the basis of where I am working from today. Later when I was able to show some abnormalities in the fluid surrounding the brain by lumbar puncture the whole situation became clearer and the story is neat, tidy and scientifically waterproof. From this base I have been able to build a model of the cause of C.F.S., which has led to vast improvement in treatment outcome and which for the last sixteen years has been indestructible, no matter how hard I try to knock this model down I cannot do so.

## PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology is really a very old concept but with advancing ability to analyse the immune response, it has relied upon new techniques to look at immunological responses in various situations. I am sure it will not come as any surprise to you to hear that people who have been under emotional stresses can be run down, mildly depressed and may be unfit. It is suggested that they are also more prone to "colds" or "viruses" and that when people are 'run down' they get everything that is 'going around'. Other people, when they feel that they are emotionally strong and physically fit will say 'touch wood I haven't had a virus infection for years'.

Going back a great number of years, in the 1930s, there was a very interesting study done on a group of workers in America that, if I remember rightly, worked for a large car making company. All of the workers were studied psychologically and the Psychologist and the Psychiatrist doing the work predicted that if there was an outbreak of a virus, some of the workers would be ill longer than others. The ones that they predicted would be ill longer would be those that had high symptom reporting for other illnesses like back strain or infections and also those that had had a previous depressive illness or neurotic illness. There was then, fortuitously it seems, an outbreak of flu and, following the prediction, some workers with these predisposing traits were ill longer than others that didn't. Thus the psychology of the patient determines how long they are going to be ill and indeed how ill they were during that outbreak. For instance some patients who have had these types of traits have also been studied when they have had hepatitis and not only are

they ill longer but the actual level of liver enzymes, (in other words the amount of damage to the liver), was found to be higher and remained so for longer. Therefore our personality contributes to the amount, and the degree of illness that we suffer.

Coming back to C.F.S., I have seen quite clearly that the vast majority, probably 99% of everybody that I have seen up to now, has had a significant history of negative stressor factors and pressures prior to their illness beginning and, furthermore, that these negative stressor factors are often multiple. They are never positive, they are always destructive and last for quite long periods of time. I haven't seen anybody who has been under negative stress for just a week or a month getting C.F.S.; the pressure is usually six months, one year or sometimes lifelong. It is especially likely that the pressures will have been lifelong in those that have had C.F.S. on at least one occasion before and have made a greater or lesser recovery from the previous episode. I am also totally convinced that when you get C.F.S. occurring in more than one member of the family, then there is a significant family dysfunction.

It is most important to identify the negative stresses and establish whether they still exist. If they do, then they need to be removed and solved if at all possible because if they exist they will inhibit the recovery process of the patient.

What stressful factors are we talking about?

In children the stressor factors are nearly always multiple and include usually a combination of: –

- The stresses of being adolescent

- The stresses of peer group

The stresses within a particular school  
Those of an academic nature

As you will see elsewhere (and this is agreed by all informed observers) the illness occurs more in women, and there is no doubt that in the patients I see who are thirteen, fourteen and fifteen years of age the pressures of being a young girl seem to be much greater than those of being a young boy. There are, of course, the enormous pressures within the body of adolescents - rapid growth, rapid change, surging hormones. In my observation, girls are very stressed within their peer groups; there is constant bickering, friends come and go and girls seem to backstab each other a lot more than boys. They scratch each other's eyes out. There is within this situation some degree of bullying, certainly hassle and aggro, which I would imagine would be normal for all adolescents. If, on top of that, you have other stressor factors, then the pressures become very great. The sorts of situations that I have seen on top of this, are those where the sufferers are perfectionists; they want to do their homework properly, they want to study hard at school, they want to get it right and they want to get it 100%. Such things as essays tend to be longer than I think would be necessary and some children just cannot seem to get themselves to cross a word out if they have spelt it wrongly and so they do the page again (this is where a computer with spell check might have come in more handy).

Academic pressure can come from all sorts of directions. There is the very academic school where high expectations are not covert but openly advertised. 'Thou shalt do well! ' Thou shalt get A\*s', not necessarily for you but certainly for the school. I remember one boy who had got C.F.S. and I reduced his curriculum down to six subjects. He was at

a local grammar school and he got six As, which I thought was absolutely excellent. However, he was publicly told off by one of the masters because they considered him to be an A\* student and he should have got A\*s. I have seen children who have pressurised themselves, and children who have been pressurised openly by their parents, to do well at the 11+ or Common Entrance and to work extremely hard in order to get through the exams.

Then, of course, if they are not naturally bright enough to pass these exams comfortably they have to work so hard to achieve passes, they are going to struggle at the grammar or other secondary school. I have seen children who were intellectually not very bright and they were struggling in a secondary school without having their problem detected.

Then of course there are other severe stressor factors when children are being bullied at school or at home, or are physically, mentally or sexually abused. All of these stressor factors make kids ill.

Adults of course have many of the same sorts of problems as children but in addition there are problems at work. People are made redundant, bullying at work is very common or the patient is in a long term job that he really doesn't like. There are also the stressor factors within unhappy relationships. There are as many stressor factors as there are patients suffering from C.F.S.

In many cases with that powerful tool the 'retrospectoscope' you can see C.F.S. coming. Patients will often tell you that prior to the actual acute viral precipitating illness process they were feeling run down, physically and emotionally, they got more tired than usual, they were

not sleeping as well as they used to and that they had started to feel unrefreshed by sleep. They, of course, appreciate that they are returning every day to the same negative pressures and it is like banging your head against a wall; you are bound to get a headache. However, what people do not realise is that by continuing to expose yourself to these horrible pressures, not only do you suffer the symptoms of long term exposure such as headache, sleep disturbance and not feeling well, but one day you are going to make yourself seriously unwell with C.F.S. It is very common for me to find with patients that there is a well-established pre-morbid pattern of increasing ill health, and then one day they go down with this virus, which is the trigger.

Of course there may not be a viral precipitation and that is the situation that you find in the slow onset M.E. and in Fibrositis Fibromyalgia Syndrome. Here there is also a long standing history of the same sort of pressures where they are outstandingly present for much longer periods of time, and during the majority of which the patient copes with them. In such cases personality traits seem to be very distinctive. People with these types of illness are often worriers as well and they have a lifetime of anxiety, often inherited or acquired from one or other or both parents. They also tend to be more obsessive, they like their work done precisely, they are very picky and very precise. They control the situation, trying to hang on to the problems that develop as a result, and I am sure then the increasing stress starts to produce the same abnormal immunological processes as are seen in the acute variety of C.F.S.. However, the stress tends, if anything, to cause more in the way of muscle pain and I believe that this is the result of chronic increased muscular tension (especially in the back of the neck), pressures in the back of the head with headaches and joint pains. Irritable Bowel Syn-

drome also is very common and is a stress-related condition in its own right.

There are other things that are known to cause C.F.S. Again, I think that in the vast majority of cases these trigger factors are also associated with people under pressure and negative stress. I am going to list Predisposing Factors from the C.F.S./M.E. Working Groups Report of January 2002 . In my experience I have not seen some of the trigger factors that they mention, but I will comment on those that I have seen a lot and put them into my context.

Under their section 3.3.1 – Predisposing Factors:

**1. Gender**

I agree that the incidence in females exceeds that in males of any age group. In my experience it is much more common in women than in men with a ratio of 3:1, and that would be counting all of the patients that I have seen over the last fifteen years.

**2. Familial**

I have already said that if there are two people, or more, within the same family with this illness then there is a family dysfunction of one kind or another. I understand that twin studies have suggested a hereditary component but I do not agree with that; I think their family environmental factors are the illness precipitators.

### **3. Personality**

I don't think I have got anything to add other than to say what my own personal feelings are. The Working Group says that there is evidence both for and against the possibility of certain personality traits predisposing to this illness, and I am sure that, generally speaking, the people that suffer from this illness process are people who like to be precise, high achieving and are worriers and self pressurising. (I have commented further with my own views on personality traits in ME/CFS further on in this article.)

### **4. Other Disorders**

I agree with the Working Group's feelings that past and current history of other disorders are particularly common factors as I have mentioned above, particularly that of a long standing history of irritable bowel syndrome prior to the onset of their acute onset of C.F.S. or the slow onset of Fibromyalgia Syndrome. To this I would add that patients, prior to them becoming ill, find themselves quite frequently subject to much more in the way of viral type infections, colds, being generally run down and sleep disturbance.

### **5. Previous Mood Disorder**

Again I would agree that most, if not all studies, have found a history of mood disorder prior to the onset of this illness. Anxiety, worry, low mood are particularly common especially in those with a history of depression in the past, again reflecting almost certainly long standing negative stressor factors in depression as well.

In Section 3.3.2 I agree with everything except references to environmental toxins. I am not suggesting for a moment that environmental toxins do not precipitate this illness as a trigger, but it is just the fact that in over twenty years I am not sure that I have seen more than one case, so from my point of view it is extremely rare.

The commonest trigger in C.F.S. is that of a history of some kind of process that suggests a virus type infection. The commonest from my point of view would be that of a non-specific flu-like illness where the virus itself is never tracked down, but as you will see I argue elsewhere that there is in fact no virus at the onset. In many cases it is abnormal initial immunological response, but it is quite clear that a glandular fever type illness is quite often the trigger factor and that Epstein-Barr Virology, specific and non-specific, can be seen to be present at the onset. But again as you will see elsewhere I argue that this is reactivation, and if there is an Epstein-Barr virus and initiator and trigger, that this again is stress related. So, other than non-specific flu-like illnesses and glandular fever, I have come across a great number of different suggested viral triggers including viral meningitis, encephalitis, hepatitis, herpes, enteroviruses, chicken pox and shingles. At the bottom of the infections trigger paragraph they are suggesting now that “available evidence suggests that abnormal persistence of infectious agents does not occur in C.F.S./M.E.”. Whilst in 1985 through to 1990 I would have said that infections are persistent and are a persistent cause, as you will see I have changed my view and entirely agree that there is no evidence that a persistent virus infection is present, and if it is, then it is not pathogenic.

## Immunisations

I have found a few people who have been made ill by immunisations. It is not a huge number, and I would never go as far as to tell people that they shouldn't have immunisations, just in case. However I suppose it may be sensible in the future to consider whether those doctors and nurses who are giving immunisations ought to raise the question as to whether there are any significant stressor factors going on within this persons life before they give vaccinations. I just don't know quite how practical that would be.

I have however seen a few, (probably about twenty in ten years), whose illness of C.F.S. was getting better until they have some kind of vaccination during their illness process. They may have had an influenza vaccine to prevent them from getting another attack of flu, they may have had a tetanus or a typhoid vaccine and in one or two cases a B.C.G. In this situation I have seen people really seriously set back, and in a few cases so severely that I have not been able to get them better. I can think of half a dozen such cases. I have, in the last six months, gone so far as to advise patients not to have any kind of immunisation when they are ill with C.F.S. unless it is absolutely essential. With the exception of a tetanus vaccine I don't know that any immunisation is absolutely essential. However, if somebody really becomes a tetanus risk then they could have a passive vaccination of the tetanus antibody as this should not upset them. As I am sure you know the commonest vaccination for tetanus is to give a tetanus toxoid which is an injection that stimulates your own immune system to make an antibody. This is called an active immunisation whereas the tetanus antibody is a passive one.

It works very quickly and would be perfectly reasonable when a patient is a very serious tetanus risk.

## **Life Events**

Here I entirely agree, and as I have mentioned already, major life events (especially those that are negative) are predisposing factors particularly if those life events are sustained. I haven't come across anybody who has been made ill simply by the obvious devastating death of a relative, even a close relative. However I have seen several people, especially children, who become extremely anxious and distressed when several members of their family suddenly depart, or indeed where they have a major life crisis such as the diagnosis of cancer or a heart attack, which then is life threatening. Of course the members of the family become very worried and anxious and they would be the ones that become ill with a C.F.S., not necessarily the person who has had the heart attack. Again, however, you will find that the people who get anxious and worry about their family member's illness will be those who worry most in general. Those people who suffer extensively from these major life event situations will often have a long standing history of anxiety of being a worrier, concerned about other people more than their own health.

## **Physical Injuries**

I personally probably haven't seen more than one or two people who have been made ill by a specific physical injury but I have seen quite a number of people who were made ill after an operation of some kind.

Again, the predisposing negative pressures apply and the anaesthetic and/or the trauma of the operation itself, or of any major post-operative infection, will be the trigger.

### **Generalised Infection**

Whilst there is no “Specific Trigger” paragraph in the Working Group’s report, I would have included a specific paragraph. I have seen a great number of people who have been made ill by specific bacterial infections such as amoebic dysentery, gastroenteritis with salmonella, and those with acute chest infections. But again, there is usually a previous history of a minor cold going on to become bronchitis and pneumonia.

### **Environmental Toxins**

As I have already indicated the Working Group have included a section specifically for this, although they suggest it is ‘not a common or widespread trigger’. I would say that I have only ever seen one case (out of around three thousand patients) with this condition. I would say that qualifies it as “rare”.

### **Others**

The Working Group has not included a section on specific end organ infections. By this I mean a specific diagnosis of a virus infection causing something that is not just simply a flu-like general infection, but a specific infection of an organ, (what is generally termed an ‘...itis’). These sorts of infections are not very common in triggering

C.F.S. because on the whole they are not stress related. They would include something like a virus attacking the thyroid gland, which would be called a thyroiditis. A virus attacking other organs such as hepatitis, viral meningitis, viral encephalitis and pancreatitis are much less common triggering factors, although I accept that they certainly occur. Some of these would not be associated with negative pre-morbid stress.

You will now note, also, that I have not included any of the well-publicised epidemic forms of this illness process. There are many medical reports of a worldwide nature where viral epidemics of various types of viruses have infected hundreds, thousands and indeed even tens of thousands of people within a specific area and population leaving a certain number with an M.E. type syndrome. This most historically is seen in a booklet termed 'The Saga of The Royal Free Disease' by Dr Melvin Ramsey. I really don't wish to comment on this illness process as I have not seen it or observed it and would take counsel from the various authors and historians of this illness. But let me say that if this illness process is looked at it has got nothing to do with the epidemiology of the sporadic case which is what I am talking about.

This then covers all of the pre-disposing factors and triggers. The Working Group goes on then to discuss the maintaining factors, and I agree with all of those, but I will go into that elsewhere. What I would like to return to now is the dynamics of stressor factors on our immune response.

As a philosophy we are, of course, people that come from and are created by our brains. Our consciousness, intellect, human features and personality lie, we believe, mainly within our cortex. The deeper and

the older parts of the brain are shared in common with most other mammals (and a lot of other living creatures who have central nervous systems) and they work in remarkably similar functioning ways.

Our bodies are effectively designed to feed our brain with food and oxygen, look after it, protect it, propel it around and reproduce it. Our bodies are not part of our personality. Whilst it is, of course, upsetting if somebody chops your leg off, it is not likely to alter you as a person, unless of course it affects your ability to cope. The same cannot, however, be said to be true of the endocrine and the immune systems. Endocrine glands secrete hormones and chemicals directly into the blood stream mainly under the control of nerve outputs and inputs from the brain, and this is particularly so in the case of your immune system. In this situation I am really concentrating on your lymphocyte response.

As I am sure you will know, your lymphocytes reside mainly in the lymph glands (of which there are hundreds), and they lie in all sorts of parts of the body. Your lymph glands are connected to your autonomic nervous system by nerves, and the relationship between your central nervous system, your endocrine system and your immune system is extremely complicated. We know a great deal about the way in which the immune response is altered by varying external stressor factors upon the brain. Many years ago the immune system was thought to be autonomous, but now we can see that the immune response involves the development of chemicals that enable the various white cells to communicate with each other. The way in which these chemicals respond and talk to the brain, and the way in which they feed back, shows that the immune system, whilst having a degree of autonomy, is mainly controlled and facilitated by the central nervous system. This control

from brain, endocrine and immune response is thus seen to be bidirectional.

Stressor factors on the brain can be extremely varied; they can be very negative, they can be very positive or they can be neutral. Their effect depends upon the patient's ability to cope with them and, therefore, upon their personality type, their moral and mental strengths or their weaknesses. Thus, there is a direct link genetically to the parental type and to the environment in which you were born, bred and nurtured. What worries you doesn't necessarily worry me, and some people become extremely anxious and worry about silly little things, at least as far as others might view them. We cope with major life events in different ways. The death of a loved one can send some people into free-fall for years never able to manage again. Others ignore it; they bury it somewhere deep in their psyche where it can remain festering for an equal length of time. There are those responses that are considered to be 'healthy' where we do the right amount of grieving and crying and talking. Most of us are able to work through these things in a period of time which medicine would consider to be 'acceptably normal'. Other major life events; marriage, divorce, house burning down, redundancy and retirement are all dealt with in similar fashions, but these events tend to be fairly acute. The event itself is probably short-lived but the response and the reaction to it can vary considerably.

Longer stressor events produce differing responses as well. Being abused physically, mentally, emotionally, sexually over a great number of years can produce major psychological changes in people. These psychological changes can be permanent and very difficult to treat. Very severe trauma can also produce long lasting effects - post-traumatic stress disorder is an example.

Less obvious long term stressors are seen in people who are extremely fastidious, obsessional, pernickety, perfectionists, want everything done right all of the time, want it to be done exactly and properly, with an ethic that is inherited very frequently from the parents. When children want to do very well at school, have to be top of the class, look for extra homework and extra-curricular activities, it can be something that is purely self-inflicted, but is often seen as the result of parental expectation and influence. People who are worriers usually come from worrying families and I find it especially so in young women who inherit the problem from their mothers and grandmothers.

As you can see most of these stressors have a negative impact, they are not good for you in the long run and all of these types of negative stressor factors are seen in the development of chronic fatigue syndrome.

### **The "Stress in Animals" comparison**

The study of the reaction that stress has upon animals seems to me as being almost unjustifiable, and then to translate the results to human beings is unreliable anyway. I, personally, must admit to the fact that I hate animal experiments but they have been done and it is difficult to ignore the results. I am reminded of the Home Office's reaction to terrorist information being obtained under torture. It doesn't come as much surprise to anybody, I would imagine, that the information obtained by torture is unreliable information and that tortured prisoners will say anything. There are those who don't want to interpret the informa-

tion and include it in justification of war, and there are those who feel that it should be ignored. Such information, therefore, should always be covered by a caveat. I am also reminded of some highly reputable scientific researchers who say that a stag standing at bay just about to be ripped to death by a pack of hounds is not stressed. I wonder what is going on in the stag's immune system at that moment. I presume even more macabre experiments could be designed on those in America on death row. I wonder if their immune systems have been studied close up to the point of the lethal injection.

There is no doubt that the information available in the early days of study of stressor effects upon immune response shows some quite conflicting results. Many years ago a study of monkeys in avoidance stress, (i.e. a stressed response by trying to avoid some horrible stimulus like an electric shock or trying to avoid another unpleasant physical punishment), showed that more of the unstressed monkeys died after being inoculated with polio virus than those that were stressed. The stress response here, apparently, enhances the anti-viral reaction and the immune responses are tighter. The reverse is also true of those that were given relaxing medications. They showed that their immune responses were less good than the monkeys that received no medication.

In the early eighties there were a whole series of studies to try and link the anatomical connection of the central nervous system and the immune system and also physiological connections between the two termed neuroimmunomodulation and immunoregulation and the response of immunoregulation. In other words, the immune response varies enormously with the types of stress that could be applied. As I

have already said, I think that it is totally cruel that animals should be subjected to what are, effectively, forms of torture for experimentation purposes. Sleep deprivation, food deprivation, total isolation, overcrowding and the overcrowding phenomena are still being studied.

I remember seeing a television programme some years ago where some rats were placed either end of a room divided by a glass screen, low enough for them to be able to jump over. If they jumped over they could breed. When the population was sufficiently increased the screen was removed and the demand for space became more intense and the rats became more aggressive. Then the food was removed so that they were then not only fighting and killing each other for space but, also, for food and water. During this overall process their immune responses were being monitored and found to be tighter and tighter and, therefore, more responsive – particularly when fighting for space. The time taken to respond to an inoculation or a viral infection was reduced. In other words their immune systems became more and more efficient but then, when the population density became so high that the killing rate between them was extensive, the immune system then collapsed very quickly.

So there seems to be a relationship between peak performance and then getting to a point whereby nobody can survive. It can also be seen in these situations that psychological influences become apparent. The rats were being very stressed, getting stress related symptoms, palpitation, rapid heart rate, increased sweating and then afterwards they were becoming depressed. They were just sitting in the corner waiting for the inevitable which then transpired with increased infections, pneumonia, death, murder and mayhem. Again rather macabre thoughts go through

my head that maybe we should be looking at the immune response of the Americans in Fallujah and the insurgent Iraqis. I wonder what that would tell us.

As you can see, all of these immune responses, maybe with the exception of the rat population studies, are observed on acute stressor factors over a relatively short period of time. You will see, elsewhere, that my suggestion is quite clear; that the stressful factors that lead to chronic fatigue syndrome, as the most significant pre-morbid factors in the development of this disease, depend upon patients being exposed to negative stressor factors over much longer periods of time. This will usually be a minimum of a year and maybe sometimes a lifetime. It is also true that the stressor factors that cause chronic fatigue syndrome are seen to be those that are more unavoidable, from the patients' point of view, i.e. they will say that they "Can't do anything about it", "But this is the way it is", "My life has always been like this". Their personality also plays an enormous part, so the study of sleep deprivation, food shortage, starvation or cold exposure in animals over a short period of time doesn't seem to me to be relevant to chronic fatigue syndrome.

To show the differences between acute stressor factors and longer ones and to the degree of stress we must return to the rats. It has been seen that rats exposed to high levels of electric shock produce lower immune responses than those exposed to lower shock levels and that the shock response on the immune system depends upon where the shock is applied to the body of the poor unfortunate rat. It is also clear that immune responses are much more suppressed when the animal is in a situation from which he cannot escape. In avoidance stress the animal is stressed by applying an electric shock and making it jump away but if you strap it down and keep shocking it you get a different immune re-

sponse. However it is also clear that you get a diminishing immunological response right across the board when you expose an animal to very long periods of stress; months as opposed to hours and days. In some cases, depending upon the animal and the shock applied, one can find that chronic stress restrained stimulation for a couple of weeks, can actually find an ability of the immune system to be more efficient and killer cell activity can be improved. However, these responses also have been found to be non-reproducible depending upon the different strain of animal and the different type of animal used.

I think I am trying to suggest that there are quite obvious changes to the immune response when animals are exposed to stress. These responses tend, if anything, to be less efficient on the whole and therefore, generally speaking, animals under stress, especially over longer periods of time, tend to be less efficient at repelling virus or bacterial infection and or inoculations. Also, the immune system doesn't make as good a response to the inoculation as it would otherwise. In fact, the responses are variable and sometimes contradictory, which I think now leads me nicely onto my reasoning to implicate chronic stress as the cause of chronic fatigue syndrome.

Once again may I apologise for the inclusion of this animal data – not nice.

### **Personality Traits in CFS/ME**

I have not done any formal studying of the personalities and personality profiles of those patients that I have seen but I have been looking at

CFS for over twenty five years and, 99.9% of the time, CFS is precipitated by a significant long-standing, overwhelming set of negative stressor factors. There is very rarely just one significant event but usually a sequence of events, over a significant period of time, and the personality of the patients that I see contributes significantly to the development of their illness process. Firstly I do not consider that there is any particular personality type that develops this illness and, certainly, they are not particularly Type A or Type B, but both. There is no doubt that there is a significant relationship between the development of CFS and a previous history of a neurotic illness process such as previous anxiety states, periods and episodes of depression, or a tendency for patients to be neurotic in the medical sense. The great majority of patients that I see are worriers and they often tell me that they are worriers about anything and everything. They tend, also, to be slightly obsessional in their approach to life; they like things done precisely, they are pernickety and they give 110% commitment; things have to be finished, neat and tidy.

The association of anxiety is probably best seen in children. They are nearly always worriers, they worry about what other people think about them and their work, they worry about the health of their family especially if one member of the family, a parent or grandma and granddad, has been significantly ill with a life threatening illness.

Internalised anxieties are very common in adolescents by the stresses of growing hormones, peer pressures at school, bullying, having to be in packs and groups. Exclusion from those is normal but can and do cause enormous anxiety. Children also are found to be worriers about their academic capabilities. Sometimes the external pressures are put upon them by parents' expectations, either spoken or unsaid, or by go-

ing to a pressurising academic school. Pressures put upon students who are expected to do well at school are also commonly seen. Then of course young children may put enormous pressures on themselves by wanting to do well, studying harder than their peers, doing more homework than is necessary, and wanting to be top of the class. Indeed if they do get to the top of the class and become a 'boff' there are then enormous pressures to stay there as the only way is down. Also, in today's young culture it is not considered "cool" to be a "boff" or a "swat", which brings separate pressures.

In adults it is well established that CFS/ME is more often seen in women. My ratio is 66% women and 34% men. Women also are born worriers. This tends to be on the whole a lifelong thing and they get it from their mothers who, in turn, get it from their mothers. I am sure it is not only genetic but acquired. After all we are born of our parents and then we live in our parents' house and our personalities are pretty much fixed by the time we are eight years old, and you can't change after that. You can be made more aware of the way things are, but I feel that as one gets older one becomes less capable of coping with stressor factors. I think that the age group of peak incidence of CFS is thirty to forty years old. I believe the reasons for this are that these are the times of the greatest pressures; financial, - mortgages, - relationships, - adolescent children, - peak performance at work, - top of the ladder, - top of the tree, - top dog being bitten from below!

There are certain occupations where stress is normally higher than others. Financial jobs in the City seem to be very common as stressful occupations in men, but increasingly so in women also. Nursing professionals and teachers also seem to feature highly, and the commonest

one after that is Mrs housewife/superstar who may also have a career of her own. I think that because men go to work and can get themselves out of the house they escape the everyday mundane problems, but mum stays at home coping with these adolescent kids. Sadly, it is not uncommon, these days, for this to be as a single parent. Financial stresses can, also, become considerable.

As previously stated, a significant history of being a worrier since childhood and, also possible difficult relationships within the family, can compound the anxiety. I also note quite often that there is a long-standing history of disturbed sleep pattern. Patients often tell me that they have had difficulty in getting off to sleep at night for a great many years and that this is worse when they have CFS/ME. It is observed, almost invariably, that sleep is not refreshing or rewarding in CFS, but I do note also that patients in the lead up to the development of their disorder process, have had occasional patches of un-refreshing sleep.

Then of course there are the significant histories of 'events'. On top of the stresses and strains of everyday life they come along rather like buses (not just one or two but three at a time). Typically these are the major life events such as death, divorce, redundancy, leaving home, going into a disastrous marriage, break-up of partnerships, significant long-term illness of siblings and relations.

To a certain extent you can see that most of the above occurs with all of us, living in our part of the world where these sorts of stresses and strains are normal. So I think there is also a great deal of truth in, 'There but for the grace of God go I', and that CFS/ME is something that we all probably get quite close to quite frequently.

As we get older and the children leave home and go away, relationships usually become more stabilised. The pressures at work start to diminish and as one goes over the hill, past middle-age, the onset of CFS is less frequent, and by the time that we all getting to our dotage CFS/ME is rare.

### **Personality and Immunological Response**

Everybody knows the Type A personality and Type B personality; the former, on the whole being 'Get up, let's go, haven't got time to be ill, stoical, somewhat aggressive maybe, independent, self-assured, self-opinionated and capable'. Type B personality is introspective, soft, gentle, tending not to push themselves forward, and probably more caring. Along with this one also finds other personality traits that are associated with the two different groups. In the Type A personality one would see more people with anxiety, with worry, things have to be done right, perfectionism, obsessional traits. In the Type B again one might find worry, but about others, about what people think of them, quiet, withdrawn, high symptom reporters, maybe a little tendency to neuroticism of a depressive type rather than anxiety. These of course are generalised statements and everybody is different, individual, but I do see that increased pressures and neuroticism are associated with fatigue syndromes – always.

Type A personality, whilst being very good for 'I haven't got time to be ill', is not a terribly good at 'coping' behaviour, certainly for recovery from virus infections. The severity of symptoms is greater in Type A

personality and so is the tendency to seek medical advice and reassurance. They seek medical advice much earlier. There is, of course, an increased incidence of high blood pressure and heart disease. A number of patients may be underweight rather than overweight, but certainly there is an increase in alcohol consumption and a lot of neurotic symptoms as a scenario.

Type B personalities, with a less stressed background and being less anxious, probably have a better coping strategy. Children at school with a less worrying approach to their exams and less obsessiveness tend to find an increase in the rate at which their blood has a positive response to vaccination. BCG vaccinations work better in a Type B personality. Response to all vaccines tends to be quicker in people who are a little bit more laid back. However, paradoxically, a study done many years ago in General Motors predicting the outcome to an infection saw a particular Psychologist interviewing the entire workforce and he suggested those that had a Type B personality would not respond to a virus infection so well and be off work longer. That in fact was the case, when there was an outbreak of flu, and those of a Type A personality tended to get back to work earlier. They had less symptom reporting, but reported their illness earlier and it was interesting to see that, with the complication of a virus infection in the liver, patients that had a pre-morbid history of depression tended to have abnormal liver enzymes for longer. There is, therefore, no doubt that ones personality has an actual effect upon the ability to recover.

There are some indications that patients who are stoical and have a Type A personality recover from surgery more quickly; their pain is less and also of shorter duration but they tend to take more tablets. Stoicism

is very good for those who have various types of cancer. The types of people, including those in denial, who are able to turn round and ignore the fact that they have had a serious cancer threat, tend to live longer. Those who adopt the attitude that they are simply not going to die have better quality outcome and do in fact live longer. There was a very big study done on breast cancer outcome with these stoical approaches and there is no doubt it works in all studies. Equally, and in contrast, those that have a more resigned approach, an acceptance of the problem, an anxious pre-disposition and depression lived less long. These psychological approaches to illness are much better predictors of long term outcome than is the size of the tumour or its aggressiveness at the early stages or time of surgery. There have also been studies to show that it is not only the patient's personality that has an important effect on their recovery rate; it is also influenced, quite remarkably, by the support of their immediate family. In fact, really good family support helps aid recovery with almost every illness process.

### **Specifics of Human Immunological Responses in the Development of CFS/ME**

As I have already indicated, at some length, in various parts of this website, almost without exception, the reason why we get CFS/ME is because of a substantive set of long standing negative stressor factors. I now strongly believe that viruses are just one of the triggers to developing CFS/ME and not the actual cause.

Up until the late eighties I was working with others demonstrating the persistence of enterovirus infection in a large subset of CFS and, in an-

other substantive subset, the relationship of this illness process with glandular fever virus (EBV). Looking back now, it is clear in my mind that persistent enterovirus infection in a great number of people, especially young children, is a normal event and in these situations they are asymptomatic. This is best seen in studying the serology and stool culture for virus in patients vaccinated against polio virus, but looking back it was clear that we were demonstrating persistent enterovirus in patients with CFS/ME. You could recover the virus from the gut, we could demonstrate enterovirus particles in the blood and in the muscle, but we could also demonstrate the fact that these patients made a normal and proper serological conversion to a long term neutralising antibody IGG. There was not the demonstration of non-conversion or a persistent short-term antibody (IGM) so, whilst the virus could be found to be persistent over a period of time, (indeed several years) the blood had shown that the patient had recovered from this infection. However, in these situations the patient did have a chronic enterovirus infection and had also demonstrated that they had CFS/ME. We tied these two things together, as cause and effect, but the problem was further complicated by the fact that, whilst there was the demonstration of a neutralising antibody IGG, the patients still had a switched on immune system and, apparently, were continuing to fight a virus. So we added all of these things together and identified CFS/ME; caused and perpetuated by a persistent enterovirus infection – **WRONG**.

We will now turn back to the immunological studies done all over the world in patients with CFS/ME. Whilst they may be called different things in different parts of the world I am sure that these illness processes are all the same, if not extremely similar, and that we are not looking at a different disease in England as opposed to Japan or Amer-

ica. There have been at least one hundred studies done on the immune responses, of which responses there are hundreds of thousands capable of being studied. All these studies agree that the immune system in adult human beings appears to be turned on in a non-specific way and that the non-specific response appears to be directed towards the immune system fighting a virus, whether there is a detectable virus or not. Also looking over the literature, it is clear that a great number of different viruses have been implicated in causing CFS/ME. As I have already said some of these are the enteroviruses and EBV. Others include the herpes viruses shingles and chicken pox, other herpes viruses and viruses that are still not known to be associated with particular disease processes, like the human herpes virus six (which is a virus still looking for a disease). There are those that believe that CFS/ME is caused by a yet undetected virus, i.e. a specific virus that causes ME so it must be the ME virus and, I am certain that these approaches are wrong.

I have mentioned elsewhere that, when you are attacked by a virus, what actually makes you actually ill with the headache, aches and pains, fever, malaise and the general symptoms of 'flu' is not the virus itself, but your immunological response to it. In other words, it is your initial antiviral non-specific response of compliment fixation and the production of interferon which then circulates through the body producing a non-specific antiviral defence. At the same time, however, it makes you ill!

In order to recover from this virus infection, to turn your compliment fixation off and to then restore and normalise immunological equilibrium (i.e. that is not turned on and fighting a virus) you have to have had a

virus. A virus has to be identified as having penetrated a cell by leaving a mark on the cell where it penetrated. Then your immune system needs to take that antiviral marker and respond by producing an antibody to that so that the antibody can turn your immune system off and let it all go back to normal. Then you recover over a period of a few days, maybe a week or a fortnight. If you don't have an antiviral antibody your immune system can stay turned on. In what situation this can occur is a matter of conjecture, however, but after careful thought, my model is as follows:-

I place you under a long standing negative stress for which it appears, there is no obvious remedy that you can think of. You are a woman married to a man who abuses you, you have got no money and no means of obvious escape other than to quit and run away to a refuge. Even this may not seem to be a good option. If you are under this intolerable pressure for a number of months, or longer, your immune system starts to fight a virus that is not there. Your cortex, i.e. your personality, stimulates your lymphocytes in your lymph glands and they start to produce a reactive change. Your natural killer cells go up, your CD48 helper cells go down, your suppressor cells alter, creating a non-specific antiviral response. This response will vary from day to day, week to week. The response becomes stronger the more stress you are under and recedes if the stress is either momentarily, or for a longer period of time, diminished. It may be that, at this point, the abuse at home is so strong, and thereby, the immune response is so activated that your immune system then starts to fight a virus in a full blown fashion. There is no virus, there is no specific trigger - just the stress, and you go down with an immune response that gives you 'flu'; an interferon re-

sponse. You get glands swelling in the neck, a very sore throat, headache, malaise, temperature, aches and pains, fatigue, intellectual concentration difficulties and you take to your bed with what, you assume, and what everybody else would also assume, is a virus type flu.

However, if there is no virus then you can't turn that off. Your stress may or may not be temporarily relieved and your symptoms then might get a little bit better. Maybe the abuse is less because you spend two or three weeks in bed and you can't respond to your spouses unreasonable demands. So you get a little better, you go back into the abusive situation and the stress increases. Your immune system responds by stressing itself further and you experience another 'flu'-like reaction one, two, three weeks or several months later. In the meantime you continue to complain of CFS/ME type symptoms and you don't get better.

Now your immune system is sensitised and turns on with a much lesser negative stress input. Now let us say that your spouse leaves you because you are ill. You are left with a couple of kids to support on your own. The immediate stressor factor of an abusive partner disappears but now, of course, the stress is 'How do you survive?'- you are ill. You bumble along with or without family support, with the symptoms and an illness process called CFS/ME. In this scenario there was no virus, so you can't turn your immune system off without some further advice and help.

We know that if you do too much, either mentally or physically or get too much stress, your immune system then turns back on again, you

get the acute and chronic symptoms sore throat, glandular discomfort, aches and pains and general flu-like symptoms. When they go away after your stress has lessened or when you don't further provoke your symptoms by the 'doing too much on a good day', scenario, your symptoms continue to flare up or diminish, depending upon how you manage your life. Hence, the development of my modified activity programme, for both mental and physical activity, which is discussed elsewhere, (**Recovery - How to Get Well PDF** ) and from which you can see that, in order to recover, you have got to do several things.

**The first** is that you must remove the stressor factor or factors, because it is quite clearly impossible to get better if you are still allowing your immune system to, metaphorically, continue to bang its head against a wall.

**The second** is that you must not do too much to stimulate your immune response thereby making it worse.

**Thirdly**, you mustn't do too little, because that perpetuates permanent ill health anyway.

**Fourthly**, we have got to turn your immune system off, permanently, and that is where antidepressants come in.

It is a little known fact that all antidepressants are immunoregulatory, i.e. they have an effect of normalising immunological responses. They turn off non-specific antiviral responses and, hence, their use in CFS/ME is axiomatic (you can't get better without using them in my opinion). The best of the antidepressants for this purpose is Amitriptyline

and its effect can be achieved by the use of small doses. I am talking in terms of 10mg, 25mg or 50mg. These are levels of antidepressants that are insufficient to achieve an antidepressant effect. They are sub-therapeutic levels, as far as depression is concerned, but they are certainly far from being sub-therapeutic when you are trying to regulate the delicate nuances of immunoregulation. All antidepressants have this effect but it is especially marked in the older type of tricyclics and, indeed, the SSRI, Fluoxetine Hydrochloride.

If you look at the cases of patients and their stress history very closely, as I have done over a great number of years, you will find that it is often the person's personality that leads to their stress. They are the fastidious, picky, obsessive, high pressure, Type A personalities, as I have mentioned above. You will find that if they are going to develop CFS/ME, they tend to have a history of being more prone, than most, to getting virus infections. In fact, they tend to get 'everything that is going about', they are always getting colds in the winter and recovering 'when the flu has gone away.' In these situations they seem to think they are getting all of these viruses which, indeed, they may be, but then, in between times when they would normally have recovered, they tend to find that the recovery takes longer. Instead of being one or two weeks after a sore throat or flu in the winter it is one or two months, and they find that their sleep pattern becomes disturbed; with mild insomnia, difficulty getting off to sleep and waking unrefreshed, they are more tired in the day - maybe a little low and irritable.

This tends to go on for months before they become more unwell. They just don't see CFS/ME coming down the track to hit them right between the eyes. At this point they are missing work, the boss is on their back,

the housework is not getting done, the children aren't being taken to school, social life disappears, the sick school-age child is missing school work so the pressure, if anything, increases in a secondary direction. We now have a self-fulfilling prophecy. The pressure increases; your immune system does not need another virus, but manages to turn itself on all by itself and you go down with this 'flu' that isn't caused by a virus and which leaves you with varying degrees of morbidity which is this chronic, horrible illness.

With the scenario I have given above, leading to a CFS/ME outcome, there is no doubt that there is a cure. It can and does get better and whilst I can get most people better using modified activity programmes and antidepressants, the one situation I can't get them better from is being themselves; in other words, the fastidious, anxious personality.

Secondly I can't get them better at handling stress in a normal way. They are always going to be vulnerable to stress. If we get them better and they go back to being the way they used to be, once more allowing external pressures to return, then people have the capability of going down with their illness process again. Their immune system is always vulnerable to stress and is likely to turn itself on and react by producing another episode of CFS/ME.

If, on the other hand, you can make sure that this illness teaches the person the lessons that it has to teach them, and that the patient learns the lessons that they have to learn i.e. that by avoiding these stressor factors to a greater or lesser extent for ever-more, then of course, patients can make an almost full recovery. However, they are never quite the same because of their experience of the illness.

# **MANAGEMENT IN ADULTS**

## **DEVELOPMENT OF MODIFIED ACTIVITY PROGRAMME** **FOR BOTH PHYSICAL AND MENTAL ACTIVITY**

In the course of treating the majority of illness processes in human beings, doctors encourage patients to do as much as they can, to struggle against their infirmity, to progress; don't sit around doing nothing because that makes your problem worse. If you have CFS, doing the latter encourages depression, sloth, loss of confidence and self esteem. The advice given to the majority of patients with CFS is to do as much as possible both physically and mentally and there is no doubt that the vast majority of patients with this condition do exactly that; they tend to try and do as much as they can. This is the rationale behind CBT and GET.

On a bad day they have to rest more because of the fatigue and increased number of symptoms and whilst resting, both physically and mentally, the symptoms begin to settle and they wake the following day feeling, perhaps, a little better. On a good day patients, I suppose quite naturally, tend to try and do as much as they can and play "catch-up". Inevitably in doing so they overdo it and this makes them suffer the next day or two days or three days or maybe even a week. Patients work this out for themselves pragmatically. They will tell me they can't simply sit around doing nothing so they go out for a party, or they go to a family dinner, spend too long there, do too much and suffer for one, three, seven maybe ten days for doing so. They have these bad days, good days, bad weeks, good weeks and bad months and good months as a result. Their illness process tends to fluctuate and "yo-yos".

They can usually identify what it is that they do too much of and makes

them suffer, especially when they look at the physical aspect of it. If they walk too far they know the following day their muscles are likely to ache, their knees are going to ache, their joints ache and their fatigue increases. They also know that when they read for too long their concentration is poor. To some extent, therefore, what I am about to enlighten you with is already fairly obvious. What is not quite so obvious is the fact that if you do this boom and bust approach you actually perpetuate the illness process itself; you make it longer and stop yourself getting better..

It is very important to realise that by doing too much one makes oneself more unwell, but what one may not realise is that every time you do too much today (for which you suffer tomorrow), you also put extra days on the end of the illness; you actually perpetuate the problem. If you have been ill for a year and "do" a little bit too much, so that you suffer tomorrow, then you also put an extra day on the end of your possible recovery time. If you have been ill for two years and you do too much today, you will suffer not only tomorrow but you also put two days on the end of your illness process and so the story continues to compile. If you have been ill for three years and overdo it you will put three times as long on the end; ten years and it is ten times as long on the end. Thus, if you do too much today and, consequently, suffer for a week and you have already been ill for five or six years, then you are going to put five or six weeks on the end of your illness and that suddenly becomes like chasing rainbows; you simply never get there. It becomes self evident, therefore, that the prognosis in patients who have been ill for four years tends to be extremely poor because they can't stick to a programme for as long as it is necessary to get better. They tend to accept the ups and downs of the illness.

Life also tends to get in the way, major family events happen, people get

married, people give birth, grandchildren arrive, etc, etc. It is very difficult to hang onto a modified activity programme indefinitely, but on the whole, treatment programmes, from my point of view, take somewhere between eighteen months and three years to get an optimal result.

You can get the majority of people a great deal better in three years or less, but sticking to the programme which is designed personally for you is the most important thing of all. Drugs don't work until you have got your programme right. You have stop making yourself worse before I can help you get better. An analogy would be that if you bang your head on the wall you will get a headache there is no point in taking an aspirin for the headache you have to learn to stop banging your head.

## **HOW DO YOU DEVELOP A MODIFIED ACTIVITY PROGRAMME?**

In essence a personal programme is to learn to understand exactly how much energy you have got in any one day and not to spend any more than that so that you do not suffer tomorrow for what you do today and you're not suffering today for what you did yesterday, bearing in mind that energy is a total concept for physical, mental and psychological energy. There is no test that is able to measure this "energy". It is measured by your own personal experience and only you know exactly how much you've got but I can tell you how to do that, how to measure it, and equally importantly how to spend it and no more.

Let us start with the physical side of things. When you were well, before all of this started, you had a normal sized battery, working at let us say at a

100 amps. This is the battery that you were born with and whilst everybody's battery is individual they all basically the same and they all work the same. If you went out and did some training you could make your battery more powerful, 110 or 120 amp. Each day you would use some or most of this energy or power and then you would go to bed, sleep well and wake up in the morning refreshed with your 110 or 120 amp battery fully recharged ready for another day. Now, because you have a Chronic Fatigue Syndrome your battery size has been reduced, let us say by 40% to 60 amps. Neither you nor I can actually measure this directly, so the best way of starting out with a programme is to assume that your battery is smaller than the 60 amps it actually is. Therefore, just to be on the safe side and not to overdo it we start work by assuming that it has a 50 amp output. So, to begin any programme I want you to do less than you can achieve.

I might say to you,

“How far do you think you can you walk?” and you might reply by saying that “On a good day I can walk XX metres.”

However, unfortunately, that is not the whole question. The question that I am asking is,

“How far can you walk every day; not on a good day, not on a bad day, but on an average sort of day? Furthermore, is this a distance that you can consistently walk every day; i.e. that is less than you can achieve and, therefore, would not make your symptoms and illness worse?”

I might ask you if you can walk a kilometre and you may say,

“No, not every day.”

“Could you walk 100 metres?” to which the answer may be,

“Yes.”

So the actual answer then lies somewhere between 100 metres and one kilometre. I want you to be absolutely sure that you can walk a certain distance before you say “Yes”.

“Could you walk 800 metres?” and the answer might be,

“Probably, yes.”

I don't want a '*probably*' to come into it. I would rather you walked 400 metres each day to which the answer is 'yes' as opposed to the '*probable*' 800 metres. Something inside you will tell you that you can almost certainly walk 400 m or something like that, (I appreciate that you cannot be absolutely certain).

So your modified activity programme for a physical walking point of view would be 400 metres every day. Having decided that it is 400 metres every day then that is what you walk. And you will walk 400m everyday come rain or shine. This would be perfection. You might not wish to do it every day and I am perfectly happy that you don't do it every day if you really don't want to, but you have to be capable of doing it every day. I will then ask the question as to whether you can do a quarter of an hour's washing-up every day or a quarter of an hour ironing, a quarter of an hour cooking, a quarter of an hour homework each day, can you play a little bit of football every day, (if you are a young adolescent male), can you phone somebody and talk to them each day, every day? So the answer is really to search for a programme which you can reproducibly do every day. It is not difficult to develop a programme for such physical 'pottering'. There are lots of things

that you can do. You can put into your program whatever you wish. You can put in a hobby, potter around the garden, do something nice in your physical pottering program and I suggest that each of them should be less than you can achieve and reproducible and can be done every day. As I've already said you don't have to do it every day but if you miss something out then you put something else into your program that would be equivalent in physical pottering energy, for example substitute an activity slot such as washing up for something that needs to be done on that day, such as washing and blow-drying your hair or sorting the recycling ready for collection. (This is outlined in more detail in **Recovery -How to Get Well** PDF).

If something makes you ill just doing it once, don't do it at all for the time being.

As this illness process is purely inside the central nervous system, i.e. within the brain, then, of course, it is very important to make sure that the amount of mental activity you use is also measured and it is with this aspect that the vast majority of people have the biggest difficulty. As I have already indicated patients can readily tell me that too much physical activity makes them worse but they haven't worked out that too much mental activity can also make their symptoms worse, especially their concentration. Most patients will also be able to tell me that they can't read for as long as they used to before their concentration goes, but they haven't worked out that watching television also makes them ill. The majority of sufferers that are off work and particularly children, who are not well enough to be at school, tend to get up in the morning, at a random hour, get washed and dressed, have some breakfast and then almost invariably turn the television on or go on the Internet. They will watch television intermittently during the day and in the evening without realising that this is the biggest potential

source of disaster. Children also have computers, play stations and X-Boxes, to join with social media and chat rooms, telephones occupy a lot of their time, and they tend to lie on the sofa in their dressing gowns watching television for hour after hour. They are making their illness process worse.

Chronic Fatigue Syndrome is a disorder of intellectual processing dysfunction with 70%, or more, of all of the information going into your brain through the eyes. Each eye has a million nerve fibres and each optic nerve works at 1000 cycles per second. You are putting two gigabytes of information into your brain every second. With all of this visual input, your brain automatically processes it up to the level at which it is presented with a picture; this is automatic and doesn't require intellectual processing. Then if you tend to concentrate on this picture you are said to 'attend' the picture. When you are unwell, your brain, is now on a timer, which nominally will last for about 10 to 15 minutes, after which the picture is disassembled and you have to concentrate to hold it in focus. At this point you have just made your illness process worse. You have gone past your visual concentration processing time. The more you try to concentrate the worse it gets and the more you will suffer for it. This is something that the majority of patients will tell you; that they have a *'reading span of ten to fifteen minutes'* but they have not realised that watching television is exactly the same process. If you watch television for more than ten or fifteen minutes, then you will make your illness worse. So will any other visual processing pastime; crosswords, puzzles, cross stitch, going to the cinema playing cards are all the same.

When you are playing with your computer, you are not only using hand eye co-ordination on the keyboard, there is a visual input and a sound input; you are doing three level multiple processing and the concentration span on the computer can go down to as little as just a few minutes. Certainly this

will be in single figures so, when we first meet and introduce the concept of the development of a programme, I always advise patients, that they should avoid visual input as much as possible. I appreciate that you can't avoid everything, that would be silly, but where possible one should avoid reading, television, computers and, also, other activities that include visual processing such as crosswords, jigsaws, scrabble, cards, close up needlework, detailed painting; in fact, anything that makes them have to use their "brain". They then usually ask, in some despair, "Well what can I do then?", "You seem to have taken away my whole life!" and the answer would be to suggest they increase the amount of auditory input into the central nervous system, listen to Radio 4, talking books or music, play an instrument, (as long as you're not reading the music too long), you can learn a foreign language or any other spoken pastime. Each one of all of these various auditory activities has an essential time base which, as it happens is fairly universally similar and I tend to advise patients to do approximately 30 minutes (or less) of any of these activities at a time. Then, of course, comes the question, "How often can I do these things?" and, generally speaking, the answer is once every hour.

You may find there are some things that you cannot do every day, in which case, do not do them at all for the time being but (on a random basis) substitute an activity slot such as washing up for something that you wouldn't usually do everyday but needs to be done, such as washing and blow-drying your hair or sorting the recycling ready for collection.

Once you have exhausted one particular part of the brain by, say, listening to a talking book for 30 minutes it takes approximately 30 minutes for that part of the central nervous system to refresh itself enough for you to be able to repeat the activity. So, in general terms, you do 30 minutes of one activ-

ity at a time per hour, wait until the end of that hour module and then you can do it again, or another auditory activity that is similar.

So, the essence of an auditory programme is to do a little bit, stop, change to do something else that is not listening, do that for fifteen minutes (or less), stop, have a break, a cup of tea or a rest and then do something else. Pottering around in this way means that your central nervous system is involved in doing different activities, a little bit of physical activity, a little bit of housework, a little bit of cooking, a little bit of gardening, maybe kick a football about or whatever. The process is then repeated to form a regular balanced cycle. There is no harm in sitting down and taking a break and doing absolutely nothing if you want to. You don't have to do things all the time but you should do things by the clock; half an hour 30 min 15 min whatever you like but don't continue to do anything until it's finished if it takes more than that time slot to finish it.

You should develop a programme that takes up the majority of your day. It should start at the same time each day, say 9am and finish at the same time in the evening, approximately at dinner time, 6pm to 6.30pm, 7pm or something like that and should contain as much as you can reasonably easily achieve and does not, in total, make your illness process worse. Whenever you start and finish your day is entirely up to you; times don't matter as long as they're the same for you each day wherever possible.

It may be that you should look around to get some new hobbies or some new activities. Always make sure that you spend some time out of the house, it's good for you, maybe not only just going for a walk but going for a ride in the car, go and sit in a café to have a coffee, go and visit a friend but don't stay too long; don't spend too long doing anything in particular - break

it up and mix it up.

This initial development of a programme is difficult, I am afraid. It is very easy in theory; it's just difficult to achieve, it takes practice. It does take a long time; patients never get it right to start with. You will not get it right first time and you will get it wrong lots of times and it needs lots of sitting down and talking to yourself about getting it right and you need a lot of support from your family, spouse, and friends. It takes me approximately six to nine months to help anybody, who has been ill for approximately two years, to get their programme right. It is restrictive and quite boring. Please don't think that you have to stay on this program for ever or for a very long time necessarily; we can start to make progress once you start to improve.

Once you have got the programme absolutely correct, or as good as possible, then you can start looking at medication. As I have said before you can't get better until you've got a program right. You can't use medication until you've got your programmes as good as you can; it can't be perfect! I strive to help people to get as good as they possibly can and then we can go forward. It is clear by now that you are going to ask me when that will be and, basically, that point is reached when you are waking every morning feeling refreshed from your sleep and your symptoms have settled. This is covered in greater detail in the '**Recovery – How to Get Well**' PDF on this site.

## **NOW TO GET THE SLEEP PATTERN RIGHT**

You have got your modified activity programme as good as you can, you are pottering around from 9am to 6.30pm doing less than you can achieve,

and you have also started to lock yourself into a regular sleeping pattern. This entails going to bed at the same time every night. I am not at all interested in what time you go to bed; that is for you to decide but whatever it is it should be the same every day. Let us assume that you are going to bed at 10pm. Between 6.30pm and 10pm, after you have had your dinner, you start to “dumb down”. You are not watching television or doing any visual processing, trying not to do anything that requires a "brain", you then start to turn off your central nervous system - so what do you do? Well again, you can potter around in a very simple fashion making sandwiches for tomorrow, do a little bit of tidying away, listen to the radio, listen to some music, listen to a talking book, talk to your parents, partner or husband, phone a friend for a few minutes, go for a stroll round the garden, have a nice hot bath, generally sit down, do not a lot and switch off!

Now you have set up a management programme and settled into a regular, daily routine we need to look at medication.

## MEDICATION

At this point you would then start looking at introducing sedative tricyclic antidepressants. Because the majority of patients with chronic fatigue syndrome have a sleep disturbance I often find that they have already been prescribed a sleeping tablet. As an example it might be Zopiclone. I do not like sleeping tablets: they actually make fatigue syndromes worse, the majority are habituating and many are addictive. The reasons for using antidepressants are discussed elsewhere (**Why Use Antidepressants At All**) but I like to make use of the sedative side effect of tricyclics to improve sleep pattern. They act as sleep regulators and they are not addictive. The commonest one to start with is Amitriptyline. It is a very old medication which is very sedative and works extremely well the majority of the time and is usually well tolerated. You would start off with the smallest dose that is made by the manufacturer and that is 10mg as a tablet, or you can take even less if you start with the liquid.

Take 10mg approximately an hour before you go to bed which in our example would be at 9pm. If you are worried about potential side effects then you could try breaking your tablet into half or even less just to make sure it doesn't upset you. You should notice that it makes you feel a little drowsy before you go to bed and hopefully your sleep will start to improve. I am not suggesting 10mg is necessarily going to be the right dose for everyone; some people (very few) can't take as much as that. As I have said, normally it is well tolerated and one would need more than 10mg. You can increase the Amitriptyline to 20mg and then to 30mg or even more, increasing at approximately 10mg aliquots at approximately weekly intervals.

## **HOW MUCH DO YOU NEED?**

You need an amount that enables you to, go to bed at 10pm (having taken your medication at 9pm) are asleep hopefully before 10.30pm, you then sleep all night long and wake by alarm at the same time every morning, let us say 7am, not feeling too groggy. There is no doubt that Amitriptyline makes you feel groggy, but this hopefully will only last for half an hour or so in the morning and be worn off by the time you finish your cup of tea. If it makes you groggy for longer or makes you feel bad, dizzy, headachy, drugged or any other horrible side effect then of course you must stop it. It is not unusual for amitriptyline to make people feel groggy in the morning and this if anything wears off after approximately a week so don't be afraid to persevere with. You must take the dose that suits you and that is always individual. However if the side-effects are unpleasant and don't wear off then you should stop it. You can try then to take something else such as 10mg of Doxepin or 10mg of Trimipramine. These are also tricyclic antidepressants and are also sedative. They are all the same, yet they are all different! (Cheddar and Gorgonzola are both cheeses but they are very different). The side effects are all the same as well but, again, they are all different. The side effects of tricyclic antidepressants are, predictably, unpredictable - what works for one person may not work for somebody else, so I suggest that you try all three. Yes, I do mean to try more than one anyway. It is also an advantage to be able to take all three; they are all different neurotransmitter regulating substances and they work on different neurotransmitters at different concentrations in the blood. 10mg of all three would be 30mg of tricyclic antidepressant (TCA) in total. If this works for you then fine, but otherwise adjustments can be made to any one of them,

or to all three, by small amounts until the perfect prescription for you is established.

TCAs are all sedative; they tend to improve the sleep but, very occasionally, they sometimes make patients not only feel bad but sometimes a little anxious and nervous. Also, they can tend to make people twitchy at night. This happens, I guess, in about 5% of cases in which circumstances these sorts of medications are not for you. There are very few substitutes for the tricyclics but in this slightly unusual situation it may be appropriate to try a quadracyclic like Trazodone instead. There are many others to try.

TCAs all make you dream; it is very common. Probably 30% to 50% of the patients that I see get dreams on TCAs; dreams which tend to be quite vivid, certainly colourful, active and sometimes unpleasant. Very occasionally, the dreams are so bad and so horrific that the tricyclic antidepressant has to be discontinued or at least a compromise is struck. Some improvement in sleep pattern can be achieved without using too much and without making the dreams bad.

Another common nocturnal complaint and side effect is that of visual hallucinations. This tends to occur in patients taking large amounts of TCA. Patients can wake up in the middle of the night and start seeing all sorts of funny things walking over the bed covers, up the walls or across the ceiling; usually unpleasant, big, creepy crawly things. The way to cope with this, again, is to reduce the tricyclic, if necessary, or simply switch the light on. On doing this visual hallucinations disappear but, unfortunately, tend to come back when you go back to sleep. Therefore, as you can see, there are benefits and down sides and it is always important to make sure that the benefits outweigh the bad.

TCA's, especially Amitriptyline, are pain killers and they are very good at treating headache and muscle aches and pains. In this case, if one of the principal complaints of the patient is of muscle pain even to the point where the diagnosis might be Fibromyalgia Syndrome, then you should stick to Amitriptyline by itself and take as much as you can tolerate.

### **HOW MUCH IS THE MAXIMUM?**

The usual maximum dose that I am quite familiar with using is somewhere between 150mg and 250mg of mixed TCA or of any one of them. The maximum dose is as much as you can tolerate. Other side effects of the tricyclics are those of a dry mouth, constipation and stimulation of appetite so it a balance of as much TCA as you can tolerate for the myalgia without making those side effects intolerable. The constipation can be relieved symptomatically by using bulk expanders like Fybogel and faecal softeners like Lactulose.

Two other serious and restrictive side effects are the very infrequent development of epilepsy and of cardiac stimulation and palpitation. Needless to say, if anyone has an epileptic attack on tricyclics then the tricyclic is either stopped or reduced to a minimum. Cardiac side effects are dose related and, therefore, would need to be monitored by an ECG and even asking for a Consultant Cardiological opinion as to the safety of the medications proposed. Any patient with known epilepsy and with known cardiac problems should seek relevant Consultant medical opinion as to the safety of using TCA's.

Another serious side effect is that TCAs cannot be taken with acute angle glaucoma.

It is very important to take one's time in developing the correct dose and mixture of the tricyclic antidepressants and can take some four to six months before the ideal prescription can be achieved.

So, now we have developed a modified activity programme that is less than you can achieve; a well balanced mixed programme of mental and physical activity. You have got your sleep pattern right with the tricyclics, you are probably already feeling a little better and, certainly, if nothing else, you should be in control.

Before we start with a modified activity program and before we start using medications to improve sleep, everybody that I see, has a sleep disturbance. They either have a difficulty in initiating sleep and lie awake for hours or they may get to sleep and find themselves waking up several times during the night or sometimes they sleep for a few hours and then, get back to sleep again after waking in the early hours of the morning. In all of these situations, when they eventually wake to get up they feel unrefreshed. If you wake unrefreshed you are not going to improve. It is the one marker in this whole illness process that will give you a money back guarantee of the outcome. Wake unrefreshed; you're not getting better. Wake relatively refreshed or quite refreshed in the morning and I can guarantee that you will improve.

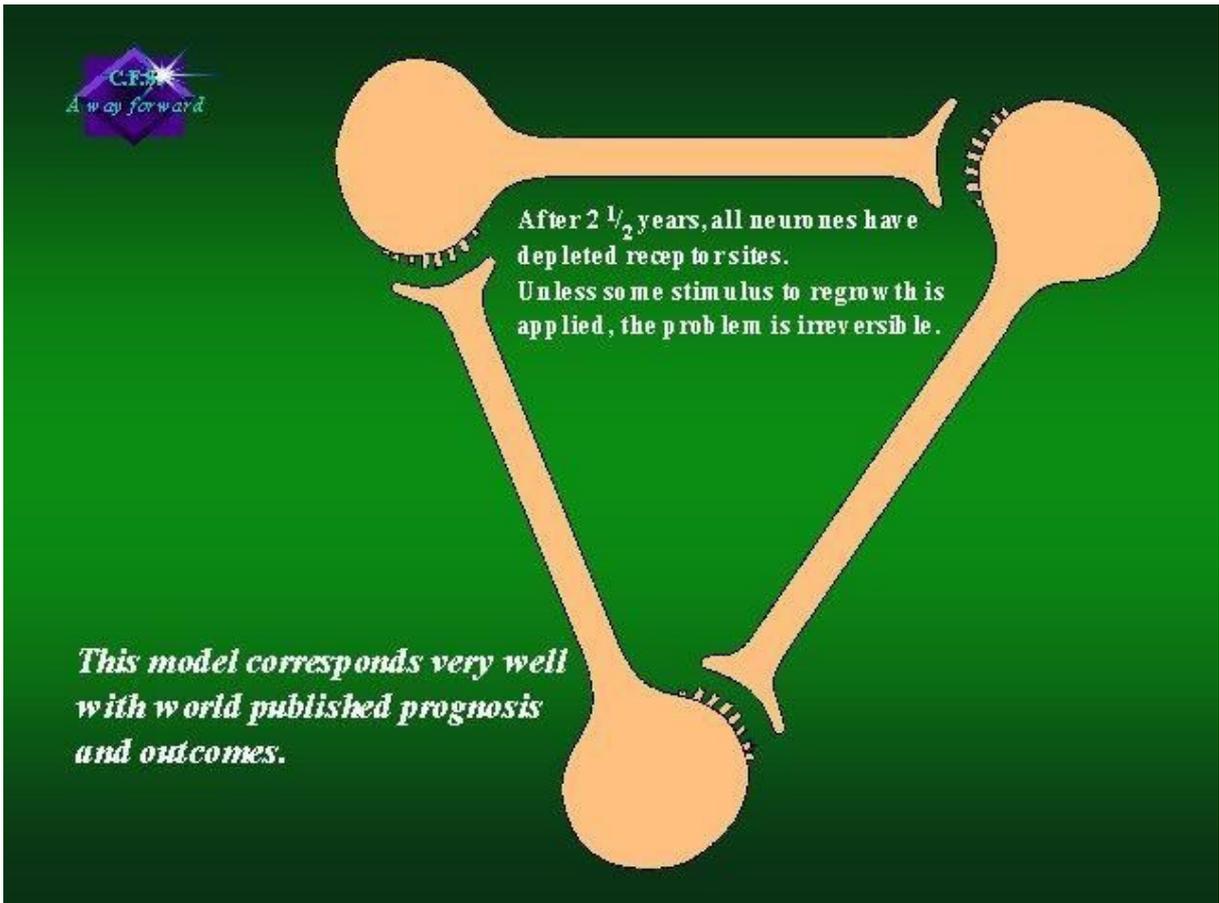
## WHY USE ANTIDEPRESSANTS AT ALL?

In 1989 I wrote an article for "The Royal College of General Practitioners" Members Reference Book. Pages 247 to 250. In there I published my outcome of studying some 3000 patients looking at their function, their recovery or lack of it over a period of time.

These patients were not being treated as I would treat them now. At that time, I believed that it was all due to a virus and therefore in that case there was nothing that I or anybody else could do about it. As I have mentioned elsewhere once you have a virus, if it's persistent and lodged inside cells of your body there is nothing that you can do to get it out especially if it's a DNA incorporated virus. My advice at that time was to rest, not do too much and, pragmatically, I was able to say that most patients gradually improve. However if they hadn't got better and back to where they were before they became ill by two and a half years then the prognosis started to become quite bleak. Patients who are been ill for this length of time do not appear to improve and they get stuck at a level of morbidity. Indeed, the longer you have it the more it tends to fluctuate and you continue to get this boom and bust because by two and a half to four years life just gets in the way; things happen.

I believe that there is a central nervous system explanation why that might occur.

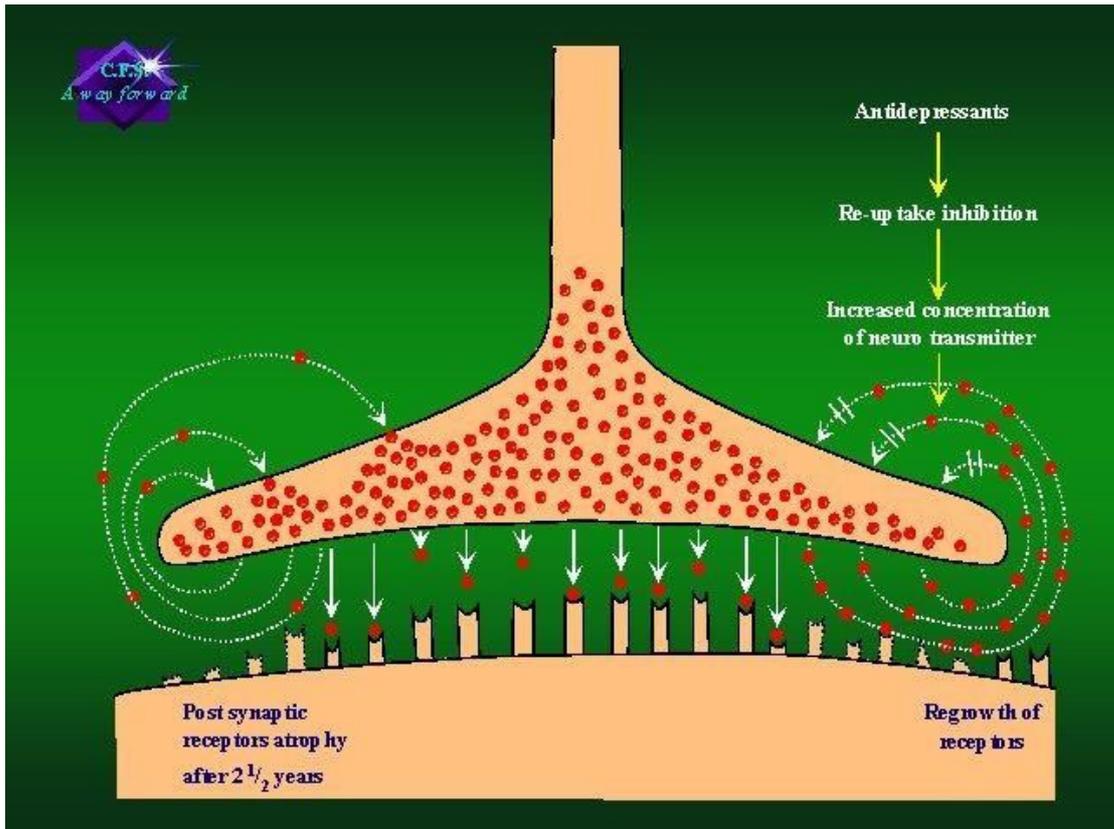
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**FIG 1**

In my first figure I am showing you the whole of your brain represented here by three neurones. Each of these neurones is able to talk to the others and they do so electrically. I have grossly simplified the process. The body of the neurone is the round bulbous bit with little spikes on the surface, the long straight bit is the axon which ends in a little foot, the space between the foot and the bristles is known as a synapse.

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**FIG 2**

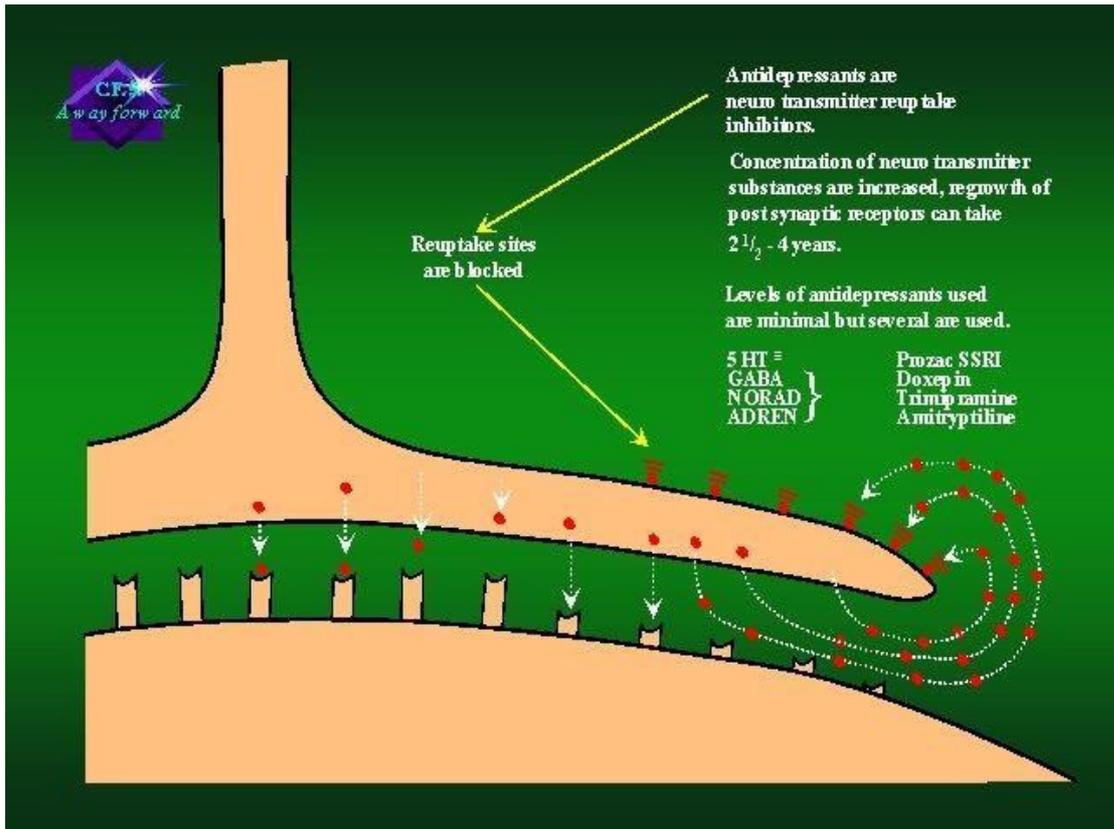
In my second figure I have shown a schematic representation of a synapse. The end of the axon is the foot, inside which you can see lots of little tiny red balls. These are little packages of neurotransmitter substances. In the normal course of events, represented in the middle the foot you will see little red packages going across in front of a little white arrow and being received by the neurone on the other side, represented by a little finger-like projection with a little cup at the end to receive the red ball. Once a cup is filled with the neurotransmitter a small area of the surface underneath the projection changes the electrical charge on the surface from positive to negative, causing an outflow across the membrane of sodium and potassium ions. This is called depolarisation and, in this way, the neuron is activated.

As I have explained elsewhere I am convinced that the amount of neurotransmitter substance in chronic fatigue syndrome is reduced and thus the number of little red balls going across the synapses is less and the receptors on the other side are not being stimulated as much as they should be. Furthermore, if you don't stimulate the receptors as much as they should be they tend to atrophy, to rot away, they degenerate and in that case once they have disappeared they can't grow back.

The question really is 'Can you re-grow synapses once they have rotted away?' and the answer is 'Yes, you can'. If somehow you can increase the number of little red balls so that there are more red balls than receptors on the other side then the concentration of the neurotransmitter would be increased and, in that situation, the constant stimulation of the chemical on the neurone receptors increases their growth and you can re-grow them but it takes time.

Now go back to my clinical outcome where I said that if patients have been ill for somewhere between 2½ to 4 years their ability to get better diminishes. Once you've got to 4 years of ill-health you are stuck with it. I believe that synapse receptors in patients with chronic fatigue syndrome begin to atrophy at about two years and this process is complete at four years.

*/continued*



**FIG 3**

In my third figure I show how antidepressants will help cure this problem. In the normal course of events once the little red package of chemical goes across the synapse and stimulates the receptor it is either destroyed by an enzyme or it will float off to the edge of the synapse, go round the back of the foot and be re-absorbed. This is called 'reuptake'. It's a form of recycling; the chemical is absorbed back into the foot, re-packaged and reprocessed.

If you can block this reuptake then the amount of red chemical left at the edges of the foot and the edges of the synapse increases and as the concentration of the chemical increases the amount of the chemical on the damaged, rotted receptors increases and stimulates them to re-grow.

It does this very slowly and may take another 2 to 4 years to be complete. So you can see that I am suggesting that medications that block this reuptake, namely the antidepressants, need to be taken for somewhere between 2½ to 4 years to be effective.

This process is mirrored and the reverse of addiction. If I give you a chemical that is not naturally occurring in your brain you can sometimes grow receptors to that chemical. These chemicals are seen in nicotine (smoking), heroine and other opiates. Let us take the example of nicotine. If you smoke for a very short period of time a few weeks or months it may be very simple to stop. If you been smoking for a long time several years you are addicted to nicotine. What has happened is that somewhere in your brain you have grown receptors to nicotine which weren't there before and when you stop smoking these nicotine receptors scream out for nicotine because the little cups' membranes are empty. Little red balls of nicotine are no longer there and the only way you can stop is not to smoke any more for a period of two and up to four years before these little receptors disappear, and that's probably true of all addiction. You grow receptors slowly over a period of time. Once you're addicted to it you have to wait for those new receptors to atrophy, to rot, and that can take a long time. There are lots of drugs like that; lots of other chemicals to which people become addicted.

So that is my explanation as to why you should consider taking antidepressants in chronic fatigue syndrome that has been present for a number of years. There is a logical pharmacological reason for doing so and bear in mind antidepressants themselves are not addictive or habituating.

If you have been ill for 2½ years you need to take the medication that will help stimulate the postsynaptic membrane and the receptors. You need to start off with a small dose and work up to one that suits you. You would then take the medication at that level for a couple of years or so and then try to reduce it. Hopefully, during this time, you will have improved and hopefully got better and then you come off the medication extremely slowly. It may take one or two years to stop the medication itself

## **SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

Now we look at introducing the medication to really begin to sort this problem out and that is the introduction of SSRIs in the morning. In using the SSRIs you are treating one of the biggest of the neurotransmitter substances inside the central nervous system. Arguably, 35% of all neurotransmission in the brain and the rest of the central nervous system is 5HT. There are several different sorts of 5HT receptors and there are several available medications to help. The commonest ones that I use are Prozac (Fluoxetine Hydrochloride), Seroxat (Paroxetine Hydrochloride), Cipramil (Citalopram), and Efexor (Venlafaxine).

### **PROZAC (fluoxetine hydrochloride)**

Using Prozac is really very difficult and must be done with great caution, because there is a potential drug interaction between all the tricyclics and the SSRIs. In America, many years ago, there was a group of very depressed, institutionalised men being treated with Trimipramine, at night and in quite large doses of up to 300mg at a time. Prozac, which

was fairly new on the scene, was added to their regime and several died of heart attacks. Obviously, this combination was immediately stopped. Further studies revealed that these two groups of antidepressants were metabolised by the liver using the same pathway; to be specific the hepatic cytochrome pathway P45011D6 isoenzyme system. There was competition for this breakdown pathway which was largely won by Prozac, and the metabolism of the tricyclic medication was inhibited. Therefore the tricyclic, in this case Trimipramine and its active metabolite Desmethyl Trimipramine, slowly went up in the blood and continued to increase to toxic levels. Toxic levels of tricyclics lead to ventricular rhythm abnormalities such as ventricular ectopics, ventricular extra systoles and ventricular tachycardia and death, so a skull and crossbones warning was written on the Prozac prescribing leaflet. This stated that Prozac must not be mixed with tricyclics at the same time or within a couple of weeks of using such other antidepressants.

Using tricyclics by themselves restores and normalises sleep patterns but does nothing for the fatigue. In fact, if anything, tricyclics increase fatigue in the day in the form of drowsiness and, maybe, have a little bit of a drugging effect. I realised, therefore, that I must use the wonderful anti-fatigue properties of Prozac and, at the same time, could I get round this potential drug interaction. The answer really is quite simple.

When you start using the Prozac you can measure the blood levels of tricyclics and their active metabolites and make sure that you always stay within safe therapeutic limits. You can't start using Prozac at the smallest prescribed capsular amount because that is 20mg and there could be an effect on the tricyclic level quite quickly and, of course, I would be in serious trouble if this happened. So I always start off using

Prozac liquid. 5ml of Prozac liquid is equivalent to 20mg of Fluoxetine Hydrochloride and the bioavailability and the effects of the capsule and the liquid are the same. So if you start off with 1ml of Prozac syrup (equivalent to 4mg of Fluoxetine Hydrochloride) this is such a small dose that it is most unlikely to have any effect at all, either good or bad. Certainly one would not expect 1ml of Prozac to have any effect upon the liver and, therefore, to have a knock on effect upon tricyclic metabolism, and that is in fact what I have found.

It is also true to say that I have very rarely used large doses of the tricyclics. The average sort of prescription would be 75mg, which is often as low as 10mg at night in total or up to the 200mg that I have used on occasion; however, the average would be 75mg.

After starting the Prozac syrup at 1ml you would leave that prescription to stabilise itself for about a month and then you would do a blood test to measure the tricyclic and its active metabolite for whatever tricyclic you are using. This is specifically measured and monitored for me by a Therapeutic Monitoring Service in London. The blood test is very specialised and is only done in one or two centres in Great Britain. The result takes about a week to ten days to come back and provided this result is normal and within safe therapeutic limits which it must be, I would then increase the Prozac to 2ml, (equivalent to 8mg of Fluoxetine Hydrochloride), wait another month and do another blood test. Then I would use 3ml and another blood test, 4ml another blood test and then 5ml (which would be one capsule), and do another blood test.

These blood tests are expensive (roughly £50 a go) so, for example, I can spend anything up to £300 just to get to 20mg of Prozac and 75mg

of Amitriptyline. Of course, on occasions I have used a little more Prozac and have gone up to 40mg and, of course one continues to do blood testing. It gets very expensive but that pales into insignificance when you bear in mind that the priority that you have is patient safety, which is paramount.

My average prescription is 30mg of Prozac (one 20 mg capsule and 2.5 mL of the liquid Prozac equivalent to 10 mg thus a total of 30) and in the fifteen years that I have been using this combination of medications I have never ever seen this potential drug interaction with tricyclics. I have, on a couple of occasions, had to write to patients to ask them to reduce their tricyclic, but it is not because of the Prozac, but due to the fact that a particular level of a prescription of, say, 100mg of Trimipramine may produce a slightly higher blood level than I would wish.

Once you have attained this stabilised prescription it remains stable. The competitive inhibition of Prozac with the tricyclic will be at a fixed level and the blood level of tricyclic will not at any point rise by itself. There are two exceptions.

The first is that Prozac, if anything, tends to make people less hungry and sometimes can promote weight loss; in that case the blood level of Prozac and the tricyclic might go up if your weight loss is significant.

Secondly, on a very hot day if you perspire a lot and do a little bit of physical exercise you might lose body fluid through perspiration and this might push up the blood levels of medication. So on a hot day, I tend to advise people to make sure they are well hydrated and if they find them-

selves losing weight you must do the blood tests again. Of course if you find yourself increasing the tricyclic you would have to repeat the blood test again, but I have very rarely had to do that, so the prescription is safe and stable once you have established it to be so. Furthermore, it will not change unless there is another medication introduced that uses the same metabolic pathway, the cytochrome 3450 system or, of course, if the patient goes down with a liver infection such as hepatitis or they start drinking heavily and produce some kind of alcoholic liver disease. On the assumption that this doesn't happen, the prescription can remain stable for several years but of course should be monitored. There is always potential for problems, human beings are only human and things never stay the same - they either get worse or they get better and hopefully better - and that is my finding.

The anti-fatigue property of Prozac, its ability to produce this feeling of well-being and the effect of sedation and improved sleep pattern of a tricyclic proves to me to be an ideal prescription. However, during all of this time the single most important thing is for the patient to remain on a stable programme and, providing they do not abuse the fact that they feel better with their Prozac, you can move them forward very slowly.

**This mixed prescription is then safe and stable.**

There is one very important proviso to this and that is that the patient must not get their programme wrong whilst on this combination of drugs. If they make themselves ill by doing too much and have a significant relapse on Prozac and tricyclics then there is nothing more that you can do, and I have seen this on a couple of occasions.

I remember, very vividly, one lady of about forty-five who had been ill for

seven years. It took me several years to get her better and she went away, knowing all of what I'd advised her to do, and more importantly what not to do and she was sticking well to her programme. She went out and bought herself a new kitchen. It was delivered but the company couldn't install it for twelve weeks and their old kitchen had been ripped out to make way for the new one, so, as her husband was a DIY specialist they decided to try and do it themselves. After a few days of mess and muck her husband's back went. She was not a person who was unfamiliar with a screwdriver so she sat her husband in the middle of the room on stool and said, "You tell me what to do and I will do it." She didn't stick to her programme and did a little bit more than she could do, day by day. She ignored the returning sleep disturbance, she ignored the unrefreshed feeling in the morning, she ignored the aches and pains and the slowly increasing sore throat. She then produced an acute flu-like reaction and found herself being bed-bound.

After a couple of weeks she came back to see me and told me that I had to help her. I pointed out to her that there was nothing I could do. I couldn't increase the already maximum doses of drugs and there is no other treatment that I know of. She could only sit back and rest and wait and see what happened. That was over five years ago and I know, for a fact, that she is still chair-bound. This is a warning and I make sure that everybody understands it. It is not meant to be a 'scare story' but you have got to stick to the programme like glue when you are on these medications.

Along the path of recovery the unplanned event will always occur that could exacerbate the situation. That is life. This might be an contemporaneous flu-like illness, the common cold, a general anaesthetic, a bro-

ken leg or an operation. In these circumstances, all you have to do is to rest and don't push it. Just lock the front door, take the phone off the hook, take an analgesic, go to bed and stay there and wait until whatever it is, has gone away. Then you slowly return back to where you were. I find these things never make people significantly unwell. They do not produce an exacerbation although, of course, a minor relapse might be experienced because of whatever has transpired, but that is safe and not a problem.

On a few occasions I have come across people who just simply do not want to, or can't, stick to a programme and, therefore, I don't want to prescribe Prozac. I tell them this so they can stick to a tricyclic at night and if they relapse because they do too much, then there is not really much of a problem with that.

I stick to Prozac most of the time (at least 90%) and, these days, I only use another SSRI if they can't tolerate Prozac. I find that most patients can tolerate Prozac very well indeed but there are one or two who say that they can't and, in these situations, they usually experience a headache or nausea. I won't go into the potential side effects of Prozac simply because these facts and information are widely available to everybody. You can find the side effects on the internet, in doctors' surgeries, in MIMS, in prescribing journals and the back of every single packet that is prescribed. You should also be able to see the side effects with regards to the TCAs in the same way.

There is some degree of notoriety with regard to Prozac – 'The happy pill' - and there is no doubt that this is true. It does lift people's mood. It can produce a slightly *laissez faire* attitude and I'll tell you about that be-

cause I have seen it on at least half a dozen occasions.

Prozac lifts mood and reduces fatigue but, also, on rare occasions, it removes inhibitory features and I have had people come back and tell me that they have found themselves doing things they would not have expected of themselves.

As an example, I had a young lady patient of about twenty two, who always enjoyed shopping. She was on 20 mg of fluoxetine. She borrowed her mother's Debenhams card, one Saturday morning, went out and blew £2,000. Debenhams' were very good about it and after an explanation they took all of her shopping back. I had to stop the Prozac. I had another lady who came back and told me that she developed road rage. She was finding herself winding the window down and swearing at all the passers by.

One gentleman brought his wife along to see me who, at the beginning, was quite a mouse. He had always encouraged her to be independent but she lived a very reclusive life. After taking Prozac she totally changed. She became flamboyant, quite extrovert, very chatty and in fact the man commented to me on this saying that he liked the lady that had come out of the Prozac bottle better than the one that was there before!!". She then looked at me and she said, "Yes and I leant over the fence the other day and told my next door neighbour exactly what I thought of him!"

These side effects are quite unusual but it does mean that they need an eye being kept upon the prescription and its effects. Whatever is going to happen it is not going to become obvious until patients are taking at least 3ml or more, usually 4ml or 5ml of Prozac, and these side effects,

good and bad, are dose dependent. The more you take, the more likely you are to have side effects, so whilst you are taking some six months or more to get the prescription stable, you have got to keep a careful eye, not only upon the potential drug interactions and their potential problems, but also upon the effects of the interactions and of the drug itself upon the patient. It is important to make sure that at all times you are doing good and never doing bad. Be reassured that these side effects and potential problems do not suddenly occur overnight, you can see them coming, you can control them. I reckon that you can improve CFS/ME at least 80% of the time, probably more with current programmes. Provided the patient can stick to their programme and tolerate the drugs then you can nearly all always get them better.

There are, however, a few that cannot tolerate the drugs and if they have been ill for a long period of time they become quite stuck. There are those that can't tolerate any of my range of drugs used, and they get stuck as well but, fortunately, they are very few. I would always encourage patients to take these medications but I do understand their concerns about taking antidepressants and all the stigmata that go with them. When used properly they are safe.

Equally when they have got better they would come off the medication extremely slowly in the reverse order. Taking them off the Prozac first and then the tricyclics at night, I would then take probably twice as long to withdraw patients from the drugs as I did to put them on. I have never had a problem getting patients off drugs. They can sometimes be a little bit difficult, and if you have been on these medications for three or four years or so then, of course, you are going to be fairly dependent upon them. Getting off is not necessarily easy but, certainly, I have never

found it to be impossible.

Whilst I would never advocate stopping these drugs very quickly that may not be the advice if you suddenly found yourself being pregnant. As I am sure we all know, the most likely time for the worst problems to occur in a pregnancy is within the first sixteen weeks, and I would suggest that you should always try and stop these drugs as soon as you know you are pregnant. The advice, these days, is that you shouldn't take even an Aspirin if you are pregnant. After twenty weeks it is not so much of a problem for the pregnancy and, of course, you must always weigh up the benefits that you have from taking these drugs with the problems that you might have in stopping them. However, as this is an unknown quantity I would suggest you should try stopping them. It would be unlikely that you would relapse all the way back to as bad as you were before and I have never actually seen that happen. I have found that patients who want to have a family and are not 100% recovered discover that when they stop the drugs to become pregnant, in a planned way, they do slide back probably 10% or 15% but not all the way back down the hill. I have had approximately ten ladies in this position of wanting to have a family and stopping the drugs. They can restart them after they have finished having their baby and finished breastfeeding, and this will be an option to be considered.

I would never let anybody else stop your drugs if you are taking the full dose of tricyclic and Prozac. If you find yourself in a hospital having to have an operation there is no problem between these two drugs and an anaesthetic. You will find yourself being questioned as to why you are taking these two together and, of course, when you process your prescription Pharmacists will, quite rightly, question why you are taking this

potentially dangerous combination. I will leave it to you to explain. If at any point you want to stop the drugs then you must always feel free to do so whether that would be my recommendation or not; the choice, of course, is always yours. However, I would always recommend trying to come off them extremely slowly. If you come off them very quickly you are likely to have a very rough ride. You will get headache, nausea, dizziness and quite profound sleep disturbances.

There is no problem in taking these drugs with other mild analgesics for headache or various aches and pains. Aspirin, Paracetamol and Ibuprofen are fine. On the box you will also see a warning that says do not mix these drugs with alcohol and that alcohol should be avoided. In my opinion that is not a problem with modest amounts of alcohol. When antidepressants are prescribed for depression then alcohol can take the antidepressant effect away and the depression can become much worse. However, we are not treating depression with these drugs; we are treating CFS/ME. Small amounts of alcohol and tricyclics, individually, make you drowsy so the combined effect of the two may help sleep as well. Too much alcohol, however, can have the opposite effect, and I am not advocating its use as part of the programme but merely commenting on likely effects.

It is also true that a lot of people with CFS/ME can't tolerate alcohol as it makes them worse but that is a different situation altogether. **(See Recovery PDF 2)**

In the event of somebody not being able to tolerate Prozac then (as I have already indicated above) I would go for Paroxetine Hydrochloride (SEROXAT) or CIPRAMIL; probably Cipramil first because it does have

a slight anti-fatigue property but nowhere near as much as Prozac. Paroxetine tends to be fairly neutral.

## **SEROXAT**

Seroxat is one of a group of antidepressants that are 5-Hydroxytryptamine reuptake inhibitors and it is a potent one.

Chemically known as Paroxetine Hydrochloride, it comes in 20mg and 30mg tablets and as a liquid 20mg in 10ml. I have been using it now for approximately five years and have often used it in conjunction with Prozac, the properties of which are mentioned elsewhere. Seroxat has recently come under quite a lot of criticism. It has been associated with an apparent increase in suicide in younger depressed patients and this association has resulted in a ban in prescribing it for patients under the age of eighteen. Having said that, if we are using it in CFS/ME in patients who are not necessarily depressed, I can see that there would be no reason to believe that there would be an increase in suicide rate in this group. I am therefore looking at what options we should be adopting in treating children under the age of eighteen with CFS/ME using Seroxat.

It became clearer to me several years ago that by using just Prozac I was excluding groups of patients who had anxiety, because there is no doubt that, in certain situations, Prozac is stimulating and actually increases some of the patients' anxiety levels. Seroxat is essentially neutral, (ie. it doesn't sedate and it does not stimulate) and it would therefore be taken in the morning. It also has other properties which can be

very useful in treating certain subgroups of patients with anxiety and degrees of obsessional compulsive disorder which I sometimes find in a few patients with CFS/ME. I am not talking about patients who have serious obsessional compulsive disorder (OCD) but in patients with whom it is possible that their anxiety is derived from a tendency to be obsessional, pernickety or precise. This is especially seen in younger people in their approach to some of their schoolwork; they like it exact, they don't like crossing things out and they tend to re-write things. Also agoraphobia and social phobia are quite common in people who have been ill for long periods of time. They become socially withdrawn and they can get anxiety and even panic attacks, very often directly as part of their personality or the result of being ill from CFS/ME for so long. It became these groups of patients in whom Seroxat would be seen to be more appropriate to be used.

Seroxat is principally an antidepressant but as I have already suggested it has licenses for treating OCD, panic disorder, anxiety disorder and social phobias. Posology suggests doses starting with 10mg (half a 20mg tablet) to 50mg in depression, panic disorder and social anxiety and phobia to a maximum of 60mg in OCD. In my experience it takes several weeks to be effective and as elsewhere in the treatment of CFS/ME I start off with tiny doses because of the possibility of drug intolerance that is found in so many people with this disorder. I would therefore always go for the liquid and start off with 2ml which is equivalent to 4mg of Seroxat and increase by 1ml per fortnight or per month.

*(Continued on page 85)*

## **Pharmacological Properties**

Paroxetine Hydrochloride is a potent selective inhibitor of 5-Hydroxytryptamine. Its metabolites are not pharmacologically active. Seroxat and its metabolites are cleared by the liver through the isoenzyme P450. Thus its use in conjunction with other drugs that also use this pathway of metabolism has to be very carefully controlled, and as I use the tricyclics which also use P450 isoenzyme, blood testing must be done to look at the levels of the tricyclics and their active metabolites to ensure they stay within safe therapeutic limits. It should be used extremely carefully in patients who are known to have renal or hepatic impairment, although in the presence of these two conditions it would be hard to sustain a diagnosis of a CFS/ME. I have rarely had to use more than 20mg or 30mg of Seroxat.

There are known to be several conditions in which special warnings and precautions should be used. Seroxat should not be used with a monoamine oxidase inhibitor, and caution exercised with anticoagulants. It doesn't have a cardiological or a blood pressure problem. It shouldn't be used in conjunction with Tryptophan because serotonin syndrome may result.

Side effects are quite common; the ones that I see most often are that patients taking Seroxat have problems sleeping and they get quite frequent gastrointestinal upsets, usually indigestion and diarrhoea. There are lots of other potential side effects and undesirable problems, but I think those should be looked up on the manufacturer's pamphlet.

In summary, I have found it a very safe medication and I simply haven't come across the problems that were indicated in the Panorama programme of 2006. I haven't found that anybody has become addicted to it even after two or three years of use, especially if it is withdrawn extremely slowly. It is one of the medications that you shouldn't come off very quickly but go back through the liquid form and come off a millilitre at a time over weeks or even months to avoid all the withdrawal symptomatology. I have found it most beneficial in patients who have got anxiety with CFS/ME.

## **VENLAFAXINE**

Venlafaxine is specifically good for chronic anxiety and stress. Unfortunately it is also true that the potential problems of prescribing Venlafaxine with tricyclics are greater than the problems that you experience with Prozac, Cipramil or Paroxetine Hydrochloride. There is a horrible problem with a potential drug interaction that can lead to acute serotonin syndrome; again, fortunately, something I have never seen but it does occur and this is potentially more of a risk with Venlafaxine. So if you are going to use this medication, then you would have to measure the blood levels not only of the tricyclic and its metabolite but also of Venlafaxine itself and make sure that all of these three lie within safe therapeutic monitored boundaries. There is also a well established cardiological side-effect so your heart should be checked out first.

I would also try a different SSRI if, despite a reasonable prescribing dosage, Prozac doesn't work. On one or two occasions I have found that, if the patient doesn't improve despite tolerating the drug, you have

got to try something else.

I do understand that there are a large number of people who simply don't want to try antidepressants for one reason or another. They have a psychological barrier to doing so in which case that is not a problem. In my opinion, whilst their chances of significant improvement are less, I am happy to continue working using a modified activity programme by itself.

## **WHAT HAPPENS IF YOU BECOME BEDBOUND?**

I have been looking at patients with chronic fatigue syndrome now for many years and fortunately I have not come across many who have been bedbound. Probably half a dozen patients that have been totally bedbound out of the approximate 3000 that I have estimated I have seen. Out of the six, I know that I could not help two; they were unable to find a way forward. Of the remaining four, two got very well and two, maybe, halfway better and they had an improved quality-of-life, so you can see that my success rate has not been startling. It is a very, very difficult problem.

As described extensively elsewhere, I will argue that the virus that you have at the beginning is simply the trigger to what is almost always a stress related condition. You get a flu like illness and the vast majority, from the very beginning, become bedbound, usually for approximately one week and then patients get out of bed, are chair bound and housebound. Whether the majority make some improvement and progress forward the degree at which they recover is extremely variable but we are talking about people with chronic fatigue syndrome and so, by definition, they have been ill with a fatigue and fatigueability for more than six months. Of all of the patients that I have seen I believe that one percent, or something like that, remain bedbound after six months from the initial illness. They remain in bed because the fatigue and the muscle aches and pains, the malaise and the exhaustion is so bad that they feel that they can't get out of bed because they are "too ill".

Let us now examine what would happen to a person who is not suffering from chronic fatigue syndrome but has another condition that confined him to

bed for a period of time. Let us say you have a compound fracture of your leg, you end up in hospital having an operation, you're then confined to bed on traction with a complicated system of pulleys and wheels and string and steel. You will find the commonest set of symptoms that are complained of once the fracture has been healed and has united is the fact that the patient will get widespread aches and pains all over their body and fatigue and this can last for weeks and, of course, because their problem is a fractured leg they are encouraged to mobilise and push forward to "get going". They fight against the fatigue and the aches and pains. If you get something less dramatic, like a cold or maybe a mild flu, you may end up in bed for two days and I'm sure we will all recall the fatigue and the headache that remains with you for days afterwards, through which one is encouraged to progress forward to get better. If you have nothing wrong with you at all and go to bed for a few days you will find that you will get fatigue and muscle aches and pains and other symptoms when you get out of bed.

A year or so ago there was an experiment conducted, I believe in France, where- by a group of volunteers were asked to reproduce a space journey in the laboratory. They were asked to lie on a mattress and were given an imaginary ceiling of 18 inches and were told to remain on the mattress and underneath the 18 inches for nine months. Their body physiology and biochemistry was studied during this time to find out how they would perform on this imaginary trip to Mars. After this experiment was over many interesting things were found, some expected and some not. They suffer from profound fatigue, muscle and joint aches and pains, loss of body weight and muscle bulk, disuse atrophy, bone thinning, blood pressure control difficulties and postural hypotension to name but a few.

When you have chronic fatigue with malaise and flulike symptoms that caused you to go to bed in the first place, and if these symptoms are quite profound, and after a few days you try to get out of bed and find that the symptoms that you went to bed with are persisting, some people will actually go back to bed believing that they are not well enough to get up yet. If, after a month of being ill with this initial virus infection, you are still suffering the same symptoms then you can see the difficulty in determining whether this is a normal reaction from lying in bed for too long or is the result of a chronic fatigue syndrome starting. The symptoms that you go to bed with are the ones that persist and increase when you get out of bed. And, from an historical point of view, I'm quite certain that is what happens; it's impossible to differentiate between the symptoms of being bedbound with chronic fatigue syndrome, and being bedbound and being bedbound for too long.

Therefore, I am sure you can see the dilemma that faces the patients who are bedbound for any length of time and who try to get up. They get an increase in their symptoms, they will feel dizzy because of low blood pressure, maybe feel weak, they will ache etc. So it is almost impossible to say when the fatigue from your virus has finished and the fatigue from being bedbound begins and it's perfectly reasonable to accept the fact that one will run gradually into the other with no perceptible difference between the two lots of symptoms. Furthermore, the longer you stay in bed the worse the symptoms will get anyway. Maybe after you have been in bed for 3 to 6 months it becomes quite clear that a lot of the symptoms that you get will be those of being in bed too long; you will get muscle atrophy and you will get your bones thinning with mineral re-absorption. You might lose your appetite and lose weight or you might not lose your appetite and gain weight; you will have a sleep disturbance, you get temperature de-regulation, (body temperature in bedbound patients tends to go down) and you will lose biological regulatory

mechanisms. These are the physical symptoms and then, of course, on top of that you get the psychological ones of loss of drive, loss of enthusiasm, depression, despair and despondency. People will try to get out of bed and their symptoms increase both so they go back to bed - it's a self fulfilling prophecy.

So where do we go from there?

As there are no blood tests for chronic fatigue syndrome and as we cannot measure the fatigue what you need to do is to assume that there are three conditions present in a patient who has been bedbound for six months.

Firstly they have a chronic fatigue syndrome.

Secondly they have disuse atrophy.

Thirdly they have been and are at the same time depressed.

.

Therefore, you need to adopt an approach of rehabilitation that will suit all three and the answer will be.

**A very very gradual mobilisation.**

**A regularisation of their day.**

**To introduce a sleep regulator.**

**To consider using medication to lift their mood.**

Let us take these one at a time.

I would start by regularising their day because they are doing nothing much at all physically; they will not be doing any physical activity that would make them naturally tired so, undoubtedly, their sleep pattern will be disturbed. They will sleep badly, will sleep at times in the day and their sleep will almost invariably be unrefreshing. It will be important to try and make sure that they go to sleep at an appropriate time at night; let us say, for example, 10 PM. The amount of sleep that they require would probably be less than you usually need and I would say they could be encouraged to wake at 6 AM. I would use Amitriptyline at night, to be given at 8:30 PM in the manner discussed elsewhere. I would make sure that they wake by alarm at 6 AM and that they do everything possible not to fall asleep during the rest of their 16-hour day. I would also make sure that they have three meals a day and no snacks in between.

It is good to encourage a visit from friends and relatives a few times a day in fixed time slots of, let us say, 20 min spaced out three or four times a day.

It should also be noted that patients who have been ill and are bedbound for any length of time, invariably, will play with their computer, watch television or try and read. This, of course, as discussed elsewhere, will perpetuate chronic fatigue syndrome so it is important to minimise visual processing to less than 15 min per hour, or something like that, and to increase auditory input from talking books, conversations, and radio. During other times a patient may be encouraged to take up a physical activity that one can do in bed, such as small amounts of stretches, exercising arms and legs using a tin of beans (*two socks tied together with small, progressing to larger, tin in each sock hung over the ankle can be used to exercise legs while sitting on*

*the side of bed or chair*), knitting simple squares, model-making or something like that for 10 to 15 min per hour as well.

### **Gradual mobilisation.**

I remember one particular patient having to lie flat all of the time when I first to see him and he was totally bedbound, unable even to use the commode. In this situation, mobilisation starts with simply raising the chest or the head, using pillows and maybe a pillow rack, to allow the patient gradually to learn to sit up. With patients who have been lying down all the time, when you start to raise them up they tend to feel lightheaded and dizzy. This because their blood pressure is almost certainly low. In order to get the circulation working again, you have to reverse the process that caused it to be dysfunctional in the first place. The patient must be encouraged to sit up more and more and not lie down except to go to sleep. They should be discouraged from having long periods of rest and encouraged to be occupied more and more, gradually to being sat on the edge of the bed, encouraged to get into a wheelchair, have a shower and to get out of their room. This might take weeks to achieve. A very tight control of the amount of physical and mental activity is essential. The patient must not be allowed to go backwards and, at the same time, mustn't be pushed forward too fast and they get into this regular pattern of trying to achieve small even minute amounts of positive physical and mental progress. It is these early days, weeks and possibly months, indeed probably months, that have to be taken with huge strength and control by the patient and support and understanding by their carer or carers.

Chronic fatigue syndrome is a loss of regulatory and control mechanisms within the central nervous system and is biochemical. To reverse this proc-

ess takes time and patience. You mustn't do too little and you mustn't do too much; it is fraught with difficulty. If one progresses forward in such a fashion it is impossible to produce a relapse. You must remember that it is the patient that will dictate the rate at which they can improve. The therapist, be that a Doctor, a nurse, physiotherapist, a brother, sister, parent, is there to give support and not to dictate the rate of recovery. Whatever happens the sufferer must be encouraged to go forward. It is not unreasonable, however, to allow a day or two of stabilisation, of not making progress, of not going forward all of the time, but to be able to take a breather; not to go backwards but to stabilise.

I have found that to give the advice that I have given here is difficult because every single patient is individual and their problems are personal and it is very difficult to give a one size fits all approach to recovery, so I would say, therefore, that you take what I've given above as a general rule of thumb but make sure that the advice fits the sufferer.

Anybody who has been bedbound for weeks or months, almost certainly, will be depressed but it might be difficult for the sufferer to see that there would be an element or a component of depression and I often find that patients deny being depressed and I'm not sure that it's easy to differentiate between chronic fatigue syndrome with some depression and chronic fatigue syndrome without it. In any event it would be better to try and lift their mood and encourage them to try a small dose of an appropriate medication. As discussed elsewhere I prefer Fluoxetine hydrochloride or Citalopram to do this job. Having said that if the medication helps then I would continue with it if it doesn't do anything then of course there's no point in taking it.

## MANAGEMENT IN CHILDREN

Chronic Fatigue Syndrome is a stress related problem and is no better demonstrated than in children with this condition. I think the youngest one that I have ever seen was seven years old. At this age, fortunately, it is uncommon but it gets more so, in children around the age of 13, 14 and 15 and, in my experience, almost exclusively young girls by a ratio of about 8 to 1. I have written about children with chronic fatigue syndrome quite a lot and in October 2003 I did a paper which was peer reviewed and published in the BMJ publication **Archives of Diseases of Childhood (Vol. 88 pages 894-898)** I did this paper with three others and the author was Dr. Maxine Patel, the other co-authors being Prof Simon Wesseley and Prof Trudie Chalder.

In children, chronic fatigue syndrome is much easier to treat than in adults as the stressor factors are more easily removed. I think the only exception to this is in children who have been abused and, unfortunately, this can go undetected for some years only to come back in the development of chronic fatigue syndrome in adults later when they are maybe 20 or 25 years old. So it is important that on, at least one occasion, the child should be interviewed by themselves. This should always be done in the presence of supportive staff and not done by the Doctor on their own.

Young girls aged 14 compose the biggest group here; they are physically growing, hormones are raging and peer pressure is huge, academic stress is great and relationships with one's parents is no doubt difficult in both directions. It is almost axiomatic to make sure that the child and the family, if necessary, are supported by talking therapies. Counselling is essential espe-

cially in young girls who have a significant degree of worry. There is no doubt that worry is an acquisition passed on from mum most of the time. This is especially so in twins, of which I've seen a couple, and the anxiety seems to feed from one to the other.

Treatment of chronic fatigue syndrome in children is, essentially, the same as that in adults, the difference being that the treatment in adults is down to the adult; treatment in children is very much down to mother and father and whether the child has a good relationship with the parents. When a children become ill they stay off school, lounge around the house in their pyjamas, lie on the sofa and watch TV or go onto their computer and involve themselves with a lot of social networking. As you will see elsewhere, visual processing is lethal in chronic fatigue syndrome and saying to a 14-year-old girl, "You mustn't watch your TV, use your computer or hang on your phone for more than 10 min per hour" does not go down well and, therefore, compliance with a programme in children, especially girls, is very, very difficult. Left to their own devices they will not adhere to a programme so mother, who may have to give up her job to look after the child whilst at home, has to be the gatekeeper of the programme and the treatment and this, almost invariably, produces friction between them. If the mother has to continue to work for financial reasons and can't take time out then the child would be left at home on her own and I have not found one young lady of 14 who will stick to a programme if left by herself.

Medications in children are also very restricted. Under the age of 18 the only medication that is licensed is Amitriptyline at night and I also use Melatonin but this has to be purchased as, probably, it's not easily prescribed by the general practitioner but it is fairly easily obtained from reliable sources on the Internet. I would always use Amitriptyline as a first line medical approach to

get the sleep pattern right, the way in which this is done this done being exactly the same as in an adult. It is usually very well tolerated and an average dose would be 20 to 30 mg.

Continuity with the school and a child's education is hugely important and so is the social aspect to the child's life. It's important that friends continue to come round, that they continue to get support from their peers and not break away from school and its social aspect any longer than is absolutely necessary and when there is any sign of improvement the first thing to try and do is to get the young sufferer back-to-school, even if it's just to go in for lunch with no academic input at all so that they don't lose their peer group. If possible, it's preferable that the school sends work home and, if the child has been off for any significant length of time, that home tuition is provided. It is important that the young child's General Practitioner is involved very early on and asked to write to the school to explain what's happening, to make sure the school understands, and that the child is not pressurised in going back to school any earlier than he can possibly manage.

It is important that the child be referred to a Consultant Physician or Paediatrician, depending upon the age, to make sure there's nothing else causing problems, and that the relevant blood tests, which are essentially the same as for an adult, be performed. It is very common that anxiety and depression become a component part earlier in children than in the adult and then you get stress-related symptoms on top of chronic fatigue syndrome headache irritable bowel syndrome; abdominal pain is common and often referred to as abdominal migraine. Frequent infections, colds and sore throats are more common in children than in the adult because, of course, at school there is a lot of it about.

As I have already said the outcome in children is much better than in adults as the peer pressures and the stresses are more easily removed. As children improve it is important to get them back to school as soon as possible and if they go back to school they should go back, on a daily basis, to a programme which would start with homework being sent home and, when at all possible, for the child to attend school, daily, for lunch. As the improvement continues they would start to go to school and do one lesson every day. I would suggest that the first lesson to be attended would be one immediately before or after lunch. As improvement continues they would go to another lesson (which has been gradually built up at home) before or after lunch so the programme would be going to school at say 12 o'clock midday, doing one lesson, having lunch and then another lesson at 1:30/2pm o'clock in the afternoon, depending upon the school program and then to return home.

It is important that they should also attend school for physical exercise. Of course, they will not be well enough to undertake a significant amount of physical activity but the period on the afternoon when physical exercise is part of the curriculum should be attended and the activity would start with just a few minutes. Again it is important that the school understands this and how it should be managed.

As the young child improves, attendance at school would increase. Unfortunately, as you will know, when the child is 14 years old they are just starting their GCSE syllabus. If the child has lost a significant amount of schooling then it is important to reduce his curriculum and you should start by making sure that the cuts to the curriculum are adequate. If the child goes back to school and does little bit too much they can struggle, coursework gets behind as they are unable to do it, and this increases the anxiety and tension. As they fall further behind it's important that, if you do reduce the curriculum,

the reduction remains permanent until the end of the GCSE coursework at the age of about 16. As they improve they shouldn't have subjects reintroduced again; you've got to cut back sufficiently so that the child can cope.

*There is much more on the subject of returning to school and education generally on the **Get Well Guidelines PDF**.*

## Psychology and Chronic Fatigue Syndrome

Over the last twenty years of treating CFS/ME I enjoyed the support of a Consultant Clinical Psychologist. However, he retired about five years ago and, as the waiting list for patients to see a Clinical Consultant Psychologist in this area has been inordinately long, I have had to provide the necessary cognitive behavioural therapy and give stress management advice etc. As I am not a qualified Psychologist I am sure that a lot of it has not been terribly good. If it is not available on the NHS and patients cannot afford to 'go private', then they don't get help in this area at all.

As you will see elsewhere, I know that the most important predisposing factor to CFS/ME is an unremitting set of negative stressor factors, and it is very important that patients remove these before they can start to improve. I tend to be very confrontational with these problems, in as much as I would say to a patient, in essence, "If you have a problem then you must sort it." That, however, may not always be possible and my approach may not always be entirely helpful in this area, but if you have a one man band you might end up having just one tune played in the same way each time. In my defence, however, I do try to make sure that my approach is sensitive and varied, although I am afraid I may not always be successful at that! When it boils down to managing internalised negative anxieties born of the patient's personality, an entirely different set of management applications are required, and these are best supplied by a Psychologist.

A Psychologist in this respect will help a patient understand their own anxieties and how to best cope with and manage them, applying a whole series of techniques to do so. Psychologists do not use medications. Indeed when I have been able to refer some patients to a Consultant Psychologist on the NHS, when these services were available to me, and where the waiting list

wasn't as long as they usually are, the Psychologist concerned usually wants the patient to stop their medications before they feel they can help him or her. Their approach would be perfectly right by saying that if you cover up your anxieties and stresses by taking pills to get rid of them then you can't learn to handle such anxieties and stresses in another and better way.

In an ideal world we shouldn't use drugs to remove anxieties but learn how to keep them in perspective. In the sixties, of course, Doctors used 'mother's little helper', Valium, rather than sort out the patient's problems. If somebody had a bereavement, it was felt that they should be given an anti-depressant or Valium to make them feel better, and not go through the appropriate grieving process. This seems to be a very English thing; that you should not be seen crying your eyes out or screaming and jumping up and down, but doing the 'stiff upper lip' thing by burying your anxieties and stress in some cupboard in the back of your brain. This doesn't help because, I promise you, that cupboard keeps banging open and these red hot skeletons have a horrible habit of coming back from time to time to haunt us all.

Psychologists can help patients to go back over their anxieties and their previous stresses, to work through them in an appropriate fashion so, eventually, the skeletons become white, dead, cold bones. Then you can bury them and they don't rattle any more.

*(Continued on page 102)*

## What is Psychological Therapy?

(We are grateful to The Atrium Clinic of Southend-on-Sea for the following notes ( © Atrium 2004) on this subject and you can visit their website by copy and pasting the web address into your browser.



[www.atriumclinic.co.uk](http://www.atriumclinic.co.uk)

Psychological therapy is also known as counselling and is a talking and listening therapy to enable and facilitate a change or a move for the client. Therapy does not change people - people change themselves. However, if a person wants to change, counsellors/therapists have the skills, knowledge and the imagination to help people work towards their goals or outcomes.

One of the best known therapies is **cognitive behavioural therapy** (CBT), particularly used for stress, anxiety and depression. It looks towards challenging and changing negative thoughts, which in turn change feelings and behaviours.

Other therapies include:

**Person Centred** - This therapy, as the name suggests is designed around the client. The theory underpinning this therapy is that it is important for the client to learn to understand himself/herself and make independent choices that are significant in understanding the problem.

**Rational Emotive Therapy (REBT)** teaches individuals to be responsible for their own emotions and gives them the power to change and overcome their unhealthy behaviours that interfere with their ability to function and enjoy life.

**Transactional Analysis (TA)** The theory of TA is based on the fact that the human personality is made up of three "ego states" *parent, adult* and *child* and within counselling TA works towards creating changes desired by the client and involves using the *adult* state to sort out behaviours, emotions and thoughts that are preventing the development of a client's full potential.

**Neuro Linguistic Programming (NLP)** was developed from studying the thinking and behavioural skills used by particularly effective and successful people. **Neuro** refers to how the mind and body interact. **Linguistic** refers to the insights into a person's thinking that can be obtained by careful attention to their use of language. **Programming** refers to the study of the thinking and behavioural patterns or 'programmes' which people use in their daily lives.

**Solution Focused Brief Therapy (SFBT)** is a short-term goal-focused therapeutic approach, which helps clients change by constructing solutions rather than dwelling on problems. Elements of the desired solution often are already present in the client's life, and become the basis for ongoing change.