TRANSCRIPT OF VIDEO OF LECTURES GIVEN ON 23rd NOVEMBER 1995 AT THE COVENTRY AND WARWICKSHIRE POST-GRADUATE CENTRE BY Dr ALAN FRANKLIN AND PROFESSOR PETER BEHAN

NOTE: **The emphases used throughout are those of the speakers themselves**

On 23rd November 1995, as a result of the hard work and determination of Robert Ennis Chairman of the Coventry and Warwickshire ME (myalgic encephalomyelitis) Support Group,two eminent speakers were welcomed to the Post-graduate Centre; the audience of about 70 consisted of general practitioners and consultants,with representatives from the Coventry and Warwickshire Health Authority and Social Services, together with representatives of the education and nursing professions.

The credentials of the two speakers were impressive: Dr Alan Franklin is a consultant paediatrician at St John's Hospital, Chelmsford who specialises in children with ME and he is a leading member of the Task Force set up by the Government to study ME. Professor Peter Behan, Professor of Neurology at Glasgow, is head of the European team investigating the cause and treatments of ME and had just returned from a world Congress on ME held in Brussels; he is, in addition, a psychiatrist.

Dr Franklin started by adressing the question of whether "ME" exists in children,as the original reports dealt only with adults; he at once said that the fact are that it **is** the same illness: although the **onset** may be slightly different, after some months the signs and symptoms and the progress and course of the disease leave little to choose between children and adults, and indeed, in the introduction, we were told that children and young adults constitute one third of all sufferers from ME. A recent epidemiological study by Dr Betty Dowsett (a former President of the MEAssociation) has shown that the majority of children away from school for any length of time are probably, unless they have had some major disability or accident, children with this illness.

Dr Franklin said that the usual criticism is that ME does not exist as a separate entity,and that children who are school-phobic use it to avoid school,or that it's really somatisation (a psychiatric disorder characterised by multiple recurrent changing symptoms in the absence of physical disorders to account for them; it is treated with cognitive therapy,which is a form of psychotherapy based on the belief that psychological problems are the products of faulty ways of thinking). Dr Franklin said that there are without doubt children who are school-phobic,but when that group has been accounted for,there has been a great increase in children who have been ill for a very long time for reasons which cannot be otherwise explained.

Dr Franklin noted that doctors find it difficult to make the diagnosis of ME and acknowledged that in his own training, he had been taught nothing about it,so when he first encountered it, his immediate opinion was that it was an hysterical disorder, but further assessment by child psychiatrists showed that such children are **different** from those normally referred for psychiatric help: they are not depressed; they are not school-phobic;if they have been out of activity for a long time, they are weak, bu the characteristic feature is not weakness,it is **fatigue**, which is disabling.

Dr Franklin stressed that he hoped we have all now abandoned the tendency to suggest that if no physical cause can be found for an illness,then it **must** be psychological: he remined us that in order to make a psychological diagnosis, there **must** be positive psychological factors. He said that unfortunately,the papers by McEvedy and Beard (two psychiatrists from the 1970s who were looking for a vehicle for a PhD thesis and who chose the 1955 Royal Free outbreak of ME for their purpose; without seeing a single patient for follow-up,and relying only on their own interpretation of the case notes, ie. over-ruling the clinical findings of the doctors who were actually involved in the outbreak,they concluded that the disease wasnothing more than an outbreak of hysteria),together with the work of some more recent psychiatrists, have **played up** the idea that psychiatric factors are predominant whereas they certainly do **not** account for the origin of the disease.

Dr Franklin went on to say that historically,there are quite a number of diseases which have gone through this kind of process; he cited asthma,which a hundred years ago was considered a very minor condition which should be more or less put on one side,so it was dismissed as a psychological illness,but it is now known that asthma is a very complicated immunological process.

He pointed out that there is a tendency for doctors to mislead themselves,and this is particularly so in relation to ME.

Dr Franklin then addressed the vital issue of how ME is diagnosed,saying that despite all the talk of pain and muscle and stomach aches, we should recognise the disease as a **brain disease.** Recent guidelines published in the Annals of Internal Medicine and drawn up by a combined international committee including Professor Behan state that fatigue as a primary symptom for which no other cause can be established is mandatory; this fatigue must be of new onset and be persistent or relapsing, so TATT (Tired All The Time) is immediately excluded. The fatigue is usually accompanied by tender lymph nodes, recurrent sore throat,tender spots in the muscles,headaches, pain in the joints, and unrefreshing sleep made worse by vivid dreams. There is no muscle wasting, as the peripheral neurology is intact. There may be a depressive element. When all other causes of gross fatigue have been ruled out,there remains a group distinguishable as having idiopathic chronic severe fatigue, the intensity of which makes it a recognisable syndrome: the quality of this fatigue is incapacitating. Children are pale and **exhausted** after doing very little; they feel ill all over; they are dizzy; there are changes in appetite and body temperature regulation; there is often photophobia and hyperacusis,which are **unusual** and distressing in children, whose normal world is noisy. There may be episodes of shaking: Dr Leslie Findley (consultant neurologist in Essex) has found that EEGs **are** altered,but this is not epilepsy. There may be hallucinations,which are not auditory but visual, and there may be the more difficult symptoms of lack of swallowing and lack of voice,which are probably due to muscular involvment.

At such a level of exhaustion,it is very tiring to work through a meal,and sometimes children do lose weight and do require naso-gastric feeding or a gastrostomy.

The cognitive symptoms include impaired concentration,reading difficulties,and confused thought and speech,and it may be that it is a teacher who first becomes aware of a child's illness; there may,however, be pressure brought by the school doctor,but children **cannot** learn if they have that sort of problem.

There is no pathognomonic test: the diagnosis is a **clinical** one based on a recognisable pattern of symptoms which are fairly consistent. SPECT (single photon emission computerised tomography) scans do, however, show in **every** case that there is hypo-perfusion of the **brain stem**, not just the cortex.

Having diagnosed ME, how do we treat it and how is it managed? Dr Franklin then gave some tragic examples of how cases should **not** be managed,telling how a child with ME was left alone in hospital on the premise that "hysterics" never harm themselves; the girl fell out of bed;she cut her lip and was badly bruised;she also fractured her skull,yet she was still deemed hysterical by the staff. After about a year, this girl recovered sufficiently to be able to return to school,but there were horrendous residual psychological problems,and whenever this child comes under pressue, some of her symptoms return.

Dr Franklin said this raises the question of whether we are dealing with an illness which goes on for many years: a lot of people would like to think it is just one acute episode: the probablity is that there is a genetic factor which means that patients are likely to succumb to future stresses.

Still under the broad topic of management, Dr Franklin quoted from the recent GMC Guidelines,which state "Patients must be able to trust doctors with their lives and well-being. To justify that trust, we as a profession have a duty to maintain a good standard of practice and care and to show respect for human life". Notwithstandin Dr Franklin said he has had the sad experience of meeting families whose doctors

have treated them worse than they would their domestic animals; he continued (quote) "there **are** colleagues who **do** try to trivialise this illness and put patients down, and I don't think that's on. I think that's very unjustified".

He then discussed the two contrasting methods of current management: the first method is to remove the child from home and push it through a programme of rehabilitation, but this route should **only** apply to a child who is well on the way to getting better. If this method is employed in the early stages, it results in further collapse, causing distress, fear and mistrust.

The alternative method is to keep the parents totally involved throughout, and to try to give the child some control of the illness,which must be **staged:** the most important measure in getting better is to pace oneself. There should be a **gradual** increase in activity; the pace must **not** be forced. If so, it will exhaust the child further and will usually precipitate a relapse.

There is a need to stay opimistic,as most young people do get better, even if not totally so.

There are no drugs which make a big difference to this illness: hypnotics (sleeping tablets) do not help **at all**, and pain-relieving drugs,even massive doses of opiates, seem to be very ineffective.

Occasionally,however, Dr Franklin has found that the most effective useful drug for children is a very small dose of amitriptyline (an anti-depressant which has a mild tranquilising action) given in the evening. In general, however, anti-depressant do not help in ME; Dr Franklin said that at the recent Brussels conference, it was demonstrated via a double blind study that the use of Prozac (much promoted by certain psychiatrists with a particular interest in ME) made **no** difference at all if the patient is not clinically depressed.

Complementary medicine is an area where there needs to be some care; Dr Franklin described it as a "suck it and see" situation.

He then went on to discuss possible models for this illness; he stated that stress and toxins, especially organo-phosphates (OPs) produce a similar illness,and that the post-polio syndrome (PPS) is virtually indistinguishable from this illness. He mentioned the work by Demitrack et al, which has demonstrated that hormonal factors are involved.

In children, the age range is from 5 - 20 years,with the average age being 12.9 years; if symptoms are established and stable for 3 - 4 months, then it is likely to go on for a much longer period,and can last up to seven years.

There is a ratio of two females to one male.

Overall, it is likely that there are genetic markers: subsequent infection and stress are seen to be the **precipitating** factors which lead to a disturbance of the hypothalamus, which in turn leads to a reduction in circulating levels of cortisol, which can be demonstrated. (Cortisol is a steroid hormone important for carbohydrate metabolism and for the normal response to any stress).

Dr Franklin then returned to an aspect which clearly caused him concern: he said that his experience is that there is a tendency to **overemphasise** the psychiatric aspects of ME: he told of a young undergraduate at Oxford who had previously had ME; this young man then got flu and took several weeks to get over it. When he returned to college,he was sent down on the grounds that he had a previous **psychiatric** diagnosis. Dr Franklin showed that this story served to illustrate one of the problems of making a psychiatric diagnosis; he made the point, however, that psychological factors **do** need to be taken seriously if they occur in ME,because **fear** may sometimes hold patients back,and **phobias** are found during and after the illness,but these are likely to be a **consequence** rather than a cause. Dr Franklinmade the point that

there is absolutely **no** secondary gain in ME.

In conclusion, Dr Franklin gave a useful summary; he said

1.there are three phases of ME: the toxic phase where the patient is still getting worse; the convalescent phase where the illness has stabilised but where doing anything increases the symptoms, and the recovery phase.

2.ME is a disease that can affect people of all ages

3.it is often not recognised, and can even be denied

4.it is difficult to diagnose

5.it runs a variable course from day to day and even from hour to hour: this is very characteristic, and the change is dramatic,which is confusing for doctors

6.the cause is unknown

7. it is often dismissed as trivial and unimportant,but it can lead to great disruption of life

8.there is nothing very positive available from a therapeutic standpoint

9.the illness **must** be recognised correctly

10.special problems occur in children:

patients cannot go on as before,and this is a hard thing to say to a child

children need to be believed, and we must **listen** to them

education is important,but school can be very stressful in that all the noise and bustle and activity may exhaust a child even before it starts to learn; some schools take on an "all or nothing" attitude,which is definitely contraindicated in ME; part-time schooling or even home tuition may be required,and there are some children who are too ill for any schooling at all

family relationships are especially difficult for young people with ME: normal adolescents want to leave home and be independent,but those with ME are forced to become **more** dependent

young adolescents find a restricted social life particularly hard to cope with: they opt out of going to parties because they are ashamed to have to leave after the first half hour through exhaustion

youngsters should be taught that there is a need to **negotiate** with this illness: they must recognise that it now takes much longer to get from A to B,but that even though it is now necessary to get from A to B via C, it **can** normally be done.

Dr Franklin finished by reminding us that ME is a complex disease, and although there i no diagnostic test,there **are** diagnostic patterns; improvement depends on quite a number of things.

Whereas Dr Franklin gave an overview of the clinical aspects of ME,Professor Behan dealt with current research perspectives. He began in his usual robust manner by making sure the audience was left in no doubt whatever of his view of those psychiatrists, often powerful, who have brought to patients with ME what Professor Behan termed "**enormous** trouble"; he believes this actually contains a degree of malignancy because of the harm caused by these psychiatrists' "psychobabble". Like Dr Franklin, he at once confirmed that ME is an **organic** illness,and clearly stated that the current subscription to a psychiatric aetiology is the result of the involvment of psychiatrists. He was adamant that there could not be a persisting psychic disturbance when 70% of patients have **no** abnormality of the psyche.

Professor Behan said ME is not a new illness: it was well described in 1750 by Manningham in a book called 'Febricula' (little fevers), and was equally well described in the 18th and 19th and early 20th centuries.

Although it remains essentially a diagnosis by exclusion,there **are** now laboratory techniques which will confirm the diagnosis.

He said that when his team first started studying ME,they thought it was precipitated only by a virus,but there is now no question that some cases of the same illness are precipitated by certain toxins,notably those of the ciguatera fish,from which two separate poisons have been isolated. Patients who develop the condition following such poisoning are **supersensitive** to 5 H-T reuptake inhibitors (5-hydroxytryptamine) and if they are given for example 50mg of sertraline (Lustral, an anti-depressant which works on the neurotransmitter 5 H-T,also called serotonin),they will be absolutely destroyed and will develop every complication.

Interestingly, on **second** exposure, patients do not require the same dose of toxin: a **miniscule** dose will do the same thing,and this is true also of organo-phosphate (OP) poisoning,which precipitates an identical illness; again, just a whiff of the chemical will cause deterioration.

Professor Behan stated that in his opinion, it is stupid for people simply to say this is not so, without any explanation for **why** it should not be so.

He said one has to explain **why** minute doses of toxin re-exposure cause the illness, or why, if there is an acute precipitant such as a viral infection,the illness goes on for twenty years; he said it was ridiculous to say this is due to the first exposure. Instead,he believes the first exposure **must** have induced in the patient a lesion **at the DNA level**,or else the virus must be persistent. His view now, however, is that there is **no** persistent virus in ME, and that there is no persistent enterovirus,no retrovirus, nor any other virus: his view has changed, because by using pcr (polymerase chain reaction), a very specific technique used in studying muscle biopsies,and by looking at the non-replicating part of the enterovirus, they were able to detect viruses in one in 300,000 cells in tissue culture. These findings were published, but when they then went on to do a very large number of biopsies with very detailed controls,the viral findings were the same in the controls as in the patients. As a result, Professor Behan changed his mind about the role of viruses as the aetiological factor.

Professor Behan then compared a condition known as myeloadenamate deaminase deficienc from which patients they had taken a piece of muscle and had stained for the enzyme and found it to be missing; it is known that the enzyme is missing due to a viral attack. Similarly, in ME, they have looked with probes and have found the gene and the messenger RNA to be present, but **at the level of translation**, there is a defect in that the enzyme is not present in muscle,which shows that there **must** be some persistent abnormality.

He then went on to address the nature of the fatigue found in ME; he stated that it occurs **acutely** and is exactly the same fatigue which occurs in other conditions such as multiple sclerosis, even going so far as to state "patients with multiple sclerosis have chronic fatigue syndrome and the fatigue is **exactly** the same".

Some patients with endogenous depression have exactly the same fatigue, as do patients with Gilbert's syndrome (a familial condition due to an inherited deficiency of an enzyme in the liver cells causing a form of jaundice). Professor Behan looked up the literature on Gilbert's syndrome dating back to 1901,all of which documents that patients develop ME-like fatigue after **stress**, or after a **viral infection**, or after **exposure to toxins.** Why, asked Professor Behan, should that lesion in the liver give patients fatigue?

Post-polio syndrome is another in which fatigue is a prominent feature; we were reminded that polio does not invariably result in a wasted arm or leg: in studies on identical twins, it has been found that 20 or 30 years later,**both** will develop incapacitating fatigue even when the twins are separated. In polio, the cells involved in the **brain stem** are neurons that have on their surface a receptor for glucocorticoids, especially the S-2 (steroid) receptor, and **particularly** the 5 H-T receptor; the neurons may not die,but there can be a defect in oxydative metabolism and in glucose utilisation; in other words, in polio, the virus gets into the brain stem and into the neurons which have steroid receptors and biogenic amine receptors; the virus does **not** just affect the anterior horn cells. In line with other recent research findings on the post-polio syndrome, Professor Behan stated categorically that "PPS is identical in every way to chronic fatigue syndrome".

Another condition in which fatigue occurs is idiopathic cyclic oedema, in which the woman is water-logged throughout the menstrual cycle due to hypothalamic disturbances; also, there is **classic** fatigue in Parkinson's disease, a condition in which the fatigue is grossly incapacitating.

Professor Behan then turned to the **laboratory tests** which can now be done in patients with ME. In passing, he referred to the man who claimed that ME was hyperventilation syndrome (Dr Peter Nixon, lately of Charing Cross Hospital); Professor Behan said that elegant physiological studies have been done on ME patients, including measuring carbon dioxide and tidal volume,and there is no evidence whatsoever of hyperventilation syndrome, but what **is** found is that patients' oxygen consumption is lowered. He and his team at Glasgow have been carrying out tests on ME patients, alon with a group of excellent controls, in which participants are exercised until they are very tired; they are then left alone until the next day when the exercise tests are repeated. In well-defined cases of ME,by using refined techniques for measuring gait disturbance,and using an ergometer for measuring muscle power,there is a **phenomenal** drop off in maximum oxygen consumption.

Professor Behan then mentioned single fibre EMG studies (electromyogram,which is a continuous recording of the electrical activity of a muscle by means of electrodes inserted into muscle fibres); in the Glasgow tests, a needle is put into the centre of two normal muscle fibres; if there is a lesion in the the nerve, or in the terminal neuron, or at the neuromuscular junction, or in the muscle membrane,there are determinable abnormalities in the action potentials for each of these fibres: by using a computer to fix one of the action potentials, a variation occurs, recorded as a jitter, which can be measured. In patients with ME there are **gross** abnormalities about 80% of cases show the biggest jitter value obtainable,suggesting that something is wrong with the muscle.

Professor Behan then observed that if the same thing that is demonstrably wrong with **muscle** may be wrong with **other cells**, then it is necessary to come back to the concept of a primary stimulus that is cauing something to go on,so what might this be?

He turned next to NMR imaging (nuclear magnetic resonance; a technique of chemical analysis used in the diagnosis of brain abnormalities based on the absorption of specific radio frequencies by atomic nuclei,enabling imaging of soft tissues anywhere in the body in any plane); he said NMR studies showed that in ME, there is **very** early excessive intracellular lactic acidosis with exercise,and that this tends to persist, suggesting that there is something wrong with the glycolytic pathway.

(Glycolysis is the conversion of glucose to lactic acid,which process involves the production of energy; during strenuous exercise,pyruvic acid (a compound derived from carbohydrates) is reduced to lactic acid,which then accumulates in the muscles and causes cramp). These NMR studies on ME patients have also been done in Oxford, in Canada and in Belgium,and the abnormal findings cannot be dismissed: in ME, there are two indicators that there is undoubtedly something wrong; one is nuclear magnetic resonance and nuclear imaging; the other is in the field of neuroendocrinolo

Still on tests for muscle pathology, Professor Behan emphasised that when doing muscle biopsies on patients with ME,it was necessary to look at them **expertly**. He showed a slide of a normal muscle biopsy in which the mitochondria (the sites of the cell's energy production) appeared as little red dots: only careful and expert study revealed an **increase** in the mitochondria in ME. The Glasgow team have now done about 400 such biopsies,and they have found another abnormality, in that the cristae (the infoldings of the inner membrane of mitochondria) have gone, leaving honeycombed patterns. This honeycombing suggested to Professor Behan a toxic or a stress phenomenon in the mitochondria,so he arranged for the slides to be looked at by a Canadian professor who is the world authority on honeycombing patterns in mitochondria; he, too, believes this is a mild **toxic** phenomenon going on in the cell.

When cells of ME patients are looked at in tissue culture,a most extraordinary finding has been observed,in that the lactic / pyruvic ratio of patients falls into two groups: patients are either producing too little or too much. Recently, Professor Behan has been interested in Syndrome X,where an individual presents with what seems to be a coronary thrombosis; they may have very very severe angina, but all the usual test results are normal: treadmill tests are normal, the ECG is normal, a coronary angiogram is normal,coronary and myocardial biopsies are normal **but** there is an abnormality of the lactic / pyruvic ratio, together with conspicuous abnormalities of carbohydrate metabolism. This Syndrome X has been reported from the Hammersmith Hospital in London, and also from Sweden. What has been a breakthrough for Professor Behan's team is that they have discovered that these Syndrome X cases have gone on to develp chronic fatigue syndrome: the team at Glasgow has done thallium scans on patients with chronic fatigue syndrome, and in 100% of cases the scans are abnormal,yet again suggesting a cellular abnormality (Thallium scans are a method of studying blood flow through the heart muscle using an injection of the radioisotope thallium-201). Professor Behan showed a thallium scan of a young girl of 21 with ME; he said he currently has a paper in press about these cases, who all have **gross** abnormalities of the myocardium. Referring to Syndrome X, Professor Behan said that other data using PET scans (positon emission tomography) which measured the flow showed **no** ischaemia and no impairment,and **this is a metabolic abnormality.** Professor Behan said that thallium is treated in the body exactly the same as potassium,so the reason why thallium should be taken up in such an abnormal way in the heart and in skeletal muscle is unknown,but experiments in animals and some in man have suggested it is due to an abnormality of potassium channels,which are abnormal secondary to a missing or reduced enzyme.

Other tests have produced the significant finding that patients with ME have reduced levels of acylcarnitine,and carnitine is an amino acid used in mitochondrial oxydation for transpo rting fatty acids across the membrane.

At this point, Professor Behan delivered one of his famous interjections about "these great experts who tell me that in their opinion, chronic fatigue syndrome does not exist".

Resuming his review of tests which are abnormal in ME, Professor Behan said that one of his Lecturers had a special interest in liver function abnormalities,and had noted that patients with ME had raised cholesterol levels,so they did a study of 30 well-defined cases, looking not only at cholesterol levels but also doing a full lipid profile: of the 30 patients in the study,27 showed not only gross but **grotesque** abnormalities. Exactly these same abnormalities have also been observed by Professor Anthony Komaroff at Harvard Medical School. Professor Behan said that

in ME, there is not only abnormal carnitine metabolism,but abnormal lipid metabolism as well,and that this has not so far been **looked for** in these cases.

He then mentioned briefly that there is abnormal immune function in MEand that there is non-specific impairment of NK cells especially (natural killer cells are able to kill certain types of cancer cells),and this is another abnormality in which there are **gross** differences between these patients and normal controls.

Professor Behan then moved on to SPECT scans,which his team have been doing for some years; they do not only SPECT scans, but **serial** SPECT scans to see if the abnormality which was present on one scan would have disappeared the next time. The biggest series of SPECT scans ever done on ME patients has been done in the radiology department at Glasgow; the important thing the team found is that the dye gets inside the intravascular space and is taken up as a **metabolic index**,showing that it is the **metabolism** of the cell which **absorbs** the substance; in other words, if the **metabolism** is impaired,the substance does not get taken up,resulting in a flow deficit. Patients with ME demonstrate such flow deficits: there are temporal deficits,occipital deficits and fronto-parietal deficits,all amounting to **gross** lesions in these patients.

Another test used by the Glasgow team in ME patients is the water-loading test, which is given in the morning; the urinary output is measured over the next three hours,and in ME patients,the results were mostly **grossly** abnormal.

This study done by the Glasgow team was to measure the serum osmolarity and the urine osmolarity,and also to measure the product of the posterior pituitary, ie. argenine vasopressin (AGP) (Argenine is an amino acid which plays an important role in the formation of urea (the main breakdown product of protein metabolism) by the liver, and vasopressin is the anti-diuretic hormone, or ADH). The stimulus for AGP comes from the paraventricular nucleus of the hypothalamus,and when patients were given the water deprivation and water loading tests, there was **erratic,crazy** production in these cases.

At this point, Professor Behan stated that in his opinion, these test results bring home the **fallacy** of simply examining someone in a clinic with a tendon hammer and a stethoscope and pronouncing the patient to be normal.

He then showed a slide of the paraventricular nuclei of a perfectly healthy rat which was stained to look for activated receptors on neuroendocrine cells and to measure a hormone, the presence of which is an index of the activity of that part of the gland. He told us that Professor Christiansen of Sweden had injected these normal rats with trypanosomes (microscopic parasites) and that the trypanosome does not get into the hypothalamus,but **does** get into other parts of the brain stem where the blood-brain-barrier is broken down (BBB is the mechanism whereby circulating blood is kept separate from the tissue fluids surrounding the brain cells and which excludes solid particles and large molecules ; this can break down after injuries such as whiplash). Having got into parts of the brain stem,an immune reaction is elicited,and these activated T cells produce cytokines (chemical messengers),and once these cytokines are produced, an **enormous** turn-on of the hypothalamus occurs; this is a **selective** turn-on of the paraventricular nuclei.

Professor Behan then showed a slide of the brain stem demonstraing the reticular formation and various nuclei in the hypothalamus to which he had been referring, stating that these nuclei are the ones involved in viral infections,particularly polio infections. He said it is known that in the post-polio syndrome (PPS),if patients with severe fatigue have their growth hormone measured,it is low. Growth hormone has rapid daily fluctuations,but it is carried by a protein which does **not** fluctuate. A colleague of Professor Behan's (Professor Martin, a neurologist) has described cases where after hypophysectomy (removal of the pituitary gland), if all the hormones **except** growth hormone are administered,the fatigue continued, so the Glasgow team decided to measure growth hormone levels in patients with ME,in patients with depression and in controls; they found that in ME,at base line,the

growth hormone levels are very low; moreover, if patients are then stimulated by being given steroids (which should result in a massive up-swing),there is no questi that compared with controls,ME patients have no response. This work has been repeated in five different laboratories and the growth hormone abnormality in ME has been absolutely confirmed. (Among other things, growth hormone increases protein synthesis).

To tie the whole thing up, Professor Behan explained that 5 H-T is particularly interesting: it is produced in the median eminance of the midbrain and sends fibres **directly** to the paraventricular nucleus and from there to the median eminanc **controlling the release of steroids.** Thus if you give a 5 H-T **agonist**,there would be a rise in cortisol,so with this in mind, the team did an experiment with a **pure** 5H-T_1 agonist and found that in patients with ME,there is a very blunted response. This demonstrates that there is something wrong between the 5 H-T axis and the production of cortisol (the hormone required for normal response to any stress). This test has also been done with prolactin; again, there is a conspicuous differenc between patients with ME,with depressives, and with controls; notably, the depressi react entirely differently from patients with this syndrome.Professor Behan noted that with any adrenal damage, there is supersensitivity to 5 H-T_1 receptors.

So, what causes this illness? Is it a defect of carbohydrate metabolism? Is it a muscle abnormality? The illness cannot be due to **all** of these,but if you have a **central cellular deficit** which was giving rise to a number of **other** abnormalities, that might explain the whole picture.

The thinking at the moment is that in patients who are perhaps genetically susceptib and depending on the stimulus and upon the time the stimulus is given,whether this i a virus or a toxin, a **damage occurs;** this damage has to be fundamental because of th number of tissues involved,and is almost certainly **at an enzyme level**, which affects the subtle metabolism of the cell,probably in relation to potassium channels.

At present, professorial departments in Sweden, London, Harvard and of course Glasgo are looking carefully to see if they can dissect out this abnormality in very subtle ways, to see what the lesion is. This lesion will have enormous importance,not only ME but particularly in multiple sclerosis and in all those diseases where fatigue is a feature. Until this particular lesion is understood, a rational mode of therapy cannot be brought about.

Professor Behan said he hoped the audience had got the idea that this is not just a crazy illness,but that it is a very exciting, challenging, and indeed a very importa illness.

He then wished to re-emphasise what Dr Franklin had said: in his own time of looking ME, he has seen far, far too many people who have been told that it's all in their head and that they are crazy; the end result has been that several have committed suicide and others have been caused the most terrible distress.

He related the story of how he had been approached by a consultant psychiatrist; this man and his wife had been to Spain where the man got severe gastro-enteritis, followed for nine months by attacks of sweating; he was greatly fatigued: he couldn't dig his garden,and was in serious danger of losing his job. Mischievously, Professor Behan responded in "psychobabble",whereupon the consultant psychiatrist very quickly told him to cut that rubbish; he was sick and needed treatment, not psychotherapy.

Having come full circle, Professor Behan ended his lecture at this point,but then dealt with a question and answer session with Dr franklin.

Dr Franklin addressed questions about the recovery phase of ME; about diet and food intolerance,which is common in ME,and about what opportunities there are in the NHS to determine such intolerances, which are highly individual and which can only be picked up by elimination and challenge dieting.

Professor Behan addressed the fact that **myalgia** is explained through the breakdown in metabolism, going on to say that some patients have **incapacitating** myalgia. He went on to say that myoadenalate deaminase is a specific enzyme in muscle,but after viral infection,although stained for, it has **gone.** If one did not know that this enzyme **should** be there, one might think the muscle was normal, as other tests would be normal. This is but one metabolic lesion: all these lesions have a feature in common,in that there is lactic acidosis or pyruvate disturbance, **particularly** in those patients where there is marked myalgia.

Professor Behan was then asked if there were any useful drugs; he said if **and only if** there was depression, then small doses of sertraline may be of benefit. In children, an anti-convulsant had an effect on various channels,but this was only a symptomatic improver. The standard two-week treatment for getting rid of lactic acidosis could be tried.

He then mentioned that it has been confirmed that in ME, 24-hour urinary cortisol is low,with some bizarre ACTH and cortisol responses that suggest mild Addisonian disease of the brain; there is some evidence that if normal physiological rather then pharmacologial levels can be maintained,then patients appear to be better.

He was then asked about the role of Efamol (GLA) : he replied that in diabetes and in conditions where the cholesterol is abnormal,there is associated chronic fatigue; in diabetes, it has now been shown **conclusively** that where there is peripheral neuropathy causing pain,the actual nerve conduction can be measured, and if these patients are given very large doses of Efamol, then at three months there is or is not a little improvement; at six months, there is defintie improvement; at nine months,it is statistically significant, and at a year, there is marked improvement. From this, it is emerging that if Efamol is to be taken, it should be for a very long time at very high doses.

Then followed an interesting contribution from a member of the audience who had done her own research and who knew that there is good evidence of fatigue not only in secondary growth hormone deficiency but also in primary growth hormone deficiency, and that there may be secondary cortisol dysfunction from the growth hormone deficiency. She had also done muscle biopsies in patients with growth hormaone **excess** in which she had observed the same muscle biopsy changes described by Professor Behan; most interestingly, she had also noted cholesterol disturbances as well. Professor Behan completely agreed,saying that work in Glasgow on muscle biopsies from human midgets who had been given growth hormone showed some apparent abnormality of the muscle architecture which is not dependent on the **level** of hormone.

This same questioner then raised a particularly pertinent matter,saying that post-head injury syndrome is very similar to chronic fatigue syndrome; she felt it was important that people realise this,and that the same method of treatment outlined by Dr Franklin for ME should also apply to the post-head injury syndrome. Professor Behan's response to this was possibly the most significant aspect of the whole meeting. He said that ever since he was a junior resident in neurology, he **knew** that when he got a patient with post-head injury syndrome,he'd got someone who was not going to respond to conventional treatment. He and Professor Dinan and a number of others have done some very interesting work which has shown that patients with post-head injury syndrome have quite marked neuroendocrine disturbances; they do not respond to conventional anti-depressants. Often the case comes up in Court, and the interesting thing is that that nearly always the injury is not a head injury as such,it is a **posterior** head injury involving the back of the head and neck. He mentioned that he is currently preparing a book for Oxford University Press in which

he is showing that this type of injury in the neck can precipitate multiple sclerosis. He said there is a reason to think that these posterior head injuries are very very important,and that the nature of their depression is probably endocrine. The same questioner replied that these posterior head injury patients are in a group who are less likely to have lost consciousness and are therefore dismissed as not having had a bona fide head injury,a view with which Professor Behan absolutely agreed.

There was no time for further questions,but Robert Ennis spoke briefly about his own personal situation and the difficulties he had encountered in getting a diagnosis. He drew attention to the fact that patients with ME are still being left alone,or they are bullied; they had no hope; they lost friends and families became divided. Even a local doctor whose daughter had ME had experienced difficulties of credibility with his own colleagues.

He compared this state of affairs with the situation in America, telling the audience that three top ME researchers gave a testimony to Congress in which one of them, Dr Mark Loveless, testified as follows: "A patient with chronic fatigue syndrome feels every day significantly the same as an AIDS patient feels two months before they die".

Robert Ennis concluded by saying that Warwickshire is called the black hole of the Midlands; it has a lot of patients with ME and a lot of doctors who do not understand the condition,nor do they wish to understand it,nor do they even try to find out about it. Meetings with prominent ME experts have been arranged,and doctors have been begged to attend, to no avail.

Robert Ennis deserves special commendation for his efforts to overcome entrenched medical ignorance and arrogance about ME,of which there are pernicious enclaves in Warwickshire and Leicestershire; let us hope that those colleagues who attended this meeting will spread the word about the devastation ME can and usually does cause.

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