The National Archives

MEDICAL RESEARCH COUNCIL

HEADQUARTERS FILE

S 1528/1

SERIES SUBJECT

MYALGIC ENCEPHALOMYELITIS: (ME)
POSTVIRAL FATIGUE SYNDROME. (PFS).

FILE TITLE

CORRESPONDENCE.

RELATED TO:
A203/371
A201/618

8000

S1528/4.

REFER TO	Initials	REFER TO	Initials	REFER TO	Initials
Dr Dowman.	JS	Dr Karen Finlay	✓		
Miss Buckley	✓	Dr. Anne-Marie Coriat	✓		
Miss Ravey.	KAM	BMS			
Dr Levy	✓				
Miss Breen.	✓				
Dr D Cox	Dr				
Dr Cox	Dr				
Miss Ravey.	KAM				
DR Jepson.	MWJ.				
Miss Ravey.	✓				
Miss Abbott	✓				
P Dukes.	✓				
Dr Jepson	✓				
Registry	✓				
M Jepson	✓				
Chris Cansell.	✓				
M. Jepson	MJ				
Registry	RC ✓				
Miss Anne-Martinez	✓				
Dr. M. Jepson	MJ				
Miss A. Martinez	✓				
Dr D Colson	✓				
Dr Gower.	✓				

PLEASE ENSURE THAT THIS FILE HAS BEEN ENTERED ON YOUR TRANSIT SHEET

* 016487 *

DISPOSAL INSTRUCTIONS	Signature	Date
REVIEW FOR DESTRUCTION IN ....YEARS		
DESTROY		
RETAIN FOR A FURTHER ....YEARS		

Miss Buckley: File, for info.

DJ
8/6/88

Miss R[illegible]

You might like to be aware of this file.

Thelma
14.6.88

Mrs Breen

To note KL's letter of 10.4.89 for information.

Thelma
11.4.89

Dr Tapsell

You might wish to be aware of this file

Dr Glover

To see letter of 6 Nov for info.

6-11-89

S1528/1 please file

CHRONIC FATIGUE SYNDROME

CIBA Foundation Symposium, 12-14 May 1992

HIGHLIGHTS

The Symptom Library Ned Shorter (Toronto) fascinated the audience with his historical perspective on how symptoms of disease without apparent organic illness vary over time. For example, fits and paralysis were quite common in the 19th century, before improved neurological tests were able to demonstrate that many patients had nothing wrong with them. The symptoms became discredited, so the patients moved on.

Chronic fatigue was first described in the so-called "sofa cases" among middle class females in the late 19th century. The number of cases declined rapidly in the period before the First World War. It coincided with the increased safety and thus popularity of abdominal surgery. Surgeons became increasingly eager to open up women in order to try and detect organic disease in such cases. Again, the symptoms became unappealing to patients in the face of such "treatment".

Since the 1930s, a number of different concepts of chronic fatigue, including "chronic Epstein-Barr virus" infection, "atypical poliomyelitis", "myalgic encephalitis", and "fibrositis" or "fibromyalgia", have converged into the diagnosis of chronic fatigue syndrome.

Why is chronic fatigue so appealing to patients and their doctors? One factor must be that fatigue is difficult to disprove. There is a desire among patients and doctors to upgrade their symptoms in order to stay abreast of science. Virology and immunology are dynamic, progressive branches of science, and patients are irresistably drawn to them in order to explain the mysterious origin of their symptoms. This is evidence of a somatization disorder, in which patients believe their symptoms, which are psychogenic in origin, are evidence of organic disease. Many patients and their support groups aggressively deny that CFS has any psychological component.

It remains to be determined whether there is an unknown core of organic pathology which can account for the subsequent symptoms.

The anthropological viewpoint The Chairman (Arthur Kleinman, Boston) and several of the speakers pointed out the danger of over-emphasising the reductionist paradigm: this is a peculiar feature of Western medicine and may be particularly unhelpful in approaching CFS. In future, there should be integration of the approach to mind and body, thus eliminating the need to define CFS as either a medical or a psychiatric condition.

The experience of non-western investigators should be sought in future in order to benefit from the different viewpoints that these would bring.

CFS should be seen as an interweaving of mind, body and society.

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Epidemiology

The prevalence of CFS is difficult to determine for a wide variety of reasons. It is a collection of symptoms, not a disease, and is relatively uncommon. Many sufferers are probably not seen by health professionals and revert to non-traditional medicine for relief of symptoms.

Prevalence rates in a US study (Gunn, Atlanta) varied from 2.0 to 7.3 per 100,000 of the general population. More than 80% of cases were female, with most patients being white with an average age at onset of 30 years.

In a prospective study of a large number of chronic fatigue cases, Manu (Farmington, CT) found only a few had an identifiable physical disorder. However, most patients suffered from major depression, panic disorder or somatization disorder. In the majority of patients, the onset of psychiatric disorder preceded the onset of chronic fatigue by at least a year. Manu concluded that CFS is usually diagnosed in middle-aged white individuals (mostly women) with a high lifetime prevalence of major depression and somatization disorder and a strong belief in the physical nature of the illness. In such cases, it is probably inappropriate to subject the patient to an exhaustive battery of physical tests (see "The Treatment Process").

Muscle fatigue

This is a common symptom of CFS. Edwards (Liverpool) carried out light and EM tests on biopsies from CFS patients and controls. He concluded that on physiological and pathological grounds, CFS is not a myopathy; a primary role for psychological/psychiatric factors was deduced from a formal comparison between CFS and myopathy patients.

Virology

Straus (Bethesda) presented results on the association between herpes viruses and CFS. He concluded that these viruses are not primary causes of CFS and may not even be necessary for the perpetuation of the illness. He believes that it is the host response to the virus, not the agent itself, which leads to the symptoms. Cedric Mims agreed that the concept of a viral trigger was similar to that in other diseases, which resulted from a unique individual reaction to a common event.

A presentation was scheduled on retroviruses in CFS. However, the speaker did not turn up. . A replacement speaker, (Folks, Atlanta) drafted in at the last minute, produced results showing the absence of retroviral sequences in the samples studied and gave a detailed analysis to explain the discrepancies with the De Freitas paper. There was no evidence for an association of CFS with HTLV-II or other human immunodeficiency virus, but other known or unknown retroviruses could not be ruled out.

Behan (Glasgow) presented results which he claimed showed that enteroviral sequences could be detected by PCR in muscle biopsies from CFS cases.

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The meeting concluded that exhaustive analysis had failed to prove that CFS is caused by a virus or viruses. However, Mims reminded the audience that "absence of evidence is not evidence of absence". While keeping an open mind on the virus issue, members were increasingly drawn to the idea that the search for a single identifiable cause of CFS is meaningless because it is a multifactorial disorder.

Immunology

Lloyd (Frederick, MD) presented data showing disordered immune responses in CFS patients. However, no causal link between abnormal immunity and CFS was found, and the alterations may be secondary to some other disease process or co-factor.

Psychiatry

Fatigue is very common in the community, with surveys finding that 20-25% of both men and women "always feel tired". Fatigue is associated with high psychiatric morbidity in community, primary care and tertiary care samples. The high rates of psychiatric disorder have several explanations: for example, it could be due to a psychological reaction to physical illness. However, studies have shown that the relative risk of psychiatric disorder is increased 2-6-fold in CFS cases compared to controls with physical diseases.

Various themes emerged. One is of a subcortical dysfunction analogous to the cognitive problems seen in illnesses such as Parkinson's disease. The most impressive evidence of CNS disturbance was quoted by Wessely (Institute of Psychiatry) as coming from neuroendocrinological studies, suggesting a role for hypothalamic disorder as a final common pathway for CFS.

Sleep Disorder

Moldovsky (Toronto) is an expert in this subject and appeared to be [redacted] He postulated a three-way interaction between the immune system, the neuroendocrine system and the sleep/wake system:

immune system — neuroendocrine system

sleep/wake system

There did not seem much support in the meeting for the importance of the sleep/wake system's part in this interaction, apart from McLusky (Belfast) who in his own words "stuck his neck out" to assert that CFS is the results of a primary or secondary sleep disorder. He believed that neurotransmitters such as serotonin had a role in the sleep/wake cycle and also in depression, pain, and changes in mood which were all features of CFS. McClusky proposed that large scale trials were needed of drugs which modulated the sleep patterns, such as the tricyclic antidepressants and 5HT re-uptake inhibitors. There was some support for the probable importance of neurotransmitters but recognition of the difficulty of conducting trials.

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(3)

Non-pharmacological treatment of CFS

Sharpe (Oxford) described a trial of cognitive and behavioural therapy which he is just starting at the Warneford Hospital. The aim is to help patients re-evaluate and, if appropriate, change, unhelpful feelings about their performance and symptoms, and thus break the vicious circle. He admitted that the trial was a purely pragmatic approach without theoretical foundation.

The Treatment Process

Mechanic (Rutgers University) stood back from the arguments over causation and gave a thoughtful account, punctuated by wise epithets, of how the clinician should approach the patient with CFS.

Treatment is influenced by a large number of factors: on the one hand, by the peculiar definition of CFS by exclusion criteria, thus promoting the expenditure of large sums on diagnostic tests; and on the other, by the way patients present and are filtered out by the medical system, by organisational factors, by how the doctor is paid, and by the culture of medical care and practice styles.

The first duty of the doctor is to support as much useful function as possible and avoid the legitimisation of symptoms and reinforcement of disability.

Gender issues

Surprisingly, gender did not appear to be an issue, given that most CFS sufferers are said to be female. Buchwald (Seattle) drew attention to the difference in the sex ratio between community care and clinic samples, with women being more common in the latter. There were many possible explanations: the higher prevalence of psychiatric disease in women, the greater health care-seeking behaviour of women, the role of sex hormones, occupational and socio-economic differences, the doctor/patient relationship, and so on. There was no suspicion that CFS was an example of the male-dominated medical profession labelling a section of the female population as "malingerers".

General discussion

Shorter felt that from a historical perspective, CFS was an example of a disordered mind/body relationship that would not survive, just as many earlier manifestations had mysteriously disappeared, to be replaced later by others. It was important to step back and look at the whole phenomenon of somatization.

The meeting agreed that different countries had varying definitions of CFS and this made international comparisons difficult; laboratory tests needed to be standardised; and the control of medication in case-control studies should be improved.

The main benefit of the meeting was felt to be in moving away from the confrontations between single paradigms to the realisation that multiple paradigms are involved.

Summarising, the Chairman (Kleinman) predicted that in 10 years' time, as in the pain field, the central issues in the CFS field would be social rather than medical or scientific, partly driven by the economics and funding of the disability systems in various countries. He also emphasised the importance of

variation and pluralism in patients, and spoke of the importance of ethnic as well as gender issues in future research.

Finally, he emphasised the importance of CFS in knowledge creation itself. The realisation among investigators that so many disciplines were involved, from infectious disease to immunolgy, would be a powerful force for bringing a truly multidisciplinary approach to the problem.

SD:704

(4A)

MRC
Medical Research Council

Medical Research Council
20 Park Crescent,
London W1N 4AL

Telephone: 0171-636 5422
Facsimile: 0171-436 6179

From the Chief Executive
Professor George K.Radda CBE FRS

Tel: 0171 636 5422 ext 6217
Fax:0171 636 3427

6 March 1997.

Dear [redacted]

Re: MRC support for research in ME/CFS.

Thank you for your letter to our Chairman, Sir David Plastow, of 5 March I would like to reply on his behalf.

As you rightly note the MRC is accountable to parliament and the public, this is a responsibility that we take very seriously indeed. However, as I explained in my letter of 5 March it would be a breach of confidentiality for us to release details of proposals we have not funded. All applications we receive are handled in confidence, only details of applications that are successful in winning support are released publicly.

I am sorry not to be more helpful on this occasion.

Sincerely,

Redacted under FOI exemption (s) 40(2).Closed until 2071

Anne-Marie Coriat PhD
Deputy Executive Board Secretary
Neurosciences and Mental Health Board,

[redacted]

cc Sir David Plastow

(4B)

Author: Geraldine Healy at MRC_M1
Date: 06/03/97 11:59
Priority: Urgent
TO: Anne Coriat
CC: Karen Finney
Subject: [redacted] re ME/CFS
---------- Message Contents ----------

Ann-Marie

In the Chairman's absence I have today (6/3) received another letter from [redacted] asking for the "names of the applicants" question to be answered. After talking to Private Office, they have suggested that you reply to [redacted], in Sir David's absence, either providing him with the names etc he requests or replying that we cannot as it would be a breach of confidentiality - for you and Karen to discuss? (Penny not sure what the position re giving this kind of info. out was).

I'll pop down with the letter straight away, so a response can go out, if possible, today please (again, with a copy for Sir David).

Thank you.

Geraldine

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(4C)

-6 MAR 1997

Sir David Plastow
Medical Research Council
20 Park Crescent
WIN 4AL.

March 5, 1997.

Dear Sir David,

I received a letter this morning from Dr. Anne-Marie Coriat, dated March 3. The reply was very general and did not answer the specific question that I have asked - what specific research proposals on M.E./ C.F.S. has the MRC received, 1994-6?

Dr. Karen Finney informed me that there have been four, (telephone conversation with Dr. Karen Finney, Feb. 6, 2.00. p.m.)

Could I please have this in writing please and the names of the respective applicants.

The MRC is accountable to Parliament and the public, (MRC, Scientific Strategy, 1995, p.5.)

sincerely,

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c.c. Bromley and Chislehurst M.E. persons
Lord Nolan
The Rt. Hon. Roger Sims and other selected M.P.s.

(5)

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Section: 40 (2)

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(5A)

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24 MAR 1997

3
~~23~~/3/97.

To Sir David,

I telephoned the MRC on January 10, 1997 to enquire about research applications into ME/ C.F.S.

I asked Dr. Karen Finney to send me research applications into ME/CFS for the period, 1994.

I telephoned again on February 6 to ask for the information in writing. I have had no response. Would you please look into this matter, pleas

I ask for the names and titles of each project

I also ask for a copy of the White Paper Health The Health of the Nation, published in 1992.

Sincerely,

[redacted]

c.c. The Rt Hon Roger Sims and other selected M.P

5B

MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 0171-636 5422
Facsimile: 0171-436 6179

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Tel: 0171 636 5422 ext 6217
Fax:0171 636 3427

5 March 1997.

Dear

Re: MRC support for research in ME/CFS.

May I first apologise for mis spelling your name in my previous correspondence. Secondly, thank you for your letter to our Chairman, Sir David Plastow, of 3 March I would like to reply on his behalf.

I hope that recent correspondence (and publications) you will have received from Dr Finney and myself (letters of 15 January and 3 March respectively) have helped clarify how the MRC supports research.

As Dr Finney and I explained although we are not currently funding any research specifically on ME/ CFS we do fund a substantial amount of basic research that underpins any search for the pathophysiology of Chronic Fatigue Syndrome. Whilst is difficult to be precise about which research is specifically related to CFS (some studies will be more relevant than others) I hope the MRC Handbook which I forwarded to you 4.3.97 provides a flavour of the diverse range of potentially relevant research that we do support. I should point out that the Handbook does not provide a list of our project grant support but rather details long term investments such as Units, Institutes and 5 year programme grant awards.

Turning to your request for copies of applications we have received, but have not funded, that are relevant to ME/CFS. I am afraid that we are not at liberty to release details of such proposals. All applications we receive are confidential documents, only details of applications that we fund are released publicly. As I am sure you will appreciate to release such data would constitute a breach of confidentiality. I am sorry I can not be of more help with this request. I do hope however that our correspondence has reassured you that MRC continues to maintain an awareness of developments in research relevant to CFS, and that although we do not commission research directly, we always welcome high quality research proposals in any field for review in open competition.

(5c)

Concerning your request for a copy of the White Paper " The Health of the Nation " I am afraid that we do not keep spare copies of the document but have been assured that these can be obtained directly from HMSO stationers.

I have enclosed, for your information, some additional MRC publications which I hope you will find of interest i) MRC Annual Report , ii) Autumn/ Winter MRC News: This is the "journal" of the MRC and is published quarterly. I would be happy to add you to the mailing list for this publication (at no cost) if that would be helpful?

I hope this helps reassure you that Council is indeed committed to supporting high quality scientific research in all fields including proposals relevant to CFS.

Sincerely,

Anne-Marie Coriat PhD
Deputy Executive Board Secretary
Neurosciences and Mental Health Board,

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cc Sir David Plastow

(SD)

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E-mail anne.coriat@headoffice.mrc.ac.uk
Tel: 0171 636 5422 Ext 6217
Fax: 0171 636 3427

PLEASE NOTE NEW FAX & TEL EXTENSION

4 March 1997

Dear [redacted]

Re: Research support for Chronic Fatigue Syndrome: ref S1528/1

As we discussed on the telephone today the MRC funds a substantial amount of basic research that underpins any search for the pathophysiology of Chronic Fatigue Syndrome. This includes research in psychology, basic virology, immunology, neuroendocrinology and various imaging technologies such as magnetic resonance imaging and computed tomography. As I explained it is difficult to be precise about what we support that is specifically related to CFS since some studies will be more relevant than others, but I hope the enclosed copy of the MRC Handbook gives a flavour of the diverse range of potentially relevant research that we do support.

In terms of research specifically on CFS, we did fund an epidemiological study on CFS costing approximately £91,000 which was recently completed by the Institute of Psychiatry. A number of factors were investigated and the study was not purely of a psychiatric nature. The study demonstrated that attendees with symptoms consistent with a viral illness appeared to be a vulnerable group with more cases of chronic fatigue identified. I should point out that we receive very few research applications directly related to CFS, and apart from the epidemiological study mentioned above no applications received to date have been of sufficiently high scientific quality to merit funding.

You may also be aware that the Linbury Trust, a family Trust of Lord & Lady Sainsbury, funds some work in CFS.

In addition the MRC was involved in a consensus meeting in 1994 which helped revise the document subsequently published as the report of the National Task Force on Chronic Fatigue Syndrome (an initiative of the Charity Westcare, supported by the Department of Health). The report made clear recommendations about the need to clarify the definitions of various CFS, to enable further research into the underlying pathophysiology and for

MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL
Telephone: 0171-636 5422
Facsimile: 0171-436 6179

SE

assessment of the value of potential treatments. Unfortunately the report also made very clear that this area of research continues to be hampered by lack of consensus about the definition of CFS.

You may also be aware that, following publication of the Task Force report, the CIBA Foundation held a symposium on the neuroendocrinology of CFS.

The MRC continues to maintain an awareness of developments in research relevant to CFS, and we hope that continued activity in this area, for example through workshops such as those mentioned above, will stimulate submission of grant applications of sufficiently high scientific quality to warrant support. Whilst we do not commission research, we welcome high quality research proposals which we evaluate by peer review against specific criteria, critically and in open competition.

Please also find enclosed for your information copies of our Annual Report and a copy of the Autumn/ Winter edition of MRC News the "journal" of the MRC which is published quarterly. I would be happy to add you to the mailing list for this bimonthly publication (at no cost) if that would be helpful?

I hope this helps reassure you that Council is indeed committed to supporting high quality scientific research in all fields including proposals relevant to CFS.

Yours sincerely,

Anne-Marie Coriat PhD
Deputy Executive Board Secretary
Neurosciences and Mental Health Board,

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(SF)

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 0171 – 636 5422
Facsimile: 0171 – 436 6179

E-mail anne.coriat@headoffice.mrc.ac.uk
Tel: 0171 636 5422 Ext 6217
Fax: 0171 636 3427

PLEASE NOTE NEW FAX & TEL EXTENSION

4 March 1997

Dear [redacted]

I thought you might find the enclosed MRC Handbook of interest, it has just been issued this week.

Sincerely,

Redacted under FOI exemption (s) 40(2).Closed until 2071

Anne-Marie Coriat PhD
Deputy Executive Board Secretary
Neurosciences and Mental Health Board,

[redacted]

(6)

TI Virus-induced changes in 5-hydroxytryptamine receptor Small pro-subtypebin mouse brain

TYPE Small Project Grant

END 01-JAN-97

DUR 12

ORG University of Surrey, University of Surrey

A ; The effect of Semliki Forest Virus (SFV) infection, which is being used as an animal model of ***Chronic Fatigue*** Syndrome, on 5-hydroxytryptamine (5-HT) receptors has been studied in mouse brain We have shown selective up-regulation of 5-HTlA receptors in virus-infected mice which is localised to specific areas of the cortex and hypothalamus. The proposal is for studies to assess the specificity of the virus targeting of 5-HT receptor subtypes in the brain by receptor autoradiography concentrating on those receptors which have been associated with the pathophysiology of depressive illness in man. We will study by autoradiography mapping the effects of SFV on 5-HT2 and 5-HT4 receptors in mouse brain. In addition, the project will address if the virus-induced changes in 5-HTlA receptors are manifested at the genetic level byHT carrying out quantitative in situ hybndisation using probes for the 5- 1A receptor. Salary for a postdoctoral researcher for this project has been provided by a charitable foundation for 12 months and funding from the MRC is sought to provide the consumable costs of this project.

APPL

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G9535159
Incomplete

(6)

TI A follow-up of ***chronic fatigue*** in primary care.
TYPE Small Project Grant
END 31-OCT-97
ABS Epidemiological work shows that ***fatigue*** is best viewed on a continuum with those most severely affected fulfilling criteria for ***chronic fatigue*** syndrome (CFS). A number of studies have examined predictors of outcome in ***chronic fatigue*** and CFS. However, most have been conducted in the hospital setting. There is no study to date which has followed up patients with ***chronic fatigue*** syndrome in primary care. We therefore propose to carry out a follow up of 229 patients with ***chronic fatigue,*** including 75 with CFS, already identified and extensively assessed, both physically and psychologically, as part of previous MRC and Linbury Trust funded research in this setting. This sample of patients was drawn from larger surveys of G.P. attenders in the South East of England, so is relatively free from selection bias. We predict a better outcome in those seen exclusively in the primary care setting and those with ***chronic fatigue*** who do not meet criteria for CFS, and that this will be explained by greater psychiatric morbidity and stronger illness attributions. We will also compare CFS patients from primary care to a published age-matched hospital series and we predict greater overall improvements in the future.
PRIM ***Fatigue*** Syndrome ***Chronic*** .EPIDEMIOLOGY
SEC HUMAN
Fatigue Syndrome ***Chronic*** .REHABILITATION
Follow-Up Studies
Primary Health Care
Family Practice
Great Britain .EPIDEMIOLOGY
MRC CLINICAL RESEARCH
APPL

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result - 1 year

TI PSYCHOSOCIAL FACTORS OF IMPORTANCE IN THE AETIOLOGY OF ***CHRONIC FATIGUE*** SYNDR (CFS): ACASE CONTROL STUDY
TYPE Standard Project Grant
DUR 0
PRIM Community Medicine
Human Experimentation
Mental Disorders/psychology
SEC Affective Disorders/psychology
Behavior
Cognition
Fatigue/psychology
Human
Perception
Population
Psychology/methods
Stress Psychological/psychology
MRC Clinical Research
APPL Dr A O House

(6)

G9328415
1)

TI AN EPIDEMIOLOGICAL APPROACH TO THE STUDY OF ***CHRONIC FATIGUE*** IN PRIMARY CARE SETTINGS

(6)

TYPE Standard Project Grant
STR 01-JAN-90
END 01-APR-93
DUR 39
ORG Institute of Psychiatry, University of London
PRIM Affective Disorders/psychology
Cognition
Fatigue/psychology
Mental Disorders/diagnosis
Mental Disorders/psychology
Neurotic Disorders/psychology
Stress Psychological/psychology
SEC Affective Disorders/diagnosis
Behavior
Diagnosis
Family Practice
Fatigue/diagnosis
Fatigue/epidemiology
Human
Medical Records
Neurotic Disorders/diagnosis
Psychology/methods
Sex Behavior
Stress Psychological/diagnosis
Stress Psychological/epidemiology

(1)

8905952

MRC Clinical Research
AWRD 01-DEC-92
TOT 94610
APPL DR A H MANN
DR H COPE
Dr A J Pelosi
Dr A S David

TI THE AETIOLOGY AND TREATMENT OF ***CHRONIC FATIGUE*** SYNDROME

(6)

TYPE Standard Project Grant
DUR 0
PRIM Drug therapy
Human Experimentation
Mental Disorders/psychology
Mental Disorders/therapy
Rehabilitation
Virus Diseases
SEC Affective Disorders/psychology
Affective Disorders/therapy
Behavior/pharmacology
Cognition
Exercise
Fatigue/psychology
Fatigue/therapy
Immune System/drug effects
Neuromuscular Junction/drug effects
Neuromuscular Junction/immunology
Psychology/methods
Stress Psychological/immunology
Stress Psychological/psychology
Stress Psychological/therapy
Therapeutics
Virus Diseases/immunology
MRC Clinical Research
APPL Dr A O House

Dr S Hatcher

G9019698

(1)

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TI IMMUNOLOGICAL ABNORMALITIES IN ***CHRONIC FATIGUE*** SYNDROME: CAUSE OR EFFECT
TYPE Standard Project Grant
DUR 0
ORG Department of Psychological Medicine, King's College Sch Medicine & Dentistry
PRIM Affective Disorders/psychology
Behavior
Fatigue/psychology
Immunity Cellular
SEC Affective Disorders/therapy
Cognition
Fatigue/therapy
Psychology
Therapeutics
MRC Clinical Trials
APPL Dr M Peakman

(6)

G9229693
D

TI MULTIDISCIPLINARY CONTROLLED STUDY OF ***CHRONIC FATIGUE***
TYPE Project Standard
DUR 0
PRIM Infection/blood
Infection/immunology
Infection/metabolism
Muscles/immunology
SEC Antibodies
Complement
Fatigue
Herpesviridae
Human
Immunity Cellular
Leukocytes/immunology
Oxygen
Proteins/metabolism
MRC Clinical Research
APPL

(6)

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G0815355
D

TI PSYCHOLOGICAL ASPECTS AND QUALITY OF LIFE ASSESSMENT FOLLOWING LIVER TRANSPLANTATION
TYPE Small Project Grant
STR 11-DEC-95
END 10-DEC-97
DUR 24
ABS Patients undergoing liver transplantation for ***chronic*** liver disease have often been chronically unwell for years, whilst those with acute liver failure lack the opportunity to be prepared for major surgery. Although orthotopic liver transplantation has become an accepted medical treatment there has been very little work carried out regarding the psychological status and quality of life following surgery. This study will assess the quality of life in patients undergoing liver transplantation and compare this with a control population with similar liver disease but not transplanted, using the Rotterdam scale and the sickness impact profile; assess neuropsychological functioning in the same populations using the CANTAB and Rivermead behavioural memory test and finally use the BENTAL ***fatigue*** inventory to assess ***fatigue*** in this population. The long term psychosocial outcome of patients transplanted for ***chronic*** versusacute liver failure will be studied.
PRIM Quality of Life
Liver Transplantation .PSYCHOLOGY
SEC HUMAN
Treatment Outcome
Liver Diseases .SURGERY
MRC CLINICAL RESEARCH
TOT 55892
APPL Dr P C Hayes

(6)

Not relevant

(6)

TI Analysis of B-cell differentiation in relation to primary and persistent Epstein-Barr virus infection.

TYPE Standard Project Grant

END 31-JUL-99

DUR 36

ABS The Epstein-Barr virus (EBV) infects over 90% of the adult population world-wide and persists for life in infected individuals. In vivo, EBV can infect both B lymphocytes and epithelial cells, however, the relative contributions of these two cellular compartments to EBV persistence and replication are controversial. Recent studies have raised the possibility that primary EBV infection as well as virus persistence and replication may be mediated chiefly through B-cells. The purpose of this project is, therefore, to study the differentiation of EBV-carrying B-cells in vivo at the single cell level, during primary and persistent EBV infection. EBV-positive B-cells will be isolated from tissue sections by microdissection, and the variable regions of immunoglobulin (Ig) genes will be analysed for evidence of somatic hypermutation using a polymerase chain reaction- based strategy. EBV-infected B-cells will also be studied for evidence of Ig isotype switching and for expression of the recombinase activating genes. These studies will characterise B-cell differentiation in the context of EBV infection in vivo and will provide insights into the mechanisms of EBV persistence in the B-cell pool.

PRIM ***Fatigue*** Syndrome ***Chronic*** .IMMUNOLOGY
Herpesvirus 4 Human .IMMUNOLOGY
Antigens Differentiation B-Lymphocyte .IMMUNOLOGY

SEC HUMAN
Antigens Differentiation B-Lymphocyte .ISOLATION AND PURIFICATION

MRC CLINICAL RESEARCH

APPL

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G9605472
D

(6)

TI The role of noradrenaline, 5-HT and coritsol in the neuropsychological pathogenesis of the ***chronic fatigue*** syndrome.
TYPE Standard Project Grant
END 30-SEP-99
DUR 36
ABS Cognitive difficulties ("mental ***fatigue***") are principle complaints in ***chronic fatigue*** syndrome (CFS) patients. Neuropsychological tests (CANTAB) designed to detect functional abnormalities in cognition have shown deficits in encoding memory, focused attention and executive function in CFS patients. The encoding and attention deficits in CFS can be pharmacologically reproduced in healthy volunteers, through impaired alpha2 noradrenergic function and the deficits in executive function through increased 5-HT function. CFS patients show increased 5-HT function but treatment with drugs acting on 5-HT function dos not improve cognitive function. A greater improvement in mental ***fatigue*** occurs with drugs that enhance central noradrenergic function. We hypothesise that the primary abnormality in CFS is impaired neurotransmission through alpha2, noradrenergic receptors with secondary enhancement of 5-HT2, which together cause cognitive dysfunction. A competing hypotheses, that reduced stimulation of central steroid receptors is the primary abnormality in CFS. To test the hypothesis, 95 pairs of CFS patients and matched sedentary normal controls will undergo neurophsychological testing (CANTAB) under pharmacological challenge tests with sympromatic, neurophsycological and hormonal outcomes measured. 45 pairs receive disipramine, fenfluramine and placebo challenges, 40 pairs will receive cortisol or saline infusions in randomised crossover design and 10 pairs will receive repeated neuropsychological testing only.
PRIM Serotonin .PHYSIOLOGY
Norepinephrine .PHYSIOLOGY
Fatigue Syndrome ***Chronic*** .PSYCHOLOGY
Hydrocortisone .PHYSIOLOGY
SEC HUMAN
Fatigue Syndrome ***Chronic*** .ETIOLOGY
Neuropsychology
Cognition Disorders .PHYSIOPATHOLOGY
MRC CLINICAL RESEARCH
APPL Professor J F W Deakin

G9606658
D

(6)

TI Exogenous antigen presentation by the HLA class I pathway: a pilot study in the EBV system
TYPE ROPA
END 30-SEP-97
DUR 12
ABS Our long-term objective is the developmetn and clinical testing of vaccines eliciting HLA class-I restrcted cytotoxic T lymphocyte (CTL) resonses against Epstein-Barr virus (EBV) antigens expressed in EBV positive malignancies. Here we ask whether EV antigens supplied exogenously as recombinant protein (ie not by the conventional route of endogenous expression) can access the HLA class I pathway in antigen presenting cells and be recognised by EBV-specific CTLs. We focus on three EBV latent cycle antigens, EBNA3C, EBNA1 and LMP2 each of which when expressed endogenousely is handled differently by the HLA class I Pathway
PRIM ***Fatigue*** Syndrome ***Chronic*** .GENETICS
Herpesvirus 4 Human .GENETICS
Genes MHC Class I .GENETICS
SEC HUMAN
Pilot Projects
MRC CLINICAL RESEARCH
APPL Professor D J Kerr

G9614539
D

(6)

TI Growth Hormone deficiency in rats as a potential model for the muscular aspects of human ***chronic fatigue*** syndrome.
TYPE Small Project Grant
END 31-JUL-97
DUR 12
ABS Hypophysectomy reduces the aerobid capacity of rat muscle. However, this deficiency appears to e entirely reversed by replacement therapy with growth hormone (GH) alone.
Patients with chromic ***fatigue*** syndrome (CFS) also have reduced aerobid capacity and frequerntly experience myalgia, which is probably attributable to a pathologically increased reliance on anaerobic metabolism. Recently, we have reported that severe CFS patients also have very low serum GH titres.
A strain of rats genetical deficient only in GH is now available. The aim of this project is to investigate histochemically, ultrastructurally, molecular biologically and physiologically whether the muscles of low-Gh CFS patients are modelled by those of the GH-deficient rats, and whether the abnormalities of the latter can be reversed by specific replacement.
PRIM ***Fatigue*** Syndrome ***Chronic*** .PHYSIOPATHOLOGY
Growth Substances .DEFICIENCY
Muscles .PHYSIOLOGY
SEC ANIMAL
HUMAN
RATS
MRC CLINICAL RESEARCH
APPL Dr W M H Behan
Professor P O Behan

G9616810
D

(6)

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Initial & Date

F.B 16/11/07

Darren 24/05/11

6A

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E-mail anne.coriat@headoffice.mrc.ac.uk
Tel: 0171 636 5422 Ext 6217
Fax: 0171 636 3427

PLEASE NOTE NEW FAX & TEL EXTENSION

3 March 1997

Dear [redacted]

Re: Research support for Chronic Fatigue Syndrome:

I understand that you have been discussing MRC's support for research on Chronic Fatigue Syndrome (CFS) with Dr Karen Finney I would like to follow up these discussions.

As Dr Finney correctly noted in her letter to you of 15 January 1997 the MRC funds a substantial amount of basic research that underpins any search for the pathophysiology of Chronic Fatigue Syndrome. This includes research in psychology, basic virology, immunology, neuroendocrinology and various imaging technologies such as magnetic resonance imaging and computed tomography. I have enclosed for your information a copy of our Annual Report which provides an illustration of how the MRC supports research. It is difficult to be precise about what we support that is specificaly realted to CFS since some studies will be mor relevant than others.

In terms of research specifically on CFS, as I believe Dr Finney discussed with you, an epidemiological study on CFS costing approximately £91,000 was recently completed by the Institute of Psychiatry. A number of factors were investigated and the study was not purely of a psychiatric nature. The study demonstrated that attendees with symptoms consistent with a viral illness appeared to be a vulnerable group with significantly more cases of chronic fatigue identified. I should point out that we receive very few research applications directly related to CFS, and apart from the epidemiological study mentioned above no applications received to date have been of sufficiently high scientific quality to merit funding.

You may also be aware that the Linbury Trust, a family Trust of Lord & Lady Sainsbury, funds some work in CFS.

6B

As I know you have discussed previously with Dr Finney, the MRC was involved in a consensus meeting in 1994 which helped revise the document subsequently published as the report of the National Task Force on Chronic Fatigue Syndrome (an initiative of the Charity Westcare, supported by the Department of Health). The report made clear recommendations about the need to clarify the definitions of various CFS, to enable further research into the underlying pathophysiology and for assessment of the value of potential treatments. Unfortunately the report also made very clear that this area of research continues to be hampered by lack of consensus about the definition of CFS.

You will also no doubt be aware that, following publication of the Task Force report, the CIBA Foundation held a symposium on the neuroendocrinology of CFS.

The MRC continues to maintain an awareness of any developments in research relevant to CFS, and we hope that continued activity in this area, for example through workshops such as those mentioned above, will stimulate submission of grant applications of sufficiently high scientific quality to warrant support. Whilst we do not commission research, we welcome high quality research proposals which we evaluate by peer review against specific criteria, openly, critically and in open competition.

I hope this helps reassure you that Council is indeed committed to supporting high quality scientific research in all fields including proposals relevant to CFS.

Yours sincerely,

Anne-Marie Coriat PhD
Deputy Executive Board Secretary
Neurosciences and Mental Health Board,

(6C)

DRAFT

25 February 1997

Dear Ms Jones,

Thank you for your letter of 14 February concerning research into Myalgic Encephalomyelitis (ME).

The Medical Research Council has supported an epidemiological study which was completed by the Institute of Psychiatry just over a year ago. The study was designed to investigate aspects of chronic fatigue in general practioner's attenders. Its aim was to develop aproaches which can be used in a primary care setting to help sufferers from chronic fatigue to cope with their illness and regain their health. A number of factors were investigated and the study was not purely of a psychiatric nature. Indeed the study showed that attenders with symptoms consistent with a viral illness appeared to be a vulnerable group with significantly more cases of chronic fatigue identified.

Although the Council is not currently supporting research into ME that is of direct relevance, it does support a considerable amount of basic research that would underpin any search for the pathophysiology of ME. Areas such as Psychology, basic virology, immunology, neuroendocrinology and the various imaging technologies (magnetic resonance imaging (MRI), Single Photon Emission Tomography (SPET), and Computed Tomography (CT) etc). It is difficult to be precise about what we ~~do~~ support since some studies will be more relevant than others. most is specifically related to CFS

The Council does not commission research, but welcomes high quality research proposals relevant to important questions surrounding ME and chronic fatigue syndrome, and evaluates them by peer review against specific criteria openly, critically and in competition ~~with all other research proposals it receives~~. In recent years some applications have been received, but none have reached the highly competitive standard for award.

Yours sincerely,

Anne Martinez-Townsend (Miss)
Public Communication

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Ms D Jones

(7)

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Dr Bryant
Dr Cowan

Re: Chronic fatigue syndrome (CFS) and

On 15 January 1997 a query concerning MRC support for ME was referred to me via Joanne James and Dr Davies (see copy of cc-mail messages on file). Although CFS or ME most often falls within the remit of Neurosciences Board, I agreed to speak to the member of the public, , to see if I could be of assistance.

explained that he suffered with ME and i) was interested in the work of the MRC (i.e. what type of organisation was it, how did it fund research?) ii) wished to know if MRC was funding any specific work on ME/CFS - if not, what was the extent of scientific interest in the area i.e did MRC receive many proposals on the subject? In reply, I said that I thought the MRC did not receive many proposals on ME/CFS but I would check our database. However, was aware of a study supported by MRC and carried out at the Institute of Psychiatry. He was not happy with the fact that MRC had supported this work because ME 'was a real illness and not all in our mind'. I explained the peer review process and said that MRC had no fixed ideas on the pathophysiology/causes of ME/CFS, and welcomed high quality proposals in this area. I also asked whether belonged to any patient/support groups which might also provide him with useful information on the condition. He answered that he was aware of these bodies but 'did not really bother with them'.

Following my telephone conversation, I asked Mr Goldstein (CAG) to run a search for applications on CFS/ME that we had received over the last year, funded or declined. In the meantime I wrote a very general letter to answering some of his questions, using briefing notes provided by Dr Gower (copy of letter on file).

Mr Goldstein's search took a little while due to other pressing matters (OST requests, PQs etc.). Between 15/1 and 7/2 rang on average twice a week to ask about progress.

When rang on 7/2 I let him know, in general terms, the results of the search (on file) i.e. that during 1996 we had received four applications which had been declined on scientific grounds. I provided with a summary of the areas which the applications addressed. wished to know the applicants' names. I explained that although MRC publishes details (titles, applicants' names and affiliation) for applications that we have awarded, applications declined by the MRC are a different matter and it would be a breech of confidentiality to provide him with names.

went on to talk about an orange booklet that had been published by the Royal College of Physicians "Chronic Fatigue Syndrome" (IFBN 1 860160468) and pointed out that this states that MRC is funding research on CFS. I reminded that we do fund a lot of research that underpins the area. requested that I put the result of the search in writing.

Before writing back to I have attempted to obtain a copy of the RCP booklet to check exactly what it says MRC is funding (it may refer to research which underpins the condition). However, RCP have informed me that at the present time this is being re-printed and may be available in the next 2-3 weeks. CIBA do not have a copy. I cannot locate it on any of the files within the S1528/2 series on CFS. I am aware that the follow-up letter requires careful drafting.

telephoned again on 13/2 to say that he needed my letter urgently; he intended to fax a letter to Ken Calman concerning the Council's lack of support for the area, and also other issues surrounding the RCP review.

Dr Davies and the Press Office have been kept informed of developments.

I think a carefully worded letter of reply from someone higher up in the Office might put this matter to rest.

Karen Finney 14.2.97

Chronic fatigue syndrome (applications for indirect support, 1/4/93 to date) - Universe CAG1 Report M-E1.EO1

Registry File Ref	Principal Applicant	Agreement Title Full	Agreement Type	Index Term	Index Type	Tot Amnt Awarded	Expected End Date	Agreement Status
G9614539	Professor A B Rickinson	Exogenous antigen presentation by the HLA class I pathway: a pilot study in the EBV system	ROPA	Fatigue Syndrome Chronic GENETICS	PRIM		30/09/97	DECLINED
G9616810	Dr N C Spurway	Growth Hormone deficiency in rats as a potential model for the muscular aspects of human chronic fatigue syndrome.	Small Project Grant	Fatigue Syndrome Chronic PHYSIOPATHOLOGY	PRIM		31/07/97	DECLINED
G9605472	Dr G Niedobitek	Analysis of B-cell differentation in relation to primary and persistent Epstein-Barr virus infection.	Standard Project Grant	Fatigue Syndrome Chronic IMMUNOLOGY	PRIM		31/07/99	DECLINED
G9606658	Dr R K Morriss	The role of noradrenaline, 5-HT and cortisol in the neuropsychological pathogenesis of the chronic fatigue syndrome.	Standard Project Grant	Fatigue Syndrome Chronic PSYCHOLOGY	PRIM		30/09/99	DECLINED
	Dr R K Morriss			Fatigue Syndrome Chronic ETIOLOGY	SEC			

All applications

No returns for direct support.

see also project grant G8905952 (prior to the parameters of this report) covering a funded pilot study on 'predictors of chronic postviral fatigue' (H. Cope et al)

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Leicester	0		+1*	- 0 or 1
Nottingham	2			- 2
Oxford	1			- 1
Reading	1			- 1
Southampton	1			- 1
Industry	1	-1	+1*	- 0 or 1

* The four recommendations are for two vacancies (molecular biology and neuropharmacology) and comprise two first choices (London and Leicester) and a pair of alternates (London and [redacted] (Cambridge)).

It could be considered that the Board recommendations would result in over-representation by Cambridge (3 - University, 1 - MRC Unit, possibly 1 - independent research unit) and London (4 - separate institutions).

4. Proposed new membership for Board 3

4.1 Council is asked to consider the following nominations to the Board:

Expertise & Name	Age	Location	Nomination
Neuropathology (1 vacancy)			
[redacted]	[redacted]	[redacted]	[redacted] Board first choice (no alternates)
Molecular Biology & Neuropharmacology (2 vacancies)			
[redacted]	[redacted]	[redacted]	Board first choice$
[redacted]	[redacted]	[redacted]	Board first choice
Redacted Under FOI Exemption S40 Closed until 2071		[redacted]	Board alternate choice; also a first choice for Grants Committee
[redacted]		Redacted Under FOI Exemption S40 Closed until 2071	Board alternate choice
[redacted]	[redacted]	[redacted]	[redacted] nominee
[redacted]	[redacted]	[redacted]	Board first choice (no alternates)

8A

MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 0171 636 5422
Facsimile: 0171 436 6179

local fax: 0171 636 3427
email address: karen.finney@hq.mrc.ac.uk

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15 January 1997

Dear [redacted],

Re: Myalgic Encephalomyelitis (ME) or Chronic Fatigue Syndrome (CFS)

Thank you for your enquiry about ME and your interest in the research work supported by the Medical Research Council (MRC).

The Medical Research Council is a body corporate established by Royal Charter. This gives it an important and valuable freedom to decide its scientific strategy and what research should be funded, taking account of scientific opportunities and health needs. The MRC is largely publicly funded and is accountable to Parliament and to the public for the work that it does. It has special responsibility to work closely with users of its research output, especially the Health Departments, and to take account of their needs. The MRC's mission is as follows:

- to promote and support high-quality basic, strategic and applied research and related post-graduate training in the biomedical and other sciences with the aim of maintaining and improving human health;
- to advance knowledge and technology, and provide trained researchers which meet the need of its users (including providers of health care), thereby contributing to the maintenance and improvement of human health, the economic competitiveness of the United Kingdom, and the quality of life;
- to provide advice on, and disseminate knowledge and promote public understanding of research in the biomedical sciences.

The MRC has a broad remit and has to be alert to new needs and opportunities in any area of science relevant to human health. Thus, its research work covers molecular and cellular biology, developmental biology, genetics and inheritance, infections and immunity, physiological systems (e.g. cardiovascular, respiratory and reproductive systems, muscles, bones, joints, teeth and skin), nutrition, metabolism and endocrinology (hormones), neurosciences and mental health, cancer, environment, child health, and health services and public health research.

The Council has not had a specific initiative on CFS. The Council receives grant proposals from scientists and clinicians which are judged in open competition. Funds are awarded to researchers on the basis of the scientific quality of their research proposals. It is through this mechanism that the Council awarded a grant to Professor Mann, Dr David and Dr Pelosi (Institute of Psychiatry, London) to study aspects of chronic fatigue in general practitioner's attendees. Its aim was to develop approaches which could be used in a primary care setting to help sufferers from

8B

chronic fatigue to cope with their illness and regain their health. A number of factors were investigated and the study was not purely of a psychiatric nature. Indeed the study showed that attendees with symptoms consistent with a viral illness appeared to be a vulnerable group with significantly more case of chronic fatigue identified.

A recent survey of our funding database indicated that the Council was not currently funding any research specifically on CFS. However, I will run this search again and let you know if any new grant applications have been received or funded. It is important to note that the MRC funds a substantial amount of basic research that would underpin pathophysiological investigations of Chronic Fatigue Syndrome. This includes research in physiology, basic virology, immunology, neuroendocrinology and various imaging techniques.

The MRC is maintaining an awareness of any developments in research relevant to CFS and is always willing to accept grant applications in this area. The Council has been involved in a number of policy meetings including a National Task Force on Chronic Fatigue Syndrome, an initiative of Westcare in 1994, and a CIBA Foundation Symposium held in 1996 on the neuroendocrinology of CFS.

I have enclosed some documents which describes research supported by the Council. I do hope that you find these of interest.

With best wishes

Yours sincerely,

Dr Karen Finney
(Research Management Group)

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MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 0171 636 5422
Facsimile: 0171 436 6179

local fax: 0171 636 3427
email: d.colson@hq.mrc.ac.uk

Ms Heather White
Department of Health
Room 414
Eileen House
80-94 Newington Causeway
London SE1 6EF

6 November, 1995

Dear Ms White

Re : Chronic Fatigue Syndrome

Thank you for your telephone call asking for information about MRC involvement in research on Chronic Fatigue Syndrome (CFS).

The MRC funds a substantial amount of basic research that would underpin any search for the pathophysiology of Chronic Fatigue Syndrome. This includes research in psychology, basic virology, immunology, neuroendocrinology and various imaging technologies such as magnetic resonance imaging and computed tomography.

In terms of research specifically on CFS, an epidemiological study on CFS costing approximately £91,000 was recently completed by the Institute of Psychiatry. The investigators planned to study the prevalence of CFS amongst consecutive general practice attenders aged 18-45 years, together with exploration of associated demographic, clinical and psychosocial variables. In addition, they planned to identify patients suffering from prolonged fatigue following viral infections and determine how many met a strict case definition of CFS. We have not yet received a final report detailing the findings of the study.

I should point out that we receive very few grant applications concerning CFS, and apart from the epidemiological study mentioned above, none have been of sufficiently high scientific quality to merit funding.

You may be aware that the Linbury Trust, a family trust of Lord and Lady Sainsbury, funds some work in CFS.

The MRC was involved in a consensus meeting in 1994 which helped to revise the document subsequently published as the report of the National Task Force on Chronic Fatigue Syndrome (an initiative of the registered charity Westcare, supported by DH)

with which you are probably familiar. The report made clear recommendations about the need to clarify the definitions of the various chronic fatigue syndromes, for further research into the underlying pathophysiology and for assessment of the value of potential treatments. Unfortunately, as the report also made clear, this area of research continues to be hampered by a lack of consensus about the definition of CFS - eg whether CFS is a physical or psychological disorder or both, and even about the existence of CFS as a distinct illness.

You will no doubt also be aware that, following the publication of the Task Force report, the CIBA Foundation held a Symposium on 18 October this year on the neuroendocrinology of CFS.

The MRC is maintaining an awareness of any developments in research relevant to CFS, and we hope that the continued activity in this area will stimulate some grant applications of sufficiently high quality to warrant support.

If I can be of any further help, please let me know.

Yours sincerely

Deborah Colson PhD
NHS/HDs Liaison Group

Telephone query
23 October 1995

I spoke to Ms Heather White from DH following the message she left for Dr Box, asking for details of MRC-supported research in Chronic Fatgue Syndrome.

She has recently taken over (August) policy responsibility in this area - especially wrt hospital services - from Richard Freeman.

She is trying to familiarise herself with her new patch, & in addition Lady Cumberlege is talking to the Townswomen's Guild in November on CFS. HW would find any info we can give her useful for Lady Cumberlege's brief.

She is particularly keen to know if there are any results from the epidemiological study funded at the Inst of Psychiatry (she has the figure of £91k for this project).

HW didn't seem familiar with the Task Force report on CFS or the recent CIBA symposium.

D Colson

(10)

13 July 1995

Dear [redacted]

Thank you for your recent letter concerning the research into Chronic Fatigue Syndrome.

The Medical Research Council supports very little research of direct relevance to Chronic Fatigue Syndrome. The Council supported an epidemiological study, recently completed by the Institute of Psychiatry.

Although the Council supports little that is of direct relevance, it does support a considerable amount of basic research that would underpin any search for the pathophysiology of Chronic Fatigue Syndrome. Areas such as psychology, basic virology, immunology, neuroendocrinology and the various imaging technologies (magnetic resonance imaging (MRI), Single Photon Emission Tomography (SPET), and Computed Tomography (CT) etc). It is difficult to be precise about what we do support since some studies will be more relevant than others.

As you may know, the Council does not commission research but welcomes high quality research proposals relevant to important questions surrounding Chronic Fatigue Syndrome, and evaluates them by peer review against specific criteria openly, critically and in competition with all other research proposals it receives. In recent years some applications have been received, but none have reached the highly competitive standard for award.

Yours sincerely,

Anne Martinez-Townsend (Miss)
Public Communication

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[redacted]

Dr M Jepson MRS.

(11)

11 July 1995

Please see draft reply dated 11/7 to [redacted] concerning his query on CFS.
I would be grateful for your comments.

Many thanks,
Anne Martinez
Public Communication

Just small additions.
Fine by me!
M Jepson 14/7/95

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(12)

DRAFT

The MRC ~~does~~ supports very little research of direct relevance to ME. ~~As~~ the Council supported an epidemiological study, recently completed by the Institute of Psychiatry.

11 July 1995

Dear [redacted]

Thank you for your recent letter concerning the research into Chronic Fatigue Syndrome.

Although the MRC supports little that is of direct relevance, it does support a considerable amount of basic research that would underpin any search for the pathophysiology of Chronic Fatigue Syndrome (CFS). Areas such as psychology, basic virology, immunology, neuroendocrinology and the various imaging technologies (magnetic resonance imaging (MRI), Single Photon Emission Tomography (SPET), and Computed Tomography (CT) etc). It is difficult to be precise about what we do support since some studies will be more relevant than others. ~~The MRC will continue to support this basic science.~~

As you may know, the MRC does not commission research but welcomes high quality research proposals relevant to important questions surrounding CFS, and evaluates them by peer review against specific criteria openly, critically and in competition with all other research proposals it receives. In recent years some applications have been received, but none reached the highly competitive standard for award.

Yours sincerely,

Anne Martinez-Townsend (Miss)
Public Communication

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[redacted]

(13)

11/7/95

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Date as postmark

Dear Sir,

I am writing this letter concerning the illness myalgic encephalomyelitis (M.E) which I suffer from.

Can you please tell me why the medical research council (MRC) does not fund any research into M.E? I have already written to the Department of Health (DOH) asking how can they justify this lack of action. I am not asking for M.E to get

special treatment over other serious illnesses such as multiple sclerosis (M.S) or Parkinson's disease but just for some government money to be spent on research into cause(s) and treatment. At the present time any research into M.E which is carried out is paid for by charitable organisations or from people with the illness donating money to the M.E Association who donate grants to fund it.

Despite such supported recent medical research which has been carried

out on M.E including SPECT scans showing a reduced blood flow to the brain, studies pointing to a hypothalamus dysfunction and various abnormalities of the immune system a large number of G.P's still do not believe that the illness exists and many of those who do, completely fail to understand it's severity and also how debilitating it can be.

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At the present time G.P's have no training of M.E when they are medical students and it still isn't included in neurology text books despite being classified as a "neurological disease" by the WHO. It isn't surprising that sufferers of M.E who get such little help from their G.P's waste money on

alternative medicine which does little good and in some cases even makes the illness much worse.

At this point can I draw your attention to some people who have carried out such good work into M.E. these include Professor Peter Behan, Dr. John Gow and Dr. E Dowsett. Also there are two doctors who have worked on behalf of M.E sufferers despite having the illness themselves who should be applauded, they are Dr. Charles Shepherd of the M.E Association and Dr. Anne Macintyre of M.E

Action. Last but by no means least I applaud the late, great Professor Melvin Ramsay who did more than anyone in trying to convince the medical profession that M·E was an organic disease and that they should try to help sufferers as much as possible instead of labelling them as malingerers.

Thank-you for taking the time to read my letter and I look forward to hearing from you concerning this issue as soon as possible.

Yours, Sincerely.

[redacted]

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MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 071 - 636 5422
Facsimile: 071 - 436 6179

Local FAX: 071 636 3427
Email:Chris.Counsell@headoffice.mrc.ac.uk

Your reference:

Our reference:

20 December, 1994

Dear Mr Waldegrave,

Thank you for your letter to Sir David Plaistow enquiring about Chronic Fatigue Syndrome (CFS/PVFS/ME). I apologize for the length of time taken to reply.

The simple answer to your question is that the MRC supports only a very limited amount of direct research in CFS, most notably at the Institute of Psychiatry, where an epidemiological study into chronic fatigue in primary care settings has been carried out over the past 5 years. In recent years a few other applications for funds have been received, none relating to the epidemiology of CFS, and unfortunately none have been awarded.

As you say in your letter, Dr Richard Sykes is Director of Westcare, which campaigns vigorously for ME sufferers. The MRC was involved in a concensus meeting earlier this year which helped revise the document produced by the National Task Force. The report makes clear recommendations about the need to clarify the definitions of the various chronic fatigue syndromes, for further research into the underlying pathophysiology and for assessment of the value of potential treatments. Unfortunately, as the report also makes clear, this area of research is dogged by a lack of concensus about the definition of CFS, about whether CFS is a physical or psychological disorder or both, and even about the existence of CFS as a distinct illness! Nevertheless this should not stop well argued research proposals from being assessed favourably under peer-review. I understand that a meeting is planned to consider how to implement the recommendations of the Task Force report, and the MRC have offered to send a representative to explain the Council's position and procedures for making applications.

Although, the MRC supports little that is directly relevant, it does support a considerable amount of basic research that would underpin any search for the pathophysiology of CFS. Areas such as psychology, basic virology, immunology, neuroendocrinology and the various imaging technologies (magnetic resonance imaging (MRI), Single Photon Emission Tomography (SPET), and Computed Tomography (CT) etc). It is difficult to be precise about what we do support since some studies will be more relevant than others. The MRC will continue to support this basic science.

As you know, the MRC does not commission research but welcomes any applications more directly related to CFS research, as it does applications in any areas of its remit. These are assessed in competition with other applications and decisions made on the basis of the quality of science. Dr Sykes recently met with the Secretary to the MRC Neurosciences and Mental Health Board, Dr Margaret Jepson, to discuss many of the points raised in this letter and to explain the procedures for applying support.

I hope that this has been of help both to you and Dr Sykes. If I can be of more help, perhaps you or Dr Sykes could contact me again.

Yours sincerely,

Christopher Counsell, PhD
Research Management Group

The Rt. Hon. William Waldegrave, MP
House of Commons
London SW1A 0AA

MEMORANDUM

TO : Dr Counsell
FROM : Penny Snell
SUBJECT : Letter from William Waldegrave dated 1.11.94
COPY :
DATE : 7 November 1994

Please see attached letter from William Waldegrave dated 1.11.94.

Sir Dai would be grateful if you would deal with this on the Chairman's behalf.

The letter has been acknowledged and your name given as the contact point.

Thank you.

Penny

From: The Rt. Hon. William Waldegrave, MP

HOUSE OF COMMONS
LONDON SW1A 0AA
071- 219 4574

03 NOV 1994

(17)

1 November 1994

Dear David,

I see, from time to time, my constituent, Dr Richard Sykes, who has founded a very useful organisation called Westcare supporting those with M.E., and has been a member of the National Task Force on CFS/PVFS/ME. He asked me to see if I could get from you an up to date of the work done in relevant areas by the MRC on the basic science concerned. I suspect that there is much more to be done, both on the epidemiology and on the causation of these various so far rather ill-defined conditions. I think that your people would probably agree that it is now becoming accepted that there are some serious and interesting diseases involved, worth investigating; if you could give me the current position on the research and whether there is any chance of additional funds being invested in this area, I know Dr Sykes would be very interested.

Yours,

Sir David Plastow
Chairman
Medical Research Council
20 Park Crescent
London W1N 4AL

7 November 1994

The Rt. Hon. William Waldegrave, MP
House of Commons
London
SW1A OAA

Dear Mr Waldergrave

I write on behalf of Sir David Plastow to acknowledge your letter of 1 November 1994 and to let you know that it has been passed on to Dr Chris Counsell in the MRC's Research Management Group. Dr Counsell will be in touch with you shortly.

Yours sincerely

Penny Snell
Private Office

19.12.94

- Dr Counsell
- Thank you for letting me see this draft.

It appears we have both been working on related aspects of same issue in recent weeks (this would have been clear if Penny had copied the minute to me - but never mind...).

1. I met with Dr Eyles on 15 November and explained all the points you make in your letter.; I have added a sentence that covers the outcome of that meeting.

2. I also made the point that the Task Force report is analogous to the topic review that MRC conducts when it wants to stimulate research in a particular area. The Task Force is therefore to be congratulated on that positive step forward. Continuing the MRC analogy; we usually publish and disseminate the report and so communicate the recommendations to the research community and the Council is open to those applications. We ~~do~~ take specific steps beyond such communication only exceptionally ~~and~~ You may want to add this point in para 3 of your letter.

3. I have recently written to Board members for their comments on the report, with a view to deciding if it should be an MRC Head Office representative only at their implementation meeting, or a Board member as well. Does

This effectively duplicate your consultation (re: para 3 of your letter)?? I will make a phone call to clarify if so. I am a little hesitant about selecting certain recommendations for mention in case that is interpreted as a particular vice interest.

Perhaps we should discuss to clarify these points.

M Jepson

MRC
Medical Research Council

Medical Research Council
20 Park Crescent, London W1N 4AL

Telephone: 071 - 636 5422
Facsimile: 071 - 436 6179

Local FAX: 071 636 3427
Email:Chris.Counsell@headoffice.mrc.ac.uk

Your reference:

Our reference:

Dear Mr Waldegrave,

Thank you for your letter to Sir David Plaistow enquiring about Chronic Fatigue Syndrome (CFS/PVFS/ME). I apologize for the length of time taken to reply.

The simple answer to your question is that the MRC supports only a very limited amount of direct research in CFS, most notably at the Institute of Psychiatry, where an epidemiological study into chronic fatigue in primary care settings has been carried out over the past 5 years. In recent years a few other applications for funds have been received, none relating to the epidemiology of CFS, and unfortunately none ~~have been~~ awarded. Met the competitive standard for but award.

As you say in your letter, Dr Richard Sykes is Director of Westcare, which campaigns vigorously for ME sufferers. The MRC was involved in a concensus meeting earlier this year which helped revise the document produced by the National Task Force, and it would certainly concur with many of the recommendations in the report. Particularly with regard to clarification of the definitions of the various chronic fatigue syndromes, the need for further research into the underlying pathophysiology and assessment of the value of potential treatments. Unfortunately, as the report makes clear, this area of research is dogged by a lack of concensus about the definition of CFS, about whether CFS is a physical or psychological disorder or both, and even about the existence of CFS as a distinct illness! Nevertheless this should not stop well argued research proposals from being assessed favourably under peer-review.

Have you contacted Ford Menzies? (I have recently sent report on asking for comment)

Although, the MRC supports little that is directly relevant, it does support a considerable amount of basic research that would underpin any search for the pathophysiology of CFS. Areas such as psychology, basic virology, immunology, neuroendocrinology and the various imaging technologies (magnetic resonance imaging (MRI), Single Photon Emission Tomography (SPET), and Computed Tomography (CT) etc). It is difficult to be precise about what we do support since some studies will be more relevant than others, but examples of the type of research include:

Enterovisuses (Coxsackievirus)

Suggest some examples ∴ general part above sufficient

Dr G Stanway, University of Essex, "Molecular analysis of receptor specificity in coxsackie virus A9"

Herpesviruses (Epstein-Barr virus)
Dr G Niedobitek, University of Birmingham, "Characterisation of persistent Epstein-Barr virus infections *in vivo*"

Immune function during infection.
Dr A Holder, National Institute for Medical Research, Parasitology Division

Neuroendocrinology.
Dr P Cowen, University of Oxford, "Clinical pharmacology of 5-hydroxytryptamine"

Depression
Work at the Institute of Psychiatry. Also
Professor G Brown, Royal Holloway College, "Social factors in the aetiology and course of affective disorders"

The MRC will continue to support this basic science.

As you know, the MRC does not commission research but welcomes any applications more directly related to CFS research, as it does applications in any areas of its remit. These are assessed in competition with other applications and decisions made on the basis of the quality of science. *We understand a meeting is planned to consider how to implement the recommendations of Task Force Report, and we have offered to send MRC representative to explain Council's position and procedures for making applications.*

I hope that this has been of help both to you and Dr Sykes. If I can be of more help, perhaps you or Dr Sykes could contact me again.

Yours sincerely,

Christopher Counsell, PhD
Research Management Group

Dr Sykes recently met with the secretary to the MRC N— and the —H—S—, Dr [illegible], and she explained these procedures. ~~and~~ [illegible] As a result of that meeting.

file - chronic fatigue file

NATIONAL M.E. SUPPORT CENTRE
AND CENTRE FOR CHRONIC FATIGUE SYNDROMES

To : Mr P Dukes MRC

From : Sue Orrock, Information Officer

Date : 10.1.94

Thankyou for your enquiry. I enclose a leaflet about our services and activities and an order form for our information sheets and/or professional pack.

I am sorry if there has been a delay in replying to your letter, but you will understand that at times the requests for information (especially following any media coverage) are quite overwhelming for a service that is provided by the voluntary efforts of people who are ME sufferers themselves.

Harold Wood Hospital, Disablement Services Centre,
Gubbins Lane, Harold Wood, Romford, Essex RM3 0BE Telephone: (0708) 378050 Fax: (0708) 378032

Registered Charity No. 1015161

NATIONAL M.E. SUPPORT CENTRE
AND CENTRE FOR CHRONIC FATIGUE SYNDROMES
Hon. Life President: Dr Betty Dowsett MB, CHB, Dip. Bact
Hon. Medical Advisor: Prof Peter Behan MD, FACP, FRCP
Medical Advisor: Dr Leslie Findley TD, MD, FRCP, DCH

WHO ARE WE ?

We are a charity linked to, and supported by, a diagnostic outpatient clinic and inpatient facilities. These are part of the regional neurological unit of Havering Hospital Trust. We see patients from all over the country.

Our ultimate aim is to establish an in patient and out patient unit for sufferers from M.E. and related fatigue syndromes under the auspices of the NHS.

The Support Centre is a <u>non-diagnostic</u> centre open to all M.E. sufferers who have been previously diagnosed

❖ ❖ ❖ ❖ ❖ ❖

Begun in 1989, it was set up following the successful and pioneering ROMFORD NEUROCARE PROJECT (initiated by DR. MARIE OXTOBY and Dr. L. J. FINDLEY in 1986 to co-ordinate the care and support of patients with chronic neurological disabilities such as Parkinsonism, M.S., M.N.D. etc.,)

A parallel service for patients with M.E. (Myalgic Encephalomyelitis) was suggested. These patients were being referred in increasing numbers from Essex and other parts of the U.K. to the diagnostic, inpatient and outpatient services uniquely provided for this illness in the Barking, Havering and Brentwood Hospitals.

In 1989, a group of volunteers with a specialised knowledge of M.E., including medical and nursing professionals co-ordinated by Dr. E. G. Dowsett, initiated the:

NATIONAL M.E. SUPPORT CENTRE at Harold Wood Hospital.

The service provided at that time (including counselling welfare advice and general information about the illness one half day per week), was funded entirely by voluntary donations from patients, friends of the M.E. sufferers, and the volunteers themselves.

By 1992, demands on this service had increased so much that it became essential to;

- ❖ Employ a full time administrator.
- ❖ Equip a modern office.
- ❖ Provide a telephone information line.
- ❖ and extend consultation hours.

❖ ❖ ❖ ❖ ❖

Harold Wood Hospital, Disablement Services Centre,
Gubbins Lane, Harold Wood, Romford, Essex RM3 0BE Telephone: (0708) 378050 Fax: (0708) 378032

Registered Charity No. 1015161

Apart from our administrator, all our staff are volunteers, have personal experience as either sufferers or carers and can offer companionship and a listening ear

The volunteers attend, updating and further counselling advice sessions on a wide range of subjects provided by professional bodies.

While our advisers endeavour to give the best advice they can within the limits of their knowledge and experience, it is necessary occasionally to redirect patients to other advisory and specialist agencies

❖ ❖ ❖ ❖ ❖ ❖ ❖ ❖ ❖ ❖ ❖

OUR PURPOSE !

To provide advice in the areas of:-

- ❖ MEDICAL questions
- ❖ GENERAL PROBLEMS - Management of M.E.
- ❖ NURSING - including pre & post pregnancy counselling and related problems,
  - relationship difficulties.
- ❖ FINANCE - advice on difficulties that can be a consequence of M.E.
- ❖ WELFARE - help and signposting with benefits, etc.,
- ❖ EDUCATION
- ❖ CHILDCARE - Help with management

To lend a listening ear, to give support and understanding, to give the sufferer the opportunity to regain confidence in themselves, to rebuild their lifestyle around their illness and to improve the quality of their life.

❖ ❖ ❖ ❖ ❖ ❖

OUR FUNDING!

The Support Centre is housed within the Hospital, but no direct funding is received from the N.H.S., so a separate charitable trust has been set up to fund

'M.E. within the N.H.S' at the National M.E. Support Centre.

The full cost of seeing a patient is between £75 - £100 but this is heavily subsidised by the Charitable Trust Funds are raised by:-

Projects undertaken for us by sufferers, their carers and friends.

Donations are given independently.

Payment for literature which is available from the Centre.

Our " 200 CLUB " which costs £12 a year to join.

and finally the formation of "FRIENDS OF"

❖ ❖ ❖ ❖ ❖ ❖

WHAT WE HAVE ACHIEVED !

Almost 1200 patients and carers have visited the Centre to date and have judged the various services provided as between 68 % and 100% good or excellent (by anonymous assessment). Referrals from medical practitioners have trebled within the same period.

We currently assist research, provide support and rehabilitation for inpatients and outpatients,
some training for doctors, nurses and other hospital staff, and for volunteers and visitors.

We have a strong young peoples group, we are educating the Educators, we provide essential information for Government Committees, and are representing M.E. groups on the new Health Authority and Community Care Trusts locally

We work together with the other main national and international M.E. groups.

❖ **It is obvious that the M.E. SUPPORT CENTRE has fulfilled a long felt need.** ❖

YOUNG M.E. SUPPORT GROUP

- Meets every month at The Centre in Harold Wood Hospital.
- There are 150 members, ranging in age from 9 - 30 yrs.
- They produce two newsletters, one for younger ones and one for the older ones. The latter has in fact just merged with the Young Tymes. This will now be edited at The National M.E. Support Centre and sent out nationwide.

Their Committee is hoping to set up a home and Hospital visiting scheme and a Penfriend Club.

If you are interested in becoming a member or joining please contact Claire White ..... c/o The National M.E. Support Centre enclosing an S.A.E. please.

❖ ❖ ❖ ❖ ❖

Why " FRIENDS OF " the NATIONAL M.E. SUPPORT CENTRE

BECAUSE WE NEED YOUR HELP IN RAISING FUNDS FOR OUR WORK

we already spread ourselves very thinly indeed, in running the Centre in all its aspects and educating the public, medical, governmental and educational worlds.

BUT this is unfortunately our / your illness and therefore as sufferers, carers and friends we/you have to take some responsibility for funding such support, education and research.

We know the problems, as we have said before, all our staff are either sufferers or carers

BUT

We need groups of volunteer Friends who will arrange Fund raising events small and large. As individuals, groups, firms, schools, colleges or working together for an area, town, county or national event.

PLEASE BECOME A FRIEND AND/OR JOIN THE 200 CLUB

A strong Fund raising team is vital!

We need the fit and healthy as well as sufferers!

Can you join us and help to support our work.? If you want to be on the mailing list to receive a newsletter, please return the enclosed form with the subscription you can afford. Or if you feel you can help

FUNDRAISE

in any way, please return the form stating how you can help.

The Support Centre is a NON-DIAGNOSTIC centre open to all M.E. sufferers who have been previously diagnosed.

OUR CLINIC DAYS

Monday a.m. & Wednesday a. m. / p.m.
Medical Consultants are available on Monday mornings/ Wednesday afternoons

These are the services we offer: -

❖ MEDICAL	-	(with consultant) times above only
❖ GENERAL PROBLEMS	-	Management of M.E.
❖ NURSING	-	including
	-	pre & post pregnancy counselling and related problems.
	-	relationship difficulties.
❖ FINANCE	-	**advice on difficulties that can be a consequence of M.E.
	-	including mortgage arrears, occupational pensions and rearranging present debts.
❖ WELFARE	-	** help and signposting with benefits, appeals, etc..
❖ EDUCATION	-	
❖ CHILDCARE	-	Help with management
❖ Other than the above		

We are happy to share and discuss all your problems arising from your M.E. and will be happy to refer to appropriate agencies if we feel that they can help you.

While our advisers will endeavour to give the best advice they can within the limits of their knowledge and experience, it will be necessary occasionally to redirect you to other advisory and specialist agencies

Please note - we charge £40 the first visit and £25 for second and subsequent visits if an appointment is requested with a medical consultant. This is **not** to pay the consultant but to help raise money for our administrative costs only, as **consultants** and **advisers** are all **volunteers. We have no funding from the N.H.S. and rely entirely on people fund raising for us and on these charges.**

We do however, realise that many people with M.E. are on benefits or disability payments and do not have the financial resources to meet this charge .....so please do not be deterred from booking an appointment or attending. **No one is turned away for a lack of funds.**

NATIONAL M.E. SUPPORT CENTRE
AND CENTRE FOR CHRONIC FATIGUE SYNDROMES
Hon. Life President: Dr Betty Dowsett MB, CHB, Dip. Bact
Hon. Medical Advisor: Prof Peter Behan MD, FACP, FRCP
Medical Advisor: Dr Leslie Findley TD, MD, FRCP, DCH

PROFESSIONAL PACK

£5 inc., p&p

INDEX

Harold Wood Hospital, Disablement Services Centre,
Gubbins Lane, Harold Wood, Romford, Essex RM3 0BE Telephone: (0708) 378050 Fax: (0708) 378032
Registered Charity No. 1015161

INFORMATION LEAFLET ORDER FORM

NUMBER	TITLE	PRICE	NUMBER	TOTAL
	M.E. - WHO CARES?	£0.35		
15	ME IN A NUTSHELL	£0.35		
6	ANTI - DEPRESSANT DRUGS	£0.35		
4	ANAESTHESIA	£0.35		
3	AMPLIGEN	£0.10		
5	ANTIBIOTICS	£0.35		
13	MAGNESIUM	£0.10		
7	DEPRESSION	£0.10		
11	IMMUNISATION	£0.10		
17	MOBILITY	£0.10		
19	M.E. and Occupational Therapy	£0.15		
20	PREGNANCY	£0.10		
21	M.E. and Sexual Activity	£0.10		
22	RESPITE CARE	£0.35		
10	GUIDELINES FOR SCHOOLS	£0.35		
From Professional Pack - Management of M.E. (for sufferers		£0.35		
	PROFESSIONAL PACK	£5.00		
	CASSETTES			
Post graduate lecture / Dr Dowsett / Hull Royal Infirmary 92		£3.00		
Post Graduate lecture / Dr Dowsett / Cheltenham 1992		£3.00		
			TOTAL	
The following papers are available from Action for M.E.				
P.O.Box 1302, Wells, BA5 2WE				
	ADVICE FOR YOUNG ME SUFFERERS	£0.10		
	A GUIDE FOR THE NON SUFFERER	£0.35		
	INFORMATION FOR EMPLOYERS	£0.35		
	WHAT M.E. IS NOT....	- -		
And the following from the M.E. Association,				
Stanford House, High Street, Stanford - Le - Hope, Essex. SS17 OHA				
	Bibliography (Medical)	£1.00		
	IFMEA (International Medical update)	£2.00		

NAME **ADDRESS**

POSTCODE

Cheques should be made payable to The National M.E. Support Centre - Harold Wood

1. Call up file.
2. Reply.

(16)

Rec'd 25/10

Tel. 081-554-3832

[redacted]

Redacted under FOI exemption (s) 40(2).Closed until 2071

23.10.1993.

Dr. Peter Dukes,
Medical Research Council,
20, Park Crescent,
London, W1N 4AL.

Your Ref. S 1528/1

Dear Dr. Dukes,

Further to earlier correspondence under the above reference, I take the liberty of enclosing a copy of a testimony given by Dr. Paul R. Cheney to the FDA on 18.2.1993. This relates to his experiences with CFS patients in the States.

You will note that he, too, describes a growing number of cases with very severe complications. This seems in accord with observations made on some subjects of my own study (see point 4 of my letter of 14.1.1993), as well as reports I am receiving from elsewhere. These observations are in stark contrast to numerous letters and articles which have recently been published, particularly those in The Times, following the showing of two TV programmes on M.E. (1,2), and in response to the recent 'Action for M.E.' campaign (3,4,5,6,7). Particularly disconcerting is the fact that antidepressant therapy, often linked to graded exercise programmes, are freely recommended as universally beneficial remedies for M.E./C.F.S. patients, when in reality such treatments have been shown to be harmful in many cases (8,9,10,11,12). Although these facts were pointed out to the editors of The Times and the BMJ, such details remain unpublished. This problem is particularly worrying in view of assertions made in Peter Breggin's recent publication 'Toxic Psychiatry' (13) in relation to effects of antidepressant drugs.

I trust you will be able to give the unresolved problems of M.E./C.F.S. your renewed attention.

Yours sincerely,

Doris Jones

(Doris Jones)

c.c. Dr. Judith Hilton, DOH.

Encl.
Testimony by Dr. P.R. Cheney to the FDA, copy for information.
List of References

REFERENCES

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TESTIMONY BEFORE THE FDA SCIENTIFIC ADVISORY COMMITTEE
February 18, 1993
by
Paul R. Cheney M.D.,Ph.D
Charlotte, NC

My name is Dr. Paul Cheney. I am a general internist in Charlotte, NC.

I was invited by the CFIDS Association, a patient group of some 23,000 members, to present the perspective of a clinician **in the trenches** treating chronic fatigue syndrome. It has now been over eight years since I first became conscious of this disorder as a distinct clinical entity. I watched in awe as over 200 cases appeared over a span of six months in a small community on the north shore of Lake Tahoe where I practiced in 1984 . Since then I have evaluated over 2500 cases of chronic fatigue of which over 2000 cases meet the CDC case definition.

I currently direct The Cheney Clinic in Charlotte, NC. (*which, with a staff of fourteen is devoted entirely to the diagnosis and management of CFS*). We have carefully evaluated in the three years of our existence over 1200 cases from 44 states and 6 foreign countries or territories. 78% meet the CDC case definition. We have seen the worst and the best of the range of scenarios that can befall a patient with this disorder. At best, it is a prolonged post-viral syndrome with slow recovery or improvement within one to five years. At worst it is a nightmare of increasing disability with both physical and neurocognitive components.

The worst cases have both an MS-like and an AIDS-like clinical appearance. While CFS is not generally fatal, we have lost five patients in the last six months. Two by suicide and three by intercurrent infections. All were in a progressive, debilitated state. The most difficult thing to treat is the severe pain. The most frustrating is the fatigue. The most alarming is the neurologic and neurocognitive elements of this disease. Half have abnormal MRI scans, 80% have abnormal SPECT scans, 95% have abnormal cognitive evoked EEG brain maps. Most have abnormal neurologic examinations. (*The most severe cases have neurologic findings which are striking but at the extreme end of a continuum of abnormalities which are subtle in most cases.*)

We have 155 cases with random CD4 counts below 500, 62 cases below 400, 21 below 300 and 3 below 200. An estimated two thirds of these cases will persist below 500 on repeated determinations. Only a few will meet the current case definition of ICL. None have shown progressive CD4 depletion as seen in AIDS. (*Many with low CD4 levels are clinically quiescent and quite stable.)* However, we have had four cases of AIDS defining opportunistic infections including MAI and pneumocystis pneumonia and two cases of spontaneous esophageal candidiasis. (*One of these patients has had repeated bouts of opportunistic infections but only one has CD4 depletion.*) 40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation. 80% have an up-regulated 2-5 A anti-viral pathway on a single determination.

From an economic standpoint, this disease is a disaster. 80% of the cases evaluated at my clinic are unable to work or attend school. The average length of illness at the time of presentation is 3.8 years. 90% have become ill since 1980. The yearly case production, if plotted, is exponential. Most are already on or will shortly be on some sort of disability plan, public or private. In a recent patient survey at our clinic, the average dollar figure spent on medical care before coming to our clinic was $25,000 with a range of from $6,000 to $40,000. Most patients had seen more than ten physicians. (*Very few were happy with their care or treatment at the hands of ordinary physicians, but especially medical specialists. The worst care is rendered by HMO's and national diagnostic clinics. The best care is rendered by caring family physicians.*)

The most common reasons given to come to our clinic are 1) To obtain a definite diagnosis 2) To seek treatment options and 3) To document disability for subsequent social security disability applications. We are frequently depositioned for disability and other types of litigation. (*Many cases involve divorce as we witness the disintegration of the family unit. We have seen litigation against schools to force homebound teaching of impaired children with CFS.*) The medical legal aspects of our practice steadily grow as this disease eats at the fabric of our communities.

We admit regularly to the hospital. The most common admitting diagnoses are acute and chronic encephalopathy, uncontrolled head pain and debilitating fatigue with inability to care for self. The longest hospitalization is 5 months to date. That patient has encephalopathy, seizures and apraxia and is currently awaiting nursing home placement at the age of 37. Medicare/medicaid has to date paid $150,000 to the hospital for her care which has exceeded $250,000 since August 1992.
Another patient, age 28 and also on medicare, spent 8 weeks at Emory University Rehabilitation Hospital. During her stay at Emory, she steadily worsened under standard rehabilitation protocols and was eventually transferred to me for an additional 1 month hospitalization. (*She has been confined to a wheelchair for 18 months with severe lower extremity extrapyramidal motorneuron disease.*) Both of these cases are summarized in two case reports for your review.

In summary, CFS is an emerging, poorly understood disorder with a distinctive clinical presentation. I am not at all sure that it is as heterogeneous as some would lead you to believe. (*I am also not at all sure that much of what I and others have been witnessing since 1980 is necessarily an old disorder. Post-viral syndromes are certainly old and certainly related but most CFS cases are much more distinctive than that. The boundaries of this disorder are certainly vague but that is true of many otherwise distinctive clinical entities.*) This disorder is a socio-economic as well as medical catastrophe that will not end. I believe that government and university clinicians have spent too little time or thought too narrowly about these patients. This disease is too complex to rely wholly on standard medical orthodoxy to explain it. When in doubt listen to a thousand patients with an open mind. Failing that, then listen to those who have spent countless hours with a thousand patients. Most of us have some wisdom to impart and most of that came from patients.

Thank you for listening,

S1528/1 22 December 1992

Dear Ms Jones

I am replying to your letters of 26 May and 19 November concerning the Ciba Foundation meeting on chronic fatigue syndrome (CFS), which took place in May this year. I apologise for not having done so sooner.

I attended the Ciba symposium myself (12-14 May). It was, as you suggest, very interesting even if it did not perhaps manage to convey the feeling of desperation and frustration of sufferers as eloquently as the letter in JAMA that you sent me.

The Council looks to the wide variety of professionals researching in the field - virologists, epidemiologists, psychiatrists etc - to develop and test plausible hypotheses with appropriate approaches likely significantly to inform understanding of the aetiology of CFS and how it may be managed, treated and prevented. The MRC does not have a view on what CFS is and what is not: it does not instruct the scientific community as to whether CFS has an instrinsic or extrinsic basis. Nor would the Council accept the implication of some critics of CFS research that 'psychiatry' means 'non-biological' or imagined. However, the members of our research Boards are undoubtedly influenced by informed debate such as that organised by Ciba Foundation in May, and briefings such as that by the Royal Society published in September 1990.

One observation that my colleagues and I made at the Ciba Foundation meeting was that participants were largely of the view that a search for a single identifiable cause of CFS was inappropriate - indeed misleading - and that it was almost certainly a multifactorial disorder. Evidence for a viral aetiology was unconvincing although, as suggested by one participant, "absence of evidence is not evidence of absence". You suggest that there may be a link between vaccination and CFS. The sequelae of immunisations in general is an area in which the Health Departments in particular have a special interest. The problem is to establish the specificity of that link to CFS. I can, however, assure you that the MRC is certainly not reluctant to support research in this area or any other that may be related to CFS, as long as it is scientifically competitive.

The epidemiology of CFS would appear to be difficult not least because CFS sufferers (in the widest sense of the term CFS) are generally particularly susceptible to physical explanations of their illness and to recalling "significant" antecedent events (illness, immunisation ...) by comparison with control populations. Interestingly, one might expect students to be similarly susceptible, albeit for other reasons (especially if studying medicine or allied subjects). I suggest this not in an attempt to write off CFS as "all in the mind", but to illustrate one of the practical difficulties involved. Another problem is that of differentiating between secondary and primary effects - both in causation and clinical presentation. These problems are,

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however, not unique to CFS and it may be that appropriate methodology can (and has?) been devised to provide definitive answers to important questions.

Finally, I should like to reaffirm that the Council welcomes applications for research in this as in any other area of its remit, in competition with other applications and making its decisions on the basis of quality of science.

I hope I have been helpful - albeit very late to reply.

Yours sincerely

Redacted under FOI exemption (s) 40(2).Closed until 2071

Peter Dukes

2b:249:26

(18) S1528/1 Ko.'d 23/11

Tel. 081-554-3832.

19.11.1992.

Dr. Peter Dukes,
Medical Research Council,
20, Park Crescent,
London, W1N 4AL.

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Dear Dr. Dukes,

Ciba Open Meeting on C.F.S. - 15.5.1992.

I refer to my letter of 26.5. concerning the above. This was acknowledged in your absence from the office by Miss R. Abbott on 28.5.1992, ref.PD:231, stating you would be out of the office until 8th June and that you would reply to my letter on your return.

So far I do not appear to have received any further communication from you and whilst I realize you must be very busy and the problem I have presented to you is both complex and controversial, I wonder whether you have been able to give the matter any further thought, and what should and could be done about it in your view.

Dr. Judith Hilton from the Dept. of Health, whom I had also contacted, has subsequently written to me and has asked for further details of the study. I am now in a position to compile these, having received agreement from the editors of journals who are considering publication of some of these results. An earlier visit abroad, followed by my being summoned to jury service on a protracted case, has unfortunately resulted in some inevitable delay in submitting these details to Dr. Hilton.

In the meantime a very comprehensive and authoritative publication on M.E./C.F.S. has become available. I enclose details of this new Encyclopaedia. It contains a full record of the papers and data presented at the 1990 first World Symposium on M.E./C.F.S., held at Cambridge, U.K. Whilst for various complex reasons this event was not the success it deserved to be, it nevertheless brought together 45 researchers into this disorder from around the world, doctors and professors, many of whom have devoted much of their lives to exploring the complexities of this disease. Significantly perhaps, the possible link with vaccinations and immunizations was also discussed at this symposium, and indeed it is re-emphasized in this latest publication by B.Hyde et al.

I have also in the meantime prepared and submitted an article on vaccination and antibiotic details and relevant results from my study to a conventional medical journal and I hope this will be accepted for publication. A further article and case study reports in relation to allergies and allergic reactions will be submitted shortly, as will a final article on the remaining results of the study.

May I hope to hear from you soon in this matter. I understand the publication based on the Ciba Conference and Open Day will become available in January, 1993. I do feel you would be wise to study the Ciba Conference book alongside the Hyde et al Encyclopaedia on M.E./C.F.S. and when making decisions on future research into this disorder, take into consideration the illuminating and authoritative studies which this book contains.

-2-

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Oh, I have also now at long last been able to secure a copy of Sir Graham S. Wilson's remarkable book 'The Hazards of Immunization', published in 1967 by the University of London, The Athlone Press. It appears to have been hidden away in the vaults of a few libraries, classified as 'CLXX', i.e. not available to the general public, unless specifically asked for.

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I look forward to hearing from you.

Yours sincerely,

Doris Jones

(Doris Jones).

Encl.
New Book Information on B. Hyde et al's 'The Clinical and Scientific Basis of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome'.

New Book Information

Published by The Nightingale Research Foundation simultaneously in Ottawa, Canada and Ogdensburg, NY, USA

The Clinical and Scientific Basis of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

Edited by
Byron Hyde, M.D., Nightingale Research Foundation, Ottawa, Canada
with editorial and conceptual advice from
Paul Levine, M.D., NIH, Bethesda, Maryland, USA
Jay Goldstein, M.D., Chronic Fatigue Syndrome Institutes, California, USA

More than eighty of the world's leading M.E./CFS authorities have contributed their knowledge to produce a **750-page encyclopedia** on the disease process that may be one of the biggest single causes of chronic illness in the world today. Known in the United States as Chronic Fatigue Syndrome and in Great Britain as both Myalgic Encephalomyelitis and Post-Viral Fatigue Syndrome, M.E./CFS has provoked a chronic disabling illness in an estimated 1,000,000 persons in North America and Europe.

This book provides, in one superb 75-chapter source, an up-to-date, comprehensive account of current knowledge concerning the history, epidemiology, children with M.E.; investigation, virology, immunology, muscle pathology, host response, food intolerance, brain mapping, neurophysiology, neuropsychology, psychiatry, sleep dysfunction, fibromyalgia syndrome, treatment and management.

This is an essential reference book for medical, government and public library reference rooms. With some United States researchers linking M.E. / CFS to a newly discovered and possibly easily transmitted retrovirus, this book is especially timely.

ORDER FORM

Please send me _____ copy(ies) of:

Hyde: **The Clinical and Scientific Basis of M.E./CFS**
ISBN no. 0-9695662-0-4
Library of Congress Catalogue Number 92-064489

Cost per book (includes surface postage and handling):

£ 70 Sterling, surface mail

£ [redacted] airmail

I enclose a cheque/bank draft (payable to **The Nightingale Research Foundation**) for _____

OR

Please charge my credit card account as indicated:

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Amount: _____

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Please return to:

The Nightingale Research Foundation
c/o Dr. John Richardson
Belle Vue, Grange Road
Ryton on Tyne NE40 3LU
United Kingdom

New Book Information

Contents

(20)

Tel. 081-554-3832.

[redacted]

26.5.1992.

Dr. Peter Dukes,
Medical Research Council,
20, Park Crescent,
London,
W1N 4AL.

Dear Dr. Dukes,

Ciba Open Meeting on C.F.S. - 15.5.1992.

As a postgraduate research student into this disorder, I was particularly interested in the way in which this illness is now portrayed to G.P.'s by other investigators. To attend the above meeting was therefore a unique experience for me. I do not belong to the medical profession, neither am I affiliated closely to either of the patient organizations, nor suffer personally from the disorder. [redacted]

It was gratifying to note that most presenters showed an enhanced understanding of problems concerning C.F.S., supported by recent research results, and Dr. Gunn's findings were of particular interest. However, one aspect struck me rather forcibly on numerous occasions during this one day event, and that concerned a huge chasm between how this illness is perceived by G.P.'s and Psychiatrists, compared to how it affects sufferers in real life and what its true nature may turn out to be. I have outlined these fundamental differences in more detail to Dr. McBride.

I have recently completed a comprehensive multifactorial epidemiological research project into this disease, and take the liberty of enclosing a copy of the Abstract for your information. You will note that details on associated factors like vaccinations, antibiotics and allergies may be especially relevant, as may those on diet, stress and earlier infections. It is disconcerting that some of these associated factors can also be seen in certain apparently healthy subjects, notably in normal students, which seems to coincide with concurrent emergence of similar symptomatology. [redacted]

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I am sure you will appreciate the far reaching consequences these observations and my study results could have if indeed they are representative of the problems seen in this disorder and perhaps in associated diseases like M.S. and others. Various researchers have made similar observations (1,2,3,4,5). Indeed one of Professor Behan's research teams recently identified sequences of an enterovirus which were identical to the polio vaccine virus in a proportion of carefully selected PVPS patients (6). There is even more alarming

literature on this subject, perhaps the most significant is that written by the U.S. Medical Historian H.L. Coulter (7,8). - Problems associated with extensive use of broad spectrum antibiotics and candida have been widely reported both in journals such as the B.M.J. and the Lancet, as well as in more journalistic publications such as 'What Doctors Don't Tell You' (W.D.D.T.Y.) and others.

You may agree that in the circumstances an in depth large-scale epidemiological research project into this disorder would seem advisable. Whilst possible consequences for the pharmaceutical industry need to be considered of course, these surely should be offset against not only an incalculable amount of perhaps unnecessary human suffering, but also against what may be a rapidly growing number of middle-aged or even quite young incapacitated, perhaps permanently disabled and STATE-BENEFIT-DEPENDENT subjects! What appears to me particularly urgent is the

IDENTIFICATION of PREDISPOSING RISK FACTORS for PVFS/ME/CFS.

This was the principal reason for the multifactorial study into this affliction, which I commenced in 1989. So far I have analysed approximately 50% of all available data, and the study will probably be extended into a PhD, if certain problems can be resolved. I recently approached the M.R.C. regarding funding for the proposed PhD, as so far the project has been financed entirely by my (debilitated!) family members. The reply I received dated 12.5.1992 implied that I should contact certain charitable trusts such as the Nuffield Foundation and others.

It is hoped that some results of my completed study can be published in conventional medical journals. So far response has been rather less than enthusiastic though.

To conclude these somewhat lengthy elaborations, I would like to point out that a remarkable set-up to diagnose and treat PVFS/ME/CFS subjects has been established at Harold Wood Hospital. It seems a pity that the Consultant Neurologist in charge of this unit was not invited to the Ciba meeting. Research funding for finding ways of helping such patients assuredly would also be most appropriate. - This disorder affects a disproportionately high number of subjects associated with the medical and health care professions. It seems to be singularly bizarre that the psychiatric sector should feel compelled to persist in somehow berating and trivializing the disorder, even now, and underscoring psychiatric problems in many cases. - I enclose a copy of an article written by a U.S. surgeon affected by C.F.S. and addressed to his colleagues, published in JAMA, 27.2.1991. It describes more aptly than anything I have read how this disease affects the lives of sufferers.

I trust these explanations will provide you with a wider perspective of the problems of PVFS/ME/CFS or any other description you may care to choose for what almost certainly is a serious and potentially chronic and debilitating disease.

I would be pleased to provide further information if this is desired.

Yours sincerely,

Doris Jones

(Doris Jones).

Encl.
Abstract of MSc Study.
Copy of JAMA article 'Skeptical of Skeptics'.

References (Selected).

(1) H.Miller, W.Cendrowski, K.Schapira: 'Multiple Sclerosis and Vaccination. B.M.J. 22.4.1967,p.210-13.

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(3) A.D.Allen: 'Is RA27/3 Rubella Immunisation a Cause of Chronic Fatigue?' Medical Hypotheses, 1988, Vol.27, p.217-20.

(4) A.D.Lieberman: 'The Role of the Rubella Virus in the Chronic Fatigue Syndrome'. Clinical Ecology, 1990, Vol.7,No.3,p.51-4.

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(7) H.L. Coulter: Vaccination, Social Violence and Criminality' (subtitled 'The Medical Assault on the Americal Brain'). North Atlantic Books, Berkeley, California. The Center for Empirical Medicine, Washington,D.C.

(8) H.L.Coulter, B.L.Fisher: 'A Shot in the Dark'. Avery Publications Group Inc., Garden City Park, N.Y., 1991.

ABSTRACT

M.E. - JUST ONE SILENT EPIDEMIC D.Jones

A multifactorial study was conducted on 225 M.E.(Myalgic Encephalomyelitis) subjects, based on questionnaires completed by volunteers, secured with cooperation from the M.E.Action Campaign, M.E.Association and Open University. Studied are a multitude of symptoms before and after M.E. onset, general life-style factors in previous 5 years, including infections, antibiotic -, oral contraceptive - and vaccination use, stress, diet and precipitating factors. M.E.students are subgroups, enabling comparison with 44 normal students. 29 non-students represent a second control group.

Analysed results show the illness often develops gradually. 30 common symptoms after M.E.onset were identified in many sufferers and 20 before onset. Specific symptoms often seem to crystallize out of candida symptoms, using Crook criteria. Normal students experience similar symptoms; these are less prevalent in healthy non-students. Over half of M.E.subjects may have serious candida problems, by Crook's criteria.

Many antibiotics were used by M.E.subjects, especially broadspectrum types, often prescribed for viral infections, including those resulting in M.E. Septrin was frequently mentioned. Vaccinations were widely used, notably Tetanus. Earlier adverse reactions to antibiotics and vaccinations were common. Over 12% of M.E.subjects were vaccinated the month before M.E.onset. Interactions between viral infections and vaccinations appeared to result in M.E.

Precipitating factors varied; viral infections predominated; childbirths, accidents, vaccinations, insect bites and others resulted in similar malfunctions. Many M.E.subjects had earlier ill health, notably recurrent respiratory tract infections. Most experienced much stress, persistent minor stress problems more frequently than major life-event stress. Loss of stress control affected most. There were frequent cravings for sugary foods, sweets and excesses in carbohydrates and chocolate. Intake of magnesium rich foods was low. Food allergies affected 40% of M.E.subjects before M.E.onset; family histories of such allergies and/or atopy were common.

Analysis suggests various factors contribute in lowering immune competence. Affected subjects seem more vulnerable to viral infections. Frequent and/or repeated vaccinations, antibiotics or other drugs tend to result in increasingly severe adverse reactions in M.E.subjects.

Skeptical of Skeptics

Skepticism permeates our profession. It is ingrained during medical training and reinforced by professional experience. Who among us has not repeatedly seen claims for fourth-generation drugs with no side effects, new operations that yield glowing results with minimal complications, or the latest infallible, high-tech diagnostic procedure . . . only to discover months or years later that these claims missed the truth by miles. Small wonder most of us are skeptics. To be skeptical is to be detached, rational, and objective. Skepticism is widely perceived as the prudent, conservative way to deal with ambiguous situations—times when even experts are confounded. Healthy skepticism is the "in" attitude for intelligent, discriminating physicians.

But healthy for whom?

Four years ago I was diagnosed as having chronic fatigue syndrome (CFS). The experience has given me a new perspective of my profession, one that is not always flattering. In one early report, the average CFS patient had previously consulted 16 different physicians. Most were told that they were in perfect health, that they were depressed, or that they were under too much stress. Many were sent to psychiatrists. The situation is better today, but not by much.

Though many CFS patients are depressed (small wonder), CFS is not depression. Antidepressants may treat that depression, but CFS persists. Likewise, therapists may support but not cure; some patients find their psychiatrist is the only one who believes they are physically ill. Careful scrutiny with an open mind reveals that the fit of CFS symptoms into traditional psychiatric molds is uncomfortable at best.

Is CFS a real disease? I believe it is, but I cannot settle that here. I would only plant this seed in the mind of skeptics: *What if you are wrong?* What are the consequences for your patients?

Imagine for a moment that you are the Subjective patient, not the Objective physician. You catch "a cold" and thereafter the quality of your life is indelibly altered. You can't think clearly . . . sometimes it's all you can do to read the newspaper or to follow the plot of a television program. Jet lag without end. You inch along the fog-shrouded precipice of patient care, where once you walked with confidence. Myalgias wander about your body with no apparent pattern. Symptoms come and go, wax and wane. What is true today may be partially true tomorrow or totally false next week. You know that sounds flaky, but, damnit, it's happening to you.

You are exhausted, yet you can sleep only two or three hours a night. You were a jogger who ran three miles regularly; now a walk around the block depletes your stamina. Strenuous exercise precipitates relapses that last weeks. *There is nothing in your experience in medical school, residency, or practice with its grueling hours and sleep deprivation that even approaches the fatigue you feel with this illness.* "Fatigue" is the most pathetically inadequate term.

You too might wonder about some of your symptoms had you not talked to other patients with similar experiences . . . or talked with physicians who have seen hundreds of similar cases. With experience, a pattern emerges: the bizarre and implausible become commonplace and credible. "Armchair analysis" of CFS understandably generates doubt; to comprehend this illness, one must heed Osler's advice to study the patient firsthand: "Learning medicine without books is like going to sea without charts. Learning medicine without patients is like not going to sea at all." I have only skimmed the surface of the myriad symptoms CFS produces—persistent headache, sore throat, loss of fingerprints, a variety of neurological symptoms, seizures, adenopathy—but you are, I hope, beginning to get the picture.

Iron-man determination to be tough is self-destructive: you merely become Sinking Sisyphus. Perhaps you take a few weeks off; rest helps. Though you improve, you are still light years from your former self.

By now you are literally disabled, but the bills still roll in. Will you qualify for disability if your physicians determine that your only problem is "too much stress"? Maybe you will be lucky enough to find a doctor who can properly diagnose and treat you, and maybe you have disability insurance with a competent company that has informed consultants. Maybe.

I have talked with scores of fellow patients who went to our profession for help, but who came away humiliated, angry, and afraid. Their bodies told them they were physically ill, but the psychospeculation of their physicians was only frightening and infuriating—not reassuring. It told them their doctors had little understanding of the real problem. Many patients had depleted themselves financially, dragging in vain through expensive series of tests and consultants as their lives crumbled around them. They had lost careers, homes, families, in addition to the loss of stamina and cognitive skills. *There is nothing that you hold dear that this illness cannot take from you. Nothing.*

Are we to believe that just because symptoms are strange and unfamiliar they cannot be real? Are we to assume that our laboratory tests are capable of screening for new diseases as well as old? Distrust of new ideas is as old as humankind; so are the harmful consequences of that distrust. The doctrines of Lister and Semmelweis were not generally accepted for more than 50 years. I shudder to think of the death and misery caused by the skeptics during that half-century.

I have been very lucky. After being ill for a year and a half, I began painfully slow improvement. Despite repeated setbacks, I have progressed to the point where I am no longer continually miserable. My career, however, is but a faint memory. There is little demand for absentminded surgeons, even if I had the stamina. Too, I harbor the lingering fear that I might transmit my illness to a patient. The satisfactions of the operating room are a thing of the past. So I wait. I hope. I pray.

My activities are narrowly circumscribed. I can read again, but I avoid difficult material. I can handle light exercise, but the backpacking that was my previous delight is evanescent fantasy. I swallow my pills, follow my diet. (Treatment is palliative and based on trial-and-error application of anecdotal evidence, but it helps most patients. I enjoy passable existence, not a miasma of misery. I lack the strength to wait years for controlled studies; life is short, science is slow.) I try to educate other patients and "convert" other physicians. Sometimes I succeed.

I have survived because of caring friends and fellow patients and because of a few committed physicians who kept their minds open. They truly listened. They thought long and hard. Many were and still are ridiculed for taking CFS seriously.

Internists have long prided themselves on incisive intellects and superior diagnostic skills. It is time for those skills to focus on the complex subtleties of this illness. I ask for your patience. CFS is sufficient indignity by itself; do not compound it. It takes considerable time and infinite patience to take an accurate history from a frail patient with impaired memory and concentration, especially if that history is long and complex. But if you take that time, you can do a world of good. CFS may frustrate you, but it is equally fascinating and rewarding. Resist the temptation of hurried, superficial evaluation. This is no illness for cookbook doctors. It is a disease for medical intellectuals with supple and open minds.

Thomas L. English, MD
Asheville, NC

Edited by Roxanne K. Young, Associate Editor.

(21) 12/3-92

Pat

Please could you:

(i) ~~draft~~ prepare the attached letter to [redacted]

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(ii) send a copy of the letter (the typed version) to Dr Bayri (+ the attached minute);

(iii) send a copy to Mr Laycock (+ attached minute).

(iv) ensure that Dr Bayri + Mr Laycock have replies to me by 18 March.

Thanks

T.

(22)

12th March 1992

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Dear

The Secretary, Dr. Rees, has asked me to reply on his behalf to your letter of 3rd March 1992 concerning MRC supported research into Myalgic Encephalomyelitis. Unfortunately, a colleague I would like to consult is currently on leave. Consequently, I hope you will forgive me if I delay addressing your points in detail for another fortnight, when I shall write to you again.

Yours sincerely

Peter Dukes PhD
Secretary, Neurosciences Board

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There are so many other aspects of ME which could be researched with a far higher probability of a positive outcome. For example the effect of virus attack for long periods on the immune system, the breakdown products of viruses and indeed, viruses in more general terms.

Another possible valid use of research would be the epidemioly of ME. No one presently knows its time extent and it could be very revealing to know. The present cost of benefits could be as much as £260,000,000 assuming 100,000 sufferers are eligible and receive £50 per week. If this were shown to be fine, there would even be a financial incentive for any Government to find research - and there could be benefit for the sufferers.

Yours faithfully

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MEMORANDUM

TO: Dr Jepson
FROM: Deborah Cash
SUBJECT: ME Syndrome
DATE: 4 March, 1992

Please see [redacted]'s letter of 3rd March.

Dr Rees would be grateful if you could deal with this on his behalf.

D. Cash

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or body tissues (27) with their "blind eyes" it is not to be expected that the Institute will take any notice of their research findings.

It cannot, of course, be denied that people with ME suffer from depression. For most it is a life sentence, to prove treatment, the instability of the medical profession and to support, in some cases, the family and relations. With such a background of past that research into the depressive aspects of ME is obvious.

There are so many other aspects of ME which could be researched with a far higher probability of a positive outcome. For example the effect of virus attack for long periods on the immune system, the breakdown products of viruses and toxins, viruses in more general terms.

Another possible valid line of research would be the epidemiology of ME. No one presently knows its true extent and it could be very revealing to know. The present cost of benefits could be as much as £260,000,000 assuming 100,000 sufferers are eligible and receive £50 per week. By this very token a cure, here could even be a financial incentive for any Government to fund research - and there would be benefit for the sufferers.

Yours faithfully

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G890595-2

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24 March, 1992

Dear

I am writing to follow up my earlier letter in reply to your letter of 3 March 1992 concerning MRC supported research on myalgic encephalomyelitis (ME), more correctly termed chronic fatigue syndrome (CFS).

As you suggest, the Council does fund work on CFS at the Institute of Psychiatry, an institution with a distinguished record of research spanning disciplines such as neurology and neuropathology and not only psychiatry. The project which I believe you may be referring to is entitled "An epidemiological approach to the study of chronic fatigue syndrome". It addresses the following important questions:

- How should fatigue be measured?

- What is the prevalence of CFS - as opposed to general "everyday" fatigue ?

- What are the clinical, demographic and psychosocial factors associated with CFS ?

The study should provide some of the groundwork necessary to allow further, more highly focused studies of causes and mechanisms, and to the identify factors that predispose to, precipitate and perpetuate CFS - whether they be neurobiological, psychosocial or environmental. MRC support for this particular study does not imply that the Council favours one particular hypothesis concerning the causation of CFS/ME over any other. Indeed, the Council welcomes applications for research on CFS/ME relevant to any area of its remit - in competition with other applications and making its decisions on the basis of quality of science.

You suggest that research findings on physical damage to the brain and other tissues have been ignored. This is a difficult suggestion to examine and to substantiate. The Council does not collect or have information on the uptake of specific research ideas or "products" into clinical practice. However, the information I have is that research in this area of work has not yet been conclusive.

I hope that I have been able to allay your disquiet. Please do let me know if I can be of any further help.

Yours sincerely

Peter Dukes

off\cfs-oil

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Another possible valid use of research would be the epidemiology of ME. No one presently knows its time extent and it could be very revealing to know. The present cost of benefits could be as much as £260,000,000 assuming 100,000 sufferers are eligible and receive £50 per week. If this were shown to be fine, there would even be a financial incentive for any Government to find research - and there could be benefit for the sufferers.

Yours faithfully

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MRC
Medical Research Council

D.I.O.
To CFS file

Rec'd 13/9

MRC Applied Psychology Unit
15 Chaucer Road
Cambridge, CB2 2EF

telephone Cambridge (0223) 355294

reference ADB/JLD

10 September 1990

Dr J E Dowman
Medical Research Council
20 Park Crescent
London W1N 4AL

Dear John,

It occurred to me that you might possibly be interested in a brief account of my activities during my Australian visit, and some broad impressions of Australian psychology. I was able to combine the journey out here with attendance at a very good memory meeting in Toronto, a Festschrift to a retiring memory expert, Ben Murdock who had spent a year at the APU back in the 1960s, and who kept up links with us since that time. It was a good meeting with many of the papers, including my own, referring to Murdock's memory model which involves parallel distributed storage. This was likened to Sir Frances Galton's composite photograph technique, whereby one superimposes a brief exposure of many faces to come up with the archetypal example of a particular category, for example the "typical criminal". Someone had the bright idea of substituting a Galton photograph of the participants for the usual group photograph, so we should know in due course what a typical memory research worker looks like!

We travelled out during the Australian mid-term break, and so had time to visit departments in Hawaii and New Zealand en route. That also meant that my host, the Queensland Department wanted us to do the bulk of our travelling at the beginning rather than the end of our trip. That fitted in quite well since it allowed me to attend a Developmental Psychology meeting in Perth as a guest speaker. It was a relatively large meeting with a number of key speakers from both Britain and the U.S., and as my first ever developmental meeting, I felt that I learnt a good deal. The University of Western Australia is considering setting up a group concerned with applied cognitive psychology, and I had a very interesting afternoon talking to them about our experience at the APU. We went back to Brisbane via Adelaide, where I gave a number of talks and visited the Julia Farr Centre. This is a very large and modern neurological rehabilitation centre that appears to be very keen to develop research. They have created a joint chair with Flinders University which has been taken by Gina Geffen, who is doing work on post-traumatic amnesia not dissimilar from the work currently going on at Southampton.

My commitment to the University of Queensland involved presenting a one-hour colloquium on each of six successive Friday afternoons, not a particularly onerous load. It is the biggest and probably one of the most active departments in Australia, with some 50 staff. They have good buildings and facilities, coupled with more students than they care to teach, and probably rather more posts than they can fill with really top-quality people. I was very impressed with the current Chairman, Steve Schwartz who has interests in both clinical and cognitive psychology, and in particular works on medical decision making. He has previously had a fair amount of contact with Donald Broadbent, who you may recall also spent a spell at the Queensland Department.

cont'd/...2

Possibly because of the size of the Department, I found it difficult to get a good feel for exactly what was going on. My colloquia were well attended, but the questions on the whole tended not to be particularly searching. However, as time went on I increasingly found people coming to talk about their research, and it is clear that there is a broad range of good work going on.

Probably the closest to my own work in emphasis is that of Graeme Halford who is interested in cognitive development, and in working memory in children. There is a relatively strong memory group here, with the most senior person being Michael Humphreys, an American with a strong interest in mathematical modelling, an area that is fairly strong in the Department.

Some of my most fruitful discussions somewhat surprisingly were in the area of psychometrics. As you may recall, I have an interest in developing memory tests, and there are a number of people here with interests in test design and its application to clinical, educational and occupational issues. I also had some useful interactions with a number of the clinicians, for example with Robert Schweitzer who is beginning a project on post-viral fatigue syndrome, and who appears to be picking up quite marked complaints of memory problems.

In between my "arduous" teaching load, I was able to make trips to Melbourne (Monash and the University of Melbourne), Sydney (Sydney and Macquarie Universities) and to the University of New England at Armidale. The trip ended up with a two-day cognitive science meeting in Brisbane, sponsored by the Australian Research Council, and attended by interested people from around Australia, and by a couple of U.S. keynote speakers, Gary Dell from Illinois and Geoff Ellman from UC San Diego. It comprised a series of one-hour presentations, followed by discussion, and worked very well.

In general it reinforced my impressions of Australian cognitive psychology. There are some good people, but with one or two exceptions, they suffer from dispersal and isolation. Psycholinguistics seems to be reasonably strong in Melbourne, although it may well suffer from the recent emigration to the U.S. of its leading light, Ken Forster. Max Coltheart seems to be doing a very good job at Macquarie, and seems to be broadening his interests to include both PDP modelling and psychophysiological brain-scanning approaches to cognition, which I would regard as an excellent development.

All in all then, although I have not managed as much writing as I had hoped (the age-old sabbatical story!), it has been an interesting and fruitful trip.

With best wishes,

Yours,

Alan Baddeley

S1528/1 10 April 1989

Dear Dr White,

Research on post-viral fatigue

Dr Rees has asked me to reply to your letter of 21 March. I am afraid you have been misinformed: the Council has no plans for any type of special funding in the field of post-viral research.

It is of course, as you recognise open to you to apply for project grant support in open competition in the usual way. I am therefore enclosing a project grant form which you may care to complete in due course.

Yours sincerely,

Katherine Levy

Dr P White
Department of Psychological Medicine
St Bartholomew's Hospital
West Smithfield
London EC1A 7BE

ENC

S1523/1

MEMO FROM THE SECRETARY

Date 30th March 1989

To Katherine Levy

Reply to Secretary by:

Post Viral Fatigue: Dr P White

Dr Rees would be most grateful if you would deal with the attached letter from Dr Peter White of St Bartholomew's on his behalf.

GMB

Gillian Breen

DEPARTMENT OF PSYCHOLOGICAL MEDICINE

St. Bartholomew's Hospital

Dr D A Rees
Secretary
Medical Research Council
20 Park Crescent
London W1

March 21st 1989

West Smithfield, London EC1A 7BE
Telephone 01-601 8888

DIRECT LINE: 01-601-8106/7/8

Dear Dr Rees

RESEARCH ON POST-VIRAL FATIGUE

I understand the Medical Research Council may be considering special grant awards for research in this area. If this is the case, I would like to forewarn you that I shall be looking for funding for substantive projects to test various hypotheses regarding the physical and psychological aspects of this putative diagnosis.

I am currently completing a prospective six month follow-up study of 249 people following a definitive upper respiratory tract infection. The majority of these patients suffered from infectious mononucleosis and I, and my collaborators, have measured psychiatric morbidity and physical morbidity following the illness, correlating these independent variables with psychosocial, immunological and virological independent variables.

I am also currently undertaking a pilot questionnaire study of 950 people who consider they have had problems in recovering after infectious monomucleosis. I shall be seeking funding to fund a laboratory and interview study of sub-groups of those 950 people.

The last two studies, for which I will be seeking funding in due course, concern a placebo controlled trial of treatment with monoamine-oxidase inhibitors, and a treatment trial of a graduated return to physical activity and exercise.

Please let me know if you require further details at the moment. The protocols are not yet prepared, since they depend results of the two above mentioned current studies. Obviously if the MRC is not considering special funding, I shall apply through the normal channels.

Yours sincerely

Peter White.

Dr Peter White
Recently appointed Senior Lecturer
in Psychological Medicine (awaiting university approval)

File No.

Dr Levy:

Dr Dowman 3/6/88 1/6/88

Through Professor Wolpert's intervention (and some difficulties in our press office) I have got caught up in an enquiry from HORIZON on MRC support for myalgic encephalomyelitis. Mrs Currie is on record - I believe in answer to a PQ on which we were consulted by the DHSS in November 1987 - as saying the MRC is supporting nothing. The question is:

> Is this true and if so why: ie. no applications or applications turned down?

I had a preliminary word with the producer Katherine Everitt (895-6403) on the basis of a very preliminary search by David Cox. Answer - nothing because no applications. However she has now extended the deadline (said to be lunch time today 1.6.88) to Friday pm. She evidently wants to quote us and while I do not wish great work to be created I do not want us quoted as saying we think we have nothing because we have considered nothing but cannot be sure. They would make a meal of it!

Would it be possible to do a check so that we can give a definitive answer: say agendas for Neurosciences Grants Committees over the last 2/3 years? Or is there something quicker and easier?

I am in HSRC tomorrow but do not mind - in principle - being interrupted.

Katherine Levy

K1

Dr. Pearl 7/6

Dr. Snyder 7/6

Dr. Dowman 7/6

Many thanks: I got away with no mention of Radda, the Unit or Oxford.

K 6/6/88

G8210913.

Also page 16 for other metabolic myopathies.

P

1. I do not think x is altogether correct: Professor George Radda (whom we support currently by a programme grant) has been using NMR methods to look at mitochondrial encephalomyopathies (page 27 of his progress report for the period 1982-86) and this line of investigation is continuing under the current programme (page 11 of renewal request considered by the Cell Board in 12/86).

2. Is this not the Royal Free Hospital Syndrome and perhaps of controversial status as a disease entity?

DNE

316

The National Archives

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Myalgic encephalomyelitis:

* POSTVIRAL FATIGUE SYNDROME

Peter O. Behan MD FACP FRCP(L)(G)(I)

Reader in Neurology(1)

Wilhelmina M.H. Behan MD FRCPath

Senior Lecturer in Pathology(2)

from the Departments of Neurology(1) and Pathology(2)

Glasgow University, Glasgow G12 8QQ, Scotland, G.B.

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INTRODUCTION

Postviral fatigue syndrome (PFS), epidemic myalgic encephalomyelitis (EME), also known as epidemic neuromyasthenia, has attracted increasing attention during the last five years leading to a clearer definition of its clinical and laboratory features and general agreement that its distinguishing characteristic is severe muscle fatiguability, made worse by exercise[1].

The illness occurs both sporadically and in epidemics, with cases being reported from all over the United States, Europe, Australasia and South Africa[2]. The difficulty in making the diagnosis, however, usually means that it is not until an epidemic occurs that random cases which presented in the preceding years are realized, in retrospect, to have had PFS[3]. Single cases may continue to appear after the epidemic has ended[4]. Thus it is stressed that the syndrome is an endemic disease with periodic outbreaks of epidemic prevalence[5].

PFS may appear at any age but is most common in young and middle-aged adults, and more frequent in females[6]. There is an unusual predisposition for medical and nursing personnel to be affected[1,6]. Many of the epidemics have occurred in hospitals, including the famous outbreak at the Royal Free Hospital[7], and a disproportionate number of staff compared to patients have been involved.

In the epidemics of PFS, a multitude of clinical symptoms but few clinical signs are present and, apart from the lassitude and undue fatigue on exertion, there are no other consistent features. Thus the view has been promoted that mass hysteria is the cause[8]. This is one reason why, although innumerable

patients have been affected, scientific analyses of the syndrome have been few. Another reason for the lack of professional interest is due to the symptomatology: the central complaint is of perpetual exhaustion and a feeling of chronic ill-health but secondary symptoms with behavioural abnormalities are almost invariably present(1). When the busy physician is confronted by a patient who dwells on these complaints and has no objective abnormalities, it is tempting for him to propose a psychiatric diagnosis.

Even now the name of this disease evokes controversy. The true syndrome always follows an apparently viral infection and its chief characteristic is fatigue so that the term "postviral fatigue syndrome" seems most appropriate but it has a large number of eponyms, depending on the location of the epidemic which occurred, or on the clinical features which predominated. Thus it is also known as Iceland(9), Akureyri(10) or Royal Free disease(7), epidemic myalgic(11), benign myalgic(12), or acute infective encephalomyelitis(13), epidemic vegetative neuritis(14), atypical poliomyelitis(15), a disease resembling or simulating poliomyelitis(16,17), encephalomyelitis resembling poliomyelitis(18), persistent myalgia following a sore throat(19), epidemic diencephalitis(20), epidemic neuromyasthenia(21) and the postviral fatigue syndrome (PFS)(1).

It is important to have one acceptable name for the disease because otherwise the fact that it occurs all over the world, is not a well-defined clinical syndrome and shows variation in the symptoms which predominate, will certainly mean that new information will not be collated or recognized as relevant. Epidemic neuromyasthenia, although a widely used term in the USA

for the past 20 years(21) suggests neuromuscular junction abnormalities and, since this has not been confirmed, should be dropped, while "benign" or "epidemic" applied to myalgic encephalomyelitis is incorrect since the morbidity is high and sporadic cases are common. Thus we feel that "postviral fatigue syndrome" which draws attention to the chief clinical features, is most satisfactory.

It is plain that infection plays a major role in PFS. Epidemic and sporadic cases are almost always precipitated by a flu-like syndrome, and the relapses which occur are also often associated with infection. No one agent has been implicated but well-documented cases have followed illnesses due to for example, Coxsackie(22), Epstein-Barr(23), rubella or varicella viruses(1) (see later). The chief organ affected is skeletal muscle and severe fatiguability, with or without myalgia, is the main symptom. The results of biochemical, electrophysiological and pathological studies(1,24,25) support the view that muscle metabolism is disturbed but there is no doubt that other systems, nervous, cardiovascular and immune,(1,23) are also affected.

Recognition of the large number of patients affected, together with the recent accumulation of relevant data and the fact that there is no effective treatment at present, indicates that a review of this intriguing disorder is merited.

HISTORICAL ASPECTS

The first epidemic of PFS occurred in the summer of 1934, affecting nearly 200 members of the medical and nursing staff of the Los Angeles County Hospital(15). It followed an outbreak of poliomyelitis and at first appeared to have similar clinical features. The epidemic ended but sporadic cases have continued to

appear in Southern California during the ensuing 30 years(4). Meanwhile, three epidemics were described from Switzerland, two in military camps, at Erstfeld(26) and Degersheim(27) and the third in a hospital(28). One hundred and thirty soldiers were ill at the first camp and seventy-three, at the other - of special interest since this syndrome is often considered to affect mainly women. At the hospital, there was a wide spread of illness between staff and patients. Again a relationship to poliomyelitis seemed likely since the Degersheim outbreak occurred during an epidemic of this disease.

Smaller outbreaks occurred in London and Pennsylvania(19,29) to be followed by a major epidemic in Iceland, in 1948(16). Once again the clinical features were thought to resemble poliomyelitis. In the town of Akureyri, more than 1000 cases were diagnosed, mainly high school children. Overall, 5% of the male and 8% of the female population were affected, with an attack rate calculated as 6.7%. The clinical characteristics of what was now called "epidemic neuromyasthenia" were obvious, with exhaustion, fatiguability, emotional instability, disturbed sensation and a mild fever. Follow-up of the patients showed that the other major characteristic of this syndrome was its chronicity(10).

The spread within the community pointed to an infectious agent but all attempts at isolation were negative. Analysis of faecal samples, testing sera for antibodies to known viruses and even intracerebral inoculation of monkeys and other laboratory animals with tissue samples, produced negative results(16). The only hint as to a possible aetiological organism was that, five years later, a large outbreak of poliomyelitis due to Type I virus occurred in Iceland, affecting all areas except those where Akureyri disease (Iceland disease) had occurred in 1948(30).

Antibody studies at this time showed that 50-95% of the schoolchildren in the areas affected by poliomyelitis had antibody to Type-I virus, but the children in Akureyri had no specific antibody, although they were apparently not susceptible to the infection. After immunization with the polio vaccine in 1956, however, the latter children produced unusually high specific antibody titres, suggesting that they had already been exposed to an agent immunologically similar, but not identical, to the poliomyelitis virus(30). Another related and intriguing observation made was that, when an American airman who had caught poliomyelitis in the 1955 Iceland epidemic returned home to Pittsfield, Massachusetts, a small outbreak of PFS followed(21,31).

The worldwide nature of the disease is indicated by the fact that the next epidemics were reported from Kentucky, USA(32) and Adelaide in Australia(17). In the latter, a clinical resemblance to poliomyelitis was again remarked on. Material from two patients was inoculated into monkeys and an agent was repeatedly transmitted which produced a radiculitis of the sciatic nerves(33). The findings were similar to, but much milder than, those seen when the agent causing poliomyelitis in a child in Boston, USA, was transmitted to monkeys(34). The Australian findings, however, have never been confirmed.

During the 1950s, outbreaks were also recorded from Denmark(14,35,36), Greece(37), New York State(38) and Coventry in Great Britain(39). In both the latter, the cases were discovered at the same time as a widespread epidemic of poliomyelitis: indeed, in Coventry it was nurses looking after patients with polio who were affected. In 1955 perhaps the most discussed and

controversial PFS outbreak of all was recorded, involving the staff of the Royal Free Hospital, London(7). It started in July 1955 when a doctor and a nurse from the hospital were admitted as inpatients with an obscure illness. Within two weeks, 70 other members of staff had similar symptoms and eventually a total of 292 staff were affected and the entire hospital had to be closed for four months, until the epidemic subsided.

The earliest symptoms complained of were malaise and headache, often accompanied by dizziness. The majority of patients had a sore throat but some had vomiting and diarrhoea. Myalgia was common and as usual in PFS affected chiefly the back and the neck. The majority of cases had mild, transient, objective neurological abnormalities. Mild to moderate lymphadenopathy was detectable. Intensive laboratory investigations failed to find any agent. The course of the disease was prolonged, with relapses of varying intensity occurring in most of the patients. By two years later, however, all but four cases had a complete physical recovery although a few subjects still had depression.

The Royal Free outbreak gave rise to a large literature(7,39,40,41,42,43) with reports, leading articles and correspondence in the medical journals. The important points it raised will be dealt with later but it has to be stated at this time that the epidemic was confidently said to be due to hysteria by some workers(8,44), a conclusion indignantly repudiated by others(40,42,45). It is of importance that sporadic cases of the postviral fatigue syndrome had in fact been reported in London before the Royal Free outbreak and continued to be so afterwards(3).

Epidemics of PFS continued to be reported during the 1950s,

including the first ones from Africa, in Johannesburg and Durban(46,47). Detailed reviews of all the previous epidemics have been given by Acheson(2) and Henderson and Shelekov(21).

The concept that the epidemic illness was due to mass hysteria was now frequently put forward but in 1974 an important report by Dillon et al(48) drew attention to the presence of objective signs and laboratory features. They had studied another hospital outbreak, this time affecting nearly 150 of the staff (but none of the patients) at the Hospital for Sick Children in Great Ormond Street, London. They noted cervical lymphadenopathy early in the disease course and confirmed that mild neurological abnormalities developed. Laboratory investigations revealed atypical lymphocytes and circulating immune complexes in the peripheral blood. In addition, occasional positive Paul-Bunnell (heterophile antibody) tests were detected although serological tests for Epstein-Barr virus, and indeed for cytomegalovirus, adenovirus, herpes simplex, influenza A and B, parainfluenza 1 and 3, mumps, rubella, measles and mycoplasma pneumoniae were all negative. The only positive virological finding was of Coxsackie virus B1 which was grown from one throat swab. Intensive attempts at virus isolation, including the inoculation of faecal and throat swab material into suckling mice, cell and organ cultures, were negative.

These workers, however, were convinced of the organic nature of the illness and drew attention to several features which they considered ruled out the diagnosis of hysteria: namely, the length of time the patients were ill, the number of relapses which occurred after the original attack, the lack of previous psychiatric illness in those affected, the wide age range from

teenagers to the middle aged and the presence of males among those affected. As in the Akrureyri epidemic, the attack rate was calculated as 7-8%.

In the ensuing years epidemics continued to be reported and their nature continued to suggest that an infectious agent although not detected, must be responsible, with a probable incubation period of between 8 and 10 days, perhaps reaching 3-4 weeks in some outbreaks. The mode of spread was unknown but personal contact seemed likely. In most cases an acute illness resulted, lasting for a few weeks but in others, the syndrome persisted for months or even years.

An outbreak which occurred between 1980 and 1983 in Ayrshire, Scotland, however, provided evidence suggesting a possible agent(49). Twenty-two patients were seen, complaining of the characteristically severe exhaustion, most obvious after exercise. The disease had started after an acute or subacute illness with symptoms of vertigo, hyperacusis and tinnitus, or with palpitations and chest pain. This time, virological studies revealed that 82% of the cases had increased neutralizing antibody titres to Coxsackie B virus. Titres of 512 or more were present in 59% of the cases and of 256 in another 23%. These figures can be compared to titres of 512 or more, and 256, in 4% and 10% respectively of a control population of 950 subjects from the same area of Scotland(50).

A report on a further 20 cases with an ill-defined but similar syndrome followed and again increased antibody titres to Coxsackie B viruses were present, in 16 of the patients. These were random cases, all of which presented, however, in the same rural practice near Glasgow(51). These two reports caught the interest of general practitioners in an area 30 miles away, at

Helensburgh[52]. They realized that 81 cases with like symptoms had presented in their practice during the preceding four years. This time, 47% of the cases had significantly increased neutralizing antibody titres to Coxsackie B viruses. These workers stressed that the disease plainly had an endemic form and sporadic cases could be recognized once clinicians were made aware of the syndrome.

The same workers then carried out a prospective study in their practice,[53] examining sera from 140 cases whose symptoms suggested the postviral fatigue syndrome. 46% of the patients had significant neutralizing antibody titres to Coxsackie B viruses, compared to 25% of control subjects. Approximately one half of the cases were still unwell a year later and all except two still had high antibody titres. As will be discussed later, the significance of increased but unchanging immunoglobulin G (IgG) Coxsackie B antibody titres are very difficult to interpret but past studies[54,55] indicate that the higher the titre observed, the greater the probability of recent infection. A test to detect specific IgM antibody to these viruses was not available when the above studies were done, but is now in routine use[56,56].

Coxsackie B2 virus has been isolated from the cerebrospinal fluid of one typical case, as reported by Innes[58]. He described four cases: of the other three, serological tests suggested Coxsackie B2 and B5 infection in two while an echovirus type 3 was grown from the faeces and cerebrospinal fluid of the fourth case. Other evidence implicating the echovirus group of the enteroviruses is provided by Lyle's report[59] of the isolation of Echo type 9 in an outbreak.

Other viruses e.g. varicella, hepatitis, rubella, influenza

and a new human B cell-lymphotrophic virus have been linked to occasional cases of PFS (see later) while similarities between this syndrome and that due to chronic infectious mononucleosis(60,61,62,63) have also become apparent. No virus, however, has been confirmed as the pathogenetic agent. The lack of diagnostic tests has severely hampered investigation of the postviral fatigue syndrome in the past but with the prospect of increasingly sophisticated techniques becoming available, such as nuclear magnetic resonance and viral hybridization tests, an intensive study of the cases becomes feasible. Indeed, in the latter, evidence of specific Coxsackie virus involvement of muscle has now been found (see muscle biopsy findings).

PFS is not an uncommon disease. No formal epidemiological studies have been done but a similar attack rate, of about 6%, has been reported in several outbreaks, suggesting that the agent is one to which the community had not been exposed previously(21). It is difficult to give figures for sporadic cases but, for instance, a general practitioner working in Otago, New Zealand, reported that 28 patients in his practice of 5000, presented over a period of nine months(64). They all complained of extreme fatigue which developed 4-6 weeks after a flu-like illness and rendered them incapable of employment. In retrospect, the physician felt that he had seen isolated cases during the several preceding years, most commonly in early summer. In the practice of one of us (POB) sporadic cases are felt to be approximately ten times as common as those of another muscle disorder, polymyositis, which has an incidence of five per million(65). General practitioners are now aware that sporadic cases are more common than those occurring in outbreaks, and they are more familiar with the clinical features. The careful delineation of this illness is

an essential prelude to any hope of successful treatment.

CLINICAL FEATURES

The postviral fatigue syndrome is defined as an illness developing insidiously after an apparently viral infection and characterized by excessive fatigue and myalgia. The true syndrome is always associated with an infection although sometimes the initial illness is temporarily overlooked. Most cases occur below middle age, with a mean age of 30 years in both the sexes. All ages can, however, be affected including, in our experience, children over the age of seven years. The female to male ratio is approximately 3 to 2.

In contrast to other post-infectious neurological syndromes such as acute disseminated encephalomyelitis or the Guillain-Barre syndrome[66], there is no disease-free period between the initial symptoms and the development of the characteristic features. The exhaustion and malaise may gradually become more severe after the onset but they are present in each case from the inception of the illness.

Modes of presentation

Reports of the different epidemics and the major reviews have delineated the protean clinical features, of which the main ones are an abrupt onset with headache, nausea, fever, dizziness, severe myalgia and intense malaise, the latter out of proportion to the mild pyrexia[2,3,7,12,15,21,41,48]. It is the sporadic cases which cause the diagnostic problems and one of us (POB) has now seen approximately 500 such cases, referred from all areas of the United Kingdom, Australasia and North America. These cases show at least three recognizable patterns of presentation.

The commonest is that of a banal flu-like illness with a sore throat or diarrhoea. Myalgia is usually conspicuous, almost always generalized but with a propensity to affect the neck and shoulder muscles worst. Mild to moderate fever is present. In the majority of cases the symptoms prevent the patient working and make him take to his bed complaining of exhaustion and fatiguability.

An equally common mode of onset is with a syndrome akin to Bornholm disease with severe myalgia of the anterior chest wall and evidence of myocarditis. The persistent tachycardia usually requires treatment with propanolol or similar therapy. As the disease continues, the myalgia becomes generalized and disproportionate exhaustion appears.

A more unusual presentation is with acute vertigo, lasting for a week to 10 days on average and then leaving the patient with a constant feeling of unsteadiness or dysequilibrium. The patient complains chiefly of this symptom but also mentions exhaustion and a varying degree of myalgia. The dysequilibrium can range from mild to incapacitating, when the clinical findings may be similar to those in patients with the gentamycin vestibular toxicity syndrome. Rarely, these patients also have evidence of myocarditis but this tends to improve on treatment. Among this group also, occasional cases develop damage to the utricle and some complain of incapacitating unsteadiness. The majority can walk and stand steadily when their eyes are open but have conspicuous Rombergism and tend to fall at night. This lesion seems to be permanent.

On examination, eye movements are normal with no spontaneous or positional nystagmus and normal responses to the optokinetic tape moving horizontally and vertically. Doll's head

movements are also normal. Caloric tests with optic fixation, however, may reveal a directional preponderance to one side, often accompanied by canal paresis. Cochlear function is normal with normal pure tone audiometric threshholds. In a study of 21 cases, however, Rosenhall[67] reported abnormal saccades and pursuit movements.

The three types of presentation described here are not mutually exclusive and can occur in any combination.

Exhaustion and weakness

The typical exhaustion may not be noticed in the first few weeks, being overshadowed by the general malaise and other symptoms. It then becomes apparent, however, that all forms of effort, even light housework or mild athletic activity, are followed by fatigue which is out of all proportion to the effort expended. Any kind of muscle exercise can cause the patient to be almost incapacitated for some days afterwards. In severe cases, the patient is usually confined to bed. In milder cases, the exhaustion is less but it is always present, varying with time and always made worse by exercise, emotional stress or intercurrent infections. A variety of other non-specific factors may also exhaust the patient e.g. a heavy meal, a prolonged hot bath or alcohol ingestion. Some patients get such a distressing reaction to the latter that they abstain entirely,

The weakness complained of may be peculiar in type: for example, one of our cases, a mechanic, noted that after a period of work, his right arm became so weak as to be useless and remained thus until he had rested it for several hours. Over a period of two to three years, however, the weakness, became generalised and accompanied by exhaustion. He finally had to give

up work.

Psychiatric symptoms

It is important to review the psychiatric symptoms because they are so common, being present in, for instance, 80% of our series of 500 cases. The most consistent findings are mild depression, often accompanied by anxiety, intense introspection and hypochondriasis. The degree of symptomatology may vary but at its most severe, every ache and pain is ascribed to the illness and carefully noted. A clinging dependency on relatives may develop, with mild emotional lability and a tendency to tearfulness. Once PFS is chronic, any abnormal premorbid traits become evident and severe hypochondriasis is typical. Often patients write long descriptions of all their symptoms and come to the clinic with interminable notes. Late in their course they undoubtedly appear as more suitable candidates for the psychiatrist than the neurologist.

Derangement of the sleep pattern is common, patients complaining of an inordinate desire to sleep which, when severe, may be indistinguishable from that seen in narcolepsy. This hypersomnolence is not accompanied by hypnagogic hallucinations, sleep paralysis or cataplexy. Sleep can be disturbed in any psychiatric disorder: but the cause in our cases may be different: the PFS patients with hypersomnolence were usually those who had excellent premorbid personalities and a definite history of a precipitating viral infection.

Possession of HLA-DR2 has recently been shown to have a highly significant correlation with narcolepsy[68]. It is of note, therefore, that determination of the histocompatibility antigen (HLA) profile in our cases revealed a significant increase in HLA-DR2 among those with hypersomnolence. (unpublished data).

Patients frequently complain of anomia. Chronic anomia has no localising value and can occur in many neurological and medical conditions but its severity suggests a clear cut organic cause as opposed to pure neuroticism. We have not found any objective defect in memory or any decrease in the Intelligence Quotient in patients given formal psychiatric tests but the subjects remark bitterly on conspicuous changes in their levels of concentration. They feel that they are not as quick or incisive in thought as before, have a decreased ability to learn and a decline in their short-term memory. Subjects who were of proven academic or research productivity showed a definite fall in output. There is no doubt that a change in personality occurs in these cases, noticed by relatives and family physicians and manifest as neuroticism, hypochondriasis or depression.

Other systemic symptoms

Joint pains are sometimes mentioned but there is no joint tenderness, a full range of movements is present and X-rays reveal no arthropathy. These pains are therefore almost certainly due to localised muscle involvement.

Evidence of cardiac involvement may be seen, usually in the cases with vertiginous symptoms. Palpitations, severe tachycardia with multiple ectopic beats and occasional dyspnoea may occur suddenly and are quite distressing. Several patients have required large therapeutic doses of propranolol.

Clinical Signs

Apart from two neurological signs (vide infra) we have not found any objective signs of disease in these patients. Mild lymphadenopathy has been reported in the epidemic cases: we have not seen it but this may be because it is an early feature and the

cases referred here tend to have had the syndrome for months to years.

The two neurological signs are first: the labyrinthine abnormality described above, seen in the small group who present with vertigo and exhibit pronounced Rombergism; the second is the presence of coarse muscle fasciculations, detectable in a very small number of those complaining of the typical fatigue. These fasciculations may be localized but are often generalized. They are much grosser than the fine quivering seen in motor neurone disease, with whole bundles of fibres contracting irregularly and, unlike in the latter illness, the patient may become aware of them himself.

Apart from these two features, which, as stated, are present only in a minority of cases, detailed clinical and neurological examination is completely negative.

Symptoms in Children

The symptoms in children are similar to those in adults but some comments are necessary. Most of the children we have seen, or those reported in other series, have been more than seven years old. The chief symptoms are psychiatric and consist of anxiety and a clinging dependency on the parents. There is reluctance to attend school, lack of interest in playing games with other children and lassitude. Like adults, the sleep pattern is disturbed: in some children this feature is so pronounced that they sleep during the entire day and are awake all night. Nightmares and irritability are common. In boys, a curious symptom similar to prostatism is seen, with strangury and difficulty in micturition. The children examined personally by one of us (POB) have often lost a significant amount of body weight. In some cases such severe weakness occurs that the child

is confined to a wheelchair for several months.

Nearly all affected children are diagnosed first as hysterical, with depression or "parental over-involvement" being commented on. In some cases, when this misdiagnosis has been made by the pediatrician and the child psychiatrist, the child has been forced to attend school and take part in physical exercises: this has been followed by a disastrous deterioration in the clinical condition with overwhelming exhaustion and weakness supervening.

Prognosis

It is difficult to give a prognosis because there are obvious variations in the clinical course and this disease is undoubtedly characterized by relapses and remissions. Epidemic and sporadic cases have also to be distinguished because the latter tend to present at a much later stage in the disease. Acheson[2] summarized the clinical course in the epidemic cases: most patients recover completely within one to two months but in a proportion, varying from outbreak to outbreak, relapses occur. Even in these cases, however, there is a trend towards improvement except for a minority in whom the PFS becomes chronic.

Dillon in 1978[69] reviewed the cases he had originally described in the epidemic at the Hospital for Sick Children in 1971: he also reported that, in the majority, the initial illness lasted 2-3 weeks and then gradually resolved over the next 2-3 months. In at least 20% of patients, however, there were severe relapses, often with intervening periods of between 2-6 weeks in which the patient was almost restored to normal health. Most cases were symptom-free at 12 months but others still had relapses for several years after the initial attack. Others report similar conclusions[3,45].

The cases referred to one of us (POB) tend to be sporadic cases in which the symptoms may have been present for many years. In these the prognosis has to be guarded since, although they do may improve, prolonged relapses, often associated with other infections, may occur at anytime; indeed disease-free intervals of up to four years have been noted. Most of the cases seen do not improve, give up their work and become permanent invalids, incapacitated by excessive fatigue and myalgia.

LABORATORY FINDINGS

General

In our experience, routine laboratory tests rarely reveal any abnormalities in the acute or chronic phase of the illness. An occasional acute case may show a relative lymphocytosis with atypical lymphocytes present, in the absence of a positive heterophile antibody (Paul Bunnell) test. The erythrocyte sedimentation rate is normal as are urea and electrolytes, liver and kidney function tests. The only abnormality is that approximately 5% of patients seen in the first six months of the illness, will have an increased creatine kinase serum concentration - raised to about twice the normal value.

Serum electrophoresis and measurement of immunoglobulin concentrations often reveal non-specific abnormalities, e.g. decreased IgA and increased IgM concentrations, with, however, normal IgG and IgE levels. X-rays of chest and joints are normal. Routine electrocardiographs are usually normal but occasionally tachycardia is demonstrable. We have examined the cerebrospinal fluid for cytology, culture and immunoglobulin levels in 40 cases, both acute and chronic, and found no abnormalities. Electroencephalograms are also unremarkable.

Muscle biopsies

We have carried out needle or open muscle biopsies on a total of 150 patients and examined them using routine histological stains and a battery of histochemical stains, together with electron microscopy. No consistent abnormality was found but a variety of non-specific findings were recorded. In about 30%, scattered atrophic fibres were seen. Another 30% showed Type II fibre hypertrophy and predominance but Type II fibre atrophy was also noted occasionally. 30% of biopsies were entirely normal. Similar non-specific Type II fibre atrophy was also reported by Byrne et al[70] in two cases of persistent myalgia.

Of the 60% of biopsies with fibre changes, rare cases revealed evidence of myoadenylate deaminase deficiency[71]. At present, there is no consensus on the implications of such a finding, except that it has been reported after a viral infection[72] and in association with myalgia[73]. It has also been recorded, however, with collagen vascular diseases, myasthenia gravis and facioscapulohumeral dystrophy[73]. Since it can follow a viral illness, it may be that its depletion is associated with that of other enzymes in the metabolic disturbance found in PFS. Viral infections in muscle can indeed be associated with a variety of enzyme abnormalities: subtle mitochondrial damage has been indicated by reduced activity of triosephosphate dehydrogenase, citrate synthetase and lactate dehydrogenase[74]. In a preliminary study, we detailed mild abnormalities of fatty acid metabolism in our cases (unpublished data), a finding which may possibly account for the clinical similarities between PFS and the carnitine deficiency syndromes[75].

On electron microscopy, muscle biopsies from our cases showed occasional bizarre tubular structures and minor mitochondrial abnormalities. Other workers[70] have also reported mitochondrial abnormalities with paracrystalline inclusions and evidence of depressed mitochondrial function in vitro. The same caveat in regards to specificity as expressed above should be made, however, about 1% of our cases had tubular aggregates but this figure is comparable to that given by others[76] in a muscle biopsy study of a wide variety of neuromuscular diseases. It thus appears that patients with fatigue and myalgia may have evidence of myoadenylate deaminase deficiency and tubular aggregates but the significance of these findings is unknown.

Electrophysiological Findings

Nerve conduction was normal in all our cases, as was routine electromyography in 60%. In the remaining 40%, however, a reduced recruitment pattern of voluntary motor units with "grouping" of motor units on maximum voluntary contraction was detected, as found by others[42].

Forty patients were subjected to single fibre electromyography and this yielded the highest level of positive findings: more than 75% had prolonged jitter values with no evidence of impulse or concomitant blocking[25]. This electrophysiological data is considered to provide evidence of an abnormality in the peripheral part of the motor unit, most likely the muscle fibre membrane.

It is known that patients with acute viral infections may have abnormal single fibre electromyographic results[77]. This has been interpreted as representing an abnormality of neuromuscular transmission, possibly responsible for the fatigue, lassitude and muscle weakness found[77]. In PFS, such results are

important in showing the organic nature of the illness and suggesting that muscle abnormalities persist after the acute infection.

Seven patients have been examined by Professor G.K. Radda, using 31 P nuclear magnetic resonance. The first case showed abnormally early intracellular acidosis, out of proportion to the associated changes in high energy phosphates during exercise[24]. It was considered to be due to a perturbation in the control functions responsible for co-ordinating oxidative metabolism with anaerobic glycogenolysis. This derangement in muscle energy metabolism could therefore be classified as a metabolic myopathy and was entirely consistent with early fatiguability and slow recovery after exercise. Of the six other patients, four showed similar changes[78]. These abnormalities could not have been identified by traditional diagnostic techniques.

Immunological Findings

We carried out immunological investigation of 50 patients. Immunoglobulin concentrations (IgG, IgA and IgM) were normal. Three different immune complex assays were carried out: the staphylococcus aureus binding, C1q binding and anti-complementary assays and they revealed positive results in 58 of the 100 samples taken[1]. These findings are in agreement with those of others[45]. Complement studies revealed reduced CH 50 values in four of the 50 cases and a significantly decreased C4 concentration in nine. 18 patients had significant autoantibody titres to smooth muscle, 13 to thyroglobulin, six to nuclear constituents and four, to gastric parietal cells.

In vitro lymphocytic mitogen responses were severely decreased in 35 of 50 cases. We used monoclonal antibodies to the

lymphocyte subpopulations, to analyse the peripheral blood subsets in forty of the 50 cases. Detectable abnormalities in the suppressor/cytotoxic and helper cell subsets were present. In eleven patients who had had PFS for up to six months (the "acute" group) the suppressor/cytotoxic (T8-positive) lymphocyte percentage was significantly decreased ($p = 0.001$), to 17% instead of the normal 24%. A lesser but still significant decrease in the total number of T cells was noted while helper, B cell and natural killer cell percentages were within normal limits.

In the 29 cases who had been ill for from one to 20 years (the "chronic" group) it was the helper/inducer (T4-positive) lymphocytes which were significantly decreased ($p = 0.001$). Only four of the 29 subjects had normal values. The T4/T8 ratio was also reduced, to 1.6 ± 0.1, compared to a normal value of 2.2 ± 0.3 and a value of 2.4 ± 0.2 in patients with other neurological diseases. The percentages of T8 positive and natural killer cells were normal but a moderate increase in B cells was present.

Five patients were examined at intervals over periods of up to 2 years; the decrease in helper (T4 positive cells) was found to persist.

We are repeating these tests in a much larger group of cases, with careful controls, and have not as yet found such clear-cut differences. As they stand, however, the results above do provide evidence of some deficiency in the immune system in PFS. They are similar to those reported by others in the chronic Epstein-Barr syndrome[23,60,63,79].

Viral hybridization studies

Coxsackie B virus-specific probes have been prepared by reverse transcription of purified virus genomic RNA and molecular cloning techniques[80]. These probes have now been used in

quantitative slot-blot hybridizations to test for specific Coxsackie virus RNA in skeletal muscle biopsy specimens from a total of 96 cases with PFS(81). The disease had been present for from six months to 20 years in this group. 20 of the biopsies were positive, with virus-specific RNA hybridization indices more than three standard deviations greater than those found in the normal muscle controls. The remaining 76 biopsies were negative. These data show that Coxsackie virus is present in skeletal muscle in cases of PFS and support the hypothesis that this virus has an aetiological role in the disease. There is a possibility that the viral infection is focal and therefore Coxsackie virus has not yet been excluded as an agent in the remaining 76 cases.

DIFFERENTIAL DIAGNOSES

These are many because numerous conditions may mimic the postviral fatigue syndrome. Psychiatric diagnoses abound: many patients will already have been labelled as neurotic, neurasthenic or depressed. Since some subjects take a large amount of time off work because of their continual exhaustion, they are often considered hysterical or malingerers. The problem is compounded because, once the disease has become chronic, secondary psychiatric symptoms are almost certain to appear.

It should be possible to make the correct diagnosis, however, based on the history of a good premorbid personality with an entirely satisfactory work record, the abrupt onset of an illness related to an infection, the story of the typical fatigue or exhaustion made worse by exercise, with myalgia, and with or without a low grade fever. The absence of any family history of psychiatric illnesses, or any psychiatric stress factors, failure to benefit from psychotropic drugs and the severe resentment felt

at being labelled with a psychiatric diagnosis, also help to indicate the true syndrome.

A number of neuromuscular disorders resemble the postviral fatigue syndrome e.g. occult multiple sclerosis (especially the spinal form in men), the familial periodic paralyses, certain endocrine myopathies and myasthenia gravis. We have seen cases of McArdle's syndrome developing after a viral infection and having a striking similarity to the disease. Patients with post-infectious polymyositis may also have a similar picture[82].

Patients with mitochondrial myopathies can be difficult to distinguish from those with PFS. We have observed a number of cases of nemaline rod myopathy in which severe muscle disease was precipitated by a viral infection. These cases complained of exhaustion and generalised weakness and, until the results of appropriate investigations were known, the diagnosis was in doubt. Carnitine deficiency syndromes may resemble PFS also. L-carnitine is an essential co-factor in the transfer of long-chain fatty acids across the inner mitochondrial membrane. Primary carnitine deficiency is associated with episodes of encephalopathy which are similar to Reye's syndrome while the secondary syndromes may present with muscle weakness and fatigue[75]. Certain other disorders can give rise to misdiagnosis early in their course: these include myotonic dystrophy, Thomsen's disease and mild peripheral neuropathies.

Patients with other generalised infections, e.g. toxoplasmosis, brucellosis and Borrellia burgdorferi (Lyme disease) can also cause diagnostic confusion.

Thus a patient who presents with exhaustion and myalgia, developing after a viral illness, will need a complete evaluation to exclude the other disorders mentioned, on the basis of

histological and histochemical muscle analyses, metabolic studies, serum creatine kinase estimation and electromyography. There is no diagnostic test for the postviral fatigue syndrome but, nonetheless, the clinical picture with the negative laboratory findings is reasonably typical and can be made confidently after a thorough investigation of the patient.

TREATMENT

Patients with PFS have proved very difficult to treat. When first seen, our method is to try a variety of simple analgesics to reduce the myalgia. Unfortunately aspirin and paracetamol give only mild relief while trials of sodium naproxen and compound analgesic preparations such as solpadeine (effervescent tablets of paracetamol, codeine phosphate and caffeine) have been ineffective. We have used steroids (prednisolone 10-60 mg/day) in patients with such incapacitating weakness that they are in danger of losing their jobs but again, no benefit was seen. A two-month course of prednisolone 30 mg/day, with or without azathioprine 150 mg/day, was also tried in ten such cases but no change was seen in their condition. Indeed, the patients seemed to have more complaints at the end of the course than at the beginning.

Intramuscular or intravenous gammaglobulin therapy has been advocated for patients with pericarditis and/or myocarditis associated with Coxsackie virus infection(83). In these patients, significant benefit has been claimed, especially when pooled normal immunoglobulin or immunoglobulin from an extrafamilial source was used. Because of the evidence that PFS is related to Coxsackie virus infection, therefore, plasma exchange followed by infusion of gammaglobulin or fresh frozen plasma, was given to cases with high titres of neutralizing antibodies to Coxsackie.

Thirty-five patients were given pooled normal gammaglobulin, gammaglobulin from family members, dimeric immunoglobulin or fresh frozen plasma, with or without preceding plasma exchange. None showed any objective improvement. Four stated that they had mild benefit after a 12-litre plasma exchange accompanied by fresh frozen plasma replacement but the improvement disappeared after two weeks: it could have been a placebo effect. The other patients each received more than 30 g of immunoglobulin but complained of the same degree of symptoms as before[83].

A number of reports have appeared demonstrating the efficacy of acyclovir in chronic viral infections[84,85]. We carried out a double-blind trial in a few patients who had developed PFS after herpes zoster. No objective improvement was found and, although some patients claimed they felt much better taking the drug, this was shown to be a placebo effect. Immunovir (inosine pranobex) which may produce an effect in chronic viral infections was also tried in some cases but no benefit was obtained.

Since there are clinical similarities between patients with PFS and those with carnitine deficiency[75], a double-blind trial of essential fatty acid therapy was also arranged, in 60 cases. No patient on placebo reported improvement but some on the therapy stated that their myalgia had improved, they had increased energy and an overall feeling of better health. The trial is still underway but it can already be stated that although essential fatty acid supplementation to the diet produced a mild degree of improvement, no patient had complete symptom relief.

Individual cases have reported benefit with cimetidine. This H2-receptor antagonist, and ranitidine, have been associated with clinical improvement in patients with chronic Epstein-Barr virus disease[86]. It has been suggested that these drugs may act,

through the H2-receptor, on suppressor cells. The results are, however, unconfirmed.

Some patients have claimed that a gluten-free diet helped their symptoms - again these results have not been confirmed.

AETIOLOGY

The viral association

The epidemiology of PFS, the incubation period and the abrupt onset of a feverish illness with upper respiratory or gastrointestinal symptoms, all suggest that a viral infection is responsible. No one virus, however, has been identified in the epidemics in spite of the most careful and exhaustive investigations and, in cases presenting after an epidemic is over, no antibodies specific for one virus have been detected. Instead, one or two different viruses have been isolated from occasional patients in the epidemics e.g. in the Royal Free epidemic, one nurse had poliovirus Type 3 in her faeces[7], while in the outbreak at the Hospital for Sick Children, Coxsackie B1 was isolated from the throat of one case, adenovirus type 3 from the throat and rectal swabs of another and adenovirus type 5 from the throat swabs of a third[48]. The epidemic described by Lyle[59] was the exception in that the same virus, Echovirus 9, was isolated from the stools of four cases.

Other viruses have been associated with single, random cases, e.g. Coxsackie B2 and echovirus type 3[58]. We have studied one case in which PFS developed after varicella infection, in a 31 year old general practitioner[1,24] and two others, in which rubella appeared to precipitate the syndrome. In other individual cases influenza or hepatitis have been implicated. The Epstein-Barr virus has also been considered and this is certainly

associated with a related clinical syndrome (see later) but has been specifically excluded in many of the epidemics and single cases.

There are three main possibilities in regard to a viral aetiology for PFS: first, that the syndrome resembles para- and post- infectious encephalomyelitis (acute disseminated encephalomyelitis, ADEM), and is due to an autoallergic reaction following any one of a wide variety of different viruses; second, that it is caused by a persistent or latent infection, again due to one of a wide variety of different viruses; and third, that a so-far unidentified virus is responsible.

With regard to the allergic hypothesis, PFS is unlike ADEM in that there is no latent period after the initial disease and before the characteristic symptoms develop; the myalgia and fatigue are present from the onset, together with other symptoms. The other symptoms disappear but the persistent weakness, although improving slightly, remains. PFS is also unlike ADEM in that the latter usually has a short, self-limited course while histological examination reveals typical lesions, in the central nervous system[66]. The two conditions are similar, however, in that each develops after an apparently viral infection but with all attempts at virus isolation fail. Since a viral aetiology is beyond doubt in ADEM[87], however, it certainly remains a possibility in PFS.

One of the reasons for the lack of success with viral isolation may be that patients tend to be investigated long after the acute phase is over, especially the random cases, when virus is perhaps no longer present in faeces or throat washings. Thus, evidence for viral involvement has often depended upon the interpretation of specific antiviral antibody titres. Now that sophisticated techniques are available to detect latent or

persistent virus infection in tissues, the possibility of detecting the agent in PFS is within our grasp. Indeed, as described already, there is good evidence that Coxsackie B virus is present in the affected muscle in some cases.

Enteroviruses

The most consistent group of viruses associated with PFS are the enteroviruses: polio-, Coxsackie and echovirus. These are common infective agents, entering through the gastrointestinal tract and then infecting nervous and muscular tissue with the production of a variety of syndromes. They share epidemiological, physical, chemical and biological characteristics and most were discovered as part of research into poliomyelitis.

a) Polioviruses

As indicated in the Introduction, the first episodes of PFS were considered to resemble poliomyelitis and the disorder was originally described as "a disease resembling or simulating poliomyelitis" or "atypical poliomyelitis"[2]. At least four major epidemics of PFS occurred after or during outbreaks of poliomyelitis, in New York State, Los Angeles, Adelaide, and Durban[9,15,17,47]. In one case nurses looking after patients with poliomyelitis were affected[39]. Development of PFS seemed to provide protection against poliovirus when an epidemic of the latter followed an outbreak of "Iceland disease"[10]. From the Adelaide epidemic[17], there was also an unconfirmed report that an agent had been isolated and transmitted to monkeys where it produced lesions similar to those of poliovirus. It is unlikely to be the paralytic polioviruses which are involved in PFS, since the disorder is just as common since immunization against these viruses was introduced but a related virus cannot be excluded.

b) Coxsackie viruses

These are the strongest candidates as the cause of PFS. Coxsackie viruses are divided into two groups, A and B, depending on the different tissues they affect in suckling mice. Group A viruses produce a diffuse myositis with acute inflammation of skeletal muscle fibres while Group B are associated with more wide-spread lesions and local necrosis of the central nervous system, skeletal muscle, and the heart[54,55,88]. The role of these viruses in causing myocarditis has long been suggested[54] and now confirmed[80] in a recent study demonstrating Coxsackie B-virus-specific sequences in endomyocardial biopsies of patients with chronic myocarditis or dilated cardiomyopathy. It is thus of great interest that some patients with PFS have evidence of myocarditis.

Thirty different types of Coxsackie viruses are recognized, 24 Group A and six Group B. All Group B and one of Group A (A9) share the same group antigen but there are many major antigenic variants in each of the Group B viruses, starting to be unravelled by the use of monoclonal antibodies[89].

Coxsackie viruses are very common in temperate and subtropical climates; they spread from person to person and are highly contagious. They produce a variety of different clinical syndromes in man, usually associated with headache, myalgia, nausea and vomiting, occasionally with a rubella-type rash, and including aseptic meningitis, encephalomyelitis (with a paralytic polio-like form), Bornholm disease, myopericarditis and acute onset diabetes[55,88]. Thus the epidemiology and the symptomatology of these viruses are consistent with known features of PFS, especially their muscle tropism, as seen in both Bornholm disease and in infected mice.

Unless the virus is isolated, however, there are severe difficulties in making the diagnosis of Coxsackie B infection in neurological disorders and even when there is very good presumptive evidence that these viruses are the agent, isolation can be difficult. For example, study of patients with aseptic meningitis due to Coxsackie infection has revealed failure of attempts at viral isolation in 82% of cases[90]. Current infection is diagnosed on the basis of a 4-fold or more rise in specific neutralizing antibody and/or viral isolation but identification of recent or persisting infection by serology has, until recently, been unsatisfactory. It has been based on neutralizing antibody titres because until 1985, a routine test for IgM specific antibodies was not available. In the past therefore, the Enterovirus Laboratory in Scotland carried out careful studies on the incidence and titre of neutralizing antibody to various Coxsackie B infections in the community. These "background" results were shown to vary with the season, from year to year, and with the age distribution of the population studied but it was confirmed that 4% of a control group of 950 individuals from the same area of Scotland, had titres of more than 512 to various Coxsackie B viruses[50]. These figures therefore can be contrasted with titres of > 512 in 70% of patients with PFS syndrome[1] in 80%[51] in 47%[52] and, in a larger study, 65%[53].

Increased but unchanging anti-Coxsackie neutralizing antibody titres are difficult to interpret but past studies have suggested that the higher the titre, the greater the probability of recent infection[54,55]. In our study of 50 patients with PFS, we were able to combine neutralizing antibody tests with a search

for specific Coxsackie B IgM and found that 6 of the 35 patients with titres of > 512, did have specific IgM antibodies[1]. Such results imply a Coxsackie B virus infection within the previous three months, or a persistent infection.

At present a carefully controlled study of IgM anti-Coxsackie antibodies in patients with PFS is underway, using an ELISA technique[57] but meanwhile evidence of Coxsackie virus involvement in the disease has been provided by a different technique, namely detection of Coxsackie B-virus-specific RNA sequences, using a hybridization probe to test for the presence of virus nucleic acid sequences in muscle biopsies[81]. This technique was used successfully in identifying persistent Coxsackie infection in the myocardium of patients with chronic myocarditis or dilated cardiomyopathy[80]. We have used the same technique to study muscle samples from 96 patients with PFS, for the presence of virus-specific RNA. Twenty of the 96 patients were positive, with virus-specific RNA hybridization indices more than 3 standard deviations greater than that in the mean of normal control samples. The remaining 76 were negative. There seems no doubt therefore, that Coxsackie virus persists in the muscle of some patients with PFS and is likely to have an aetiological role. The fact that some of the biopsies were negative may be because the infection is focal.

These findings are also of interest in linking PFS to another well-known group of muscle disorders, namely polymyositis/dermatomyositis, where Coxsackie viruses have been suggested as aetiological agents since the 1950s. There are reports of Coxsackie A9 being isolated from two cases of chronic myositis as well as ultrastructural evidence of picornavirus-like particles in muscle biopsies (reviewed in 91). The condition

described as "benign post-infection polymyositis"(82) is very similar, and indeed almost certainly identical, to PFS (see later). It is therefore fascinating to note that the same viral hybridization techniques have identified Coxsackie virus in childhood dermatomyositis and adult polymyositis(92).

Altogether, there is now much evidence to support the hypothesis that, in some cases, PFS is due to persistent Coxsackie virus infection. The problem of how the damage is caused is still unsolved: the extreme scarcity of fibre necrosis and the absence of inflammation makes it seem likely that the virus must have an unusual, subtle effect in interfering with cell metabolism without causing cell death. Such a new concept of a virus altering some functions of the differentiated cell without interfering with vital processes, has recently been put forward to explain the effects of possible persistent viral infections(93).

Experimental evidence supports the view that Coxsackie viruses can cause persistent damage: cytotoxic T cells generated in mice during infection with Coxsackie virus B3 have been shown to attack viral-infected myocardial fibres in vitro(94). The myocarditis in infected animals has been shown to be predominantly due to T-cell mediated(95)immunological injury. The viruses also have a detectable effect on the immune system in general: infection with B3 causes an impairment of immune responses in mice, possibly due to activation of the host's suppressor cells(96).

c) Echoviruses

This group is also suspected of an aetiological role in PFS, since these viruses are known to be associated with encephalomyelitis. Echovirus Type 9 was implicated in an outbreak

in Newton-le-Willows[59] in Lancashire, while Type 3 was isolated from the cerebrospinal fluid of one of the four typical cases described by Innes[58].

Epstein-Barr virus

This herpes group virus has been studied extensively in relation to PFS. Isaacs[97] originally reported the clinical details of 206 patients with infectious mononucleosis and drew attention to 25 who had symptoms lasting for a year or more. Later workers [23,60,61,62,63] have also described patients with a prolonged illness characterized by malaise, fatigue, low grade fever, loss of weight and myalgia developing after infectious mononucleosis. It is plain that a minority of patients who develop glandular fever may go on to have chronic or recurrent symptoms for a period of at least a year or longer and to show an unusual pattern of anti-EB virus antibodies with increased anti-EA (early antigen) and/or absent anti-EBNA (EB nuclear antigen) titres. These cases have no evidence of any previous immunological abnormality or other infection[63].

Impaired or reduced anti-EB-virus cytotoxic T cells[63], increased non-specific suppressor T cells and T cell activity[23,62] have been noted. A pattern of antibodies indicative of persistent EB virus infection has been suggested[60,63,98]: significantly increased or low titres of IgM antibodies to the viral capsid antigen (VCA), together with antibodies to the R component of the early antigen (EA) complex. Other workers have agreed about the increased titres to VCA but have detected IgG antibodies, not IgM[61,99]. Studies on these patients have also revealed that T cells isolated from their peripheral blood, when mixed with mononuclear cells from normal controls, in vitro, will produce a severe decrease in the expected

production of immunoglobulin. The suppressive effect was clearly exerted on T cells and may also have involved B cells[79]. All these immunological findings have been interpreted as indicating the syndrome is associated with a specific defect in the immune response to the EB virus and therefore has an immunological basis[63].

The clinical resemblance between this syndrome and PFS, makes one suggest that persistent EB virus is also a candidate as a pathogenetic agent in the latter syndrome.

Other viruses

A recent epidemic of PFS has been described from around Lake Tahoe in Nevada[100,101]. At first the patients were thought to show the typical features of chronic Epstein-Barr virus infection but serological studies showed no evidence of positive IgM antibodies to VCA, although there were higher titres than expected of IgG antibodies to the diffuse (D) component of EA and the VCA. The patients also had higher IgG antibodies to cytomegalovirus, herpes simplex viruses HSV-I and HSV-II and measles virus. This outbreak showed clustering of cases, with two groups arising around members of high schools and one, involving 19 of the 66 employees of a hotel casino. A variety of immunological abnormalities were detected including abnormal T4/T8 lymphocyte subset ratios, dysfunction of natural killer cells, abnormal proliferation of B cells and decreased IgG concentrations[102].

The clinical symptoms were typical of PFS with by far the commonest being fatigue, accompanied by minor cerebral dysfunction e.g. anomia and lack of concentration were reported by 80% of subjects while emotional lability and neurotic features were also found in the same number[102]. Lymphadenopathy, especially

posterior cervical, was noted in 60%, and rashes in 10%. These latter features are different to the cases of PFS we have seen but may be related to the fact that the Lake Tahoe cases were acute when investigated.

A new strain of Epstein-Barr or other virus has been suggested as the agent. Some of the sera of the Lake Tahoe cases were tested with the latter in mind: it was found that 60% of the patients but only 30% of the healthy population had specific antibodies to a new herpes virus, HBLV[100]. This new virus is propagated in B lymphocytes[103] and its presence might therefore be expected to correlate with immune abnormalities such as are found in PFS. The significance of its finding, however, is still unknown. How the weakness and fatiguability are brought about at the cellular level also needs to be unravelled but one possibility suggested has been the effect of abnormally high levels of interferon[102].

Influenza A and B, herpes zoster, rubella, hepatitis B and the Epstein-Barr virus have all been reported as causing acute or subacute myositis[91], and hepatitis B has also been associated with severe myalgia and lipid storage myopathy but the cases described do not have the clinical features of PFS[104].

One of us (POB) has been struck by the severity of PFS when it follows varicella infection. Such a case was the first one in whom nuclear magnetic resonance 31 P abnormalities were shown[24]. Varicella is one of the viruses implicated in Reye's syndrome[105] and is a well recognized precipitant of ADEM and the Guillain-Barre syndrome[106]. The lesions in these latter varicella-associated diseases show no neuronophagia, round cell infiltration or intraneuronal inclusions and virus cannot be isolated from the damaged tissue. Immunological mechanisms or metabolic effects

produced at a distance from the damage, could be involved. The fact that varicella is so consistently linked to Reye's syndrome, with its metabolic disturbances and cerebral oedema in the absence of a cellular infiltrate, suggests the virus's main effect is on a metabolic pathway.

Relationship to other postviral syndromes

There are several other postviral neurological syndromes, most occurring on an immunopathological basis. They include acute haemorrhagic leucoencephalitis, ADEM, transverse myelitis and in Reye's syndrome in all of which the central nervous system, mainly the white matter, is damaged to a varying degree by an immunological reaction(66). Other syndromes thought to have a similar pathogenesis are the Guillain-Barre syndrome, in which peripheral nerve myelin is the target(66) and polymyositis/dermatomyositis (PM/DM) in which muscle is the site of attack(91).

The precise nature of the immune reaction is not known: attack by sensitized lymphocytes to specific antigens or deposition of immune complexes causing a vasculopathy are the two main theories. In this regard it is interesting that, in Coxsackie-induced myocarditis in mice, the specifically sensitized T cells which are induced are capable of attacking normal, as well as infected, myocytes(94).

The diagnostic distinction between ADEM and PFS can be difficult in atypical cases of the former, although in typical cases it poses no problems. Usually laboratory tests, including the cerebrospinal fluid findings, resolve the doubt. Differentiation between PM/DM and PFS can also be difficult but in the former there is laboratory evidence of muscle damage:

electrophysiological, serological and/or histological. Myositis can be closely related to a preceding viral infection: indeed influenza and Coxsackie viruses have often been implicated in these cases (reviewed in 91) but these are usually acute or subacute illnesses rather than chronic disease like PFS. The benign post infection polymyositis which has been described, however, is in our experience, identical to PFS[82]: Schwartz et al drew attention to 6 patients who developed persistent muscle cramps, aching pain and persistent fatiguability after a flu-like illness[82]. All but one had normal laboratory values, the exception being a mild increase in CPK concentrations. Muscle biopsy suggested an increase in centrally placed nuclei, EMG, including single fibre EMG, was abnormal in showing myopathic changes. All but one of the patients showed some improvement within two years. This syndrome is identical to the 50 patients with PFS we have described[1], except that the majority of our patients did not recover.

Myalgia itself is a common feature of viral illnesses, especially influenza and many patients complain of weakness and fatiguability after a viral infection. If the muscle enzymes are measured, there is often a slight increase[107]. Detailed electrophysiological studies in influenza and Echovirus infections have also shown changes in neuromuscular transmission[77]. The clinician, however, is faced with the problem of measuring weakness objectively. Some investigators have used an isometric muscle-strength measuring apparatus[108] to demonstrate that there is indeed weakness after, for example, influenza.

Reye's syndrome should be mentioned here because it is also post-infectious, with 75% of children having antecedent respiratory infection, 15% having diarrhoea and 15%

varicella[105]. The syndrome consists of "toxic encephalopathy" with hepatomegaly and its clinical features i.e. lethargy progressing to stupor, coma, decerebrate or decorticate posturing are different to PFS but the pathological findings are relevant. There is a singular lack of inflammation in the brain, the liver or any other viscera. Fatty changes only are seen with ultrastructural evidence of mitochondrial abnormalities. Serum carbamyl phosphate synthetase, ornithine transcarbamylase and other mitochondrial enzymes are decreased but cytosolic enzymes are normal.

Various hypotheses as to its causation have been put forward: direct viral precipitation of a genetically determined metabolic defects or virus acting in concert with some cofactor[105]. There is some evidence to support each of these in Reye's syndrome and by analogy, to suggest mechanisms of damage in PFS. The second one, in particular, is of interest in view of our observation that PFS has occurred in several patients who already have a metabolic congenital e.g. nemaline, myopathy.

The possible role of a persistent virus

Acute viral infections have traditionally attracted most interest but it has gradually become apparent that numerous viruses, e.g. the herpes simplex, cytomegalo-, Epstein-Barr, rubella and adenoviruses can cause chronic viral disease[93]. A variety of clinical patterns can be produced by such chronic infections and, indeed, since the pattern depends on the host's response as well as the virus, the same agent can be responsible for more than one syndrome[109].

Chronic viral infections can be divided into two main groups: persistent, when infectious virus can be identified and

latent, when it cannot[93]. Examples of persistent virus infection include those due to measles, rubella, the papova group and some of the herpes group, while others of the herpes and retro virus group are associated with latency, e.g. herpes simplex and zoster. In both types, infectious virion can be assembled and therefore the complete viral genome is present.

The main areas of interest in regard to a possible relationship between a chronic viral infection and PFS are first, could the disease features be produced by an undetected virus? and secondly, how might such a virus be identified in future studies?

In a chronic viral illness, the virus is limited in its effects but not eliminated: at any one time only a few cells are involved and any tissue injury is repaired. The infected cells may not be killed and may, in fact, be able to reproduce but they are likely to be unable to carry out differentiated or specialized functions[94,109]. This is one of the most interesting facts to emerge from the study of chronic viral disease: that the viruses cause disease by destroying function in differentiated cells, but not by killing them or interfering with their basic "house keeping" effects[93]. A good example of this is seen in lymphocytic choriomeningitis virus infection of murine neuroblastoma cells: the cells grow normally and reproduce efficiently but the intracellular enzymes normally available for the synthesis and degradation of acetylcholine are severely decreased[93]. Thus the specialized electrophysiological and nuclear magnetic resonance studies of muscle described here, showing interference with the normal muscle metabolism, could be relevant to the hypothesis of a chronic viral aetiology for PFS.

For a virally-infected cell to survive in the body, it has to avoid the host immune system and one of the ways of doing this is

by interfering with the function of immunocompetent cells. The end result can be specific or non-specific immunosuppression[110]. It is important to stress therefore, that there is evidence of general immune abnormalities in PFS: we and others have shown changes in the immunoregulatory subsets, decreased mitogen responses and the presence of immune complexes in the disorder[1,48,111] while Coxsackie viruses are known to produce impairment of lymphocyte responses in infected mice[96].

Under the conditions described above, there may be no histological evidence of cell damage, also in keeping with the findings in PFS.

It is not surprising that, if the virus succeeds in evading the host immune response, evidence of its presence is difficult to detect. It may be impossible to isolate by the usual methods, may not show cytopathic effects in tissue culture or may indeed require special cell lines not available in routine laboratories. The patient cannot be expected to show a rising titre of specific antibody, although there may be a constant high level of antibody: as has been demonstrated frequently in patients with PFS in regard to Coxsackie virus[1,49,51]. Light microscopy and electronmicroscopy may not reveal virus particles and immunostaining of infected cells will be negative if viral antigen is not expressed.

Growth of explants and co-cultivation have led to identification of some latent viruses e.g. herpes simplex, and may be necessary in the study of PFS. Nucleic acid hybridization indeed has already yielded positive data. This technique is of particular use in chronic infections because it can detect inactive or even incomplete viral genome in a cell. The test

conditions, however, must be "stringent" i.e. specific virus antigen rather than group antigen must be identified and it has to be borne in mind that regions of, for instance, mammalian DNA are identical to herpes virus sequences[109]. In situ hybridization, to localize individual infected cells, is the next stage in this investigation of PFS.

The presence of virus detected in this way, however, does not establish absolutely that it is the aetiological agent, although it goes a long way. Koch's postulates are difficult to apply in the case of a persistent viral infection. We may be dealing not with a known Coxsackie virus but with a mutant type, or with superinfection by another virus, or even with a zoonotic infection.

CONCLUSION

What is certain is, that when one reviews the postviral fatigue syndrome with its epidemic and endemic data, clinical features and laboratory results, it becomes plain that this is an organic illness in which muscle metabolism is severely affected. The latest developments lead us to hope that the agent, if it has not been already, then soon will be, identified.

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