

THE EPIDEMIOLOGY OF MYALGIC ENCEPHALOMYELITIS (ME) IN THE UK - 1919-1999

INTRODUCTION

Although ME is one of the commonest chronic neurological diseases in the UK today no official government sponsored statistical evaluation has yet been made. We therefore have to rely on individual studies which suggest a point prevalence of some 300,000 sufferers. The illness mainly affects young to middle aged adults with a secondary peak at puberty, after which female subjects significantly outnumber males throughout the childbearing years. Chronic disablement affecting the most socially, economically and educationally active sector of the population, many of whom have lost education, training or the ability to work, will pose grave economic problems for the future.

A comprehensive demographic survey (including age, gender, occupation, geographical location, length and severity of illness) is urgently needed.⁽¹⁾ Forward planning based on rational assessments of diagnostic, therapeutic, preventative medical strategies and/or the social, financial and educational support required, is impeded by lack of this vital information. Currently, sufferers from ME require access to NHS and special educational facilities, as for those with any similar chronic illness. Without an epidemiological study no government can hope to stem the true health costs of this disability, to say nothing of delayed diagnosis poor management and the expensive or inappropriate prescription of drugs. Realistic long term planning to provide the care and assistance needed for stabilisation of this illness must surely offer the most cost effective strategy.

WHAT IS ME/CFS?

DESCRIPTION AND CLASSIFICATION

ME/CFS is a syndrome (a linked group of symptoms) which usually follows a common and apparently trivial virus infection (often described as a self limiting respiratory/gastro intestinal upset with headaches, malaise and dizziness from which the majority of people recover). However, after an interval, a second more serious multi system disease can develop with variable involvement of cardiac or skeletal muscle, liver, pancreas, lymphoid or endocrine organs. Nevertheless, ME is primarily a neurological illness with well documented encephalitic features and classified as such by the WHO international classification of diseases (ICD 10).

CHARACTERISTIC SYMPTOMS INCLUDE:^(2,3,14)

- (a) An episodic and unpredictable state of central nervous system exhaustion, triggered by mental or physical over exertion often with delayed onset and prolonged recovery.

- (b) A profound neuroendocrine disturbance affecting the hypothalamic/pituitary/adrenal response to stress as well as the normal homeostatic control of sleep and temperature rhythms, of fluid balance, and of growth and reproductive hormones.
- (c) Defective control by the autonomic and sensory nervous system of cardiovascular and gastro-intestinal function and of pain and other tactile sensations.
- (d) Brain dysfunction includes cognitive problems such as defective attention span and memory, impaired verbal and mathematical ability as well as difficulties with balance, fine motor control and spatial perception and disturbance of auditory and visual function as well as seizure activity often misinterpreted as “panic attacks”.
- (e) Musculo-skeletal problems affect some 70% of patients, one third of whom have an abnormal metabolic response to muscular exercise.
- (f) The disease pursues a chronic, relapsing and unpredictable course.

DIFFERENTIAL DIAGNOSIS FROM “CHRONIC FATIGUE SYNDROMES”

ME has a characteristic clinical presentation, an unique neuroendocrine profile and a distinguishing epidemiological pattern which clearly separate it from some 30 other pathological and physiological fatigue states. Supplementary evidence supporting the clinical examination and symptoms (a-f above) may be obtained from:

- (a) Tests of adrenal response to stress.^(4.)
- (b) Estimation of pituitary hormones.^(5.)
- (c) Tests of autonomic function including tilt table testing for cardiovascular response.^(6,7)
- (d) Brain imaging and neuropsychometric testing.^(8,9)
- (e) Response to subanaerobic exercise tests.^(10.)
- (f) Extension of clinical records and observation periods from weeks and months to years.^(2,11,12,13,14)

HISTORICAL ASPECTS – THE PARADOX AND ENIGMA OF “DISEASES OF AFFLUENCE”^(11,12,15,16,17)

ME is not a new disease and, until the late 1950s, it was generally considered to be an atypical, non paralytic or milder form of poliomyelitis. However, a new awareness of its disabling potential was first recognised in the more affluent communities of North America and Europe, then engaged in vast housing and public hygiene improvements accompanied by major redistribution of population from inner cities to suburbs. These laudable plans paradoxically destroyed the age-old circulation of asymptomatic, but naturally immunising childhood infections, while the burden of severe disease (with previously unrecognised complications) fell upon non immune adolescents and adults. These “diseases of affluence”, of which poliomyelitis is the classic example, are largely confined to geographically temperate climates, where bowel and respiratory infections are seasonally interrupted, compared with tropical areas, many of which still maintain solid adult herd immunity by reason of continuous exposure to infection and lesser standards of hygiene. It

was these social changes, rather than any sudden viral mutation, that led to another 20th century phenomenon – major epidemics, then pandemics of polio, followed seasonally and sequentially by the milder but more chronic and relapsing form of illness, previously referred to as “atypical” or “non paralytic” polio, but following the major Royal Free Hospital epidemic in 1955, as “Benign” Myalgic Encephalomyelitis. Some 70 outbreaks are clearly recorded in medical literature, 38 before successful mass polio immunisation in selected countries interrupted the natural circulation of 3 polio virus strains in 1965. During the next 30 years, a further 32 epidemics of ME have been recorded along with a rising incidence of the disease. This rise culminated in a 5-8 fold increment world wide, during the period 1980-1989, since when it has remained an endemic disease with periodic epidemic potential. 40 years ago ACHESON^(17.), in his seminal review of 14 geographically widespread epidemics, had already suggested that the illness follows infection by a group of related agents.

EPIDEMIOLOGICAL DATA RELATING TO ME IN THE UK

Apart from the USA, no government has yet adequately funded epidemiological studies of ME and, in the UK, we still have to rely upon data based on a relatively small number of subjects collected by individual workers and mainly related to medical referrals. These have the defect of excluding the many patients (especially the severely affected, the house bound and those disillusioned by conventional medicine) who are seldom seen by doctors.

LOCAL PREVALENCE STUDIES 1975-1997

Figures for point prevalence of ME in the general population of the UK are unknown, therefore those derived from local studies (below) can only be speculative:

Location & Number of Subjects	Years Of Study	Local Prevalence (Range)	Projection to Adult General Population	Source Of Data	Notes
A) Mainly Southern England (420) ⁽²⁾	1975 -1987	272/100,000 -545/100,000	155-300,000	GP referrals to hospital infectious diseases facility	Three times the local prevalence of MS
B) North Scotland Including Highlands And Islands (289) ⁽¹⁸⁾	1990	0.3 – 2.7/1,000 (average 1.3/1,000)	17 – 150,000 74,000	Postal Survey Of GPs using hospital Infectious Diseases facility	Epidemic of BORNHOLM DISEASE in Area of highest Prevalence Within past 5 years
C1) Southern England & Midlands (27,327 School staff) ⁽¹⁹⁾	1991-1995	400-700/ 100,000 (average 500/ 100,000)	230-400,000 285,000	medical certification of long term sickness absence in local education Authority areas	Figures highly variable in different locations with evidence of clustering
C2) Same Location 333,024 (school)	1991-1995	38 – 102 / 100,000	Projection to general population of school children 4,000 – 9,000	“	“

pupils) ⁽¹⁹⁾		(average 70/ 100,000)	6,300		
D) 4 schools In <u>one</u> of The locations Studied in C2 Above (32,924 school pupils (20)	1996/1997	0.05% -0.1% individual schools (combined schools 70/100,000)	Projection as Above 49 – 9,000 6,300	Postal Questionnaire addressed to Local education Authorities, Community Paediatricians & Child psychiatrists and to parents of children on “special needs” register	As above with Possible Evidence of Clustering

THE INCIDENCE OF ME IN EPIDEMIC AND PANDEMIC YEARS

Apart from 2 UK studies and one each in Canada and the USA, little information is available about the chronic aspects of ME or the significant numbers of patients involved. Although many incidence studies have been published for individual hospital and other epidemics, there has been no serious attempt at nationwide or long-term follow up of those affected. Some comparisons are now made between 3 UK studies and one Canadian, during the period of the recent North American pandemic of ME between 1980 and 1989.

Figure 2

STUDY (A) PERIOD OF STUDY: 1954-1992; SOURCE OF INFORMATION: Enteroviral related illness over 4 decades in General Practice; GEOGRAPHICAL AREA: Widespread but mainly Northern England and Scottish Borders; SUBJECTS : 5,348 PATIENTS WITH ENTEROVIRAL INFECTIONS; categories of illness: G1: Acute enteroviral infection, G2: Recurrent enteroviral infection, G3/4: patients with single or multiple end organ pathology including those with ME. G5: Deaths (all within category G3/4)

Figure 1

STUDY (B) PERIOD OF STUDY: 1965-1998; SOURCE OF INFORMATION: Patients with all types of infection referred to a hospital Infectious Diseases facility; GEOGRAPHICAL AREA: Widespread but mainly Southern England and the Midlands. SUBJECTS: Of some 9,000 patients referred for investigation, 3,031 were considered to have ME as the main diagnosis or, in conjunction with other illness.

STUDY A⁽¹²⁾ Figure 2

Patients with ME
Decades of Attendance

STUDY B⁽²⁾ Figure 1

Patients with ME
Charted by Year of Onset

		G1	G2	G3/4	G5		
(1)	1954-64	315	0	28	17 (7%)	(1)	133 (5%)
(2)	1965-74	659	5	63	22(14%)*	(2)	239 (9%)*
(3)	1975-84	78 4	131	263	46 (23%)	(3)	800 (30%)
(4)	1985-92	189	565	540	19(56%)*	(4)	1480 (55%)**
TOTAL	(5349)	3560	701	894	104	TOTAL	(2712)

Percentage of Illness (In Epidemic (2)* and Pandemic Years (4)**)

6. Figure 4

STUDY (C)⁽²¹⁾ PERIOD OF STUDY 1935-1992; SOURCE OF INFORMATION: Patients referred to a medical clinic in Ottawa, Canada; GEOGRAPHICAL AREA: Widespread in Canada and North America; SUBJECTS: a pilot study of 1,826 patients with chronic ME which also provides detailed demographic information.

INCIDENCE OF ME IN CANADA (BY DATE OF ONSET OF ILLNESS) DURING NORTH AMERICAN PANDEMIC.

(1)	PRIOR TO 1977	105	6%
(2)	BETWEEN 1977 and 1979	451	25%
(3)	BETWEEN 1979 and 1992	1,260	69% ** pandemic years
		—————	
	TOTAL	1,826	

Figure 3

STUDY (D)⁽¹⁴⁾ PERIOD OF STUDY: 1995-1998. SOURCE OF INFORMATION: Participants sought through patient organisations and individual physicians. Data collected by means of self report questionnaires. (Evidence of chronicity required:- illness not less than 2 years duration with specified level of disability eg. inability to leave home without assistance).

GEOGRAPHICAL AREA: Widespread in UK

YEARS OF <u>ONSET</u> OF ILLNESS	NUMBER OF CASES	
(1) 1943-1980	43 (19%)	
(2)** 1981-1984	28 (12%))
(3)** 1985-1986	26 (12%)) 158 (70%)
(4)** 1987-1988	36 (16%)) ** total in
(5)** 1989-1990	40 (17%)) pandemic years
(6)** 1991-1992	28 (12%)	
(7) 1993-1994	24 (11%)	
		—————
	TOTAL	225

COMMENT:

Though the information in all Incidence Studies (A-D) was collected independently, they reveal a staggering increase in the incidence of ME between 1965-1990, when between 50% and 70% of the patients recorded in individual studies fell ill or presented to the investigator. Though records in Study A were entered by date of attendance and might reflect medical or lay press publicity, those in studies B-D were recorded by date of onset of illness and were free of this bias. The smaller increases between 1965 and 1975 coincided with widespread epidemics in the UK of BORNHOLM DISEASE^(12,18) (epidemic pleurodynia – a well recognised enteroviral infection associated with neurological and cardiac complications) of which some 340

cases were recorded in Study A, representing 18% of patients with ME, their family members or social contacts. The major increases in all studies between 1980 and 1990 coincided exactly with the North American pandemic years, followed by a decline in incidence to that of the late 1970s in 1998 but by no means to the earlier base levels.

LABORATORY EVIDENCE OF ENTEROVIRAL INFECTION BETWEEN 1980 AND 1990^(2,12)

	Enterovirus Serology	Immunology	Comments
<p>1. Dowsett/Ramsay: (420 patients) (a) 205 seen before 1985</p> <p>(b) 124 seen when the more accurate enteroviral (EV) IgM test became available</p>	<p>Neutralisation Tests 68/205 (33%) indicative of recent infection</p> <p>EVIgM +ve 38/124 (31%) evidence of recent/active infection <u>*controls (12%)</u></p>	<p>Circulating Immune Complexes 128/276 (46%) positive</p> <p>(evidence of antibody/complement activation)</p>	<p>16 Patients (13%) when retested annually for 3 years, were shown to be persistently or intermittently positive for (EV) IgM * Local Blood Transfusion Service</p>
<p>1. Richardson: (898 patients)</p>	<p>EVIgM +ve 295/898 (33%) <u>*controls 4-9%</u></p>	<p>146/898 (16%) positive</p>	<p>*Local Blood Transfusion Service</p>

COMPLEMENTARY AND SUPPORTIVE EVIDENCE OF NEURO HORMONAL DISTURBANCE AND IMPAIRED CENTRAL NERVOUS SYSTEM METABOLISM IN PATIENTS WITH PERSISTENT ENTEROVIRAL INFECTION – 1994-1998⁽⁹⁾

RICHARDSON published evidence of hypothalamic disturbance in 30 patients with ME (95 males and 25 females) who had persistent enteroviral infection, by means of Buspirone stimulation of the pituitary and adrenal hormones, prolactin and cortisol. This study was followed up 3 years later by the correlation of this biochemical disturbance with SPECT Scan evidence of impaired metabolism in the hypothalamic and related areas of the brain in 39 patients. More sophisticated methods of detecting persisting enteroviral infection were available than in earlier studies (eg. PCR)

THE SEASONAL AND GEOGRAPHICAL CHARACTERISTICS OF ME⁽²⁾

These rely entirely upon the interaction between climate and hygiene. The majority of patients (between 60% and 80%) report that a “flu-like” illness ushers in the onset of ME, which is more common in Summer and Autumn than in Winter and Spring (63% compared with 37% in a study of 225 patients). The geographical distribution of the disease bears a striking resemblance to that of polio, multiple sclerosis and several other disabling neurological conditions which are uncommon in tropical areas of the world but share the same incidence as that of the adopted country in ethnic minorities who are born in countries with well developed sanitation.

GENDER AND AGE OF ONSET OF ILLNESS^(2,14,21) Figures 5-7

The commonest age at onset in both sexes lies between the third and fourth decade (30-45 years). However, there is a secondary peak at puberty, more marked in females than in males. From this point for F:M ratio rises sharply from near unity before puberty to a 3:1 ratio (or 5:1 in the more severe and prolonged cases) throughout childbearing years until the menopause. Clearly, when girls enter the endocrine differentiation of an adult female they also undergo hormonally determined changes in T cell response to infection and may therefore suffer a more severe and chronic illness (with a greater liability to auto immune disease) than males.

After 50 years of age in both sexes, there is a gradual decline of new illness. However recent experience (combined with prolonged follow-up of sufferers who may well have stabilised over 30-40 years) indicates that a proportion may relapse with new muscular weakness and other late effects, indistinguishable from those described in the post-polio syndrome and register as “new” patients in ME charity self help groups.

OCCUPATIONAL RISKS OF ME

Apart from a single epidemiological survey of school staff, 3 hospital based infection studies and innumerable small anecdotal surveys made by patients (e.g. survey No.6, below), no serious investigation of occupational liability to ME has been published in the UK. However, a major epidemiological study of patients presenting to a Canadian Medical clinic is available for comparison;

1. CANADA 1935-1992(1,826 subjects).⁽²¹⁾ The seven most commonly reported occupations at onset of illness (with risk factors in parenthesis) were:-
 - a) nursing (3.59). b) teaching (3.26). c) medical laboratory

technicians (2.86). d) secretaries (0.88). e) bank clerks (0.48).
f) bookkeepers (0.28).

Male employees in teaching had only half the risk of developing ME compared with their female colleagues while the figures for all occupations suggest that contact with infections as in health care and teaching, presents a greater risk than in other stressful jobs such as Banking.

2. UK 1991-1995 (27,327 school staff).⁽¹⁹⁾ The prevalence of ME in this population bears a close relationship to that reported from Canada - that is, between 400 and 700/100,000 (average 500/100,000) or some 2 to 3 times the average in the general population
3. UK - 1990 (289 patients with ME)⁽¹⁸⁾ Postal Survey of Doctors Referring Patients to hospital Infectious Disease facility; teachers or students and hospital staff (29%), skilled or unskilled manual (17%), not employed (16%), homecare (13%), Service industries (11%), Secretarial (9%), Other Professional (5%)
4. UK 1974-1987 (420 patients with ME)⁽²⁾ referred to a hospital Infectious Diseases facility; Teachers/Healthcare (41%); clerical and administrative (26%); skilled or unskilled manual (21%); not gainfully employed including children and pensioners and homecare (12%). Corresponding figures for 6,000 patients attending with other disorders: 4%, 21%, 12%, 63%.
5. UK Hospital Infection Surveys^(2,23) - area and years of study as in (4): Staff locations at highest risk of ME -
Theatre and intensive care; paediatrics, midwifery, dental and eye clinics, physiotherapy; Mental subnormality and chronic care facilities. OTHER OCCUPATIONS OUTSIDE HOSPITAL: Ambulance and paramedical; parents/playgroup attendants; prison and similar institutional staff; sewage and water workers; participants in recreational water sports; visitors to the tropics.
6. UK POSTAL SURVEY OF 1,883 holiday makers (mainly to the Mediterranean region) in 1992.^(22,23) 882 of the travellers (49%) developed an initial respiratory/gastrointestinal illness of whom 474 (52%) later suffered from ME - a 25% attack rate

THE PROGNOSIS OF ME^(2,11,12,14)

Of 420 patients (41% of whom presented early to a hospital Infectious Diseases facility - between 10 days and 2 years after onset of their illness), 31% were judged to be improving; 20% were still fluctuating between relapse and remission; 25% had achieved a steady level of disability; 24% had experienced no remission or were deteriorating.

ME is not a short term illness and improvement does not proceed in linear progression. After an initiating virus infection, which commonly circulates in the

local population (often asymptomatic or so trivial as to be overlooked) the vast majority of those exposed make a complete recovery. Others may enter an indeterminate period of fluctuation before complete resolution. After a variable period, some 6-10% of those exposed may develop neurological (encephalitic) complications, from which recovery is still possible. However, others proceed to a more serious, multisystem disease involving cardiac, endocrine and other end organs which, with careful management, may yet stabilise at a level of disability which permits gradual return to education, training or work. Unfortunately, some 25% of patients enter a slow but inexorable downhill course over many years. The death rate in this group is about 10%, mainly from end organ failure (eg myocarditis or pancreatic disease) which is certified as such, rather than from ME. Others succumb to age related degeneration or malignant growths but some, tragically, to preventable causes such as suicide and inappropriate management of undetected complications (such as myocarditis).^(12,24) Unfortunately, there appears to be a lifetime risk of relapse in all patients.

FACTORS AFFECTING PROGRESSION OF THE ILLNESS

- (A) **PERSONAL:** The patients immune status at onset (though prior contact with the initiating infection in earlier years may be protective); The type of infecting agent, depending on its potential for inducing neurological, and other serious complications; the degree of exposure to secondary cases in family and social contacts. Though suspicion has been cast on genetic risk and a significant number of patients (between 31% and 90% in different surveys)^(2,21) report 2 or more cases in the family, clustering of cases is equally common in the staff of schools and health care institutions, suggesting cross infection rather than genetic susceptibility to be the underlying cause.
- (B) **DELITERIOUS FACTORS NOT SHOWN TO BE CAUSAL WHICH MAY NEVERTHELESS TRIGGER ONSET OR RELAPSE OF ME:** The commonest triggers of relapse still remain mental or physical over exertion/stress and secondary viral, bacterial or other infection. **OTHER RISK FACTORS INCLUDE:** (1) **IMMUNOSUPPRESSION:** partial or temporary following immunisation, pregnancy, the use of steroid or cytotoxic drugs, cigarette smoking (which alters mucosal immunity) (2) **HORMONAL IMBALANCE:** Following puberty and childbirth the use of certain contraceptive preparations and hormone supplements (eg thyroid) without supervision. (3) **PHYSICAL STRESS:** Following surgery, head injury, climatic change, malnutrition. (4) **EXPOSURE TO :** psychoactive and vasoactive drugs or substances (including alcohol) and environmental toxins, especially those which are neurotoxic, cholinergic or muscarinic eg. Organophosphates and similar agents.

CONCLUSION

- (1) **ME is a physical illness distinguished by its encephalitic features, its unique neuroendocrine profile and close epidemiological similarity to poliomyelitis.**

It has the potential to cause serious long term disability in the most economically and socially active members of society.

- (2) Research into the cause, diagnosis, prevention and management of the illness is seriously under funded and the late chronic phase is almost devoid of attention.
- (3) In the absence of an early government sponsored epidemiological survey (including patients in the community who do not present to medical clinics) it will be impossible to plan or cost suitable management strategies.
- (4) **Redirection** of research into institutions, occupations or communities shown to be at high risk of developing ME (eg school populations, teaching and health care) indicates that this is a simple and economical method of identifying the infective agents capable of triggering the onset or relapse of ME and of quantifying long term problems. Rapid diagnostic tests, antiviral drugs and vaccines in the process of development (in response to the rising tide of viral meningitis and myocarditis, worldwide) could well be applied to ME, possibly providing a means of diagnosis, prevention and management in the short term.
- (5) The many individual studies recorded in this paper, which have been conscientiously and economically collected, undoubtedly broaden our knowledge of the problems to be tackled. The current implications of these findings in respect of future management of the illness are:-
 - a. They should be pursued in relation to possible reparative treatment which may involve immunological and other methods, although according to our present state of knowledge, in neurological conditions, healing and repair are notoriously imperfect.
 - b. That they should engender a more sympathetic attitude to the ME patient.

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With special thanks to CHRIS RICHARDS and RAY GIBBONS of the CHROME Database.

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Ray Jenkins BSc and Chris Richards PhD inaugurated a database of patients severely disabled by chronic ME in 1995, in order to monitor progress over the next 10 years. They have already disclosed the exceptional severity of the disease in those who develop ME below the age of 16 years and currently have over 300 patients registered. Address: CHROME, 3 Britannia Road, London SW6 2HJ

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