

# THE IMPACT OF PERSISTENT ENTEROVIRAL INFECTION UPON CHRONIC NEUROLOGICAL DISEASE IN 2002

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## A. INTRODUCTION(1)

Viruses have been aptly described as “a piece of bad news wrapped up in a protein parcel”. Traditionally these minute microbial parasites have been considered difficult to detect by routine microscopic examination and culture. Evidence of their activity is usually based on the damage inflicted by the host’s immune response upon the host’s own tissues, such as cell damage and inflammation. In the absence of such evidence, the disease under investigation is often considered not to have been caused by a virus and indeed not to have any organic cause. This is a dangerous conclusion and may even lead to prejudice against many sufferers from serious, chronic life-long neurological diseases such as ME, Polio and their late effects as well as the autoimmune and other forms of damage arising in MS and Parkinsons disease which may sometimes overlap with ME and Polio.

## B. HISTORICAL ASPECTS

We have much to learn from history and even more to glean from modern technology, which can now explain the clinical facts well known to research workers for the past half century :-

For example: -

**(i)** In 1910(2), a non-paralytic form of polio was described which differed from the paralytic form only in respect of the degree of weakness. It was associated with “paresis” (transient paralysis or muscle weakness) usually accompanied polio epidemics and was generally referred to as “atypical” or “abortive” polio.

**(ii)** In 1948(3), the year in which polio viruses 1,2,3 were first grown in the cells of human or animal tissues (“tissue culture”), Coxsackie viruses (typical of some 12 species of “non polio” enteroviruses with potential to attack neurological tissues in the same way as polio viruses 1-3) were isolated during an epidemic of poliomyelitis in Coxsackie, New York State, USA from 2 boys with typical symptoms.

**(iii)** In 1955(4), an epidemic of neurological illness (later called myalgic encephalomyelitis) affected some 300 members of the staff at the Royal Free Hospital, London causing encephalitis accompanied by paresis but without permanent paralysis.

However, many nurses remained chronically disabled and unfit for strenuous hospital duties for the rest of their lives. Some 15 years after this outbreak (1970) two psychiatrists (McEvedy & Beard)(5) studied the case histories of these sufferers and, without seeing or examining a patient, declared the whole incident to be an example of “mass hysteria”. Unfortunately, this opinion was to have a profound affect upon the fate of future generations of sufferers from the same illness in the 1980-1989 pandemic. As for McEvedy, he went on to declare an outbreak of “winter vomiting disease”, affecting a boy’s school, to be another example of “mass hysteria”. By this time further advances in technology (e.g. the electron microscope) clearly indicated a common virus infection to be at fault.

## C. 1972-1987 HALCYON YEARS FOR ME RESEARCH

By 1972, a distinguished group of clinicians and scientists had set out to share information, form research groups and hold national and international conferences related to the problems of ME. Following successful vaccination against the three polio viruses during the early 1960s over 60 epidemics of atypical, non paralytic polio had been recorded in the UK alone. It was obvious that (since Nature abhors a vacuum) the non polio enteroviruses were naturally filling the gap(6),

and demonstrating their potential for inducing a serious neurological disease of considerable chronicity, mainly affecting school children and middle aged adults in the most important and productive years of their lives. Most of the famous London teaching hospitals were involved, at that time in investigating epidemics and in subsequent research while links were forged with international institutions in USA, Canada, Europe and Australasia, facing the same problems. Research first published in 1975(7) indicated that the enteroviruses (which triggered the illness) belonged to a vast group of viruses (many of them at that time yet to be discovered) which were able to survive persistently in the human body as an uncoated form of intracellular genetic material, thus avoiding direct challenge from the immune system. Simple (indirect) laboratory confirmation of their presence based on blood tests, was available in most NHS laboratories without let or hindrance, while the European enterovirus reference centre at Ruchill Hospital in Glasgow, provided expert identification. It was clear from their work that epidemics occurred at 10 year intervals and pandemics (world wide spread) were approximately 20 years apart. By 1987, famous research workers, including Drs Ramsay, Richardson and (from Canada and the USA) Byron Hyde and David Bell, Professors Mowbray and Banatvala and scientists of the status of Len Archard and (from the USA) Roger Loria and Richard Bruno and Nancy Frick, were able to enlighten and to back up the hundreds of GPs and NHS consultants dealing with an ever increasing number of seriously disabled patients. The potential of this disease to disable children and interrupt their education was realised(8) and (in the early 1980's) the late effects of polio were rediscovered (earlier reports dated from the late 19th century).

#### **D. THE 1980-89 PANDEMIC OF ME**

This began at Lake Tahoe (a world famous holiday resort near Reno, USA) and spread rapidly to Canada, the UK, Europe and Australasia. Insurance claims for chronic disability due to this serious illness rose rapidly between 1988 and 1994 to a point where they were 5 times higher than claims arising from the concurrent AIDS epidemic. It soon became uneconomic for the insurance companies to take on this burden. Possibly with hindsight and with vague memories of McEvedy's evaluation of the Royal Free Hospital epidemic in 1955(9), insurance brokers chose to send patients for insurance assessment to doctors professing similar views, since mental illness is not generally insurable in the USA. As the impression spread world wide (!)(13) that ME was merely a psychiatric illness, easily remedied by antidepressant drugs, cognitive behaviour therapy and progressive exercise, funding for fundamental research ceased. Moreover, undue optimism about the success of polio vaccination led to apathy among a new generation of doctors. Some 15 years elapsed before (in the UK at least) the Chief Medical Officer's Working Party on ME reported in January 2002 that ME was indeed a long term seriously disabling illness and that no one had any grounds for disbelief or for withholding support.

#### **E. PERSISTENT VIRAL INFECTION (7)**

When the study of viruses, using the light microscope, began in the early 20th century, they were described as sub cellular entities (so primitive that they must use the host cell facilities for sustenance and replication) thus inviting an immune response, which caused distinct tissue destruction and invasion of immune cells, recognised by light microscopy. However, a different mechanism by which viruses may cause minimal tissue disturbance has been recognised over the past 40 years. It permits the virus to live symbiotically with the host cell for a lifetime and avoids the gross cell damage which will attract inflammatory retribution from the immune system. It is believed that the vast majority of virus species adopt this successful strategy, allowing "free board and lodging" for life for the virus and minimal damage to the host cell. This usually means that a partnership involving adaptations on both sides is set up but, unless the sacrifices are perfectly equal the host cell will risk losing some of its specialised functions (e.g. the production of enzymes, hormones, neurotransmitters etc.) whilst retaining the essential "house-keeping" functions which sustain and support both cells and virus. In the case of enteroviruses, after the initial infection, which evokes an immune response, the viruses discard their protein coat and remain hidden in the form of genetic material (RNA) within many body structures and tissues, supposedly, for a life time, causing minimal disturbance to body homeostasis.

## **F. CURRENT TECHNOLOGICAL ADVANCES**

These include:

### **(i) Diagnosis (10)**

Rapid diagnosis using detection and amplification of virus genetic material (PCR). This technique enables acute enteroviral infection (e.g. in viral meningitis and encephalitis) to be detected within 5 hours.

### **(ii) Treatment(10)**

Antiviral agents for acute infection (and possibly for instances of virus reversal) (14) are now being developed in the USA.

**(iii) (11)** The discovery of interfering DS(RNA)i - a natural method of limiting viral multiplication which can be used to limit persistent viral infections or minimise the spread of viral induced malignancy.

**(iv) (15)** The discovery of embryonic stem cells which remain naturally in

certain areas of the brain carrying out "running repairs" over a lifetime, but which can be harvested, amplified and used for treatment in selected cases.

**(v) (12)** The discovery of defects and imbalance in the production of inactive and active genetic strands of viral RNA, providing further diagnostic and therapeutic opportunities.

**(vi) (8)** Possibilities for preventing epidemics of viral infection leading to ME in school children using rapid diagnostic tests and immunisation as applied previously for polio in schools.

**(vii)** Modern technology applied to rehabilitation and equipment, enabling patients to live and work independently.

**(viii)** Modern information technology enabling international communication and exchange of information between research workers and patients.

## **G. THE FUTURE**

After 15 years in the wilderness of discrimination and disbelief, technology has advanced beyond our wildest dreams, patients have access to the internet and have become expert in information relating to their illness, new methods of rehabilitation are available, new drugs, new methods of detecting and of treating virus infections of the brain as well as other important "end organ" damage (e.g. degenerative cardiac disease). Perhaps the most important advance of all, is the current trend for patients with serious neurological debility to form Neurological Alliances with the aim of sharing facilities for rehabilitation.

We must now look forward to the enlightenment and empowerment of patients suffering from a series of interconnected neurological illnesses and to treatment and support on an international scale to enable them to live a life of fulfilment and independence.

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