**ENTEROVIRAL MYALGIC ENCEPHALOMYELITIS… EvME [ME/CFS]**

**Introduction**: CFS is an "umbrella" classification of illnesses whose aetiology is thought to be unknown. As the classification implies, the prominent symptom is fatigue. Fatigue occurs in a wide range of illnesses. Neurological - Endocrine - Immune - Malignant - Infective - Toxic - Genetic. Advances in cellular biology and revisiting the past have re-defined illness hitherto classified.

***Background***: Myalgic Encephalomyelitis is recognised by the WHO as a neurological disease. It is well annotated in medical literature, from the Polio epidemics in 1930s-40s [Gilliam]. Defined by Melvyn Ramsay in the 1950s – Royal Free Disease and in the 1960s by Luis Leon Sotomayor " Epidemic Diencephalomyelitis; A possible cause of Neuro-psychiatric, Cardiovascular and Endocrine disorders". In 1970 the BMA published a paper by two psychiatrists. Dr C P McEvedy and Dr A W Beard which concluded that the Royal Free outbreak was largely due to hysteria. The effect on medical opinion was far reaching and still prevails. The effect on patients was and remains catastrophic. The enteroviruses, ubiquitous in nature, are responsible for a variety of human diseases ranging from mild gastroenteritis to fulminating multi-organ failure. They are the cause of Myalgic Encephalomyelitis and it is no surprise that this disease has multi-organ involvement with protean manifestation.

***Pathophysiology:*** Enterovirus genus is comprised of Polioviruses, Coxsackieviruses A&B, Echoviruses and E71. They are members of the Picornaviridea family. The Picorna family is marked by its extremely small size. The virion is a naked icosahedron about 30 nm in diameter. The genome is comprised of single-stranded monopartite RNA. While Poliomyelitis has virtually been eradicated in the Western world, others of the genera have filled the vacuum so created [E71]. Enteroviruses, as the name implies, persist in the gut and are remarkably resistant to its harsh conditions. They mutate slowly, en passage, to re-challenge host resistance; pandemics occurring every 2-4 years. Diseases can range from relatively minor gastrointestinal upset to paralysis, meningitis, encephalitis, cardiac damage and birth defects. Sub clinical and mild infections are by the far most common.

| | Poliovirus | Coxsackie A | Coxsackie B | Echovirus | Enterovirus 71 |
|---|---|---|---|---|---|
| MENINGITIS | + | + | + | + | + |
| ENCEPHALITIS | + | + | + | + | + |
| MYELITIS | + | + | + | + | + |
| PARALYSIS | + | + | + | + | + |
| MYALGIA | + | + | + | + | + |
| CARDITIS | + | + | + | + | + |
| EXANTHEMS | | + | + | + | + |
| GLANDULAR | | | + | + | |

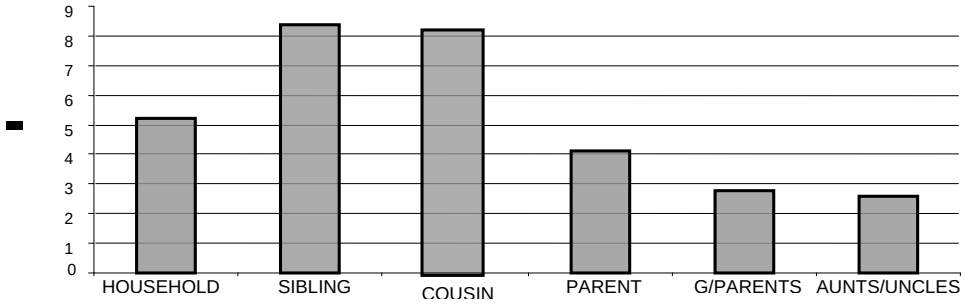
Coxsackie B viruses are increasingly recognised as a major cause of meningitis, myositis, pericarditis, myocarditis and DCM. A recent study in children infected with EV71 "rhomboencephalitis" showed that 19% developed cardiac abnormalities. EV71 now mimics Poliovirus".[JAMA 2004;291:222-227] While Coxsackie A16 usually causes Hand, Foot and Mouth disease, Coxsackie B2 and B5 have also been implicated. Coxsackie B has been implicated in direct inflammation of major glands - pancreas and thyroid glands with potential subsequent autoimmune disease leading to insulin dependent diabetes and primary thyroid failure.

Coxsackie B viruses can initiate "insurgent" persistent, non-cytolytic infection e.g. EvME. The reason why infected cells are "protected" from cytolysis unknown. It may simply be that the host tolerates the virus to preserve the cell albeit at the cost of loss of specialised function. It is not known how many cellular metabolic deficits are directly due to persistent virus in situ or to viral interference with transport function of small associated blood vessels [vasinervosum].

It may be a summation of both. Understanding the balance between host and insurgent virus underpins treatment. See annex 11.

Host range and transmission: Direct faecal/oral spread from the human, animal and bird alimentary canal is the usual route. The viruses are recycled in sewage to rivers, estuaries, beaches, recreational water and agricultural irrigation to re-infect via food and drinking water. Shellfish present a special hazard as they concentrate pollutant enterovirus, which in many cases survive cooking. Also sea birds, feeding in estuaries, recycle the virus when they roost on reservoirs. [Richardson]. Enteroviruses survive chlorination and freezing. It is also possible in developed countries for spread to occur via aerosol from flush toilets and fomites from eye to eye. Indirect spread may also occur via table utensils, handkerchiefs and hospital equipment or mouth-to-mouth resuscitation. Social policies in developed countries – childcare – retail parks – fast food – global holidays – global warming - open borders – absence of surveillance; promote endemic disease.

Transmission rates: JAMA 2004,291,222-227




Incubation period: This is commonly 2 – 5 days. Initial replication takes place in the oropharynx or GI tract. Spread then occurs into deeper lymphoid tissue i.e. Payers patches. From day 2, viraemia and dissemination of virus to distant organs takes place. Different enteroviruses have different receptors, among which are some intercellular cell surface adhesion molecules (ICAMs). The expression of these molecules determines tissue tropism. Coxsackieviruses bind to ICAM-1, an adhesion glycoprotein expressed on the surfaces of a variety of cells (epithelial, endothelial, fibroblasts). Poliovirus binds to another cell surface glycoprotein known as CD155. For example, CD155, the poliovirus receptor, is expressed in spinal cord anterior horn cells, dorsal root ganglia, skeletal muscle, motor neurons and some cells of the lymphoid system. Expression of CD155 within embryonic structures giving rise to spinal cord anterior horn motor neurons may explain the restrictive host cell tropism of poliovirus for this cellular compartment of the central nervous system. When the virus binds to its receptor, the VP4 protein is released from the protomer. This allows the escape of the viral RNA from the nucleocapsid when the virus is internalised via coated pits into the endocytic pathway. In the endosome, the nucleocapsid disassembles in the acid environment. Viral protein synthesis is detectable within 15 minutes of infection. This takes preference to cellular protein whose mRNAs are "capped".
IgM antibodies can usually be detected from about 7 days to 6 months and IgG antibodies for 1 – 2 years after recovery. Most enterovirus infections, with the exception of EV70 conjunctivitis, which is superficial, confer lifelong immunity.

Tissue Trophism

| VIRUS | DOCKING RECEPTOR | TISSUE TYPE | ORGANS AFFECTED | "FERTILE FIELD" |
|---|---|---|---|---|
| POLIO E71 | CD155 | ANT.NERVOUS SYSTEM. MUSCLE | CNS/PNS. [MOTOR COMPARTMENT] HEART | |
| COXSACKIE A&B. ECHO | ICAM-1 | EPITHELIAL ENDOTHELIAL. FIBROBLAST. LEUKOCYTE | OROPHARYNX. GI TRACT, SKIN, MUSCLE. POST CNS/PNS [SENSORY AND HOMEOSTATIC COMPARTMENT]<br><br>GLANDULAR.<br><br>THYROID. PANCREAS<br><br>FOETAL ABNORMALITIES:<br><br>CNS AND CVS AGENISIS | AUTO-IMMUNE DISEASE<br><br>PTF, T1D, PA, MG, MIXED CONNECTIVE TISSUE DISORDERS<br>TUMOURS<br><br>ASTROCYTOMA, GLIOMA, RETROPERITONEAL, THYROID |

Frequent occurrence of varying degree of multi-organ involvement. i.e. HFM, Dermatomyositis, EvME + Myocarditis + PTF.

***Myalgic Encephalomyelitis (EvME)***

Nowhere is the variety of systemic symptoms seen more often than in EvME. While it is a defined entity, other organ pathology is not infrequent and can obscure the picture. Onset may be acute and be suspected when symptoms fail to clear within 14 days or may follow another acute enteroviral illness i.e. Bornholm's Disease

*Prevalence*: Northern Region of UK, over a ten-year period, number of cases approximately 400 per 100,000. This compares with MS prevalence over a similar period of 200 per 100,000 Internationally prevalence is unknown because of misclassification of this illness.

*Mortality/morbidity*: [Enterovirus]
Mortality : In 1783 cases [adults] - no of deaths 111, 6.2%. Of these deaths: 53% were cardiac - 15% were retroperitoneal tumours. 12% were CNS tumours. The remainder were multiorgan failures. [Richardson]

In 183 children at 6 month follow-up - no of deaths 10. [5.46%] JAMA 2004;291:222-227.

Because of the persistent nature of enteroviral disease and to-date incorrect treatment, long-term disability is inevitable.

*Sex ratio:* Female to male 3:1.

*Age*: 50% of cases occur between the ages of 20-40 years.
25% of cases occur during puberty.
25% of cases occur after the age of 40

*Pregnancy:* In the infected mother, unprotected by IGG injections, all foetuses were abnormal. [Richardson]

**This illness has an acute and chronic phase during the progression of which symptoms and signs become more defined.**

***Clinical findings*:**
*History:* History is the most helpful component in diagnosing EvME. As with poliomyelitis EvME may be epidemic, endemic and also sporadic. It may follow an acute viral illness, such as Bornholm's disease, pericarditis, labyrinthitis or meningoencephalitis. A more vague flu-like illness with chest or bowel disturbance may be the harbinger of a more insidious onset. Apparent malaise not only fails to end but becomes more defined with development of symptoms such as anomia or severe concentration difficulty in a previously highly accomplished person who now cannot recall a paragraph, even after reading it several times.

A score chart devised by Dr J R Richardson in the 1970s defines symptoms. [Annex1]. This has been validated by VP1 - Buspirone/Prolactin stimulation test - SPET brain perfusion scans.

***Physical Examination findings*:** Like history, are often non-specific - to the untrained. Examination should begin, outside the consulting room, by observing the patient's mobility.

- Peripheral skin colour. Pearlescent grey with activity. [vasomotor dysfunction]
- Muscle infarcts are frequently found on palpation of myalgic limb muscles.
- As cardiac involvement occurs frequently, a full CVS assessment is mandatory.
    1. Dysrrthymias
    2. Murmurs. Notably pericardial
    3. BP – Tilt Table. Variable Autonomic dysfunction

- A thorough nervous system examination should be carried out concurrent to " *minimal exercise"*
    1. A short-term memory test - requesting patient to recall a simple statement at the end of the examination.
    2. Rombergism. Present in 80% of cases. Heel toe co-ordination may be deficient in severe cases.
    3. Visual fields. Eye movement and pupil reaction. A reverse Argyll Robertson pupil is present in 60% of cases
    4. Seated patient - Test for muscle jitter in quadriceps- present in 60% of cases
    5. Muscle power in all four limbs is assessed followed by immediately checking for cogwheel rigidity in last limb tested; usually left upper biceps. This extra-pyramidal sign is present in 80% of cases.
    6. Pronator sign. - present in 60% of cases.
    7. Full sensory examination. Often asymmetric hypo-analgesia of face and limbs
    8. Reflexes. Often altered. May be crossed over to opposite side. Clonus is present in severe cases.

**Laboratory findings**. Standard haematological and biochemical tests are often unremarkable.

- *Haematology:* Essentially normal. Esr only raised if autoimmune or neoplastic sequellae present.
- *Biochemistry:* Minor abnormalities of LFTs. Marginally raised CPK. If chest pain present Troponin T may be raised
  Buspirone/prolactin stimulation test. Positive in EvME. [Richardson]
- *Virology:* PCR for enterovirus is essential, particularly in acute phase. In the chronic [persistent] phase, PCR is understandably less reliable. PCR should be available in all Regions. Mortality from significant enteroviral illness is 5-6%. Morbidity in financial terms re treatment cost, lost working days and benefits payment is potentially huge.

**Radiology findings**

- MRI brain scan demonstrates UBOs in 50% of cases. This reflects cellular exudate in Virchow-Robin spaces.
- The most valuable radiological tool, in diagnosis of EvME, is a SPET brain perfusion scan. That is because EvME is primarily physiological not anatomical. Hypoperfusion to the brainstem is the most common abnormality. Followed by caudate nuclei and temporal lobes. [De Costa. Richardson]

**ECG.** In the acute phase, inflammation occurs in the A/V septum Bundle of His and near S/A and A/V nodes causing abnormalities in rhythm. In the chronic phase, fibrosis can act similar to A/V node as a "capacitor" and initiate ectopic beats. [Richardson]. & Woodruff [1980] Viral myocarditis. AJP, 101: 427-429.

**Immunological findings**: to date, are ambiguous due to imprecise research. Nevertheless, an autoantibody screen with target organ hormone output should be measured at outset. Then monitored as necessary.

PCR + Buspirone/Prolactin stimulation test + SPET brain scan are the "Gold Standard" investigations.

**Differential diagnosis**

An acute illness may be as follows: Bornholm's disease; viral meningitis or encephalitis; labyrinthitis; cerebella syndrome; Hand, Foot and Mouth disease; GI syndrome; pancreatitis; viral pneumonitis; spinal radiculopathies; non-specific influenza-type febrile illness. In considering the differential diagnosis, the following section is a brief survey of variables.
*Acute* presentations

- Flu-like illnesses may have varied and obscure causes. These may range from GF to Sheep Dipper's Flu [acute pesticide poisoning]. A pesticide screen can achieve distinction of the latter.
- Bornholm's disease which may mimic gallstones or renal colic, torsion of the bowel and pleurisy, or even myocardial infarction.
- Meningitis and encephalitis, which may be bacterial
- Labyrinthitis is viral in most cases, but may mimic a basilar artery insufficiency syndrome.
- Cerebella syndrome may again mimic a vascular-mediated syndrome.
- Hand, Foot and Mouth disease, with or without iritis, is usually viral but Erythema Chronicum Migrans (ECM) must be kept in mind as Lyme disease can closely mimic EvME. The tick Ixodides dammini exists on deer in New Forrest. In the Highlands, 40% of deer and sheep carry the tick.
- GI syndromes, e.g. gastroenteritis and also pancreatitis may also be bacterial, toxic or viral.
- Radiculopathies also occur and may have varied aetiologies, but a viral cause should always be considered.

**Virology titres often are not performed although it may well be wise to do so for future reference, in case chronic sequelae occur.**

*Chronic sequelae*
The more challenging task involves chronic sequelae which is particularly true in EvME as the effects may be neurological, hormonal, autoimmune or myalgic in varying degrees and the latter may involve the myocardium. All of these may be discrete but also may occur as an additive in EvME, which, of course, tends to cause problems. Moreover, the difficulty lies in the fact that the pathogenesis of the acute stage may not have been accurately defined. Some

patients with flu-like illness do not present until secondary effects develop. In these, viral titres may have fallen and culture may be negative but the VP1 test (Mowbray) and PCR are a value in suggesting ongoing enteroviral infection.

- Brucellosis: this may be difficult to define. However, it can produce all the acute and chronic symptoms. In the CNS diverse spinal and cerebral symptoms occur, sometimes with paranoid delusions. Endocarditis may cause emboli with remote effects. As with toxins, this should be considered in those who work with animals. However, the ESR is high and lesions may develop that mimic sarcoidosis. The Elisa IgM in the acute stage or IgG in the chronic stage should be assayed.
- Lyme disease. As with Brucellosis it is difficult to prove in the chronic stage. Lyme disease causes ECM skin lesions in the acute stage, which may be confused with Hand, Foot and Mouth disease. In the later stage neurological cardiac arthritic conditions may follow, as with viruses. Lyme disease, however, is due to a spirochete transmitted by ioxidid tics.
- Tuberculosis: Laboratory tests, together with radiology and high ESR should differentiate.
- Carcinomas: Again, they usually have high ESR. They may be primary or sequential.
- CVS: Pericarditis, perimyocarditis and myocarditis have all been noted in enteroviral infection as discrete or additive. The additive cases still manifest the symptoms of ME after the cardiac condition resolves.
- CNS: Other syndromes that have followed well-documented viral illness can be excluded by careful examination and MRI scans etc
- Autoimmune: This is a difficult area and autoimmune sequelae are well recognised following viral infection. However, they should be differentiated clinically as a separate entity or as an additive factor in EvME.
- *Toxins*;
- Organophosphate toxicity is characterised by a triphasic clinical picture involving an acute cholinergic phase, an intermediate syndrome and a disabling chronic delayed polyneuropathy. The latter is due to phosphorylation of a receptor protein - neuropathic target esterase. The clinical picture is often similar to EvME but can be differentiated in the laboratory.
- Organochlorates; Lindane is neurotoxic, interfering with the GABA and sodium conduction. It also interferes with apoptosis creating an environment for autoimmune disease. With a half life of 15yrs differentiation from EvME may be difficult and indeed enterovirus and Lindane may act synergistically.

**Management**

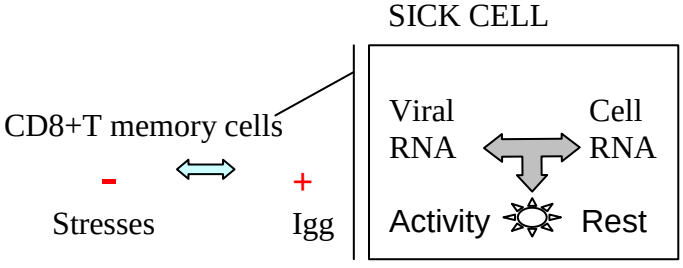
Management should commence when an enteroviral infection fails to resolve within 14 days of onset. This is a direct challenge to Public Health surveillance. Regional monitoring by PCR of all viral outbreaks within a community should be undertaken. This alone will enable any advance in antivirals to be effective. Enterovirus infection should be notifiable.

*Aims*

***The balance between host and virus should be redressed in favour of host to allow viral capture and or decay.***

***Reduction of demand upon infected cells to minimise viral replication***

***Reduction of Stress: < ACTH < Glucocorticosteroids: >Immune function.***




Virus has a cellular activity "sense" switch which benefits production of viral RNA and infectious virus. Purpose of treatment is to rest sick cells and to help viral containment with Igg. [modus operandii yet to be researched] Appears to be clinically effective.

*Acute phase*. Patients suspected with concurrent major organ involvement should be hospitalised i.e. children with cardiac abnormalities.
*Convalescence*. Correct pacing of activity. This will reduce demand on "sick" cells. Activity should be increased in small steps. In the event of symptom exacerbation patient should rest. This discipline is contrary to patient's own expectations. Professional counseling would be helpful
*Work/College/School*: Carefully graded from home activity to school or workplace.
*Stress*: Minimised by correct management and readily available social benefits for home care.
*Diet*: Patient advised about a strict elimination diet, eliminating chemicals toxic to the immune system i.e. pesticides. Added to which a Choline/Vit C mixture is recommended. Choline/Vit C mobilizes cholesterol then lowers. Lipophilic viruses being exposed to the immune system. Pesticides, being lipophilic, are also mobilized. Then sulphonated and excreted. Choline inputs into neurons to improve acetylcholine synthesis. Choline is also a vital component of all cell membranes and nerve sheaths.

*Immune system modulation and passive immunity:-*

- *Igg* : Subcuvia . *5ml.im. every 7 to 14 days [Richardson]. & JAMA 26/12/90.Vol 264:24

## Prevention

- VACCINATION. Because of [a] chronicity and [b] potential embryological, cardiac, autoimmune and tumorigenic sequelae; a vaccine should be developed.
- Genuine " Early warning " viral surveillance.
- Reversal of the current social trend of not isolating infants and children. This will help prevent the spread of the causal virus.
- At present, there are no effective antiviral drugs for enteroviruses.

## Conclusion

**TB was originally treated as a psychiatric illness. Are we not beyond this phase with EvME**

How would our forebears have responded when treating TB, if told:- [Current NHS protocols]

- Patient must be ill for 6 months before diagnosis.
- All tests known to medical science should have been performed.
- The main " plank " of treatment will be cognitive behaviour therapy.

**Dr J I Spurr**

**Ref** 1. Archives of Disease in Childhood 2004; 89:368-373
Dr A Gilliam MD. Epidemiological Study of an Epidemic, Diagnosed as Poliomyelitis, Occurring Among the Personnel of the Los Angeles County General Hospital, During Summer of 1934. Public Health Bulletin No 240.

**Acknowledgement**
I thank the family of the late Dr J Richardson for their support and for permission to extrapolate data from his book " Enteroviral and Toxin Mediated Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Other Organ Pathologies." The Haworth Medical Press.
And: Myalgic Encephalomyelitis. - Guide lines for doctors.

**ANNEX 1:**

**John Richardson Research Group Score Chart:**

*Symptoms can be broken down into four sections*

- *Fatigue.* This can be either central fatigue or muscle fatigue. Central fatigue is probed in question 2d while peripheral fatigue is indicated by questions 2c and 8. Question 2a and b would suggest resulting combination. Muscle fatigue is known to be related to an excess of lactic acid after work effort. In this condition, however, excessive activity is usually reflected the following day and it may take days for the patient to recover.
- *Mental Activity*. Question 7a indicates anomia which is a very well recognised symptom in this condition while question 7b reflects the motor fatigue involved in transposing verbal to written language. This may indicate the involvement of supra and infra sensorial mechanisms within the brain.
- *CNS instability*. This is seen in varying degrees of severity in 80% of cases, hence the two grades of response to question 3b. Question 9a relates to the vasomotor instability reflected in temperature or sensory changes, which again may reflect abnormal reception in the hypothalamic nuclei.

*Overall result.* Finally, question 8 is obviously the result of a conglomeration of the other symptoms.

| | **JRRG SCORE CHART** | | ***Con Dates*** |
|---|---|---|---|
| 1 | Has there ever been any evidence, either illness or titre, of past infection | 1 | [ ] [ ] [ ] |
| 2 | **FATIGUE** | | |
| | a) Are you less than 33% efficient per day (i.e. this relates to a full day with hobbies and social activities after work) | 2 | [ ] [ ] [ ] |
| | b1) Do you need a period of bed or settee rest during each day | 3 | [ ] [ ] [ ] |
| | or b2) Do you need a period of bed or settee rest on 2 or 3 days each week | 2 | [ ] [ ] [ ] |
| | c) Have you excessive fatigue and muscle pain after work effort | 2 | [ ] [ ] [ ] |
| | **WALKING DISTANCE.....** | | |
| | d) Do you feel fatigued upon waking? | 1 | [ ] [ ] [ ] |
| 3 | **CARDIAC/VASOMOTOR EPISODES** | | |
| | a) Do you have chest pain | 1 | [ ] [ ] [ ] |
| | b) Do you tend to have faint attacks and lose consciousness | 3 | [ ] [ ] [ ] |
| | or Do you have attacks without loss of consciousness but have to sit or lie down | 2 | [ ] [ ] [ ] |
| | Either accompanied by abnormal heart beat Y/N | | |
| 4 | **THERMODYSREGULATION** | | |
| | Do you have nocturnal sweats or cold feelings | 2 | [ ] [ ] [ ] |
| | Is your appreciation of temperature the same as other family members? | | |
| 5 | **SLEEP** **Norm** [0] **Owl** Stage 1/2 [1] Stage 3/4 [2] | 1 or 2 | [ ] [ ] [ ] |
| 6 | Do you have bizarre dreams | 1 | [ ] [ ] [ ] |
| 7 | **EVIDENCE OF DISTURBED MENTAL ACTIVITY** | | |
| | a) Do you have difficulty finding the correct words | 1 | [ ] [ ] [ ] |
| | b) Can you write a long letter with uniformity of words. | 1 | [ ] [ ] [ ] |
| | Does your voice become hoarse or weak Y/N | | |
| 8 | Is your gait consistent with your age or unsteady | 1 | [ ] [ ] [ ] |
| 9 | a) Do you have cold or numb feelings in extremities or face. | 2 | [ ] [ ] [ ] |
| | b) Do you have disturbed vision or disturbed hearing | 2 | [ ] [ ] [ ] |

15 is the lowest score we find Maximum total 25 Patient's total ___ ___ ___

Annex 11:

To institute correct management of ME/CFS you need to understand Host v Virus interaction.

From the virus's perspective, if it is too virulent it will kill the host before it can spread to other susceptible hosts or it will kill all the susceptible hosts; in either case, the virus will disappear from nature. However, if the virus is not virulent enough, the host's immune system will eliminate it before it can spread to other hosts, and the virus will become extinct.
From the host's perspective, too weak an immune response may allow rapid viral dissemination, leading to death; but too strong an immune response may cause dramatic immunopathology, which in some cases, may also be lethal.
Thus, the virus is trying to evade the host's immune response and spread to other hosts, and the host is attempting to eliminate the virus without causing too much tissue damage. The longer the virus and the host interact, the more the two seem to adapt towards peaceful coexistence. For example, herpesvirusus are carried by almost all-adult humans but cause only sporadic [and usually mild] disease; and papovavirus JC virus can persist for the life of the host, usually without ever causing disease. Not so with enterovirusus they are "insurgent" viruses constantly seeking to exacerbate existing disease [ME/CFS] and to create a fertile field for chronic sequelae [Autoimmune thyroid failure and diabetes – dilated cardiomyopathy – malignancy]
It is therefore essential that enteroviruses be eradicated at outset. Mortality rate in susceptible cases being approximately 5% due to cardiopulmonary failure. If they are not eradicated and become "insurgent", measures to bolster the host's immune response become vital. There is no place for psychiatric measures in the treatment of ME/CFS; indeed, CFS should be dropped from the nomenclature. That nomenclature should be EvME.