Questions for Professors Frank J M van Kuppeveld and Jos W M van der Meer

Margaret Williams 4th February 2012

Professors Frank J M van Kuppeveld and Jos W M van der Meer have recently stated in plain terms that *"In the past, several infectious agents have been associated with CFS but none of these could be confirmed in subsequent studies…."* (Lancet 4th February 2012: 379: 9814, e27 – e28 doi:10.1016/S0140-6736(11)60899).

Where is their evidence for the assertion that no infectious agent "*could be confirmed in subsequent studies"* in (ME)CFS patients?

Is their assertion correct? Did The Lancet's editorial team check the authenticity of that assertion before publishing it?

Here is some evidence that Professors van Kuppeveld and van der Meer (and The Lancet's editors) seem to have overlooked:

1983

"Virological studies revealed that 76% of the patients with suspected myalgic encephalomyelitis had elevated Coxsackie B neutralising titres *(and symptoms included) malaise, exhaustion on physical or mental effort, chest pain, palpitations, tachycardia, polyarthralgia, muscle pains, back pain, true vertigo, dizziness, tinnitus, nausea, diarrhoea, abdominal cramps, epigastric pain, headaches, paraesthesiae, dysuria)….The group described here are patients who have had this miserable illness*" (BD Keighley, EJ Bell. JRCP 1983:33:339-341).

1987

*"Recently associations have been found between Coxsackie B infection and a more chronic multisystem illness….referred to as…myalgic encephalomyelitis…140 patients presenting with symptoms suggesting a postviral syndrome were entered into the study…Coxsackie B antibody levels were estimated in 100 control patients…All the Coxsackie B virus antibody tests were performed blind…****Of the 140 ill patients, 46% were found to be Coxsackie B virus antibody positive****…****This study has confirmed our earlier finding that there is a group of symptoms with evidence of Coxsackie B infection.*** *We have also shown that clinical improvement is slow and recovery does not correlate with a fall in Coxsackie B virus antibody titre"* (BD Calder et al. JRCGP 1987:37:11-14).

1988

"These results show that chronic infection with enteroviruses occurs in many PVFS (post-viral fatigue syndrome, a classified synonym for ME/CFS) patients and that ***detection of enterovirus antigen in the serum is a sensitive and satisfactory method for investigating infection in these patients****….Several studies have suggested that infection with enteroviruses is causally related to PVFS…The association of detectable IgM complexes and VP1 antigen in the serum of PVFS patients in our study was high…This suggests that enterovirus infection plays an important role in the aetiology of PVFS*" (GE Yousef, EJ Bell, JF Mowbray et al. Lancet January 23rd 1988:146-150).

1988

"The main features (of ME) are: prolonged fatigue following muscular exercise or mental strain, an extended relapsing course; an association with neurological, cardiac, and other characteristic enteroviral complications. ***Coxsackie B neutralisation tests show high titres in 41% of cases compared with 4% of normal adults****…These (chronic enteroviral syndromes) affect a young, economically important age group and merit a major investment in research*" (EG Dowsett. Journal of Hospital Infection 1988:11:103-115).

1990

*"Skeletal samples were obtained by needle biopsy from patients diagnosed clinically as having CFS (and) most patients fulfilled the criteria of the Centres for Disease Control for the diagnosis of CFS (Holmes et al 1988)…****These data are the first demonstration of persistence of defective virus in clinical samples from patients with CFS****…We are currently investigating the effects of persistence of enteroviral RNA on cellular gene expression leading to muscle dysfunction*" (L Cunningham, RJM Lane, LC Archard et al. Journal of General Virology 1990:71:6:1399-1402).

1990

*"Myalgic encephalomyelitis is a common disability but frequently misinterpreted…****This illness is distinguished from a variety of other post-viral states by a unique clinical and epidemiological pattern characteristic of enteroviral infection****…****33% had titres indicative and 17% suggestive of recent CBV infection…Subsequently…31% had evidence of recent active enteroviral infection****…****There has been a failure to recognise the unique epidemiological pattern of ME****…Coxsackie viruses are characteristically myotropic and enteroviral genomic sequences have been detected in muscle biopsies from patients with ME.* ***Exercise related abnormalities of function have been demonstrated by nuclear magnetic resonance and single-fibre electromyography including a failure to coordinate oxidative metabolism with anaerobic glycolysis causing abnormal early intracellular acidosis, consistent with the early fatiguability and the slow recovery from exercise in ME****. Coxsackie viruses can initiate non-cytolytic persistent infection in human cells. Animal models demonstrate similar enteroviral persistence in neurological disease… and* ***the deleterious effect of***

forced exercise on persistently infected muscles. These studies elucidate the exercise-related morbidity and the chronic relapsing nature of ME" (EG Dowsett, AM Ramsay et al. Postgraduate Medical Journal 1990:66:526-530).

1991

*"Persistent enteroviral infection of muscle may occur in some patients with postviral fatigue syndrome and may have an aetiological role….The features of this disorder suggest that the fatigue is caused by involvement of both muscle and the central nervous system…We used the polymerase chain reaction to search for the presence of enteroviral RNA sequences in a well-characterised group of patients with the postviral fatigue syndrome…**53% were positive for enteroviral RNA sequences in muscle**…Statistical analysis shows that these results are highly significant…On the basis of this study…**there is persistent enteroviral infection in the muscle of some patients with the postviral fatigue syndrome and this interferes with cell metabolism and is causally related to the fatigue***" (JW Gow et al. BMJ 1991:302:696-696).

1991

A major publication (Postviral Fatigue Syndrome. British Medical Bulletin 1991:47:4: 793-907, published by Churchill Livingstone for The British Council) contains the following:

"Molecular viral studies have recently proved to be extremely useful. They have confirmed the likely important role of enteroviral infections, particularly with Coxsackie B virus"(Postviral fatigue syndrome: Current neurobiological perspective. PGE Kennedy. BMB 1991:47:4:809-814)

"*We conclude that persistent enteroviral infection plays a role in the pathogenesis of PVFS…The strongest evidence implicates Coxsackie viruses…**Patients with PVFS were 6.7 times more likely to have enteroviral persistence in their muscles***" (JW Gow and WMH Behan. BMB 1991:47:4:872-885).

1992

*"We will report at the First International Research Conference on Chronic Fatigue Syndrome to be held at Albany, New York, 2-4 October 1992, our new findings relating particularly to enteroviral infection…We have isolated RNA from patients and probed this with large enterovirus probes…detailed studies...showed that the material was true virus…Furthermore, this virus was shown to be replicating normally at the level of transcription. Sequence analysis of this isolated material showed that it had 80% homology with Coxsackie B viruses and 76% homology with poliomyelitis virus, **demonstrating beyond any doubt that the material was enterovirus***" (Press Release for the Albany Conference, Professor Peter O Behan, University of Glasgow, October 1992).

1993

"Samples from 25.9% of the PFS (postviral fatigue syndrome) were positive for the presence of enteroviral RNA, compared with only 1.3% of the controls*…We propose that in PFS patients, a mutation affecting control of viral RNA synthesis occurs during the initial phase of active virus infection and allows persistence of replication defective virus which no longer attracts a cellular immune response*" (NE Bowles, RJM Lane, L Cunningham and LC Archard. Journal of Medicine 1993:24:2&3:145-180).

1993

"These data support the view that while there may commonly be asymptomatic enterovirus infections of peripheral blood, it is the presence of persistent virus in muscle which is abnormal and this is associated with postviral fatigue syndrome*…Evidence derived from epidemiological, serological, immunological, virological, molecular hybridisation and animal experiments suggests that persistent enteroviral infection may be involved in… PFS*" (PO Behan et al. CFS: CIBA Foundation Symposium 173, 1993:146-159).

1994

"Individuals with CFS have characteristic clinical and laboratory findings including…evidence of viral reactivation*…The object of this study was to evaluate the status of key parameters of the 2-5A synthetase/RNase L antiviral pathway in individuals with CFS who participated in a placebo-controlled, double-blind, multi-centre trial…The present work confirms the finding of elevated bioactive 2-5A and RNase L activity in CFS…RNase L, a 2-5A-dependent enzyme, is the terminal effector of an enzymatic pathway that is stimulated by either virus infection or exposure to exogenous lymphokines. Almost two-thirds of the subjects…displayed baseline RNase L activity that was elevated above the control mean*" (Robert J Suhadolnik, Daniel L Peterson, Paul Cheney et al. In Vivo 1994:8:599-604).

1994

In his Summary of the Viral Studies of CFS, Dr Dharam V Ablashi concluded: ***"The presentations and discussions at this meeting strongly supported the hypothesis that CFS may be triggered by more than one viral agent…Komaroff suggests that, once reactivated, these viruses contribute directly to the morbidity of CFS by damaging certain tissues and indirectly by eliciting an on-going immune response"*** (Clin Inf Dis 1994:18 (Suppl 1):S130-133).

1995

"These results suggest there is persistence of enterovirus infection in some CFS patients and indicate the presence of distinct novel enterovirus sequences…Several studies have shown that a significant proportion of patients complaining of CFS have markers for enterovirus infection….It is worth noting that the enteroviral sequences obtained from patients without CFS were dissimilar to the sequences obtained from the CFS patients…This may provide corroborating evidence for the presence of a novel type of enterovirus associated with CFS*"** *(DN Galbraith, C Nairn and GB Clements. Journal of General Virology 1995:76:1701-1707).*

1995

"In the CFS study group, 42% of patients were positive for enteroviral sequences by PCR, compared to only 9% of the comparison group*…Enteroviral PCR does, however, if positive, provide evidence for circulating viral sequences, and has been used to show that* ***enteroviral specific sequences are present in a significantly greater proportion of CFS patients than other comparison groups***" (C Nairn et al. Journal of Medical Virology 1995:46:310-313).

1997

"To prove formally that persistence rather than re-infection is occurring, it is necessary to identify a unique feature retained by serial viral isolates from one individual. ***We present here for the first time evidence for enteroviral persistence (in humans with CFS****)…"* (DN Galbraith et al. Journal of General Virology 1997:78:307-312).

2001

"Over the last decade a wide variety of infectious agents has been associated with CFS by researchers from all over the world. Many of these agents are neurotrophic and have been linked to other diseases involving the central nervous system (CNS)*…Because patients with CFS manifest a wide range of symptoms involving the CNS as shown by abnormalities on brain MRIs, SPECT scans of the brain and results of tilt-table testing, we sought to determine the prevalence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and* ***Coxsackie virus in the spinal fluid of a group of patients with CFS.*** *Although we intended to search mainly for evidence of actively replicating HHV-6, a virus that has been associated by several researchers with this disorder,* ***we found evidence of HHV-8, Chlamydia species, CMV and Coxsackie virus in (50% of patient) samples…It was also***

surprising to obtain such a relatively high yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged" (Susan Levine. JCFS 2002:9:1/2:41-51).

2003

*"**Differences in bacterial and/or viral infections in (ME)CFS patients compared to controls were significant…The results indicate that a large subset of (ME)CFS patients show evidence of bacterial and/or viral infection(s)**, and these infections may contribute to the severity of signs and symptoms found in these patients*" (Nicolson GL et al. APMIS 2003:111(5):557-566).

2003

Seeking to detect and characterise enterovirus RNA in skeletal muscle from patients with (ME)CFS and to compare efficiency of muscle metabolism in enterovirus positive and negative (ME)CFS patients, Lane et al obtained quadriceps biopsy samples from 48 patients with (ME)CFS. Muscle biopsy samples from 20.8% of patients were positive, while 100% of the controls were negative for enterovirus sequences. Lane et al concluded: ***"There is an association between abnormal lactate response to exercise, reflecting impaired muscle energy metabolism, and the presence of enterovirus sequences in muscle in a proportion of (ME)CFS patients"*** (RJM Lane, LC Archard et al. JNNP 2003:74:1382-1386).

2005

In a review of the role of enteroviruses in (ME)CFS, Chia noted that initial reports of chronic enteroviral infections causing debilitating symptoms in (ME)CFS patients were met with scepticism and largely forgotten, but observations from *in vitro* experiments and from animal models clearly established a state of chronic persistence through the formation of double stranded RNA, similar to findings reported in muscle biopsies of patients with (ME)CFS. Recent evidence not only confirmed the earlier studies, but also clarified the pathogenic role of viral RNA (JKS Chia. Journal of Clinical Pathology 2005:58:1126-1132).

2006

*"Early beliefs that (ME)CFS may be triggered or caused by a single virus have been shown to be unsubstantiated (and) it is likely that different viruses affect different individuals differently, dependent upon the …immune competence of the individual…**Infections are known to trigger and perpetuate the disease in many cases. Therefore, one valuable approach that has not been widely adopted in the management of (ME)CFS patients is to exhaustively investigate such patients in the hope of identifying evidence for a specific persistent infection*** (but in the UK, NICE specifically does not permit such investigations*)….**Enteroviruses have been reported to trigger approximately 20% of cases of (ME)CFS…Antibodies to Coxsackie B virus are frequently detected in (ME)CFS patients, and***

enterovirus protein and RNA occur in the muscle and blood of (ME)CFS patients and their presence has been associated with altered metabolism in the muscle upon exercise in the context of (ME)CFS*"* (LD Devanur, JR Kerr. Journal of Clinical Virology 2006: 37(3):139-150).

2006

"(ME)CFS is associated with objective underlying biological abnormalities, particularly involving the nervous and immune system. ***Most studies have found that active infection with HHV-6 – a neurotropic, gliotropic and immunotropic virus – is present more often in patients with (ME)CFS than in healthy control subjects****…Moreover, HHV-6 has been associated with many of the neurological and immunological findings in patients with (ME)CFS" Anthony L Komaroff. Journal of Clinical Virology 2006:37:S1:S39-S46.*

2007

*"****Research studies have identified various features relevant to the pathogenesis of CFS/ME such as viral infection, immune abnormalities and immune activation, exposure to toxins, chemicals and pesticides, stress, hypotension…and neuroendocrine dysfunction….Various viruses have been shown to play a triggering or perpetuating role, or both, in this complex disease….The role of enterovirus infection as a trigger and perpetuating factor in CFS/ME has been recognised for decades***" (Jonathan R Kerr. Editorial. J Clin Pathol 14th September 2007. Epub ahead of print).

2007

*"Since most (ME)CFS patients have persistent or intermittent gastrointestinal (GI) symptoms, the presence of viral capsid protein 1 (VP1), enterovirus RNA and culturable virus in the stomach biopsy specimens of patients with (ME)CFS was evaluated…****Our recent analysis of 200 patients suggests that… enteroviruses may be the causative agents in more than half of the patients****…At the time of oesophagogastroduodenoscopy, the majority of patients had mild, focal inflammation in the antrum…95% of biopsy specimens had microscopic evidence of mild chronic inflammation…82% of biopsy specimens stained positive for VP1 within parietal cells, whereas 20% of the controls stained positive…An estimated 80-90% of our 1,400 (ME)CFS patients have recurring gastrointestinal symptoms of varying severity, and epigastric and/or lower quadrant tenderness by examination…****Finding enterovirus protein in 82% of stomach biopsy samples seems to correlate with the high percentage of (ME)CFS patients with GI complaints…Interestingly, the intensity of VP1 staining of the stomach biopsy correlated inversely with functional capacity…A significant subset of (ME)CFS patients may have a chronic, disseminated, non-cytolytic form of enteroviral infection which can lead to diffuse symptomatology without true organ damage***" (Chia JK, Chia AY. J Clin Pathol 13th September 2007 Epub ahead of print).

2009

Dr John Chia, an infectious diseases specialist from Torrance, California, who specialises in ME/CFS, is on record*: **"I believe that the main reason (ME)CFS patients are symptomatic is due to continuing inflammatory response toward viruses living within the cells, enteroviruses in most of the cases I see. We have clearly documented certain enterovirus infections triggering autoimmune responses in some patients**" (http://aboutmecfs.org/blog/?p=865).

These few illustrations from the many available serve to illustrate that Professors van Kuppeveld and van der Meer's assertion that: *"In the past, several infectious agents have been associated with CFS but none of these could be confirmed in subsequent studies…."* is demonstrably incorrect.

The ignoring of the evidence-base of infection in ME/CFS is all the more disturbing given that Frank van Kuppeveld is Associate Professor (Infection and Inflammation) in the Department of Medical Microbiology, Radboud University Nijmegen Medical Centre and his research focuses on enteroviruses, and Jos van der Meer is Professor of Internal Medicine and Chairman of the Division of General Internal Medicine at Radboud University Nijmegen Medical Centre who also works in the Nijmegen Institute for Infection, Inflammation and Immunity.

Do Professors van Kuppeveld and van der Meer have no concern for accuracy?

Another article in which Professor van der Meer was a co-author appeared to show a similar lack of attention to the existing biomedical evidence-base: (A controversial consensus – comment on article by Broderick et al": http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02468.x/pdf). Professor van der Meer accuses the International Consensus Panel of bias towards the biomedical construct: "*the authors seek to discard the findings in published studies that have applied the existing international criteria, if the result do not fit with their notions of causation….In a 21st century consensus document, accounting in a balanced fashion for the strength of the evidence is an essential element"*, yet he does exactly the same by ignoring the biomedical evidence in his own articles.

From his two latest articles, one must question whether Professor van der Meer contributes to scientific progress in what everyone agrees is a controversial condition.

Equally, do editors of medical journals no longer see the need to adhere to elementary rules of procedure by assuring themselves that what they publish represents a potentially useful and original

development of knowledge, and that any contribution is squarely built on the foundations of existing knowledge?

By publishing items that disregard the pre-existing body of knowledge, authors and editors fail in their duty to provide readers with information that can be relied upon and which can serve as a dependable basis for future work.

Investigators are not free to declare established knowledge disproven simply by ignoring the data on which that knowledge is predicated.

Merely ignoring and/or denying the existing knowledge-base, as Professors van Kuppeveld and van der Meer appear to have done, serves no scientific purpose but may actively delay the advancement of science and thus prolong the incalculable suffering of people with ME/CFS.