

Anonymous 1

HHS Chronic Fatigue Syndrome Advisory Committee (CFSAC)

Private Testimony April 5, 2010 Confidential

I am a medical scientist with specialization in immunology and retrovirology. I am trained in the review of the chemistry and manufacturing of biological products, such as pooled plasma products, and have received special training in the post-market safety evaluation of biological products (pharmacovigilance of biological products). My area of expertise includes emerging bloodborne pathogens and public health.

I am writing to the CFSAC to convey concerns and suggested recommendations for follow-up with respect to Xenotropic murine leukemia virus related virus (XMRV). In the USA, XMRV has been linked with chronic fatigue syndrome-myalgic encephalomyelitis (CFS-ME) and fibromyalgia (FM) epidemics and possibly with autism and autism spectrum disorders (autism/ASD). The latter has also shown an epidemic increase since the 1980's and by 2006, about 1/110 children (8 years and older) have been diagnosed with autism/ASD. The available evidence suggests these dual epidemics might be at least 10 fold lower in Europe when compared to the USA based on XMRV prevalence in patients with prostate tumors. It is important to note that it is possible more than one agent might be causally related to CFS-ME/FM or with autism /ASD and a causal link of XMRV with these diseases remains to be unequivocally established.

I have come to understand from clinical and research experts that vaccination may exacerbate putative XMRV related disease, which depending on the age, could result in vaccination onset autism/ASD or CFS-ME/FM. Thus, my first recommendation for consideration is that contraindications should be provided in product inserts on all vaccines for patients harbouring XMRV or who have been diagnosed with CFS-ME, FM, autism or ASD. Since subclinical infection with XMRV is known to occur, warnings to this effect should also be added to the product insert encouraging testing for XMRV. This testing should be provided at no expense for those requesting it (once suitable methods are developed and validated). All vaccination should be voluntary and not mandated for school attendance or for occupational purposes. Companies should be encouraged to develop safer vaccines for persons harbouring XMRV: for example only single doses (removing the need for thimerosal), and unadjuvanted vaccines to reduce the intensity of the reactivation of XMRV should also be commonly made available. Companies will have to perform research to determine what agents can block the reactivation of XMRV while still maintain the ability to activate cellular and humoral immunity of vaccines. I suspect the latter is no easy task. Thus, there is a need by the National Institute of Health (NIH) to immediately fund requests for proposals to find solutions to this problem. As the putative XMRV epidemic continues, there will be fewer and fewer people able to safely take

vaccines. Thus the highest priority that I can think of, is to determine the source of the putative XMRV epidemic, and to curtail it; promptly.

Accumulating evidence as early as 1993 and as first noted by the CDC (Khan et al, 1993), suggested risk factors for the contagious form of CFS somehow related to infertility, particularly in women. The epidemiological record as reported by Holmes et al, 1987, DeFreitas et al, 1991, and Buchwald et al, 1992, frequently reported median ages of about 40 years and an excess of females. Similar evidence is also consistent with the notion that the risk of offspring developing ASD is linked to older age for having a first borne child rather than children born to older parents (Grether et al, 2009, Durkin et al, 2009, and reviewed in Hughes, 2009). Moreover as reviewed by Hughes (2009), parents particularly mothers of children with autism frequently share signs and symptoms with ASD, such as sleep disorders and cognitive impairment. Dr. Judy Mikovits of the Whittemore Peterson Institute has publically discussed her concerns about the vertical transmission of XMRV and vaccination-onset autism. Taken together the available evidence is consistent with the notion that both the CFS-ME and autism epidemics may relate to the same or similar infectious agent, potentially initially transmitted to the mother via infertility treatments. While it may be too early to exclude other gamma retroviruses, herpes viruses or other viruses as also being a culprit in the etiology of CFS-ME or ASD, at the very least, one might expect to track contaminated biological products using XMRV as a proxy marker.

A candidate, potentially high risk biological product frequently used for infertility treatment is human chorionic gonadotropin (HCG) purified from urine of pregnant women (uHCG). Currently the US pharmacopoeia for urine HCG does not include testing for the bloodborne pathogens HIV-1 or hepatitis C nor for viral inactivation/reduction, while in contrast the British and European pharmacopoeia has called for these safety measures since 1997. It is important to note that many of these products (also urine derived lutenizing hormone, uLH) were marketed by the early 1980's, and thus, were exempt from newer regulations introduced later. Recombinant forms of HCG and LH peptides were introduced in the late 1990's and do NOT have the same infectious disease risk profiles. The recombinant forms (rHCG and r LH) may have been favoured in the UK and Europe due to higher inherent risks of BSE contaminated donors. Thus, in the UK and Europe, the spread of infectious agents, possibly including XMRV, through uHCG and/or uLH may have been minimized due to the use of alternative safer recombinant products or via the introduction of higher safety standards for uHCG/uLH. It would be additionally useful to restrict the size of the urine pools to minimize risk, as has been achieved for plasma products.

I have already raised the issue of urine derived human chorionic gonadotropin (uHCG) used for infertility treatments and for cycles of "in vitro fertilization" as being potential candidate sources of XMRV for the CFS-ME and/or autism epidemics, with the USA FDA (February 11,

2010). They are taking this challenge seriously, and have obtained early survey evidence supporting the notion that IVF treatments (generally which employs more injections of uHCG) may carry an increased risk of severe cases of autism. This was a quick survey conducted in February 2010 on 1400 families at 15 autism treatment centres across the USA (Dr. Patricia Davis, Boston, February 26, 2010). It is important to note that recombinant HCG (rHCG) which is likely more expensive but available on the market, is thought to be highly unlikely to carry the risks of XMRV or some other viral agent potentially involved in CFS-ME or ASD. Thus, my recommendation is to have the FDA investigate uHCG and uLH as a candidate source of XMRV, and to improve the US pharmacopoeia standards on uHCG and uLH. Sequencing of viral isolates in patients versus suspect biological products should help distinguish epidemic forms related to contaminated biologicals from potential direct zoonotic transmissions to individuals such as possibly from the common house mouse.

Unfortunately, there is no known proven method to remove a retrovirus from its integration into human DNA in situ. Future therapies based on a gene therapy to specifically block the expression of a retrovirus are at least 5 to 10 years away. In the meantime, we are desperate for simple, inexpensive and safe therapeutics able to block the reactivation of XMRV. We know the virus is inducible by stress particularly the glucocorticoid steroid hormones. We also know that CFS-ME patients are low in the anti-stress hormone, dihydroepiandrosterone (DHEA). Accordingly, although it remains to be clinically proven by randomized clinical trials, daily supplementation with DHEA is likely to help prevent and minimize XMRV activation by at least, minimizing stress. In this regard, it would be useful for DHEA available in the USA as an over-the-counter product, to undergo higher stringency for potency and purity (spot testing), and since it is probably isolated from the adrenal glands of bovines, there should also be measures imposed to reduce the risks of BSE (such as reducing pool sizes and the addition of prion inactivation measures). However, I believe due to the expected growing prevalence of XMRV, and the lack of energy or disability associated with XMRV neuroimmune disorders, that making DHEA a prescription drug would be a significant barrier for most autism and CFS-ME / FM patients. Patients with CFS-ME need help in blocking the reactivation of XMRV. It has been estimated in US patients that about 25 % of patients are unable to work full-time. In Canada, DHEA is on Schedule G (restricted substance list) which means it is not available over the counter, nor by prescription but only through a paper-work intensive, special access program and is very tightly monitored. The monthly paperwork is probably too cumbersome for most patients and their doctors. In Canada, a recent report suggested about 68 % of CFS-ME and FM patients were not able to work full time with average time to withdrawal from the work force at 3 years after symptom onset (Lavergne et al, 2010). It is tempting to speculate that the higher difficulty with the control of putative XMRV in Canadians, might in part reflect the lack of availability of supplements able to control stress (like DHEA) and thus, the reactivation of putative XMRV.

DHEA is one candidate "natural product" which may exhibit at least indirect control of putative XMRV infections. I am sure if funding were made available through NIH, that a whole range of inexpensive natural products would be identified.

I also understand from interviewing CFS-ME clinical experts that in addition to the contraindication of vaccines, that they also contraindicate the use of statins due to severe reactivation of the putative XMRV. Statins are used to lower cholesterol. To the best of my knowledge, there is no contraindication in the product inserts for statin products against use by patients diagnosed with CFS-ME or FM, with those infected with XMRV, or for patients showing signs and symptoms of chronic fatigue/insomnia. Thus, taking a public health perspective, it would be useful to prevent further transmission of XMRV by ensuring reactivation does not occur due to statins. This would be best achieved by adding this contraindication to the product insert. Again, given the growing prevalence, prospective statin patients should be screened first for XMRV before statins are prescribed that is; once appropriate screening methods are developed and validated. This requirement could be handled as a warning in all statin product inserts.

The common transmission routes and shedding of XMRV needs elucidation . Is the virus found in saliva, urine, faeces, sweat as well as blood? Is there casual transmission? Is the virus only shed when symptoms are obvious? Is there vertical transmission through milk? These are prime areas for additional research where the NIH and/or the CDC may take a lead.

The Lombardi et al, Science paper of October 2009, clearly demonstrated XMRV is transmissible through blood, at least in vitro. It is important for all patients diagnosed or suspected of having CFS-ME or FM, not to donate blood. International blood safety standards indicate that persons presenting with irreversible CNS disorders should be permanently deferred as donors. CFS-ME and FM are irreversible CNS disorders. Thus, the American Association of Blood Banks (AABB) should update their donor deferral policy as soon as possible. However, this donor deferral should also apply to cells, tissues, organs, semen and urine donors, as well as blood. Once the XMRV screening test (and/or other viruses) becomes available, this should also be applied. If a donor presents who has had insomnia/fatigue only for a short period of time, I think it would be prudent to simply temporarily defer them until the next time.

So in conclusion, I believe there are a number of things which can be immediately implemented or started, even as we wait for further confirmatory evidence of the Whittemore Peterson Institute's findings linking XMRV with the vast majority of CFS-ME patients, and possibly autism in the USA. It is possible that between 5 and 10% of the USA or North American population may be already infected. This is a very real disease, with very real and often dire consequences whether it hits an adult or an infant. It has to be stopped, and it has to be

stopped now. I hope the concerns I raise and potential recommendations made, will make a difference first to the patients, secondly for public health, but also for economic recovery.

I think it is the job of the CFSAC to consider, evaluate, prioritize and provide oversight that these and other recommendations made by others, are acted on in an expeditious manner. Given the potential threat to the US GDP and the economy; due to workforce loss, loss of tax revenues, the costs of care for disabled persons and the progressive loss of effectiveness of vaccination programs, it would seem to me that XMRV associated neuroimmune disorders (XAND) are tentatively, a matter of national security, and requires funding commensurate with this possibility.