



## X Marks the Spot

Chronic Fatigue Syndrome (CFS) is one of a number of overlapping conditions that TMJD patients have reported. Like TMJDs, the cause of CFS, characterized by overwhelming and persistent fatigue, has baffled investigators. This has led some to dismiss the condition as not real, stigmatizing patients as neurotics whose problems are “all in their heads.”

It is significant, therefore, that researchers have found immune system defects and chronic inflammation in CFS patients, who frequently experience neurological problems, and also have a higher incidence of cancer. Recently, researchers<sup>1</sup> at the Whittemore Peterson Institute in Reno, Nevada, the Cleveland Clinic, and the National Cancer Institute have found evidence for a viral infection in the blood of 67 percent (68 out of 101) CFS patients, compared to 3.7 percent (8 out of 218) healthy controls. The virus, xenotropic murine leukemia virus-related virus (XMRV), is a retrovirus nearly identical to one that had earlier shown up in the tumor tissue of prostate cancer patients, a finding that stimulated the current CFS investigation. Multiple laboratory tests have established that XMRV can actively infect a range of

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## TMJA...20 Years of Advocacy

On December 31st we celebrated the beginning of our 20th year as a non-profit organization. I can think of no better time to reflect upon where we’ve been and what we’ve accomplished over these years.

- In 1992 we were responsible for a Congressional hearing on the dangers of TMJ implants. That hearing not only brought to light the disastrous results of TMJ implants, but also established that the amount and quality of research being directed toward TMJ disorders was paltry and poor. That hearing established a relationship between the Association and elected officials who were in a position to ask that funding and quality of research be increased. Concern over the potential harms of invasive and irreversible treatments for TMJDs also led the NIH to issue recommendations urging that conservative treatments, along with adequate pain relief, govern management of TMJDs.
- Persistent contact with government officials, researchers, and practitioners, combined with the testimony of patients at congressional hearings and scientific meetings, along with media publicity have resulted in the recognition of TMJDs as legitimate disorders.
- Our advocacy efforts have gained the respect of the National Institutes of Health (NIH) administrators and congressional leaders and resulted in 16 consecutive years of report language to the NIH asking for increased support for TMJD research. This has led to the reduction of the stigma associated with a painful disorder for which there is no simple diagnostic test, no understanding of the cause or causes, and no evidence-based treatments.
- We have changed the field of TMJD research by establishing that TMJ disorders are a complex disease—like diabetes, hypertension and other conditions. TMJ research requires a whole body systems approach that looks at the roles that genes, gender, age, environmental and behavioral triggers play in TMJDs. During our last scientific meeting we established that many TMJD patients suffer a number of other pain conditions.
- This discovery resulted in an expansion of the Association’s base of operations through collaboration with other patient advocacy groups in the recently formed Overlapping Conditions Alliance. By studying a number of these pain conditions along with TMJDs, we may find the trigger common to all. We’ve also brought recognition to the fact that for many TMJD patients, pain is chronic, not easily “fixed” by any one of the many treatments that have been recommended to patients by self-proclaimed specialists—treatments that in many cases cause or exacerbate the condition. *We have changed the perception that TMJ disorders are only about teeth and jaws.*
- We have provided a reliable and constantly updated source of information for patients, the public, and scientists. Anyone who cares to know more about TMJDs will find the latest and most comprehensive information through our web site, [www.tmj.org](http://www.tmj.org), our journal, *TMJ Science*, the newsletter, *TMJ Communiqué* and other publications.

We have provided support to those affected by TMJ disorders particularly at a time when there was nowhere and no one else to turn to.

I hope by now you have a smile on your face and are patting yourself on the back because this is YOUR organization and working together we’ve moved some pretty formidable mountains as we are *changing the face of TMJ*! ♦

Terrie Cowley, President & Co-founder

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# TMJ Treatments Raise Ethical Issues about TMJD Trial Conduct & Clinical Care

*The following article appeared in our e-newsletter, TMJ News Bites, in July 2009.*

High on the national agenda to reform health care in America is to conduct studies to find out what treatments really work and thus eliminate often costly but ineffective and possibly harmful alternatives. In that light, it is sad to report that a recent analysis of over 200 systematic reviews comparing surgical and non-surgical interventions for temporomandibular joint and muscle disorders (TMJDs) concluded that the poor quality of most studies precluded making any recommendations whatsoever. Indeed, the authors of the article,\* found only two systematic review articles out of 211 published over the last 40 years that met the authors' inclusion criteria for further analysis.

“Systematic reviews” have become popular in recent years as a means of validating clinical practice. The reviewers amass the published reports in the medical literature of clinical trials of a procedure—a diagnostic method or means of prevention or treatment—over a period of time, using standard databases like Medline. They then judge whether a particular trial design is of sufficient quality to merit inclusion in their review and analyze the group of trials selected to see if some definitive pattern of results emerges. In some cases the data from a number of published trials can be combined into one big “meta-analysis,” which adds weight to the statistical analysis.

In the case of the systematic reviews of TMJD surgical and non-surgical treatments, the authors could find only two systematic reviews that met their inclusion criteria. (They excluded reviews of in vitro or animal studies, reviews of non-surgical treatments only, editorials, simple narratives, letters to the editor, and articles published outside a selected set of languages). Worse, only a few subsets of studies included in each of the reviews the authors selected met high-quality criteria and these studies represented only a small percentage of all the patients involved in the studies. While both reviews found no statistically significant differences in outcomes for surgical vs. non-surgical interventions, the conclusions were based on combining results for all the studies in the reviews—whether high, low, or of middling quality. As a further caveat, the BMC authors independently evaluated the methodology employed by the authors of the two reviews themselves, using three different sets of established methodology criteria. On a scale of 0-100% one review met only 23.5% plus or minus 6.0% (mean and standard deviation) and the other, 77.5% plus or minus 12.8% of the methodology quality criteria.

To their credit, the authors of the two systematic reviews discussed the flaws in the studies in their reviews: few trials tailored specific treatments to specific sub-groups of TMJD patients, so judgments of relative efficacy could not be made. Also, trials varied in how they defined the success or improvements following treatment.

Such criticisms are not new; the lack of standardized diagnostic criteria and outcome measures for TMJDs has plagued TMJD studies for years, along with such issues as sample size and patient follow-up. The BMC authors advise that “clinical scientists need to be designing, implementing, and reporting clinical trials and systematic reviews that meet international standards.” For TMJD studies in particular, trials should incorporate international standards assessing chronic pain pre- and 3-months post-therapy, measures which would include the number and percentage of patients with 50% pain relief for both the experimental and control group.

### Ethical Concerns

The authors conclude, “The most troubling aspect of our findings involves the ethics of trials that do not meet international standards of conduct, and the care of patients that is not based on high levels of evidence.” They cite a Supreme Court ruling in which the Federal Rules of Evidence for causality of harm were applied, based on the highest level of evidence. It should not take the threat of litigation to alter clinical trial design or practice. As the authors observe, “having clinical scientists register their trials, select and implement interventions and comparisons in a standard, randomized, blinded fashion, and completely report these results...would substantially improve the evidence base, reduce the variation in care and improve knowledge of patient outcomes.” ♦

\* Bessa-Nogueira RV, Vasconcelos BCE, Belmiro CE, Niederman, R. The methodological quality of systematic reviews comparing temporomandibular joint disorder surgical and non-surgical treatment. *BMC Oral Health* 2008;8:27.

## TMJA and FDA: Past Imperfect, Future Conditional...

The Food and Drug Administration (FDA) is the federal agency charged to ensure the safety of the food we eat, the effectiveness and safety of medications we take and devices implanted into our bodies. For all too many TMJD patients, the agency's performance with regard to devices has been nothing short of disastrous. In 1982 the FDA approved the use of an implant made by the Vitek Company to replace diseased or damaged parts of the jaw joint in TMJD patients. The product was approved because of its supposed similarity to a sheeting material called Silastic, which the agency had earlier approved to treat lock-jaw (trismus). Unfortunately, the Vitek implant and jaw devices using Silastic could and did break down during ordinary jaw movements, releasing particulate matter into the bloodstream where it could trigger an immune system reaction. Worse, in some cases the material worked its way through the skull to penetrate the brain. Patients were seriously harmed, their pain intensified, and in many cases they became subject to multiple surgeries to remove the failed devices in efforts to correct the damage. Tragically, some patients, with mutilated faces, restricted jaw movements, and unbearable pain, committed suicide.

The FDA issued a recall of the Vitek device in 1990 but could not recall Silastic sheeting, because there had been no studies upon which they could base a recall. In response to the recall, the Vitek manufacturer moved his company to Switzerland until the statute of limitations expired. That left the FDA solely in charge of conducting the recall, but with little information of who had placed the implants and who had received them. Many TMJD patients were not informed of the defective devices and their dangerous potential.

The implant scandal and the realization that there was virtually no science behind the diagnosis and treatment of TMJ problems led to the formation of The TMJ Association, Ltd. (TMJA) as a local patient group in Milwaukee in 1986, and its incorporation as a national non-profit organization by 1990 (see Terrie Cowley's article on pg. 1). The Association took action to alert Congress to the ongoing problems of TMJ implants, and a hearing, "Are FDA and NIH Ignoring the Dangers of TMJ Implants?" was held in 1992. Following the hearing TMJA believed that the now much-chastised FDA would exercise extraordinary scrutiny over any future jaw device. Unfortunately, this has not been the case. A GAO report revealed the problems associated with the FDA's approval of devices since 1999. There has been a general lack of transparency, a haphazard post-marketing surveillance system, a double standard in which small companies are treated more leniently than large companies, and approval of a device without

clinical data. In part, FDA's problems with devices reflect overall issues in regard to agency operations.

At a recent scientific briefing, a researcher who has been an expert witness on the serious side effects of drugs that were not reported by drug manufacturers, was asked, "What would be your three top recommendations for improving the performance of the Food and Drug Administration as the nation's watchdog over food, drugs, and devices?" Without hesitation, he said "Leadership, leadership, leadership." And if their records are any proof, that is now what FDA has. Margaret Hamburg, M.D. is FDA Commissioner and Joshua Sharfstein, M.D. is Principal Deputy Commissioner. Hamburg will oversee food and tobacco while Sharfstein will handle drugs and devices.

Both have sterling reputations. Hamburg's was forged at the National Institutes of Health and the Department of Health and Human Services, and most recently, as New York City's Health Commissioner. Sharfstein brings to the job experience as a city health commissioner of Baltimore. Earlier in the decade he served on the professional staff of Congressman Henry Waxman of the Government Reform Committee, himself an outspoken guardian of the public's health. Both Hamburg and Sharfstein have records as excellent managers able to boost staff morale, which the FDA sorely needs. Their appointments come in the wake of a recent scandal in which the agency admitted to succumbing to political pressure to approve a knee-repair device in spite of the negative judgment of its own scientific review panel. That decision is now under review, along with steps to revise internal procedures to assure that standard protocols are followed and decisions fully documented. In addition, the agency has asked the Institute of Medicine to review the FDA's device approval process.

Meanwhile, The TMJ Association has been active in a coalition concerned with the safety of all devices. The Patient Coalition, an association of consumer and patient groups and other interested parties, has had meetings on October 5th with Dr. Sharfstein and September 8th with Dr. Jeffrey Shuren, Director of the FDA Center for Devices and Radiological Health. Dr. Shuren asked to meet with Coalition members prior to assuming his new position. Terrie Cowley, TMJA President and Co-founder, detailed the harm caused to TMJ implant patients and stated that "It was because of the incredibly low standards, lack of transparency, a voluntary and broken Medwatch system, a device tracking system that we have no evidence is being adhered to, a haphazard post-market surveillance system, inadequate IDE endpoints, a policy that abrogates its responsibility by telling the

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immune cells. Note that presence of the virus does not indicate it causes CFS; it could be a free rider just taking advantage of immune system defects. But it is a finding that scientists take seriously in light of discoveries that infectious agents like the bacterium *Helicobacter pylorus* cause stomach ulcers, and human papillomaviruses cause cervical cancer. More clinical testing and epidemiological studies will be needed to determine definitively whether the virus is causal. As commentators on the CFS study have said<sup>2</sup>, "If these figures are borne out in larger studies, it would mean that perhaps 10 million people in the United States... are infected with a virus whose pathogenic potential for humans is still unknown."

More information and commentary on this study can be found on <http://www.cfids.org>. The researcher's paper has aroused controversy as other investigators have failed to replicate the findings. Stay tuned. ♦

<sup>1</sup> Lombardi V, Ruscetti FW, Gupta JD, et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science*. 2009;585-598.

<sup>2</sup> Coffin JM, Stoye JP. A new virus for old diseases? *Science*. 2009;326:530-531.

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## **TMJA and FDA: Past Imperfect, Future Conditional...** *continued from page 3*

patient and surgeon they will share responsibility of the device and essentially a system that bows to the whims of manufacturers." Ms. Cowley advocated for mandatory implant registries, including device retrieval analysis (to determine causes of failure) and also a Unique Device Identification System, which will unequivocally determine which device a patient received in the event that a recall is necessary. The TMJ Association plans to continue efforts to see that any device implanted into a TMJD patient undergoes rigorous scientific scrutiny. All TMJD patients certainly deserve it. ♦

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### **Breakthrough: Jaw Joint Bone Graft Grown**

Bioengineers at Columbia University recently grew grafts of the temporomandibular joint. The breakthrough discovery is great news for TMJD patients who have had TMJ implants or may be contemplating implant surgery down the road. According to the *Scientific American* article on October 5, 2009, Dr. Gordana Vunjak-Novakovic states "It was the greatest challenge we could think of, the most complex piece in the skull in terms of shape, based on surgeons we asked," she says. "If we can grow this piece, we think we can grow anything." They first used real bone as a scaffold to which they added stem cells in a bioreactor which was supplied with nutrients, growth factors, and oxygen. After 5 weeks they saw functional bone tissue form of exactly the right shape.

Terrie Cowley had the opportunity to meet Dr. Vunjak-Novakovic at a November TMJ Bioengineering Conference. *TMJ Communiqué* plans an interview with her in a future issue. ♦

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### **Our New Web Site & TMJ News Bites**

We're pleased to announce we have launched a new sister web site to our current [www.tmj.org](http://www.tmj.org) site that will provide better access to information, offer more opportunities for you to interact with us and other TMJD patients, leveraging the power of social networking and allowing us to reach a broader audience. We hope you find it easy to navigate and that the information you want is easily accessible. Please visit <http://www.tmjassociation.org> and let us know what you think.

Since March 2009 we have been publishing a monthly e-newsletter, *TMJ News Bites*. If you don't already subscribe, you can sign-up at: <http://www.tmjassociation.org/site/sign-up>. ♦