The XMRV virus: Reality and artefactuality in scientific controversy.

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Abstract:

The retrovirus XMRV (xenotropic murine leukemia virus-related virus) was first identified in association with Chronic Fatigue Syndrome in 2009. Following the publication of this research there erupted a major controversy within the scientific literature over the status of the XMRV virus, that wound to a close in 2012 with the editorial retraction of the original research and the conclusion that the virus was a laboratory artefact. This paper maps the dynamics of the XMRV-CFS controversy, and how the status of the virus itself changed over the course thereof. The question of the "reality" of both the virus and its putative association with Chronic Fatigue Syndrome were pivotal to the actors involved, and the thesis focuses on how the endogenous discourses of artefactuality (along with the procedures, materials, and instrumentation with which such discourses were entangled) figured into the perpetuation and eventual resolution of the controversy.

Résumé:

Le rétrovirus XMRV (*xenotropic murine leukemia virus-related virus*) a été identifié pour la première fois en 2009 en association avec le Syndrome de fatigue chronique. Suite à la publication de ces recherches, une controverse importante a éclaté dans la presse scientifique quant au statut du virus XMRV. Cette controverse s'achèvera en 2012 avec la rétractation de l'article original et la révélation que le virus était en fait un artefact de laboratoire. Le présent mémoire retrace la dynamique de la controverse autour du couple XMRV-SFC en examinant de plu près le changement de statut du virus au cours de cette même controverse. La question de la « réalité » même du virus et celle de son lien putatif avec le Syndrome de fatigue chronique occupent une place centrale au sein du débat entre les scientifiques concernés. Le mémoire s'intéresse donc en particulier au rôle qu'ont joué dans la perpétuation et l'éventuelle résolution de la controverse les discours endogènes concernant l'artefactualité, ainsi que les instances matérielles (procédures, matériaux et équipements) rattachées à ces discours.

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Introduction

In October of 2009, research was published in *Science,* the high-profile journal of the American Association for the Advancement of Science, that found a high prevalence of a newly identified retrovirus, XMRV, in patients with Chronic Fatigue Syndrome (Lombardi et al. 2009). Chronic Fatigue Syndrome (CFS), is a poorly understood disease condition that was first identified in the late 1980s, and is associated with a collection of symptoms, defined in part by unremitting fatigue that is not alleviated by rest (Buchwald et al. 1987; Fukuda et al. 1994). The history of CFS has been politically fraught, and it remains a somewhat controversial diagnosis due to the lack of a reliable biological marker for the disease. As such, CFS may be considered a 'fuzzy' disease category, a diagnosis of exclusion (based on the presence of a collection of symptoms in the absence of some other underlying cause) that despite attempts at standardization, has ill-defined borders and an uncertain membership.[1] The search for a viral origin for CFS has yielded many candidates over the years, each of which was eventually discarded, and the suggestion of a possible retroviral cause had major potential for the characterization, diagnosis, and treatment for the condition. If XMRV was confirmed as a genuine human infection associated with CFS, it would be only the third retrovirus to be identified in humans, along with HIV and HTLV-I. However, attempting to establish the role of retroviruses in human disease has been a complicated and difficult endeavour.[2]

This 'fuzzy' status of CFS as a disease entity has made it prime material for “social construction of disease”-type analyses, and the complex relationships between CFS patients, health care providers, state and private insurance bodies are highly amenable to traditional sociological approaches to health and illness.[3] Had the XMRV-CFS association been confirmed, it would have had major repercussions

[1] Currently three sets of overlapping standards are in prevalent use. The most common is the CDC/Fukuda criteria, followed by the Oxford Criteria, and the 2003 Canadian Clinical working definition.

[2] For an overview of viral research on CFS, see Ablashi 1994. On retroviruses and human infection more generally, see Voisset, Weiss, & Griffiths 2008.

[3] See Aronowitz 1998; Dumit 2006; Rosenberg 2002; Travers, & Lawler 2008, for examples both CFS-specific and more general.

for how CFS was conceptualized, experienced, negotiated and administrated, and the controversy has been widely commented on by patient and advocacy groups, CFS and science blogs, and traditional media outlets. For the purposes of this paper I will not take CFS or CFS patients as my primary subject, but rather focus attention on the entity XMRV as the object of the controversy as it unfolded in the scientific arena. This focus was not assumed at the outset of research, but was adopted in response to the heated debate that arose among scientists in the wake of the Lombardi et al. (2009) *Science* paper. It is noteworthy that this critical attention was directed *not* at CFS as a disorder with an already disputed status, but toward the virus itself (although it has been claimed by some that the virus only became controversial because of its association with CFS specifically). Had XMRV moved swiftly and unchallenged from the laboratory "into the world," as it were, the controversy might have developed very differently. As XMRV met with such immediate resistance within the scientific journal literature, an opportunity was presented to engage in an examination of a scientific object "in the making."[4] To distinguish between "public" scientific controversies on the one hand and "technical" scientific controversies on the other, as has often been done, is tempting but disingenuous, especially if it has the effect of predetermining the scale of analysis and the types of actors that will be admitted into consideration. Nevertheless, to *begin* analysis with how XMRV figured into debates among CFS patients and activists, doctors, bloggers, blood banks, and government agencies would be to participate in the "black-boxing" of XMRV, rather than taking advantage of what can be learned by observing what goes into this very process.

This paper is based on research I conducted over the course of September 2010 through February 2012. In this period I conducted a series of six ethnographic, open-ended interviews with scientists who had published research on XMRV, including several of the co-authors of the initial Lombardi et al. (2009) paper. Interviewees were selected on the basis of their membership in the core

[4] For an early and influential example of this approach to scientific objects "in the making," see Latour and Woolgar, *Laboratory Life: The Construction of Scientific Facts* (1979)

set of participants in the controversy. Informed consent was obtained from all interview subjects, and the research was approved by the McGill Research Ethics Board. The interviews, which varied in length from 1 to 3 hours, were manually coded by myself using an open coding system that eventually yielded categories that highlighted passages concerning the ontological status of the virus, classification and nomenclature issues, contamination, experimental procedure/methodology, and replicability of results. I read and analyzed all relevant literature (based on keyword searches for XMRV using the National Centre for Biotechnology Innovation (NCBI)/United States National Library of Medicine PubMed, Web of Science, and Scopus databases), including the roughly 200 papers published in scientific journals, as well as related material in the form of commentaries by scientists, newspaper and magazine articles, newsletter items, blog and web forum postings, memoranda and press releases by state agencies and other organizations. In addition I conducted fieldwork at one scientific conference (The International Association for CFS/ME 2011 Conference, held in Ottawa, Ontario, in September 2011) where XMRV-CFS was discussed, and consulted and analyzed video recordings of three other conferences (The First International Workshop on XMRV, September 2011; The Conference on Retroviruses and Opportunistic Infections, February 2011; The National Institutes of Health State of Knowledge Workshop on CFS, April 2011). The interviews and fieldwork informed my analysis by allowing the further exploration of themes and issues prevalent in the literature, and the identification of what elements of the research, and of the debate surrounding the research, were viewed as most significant by the actors involved.

Chapter I: Scientific Controversy Examined

For the past three decades, the study of scientific controversies has been a favoured topic for the

sociology of science. Or, more precisely, across many *sociologies* of science, as well as the historical, anthropological, and philosophical investigations with which they overlap. The reasons for this interest in controversies are both conceptual and methodological. The 1970s witnessed the beginning of a double movement away from, on the one hand, a more traditional sociology of science associated with the work of Robert K. Merton that emphasized institutional formations, norms, and reward distribution, that was viewed as more of a *sociology of scientists* than a sociology of science, toward a focus on the *content* of scientific activity and scientific knowledge. And, on the other hand, away from epistemologies and sociologies of knowledge that embodied a 'whig history' approach to science, treating it as the standard for the differentiation between true and false knowledge, self-evident and immune from sociological investigation, toward an interest in how the factuality of scientific knowledge was produced and of what scientific practice consisted. For such an investigation into the content of science, controversies have proved particularly useful because they display scientific activity at its most dynamic, where what will become certainties and matters of fact are still in flux, and one can observe and analyze the processes of knowledge-in-the-making. Put another way, as the "canonical knowledge-producing institution" (Collins 1983:87) of the current era, science can be seen as a process of *world-making.* In controversies the collection of entities, facts, and forces that make up the world are destabilized, shuffled, and re-solidified, often with new elements entering into the world and others falling into disuse or obscurity. The work of contemporary science studies has made this matter of *of what the world is made*, and how it gets that way, a question of major sociological importance. As such, there has been a proliferation of research that delves into the often highly technical and esoteric domains of the laboratories, scientific conferences, and journal literature.

Methodologically, controversies have provided an excellent opportunity for research because over the course of debate, the various sides of the controversy engage in the deconstruction of each other's arguments and claims, providing an 'endogenous' analysis of the practices, procedures, and

dynamics of scientific work in a specific area. This offers insight not only into the 'inner workings' of scientific process, but also allows one to observe what goes on in the process of construction of a particular scientific object or fact. What kinds of uncertainties are introduced? What methods, materials and prior facts may be drawn upon as resources and what are put into question? What possibilities are presented or foreclosed, and how is this all achieved, in order to arrive at something that may be understood as objectively "already-there," waiting for scientists to discover it? The analysis of 'warm' or 'open' controversies, where debate is ongoing or closure only recently or precariously obtained, presents the sociologist with the chance to share in the relative uncertainties of the scientists themselves, before the lid of the 'black box' has been closed, while the temptation to view the resulting fact as inevitable is less pronounced.

Bruno Latour uses this metaphor of the "black box" to describe how once-disputed scientific facts and scientific objects come to be able to circulate freely, to be relied upon or appealed to as evidence, and taken for granted as things in the world (Latour 1987). Users do not need to understand how or why a black box works in order to make it work for them, or to use it to make someone or something else perform some action, and this use reaffirms the unproblematic status of that which has been black-boxed. Such facts, however, have their histories, and their successful deployment rests upon the obfuscation of not only the conditions of their production, but the often fierce debates that preceded their being established as 'matters of fact'. To pursue an analysis of a scientific controversy is to attempt to expose the collective work that goes into constructing and closing the black box, to highlight what is made invisible by that closure. Fundamentally it could be said that analyses of controversies constitute a sociological investigation into how the *self-evidence* of scientific facts and scientific objects is constituted.

This strand of sociology of science or science studies may be traced back to the Strong Programme for the Sociology of Scientific Knowledge that was developed at the University of

Edinburgh primarily by David Bloor, Barry Barnes, Steven Shapin, and Donald A. MacKenzie. Central to this school of thought was its opposition to what was derided as the 'weak programme' that sought only to explain instances of scientific error or false belief in sociological terms, leaving the *core* of science – scientific knowledge – uninterrogated. Bloor's 1976 *Knowledge and Social Imagery* set out four basic tenets of the Strong Programme: (1) *Causality* – The sociology of science must aim at discerning what conditions or factors bring about beliefs or states of knowledge. Ie: "The content of a belief is not to be treated as the cause of the belief" (1991:175). (2) *Impartiality* – Against the earlier 'sociology of error,' both sides of the dichotomies of truth and falsehood, rationality and irrationality, failure and success, require explanation. (3) *Symmetry* – Proceeding from the requirement of impartiality, the condition of symmetry demands that the same *type* of explanations (sociological) apply for beliefs held to be true as for those held to be false. (4) *Reflexivity* – the types of explanation produced should apply as well to sociology, itself a mode of knowledge production (Bloor 1991).

Taken together these last four tenets constitute a "methodological relativism" that allows the researcher to engage in an analysis of science while bracketing major epistemological and metaphysical questions that ultimately stand outside of empirical verification, or arguably even philosophical resolution (Bloor 1991:158). The *symmetry/impartiality* conditions (which can be seen as two sides of the same requirement) are tremendously useful for thinking outside of the teleology of cumulative scientific progress, although they do not strictly refute this teleology, nor are they intended to. Bloor asserts that this is specifically a methodological manoeuvre; the trenchant materialism of the Strong Programme affirms the existence of a knowable external world, while simultaneously insisting that this world does not solely determine what is known about it (1991: 33). Observation, it is argued, is theory-laden, always already part interpretation, and can never be 'pure' in the ideal or rhetorical sense. Furthermore, 'observation' *in the sense of a scientific practice* is mediated not only by theory, but also organized through complex systems of representation, instrumentation and procedure. Practices of

classification, experimentation, and interpretation of proofs can be seen in a similar light: “Scientific theories, methods, and acceptable results are *social conventions*,” Bloor writes (1991:43, emphasis mine).

While this methodological relativism and the principle of symmetry have become key components of the sociology of science, other aspects of the Strong Programme have been found to be distinctly limiting, specifically the type of causal explanation that it presumes to offer. Critics have argued that the “macroscopically-oriented” model of the Strong Programme, which maintains that *goals and interests* are responsible for “bringing about” scientific belief, inadequately specify how such social-structural factors can account for the actual content of scientific knowledge, and fails to attend to the actual practices of scientific work, concerned as it is more with the explanation of *why* certain beliefs are held. Knorr-Cetina writes:

> the epistemological question of how that which we come to call knowledge is constituted and accepted is not addressed in the above model . . . To attack this question, we are pressed to examine the genesis and transformation of our objects of knowledge at a level sufficiently close to the actual practices of scientists to be able to differentiate between knowledge-constitutive procedures and rationales. (1983:116)

Additionally, it has been pointed out that the form of causality proposed by such a model is of a weak and ill-defined persuasion (Latour 1999; Woolgar 1981). This criticism is part of a broader view that the attempt to *explain* science by recourse to 'social factors' is the wrong approach entirely, and one which hinders our ability to analyze scientific controversies for the complex, dynamic world-making and -remaking processes that they are. “We are led to the heart of scientific practice by arguments about focus,” writes Woolgar, “only to find that the phenomenon is then to be subject to a sociological sledgehammer” (1981:373).

An approach associated with the Strong Programme, but which in engages a more

“microscopic” analysis is that of Harry Collins, often referred to as the Bath School. In Collins's early work there is a more explicit emphasis on the study of active controversies than in the Edinburgh School, which has tended toward historical case studies. Collins also focused on in-depth laboratory studies, the running of experiments, and the construction of experimental apparatuses (such as the design of the TEA laser and gravity-wave detectors (Collins 1983)). Collins opposes what he calls an “algorithmical model” of science that sees the work of experimentation as a set of straightforward procedures that, as a mere formality, reveal or reflect the workings of the natural world, to an “enculturational model,” wherein science is a set of skilled practices that relies on a shared culture of belief and tacit knowledge. The crux of what Collins called the Empirical Programme of Relativism is the underdetermination or *indeterminacy of data*: “The natural world,” Collins writes, “must be treated as though it did not affect our perceptions of it” (1983:88). This methodological relativism, in a stronger vein than Bloor's, and which carries still further the principle of symmetry, is viewed as necessary to highlight the social or cultural dimension of science, which is to be explored microsociologically or ethnologically. For Collins, the course of a scientific controversy can never be decided by the experimental data alone, and so if closure is to be collectively achieved (or imposed) it must be so as the result of some other intervening influence.

The presumed 'social' status of this influence can prove analytically problematic (this will be discussed in greater detail in a subsequent chapter), and it is for this reason, among others, that Collins's model cannot exhaust our approach to the study of controversies. Another approach, indebted to the Strong Programme but in many ways greatly at odds with it, is that of Actor-Network Theory. Variously articulated by Bruno Latour, Michel Callon, and John Law, most prominently, Actor-Network Theory comprises less a theory in the classical sense than “a disparate family of material-semiotic tools, sensibilities and methods of analysis that treat everything in the social and natural worlds as a continuously generated effect of the webs of relations within which they are located” (Law 2009: 141).

Vigorously empirical and strongly influenced by ethnomethodology in its approach, Actor-Network Theory is highly descriptive, in lieu of attempting to offer causal explanations or predictions, and demands what can be considered a theoretical 'light touch.' Its injunction to 'follow the actors' gives priority to the arguments, explanations and reflexive activities of the actors themselves, over and above any concealed interests or hidden social forces imputed by the analyst.

The major difference between Actor-Network Theory and other sociologies of science lies in how "nature" and "society" are conceptualized, and this is what makes Actor-Network Theory most salient for our investigation of scientific controversy. Actor-Network Theory rejects from the outset the binary Nature-Culture schematic that is the basis for the very intelligibility of traditional 'social explanations of science.' Returning to the idea of controversies as sites of *world-making* activity, Actor-Network Theory views nature and society as *simultaneously co-produced* through the settlement of scientific controversy. This requires a somewhat different understanding of society as an object, as itself a *socio-technical assemblage* or *collective* that is made up of associations not only between humans, but among humans and non-humans, such as other animals and organisms, laboratory materials, machines, tools, texts. The list is of necessity inexhaustible, and more to the point, ever-changing as scientific and technological work continues to modify the collection of entities that make up the world (Latour 2005). The purpose of this re-imagination of "society" is to blur the too-easy distinctions that are made between what belongs to the "natural" versus the "social" world. Such sorting out requires the ignoring or severing of connections between what cannot realistically be disentangled, and makes little sense if our aim is an understanding of this complicated socio-technical arrangement of the world.

Latour writes, in *Science In Action*:

> Since the settlement of a controversy is the *cause* of Nature's representation, not its consequence, we can never use this consequence, Nature, to explain how and why a controversy

has been settled . . . Since the settlement of a controversy is the *cause* of Society's stability, we cannot use Society to explain how and why a controversy has been settled" (1987: 258).

The implication for Actor-Network Theory-inflected research is the suspension of analytical recourse to either scientism or to pre-decided-upon "social factors" to understand the controversy or the object(s) that are produced therein, in order that the instability of both nature and society over the course of a scientific controversy may be attended to. This position is both *relativist* and *constructivist*, but not in the senses usually understood. Relativist, in that it is concerned with "the empirical task of tracing the establishment of relations" (Latour 1999:120), and constructivist (*not* "social constructivist") in that it attends to the processes and activity through which facts are made.[5] While I will not adopt wholesale the terminology or analysis of Actor-Network Theory, several of the above elements factor into my approach to the XMRV-CFS controversy.

Chapter II: Chronology of the XMRV-CFS Debate

In order to orient the reader, it will be necessary to summarize the major events of the controversy as it has unfolded. Such an effort inevitably presents a particular version of the chronology, and risks inscribing a telos into the proceedings. Major events? Significant papers? Significant for what outcome, and in light of what resolution? In any controversy there are many ways of recounting events, as they can look quite different from different perspectives, particularly from the vantage point of an achieved or partially achieved closure. Indeed, part of the work of solidifying and realizing such closure may entail the narrativization of events in a particular way. The success with which various

[5] Which is fundamentally different than the claim that what is constructed is somehow 'unreal.' Latour emphasizes how the stark artificiality and constructedness of the laboratory setting is not at odds with the understanding of Nature that is produced. "This is why it was with great enthusiasm that we began using the expression 'construction of facts' to describe the striking phenomenon of artificiality and reality marching in step." (Latour 2005:90)

actors are enrolled in the reproduction of this account can be read as a measure of the strength of the closure, although this enrolment will rarely be universal.[6]

In light of this, the following timeline must be viewed as a practical arrangement for the purpose of navigating the controversy, not a neutral, transparent recounting. I do not detail comprehensively all of the publications related to XMRV but rather will highlight the papers, events and turning points for how they shaped the terrain of the debate. This selection process is informed in part analytically, and partly by following the indications of the actors themselves. Where other published papers have not been mentioned, it is because they fell relatively unnoticed into the fray, as it were, failing to elicit more than a passing response from the other actors involved in the controversy.[7]

Another pragmatic decision that has been made with respect to this timeline has to do with the complicated nature of the dissemination of research results within the scientific arena. It would be misleading to refer to this simply as a "system of dissemination" because it more accurately involves several parallel systems that do not always interact in a consistent fashion. I have chosen for the timeline to organize papers by their official date of publication, corresponding to the issue of the journal in which they appeared. The internet has complicated this process somewhat, as many journals also feature some manner of online publication forum that allows for the release of papers in advance of their official publication.[8] The discrepancy is not usually more than a month or two; where and when this makes a difference, or specifically where this is made an issue by scientists, I will so note in my

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[6] Collins refers to the *catastrophic crystallization of certainty* that often attends the closure of a controversy. This is especially the case for those at some remove from the debate, but even for those in the midst of the controversy, he writes "it is very hard to recapture the uncertainty of the time of creation once the debate is closed and the correct way of going on has been crystallized into the new scientific institutions." (1985:144)

[7] Highlighting how scientific claims depend on their embeddedness within networks of reference and citation, Latour writes: "There is something still worse, however, than being either criticized or dismantled by careless readers: it is being *ignored*. Since the status of a claim depends on later users' intentions, what if there are *no* later users whatsoever? . . . No matter what a paper did to the former literature, if no one else does anything with it, then it is as if it never existed at all. You may have written a paper that settles a fierce controversy once and for all, but if readers ignore it cannot be turned into a fact; it simply *cannot*" (1987:40). Still worse, however, is not to be published at all. Some actors in the controversy suggested that editorial bias rendered it difficult for positive XMRV/CFS papers to make it to publication.

[8] *SciencExpress* is a prime example of such advance online publication. www.sciencemag.org also features *Science*NOW and *Science*Insider, devoted to science news and policy developments.

analysis. A similar issue exists where is concerned the presentation or divulgence of unpublished research in the context of a conference, interview, or other public forum prior to official publication. Again, for the purposes of the timeline I will go by the publication date, unless the alternate option has a particular salience for the actors themselves or for the unfolding of the controversy.

This aspect of the dissemination of research is something that scientists are quite attentive to, and is itself a matter of debate. Scientists may be concerned with priority of publication, presentation of unpublished research, the strategic motives seen to be behind the timings of publications, or how online publishing has altered temporal dynamics of the sharing of scientific work. The activity being examined here occurs within a relatively short period of time, relative to other scientific controversies, some of which have spanned decades. XMRV was first described in 2006, and the connection to Chronic Fatigue Syndrome suggested in October of 2009. The number of papers dealing with or explicitly referencing XMRV grew dramatically from 2010 to 2012,[9] when it appeared that a sort of closure had been achieved.[10]

It is important to note that the timeline of XMRV and that of its putative association with Chronic Fatigue Syndrome are not coterminous, although they interrelate. XMRV was first identified in 2006 in a paper by Urisman and Silverman of the Cleveland Clinic, isolated from tumour cells of prostate cancer patients (Urisman et al. 2006). This research yielded the VP62 clone that was to serve as the reference sequence for further XMRV study. The unwieldy monicker, Xenotropic Murine leukemia virus-Related Virus, was derived from the virus's genetic similarity to a class of known murine leukemia viruses (MLVs), the 'xenotropic' describing its apparent ability to infect outside of that

[9] 21 articles concerning XMRV had been published between the Urisman et al. (2006) prostate cancer paper and the Lombardi et al. (2009) CFS paper. From 2009 to the beginning of 2012, this count rose to 226.

[10] The density of this time scale has been commented on in relation to how the Internet and online publication has influenced both the pace of scientific research, and how past research is narrated historically. One scientist, Judy Mikovits, commented "It took us a long time to isolate HIV. And everybody says, "Well, with HIV, the confirmatory papers came *right* out afterwards." But we were not in the internet world. We were all racing from 1980 to 1982, 1983 and 1984. All of us worked nonstop for four years to isolate that virus. Montagnier published in 1982, Gallo published in '83, Levy in '84. Come on. Those are years apart. We're two years after that [XMRV-CFS] paper." (Interview with Judy Mikovits. Reno, NV. August 11th, 2011)

species. An alternative chronology could be written for XMRV's association with prostate cancer, that would overlap in terms of several events and publications, but produce a very different story of XMRV. The XMRV-human prostate cancer association has also been a source of conflict, although neither so high-profile nor so volatile as that for CFS.

In October 2009, a team comprised of researchers from the National Cancer Institute (NCI), Cleveland Clinic, and the Whittemore Peterson Institute (WPI)[11] published a paper in *Science* reporting an association between a retrovirus, XMRV, and Chronic Fatigue Syndrome (CFS). The paper demonstrated by multiple methods the detection of XMRV in 67% of their sample of CFS patients, and 4% of healthy controls (Lombardi et al. 2009). This immediately set off a flurry of activity in the scientific and mainstream press, and among CFS patient communities. In November, under the guidance of the National Heart, Lung, and Blood Institute (NHLBI), the Blood XMRV Scientific Research Working Group (hereafter the Blood Working Group or SRWG) was formed to investigate whether XMRV posed a threat to the American blood supply. The working group consisted of representatives from retrovirology and CFS research, laboratories at the WPI, NCI, Centers for Disease Control (CDC), Food and Drug Administration (FDA), and a private contractor, Blood Systems Research. While not a major participant early on in the controversy, the role of the Blood Working Group study came to be viewed as of increasing importance as time went on.

The initial responses to the Lombardi et al. (2009) paper within the journal literature ranged from cautious excitement to skepticism. By February 2010, three studies had been published that failed to find XMRV in CFS populations in the Netherlands and UK (Erlwein et al. 2010a; Groom et al. 2010; van Kuppeveld et al. 2010), prompting questions about the discrepancy of results, followed in May by a series of critical responses in the "Technical Comments" section of *Science* (Lloyd et al. 2010; Sudlow et al. 2010; van der Meer et al. 2010). These called into question the design and conclusions of

[11] The WPI is a private translational medicine facility in Reno, Nevada devoted to the study of 'neuro-immune disorders' such as chronic fatigue syndrome and fibromyalgia.

the Lombardi et al. (2009) paper, and effectively set the terms by which its results were challenged in the initial stage of the controversy. In the same issue, Judy Mikovits and Frank Ruscetti, co-authors of the paper, published a response to their critics along with supplementary information outlining in greater detail the laboratory work that had been performed (which material had been cut from the original publication for concerns of space) (Mikovits & Ruscetti 2010a & 2010b).

In spite of this lack of consensus among researchers, blood safety organizations had in the interim begun taking measures designed to address the potential threat of a blood-borne human retrovirus. In April, 2010, Canadian authorities issued a ban on blood donation by individuals diagnosed with CFS, and were subsequently joined by Australia, New Zealand, and in June the AABB, an international advisory organization dedicated to the practices and standards of transfusion medicine and cellular therapies.

In July 2010, the first of a pair of federal studies was published by Switzer et al. of the CDC, that found no evidence of XMRV infection in an American CFS cohort (Switzer et al. 2010). The following month, Shy-Ching Lo and Harvey Alter of the FDA/NIH published a paper describing the detection, not of XMRV, but of several related viral sequences in American CFS patients (Lo et al. 2010a). The Alter/Lo paper had reportedly been held back from publication in the light of its conflicting findings with the CDC paper, in order to re-test and confirm their results (Enserink 2010a). It had been widely assumed that the results of these studies would provide closure to the controversy, but quite to the contrary, they had the effect of perpetuating and multiplying the lines of conflict. The significance of the Lo et al. (2010a) results quickly became a matter of debate. The authors, along with those of the Lombardi et al. (2009) paper, interpreted the presence of these similar viral sequences as support for the association originally reported in *Science*, whereas critics denied that the paper strictly qualified as confirmatory.

Here the identity of XMRV became somewhat “fuzzy” with the introduction of a new set of

entities. The "MLV-related sequences" of the Alter/Lo lab. had to then be taken into consideration by other actors, as to their relationship to XMRV and to CFS. The Mikovits and FDA/NIH teams argued that this group of similar viral sequences for all intents and purposes 'count' as XMRV, while others maintained that only the specific full-length sequence identified in the initial *Science* paper (based off the VP62 sequence of Urisman et al. 2006) could properly be considered XMRV. In the latter view the other sequences found by Alter/Lo could not be considered supporting evidence, and were *evidence* of something else entirely. But of what? The controversy had expanded and was no longer simply about the XMRV-CFS association, but also whether there existed an association between other *MLV-like sequences* and CFS, and about the proper relationship between the MLV-like sequences and XMRV: was it meaningfully more one of *difference* or one of *similarity*? Thus a major dimension of the controversy quickly became disputes among scientists about what the controversy was in fact "about." The appearance of MLV-like sequences on the scene had in a sense *changed* XMRV, and this was to be only one of many transformations which XMRV was to undergo. This development may be seen as an initial step toward what I will refer to as the "HGRV turn" that occurred in the XMRV controversy. HGRV, standing for Human Gamma Retrovirus, was promoted increasingly by the WPI over the course of the controversy as a substitute term for XMRV, which change in nomenclature was hotly debated. Within the journal literature and mainstream press, however, XMRV or MLV-like sequences continued to be the commonly-used terminology.

In the initial attempts to account for discrepancies between the published studies several possibilities were suggested, ranging from patient selection and problems arising from different diagnostic standards for CFS, to potential geographic variability of XMRV distribution, to the possibility that positive findings were the result of laboratory contamination. The issue of contamination came considerably to the fore in December of 2010 with the publication of four independent studies in the journal *Retrovirology* that found contamination in either human samples or

PCR reagents. Hué et al. (2010) found that PCR primers believed to be specific for XMRV also detected mouse genomic DNA as if it were a positive XMRV result. They also found that a widely used prostate cancer cell line, 22Rv1, produced large amounts of XMRV that appeared to be ancestral to the more recently detected strains, suggesting that laboratories that had worked with 22Rv1 were at a high risk for contamination. A group in Japan (Sato et al. 2010) found that a component of a popular commercial PCR kit from Invitrogen was itself contaminated with MLV sequences that could produce falsely positive results. Two papers (Oakes et al. 2010 and Robinson et al. 2010) demonstrated using a new test for contamination that what had appeared to be positive results for XMRV from cohorts in the United States, and the UK, Thailand and China, respectively, were actually the result of contamination of samples. Further, Oakes et al. (2010) demonstrated that the pattern of detection of MLV-like sequences produced by contamination fairly closely resembled the distribution of sequences identified in the Lo et al. (2010a) paper, suggesting circumstantially that contamination might account for the results, despite precautions.

John Coffin, of the NCI/Tufts University, a renowned retrovirologist and co-author on both the Oakes et al. (2010) and Robinson et al. (2010) papers, had from the early days of the controversy been a prominent commentator and a participant in many of the conferences where XMRV was discussed, as well as part of the Blood Working Group. With the publication of these papers he emerged as a vocal critic of the XMRV-CFS association. None of the studies had proven contamination in the case of either Lombardi et al. (2009) or Lo et al. (2010a), who insisted that they had taken appropriate precautions. Taken together along with the published negative studies, however, the contamination explanation was gaining considerable allies in the scientific literature. Several commentaries were published that emphasized the likelihood of contamination (Cort 2011; Martin 2010; Smith 2010; Stoye 2010; Erlwein, Kaye, Robinson, & McClure 2010; Kaiser 2011) which elicited a direct response by Alter and Lo of the FDA/NIH (Lo et al. 2010b), as well as public statement by the WPI affirming the stringency

of their contamination protocols, and reiterating that Lombardi et al. (2009) had demonstrated evidence of XMRV by several methods other than PCR (Whittemore Peterson Institute 2010).

During the first half of 2011, a number of critical papers were published that variously found no evidence of XMRV-CFS association across wide American and UK samples (Erlwein et al. 2011; Satterfield et al. 2011; Sakuma et al. 2011), claimed to reproduce the Lombardi et al. (2009) PCR protocols and serology tests (Erlwein et al. 2011; Shin et al. 2011), reported more evidence of contamination of PCR kits (Tuke et al. 2011), and produced negative results upon testing of individuals previously diagnosed as XMRV positive (Knox et al. 2011). At least one of these papers was published by a lab that had heretofore been supportive of the XMRV-CFS association (Shin et al. 2011). Other research cast doubts on the stability of XMRV's association with prostate cancer (Garson, Kellam & Towers 2011; Yang et al. 2011, Switzer et al. 2011).

In April 2011, the French newspaper of current events *Le Monde* ran a special feature on XMRV that reported new evidence that XMRV appeared to be a laboratory artefact, a "chimera" or genetic recombinant accidentally generated in the course of the production of the 22Rv1 cell line sometime in the mid-1990s (Foucart 2011). The report was based on research that had been presented in March at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) by Oya Cingöz of the Coffin lab and Vinay Pathak of the NCI. Reports followed in various news sources and scientific publications, including *Science*, *Lancet*, and an NIH News press release (van Kuppeveld & van der Meer 2011; NIH News 2011; *Science* 2011). The paper itself, "Recombinant Origin of the Retrovirus XMRV," by Paprotka et al., ran in *ScienceExpress* in June 2011, and was published in the July issue of *Science*, along with an "Editorial Expression of Concern," that highlighted the challenges posed to the XMRV-CFS association, and concluded that "the validity of the Lombardi et al. study is now seriously in question" (Alberts 2011a: 1). This document would thenceforth accompany the online version of the 2009 Lombardi et al. paper. According to the findings of John Coffin's group, XMRV was effectively

ruled out as a causal agent in CFS by identifying its origin as a laboratory artefact several decades after the identification of Chronic Fatigue Syndrome as an illness; this was widely seen as further support for the argument that contamination was responsible for the majority of positive XMRV findings, although the possibility of genuine XMRV infection had not been strictly ruled out. In the midst of this, the Mikovits team published a follow-up paper describing a distinct inflammatory signature associated with XMRV infection in CFS patients (Lombardi et al. 2011). Appearing in a lower profile journal (*In Vivo*, the International Journal of Experimental and Clinical Pathophysiology and Drug Research), the article was largely ignored.

In September, 2011 Robert Silverman, a researcher at the Cleveland Clinic and one of the co-authors of the 2009 *Science* paper, issued a partial retraction after discovering evidence of contamination in his lab's samples (Silverman et al. 2011). This development weakened the results of the Lombardi et al. (2009) paper, but did not require its full retraction. The announcement was made on the eve of the IACFS/ME (International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis) conference, which featured the presentation of new XMRV research, including the results of the Blood Working Group study, and the panel "The Case For and Against Human Gamma retroviruses (HGRV) in CFS/ME," with Coffin and Mikovits as speakers. The Blood Working Group results, published officially as "Failure to Confirm XMRV/MLVs in the Blood of Patients with Chronic Fatigue Syndrome: A Multi-Laboratory Study" (Simmons et al. 2011b) reported that none of the labs involved, the WPI and NCI included, were able to reliably detect XMRV, and concluded that XMRV did not present a threat to the blood supply.

On September 29th, 2011, Judy Mikovits was fired from her position as research director at the WPI, over disputes concerning ownership of research material. During the remaining months of 2011 several papers were published supporting MLV or PCR contamination (Hué et al. 2011; Katzourakis et al. 2011; Wolff et al. 2011; Zheng et al. 2011), negative XMRV findings in CFS cohorts in Canada and

Sweden (Cool et al. 2011; Elfaitouri et al. 2011; Steffen et al. 2011), as well as negative XMRV findings and possible contamination for prostate cancer in Europe and the United States (Stieler et al. 2011; Rusmevichientong et al. 2011). In December, *Science* issued a full editorial retraction of the Lombardi et al. 2009 XMRV paper (Alberts 2011b), that was followed days later by the retraction of the Lo et al. (2010a) paper by the authors. In their retraction, Lo et al. wrote:

> Although our published findings were reproducible in our laboratory and although there has been no evidence of contamination using sensitive mouse mitochondrial DNA or IAP assays or in testing coded panels . . . in consideration of the aggregate data from our own laboratory and that of others, it is our current view that the association of murine gamma retroviruses with CFS has not withstood the test of time or of independent verification and that this association is now tenuous. Therefore, we retract the conclusions in our article. (Lo et al. 2012)

These retractions represented a tentative closure of the XMRV controversy, and were accompanied by numerous reports and commentaries in the science press to that effect. Nonetheless, another major CFS study, headed by Ian Lipkin of the Columbia Center for Infection and Immunity, and including Judy Mikovits independently of the WPI, remained in progress as of the writing of this paper.

To summarize, in 2009 the Lombardi et al. *Science* paper suggested a strong association between the virus XMRV and CFS, and was followed by a series of negative studies and critical commentaries. The controversy expanded with the publication of the Lo et al. (2010a) paper that found that other MLV-like viruses might also be associated with CFS. Following this, several papers were published that raised the possibility that contamination was responsible for the positive findings, whether through inadequate laboratory controls or contaminated experimental materials. In Spring 2011, Paprotka et al. published research that seemed to indicate that the XMRV was a laboratory artefact, as opposed to a naturally occurring virus, which effectively ruled out any possibility of a causal relationship between XMRV and CFS. In September 2011, the Blood Working Group reported

that none of the multiple laboratories involved in their study had succeeded in reliably detecting XMRV, and by January 2012, following a partial retraction of the results of the Lombardi et al. (2009) paper (by the authors), and those of the Lo et al. (2010a) paper (by the authors), the full Lombardi et al. (2009) paper had been retracted by the editors of *Science.* Despite ongoing research into XMRV and CFS, by January 2012, the controversy was widely represented in the scientific and popular press as resolved, and XMRV a laboratory artefact in lieu of a genuine infection.

Chapter III: Experimenter's Regress, Closure, and Regulatory Objectivity

As noted above, there are certain dangers and oversimplifications involved in presenting a controversy as unfolding in a linear progression of events, notwithstanding the difficulty of avoiding the language of "progression," "development," and "unfolding." The terrain of a controversy tends to expand and contract as new entities and actors are introduced, undergo transformations, or recede. Such developments should not be presumed to lead progressively toward an elucidation of the "truth of the matter" (although upon closure they may be cast as such); as previous areas of contention are closed off, resolved or obscured, this may open up new terrains of non-agreement and debate. Nevertheless, it is worth examining the controversy at its inception: the initial claim as it was articulated, how it was taken up by or criticized and rendered controversial by others, and what strategies of argument were employed to these ends. This is perhaps the point in the controversy that is easiest to map – the first wave of papers and Technical Comments presented an orderly dialogue of argument and counter-argument that became increasingly messy as the controversy expanded and the object(s) thereof, as much as the claims made about them, proved unstable.

The central claim of the 2009 Lombardi et al. *Science* paper is this: "We have discovered a

highly significant association between the XMRV retrovirus and CFS" (Lombardi et al. 2009:588). If we briefly consider this statement in light of the schema provided by Bruno Latour in his *Science In Action* (1987), we may sketch the network of associations upon which it relies for its stability, and those consequences which, if the statement is accepted, are supposed to follow. In the first place, the statement relies upon the prior existence of two things: the retrovirus XMRV, and the disorder Chronic Fatigue Syndrome, or CFS. Chronic Fatigue Syndrome was, in 2009, and remains, itself a controversial disorder. Since its initial description in 1987, CFS patients have struggled to have their conditions diagnosed and taken seriously by clinicians and scientists among whom no consensus existed on the status, origins, or even nomenclature of the disease. Whether CFS constitutes a single disease entity or a collection of conditions with overlapping symptoms but no shared underlying cause remains a question for researchers, and so the identification of a viral agent had great potential significance for how CFS was characterized and understood.[12] Had XMRV been accepted as etiologically related to Chronic Fatigue Syndrome, a totally different controversy might have erupted.

In *Science In Action*, Latour discusses the reception of a scientific statement in terms of the *positive and negative modalities* of the statement (1987:22). A positive modality leads the reader, as it were, "downstream," away from the conditions of production, and makes the entity or statement in question "solid enough to render some other consequences necessary" (1987:23). The statement "We have discovered a highly significant association between the XMRV retrovirus and CFS." (Lombardi et al. 2009:588), if accepted, was positioned to set off a chain of consequences and new questions for the diagnosis, definition, and treatment of CFS: Was XMRV an etiological agent, or an opportunistic passenger infection? If the former, was CFS finally by way of virological validation moving out of the periphery of scientific acceptance? Could antiretroviral therapies be used to cure or alleviate the burden of the disease? Who would be in a position to provide diagnostic or therapeutic technologies? Would the once unstable and amorphous condition need to be redefined along new lines? What new patterns of

[12] See Aronowitz 1998; Dumit 2006; Fukuda et al. 1994.

nosological inclusion and exclusion could befall the CFS patient community (such as a fragmentation of the diagnosis into "XMRV-associated" and "XMRV-free" CFS?)? Indeed, with such high stakes controversy seemed inevitable. In the early throes of research following the publication of the Lombardi et al. (2009) paper, it seemed unclear what direction events would take. As it happened, it was negative modalities that proliferated, directing attention "upstream," toward the experimental conditions of the production of the statement.

Given the tenuous, uneven acceptance of CFS by scientists and medical practitioners, it is perhaps remarkable that within the context of the XMRV research, CFS was by and large tacitly accepted as a genuine condition that might have a physiological basis. The Lombardi et al. (2009) paper marked the first time research on Chronic Fatigue Syndrome had been published in *Science* magazine, arguably representing a degree of legitimacy in the scientific mainstream that had not heretofore been conferred upon the condition. Critics might have made the coherence or validity of CFS the object of debate, and indeed some early responses emphasized the unlikelihood that so heterogeneous a condition would yield such a high percentage of positives for the virus, but ultimately it was the virus itself that became the centre of controversy.

The first step for the Mikovits team was to establish the link between the virus they had detected and that identified in prostate cancer by the Urisman et al. (2006) paper. The impetus to look for this virus in CFS patients was a hypothesis about a possible shared deficiency in the RNase L pathway between CFS and prostate cancer that was believed to inhibit the antiviral response of the body's immune system (Lombardi et al. 2009).[13] In the paper the authors describe how they were able to determine by phylogenetic analysis (effectively a viral 'family tree') that the sequences isolated from their CFS patients were more more genetically similar to the prostate cancer strains (>99% identical) than to existing endogenous murine leukemia viruses. In this way the Mikovits team was able to draw

[13] Interestingly, the altered RNase L connection was later discarded, when XMRV was detected in patients with normal Rnase L pathway function (Schlaberg et al. 2009).

upon the evidence of the Urisman et al. (2006) paper, in the process strengthening it by the addition of their own lines of evidence.

Lombardi et al. (2009) details multiple methods of detection: polymerase chain reaction (PCR), serology for antibodies, Western Blot for viral proteins, and viral cell culture. These may be seen as methods of conferring, extending, and reinforcing the reality or materiality of XMRV within scientific representational conventions.[14] Each of these techniques is linked together to support the claim that 67% of their CFS cohort demonstrated evidence of XMRV infection. Three potential responses to this claim were likely: First, the paper could be ignored, which did not occur. Second, if the claim was accepted and followed 'downstream', as discussed above, questions as about pathogenesis, diagnosis, and treatment arise. Many of these avenues were in fact pursued: XMRV tests were developed and marketed by Cooperative Diagnostics (who later withdrew the test) and VIP Dx (now UNEVX), several countries imposed bans on blood donation from individuals diagnosed with CFS, and discussions began about antiretroviral treatments similar to those for HIV, along with anecdotal reports of off-label use of ARVs. These responses, however, occurred largely outside of the main arena of debate.

A third response, to challenge the claims of the paper and pursue them "upstream," occurred in the form of the three negative studies[15] from the United Kingdom and the Netherlands that failed to detect XMRV, followed by the "Technical Comments"[16] published in *Science*. The Technical Comments were co-authored by several members of the research teams that had produced the conflicting study results. By taking advantage of the independent publication of the negative studies (in

[14] Various authors in the history, anthropology, and sociology of science have written on how scientific objects achieve 'reality' through being located at the intersection of multiple practices of representation, visualization, and materialization (Rheinberger 2000, Mol 1998). Those discussed here are comparatively constrained (a wider array of clinical or subjective personal representations are not considered), but it should be noted that even within the delimited spheres of retrovirology and molecular biology, such complementary techniques are not necessarily equivalent. Issues concerning the comparative sensitivity of detection methods are explored below, and at least several of the scientists interviewed expressed the opinion that the major achievement of the Lombardi et al. (2009) paper was the isolation and culturing of the full virus (Interview with John Coffin. Boston, MA. September 2nd, 2011; Interview with Judy Mikovits. Reno, NV. August 11th, 2011; Interview with XMRV researcher. August 10th, 2011).

[15] Erlwein et al. 2010a, Groom et al. 2010, Kuppeveld et al. 2010.

[16] Lloyd et al. 2010, van der Meer et al. 2010, Sudlow et al. 2010.

the journals *PloS One*, *BMJ*, and *Retrovirology*), the authors of the Technical Comments were able to mobilize them as a form of additional evidence to buttress their critiques. That they were in part responsible for this additional evidence is neither disavowed nor explicitly stated. This is consistent with Collins's concept of the "core set," the limited group of scientists bound by their "close, if differing, interests in the controversy's outcome," who actively contribute to the debate (Collins 1985:142), although the boundaries of the core set cannot be presumed to be stable or unchanging, and a remarkable quality of the XMRV-CFS debate was how permeable it proved to be to the involvement of researchers from diverse disciplines.

Taken together, the Technical Comments presented several lines of argument: (1) The history of CFS has witnessed a long line of viruses suggested to play a role in its etiology, and none so far have been validated. This is the backdrop against which the XMRV-CFS association must be judged. (2) It is irresponsible and premature to claim that XMRV plays a causal role in CFS. (3) Two of the three pieces pointed to a lack of adequate description of how the CFS patient population was defined and characterized, and suggested that selection partly on the basis of specific immunological abnormalities and cytokine profiles greatly limited any generalizability of findings. (4) The Lombardi et al. (2009) paper did not meet the epidemiological standards for a valid case-control study. Specifically, sufficient precautions against experimenter "expectation bias" were not taken. (5) Alternative explanations were not considered. (6) Three independent studies have failed to replicate their findings, and do not support any association between XMRV and CFS.

Some of these criticisms operated in a more broadly rhetorical fashion (such as the 'false precedent' claim, that implied that XMRV was *but another* in a long line of failed explanations for CFS), whereas others employed specific methodological arguments. The response by Judy Mikovits and Frank Ruscetti of the WPI and NIH respectively, and coauthors of the Lombardi et al. (2009) paper, was published in the same issue of *Science*, and addressed the criticisms in turn (Mikovits & Ruscetti

2010b). Concerning (1), (2), and (5), Mikovits and Ruscetti pointed out that they at no point in their paper claimed a causal role for XMRV, but stated only that "These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS" (Lombardi et al. 2009:585), and left open whether XMRV could be "a passenger virus in the immunosuppressed CFS patient population" (Ibid.: 588). To (3) and (4) they countered that the study was never designed to be a case control, and that these criticisms derived from a *misreading* of their paper. Mikovits and Ruscetti also pointed out that neither immunological abnormalities nor cytokine profiles provided the basis for patient inclusion in the study, and further details about selection of patients and controls, diagnostic criteria, and blinding procedures[17] were available in the "Online Supporting Material" (Mikovits & Ruscetti 2010a) published in the same issue.

The first five lines of critique were dismissed as inaccurate, irrelevant, and ultimately "unwarranted." A different approach was taken to the 'conflicting studies'. These were referred to as the "three recently published PCR studies" (Mikovits & Ruscetti 2010b: 825-d), and their identification with PCR specifically was not accidental. Polymerase chain reaction (PCR) is a standard technique of molecular biology used widely in the study of viruses and retroviruses, that allows one to select for and amplify small amounts of DNA. It served as the initial method of detection of XMRV in the Lombardi et al. (2009) study, and the primary method in the three subsequent studies by Groom et al. (2010), Kuppeveld et al. (2010), and Erlwein et al. (2010a). Each of the negative papers positioned itself as a replication study that produced conflicting results to those of Lombardi et al. (2009), but there were methodological differences between them, and it was precisely these differences, downplayed by each of the critical papers, that Mikovits and Ruscetti seized upon:

> We contend that the three recently published PCR studies [. . .] do not qualify as being studies

[17] In response to the imputation of experimenter 'expectation bias,' Mikovits and Ruscetti appeal to the credibility and implied disinterestedness of the NCI and Cleveland Clinic, tacitly accepting that the WPI, already identified with CFS advocacy, may not have so easy access to the same claims (Mikovits & Ruscetti 2010b).

> that fail to replicate our study, as neither the same PCR methodologies were used nor did these studies draw on the additional cell culture and immunological methods that we employed to observe XMRV nucleic acids and proteins. (Mikovits & Ruscetti 2010b:825-d)

Mikovits and Ruscetti denied that the evidence produced in the subsequent studies qualified as *equivalent* to that of their own, in what was not (yet) precisely a hierarchization of evidence, but an insistence that because the specific experimental conditions were not reproduced, the results of the negative studies could not be said to contradict the findings of the Lombardi et al. (2009) paper. However, they go on to state that "Of the technologies used to identify and isolate XMRV in patients with CFS, PCR from DNA or cDNA from unstimulated peripheral blood mononuclear cells is the *least sensitive method*" (Mikovits & Ruscetti 2010b). This can be read as a counter-move to those attempts by the authors of the negative papers to firmly establish the legitimacy, equivalency, and even superiority of their own methods. The Kuppeveld et al. (2010) paper, for example, uses the same set of primers as Lombardi et al. (2009) for their PCR, although their procedures differed somewhat. Erlwein et al. (2010a) augmented their claim to the efficacy of their PCR by noting that it should have been sufficiently sensitive to pick up slight sequence variation that could be predicted to occur between American and UK strains of XMRV (2010:3). Groom et al. (2010) asserted outright the superiority of their PCR methodology: "We concluded that our assay was capable of reliably detecting as little as 16 copies of proviral DNA and was therefore likely to be as sensitive, if not more so, than the assays previously used" (2010:4). These challenges on the level of methodology were dealt with by Mikovits and Lombardi first by asserting the non-equivalence of experimental results due to different arrays of detection methods, and second by attempting to install PCR in a hierarchy of methods that diminished its power as evidence-generating. Consequently, the negative studies could be criticized in turn by Mikovits for "relying" too heavily on PCR. In this formulation, the strength of the Lombardi et al. (2009) paper resides in PCR as a *complementary method* to the immunohistochemistry, Western Blots,

and cell culture. Outside of this assemblage of techniques, its authority is undermined (Mikovits et al. 2010a). As one researcher stated:

> All of these studies are focused on primarily PCR, and that's not how we classic retrovirologists have identified either of the other two human retroviruses, particularly not HTLV-1, which was so difficult to find . . . So when you use complementary methods as we did, twenty-five, thirty years ago, when we did most of the work in HIV and HTLV-1, we used all of these methods to increase the power of defining not just a simple PCR. (Field notes; comments made during First International Workshop on XMRV. Bethesda, MD. September 8th, 2010)

This devaluation of PCR was by no means universally accepted. Many of the other actors in the controversy contested the claim that PCR was so inadequate a method for the detection of retroviruses,[18] but the issue cannot be cast simply as some actors being "pro" or "contra" PCR. The status of PCR, to what extent it could be relied upon to produce valid evidence was highly variable. The decentering of PCR, for the Mikovits team and others, took on added significance as reports on the risks of contamination multiplied. The papers by Hué et al. (2010) and Sato et al. (2010) called PCR results into question first on the grounds of specificity, finding that some primers supposed to detect XMRV would also amplify trace amounts of contaminating mouse genomic DNA as if it were a genuine XMRV infection, and second when the perceived integrity of the tool itself was compromised by the findings that several commercially available PCR kits were *already* contaminated with viral sequences that bore >96.9% similarity to some of the MLV-like sequences detected by the Alter/Lo lab (Sato et al. 2010). Further studies contributed to the solidification of the idea that in the laboratory setting the success and ubiquity of the mouse as model organism had rendered contamination nigh-inevitable (Oakes et al. 2010, Robinson et al. 2010, Garson, Kellam & Towers 2011, Paprotka et al.

[18] "I think that's a spurious argument. PCR is far more sensitive than co-culture" (Interview with John Coffin. Boston, MA. September 2nd, 2011). See also Wiecek 2011: "These PCR-based techniques are used in all other infectious diseases and used absolutely perfectly, without any controversy . . . You have to rule out an entire area of modern molecular biology in order to support the notion that XMRV is a transmissible human virus." (1).

2011, Knox et al. 2011). The effect of this perceived inevitability of contamination on the evidence-generating power of PCR was, however, asymmetrical. A positive finding was viewed as contamination, a laboratory artefact. Conversely, negative PCR results could be relied upon as always, despite the fact that if contamination was ubiquitous, one should expect similar rates of false positives among healthy controls as well. Controlling for contamination is a routine part of laboratory work, especially when dealing with highly sensitive techniques such as PCR. As contamination concerns mounted, scientists had to go to greater lengths to convince others that they had successfully controlled for it.

The above illustrates what Collins describes as the "experimenter's regress" (Collins 1985). This is the paradox that arises when replication is used as the basis for determining what experimental results are to be trusted, particularly where new phenomena or relationships are being studied. Exact replication of an experiment is impossible, and even near-replication is rare, so there will always be sufficient difference between two experiments for a critic to claim that replication has not been achieved. Because scientific work is a form of skilled practice, Collins argues, the question of whether or not the results are to be believed hinges upon whether the experiment has been correctly performed. However, the only way to judge if an experiment has been properly performed is if it achieves the correct results, and so forth.

In this case, when the Lombardi et al. (2009) paper's results were initially called into question, it was easy to criticize the negative papers for failing to reproduce the methods of the original *Science* paper. This line of argument was pursued throughout the controversy. Max Pfost, a researcher at the WPI and Lombardi et al. 2009 co-author, put it thus:

> The big thing which I started off seeing was the reproducibility. I found that to be a big hurdle. It just it boggles my mind that nobody can just follow the directions. Nobody contacts us and says, "Hey you know what, let me give you a legitimate chance. I want to find this. I want to

> see. I want to try it the way you're doing it. I want to just give this a whirl, if it's there, it's there. If it's not, it's not. (Interview with Max Pfost. Reno, NV. August 10th, 2011)

The implicit response to this, evidenced in the wealth of follow-up papers that used similar but not identical procedures, was that such close replication was not necessary to produce comparable results. This highlights the issue of exact versus generic confirmation – what degree of similarity is viewed as necessary to render results comparable? Alternately, to what extent must a condition of generalizability be met, so that other researchers using roughly the same methodology can make the same observations? If the Lombardi et al. (2009) results were in fact flawed, as critics suggested, the fault may lie precisely in their methods, therefore to reproduce them exactly would be to reproduce error. Coffin, on this topic, makes the comparison to HIV:

> So it's useful to contrast that with what happened with HIV actually, where the first paper that came out actually wasn't very good. It was not as good as this one in fact, not as good as the *Science* paper, the Montagnier paper. But everybody was able to repeat it . . . the issue was not that you couldn't repeat anything. Everybody who looked could find HIV, could find the antibodies in AIDS patients, could isolate the virus, could grow the virus and so on and so forth. (Interview with John Coffin, Boston, MA. September 2nd, 2011)

Initially, several different potential explanations were offered for the discrepant results: (1) The possibility that positive results were due to laboratory contamination (discussed above). (2) The instability of CFS as a disease entity (due to different sets of diagnostic criteria, it was speculated that CFS as a category might constitute a multiplicity of different underlying diseases conditions, not all of which might be an associated with XMRV). (3) Differences in the geographic distribution of XMRV globally, and across the United States. (4) The possibility that XMRV was but one of a number of related viruses that were associated with CFS, and that highly-XMRV-specific PCR primers were failing to detect this diversity. The second and third options were ruled out as further studies were

conducted that covered a broader sample of CFS patients from across the United States, that also produced negative results, in the process mooting the international geographic variability argument (Switzer et al. 2010, Satterfield et al. 2011, Sakuma et al. 2011.). Similarly, while the contours of CFS as a disease entity remain incompletely understood, it was easy for researchers to make recourse to existing standards, such as the CDC/Fukuda criteria, to allow for fairly meaningful comparison of results.

The fourth option, that there may be a larger subgroup of viruses involved, of which XMRV was only one, became a possibility with the publication of the FDA/NIH study by the Alter/Lo team (Lo et al. 2010a). This paper, "Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors," represents a sort of ripple in the experimenter's regress, as it does not precisely present a problem of *replication.* As stated earlier, the Lo et al. (2010a) study did not find XMRV in CFS patients, but did detect a number of related "MLV-like" sequences which, in the authors' words, "clearly support the central argument by Lombardi et al. that MLV-related viruses are associated with CFS and are present in some blood donors" (Lo et al. 2010a: 15878). Although endorsed by the Mikovits team, this interpretation of the "central argument" of the Lombardi et al. (2009) paper was not accepted by all. For many, the evidence reported in the *Science* paper pertained only to the argument that XMRV specifically was associated with CFS. As Lombardi et al. (2009) makes no claims about viruses other than XMRV, the detection of other viral sequences by Lo et al. (2010a) accordingly could not be taken as evidence for the XMRV-CFS association. The Mikovits team and Harvey Alter argued that there was a flexible equivalency between the two studies' findings, while critics, most visibly John Coffin of the NCI/Tufts University, steadfastly denied such an equivalence.

The relationship of the Lo et al. (2010a) paper to Lombardi et al. (2009) as a form of *supporting evidence* is somewhat more complex than that amongst the so-called negative papers, or between

Lombardi et al. (2009) and the negative papers: Each successive negative paper was taken as adding to a cumulative body of conflicting evidence, whereas the contribution of the Lo et al. (2010a) paper must be seen as less *additive* than *transformative.* For in no sense could the Alter/Lo paper be considered an exact *replication* of the Lombardi et al. (2009) study. In order for these two sets of results to be considered mutually supporting, the XMRV-CFS association as originally articulated had to be modified into an "*MLV-related virus*"-CFS association. Expressed differently, the identity of XMRV had to be expanded to include other MLV-like sequences, or, conversely, to be absorbed into the broader class of MLV-like sequences. This question of identity became increasingly complicated over the course of the controversy, and will be explored in greater detail below. Here it suffices to note how the object of the controversy may itself be subject to transformations and deformations throughout, resulting at some points in uncertainties and disagreement about what, in fact, the controversy is actually "about."

The "identity question," and the concerned scientists' approaches to it, are also relevant for our understanding of what attempts were made to break the experimenter's regress, and this highlights a potential shortcoming of Collins' model for these purposes. Collins argues that due to the *interpretive flexibility* of experimental data, "The scientific view belonging to both sides of a controversy can be defended indefinitely, and . . . if debate is to end, it must be brought to a close by some means not usually thought of as strictly scientific" (Collins 1983: 99). The phrase "*means not usually thought of as strictly scientific*" should give us pause. What is meant by "strictly scientific," and as thought of by whom? The claim derives from Collins' broader argument that science operates according to an *enculturational* model, emphasizing the roles of socialization, shared frameworks, and skilled practice based on *tacit knowledge* (forms of knowledge that must be accomplished and acquired through practice, that may be shared or taught, but not fully explicated). In this view science is not a social activity solely in the trivial sense that it is performed by people working together, but in the sense that

scientific knowledge is produced through complex patterns of negotiation, communication and collective consensus that can not be reduced to the formal apparatus of theories and instruments (1985: 56). The argument that something social or cultural, something *extra,* as it were, is required in order to break the regress only makes sense if we are from the outset invested in the idea of science and culture, nature and society, as *a priori* distinct domains. If, on the other hand, we adopt a position which takes nature and society to be co-produced through the activity of the controversy, we may be able to bring different formations to light without being forced to make the meaningless distinction between what kinds of activities are *cultural* and what are *scientific*, or the potentially more problematic but equally useless claim that science is "merely" a cultural activity.

In this case, the scientists involved in the controversy, quite aware of the problem posed by the "experimenter's regress," promoted their own solutions to break the regress that emphasized above all the coordination and standardization of experimental methods, materials, and criteria for the evaluation of evidence. From very early on this was seen as a necessary step. Groom et al. (2010) suggest in their conclusion that "Following the findings reported here, it would seem a prudent next step for subsequent studies to compare samples and protocols between different laboratories around the world" (Groom et al. 2010:8). This was echoed in many of the commentaries and scientific conferences,[19] and was embodied in the formation of the Blood Working Group (SRWG). The ultimate goal of the Blood Working Group was to assess the prevalence of XMRV in the American blood supply, discern whether it was transmissible via transfusion, and if so, whether it posed a health threat. In order to achieve this the SRWG decided to focus its efforts in two main areas: Developing standards for the evaluation of the various tests used to detect XMRV, and facilitating the sharing of clinical samples between laboratories. In their March 2011 report the SRWG wrote:

The discordance [of previously published results] strongly suggested the need for the

[19] Food and Drug Administration 2010; Klein et al. 2010; Kearney & Maldarelly 2010; Silverman et al. 2010; Stoye et al 2010

> development of XMRV analytical reference panels, as well as panels of samples from clinical cases and controls, to be used to validate the performance characteristics of assays for subsequent use to investigate the prevalence of XMRV/MRVs in blood donors and recipients. Thus, the development of XMRV/MRV analytical and clinical panels for characterization of nucleic acid tests (NATs) and serologic assays was identified as a first priority by the Blood XMRV SRWG. (Simmons et al. 2011a: 645)

The SRWG brought together nine laboratories, including those of John Coffin at the NCI, Judy Mikovits at the WPI, Frank Ruscetti of the NIH, Harvey Alter and Shy-Ching Lo of the NIH and FDA respectively, and William Switzer of the CDC, each of whom had played significant roles already in the controversy. The initial phase of the SRWG's research consisted of developing coded analytical performance panels that were used to compare the sensitivities of different assays for XMRV detection across laboratories, in order to rule this out as a source of divergent experimental results. Phase II consisted of a study where each lab tested the same fully blinded samples made up of healthy subjects, spiked positive controls, and patients previously identified as positive, for either XMRV or MLV-related sequences using PCR, serology, or cell-culture, in order to determine whether the available assays were capable of consistently and reliably detecting these viral sequences. To increase the comparability of results, investigators from the WPI and Ruscetti labs, the only parties to date to successfully culture the virus, provided on-site-training to the technicians of the other participating laboratories.

These measures were quite clearly framed as an attempt to address the debate surrounding XMRV: “It is hoped that this series of studies will yield protocols that can be the basis of a set of “gold standard” assays allowing the standardization of tests across laboratories to minimalize the type of controversies thus far seen in XMRV/MRV detection” (Simmons et al. 2011a: 649). However, the work of the SRWG was not explicitly directed at resolving either the issue of XMRV's association with CFS or the problem of identity posed by the Lo et al. (2010a) sequences. Although the ultimate aim was the

safety of the blood supply, on a practical level the SRWG was concerned with regulation, standardization and coordination. The report, presented at the IACFS/ME conference in September 2011, addressed only the question of whether the available assays were adequate for detecting XMRV and MLV-like sequences; by including the sequences of both Lombardi et al. (2009) and Lo et al. (2010a), the broader question of identity was skirted by what could be framed as an inclusive precautionary measure. Nonetheless, the findings that none of the nine laboratories were able to *consistently* detect the viral sequences in samples previously identified as positive was claimed by many as a final blow to the XMRV-CFS association (Cohen & Enserink 2011; Robinson, Erlwein & McClure 2011).

Returning to Collins' claim that "if debate is to end, it must be brought to a close by some means not usually thought of as strictly scientific," it is not clear that the work of the SRWG can be considered outside of the "strictly scientific." A collective, coordinated activity, to be certain, but to what extent does it suggest a specifically *cultural* dimension of scientific work? The role of the SRWG in the controversy may be better viewed as an example of what Cambrosio et al. (2006) have termed *regulatory objectivity*. "Regulatory objectivity" describes a historical modality of objectivity operating within modern biomedicine that, in the space of scientific controversy, refers to the "systematic recourse to the collective production of evidence" (Cambrosio et al. 2006). It is characterized by inter-laboratory coordination and an emphasis on the endogenous generation of guidelines and standards, a process in which scientists engage in a highly reflexive manner. This is to say that the actors involved are both cognizant and critical of the conventional character of their practice. Decisions about standards are made with an eye to anticipating what will work at least in the short term, and facilitate the coordination of future research. The SRWG seems to embody just this phenomenon, but while the work of the group explicitly served a primarily regulatory function – the production of standards for detection assays and samples – it also had the effect of producing an epistemic judgement. The results

of the SRWG validated prior concerns about the reproducibility of Lombardi et al. (2009) results, rendering the XMRV-CFS association less *real* in the process. It did not do so by providing a replication of the original Lombardi et al. (2009) study, but by incorporating elements thereof (pursuing detection by PCR, serology, and virus culture, and incorporating the skilled practice of WPI/NCI technicians), within a new framework (standardized samples, spiked positive controls, testing in parallel) that in a sense mooted the requirement for exact replication of earlier results. The epistemic *side effects* of this regulatory activity have not gone unchallenged. Commenting on this, Mikovits has stated that "The conclusion of the Blood Working Group was that we don't have reproducible assays to detect XMRVs in the blood – not that they weren't in the patients at all" (in Cohen & Enserink 2011:1695), but this has not made an appreciable difference in how the SRWG results have been taken up in contributing to the controversy's closure. While an in-depth analysis of the SRWG as a site of regulatory objectivity is beyond the scope of this paper, it seems to suggest a valuable alternative perspective on the mechanisms of potential closure than that offered by Collins.

Chapter IV: Artefacts and Artefactualities

One of the major questions concerning the XMRV-CFS association was whether the relationship reported was "real" or an artefact. Artefactuality is a concept important both to scientific work and to sociology of science, although it has different implications in each. Within scientific discourse, the distinction between fact and artefact denotes a sort of truth relation – facts are what science deals in, what it aims to uncover or express about the natural world; artefacts are intrusions, sources of confusion, mistakes that must be corrected for. An artefact may be an effect produced by the scientist or the instrument that masquerades as a real part of the phenomenon under study. Or it may be

the product of a deficiency in the experimental system, by which as the result of insufficient controls some element of the natural world interferes, breaching the tightly circumscribed limits drawn around what the scientific activity seeks to observe. Michael Lynch, in *Art and Artifact in Laboratory Science,* writes that "The danger that artifacts are said [by scientists] to present for research is that their presence can go undiscovered and be taken as evidentiary features of purportedly natural phenomena" (1985: 81). The artefact, then, can be seen as a dissembler of authentic results.

Lynch's work is one of the few in the social studies of science that explores in depth the significance of artefactuality as an endogenous or native discourse. Other scholars have addressed the fact-artefact dichotomy in science by noting that, contrary to the scientists' use of the term, the entire field of science's operation and production is in a sense artefactual. Latour points to how facts as well as artefacts are *made* or constructed in the process of scientific work, bringing out a tension in the traditional distinction between facts as pre-existing "out there," and artefacts as of human fabrication. Similarly, Knorr-Cetina emphasizes the artefactuality of the "scientific reality" that is both produced and required by laboratory work. The site of the laboratory is a highly artificial space into which the raw material of nature may enter only by way of extensive preparations that transform it into the material appropriate to scientific experimentation. This artefactual reality in which scientific activity is seen to take place is important for understanding science as a practice of construction, but it has tended to gloss over how the discourse of artefactuality works in actual research settings.

By the end of 2011, following on the results of the SRWG study and the retractions of the Lombardi et al. (2009) and Lo et al. (2010a) papers, XMRV had become widely accepted as a laboratory artefact. The artefactuality ascribed to XMRV, however, was multifaceted and signified different things over time and in within the context of different arguments. For analytic purposes, I will distinguish between the above described "scientific reality as artifact" of the sociologists, and two other modalities of artefactuality that were endogenous to the debate. These can be described as *experimental*

artefactuality (or arte1) – which refers to the sense of an artefact as a false result that is produced within an experimental system, its artefactuality an effect germane to that experimental system and its goals; and *ontological artefactuality* (arte2) – which evokes the somewhat more literal sense of an artefact as an object that has been produced by human work. In this case arte1 has largely to do with contamination concerns, and arte2 with the "Recombinant Origin" theory of Paprotka et al. (2011) that maintained that XMRV as a viral entity was itself produced in the laboratory.

"Arte1" – Contamination and Experimental Contingency

Lynch writes that "The possibility of an artifact is an almost inevitable accompaniment of research which relies on specialized techniques and machinery for making initially "invisible" theoretic entities visible in documentary formats" (1985:82). Thus, in retrovirology the processes of recognition and of distinguishing fact from artefact are complicated by the very technologies and procedures by which microscopic entities are represented. However, the artefact is not merely an excess trace produced by the apparatus, but an object or entity in its own right. The artefactuality of "the contaminant" is not simply a matter of the misuse or misreading of instruments, nor does it reside wholly in the contaminant itself. Rather, it is defined at the intersection of the experimental system, the object, and what the researchers are trying to accomplish. An entity may be a contaminant in one experimental setting and not in another. For example, the Hué et al. paper (2010) described how the 22Rv1 cell line produces high quantities of virus fundamentally identical to XMRV, raising the possibility that even laboratories that had not used 22Rv1 may have received material from other labs where the cell line was used, providing a potential source of contamination. In this case, the contaminant was not an entity "other" than XMRV, but rather was XMRV that had found its way into the samples being tested as a result of their handling in the laboratory, rather than as a genuine infection. XMRV could thus be either a "real" or artefactual result, depending on where it was detected

and from whence it was deemed to have come. In this sense, the artefactuality of a result is contingent on the experimental system of which it is a part.

Another form that contamination could take rested on the *misrecognition* of other murine viral sequences as XMRV. The Hué et al. (2010) and Oakes et al. (2010) papers demonstrated that PCR primers previously believed to be specific for XMRV also amplified many common endogenous MLVs, identifying mouse DNA as a potential source of contamination. It was argued that due to the ubiquity of mice both as preferred sources of laboratory material and highly successful model organisms, along with the difficulty of ensuring that wild mice did not infiltrate laboratory or related settings, the presence of trace amounts of mouse DNA (that harboured endogenous MLVs) could lead to falsely positive PCR results. The Sato et al. (2010) and Tuke et al. (2010) reports that MLV sequences had been found in components of some PCR kits presented the additional possibility that contamination could arise not only from the laboratory environment, but also from the very tools that were employed in order to detect XMRV.[20] Complicating matters further, the Robinson et al. (2010) paper co-authored by John Coffin claimed that the assay that had been used by Switzer (of the CDC) to test for contamination was less sensitive than their IAP (intracisternal A-type particle) assay, and therefore more likely to overlook contamination. The acceptance of the IAP assay as the new standard contributed to the production of an ever-receding horizon for the authorization of positive evidence of XMRV, to which scientists in the debate were not insensitive:

> I don't know, in my opinion the mouse mitochondria one was just as sensitive as Switzer's four probe one, but so be it, we have to go out and get a new instrument, so we can do his little assay. So we do that and then everything comes back clean. And then Coffin decides that, "Oh, Switzer's assay is definitely not sensitive enough because we couldn't detect any mouse sequences there." Because we don't have any, but we detect the positive controls he sent no problem. So then he comes up with this IAP assay which is Intracisternal A Particles, and you

[20] A more recent study headed by Switzer of the CDC additionally found six commonly used PCR kits contained some form of MLV or murine DNA contamination (Zheng et al. 2011).

> start asking yourself how many of these assays do I need to do to prove to you there is no mouse contamination? And you start really looking at it. The first assay that Lo did was just fine, it was sufficient. I can detect down into the picograms. It was so good that I can detect it and titrate it up that far. The sensitivity of assay was great. But then I had to do Switzer's. "All right, fine it's a different type of technique of PCR, let's try that one out" and that one's fine. And then, "Well that's not sensitive enough. Now we're into the IAP."
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> . . .
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> Everything is just contamination and it just -- it constantly changes, and it's brilliant, the strategy that they're going with because no matter what you do, you can't stop contamination. I don't care what it is, I can never prove to you that it's not some form of contamination. (Interview with Max Pfost. Reno, NV. August 10th, 2011)

Similarly, the sequences detected by the Alter/Lo lab were suspected of being contamination, particularly because their paper concentrated on PCR and lacked the additional evidence of the serology and viral culture, which in the case of the Lombardi et al. (2009) paper could not be easily explained as contamination. Further, the study by Oakes et al. (2010) demonstrated that in a randomly contaminated sample, a similar pattern of infection with MLV sequences to those reported in Lo et al. (2010a) could be observed. The rhetorical potency of this claim lay in the graphic device of the phylogenetic tree. The phylogenetic tree is a spatial diagram representing evolutionary relationships between entities as a series of branching lines, demonstrating what entities are descended from which others, and provides a taxonomic organization of species. By mapping where the viral sequences produced by contamination fell on the tree, and comparing these to the positions of the Alter/Lo sequences, an abstract but quite compelling argument could be made for contamination on the basis of a visual similarity between two representations. That intentional contamination *looked like* the results produced by Lo et al. (2010a) operated as a form of evidence that strengthened the contamination argument without having to strictly demonstrate the fact.

With the publication of each of the above papers it became increasingly difficult to prove that

any given lab had successfully controlled for contamination, even though it had not been proven, prior to the Silverman retraction (Silverman et al. 2011) that contamination had occurred in either the Lombardi et al. (2009) or Lo et al. (2010a) studies. Indeed, even as of the Alter/Lo lab's retraction of their paper, the authors maintained that they could not find evidence of contamination, but felt compelled to reconsider based on the inability of other groups to independently reproduce their results (Lo et al. 2012). Nonetheless, by the linking together of the various negative papers on contamination an impression was created of contamination as a ubiquitous and even *inevitable* threat.

It is important to note, however, that contamination was not from the outset a major issue in the debate. The initial wave of negative papers and Technical Comments did not focus on contamination. It was only after Hué et al. (2010) and the deluge of other contamination papers that followed in its wake that contamination came to be viewed as an increasingly likely explanation, and the contaminant an actor in its own right. This is not because contamination was by any means unknown before this point. The high risk contamination posed was considered one of the major hurtles for associating retroviruses with human disease, in part because the extreme sensitivity of methods such as PCR that were required to make elusive retroviral sequences tractable increased the risk of false positives. Early on, contamination was viewed by and large as a risk that could be accounted for by fairly routine protocols. All lab workers were aware of the dangers of contamination as an "occupational hazard," and the layouts and standard procedures (separate rooms, along with independent hoods and ventilation systems for processing and testing of samples, minimizing how often tubes containing samples were opened, rigorous sterilization, re-sequencing of all PCR products) of the laboratory were organized around reducing its likelihood.

As the controversy developed these sets of contamination controls were no longer permitted to remain unspoken or presumed adequate. Increasing scrutiny was directed at experimental practice as the controls were problematized by critics. In the initial *Science* paper only passing reference is made

to contamination; a note about phylogenetic analysis of isolated sequences indicates that it is "unlikely" that the virus XMRV is a contaminant (Lombardi et al. 2009). In Lo et al. (2010a), the issue of contamination is addressed in greater detail, perhaps as a consequence of the paper having been held back to re-check findings in light of the negative CDC paper (Switzer et al. 2010). An entire section of the Lo et al. (2010a) paper is devoted to discussion of the possibility of contamination and the extensive precautions the authors had undertaken. This explicit caution was due in part to the greater similarity of the sequences they had detected to pre-existing endogenous murine leukemia viruses. The authors explain:

> Mouse DNA contains endogenously many closely related proviruses of MLVs. Hence, contamination of the blood samples or reagents by mouse DNA could have produced falsely positive PCR results. Although we took great precautions to prevent potential contamination in the laboratory, and although multiple negative controls were always included in each assay, we took additional steps to confirm that no mouse DNA had contaminated the assays or the clinical samples prepared in this study. (Lo et al. 2010a:15876)

The paper goes on to detail the additional steps. We can see in the above how what initially were treated as mundane, routine practices became over time problematic and highly self-reflexive. What previously had been backgrounded, in effect black-boxed, were made issues by the scientists in the debate: When were standard procedures not enough? Did labs that were not primarily retrovirology labs fail to appreciate the extent of the precautions that were necessary? What additional precautions were necessitated? Under what circumstances could controls be deemed sufficient?

As "the contaminant" became an increasingly significant actor in the controversy, calling into question the adequacy of standard procedures, it began to seriously threaten the status of XMRV itself. The relationship between "the virus" and "the contaminant" has been complex and variable. "The contaminant" is not a single unitary entity, but a collecting-together of many different entities over the

course of the controversy. By times it is derived from plasmid or mitochondrial DNA, at others it is effectively XMRV 'out-of-place' (or in a place to which it does not belong). The ostensible products of contamination may be referred to as a single actor, however, by virtue of how they are placed in a binary opposition with XMRV as a "genuine human infection." While the two were not definitely mutually exclusive, at every turn the strengthening of the reality of the former contributed to a weakening of the reality of the latter. This transferal of reality did not flow in both directions, however. Part of the strength of the contaminant lay in its ability to appear and disappear without compromising its reality, a privilege that was denied to XMRV as it attempted to establish its foothold as a genuine human infection. In this way the contaminant has had somewhat of a *spectral* quality, for the type of effect that contamination has exerted in the debate has been for the most part indirect. Until Silverman's retraction in 2011 of the Cleveland Clinic's contribution to the Lombardi et al. (2009) paper, contamination had been suspected, implied, and suggested, but never confirmed. And yet, it was a criticism that could not be dispelled by Mikovits or other proponents of the XMRV-CFS association, like a ghost that haunted XMRV research.

For XMRV, with every paper that did not detect it the virus receded into a further disputed reality, regardless of the heated debates over whether "absence of evidence" could rightly be taken for "evidence of absence."[21] By contrast, when and where the contaminant was found, evidence for the likelihood of contamination was strengthened, but when no contamination was found, the possibility of contamination did not become less real, it was simply that contamination had not in *that* instance occurred. This asymmetry worked in the favour of the contaminant: as a type of *accident*, the contaminant was not required to always be readily detectable in order to be viewed as something that was authentically out there in the world. I have already noted how the conventional laboratory

[21] It is worth noting that I have only written of artefacts as objects, but not as absences. Lynch distinguishes between *positive* artefacts and *negative* artefacts. A negative artefact is a false absence, where some human, procedural, or instrumental factor in the experiment results in the failure to appear of an expected result or a phenomenon that is actually present. While from the perspective of Mikovits and the WPI team, many of the negative XMRV findings could be viewed as negative artefacts, only one paper published to date (Bacich et al. 2011) makes a specific claim about falsely negative results.

protocols ceased to be seen as sufficient to prevent contamination, but that is only half true, for whenever there were no positive results to be reported, the routine procedures had, by default, proven to be quite adequate. Indeed, despite the seeming ubiquity of contamination, many labs (all of those that reported negative findings) seemed to have no trouble avoiding it. What accounts for this adequacy or the failure thereof? John Coffin provides an explanation of how these various forms of contamination could occur:

> These [22Rv1] cells make a lot of virus. And it's passed all over the world to laboratories that aren't actually virology [laboratories]. Actually, even virology laboratories cross-contaminate cultures, you know virus-producing culture and non-producing culture. That happens all the time. A laboratory that is not virology wouldn't even think that there was the remotest possibility, they wouldn't even consider that. So almost certainly a lot of other cells had been cross contaminated with this virus and that's almost certainly how in the original paper they came to be able to isolate virus from it, and other labs that hadn't worked with the cells and hadn't been connected with labs that had worked with these cells, *weren't* finding it.
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> . . .
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> And until one has a study that's been meticulously designed, the problem with mouse DNA in a sense is worse. Because I visualize what happens is that there is -- well, one of the images I use is you've got a big storehouse somewhere and in the storehouse is a huge pile of sodium phosphate, for example. All right, at night, mice are crawling all over it doing whatever it is mice do, leaving DNA behind. During the day somebody comes in with a nice clean shovel, brings out a shovel full and that goes into the manufacturing process and ends up being in your reagent grade, your biological grade buffer that you use to make your DNA with or to assay your DNA with. Maybe that shovel got a bit of the mouse dropping and maybe it didn't. And so sometimes, so from lot to lot you'll have a huge difference. So you're not using exactly the same lot of the stuff. You may get a different results. (Interview with John Coffin. Boston, MA. September 2nd, 2011)

Another researcher describes the situation thus:

> It's so encompassing, the contamination theory, that everybody is going to assume -- and that's one of the issues about these papers. They basically say "Well, we determined that our reagents were contaminated, therefore contamination's a big concern, therefore all the papers were probably wrong." Well, this doesn't mean that our reagents were contaminated, because we screened our reagents . . . When we do work in this laboratory, we do the standard screening looking for mouse intracisternal A particles, make sure there's no mouse DNA in anything we're dealing with. But no matter what you do people just are not going to accept PCR results anymore. There's always that one chance, you can screen every reagent you got, but there's that one chance that it's going to be in there somehow. . . If you're going to do a positive study on XMRV, I mean it's basically you have to walk on water to be able to get a paper accepted. (Interview with XMRV Researcher. August 10th, 2011)

That none of the scientists could entirely rule out the possibility of contamination gave the contaminant a special evidentiary status in the later days of the controversy. The flexibility of the contaminant constituted for it a strength beyond the empirical: it did not *need* to be proved, because it could not be *disproved.*[22] The ubiquity of contamination and the imperfection of controls were evoked to weaken positive findings, however, in other studies the routine controls were determined to be adequate precisely *because they did not* find XMRV. This slippage depends upon the absorption of the virus into the contaminant, a total transformation of the evidentiary status of the entity XMRV over the course of the controversy. What in 2009 was evidence for a genuine human infection, and potentially an etiological agent for CFS, had by late 2011 become evidence for contamination.

Taking a cue from Knorr-Cetina's description of scientific inquiry as "decision-impregnated" (and decision-impregnating (Knorr-Cetina 1983:120)), we may consider the artefact as it first emerges onto the scene as something "not decided upon," that interrupts or impinges upon the carefully ordered experimental system. At this point it is elusive, its relations to other actors uncertain. Lynch writes of

[22] Technically, the situation was not quite so Kafkaesque as this, and much faith was placed in the Blood Working Group study to provide an organizational framework for independent verification: "[The SRWG] is really the acid test for this. That's what Judy has to do. She has to show that she can, with completely blinded samples reproducibly detect the patient's samples and reproducibly find and isolate XMRV. And so that that will iron itself out, it's just in the process that we're doing so right now" (Interview with John Coffin. Boston, MA. September 2nd, 2011).

artefacts as moments of *trouble* in scientific work, where routine practice becomes conspicuous, confounded and confounding. This trouble must be dealt with or resolved; in effect, decided upon. In the case of XMRV, this did not mean simply incorporating the artefact into the existing understanding of what was under investigation – the incorporation of the artefact here modified the terrain of the debate, and other entities along with it. What began as spectral and potential, was over time (and not time alone, but extensive research and debate) solidified as the contaminant became the default explanation for the appearance of XMRV, and XMRV-as-genuine-infection consigned to non-reality, the most recent addition to the many proposed aetiological agents in the history of CFS. The role that the contaminant plays in the controversy can be said to be temporally modulated; it initially introduces uncertainty into the work of scientists (not to mention patients, bureaucrats, health practitioners, public health bodies, medical technology companies, etc.), but as it gains strength, absorbs and displaces the virus, and is *decided-upon*, it in turn becomes a producer of stability, and as such, *decision-impregnating*. Decisions about blood safety, the reliability of PCR, treatment of CFS, may thereafter be made in reference to the artefactual XMRV, as opposed to its potentially pathogenic antecedent.

"Arte2" - Recombinance, Difference and the Ontological Boundaries of XMRV

The second modality of artefactuality, *ontological artefactuality*, refers to an object that is the product of human work, as opposed to a naturally occurring phenomenon. According to the study published in *Science* by Paprotka et al. in the Spring of 2011, XMRV arose over the course of a series of genetic "recombination events" that occurred during the passaging of a prostate cancer xenograft through nude mice in the mid-1990s. The virus was postulated to be comprised of material from two pre-existing murine proviruses that came together in the laboratory, rather than a naturally-occurring or "wild-derived" viral entity. The paper "Recombinant Origin of the Retrovirus XMRV" was the product of two separate lines of research. It had previously been found that a commonly used prostate cancer

cell line, 22Rv1, was infected with XMRV and produced high quantities of the virus (Knouf et al. 2009). Researchers had assumed that the cell line had been grown using material from an already XMRV-infected prostate cancer tumour, which would have been consistent with the postulated association between XMRV and prostate cancer. A research team at NCI Frederick led by Vinay Pathak, trying to trace the origins of the virus, screened a number of passages of the xenograft (samples from different mice used to perpetuate the cell line over time) used in the production of 22Rv1 for evidence of XMRV. The group found that while XMRV was present in many of the late passages of the xenograft, it could not be found in the earlier (pre-1993) passages. What was detectable in these earlier passages was a murine provirus (an endogenous MLV) that was *partly* identical to XMRV, in that it had long stretches of similarity to XMRV, but in other areas differed substantially. Independently, Oya Cingöz, a doctoral student in John Coffin's lab at Tufts University, had been working on assays to search for endogenous proviruses in mice that might be ancestral to XMRV. The project was motivated by the generally held belief that XMRV had at one point been an endogenous virus in mice, that had somewhere along the line "jumped species" and begun to infect humans. In pursuing this investigation, Cingöz screened a number of different species of mice but was unable to find any provirus that genetically matched XMRV. Like the NCI team, however, she was able to detect an endogenous MLV that contained a long stretch of genetic sequence that closely matched a portion of XMRV, albeit not the same portion as had been identified by the Pathak lab.

Taken separately, these findings would not have been of major significance, but via John Coffin (who worked for NCI Frederick as well as Tufts University), who had access to the results of both groups working on XMRV, the findings were juxtaposed and it was noted that the two partial sequences were complementary. When taken together, these two viral sequences, now renamed PreXMRV-1 and PreXMRV-2, provided a complete genome that was almost identical to that of XMRV. From which it was postulated that at some point over the course of the numerous passagings of the xenograft, through

series of genetic crossovers, the virus XMRV had been produced. This origin story explained why in passages prior to 1993, both PreXMRV-1 and PreXMRV-2 were detectable, but not XMRV, which could only be detected in the late passages, after 1996. It was further claimed, on the basis of phylogenetic analysis, that all strains of XMRV that had been sequenced to date were descendent from this original laboratory artefact.

XMRV-as-artefact in this second sense can be seen as an of *excess* of the experimental system, albeit in a manner very different than could be said of the contaminant. The contaminant is an excess of the "PCR testing of CFS patient blood samples for XMRV" experimental system, whereas the recombinant emerged from a particular manifestation of the "nude mice-passaged prostate cancer cell line xenograft" that was distributed across numerous labs over several years.[23] While produced by this experimental system, the artefactuality of the recombinant is not contingent in the same way as has been described above for the contaminant. The status of XMRV-as-contaminant is locally specific, depending on its appearance in a particular experiment with particular aims (arte1), whereas this second type of artefactuality resides in the entity itself, as it has literally moved beyond the context of its experimental origin (arte2). XMRV-as-recombinant remains an artefact wherever it goes, to whomsoever it presents itself, and this was a problem for those attempting to establish the association between XMRV and CFS. The artefactuality of XMRV effectively severed any tentative causal association between the virus and CFS by positing a date of origin a full decade later than the clinical definition of CFS. While advocates of the XMRV-CFS association had always been careful not to make causal claims, the redefinition of XMRV as a laboratory artefact was felt as a significant challenge to the "reality" of XMRV as an entity.

The significance of this ontological artefactuality must be situated in the broader context of

[23] The story of the HeLa cell line parallels that of XMRV in several ways – both entities *are* ontological artefacts and *operated as* experimental artefacts. Each proved to be sources of contamination well beyond what had previously been imagined, resulting from the widespread sharing of cell lines between laboratories. A key difference is that HeLa was an intentionally created artefact, that, unlike XMRV, was never believed to be a pre-existing natural object. For an account of the HeLa cell line, see Hannah Landecker's *Culturing Life: How Cells Became Technologies* (2007).

debates over *identity* in the controversy and in the field of virology as a whole. Since the late nineteenth century, when viruses were defined in a class unto themselves distinct from bacteria, viruses have been matters of great debate within the medical and biological sciences. The question not only of what are viruses, but how to distinguish, identify, classify, and organize them has been complicated both by the transitivity of viruses as natural objects, and the persistent difficulties involved in their representation as scientific objects. Changes in the apparatuses by which viruses have been materialized (or translated from theoretic to material entities) have been accompanied by major shifts in how viruses have been drawn both conceptually and as physical entities. Their high rate of mutation/reproductive infidelity, 'borrowing' of host genetic material, and inter-viral genetic recombination have proven very challenging for the elaboration of a stable taxonomy, and both "species" as a grounding for taxonomic identity, and even the coherence of the larger category of "virus" have been called into question. Regulatory bodies and indexes such as the International Committee on Taxonomy and Viruses (ICTV), or the National Library of Medicine's *Medical Subject Heading* (MeSH) thesaurus provide classifications that are usable and at least temporarily stable, if so at the cost of being somewhat arbitrary (Bowker & Starr 1999), but despite such efforts at standardization, the identification, naming and classification of viruses remains a controversial and somewhat *ad hoc* affair, as is born out by the XMRV controversy.

Despite such efforts at standardization, the identification, naming and classification of viruses remains a controversial and somewhat *ad hoc* affair, as was born out by the XMRV controversy. The "HGRV turn" of the Mikovits team became a central problematic of the debate that could not be reduced to semantics alone. It is difficult to determine when precisely the term "HGRV" began to be used, as it does not appear in the journal literature, and the scientists interviewed were vague in their recollections.[24] In a short video released in August of 2010 on the WPI website, Judy Mikovits

[24] A keyword search for HGRV in PubMed, the United States National Library of Medicine database, at the time of writing yielded 0 results, compared to 249 for XMRV. The term HGRV has, however, been taken up among some members of the CFS patient and advocacy community who have been following the XMRV-CFS debate.

suggested that XMRV belongs to a "family of viruses" that may be involved with CFS, which she describes as "human gammaretroviruses."[25] By April of 2011, at the NIH State of Knowledge Workshop on CFS, discussion of HGRVs figured prominently, and in September of 2011, the term was included in the title of the IACFS/ME conference panel "The Case For and Against Human Gammaretroviruses in CFS." The adoption of the term, however, remained controversial:

> We believe some of the recent media coverage about XMRV has suffered from an issue of nomenclature. In the past, we have used "XMRV" to mean viruses with sequences similar to the virus reported by Urisman et al. in 2006 to be present in prostate cancer tissues. However, "XMRV" has come to mean only the sequence of the virus molecularly cloned (but not isolated) in 2006 and the nearly identical viruses that have been found in some cell culture lines. In order to clarify WPI's position on future research on gammaretroviruses, we plan to refer to gammaretroviruses that may infect humans as "HGRVs", human gammaretroviruses. (Unpublished press release: "WPI Response to Media Reports on XMRV in CFS/ME"; personal communication with Judy Mikovits, September 26th, 2011)

> First of all, clarification of nomenclature. XMRV refers to the virus that was detected in prostate cancer samples in 2006, and then again in blood samples from CFS patients in 2009 - with those exact crossover events. To be able to call it XMRV, it should have all six crossovers, and the same genetic sequence - *that's* what XMRV is. Only after the controversial papers started coming out did the WPI change the nomenclature to say "Oh, we didn't just find XMRV, we found human gammaretroviruses," which was a little strange because they never showed the presence of any other gammaretrovirus to start with, all they ever detected was XMRV. (Interview with Oya Cingöz. Boston, MA. September 2nd, 2011)

On the face of it, "human gammaretrovirus" seems simply a broader taxonomic term than XMRV (the family *retroviridae* is broken down into six genera, of which gammaretroviruses, the genus to which XMRV belongs, is one). The HGRV turn, however, was part of a dispute over both how

[25] "Judy Mikovits Reacts to Alter/Lo Paper" http://www.youtube.com/watch?v=9ZEwQUg7o6I from http://www.wpinstitute.org/news/news_current.html, retrieved 12/12/2011.

XMRV was to be defined, and who was legitimately in a position to do this defining, with major implications for how past research was to be evaluated and future research pursued. Specifically, HGRV represented a challenge to the status of VP62 as the “reference sequence” for XMRV, that in the process reformulated what the object of the debate was taken to be. We can describe this challenging of VP62 as a form of resistance to the "Recombinant Origin" theory of Paprotka et al. (2011). While the “series of recombination events” scenario described in the paper was not directly disputed by the Mikovits team, they contested the implications and generalizability of the authors' conclusion that “because the probability that the same recombination event could occur independently by random chance is essentially negligible, any XMRV isolates with the same or nearly the same sequences identified elsewhere originated from this event” (100). In other words, they did not attempt to deny the reality of the artefact, but rather to dislodge it from its position of centrality for the definition of XMRV.

The relationship between XMRV and VP62 illustrates the complexity of matters of virus identity. It is not that VP62 “was” XMRV in the exhaustive and exclusive sense of total identity; rather, as one of the first and best-characterized XMRV sequences identified in the Urisman et al. (2006) prostate cancer study, VP62 served as a point from which degrees of difference could be measured. It is these degrees of difference (or alternately, of similarity) that constitute XMRV as an object that is simultaneously multiple but may be spoken of and treated as singular. Exact identity in viruses is extremely rare, and because of the comparatively small amount of genetic material that comprises a virus, minute differences can be major differences for species identification. Early on in the debate, Coffin and other scientists began to use the term “consensus XMRV,” which described the collection of sequences that thus far had been agreed to comprise XMRV. These included along with VP62 the two other Urisman et al. (2006) sequences (VP35 and VP42), the two sequences from the Lombardi et al. (2009) paper (WPI1106 and WPI1178), that found to be produced by the 22Rv1 cell line (described in

Knouf et al. 2009), and later the recombinant described by Paprotka et al. (2011). But the term "consensus XMRV" was misleading in that while there was general agreement that these seven sequences qualified as XMRV, it was not universally accepted that these were the *only* sequences that qualified, nor that VP62 should serve as the point of reference. Virus identity here represents a *containment* of difference, rather than its exclusion, which raises the question: What is the difference that makes a difference? There are, of course, types of similarity and difference that make more of a difference. But when, and to whom, and how is this decided?

In the original *Science* paper, the referent status of VP62 was taken for granted, as the Mikovits team attempted to establish the equivalence of their results to those of Urisman et al. (2006):

> CFS XMRV strains 1106 and 1178 each differed by 6 nt [nucleotides] from the reference prostate cancer strain XMRV VP62 . . . Thus, the complete XMRV genomes in these CFS patients were >99% identical in sequence to those detected in patients with prostate cancer. (Lombardi et al. 2009:587)

Mutations are common during viral replication, and the six nucleotide difference between the CFS and prostate cancer sequences was seen as not significant. In 2009, affirming the identity of the CFS XMRV sequences with those of prostate cancer XMRV was a necessary move to strengthen the foothold of XMRV in the world. For at that time the prostate cancer sequences embodied the extent of XMRV's existence. By the time of the "Recombinant Origin" paper by Paprotka et al. (2011), however, this association had become a liability. Close similarity conferred artefactuality. The Mikovits team and the WPI had since the publication of the Lo et al. (2010a) paper attempted to distance themselves from XMRV thus defined, emphasizing the possibility that other "variants" could play a role in human disease. The centrality of VP62 to the definition of "consensus XMRV" was declaimed by some as a dogmatic restriction that had been imposed on the field by a small group of researchers:

> This is the first time it's ever happened in human retrovirology that we've defined a virus based on a single sequence that *he* [John Coffin] calls XMRV. I mean, *we* call XMRV xenotropic MLV-related virus, that means *any* xenotropic virus that is infecting human cells. (Field notes; comments made during State of Knowledge Workshop on CFS, Bethesda, MD, April 8th, 2011)

This decentering of VP62 may be seen as an attempt to retrieve or retain a non-artefactual identity for XMRV, by redrawing the ontological boundaries of the virus. Effectively this was an argument for a subgroup of variants that were *more different* from VP62 than the sequences held to make up consensus XMRV, although still distinct from the previously reported MLV-like sequences of Lo et al. (2010a), that were also collected under the HGRV umbrella. Several of the WPI researchers interviewed tended to de-emphasize XMRV proper, and even suggested that some of the sequences detected in the original Lombardi et al. (2009) paper may have been variants unrelated to VP62.

The critical response to the variants arguments took two forms. While the possibility that another gammaretrovirus could play a role in human disease was allowed, recourse was again made to the hierarchy of methods of detection: in order for any variant to become a real possibility, it would be necessary to isolate the full virus, as had been done in the original Lombardi et al. (2009) paper, rather than just providing partial sequences by PCR, which were all that had been supplied to date. The insistence upon a group of hypothetical variants, to Coffin, remained unfounded:

> But then they're talking about all endogenous MLVs, if that's what they're saying. What's XMRV? I mean XMRV is a virus. If you isolate another virus that we can discuss what to call it but there is no other isolate. There is no other virus isolate. So there's nothing to call it . . . And to call these other things viruses until you have that virus, it just doesn't make any sense at all. (Interview with John Coffin. Boston, MA. September 2nd, 2011)

It was further argued that none of the supposed variants that had been posted to GenBank[26] were

[26] GenBank is an online, open-access database of genetic sequences maintained by the National Center for Biotechnology Information (NCBI).

substantively different from what been established as XMRV. Again, the "the difference that makes a difference" proved to be ambiguously defined and not widely agreed upon:

> The short answer is that there is no set percent cutoff value in terms of sequence identity, and the assessment also depends on how closely other members of a certain virus family are related to each other. In case of XMRV and other MLVs, because the sequences are so similar to start with, the expected percent identity should even be higher to be able to differentiate it from other MLVs . Also, the problem with the later WPI sequences, those they claimed to reflect sequence variation in patient isolates, was that they were not full length viral sequences, they only represented a very short section of the entire viral genome, which was not enough to assess its actual origin. For instance, some MLVs can have long stretches of identical sequence in certain regions of the genome, but differences in other parts allow us to differentiate them. These ones looked exactly like XMRV. (Oya Cingöz, personal communication, January 3rd, 2012)

As such, the difficulty became for the variants to distinguish themselves as sufficiently non-identical to VP62 to escape its infectious artefactuality, while at the same time qualifying as XMRV. XMRV could, through HGRV, be redeemed as a genuine human infection if researchers were able to provide strong enough evidence of variants that could not be traced ancestrally back to VP62.

The revelation of the ontological artefactuality of XMRV had a curious effect on the controversy. The "Recombinant Origin" theory was widely interpreted as support for the idea that positive results must be due to contamination, rather than genuine infection, even though nothing in the former necessitated the latter. This illustrates the persistent effect the question of causality exerted over the debate, however often it was disavowed as an explicit claim. Once ruled out as a causal factor in CFS, the prospect that XMRV-as-artefact could still be a genuine infection was quietly dispelled.[27]

[27] Research demonstrating that XMRV was highly vulnerable to human immune response contributed to the belief that XMRV was not a viable human infection (Paprotka et al. 2010), which minimized concerns about the potential ramifications of accidentally and unknowingly creating a retrovirus in the laboratory. Thus the unintentional generation of retroviruses in the laboratory was normalized as a common and unremarkable, if sinister-sounding, occurrence. From the opposing perspective, however, such research completely elided consideration of the very immune deficiencies commonly found in CFS patients.

What is most striking is how the entity XMRV was changed by this development. Before the Paprotka et al. (2011) paper, XMRV was a virus that could be believed to have existed in the world as a "natural" non-artefactual object. Prior theories as to its origins suggested that, due to its similarity to other MLVs, it had likely been an endogenous mouse virus that had 'jumped' the species boundary and begun to infect humans. After the "Recombinant Origin" paper the virus became the accidental product of human work, with a delimited life span and biography. This process could be written as the transformation of a natural object into a technological artefact, but it is also a blending of the two, as the artefactuality of XMRV does not preclude its being a natural object from the point of its origin onward. This type of ontological artefact is not essentially different than a virus that arose through recombination in the wild as opposed to a laboratory, and so its artefactuality does not constrain its future use as a potential source of information about retroviruses. In this way XMRV is simultaneously fact and artefact, in the jargons of both the natural and the social scientist.

Conclusion

In this paper I have examined the controversy over the XMRV-CFS association in terms of the "experimenter's regress" model provided by Collins, and demonstrated the shortcomings of this approach for capturing the most salient qualities of the process of the controversy's closure. I have proposed instead that the coordinated, pragmatic, standard-oriented activity of the Blood Working Group represents an example of "regulatory objectivity" at work. The treatment of the controversy's closure as a *fait accompli* here may prove to be premature, although this conclusion merely reflects the prevailing state of the scientific literature and the opinions expressed by many of the scientists involved. The largest XMRV-CFS study to date, the Lipkin study, is ongoing, and it remains to be seen

whether its results will reaffirm the growing consensus or reignite the controversy by interfering with the black-boxing of XMRV's artefactuality.

The issue of artefactuality has been central to the XMRV-CFS controversy, and has proven useful to illuminate the intersection of epistemology and ontology in the highly technologically-mediated representational spaces of retrovirology and microbiology. The two types of artefactuality I have discussed – *experimental*/*arte1*/*contamination* and *ontological*/*arte2*/*recombinance* – are distinct yet intertwined, and this is significant for the stability of the controversy's closure. However convincing the argument of the Paprotka et al. (2010) paper, it could technically be confounded by the detection and isolation of XMRV from a sample that predated the postulated recombination events. Evidence such as this would again rewrite the history of the virus as a natural, non-artefactual object. XMRV-as-ontological-artefact (arte2) is in a sense protected by the success of XMRV-as-experimental-artefact (arte1), for so long as it is understood that XMRV is not a genuine human infection, such evidence that would contravene the "Recombinant Origin" theory can be dismissed as the result of the contamination that has been shown to so widely occur. The two types of artefactuality are mutually reinforcing, in that since XMRV has been determined to have originated in a lab in the mid-1990s, therefore any XMRV detected from a sample predating 1993 by default *must* be contamination, for XMRV is believed to have been non-existent at that time. As such, the resolution that "XMRV was discovered to be an artefact" does not suffice as an explanation of the controversy's closure; only by unpacking the multiple meanings and uses of artefactuality endogenous to the debate can we describe with proper nuance how the fact of XMRV's artefactuality was produced.

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