Inferring an Autovirulent Epigenetic Etiology for the Autism Spectrum and Schizophrenia

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A commentary on and analyses of three contemporaneous co-citations:

- Daniels, J. L., Forssen, U., Hultman, C. M., Cnattingius, S., Savitz, D. A., Feychting, M., and Sparen, P. **Parental Psychiatric Disorders Associated With Autism Spectrum Disorders in the Offspring**, *Pediatrics* 2008; 121: e1357-e1362.
- Singer, H. S., Morris, C. M., Gause, C. D., Gillin, P. K., Crawford, S., and Zimmerman, A. W. **Antibodies against fetal brain in sera of mothers with autistic children**, *Journal of Neuroimmunology* 2008; 194, 165-172.
- Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., Nord, A. S., Kusenda, M., Malhotra, D., Bhandari, A., Stray, S. M., Rippey, C. F., Roccanova, P., Makarov, V., Lakshmi, B., Findling, R. L., Sikich, L., Stromberg, T., Merriman, B., Gogtay, N., Butler, P., Eckstrand, K., Noory, L., Gochman, P., Long, R., Chen, Z., Davis, S., Baker, C., Eichler, E. E., Meltzer, P. S., Nelson, S. F., Singleton, A. B., Lee, M. K., Rapoport, J. L., King, M-C., and Sebat, J. **Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia**, *ScienceExpress* Reports (Published online March 27 2008; DOI: 10.1126/science.1155174).

Key Words: Logistic Reasoning; Logistic Intelligence; Autovirulent Factors; Autism; Schizophrenia; Autotoxicity; Autotoxins; Autovirulence; Autovirions; Context-Specificity; Infectiousness; Transmissibility; Epstein-Barr Virus; EBV; Adenovirus; Hyper-endemic; *De Novo* Mutations; Autoimmune; Evolution; Etiology; Pathogenicity; Science; Philosophy of Science; Parsimony; Ockham's Razor

Abstract

Ethnomethodology teaches that disciplines have specific 'ways of knowing'. Logistic reasoning (LR) is a dynamic, interdisciplinary approach to question-asking, question-answering, inferential reasoning and problem solving that, on occasion, may be at variance with disciplined inquiry. Of these approaches, the seminal importance of question-asking often is overlooked, though it is deemed essential because the ways questions are framed could be crucial regarding how those questions are answered. LR also represents a novel form of meta-analysis in which mathematical logic is combined with assessments of numerous (*and sometimes contemporaneous*) qualitative and quantitative findings. During the early-1980s, LR gave rise to a notion of autovirulence; to wit, transmissible and infectious secondary particles (i.e., often small-RNAs) contributing to epigenetic disorders. LR now

suggests counterintuitive (albeit interdisciplinary) autovirulent etiologies for the autism spectrum, schizophrenia and a plethora of other neuropsychiatric disorders. Epigenetic consequences of stress-induced Epstein-Barr virus (EBV) autovirulence (associated with the transmissibility, infectiousness and pathogenicity of its two small-RNAs) *effectively* modify the genetic code. Molecular mimicry, cancers, autoimmune, and psychosomatic and psychoneuroimmunologic disorders are typical outcomes. Depending on titers of autovirulent secondary particles and fetal developmental cycles, their congenital (i.e., *in utero*) actions in the pregnant female can give rise to aneuploidies (e.g., mosaic Downs syndrome) and the autism spectrum. These findings challenge traditional methods, approaches and perspectives in genetics, genomics, infectious diseases, and other disciplines and professions. The LR approach also establishes parsimony in seemingly disparate reports, reveals new pathogenic biohazards, and points to experiments which should and should not be undertaken. Most important, LR provides a lens and roadmap for viewing and understanding roles of stress in the formation and alteration of attention, long-term memories (LTM), beliefs, consciousness, reality, 'common sense', cognitive and social behavior, and consequences of war, terrorism and catastrophes – including stress-activated and post-traumatic consequences surrounding events associated with September 11, 2001, the December 26, 2004 tsunami, the "financial meltdown" in late-2008, and a 2008 war and conflagration between Israel and Palestinians in the Gaza (Smith, 2009a; Smith, 2009b). Taken together, this report uses meta-analyses of contemporaneous (co-cited) findings in order to present compelling arguments for *anticipating chaos* and for advocating a novel form of *pathogen analysis.* The latter is a GPS-like discipline going beyond pathology and *gedanken* studies. It is directed toward comprehensive studies focused on logistic and anticipatory reasoning, reverse engineering, and understanding causes, faults, errors and consequences of transmissible and infectious pathogens. Pathogen analysis is akin to fault, error and tolerance studies in engineering (e.g., understanding why a bridge collapses or an aircraft crashes). Regarding the need to anticipate chaos, our findings reveal a need for ongoing and long-term *Global and National Stress Surveillance Projects* deploying anticipatory and look-ahead chaos and catastrophe detection tools that are metaphorically and analogically akin to GPS.

Background

Smith (1983) observed that research in the life sciences often is characterized by *descriptive-structuralism* (DS) approaches whereas research in physical, computer and information sciences is characterized by *heuristic-functionalism* (HF) approaches. Logistic reasoning (LR) then was introduced to fill a void created by discoveries that dynamic changes in DNA in brain are the likely repositories of long-term memories (LTM). DS did not allow for major upheavals in one's overall perspectives on the sanctity of DNA in all cells, genes, evolution or a need for alternative classificatory schemes. Although more versatile than DS, HF still was limited insofar as dynamic changes in DNA in brain represented too great a fundamental paradigm shift.

This discovery about LR could be inferred from characteristics of 'slow' and lentiviruses which, without exception, are associated with dementia in brain and immune dysfunctions (Smith, 1979). With the 1981 discovery of HIV and AIDS (i.e., an "immune dementia"; cf. Smith, 1979), it was evident that none of the traditional disciplines provided adequate tools for explicating underlying issues and phenomena. Indeed, HIV/AIDS – once an emerging infectious disease – now is a chronic infectious disease, in part, because disciplined inquiry has fallen far short of expectations.

'Switching gears', global positioning systems (GPS) rapidly are becoming everyday tools used in charting and navigating diverse geographic terrain. GPS employs look-ahead, anticipation, feed-forward and feedback, hazard and error detection and correction, and a variety of other techniques aimed at assuring that progress is accurate, safe, timely and relatively error-free. LR and logistic intelligence (LI) are GPS-like mental and meta-analysis tools developed by Smith between 1979 and 1983 for use in charting and navigating disciplines and scientific landscape (Smith, 1979; Smith, 1983; Smith, 1984). The initial challenge was to explicate and "debug" the molecular basis of LTM inferred from associations between 'slow viruses' and dementia (Smith, 1979). A 1979 application of LR and LI accurately anticipated the onset of AIDS (first reported in 1981) and the transmission and spread of bovine spongiform encephalopathies (BSE; first reported in the mid-1990s). LR subsequently was used to demonstrate associations between Epstein-Barr virus (EBV) and the epigenetic production of acid-labile α-interferon in early case reports of HIV/AIDS (DeStefano et al., 1982; Smith, 1984; cf. Preble et at., 1982), associations between EBV secondary small RNA particles with Kaposi sarcoma (Smith et al., 1984a; Smith et al., 1984b), and to disambiguate and chart crucial distinctions between the evolution of HIV (which is associated with the changing dynamics in microheterogeneity in HIV) and the evolution of AIDS (which is associated with an "island" effect; Smith, 1989; Smith, 1994). LR also revealed reasons for failures in attempts at crafting neutralizing vaccines against HIV in contradistinction to successful neutralizing circumventive vaccines against opportunistic pathogens in AIDS (Smith, 2001; Smith, 2006c; Smith, 2007), as well as probable causes of failures in several gene therapy experiments (Smith, 2001; Smith, 2006a; Smith, 2006c; Smith, 2007).

LR and LI are important meta-analytic tools, though going well beyond traditional meta-analysis methods. Typically, meta-analysis combines or aggregates results from numerous studies in order to assess some statistical hypothesis, increase sample size, improve statistical power and effect size, and/or control study characteristics. Meta-analysis generally has not been used to assess contemporaneous issues. Nor has meta-analysis been used extensively in disambiguating controversy. Most important, because of its traditional emphasis on statistical issues, meta-analysis generally ignores issues of mathematical logic and critical reasoning.

Perhaps the most interesting meta-analytic application of LR occurs in determining the "cause" of AIDS. Although many scholars are convinced that HIV is the sole cause of AIDS (cf. Commentary, 2000; Ramatlhodi, 2000/2008; Prusiner, 2002; Dugger, 2008; Chigwedere et al., 2008), in

actual fact AIDS is caused by HIV *and selected nascent ("opportunistic") pathogens*. And, not all pathogens are "opportunistic"! This only becomes evident after invoking two *axioms* from sentential logic (i.e., Modus Ponendo Ponens and Modus Tollendo Tollens). Those axioms suggest that the offending lentivirus (i.e., HIV) *and relatively rare opportunistic pathogens* are causes of lentivirus disease, and not the lentivirus alone, *and not any relatively common isolated pathogens*[1] (Smith, 1983; Smith, 1984; Smith, 2005). These axioms also teach a need for and the value in categorizing both relatively common and relatively uncommon pathogens *within specific regions* (i.e., environmental locales). Controversy concerning President Thabo Mbeki's claims about presentations of AIDS in the USA in contrast to presentations of AIDS in South Africa led to the ill-conceived Durban Declaration whereas the significant underlying issue was the distribution of opportunistic pathogens within South Africa in contrast to other regions, worldwide (cf. Commentary, 2000; Smith, 2001).[2]

It should not escape one's attention that applications of these two axioms in sentential logic also should contribute to one's understanding of failures in attempts at making vaccines against HIV. Any traditional meta-analysis of vaccine data suggests that attempts at crafting vaccines against HIV have been and will be dismal and uniform failures. Statistical studies alone provide convincing evidence that "null hypotheses" (i.e., that some vaccine against HIV is effective based on any and all sorts of evidence) repeatedly have never been rejected.[3] Perhaps more important, mathematical and logical analyses of molecular biological reasons underlying lentivirus microheterogeneity reveal the poor likelihood that vaccines could ever be crafted against lentiviruses *per se* (cf. Kawashima et al., 2009). That same logic (though focusing on Modus Tollendo Tollens) suggests that vaccines against relatively uncommon pathogens within a region can effectively vaccinate against disease (e.g., AIDS) by circumventing the *trans*-

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[1] One is reminded that there presently are no reports of polio being opportunistic in AIDS. A presumption is that polio vaccines, when administered prior to HIV infections, effectively immunize against AIDS by circumventing the activation of HIV. One also is reminded that pathogens associated with measles, mumps, rubella and chickenpox generally are not opportunistic in AIDS in adults if those adults had childhood exposures to either the disease or its associated vaccines. This cannot be said of children exposed to HIV prior to these diseases or vaccines; to wit, those pathogens are opportunistic in the HIV-infected child. Not surprisingly, these findings also are broadly parsimonious and consistent with recent reports of regional differences in the adaptation of HIV-1 to human leukocyte antigen class I (cf. Kawashima et al., 2009).

[2] Youthnet Children Under the Sun is a 501.(C).3 non-profit USA corporation seeking to establish community-oriented research clinics throughout Sierra Leone. Its initial focus will be to employ local staff in an effort to categorize common and uncommon pathogens in different regions in Sierra Leone. An ostensible goal will be to demonstrate that vaccines against AIDS can be accomplished by focusing on vaccines against relatively uncommon pathogens within a region.

[3] This author knows of more than 50 attempts at crafting vaccines against HIV, all of which were failures and none of which led to the rejection of obvious null hypotheses (<citation ###>).

activation of HIV. [NB: Selected pathogens (e.g., herpesviruses) *cis*-activate HIV and thus will require special attention in regards to vaccines against pathogens that may be opportunistic.]

Perhaps the most ambitious application of LR and meta-analysis pertains to evolutionary issues. A review of thousands of articles on the molecular biology of LTM led to a 'DNA as LTM' hypothesis (Smith, 1979). This hypothesis states that the brain is the repository of changing DNA associated with LTM. When combined with the reported 2001 findings of two human genome projects,[4] there is compelling evidence that changes in DNA in brain represent *a priori* events and the formation of neural networks in brain (i.e., the emergence of axon-dendrite connectivity) represent *a posteriori* events. This application of LR is crucial in the context of this report because constellations of aberrant *a posteriori* functions and consequences previously had never been associated with constellations of aberrant *a priori* molecular products. This was the oversight and deficiency in Smith (2003b).

This report discusses novel uses of LR to disambiguate among microscopic (e.g., disciplinary), macroscopic (e.g., multidisciplinary) and telescopic (e.g., ethnomethodological, philosophy of science, and, inter-, trans- and meta-disciplinary) epigenetic issues and perspectives associated with the EBV in relation to mental disorders. A 2003 report revealed associations among EBV and more than 92 'hit-and-run' and 'beneath-the-radar' diseases, disorders and syndromes (Smith, 2003b). The 2003 report did not consider mental disorders because there never had been any 'index of suspicion' for significant downstream *a posteriori* consequences. This investigator had seen no reports associating EBV with significant mental illness beyond the few cognitive disorders associated with autoimmune and chronic fatigue illnesses. Indeed, the sole basis for any arousal of suspicion in this report was the arrival of three seemingly disparate articles on the same day in late-March 2008 – all 'reeking' of epigenetic and 'signal-to-noise' ratio issues.

Although EBV is common and ubiquitous, this report posits that stress-activated EBV secondary small RNAs (i.e., EBER-1 and EBER-2) not only are transmissible and infectious, they could be parsimonious etiologic factors contributing to the autism spectrum disorders, schizophrenia, a variety of other neuropsychiatric disorders, and other stress-mediated phenomena. Insofar as the putative molecular mechanisms are epigenetic and generalize the prion hypothesis, LR and LI expose ethnomethodological pitfalls and the potential for significant biohazards associated with some autovirulent products. Underlying tools and techniques also underscore the importance of disambiguating signal (e.g., genes and gene products) versus noise (e.g., discoveries of *de novo* mutations, and broad and enigmatic psychiatric clinical symptoms) issues associated with scientific, transdisciplinary and professional terrain.

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[4] See February 2001 issues of *Nature* (Volume 409, 15 February 2001) and *Science* [Volume 291 (5507), 16 February 2001]. For a historical perspective, also see Berg (2006).

Overall, a central objective in using LR and LI is to promote the development and use of "scientific common sense" (SCC) going far beyond classic notions of Ockham's Razor, paradigms, verisimilitude, ill-advised and poorly designed experiments, statistical limitations, and general short-sightedness (Smith, 2007; Smith, 2008). Good SCC requires focus, proceeding along scientific roadways with proper directedness, and, by way of the GPS analogy, avoiding traveling the 'wrong way' along one-way pathways and thoroughfares. At this particular time in history, SCC would suggest a need for global and national surveillance roadways and efforts directed at prospectively documenting and understanding all stress-related illnesses associated with the late-2008 and 2009 'financial meltdown' (Smith, 2009a; Smith, 2009b).

Introduction

There are four objectives in this report. One objective is to posit a seemingly counterintuitive finding that transmission and infection by stress-activated Epstein-Barr virus (EBV) 'autovirulent' (*secondary*) particles can explain the etiology of the autism spectrum and schizophrenia. Insofar as this objective explores inapparent associations among disciplines, diseases and processes, this objective supports an expanded notion of parsimony beyond Ockham's razor.

A second objective is to describe elements of LR (Smith, 1983; Smith, 2006) used in discovering molecular mechanisms associated with EBV and of limitations on Ockham's razor as a principle in parsimony. Based on structural and functional properties of "slow" viruses (including prions) and lentiviruses, LR was used *in 1979* to accurately anticipate HIV/AIDS in the early-1980s, 'mad cow' disease in the mid-1990s, and the vast disparity between proteomic and non-proteomic regions of genomes (Smith, 1979). LR, along with reported properties of several EBV-encoded small RNAs (i.e., EBER-1 and EBER-2), also provided a basis for anticipating a large variety of EBV-related diseases (Smith, 1983; Smith, 1984; Smith, 1989; Smith, 2003b; Smith, 2007; cf. Young and Murray, 2003). LR now may find general utility in discovering new 'hit-and-run' and 'beneath-the-radar' pathogens and processes. It also has value in assessing potential biohazards insofar as autotoxic (e.g., prions) and autovirulent (e.g., transmissible and infectious small RNAs[5]) factors can pose extreme and deadly risks to individuals, groups and populations. One now can speculate about autovirulent factors possibly underlying other illnesses (e.g., amyotrophic lateral sclerosis [ALS, also known as Lou Gehrig's disease]; Guillain-Barre syndrome, Tourette's syndrome; post-polio syndrome [PPS]; multiple sclerosis [MS]; inflammatory and irritable bowel diseases and Crohn's disease (cf. Ma, 2008; Kaser et al.,

[5] Although specific small RNAs allegedly are transmissible and infectious, LR posits that one ultimately must 'rule-out' the transmissibility, infectiousness and pathogenicity of many recently discovered normal and aberrant versions of small- and micro-RNA (e.g., snRNPs, siRNA, miRNA). Most important, the fact that many small- and micro-RNA have normal biological functions does not detract from their potential transmissibility, infectiousness and pathogenicity if they are outside of their normal context. This is the basis for and importance of the term 'context-specificity'.

2008; Clevers, 2009); and, some post-traumatic stress disorders [PTSD]). LR suggests that stress-induced autovirulent mechanisms also provide a lens through which one can view etiologies of unusual stress and psychoneuroimmunogenic dermatologic presentations (e.g., HIV/AIDS associated dermatitis, cold-induced urticaria, eczema, stress-or trauma-induced premature hair-graying known as telogen effluvium, and other dermatologic and autoimmune presentations; cf. Urpe, Buggiani and Lotti, 2005; Wyller, Eriksen and Malterud, 2009). Yet, for practical considerations, this report focuses only on putative transmissible and infectious diseases involving brain and central nervous system (CNS) lesions – including the autism spectrum disorders and schizophrenia.

Third, because autism and schizophrenia are perceived to be largely diseases of brain, it is both necessary and desirable to explicate how transmissible and infectious particles can contribute broadly to neurological, psychological and social pathology. Autism and schizophrenia also are used to explore pathogenicity in the context of womb, brain, CNS, and, ultimately, evolution. Infectiousness, transmissibility, and, occasionally, replicability may have entirely different meanings in these different contexts (e.g., molecular diseases *in utero* and nervous system transmission diseases in brain and the CNS), even though a common and ubiquitous pathogen may be the putative source of underlying disorders.

A fourth objective is to situate LR and LI in a broader context of theoretical, experimental, logistic and applied sciences, on the one hand, and logic, methodology and philosophy of science, on the other hand. These are components of SCC (Smith, 2006c; Smith, 2007; Smith, 2008b) and are deemed to be essential in view of increased complexities in information and the sometimes artificial divisions of labor among sciences and scientists (cf. Editorial, 2008; Abbott, 2008). Indeed, LR and LI reveal unique approaches for resolving the "unnecessary battle" among neuroscientists and geneticists regarding the biology of mental disorders (Editorial, 2008; Abbott, 2008). A novel perspective posits that some issues should be framed in terms of 'signals' (e.g., as in selected genetic diseases) and 'noises' (e.g., as in overwhelmingly epigenetic diseases, enigmatic clinical symptoms and *de novo* mutations). If one uses the metaphor of 'not seeing forests for the trees', diseases which are consequences of autovirulent epigenetic disorders would represent a third alternative. These diseases represent distortions of both forests and trees, and require that one step back to appreciate novel impressions, distortions and consequences of molecular mimicry.

Three seemingly disparate articles provide the initial basis for this report. Daniels et al. (2008) discuss parental psychiatric disorders associated with their offspring who have disorders on the autism spectrum. Singer et al. (2008) recently reported antibodies against fetal brain in sera of mothers whose children are autistic, further affirming an earlier finding of maternal antibodies in infantile autism (Warren, Cole et al., 1990). Although Walsh et al. (2008) reveal "rare" and "*de novo*" variants associated with schizophrenia, a member of the Walsh team previously had reported *de novo* mutations associated with autism (Sebat et al., 2007). These *de novo* findings provide important clues to obscure epigenetic mechanisms.

When the "keep it simple, stupid" (KISS) version of Ockham's razor is used as a basis for reasoning, some scholars may interpret the Singer findings as evidence for the mere release of antigens from fetal brain. Other persons may find no connections between *de novo* mutations in schizophrenia and autism. Still other persons may question any connection between parental psychiatric disorders and mothers having sera with antibodies against fetal brain. Not insignificantly, the three articles also span the soft sciences (Daniels et al.), clinical sciences (Singer et al.) and hard sciences (Walsh et al.), and may have relevance for a perceived "unnecessary battle" (Editorial, 2008).

This report ties these articles and their approaches together with a singular theoretical framework representing the first known model that can explain the underlying heterogeneity in symptoms, presentations and findings associated with the entire autism spectrum, schizophrenia, and several other diseases. Perhaps more important, the proposed theoretical framework broadens traditional interpretations of genetics and genomics, transmissible and infectious phenomena, epigenetics, and evolution.

Using Logistic Reasoning (LR) and Logistic Intelligence (LI) to Make Sense and Establish Parsimony

LI refers to the ability to see connections among ideas and issues using logic and LR (Smith, 1983). Using LR[6] (Smith, 1983; Smith, 2006c; Smith, 2007) regarding the above co-citations (i.e., the three articles *logistically* must be taken together), a more plausible and *parsimonious* explanation is that maternal stress- or trauma-activated Epstein-Barr virus (EBV) small RNAs (i.e., EBER-1 and EBER-2; cf. Bauer, 1983; Kupfer and Summers, 1990; Schuster et al. 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Hardwicke and Schaffer, 1997; Schaffer and

[6] Logistic reasoning (LR) is a quasi-goal-oriented process involving asking "good" questions (i.e., question-asking involving 'why', 'why not', 'what if', 'what is taught/learned' and 'what is anticipated/next') and 'question-answering'/problem-solving, 'look-ahead', fault and error analysis (including expectations of Murphy's Law; to wit, 'when something can go wrong, it may occur'), and erotetics. Succinctly, LR is about seeing the 'big picture'. These processes are analogous to strategies used by systems designers, computer programmers, and chess and "Go" masters. The processes go beyond classic *gedanken studies* (Smith, 1979; Smith, 1983; Smith, 2006c; Smith, 2007; Smith, 2008b; cf. Platt, 1964; Nersessian, 1992). In general, LR is concerned with how 'things' and systems work together (including broad concerns about 'common sense'; Smith, 2006c; Smith, 2007; Smith, 2008b), how they fail to work together, and discerning if and when they cannot work together. An ultimate goal in LR is to see the 'biggest pictures' first, and then focus on the minutiae (i.e. to paraphrase an old saw, 'one should see the forest first, and then its trees', though also allowing for the forests to be illusory). Finally, LR should reveal an appreciation for the retrospective (both synchronic and diachronic issues), prospective and anticipatory (cf. Nadin, 1999). These often prove to be essential in characterizing feedforward, feedback and skip-ahead processes often associated with systems and processes. Overall, an aim in LR is to give concrete meaning to Louis Pasteur's quote in an 1854 lecture at the University of Lille; to wit, "in the field of observation, chance favors the prepared mind."

Hardwicke, 1997; Schaffer and Hardwicke, 2000) or other small RNA (e.g., VAI and VAII associated with some adenovirus) could contribute to the production of fetal brain antigens which both *alter* and/or *mimic* normal fetal tissue. The direct actions of stress on brain also must be considered (cf. Hunter et al., 2009).

The term *autovirion* refers to transmissible and infectious secondary particles capable of causing disease. Autovirions often are small RNAs generally derived from DNA viruses (Smith, 1983; Smith, 1984). Indirect and circumstantial clinical and experimental findings implicate autovirions in molecular mimicry possibly by effectively changing or circumventing the genetic code. *Autovirulence* is a term used to describe this scantly understood *epigenetic* mechanism (Smith, 1983; Smith et al., 1984a; Smith et al., 1984b; Smith, 1984; Smith, 1987; Smith, 2003b; cf. Brennecke et al., 2008). EBV- and adenovirus-associated autovirions particularly are noteworthy because of their association with autoimmune diseases (Lerner and Steitz, 1979) and their extraordinary mutagenic potential (Young and Murray, 2003). They also are associated with many somatic and germline *de novo* mutations. Autovirulence is widespread in nature and is one component in a general theory of autotoxicity, autovirulence and context-specificity (Figures 1 and 2; Smith, 1983; Smith, 1984; Smith, 1987). Overall, the theory represents a significant generalization of the prion hypothesis (Prusiner, 1982) insofar as transmissible and infectious *epigenetic* processes may be widespread and contribute substantially to disease *and evolution*.

Logistic Reasoning About Epigenetics, Autovirulence and Molecular Mimicry

Epigenetics is a term first introduced by Conrad Hal Waddington in the 1940s (Waddington, 1942; cf. Waddington, 1940; Waddington, 1941; Waddington, 1946; Lederberg, 2001). It often is defined as heritable changes in gene expression that do not change gene or proteome sequence. This definition is adequate for usual genetics and molecular biology studies of methylation, "imprinting," selective silencing and other heritable changes (cf. Bird, 2002; Bird, 2007; Gerstein et al., 2007; Sweatt, 2007; McGowan et al., 2008; Gluckman et al., 2008; Johannes et al., 2008; Keverne and Curley, 2008; Lubin et al., 2007; Miller and Sweatt, 2008; Sweatt, 2008; McGowan et al., 2009). More broadly defined, epigenetic phenomena are heritable *or propagated* alternative states of gene expression, molecular function, or organization *specified by the same genetic instructions* (i.e., DNA sequence). Conformational changes associated with Kuru, scrapie, Creutzfeldt-Jakob disease and other prion diseases are subsumed within this definition, but the definition is not limited to genetics and molecular biology perspectives (cf. Mead et al., 2007). Still other scholars emphasize that epigenetics refers to gene-regulating activities that *do not change the genome*. The subtle difference in these definitions is that the former refers to the proteome (i.e., that portion of the total genome focused on genes and proteins), whereas the latter refers to the total genome and its many undiscovered functions. The latter definition also can accommodate DNA dynamics associated with transpositions (i.e., transposons; McClintock, 1950), DNA rearrangements

associated with immunoglobulin hypervariable regions (Tonegawa et al., 1978; Sakano et al., 1979), and a theory that DNA *must be* the repository of LTM in brain and the immune system. Throughout this report, the theory is referred to as the 'DNA as LTM' hypothesis[7] (Smith, 1979; Smith, 2003a; Smith, 2007; cf. Berezikov et al., 2006).

The latter definition is important for another reason. Relatively recent findings from two independent human genome projects reveal that the proteome comprises approximately 1.2% of the *human* genome, with perhaps another 22.3% of the genome having some regulatory interaction with the 1.2% (see *Nature* [Volume 409, 15 February 2001] and *Science* [Volume 291 (5507), 16 February 2001]).[8] A generous (albeit debatable) interpretation of this finding is that Darwinian evolution can explain *at most* 25% of the *human* genome.[9] An equally generous interpretation is that *nature* comprises approximately 25% of the human genome, with *nurture / nurturance* comprising a larger fraction of the genome (Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007). In regard to the discipline of genetics, a generous interpretation is that epigenetic events may be far more prevalent than previously suspected. Thus, past definitions most certainly ignore the vast genomic territory beyond the paltry ~25% (≥1.2% + 22.3%) comprising genetic processes. A range for epigenetic options can accommodate a significant portion of the remaining ~75% of the human genome – pseudogenes notwithstanding!

In the end, few definitions focus on the typical meaning of the prefix "epi-," 'that which is on, beyond, at, after, beside, or akin to …' Emphasis on an even more general definition of epigenetics may be especially important in view of recent discoveries of RNA interference, a multitude of potentially transmissible and infectious microRNAs (cf. Grimson et al., 2008), new and unusual epigenetic mechanisms discussed in this commentary, and the

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[7] The term 'theory' to describe a molecular model of LTM is used advisedly. It refers to a comprehensive, anticipatory and testable explanation for a natural phenomenon that is supported with copious facts and evidence corroborating many predictive aspects of that theory (Smith, 1979; Smith, 1983; Nadin, 1999). Although the theory is not widely known, many of the corroborating facts and other evidence derive from multiple disciplines and interdisciplinary tools – including LR. The 'DNA as LTM' hypothesis is a narrow and straightforwardly testable (and falsifiable) experimental claim about changes from A*T-rich base-pair regions in brain to G*C-richer base-pair regions.

[8] None of the proffered definitions takes up a fundamental need to challenge underlying ethnomethodological assumptions about the sanctity of definitions of 'genes' and 'genetics' *per se* (cf. Pearson, 2006; Gerstein et al., 2007; Ji, 2008), even though findings and mechanisms cited in this report provide an appropriate occasion to revisit this matter.

[9] In fairness, neither Charles Robert Darwin nor Jean-Baptiste Lamarck had any knowledge of genomes. Nor were they in any significant position to argue the merits of nature versus nurture. Arguments supporting a 'tripartite' theory of evolution (Smith, 2006a; Smith, 2006c) establish the nature / nurture claims, as well as the unique roles of the womb, mirror neurons and 'DNA as LTM' as a broader basis for viewing evolution. Perhaps more important, the tripartite model will be useful in explicating the third (i.e., etiology and pathogenicity) objective in this report.

potential for actions associated with non-protein encoding DNA likely to emerge from even newer and unanticipated discoveries (cf. Footnote 8). Because of subtle underlying issues of transmissibility, infectiousness and replicability, this more general definition has important implications for evolution. Hence, the prefix "epi-" in epigenetics may best capture being 'beyond the genome' with little emphasis on genetics notions of methylation/imprinting, silencing and heritability (i.e., the proportion of a trait attributable to genetics) given rapid changes in our knowledge of genomics (Smith, 2003a; Smith, 2003b) and evolution (Smith, 2006a; Smith, 2006c).

This report posits that *some* epigenetic phenomena involve the viral hijacking of host genetic machinery to effectively "sabotage" immune and other organ systems (including brain) in an unusually stealthy manner (Smith, 1984). The *ubiquity* of EBV and other viruses that release autovirions contribute to this stealthiness by creating a "blindness" (e.g., beneath-the-radar and hit-and-run phenomena) characterized by "not seeing for looking." The phenomena should not be surprising in view of discoveries of post-transcriptional events and alternative splicing of RNA associated with some adenoviruses (Berget et al., 1977; Gelinas and Roberts, 1977; Chow et al., 1977). *The net effect is to change the "code," even though the host "genetic code" remains intact* (Smith, 1983).[10] Dubbed "aberrant translation products" for lack of any additional specificity (Figure 3), EBV and selected other viruses effectively hijack the genetic code through viral countermeasures aimed at turning "self" into "other." This mechanism challenges traditional notions of autoimmune disease in terms of underlying immune mechanisms and semantics (Smith, 1983; Smith, 2004). Although the immune system may be fully intact, products of molecular mimicry could produce an appearance of a dysfunctional immune system because "self" and "other" generally are indistinguishable.

Overall, when stress-activated aberrant gene expression patterns simultaneously involve multiple genes (because the changes to the code may involve multiple genes), one encounters vexatious situations and conundrums wherein only LR can be used to disambiguate the myriad of presentations mimicking multifactorial traits (cf. Chapters 7 and 8 in Lewis, 2008). Autovirulence would produce multiple spurious findings, whereas a multifactorial situation might arise because of some cascading consequence of some hierarchical (recursively-acting) gene. This distinction, in the long-run, may help one disambiguate and clarify among transmissible epigenetic issues (i.e., noises, as in mental disorders) and cis- and trans-acting issues (i.e., signals, as in strictly genetic diseases). Those stress-activated aberrant gene expression patterns should be viewed as *noise patterns* when

[10] Emphasis on the more general notion of "code" is not without foundation. For logistic reasons, one can anticipate that there will be one or more 'codes' associated with the 'DNA as LTM' hypothesis (Smith, 1979; Smith, 1983; Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007). Those codes are likely to focus on non-proteomic regions of the genome. They also could be targets of autovirulent epigenetic actions thereby contributing to cognitive and/or behavioral consequences.

contrasted to multifactorial traits (i.e., *signal patterns*). With noise patterns, the challenge goes beyond not seeing forests for the trees. Presentations of both the forests and trees become distorted when autovirions contribute grossly to epigenetic code changes. This precisely is the situation wherein geneticists and molecular biologists have been unable to assess systematic and scientific signals among noises and psychiatrists have not been able to assess noises among quite concrete clinical signals (cf. Editorial, 2008; Abbott, 2008). In fairness, geneticists and mental health specialists recently have begun to focus less on single gene diseases and focus on multiple influences and inputs, including multifactorial studies and genome-wide association studies (cf. Lewis, 2008; Frankland et al., 2008; Yamasaki et al., 2008).

Although precise mechanisms underlying the production of aberrant translation products remain elusive (though with aberrant splicing being one suspected mechanism [cf. Lerner, Boyle, Mount et al., 1980; Mathews, 1980; Akusjärvi et al., 1980; Hinterberger et al., 1983], aberrant translation being another mechanism [cf. Thimmappaya et al., 1982; Bhat and Thimmappaya, 1983; Bhat, Metz and Thimmappaya, 1983], and aberrant transcription being a third mechanism [Figure 3]), molecular *mimicry* is the usual outcome and autoimmune diseases are occasional clinical presentations (cf. Ehrlich's notion of "horror autotoxicus"; cf. Silverstein, 2005). The code altering viral small RNAs may not be limited to EBER-1 and EBER-2 (Lerner, Boyle, Mount et al., 1980; Mathews, 1980; Akusjärvi et al., 1980; Hinterberger et al., 1983; Young and Murray, 2003), or VAI and VAII (Akusjärvi et al., 1980; Thimmappaya et al., 1982; Bhat and Thimmappaya, 1983; Bhat, Metz and Thimmappaya, 1983). Nor should it be lost to one's attention that these small RNAs may be interchangeable. That they differ from host tRNA, mRNA and other small RNAs also should not be overlooked. Finally, autovirulent small RNAs need not be replicatable; their increased production in end-point titration studies may derive from the replication of the host virus (e.g., EBV, adenoviruses, etc.) and/or biological fission (Smith, 1983; Smith, 1984). Their non-replicatability could explain their "hit-and-run" and "beneath-the-radar" consequences.

Although not denatured, the non-self, "other" molecules generally lack the usual biological (specificity and functional) properties, even if they retain many conformational properties possibly giving rise to immune recognition.[11] Thus, particular care must be used when referring to "autoimmune" processes and autoimmunity as abnormal responses to self. The immune system could be fully intact, even though molecular mimicry could render an appearance that the immune system is dysfunctional. This semantic

[11] Immunogenic response is not a foregone consequence. Acid-labile α-interferon often elicits no immune response. Perhaps more important, the Singer et al (2008) findings provide clues that some (*though not necessarily all*) targets of autovirulent acts may produce immune responses. Further investigation is required to determine whether important byproducts of autovirulence in brain elicit no immune responses, titers of autovirions and/or aberrant translation products are factors, and/or location on the autism spectrum is a factor. Clinically, these may prove to be crucial considerations if the Singer findings logistically are a 'tip of an iceberg'.

distinction possibly has crucial importance in clinical settings and laboratory studies (Smith, 1983; Smith, 1984; Smith, 2006c; cf. Lonyai et al., 2008). Equally important, molecular mimicry sometimes could give rise to non-immunogenic aberrant molecular products and on other occasions give rise to immunogenic aberrant molecular products. This observation could explain the variable presentation wherein approximately 12% of mothers with autistic offspring have autoantibody responses (Paul Ashwood, 2008 personal communication).

One last point should be made about a fundamental need for a more expansive notion of epigenetics. Our epigenetic notions of autotoxicity, autovirulence and context-specificity (Smith, 1984; Smith, 2003; see forthcoming discussion) effectively generalize the Prusiner "prion" hypothesis (1982), the Bishop-Varmus "oncogene" hypothesis (Stehelin et al., 1976; Bishop, 1982; Bishop, 1989; Varmus, 1989; Nobel Prize press release, 1989) and neo-Darwinian-Lamarckian evolution (cf. Smith, 2006a; Smith, 2006c). The Bishop and Varmus 'oncogene' hypothesis, which subsumes cancers induced by EBV, is predicated on oncogenesis caused by mutated genes and/or aberrant gene products expressed in high titers (cf. Kelly et al., 2009; Sathish, Zhu and Yuan, 2009; Dickerson et al., 2009). Our generalization goes beyond epigenetics implicated in cancers – with this report citing the first evidence that broadly defined epigenetic mechanisms may account for many mental illnesses. Moreover, to the extent that trinucleotide repeat (TNR) diseases may represent aberrant products of trinucleotide processing associated with the 'DNA as LTM' hypothesis, the evolution of Huntington disease, Fragile X disease, X-linked spinal and bulbar muscular atrophy, myotonic dystrophy type 1 and other TNR diseases (and their severity) could be explained by this mechanism.

Autotoxicity, Autovirulence and Context-Specificity

A theory of autotoxicity, autovirulence and context-specificity (Smith, 1983; Smith, 1984) was crafted as a *parsimonious* explanation for transmissible and infectious *secondary* particles contributing to epigenetic and epigenomic diseases. Those diseases often present as slowly progressive, "hit-and-run" and/or "beneath-the-radar" disorders (Smith, 1983; Smith, 1984; Smith, 2003b). Insofar as herpesviruses were known to *cis*-activate lentiviruses such as HIV (cf. Rosadio, 1983) and other pathogens *trans*-activate HIV, autovirulence first was proposed as a parsimonious explanation for the titer-dependent role of EBV in the production of *both* α-interferon and acid-labile α-interferon[12,13] – especially in HIV/AIDS

[12] Significantly, the Kikuta et al. (1984) conference presentation did not cite finding titer-dependent increased production of acid-labile α-interferon. Those authors considered titer-dependent increased production of acid-labile α-interferon to be a negative finding which might besmirch their report. The finding only was revealed after this author cited *logistic* reasons for suspecting the finding (Kikuta et al., 1984 personal communication; Smith, 2009a; Smith, 2009c).

[13] The roles of α-interferon and acid-labile α-interferon in HIV/AIDS are intriguing, poorly understood and remain to be fully explicated. It remains to be determined if their roles relate to the evolution of HIV (and lentiviruses), the evolution of AIDS-like

(DeStefano et al., 1982; cf. Kikuta et al., 1984; Smith, 1984; Preble et al., 1982; Smith, 2009a; Smith, 2009c). The mechanism also explained the association of EBV with hairy leukoplakia, the presence of EBV antigens in classic and AIDS-related Kaposi's sarcoma tissue (KS tissue; Smith et al., 1984a; Smith et al., 1984b; Smith, 1984), and the crucial distinction between the evolution of HIV and the evolution of AIDS (Smith, 1989). Using LR, one was able to *anticipate* that several EBV "antigens" would represent aberrant translation products (of early "diffuse" [EA-D] and "restricted" [EA-R], and "membrane" [MA] products) in KS tissue and possibly tissues from other tumors (e.g., renal carcinoma and squamous carcinoma; Smith et al., 1984a; Smith et al., 1984b; Smith, 1984). Monoclonal antibodies directed at EBV EA-D, EA-R and MA antigens affirmed this *anticipated* finding (see Table 2 in Smith, 1984; Smith et al., 1984a; Smith et al., 1984b). Chang et al. (1994) subsequently reported a ~39% overlap in the EBV and Kaposi's sarcoma herpes virus (KSHV) genomes. [NB: HHV8 (=Castleman's Disease) also has a significant genome overlap with EBV. Moreover, HHV-6 (associated with roseola) may have a significant genome overlap with EBV autovirions in addition to its intriguing capability of congenital transmission (Hall et al., 2008).] Available evidence suggests that the offending autovirions are encoded in the overlapping genomic intersections of EBV, KSHV, HHV6 and HHV8. Indeed, this overlapping intersection may be a central feature of *all* gamma herpesviruses. More important, any associations among virus and disease (e.g., KSHV and KS, HHV-6 and roseola, HHV8 and Castleman's disease) must carefully disambiguate among virus and its autovirions as etiologic factors. Hence, the Henle-Koch postulates may not be an adequate methodological procedure for establishing causality in regard to gamma herpesviruses, their autovirions and diseases.

In general, EBV and gamma herpesviruses are not the only viruses producing autovirions. Autovirions also are produced by some adenoviruses (cf. Akusjärvi et al., 1980; Lerner, Andrews et al., 1981; Lerner, Boyle et al., 1980; Lerner, Boyle et al., 1981; Thimmappaya et al., 1982; Bhat, Metz and Thimmappaya, 1983; Bhat and Thimmappaya, 1983), vesicular stomatitis virus, Ebola virus (Lee et al., 2008), and may underlie mechanisms of many epigenetic disorders – *and especially many alleged autoimmune disorders*. Just as the classification of herpesviruses distinguishes among alpha-, beta- and gamma-herpesviruses, the classification of adenoviruses may benefit

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diseases and their opportunistic pathogens (cf. Munakata et al., 2008), and/or the evolution of antivirals and viral countermeasures and 'sabotage factors' (e.g., EBV, some adenoviruses et al.; Smith. 1984). Regardless, the production of acid-labile α-interferon has evolutionary advantages for both EBV and in HIV/AIDS. Perhaps more important, the distinction between the evolution of HIV and lentiviruses, on the one hand, must be considered in contradistinction to the evolution of AIDS and AIDS-like diseases, on the other hand – distinctions regarding the evolution of lentiviruses (in contrast to oncoviruses, spumaviruses and other retroviruses) that are unappreciated in a recent article by Worobey et al. (2008) and in previous reports from Beatice H. Hahn's and Bette T. M. Korber's research groups (Hahn et al., 2000; Nowak et al., 1996; Wolinsky et al., 1996; Korber et al., 2000; cf. Smith, 2001; Smith, 2003b; Smith, 2006c; Smith, 2007).

from distinguishing among those variants which may or may not encode for VAI and VAII (*or other*) small RNAs particularly in view of findings by Bhat and Thimmappaya (1983). In regard to the Ebola virus, a preliminary clue to an epigenetic mechanism is that the virus can produce two different forms of a glycoprotein from one gene (Lee et al., 2008).

It is important to emphasize that autovirions, as with autotoxins (e.g., prions), need not be replicatable (i.e., self-replicating, just as the hepatitis delta antigen may not be self-replicating; Smith, 1984). Their increased production (inferred from end-point titrations) may derive from a primary source (e.g., a virus) of a process of 'biological fission' (Smith, 1984). This is what distinguishes autotoxins and autovirions from being categorized as being viruses, and is the reason that this report emphasizes autovirulent etiologies – not viral etiologies. It may be the basis of autovirulent 'hit-and-run' and 'beneath-the-radar' profiles. Once aberrant translation products are produced, the immune system (reacting to the molecular mimicry) may contribute to the slowly progressive disorders. This may be the basis of antibodies to myelin basic protein being a finding in multiple sclerosis and autism (Singh et al. 1993). It also could be the basis for other variable autoantibody and antibody findings in autism (Todd and Ciaranello, 1985; Warren et al., 1990; Singh et al., 1993; Singh et al., 1997; Singh et al., 2002; Vojdani et al., 2002; Dalton et al., 2003; Singh and Jensen, 2003; Singh and Rivas, 2004; Ashwood et al., 2004; Ashwood and Wakefield, 2006; Singer et al., 2008; Kirkman et al., 2008; Libbey et al. 2008; Braunschweig et al., 2008), schizophrenia (DeLisi et al., 2008) and other disorders (Kiessling et al., 2003; Kirkman et al., 2008). Equally important, the immune system need not be involved in responding to aberrant translation products (see Footnote 11). This could be the basis of the differential expression of apolipoproteins and complement proteins associated with children with autism (Corbett et al., 2007). If there is any lesson learned from HIV/AIDS, the production of acid-labile α-interferon served to militate against antiviral properties of α-interferon thereby providing EBV and other potential pathogens free passage – both in the host and evolutionarily! Acid-labile α-interferon merely competed with α-interferon … a process analogous to radioimmunoassay analysis, though using non-functional (and not radio-labeled) molecules.

Autotoxins subsume all prions, which, as noted above, are epigenetic *conformational* byproducts (Figure 1; Smith, 1983,[14] Smith, 1984; Smith,

[14] It is no coincidence that the theory of autotoxicity, autovirulence and context-specificity was formulated at the same time that the prion hypothesis was reported (Prusiner, 1982). LR in 1981 revealed parsimony underlying research by Stanley Prusiner, Thelma Dunnebacke, Joan Steitz, Thomas Okarma and Gary Pearson (Smith, 1979; Smith, 1983; Smith et al., 1984a; Smith et al., 1984b; Smith, 1984). Indeed, the pun on Immanuel Kant's, *The Critique of Pure Reason* (Kant, 1781/1929/1985) in the title in Smith (1983), was a direct reference to LR about uncanny coincidences in reports by Prusiner, Dunnebacke, Steitz and Okarma (cf. Smith, 1983; see Table 1 in Smith, 1984). Moreover, in 1981 Okarma's laboratory at the Palo Alto Veteran's Hospital provided an opportunity for this author to gain 'wet'-laboratory experience thereby providing the impetus for formulating the preliophic

2003b). Naegleria amoeba cytopathogenic material [NACM] may be another autotoxin (Dunnebacke and Schuster, 1985; Dunnebacke and Dixon, 1989), thus initially establishing the generalizability of the process (Smith, 1984). Whether NACM represents an epigenetic byproduct remains to be fully explicated, although its resistance to some proteases suggests some unconventional conformational properties. Autovirions subsume small ribonucleoproteins (snRNPs; Lerner and Steitz, 1979; Akusjärvi et al., 1980; Lerner, Andrews et al., 1981; Lerner, Boyle et al., 1980; Lerner, Boyle et al., 1981; Hinterberger et al., 1983; Smith, 1984; Thimmappaya et al., 1982; Bhat, Metz and Thimmappaya, 1983; Bhat and Thimmappaya, 1983), the hepatitis 'delta' agent (Smith, 1984), other transmissible and infectious smallRNAs or microRNAs (cf. Zhai et al., 2008), and other yet-to-be-identified viral-associated *secondary* pathogens (e.g., the hepatitis delta antigen; Smith, 1984) as depicted in Figure 2.

As noted above, many autoimmune diseases are associated with autovirions (Lerner and Steitz, 1979; Smith, 1984; Smith, 2003b) and many rheumatologists have speculated that autoimmune diseases may comport with slowly progressive transmissible agents (Halstead Holman, 1981 personal communication). Context-specificity merely indicates that diseases are associated with specific aberrant or dysfunctional byproducts being produced and occurring in cells during unspecified cell or developmental cycles. In practical and philosophical terms, context has both existential and phenomenological meaning. For the broad array of autovirulent epigenetic byproducts, one should not be surprised that these virus secondary products are associated with a spectrum in presentations – whether in the plethora of

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moleculator (i.e., ***pr***otonic-***el***ectronic-***io***nic-***ph***oton***ic molecu***lar calcu***lator*** depicted in Exhibits A through E; cf. Smith and Shadel, 2003/2008). This device and its processes were schematized as Figure 1 in Smith (1983). Conceptually, cells and preliophic devices are electrofocusing (i.e., *vectorial*) devices though not electrophoresis devices (i.e., the latter devices are used to elucidate structure, not function). That was the basis for the title question: "Does Purification of Molecular Function Differ from Purification of Molecular Structure? …" (Smith, 1983). Because the "central dogma" often was cited as an impediment to the 'DNA as LTM' hypothesis, and because Crick (1970) had doubts about the dogma as evidenced in a footnote citing articles by Gibbons and Hunter (1967) and Griffith (1967), the preliophic moleculator device specifically was conceived and designed to *disprove* the "central dogma" in a simple, straightforward, elegant, and generalizable (utilitarian) manner. The invention provided an additional salient (thermodynamic) discovery. The chemiosmotic hypothesis concerned with coupling in oxidative and photosynthetic phosphorylation (Mitchell, 1966) posits that protons are byproducts of mitochondrial processes. Preliophic processes revealed an *in virtualis* observation (see Footnote 28 for an explanation of *in virtualis*) that, in theory, those protons support intracellular, cell surface and preliophic pH-gradients thereby facilitating bi-directional vectorial movements with minimal Brownian motion. Naturally occurring microtubulin-associated proteins, phosphatidyl-proteins and other phosphatidyl-moieties (e.g., phosphatidylserine, phosphatidylinositol, phosphatidylinesitol, phosphatidylglycerol, phosphatidylethanolamine, and phosphatidylethylamine), along with commercial ampholytes (i.e., molecular substrates used for producing pH-gradients during isoelectrofocusing) provided further support for the utility of this device.

EBV-associated disorders (Smith, 2003b), inheritance (Brennecke et al., 2008), the autism spectrum, hemoglobinopathies, lymphomas, carcinomas et al., and despite the underlying *ubiquity* of the parent viruses. Indeed, these findings teach that ubiquity appears to confer an evolutionary advantage on select viruses (e.g., herpesviruses and adenoviruses).

These findings also teach an important lesson about context-specificity. A mother's womb may be a veritable cauldron for context-specific changes (Smith, 2006a; Smith, 2006c; Hall et al., 2008). The fetus, *in utero*, represents a rapidly developing entity. It should be no surprise that titer-dependent production and release of autovirions could give rise to a range in slowly progressive developmental outcomes, responses and disorders depending on which 'context-specific' cells during the fetal developmental cycle become infected with those secondary products. Outcomes also could depend on titers of aberrant translation products (cf. Corbett et al., 2007). Both possibilities (i.e., autovirions and aberrant translation products) thereby may explain the autism spectrum. This may be the real lesson in Singer et al. (2008; also see Footnote 11). The Singer findings also teach that time is of the essence; a high priority should be directed at the early identification and detection of real or aberrant antigens to which the antibodies are directed (cf. Okarma et al., 1982). Among other lessons, Daniels et al. (2008) teach that parents (*and especially mothers*) of autistic children may be candidates for excess production of autovirulent products (cf. autism odds-ratios for mothers in Table 1 in Daniels et al., 2008; cf. Smith, 2007). The Daniels finding also comports with emerging data on mothers with disorders in common sense who often exhibit high anxiety and general anxiety disorder (Smith, 2007). Some of their offspring occasionally reveal autistic tendencies (Smith, 2004; Smith, 2006a; Smith, 2006c; Smith, 2007). Because disorders in common sense remain a beneath-the-radar phenomenon not being investigated in any clinical profession, much more can be learned as clinicians become more cognizant of these extremely challenging medical, psychological and social disorders.

Three other recent reports, when combined with the reports by Daniels et al (2008) and Singer et al (2008), now provide compelling evidence that much of the autism spectrum *and schizophrenia* may derive from autovirulent processes. [NB: Fragile X syndrome is not considered a part of the autism spectrum for reasons cited below.] Reports of *de novo* germline mutations associated with autism (Sebat et al., 2007) and *de novo* mutations in genes critical to brain development in schizophrenia (Walsh et al., 2008) are consistent with the autovirulence hypothesis. Other studies report idiopathic *de novo* mutations, chromosomal rearrangements, micromutations and microdeletions consistent with the autovirulence thesis (cf. Friedman et al., 2006; Mefford et al., 2008). When sampling families in which parents were cousins, Morrow et al. (2008) report mutations, deletions and other anomalies in 88 families in Turkey, Pakistan and other Middle East regions (cf. Sutcliffe, 2008). Other studies of familial autism (Arkin et al., 2008) and independent subjects (Kim et al., 2008), though focused on neurexin disruptions and dysfunctions, reveal similar findings (cf. Stephan, 2008). These findings are particularly significant because many autovirulent factors

are hyperendemic in an Equatorial region roughly bounded by the Tropic of Cancer on the north (say, below ~23.5° latitude) and the Tropic of Capricorn on the south (say, above ~23.5° latitude) - a possibility which often is neither appreciated nor anticipated (cf. Jones et al., 2008; Pennisi, 2008). In addition, familial and genetic tendencies in schizophrenia were demonstrated in persons of European ancestry and African-Americans, with suggestive evidence of linkage at 8p23.3-p21.2 and 11p13.1-q14.1 (Suarez et al., 2006). Other linkage studies implicate 10q22-q23 as a schizophrenia (SZ) susceptibility locus in Ashkenazi Jewish (AJ) and Han Chinese from Taiwan populations (Chen et al., 2009). In other words, the higher prevalence rates in families caused by germline mutations and aneuploidies in this hyperendemic region, when coupled with rare mutations in at least 10% of sporadic cases of autism (Sebat et al., 2007), provide compelling evidence that no theory of autism or schizophrenia now can be complete without ruling out autovirulent etiologic factors. Not to be overlooked are the anomalous mutations in 15% of adult-onset schizophrenia and 20% of child- and adolescent-onset schizophrenia (when compared to 5% in healthy controls; Walsh et al., 2008). Indeed, *as matters of logic and LR*, autovirulence *must* be suspected whenever *de novo* mutations or *idiopathic* processes are observed or reported[15] (cf. Smith, 1983; Smith, 2006c). This accounted for the logistically important 'Eureka!' moment which occurred when this author received the Singer et al. and Walsh et al. reports on the same day in late-March, 2008. Had each paper been perused in a separate manner which could not be co-cited, this report never would have gained any grounding or traction.

A possible future finding of *de novo* mutations in postmortem brain tissue of persons with autism, schizophrenia or other cognitive disorder would be particularly significant and could provide indirect support for the 'DNA as LTM' hypothesis particularly in regard to possible discoveries of inverse encoding schemes implicated in LTM (Smith, 1979; cf. Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007; also see Footnote 10). In schizophrenia and other cognitive disorders, the targets of autovirulent actions could be transposon-like, endogenous retrovirus-like and other molecules implicated in changing DNA. Those aberrant products then might produce *epigenomic* consequences, *de novo* mutations and *idiopathic* disorders. This could comport with a recent report of some statistically significant findings related to six genes involved in the control of maternal and affiliative behaviors in the autism spectrum (e.g., OXT=oxytocin, OXTR=oxytocin receptor, PRL=prolactin, PRLR=prolactin receptor, DβH=dopamine beta-hydroxylase, and FOSB=Fos family transcription factor complexes; cf. Yrigollen et al., 2008). This could be in contrast to recently reported epigenetic hypermethylation (largely in hippocampus) in

[15] 'Idiopathic' and '*de novo*' are catchall terms describing actions and processes of unknown origin. The terms are promulgated by investigators who are quick to invoke Ockham's razor without using LR to explore inter- and meta-disciplinary implications or underlying ethnomethodological assumptions that might explain the 'unknown origin'.

postmortem brain tissue associated with suicide and child abuse (McGowan et al., 2008; McGowan et al., 2009). Significantly, because the McGowan et al. research teams (McGowan et al., 2008; McGowan et al., 2009) revealed no knowledge of the 'DNA as LTM' hypothesis, their studies failed to rule out hypermethylation as an *anticipated* LTM response.

Insofar as the 'DNA as LTM' theory was derived from a comprehensive analysis of 'slow viruses' (i.e., prions and lentiviruses) and their potential and putative roles in the evolution of the molecular basis for LTM, trinucleotide repeat diseases (TNR diseases; e.g., Huntington's disease; Fragile X syndrome; X-linked spinal and bulbar muscular atrophy; myotonic dystrophy type 1; Cleary and Pearson, 2003) may be evolutionary consequences of autovirulence.[16] This may be the real significance of some reported familial epidemiologic findings (Daniels et al., 2008) and *de novo* germline mutations (Sebat et al., 2007). However, the specific mechanism of autovirulence proposed for the autism spectrum differs from any autovirulence associated with TNR diseases. Thus, Fragile X disease should not be considered among the autism spectrum. Finally, a report by Campbell et al. (2006) of putative genetic variants in autism associated with disruptions in MET transcription also comports with the autovirulence theory.

In a final analysis, transposon-like and endogenous retrovirus-like molecules could be significant targets of autovirulent actions. This presents an epigenetic and epigenomic conundrum: If the targets of autovirulence are host molecular translation products involved in generating *natural* changes to the genome (as would occur in the 'DNA as LTM' hypothesis, transpositions, immunoglobulin gene rearrangements, and other natural DNA dynamics processes), what is the source of the epigenetic/epigenomic malfeasance … the virus or the evolutionary consequences of the virus? This may be the real significance of TNR diseases. During past evolutionary time periods, autovirions gave rise to changes in molecules implicated in changing trinucleotides and TNRs (as in LTM).[16] Those aberrant translation products produced TNR sequences and subsequent repeats in gene products (as in *huntingtin* in Huntington disease). This is a logistically important reason for understanding boundaries between proteomic and non-proteomic regions of genomes[17] (Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007). For logistic reasons, if the 'DNA as LTM' hypothesis is true, then one can

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[16] Trinucleotides are important in the 'DNA as LTM' hypothesis because there must be parsimony and internal consistency between direct (DNA → RNA → proteins) and inverse (DNA ← RNA ← protein; or, stated differently, proteins → RNA → DNA) pathways. Insofar as trinucleotides are essential to the genetic code, inverse pathway encoding schemes also must be account for trinucleotides. However, this does not mean that inverse encoding schemes must be limited to trinucleotides sequences.

[17] With LR, one can anticipate high cytosine (C) and guanine (G) content in TNRs for syntropic and thermodynamic reasons, in addition to substantive aspects of the 'DNA as LTM' hypothesis (Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007). Adenine (A) * thymine (T) base pairings have other equally important roles in the 'DNA as LTM' hypothesis (Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007; cf. Pozzoli et al., 2008).

anticipate the need to change and/or move *trinucleotides* (cf. Sureshkumar et al., 2009). It also is an important reason to be on the lookout for *de novo* or other changes in the genome as in progeria (cf. Eriksson et al., 2003; Goldman et al., 2004). Perhaps most important, transpositions, gene rearrangements, and changes in DNA associated with LTM (as would occur in the 'DNA as LTM' hypothesis) most likely will occur after birth, and not *in utero*. This could explain the functional phenotypic differences associated with the autism spectrum.

Stress (i.e., Glucocorticoid) Activates Latent Epstein–Barr Virus and Selected Other Viruses

Glucocorticoid is known to activate a number of viruses. This includes herpes simplex virus (Hardwicke and Schaffer, 1997), EBV (Bauer, 1988; Kupfer and Summers, 1990; Schuster, Chasserot-Golaz and Beck, 1991), human immunodeficiency virus (HIV; cf. Moens et al., 1994), human papilloma viruses (HPV; Chan, Klock and Bernard, 1989), mouse mammary tumor virus (Buetti and Diggelmann, 1981), and Maloney murine sarcoma virus (Miksicek et al., 1986). It generally is agreed that the glucocorticoid response element (GRE), in conjunction with glucocorticoid receptors, are the common mechanisms implicated in stress-activated viral responses (Hardwicke and Schaffer, 1997; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000). Although stress can contribute to brain plasticity directly (Hunter et al., 2009), this report will focus only on EBV because its *secondarily produced* small RNAs (i.e., EBER-! and EBER-2) retain autovirulent potential. The specific challenge is to provide a parsimonious model for a ubiquitous pathogen causing a variety of uncommon diseases.

Once a host becomes infected with EBV, the virus generally remains latent in the human host throughout the host's life-cycles. This is the source of the ubiquity of EBV, its potential long-term pathogenicity, and, most important, the potential for its secondarily produced small RNAs (i.e., autovirions) to contribute *epigenetically* to molecular mimicry and the panoply of EBV-associated *uncommon* diseases and syndromes. Thus, a central challenge is to continually disambiguate between novel epigenetic outcomes and normal genetic events – the veritable metaphoric challenge of distinguishing 'forests', 'trees' and other 'hit-and-run' and 'beneath-the-radar' possibilities, heretofore and hereafter referred to as a challenge of distinguishing signals and noises.

Bauer (1988) demonstrated that glucocorticoid could induce the production of EBV early-antigens. Others (Kupfer and Summers, 1990; Schuster, Chasserot-Golaz and Beck, 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Hardwicke and Schaffer, 1997; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000) subsequently demonstrated that GREs are responsible for reactivation and resumption of productive infections following stress, trauma and immunosuppression. Not only can this provide opportunities for EBV to reactivate and spread to new hosts, it also creates opportunities for the release and transmission of infectious autovirulent *secondary* pathogens (i.e., autovirions). These autovirions need not be replicatable, and probably are not self-replicating. Rather, their

increased production and rising end-point titers may be artifacts and consequences of *biological fission* instead of replication (Smith, 1983; Smith, 1984).

The pregnant female presents a special challenge. Stress-activated EBV secondary autovirions could be transmitted to her intrauterine embryos, fetuses and unborn offspring – at any or all stages during intrauterine development. During early embryonic development, autovirions could contribute to aneuploidies such as mosaic Down syndrome. Indeed, the dogma that pregnancy associated with advanced maternal aging contributes to increased risks for aneuploidies now may need to be rethought and revised, especially in view of evidence that some young women give birth to children with Down syndrome (cf. Erickson, 1978/2007; Morris, Mutton and Alberman, 2002; Dianna Burns-Banks, MD, personal communication in 2008; Lorraine Barnes, MD, personal communication in 2008). Using LR, an alternative hypothesis is that psychological and other stresses associated with advanced maternal aging increases the risks for epigenetically-induced aneuploidies. Could this be a factor in the birth of a child with Down syndrome to Alaska Governor (and Republican Vice Presidential candidate) Sarah Palin whose child was conceived during her term as Governor? Could stresses associated with her political office represent the true reason for the child with Down syndrome and not Palin's maternal age? Could reports that Palin's daughter Bristol had mononucleosis during Sarah Palin's pregnancy have relevance in this regard?

Another intriguing conundrum arises when stress-activated EBV secondary particles are transmitted to and infect monozygotic and/or dizygotic twins during their intrauterine development. The consequences could mimic genetic events insofar as monozygotic twins could be equally affected, though for *epigenetic* and *congenital* reasons, and not for genetic reasons. Indeed, the womb may provide the ideal cauldron for non-Darwinian *de novo* and germline mutations and other molecular events. Could this be the real reason for the "unnecessary battle" among neuroscientists and geneticists regarding the biology of mental disorders (Editorial, 2008; Abbott, 2008)? Could this provide the basis supporting a need to distinguish between 'signals' associated with *disciplines* such as genetics and the neurosciences, on the one hand, and 'noises' associated with *interdisciplinary* and *transdisciplinary* inquiry employed in psychiatry and mental disorders, on the other hand? It should not escape one's attention that the epigenetic and mutagenic potential of EBV and its autovirions could explain a spectrum of disorders (including the autism spectrum) depending on the titers of autovirions and their context-specificity. It also can explain an increased number of reports of *de novo* mutations and increasing numbers of genes being discovered and implicated in the autism spectrum.

Still another methodological challenge presented by stress is highlighted in recent studies of DNA methylation plasticity (cf. Kubota et al., 2008). Their findings are interesting, in part, because methylation is one of several epigenetic mechanisms alluded to above. Heretofore, patterns of DNA methylation were thought to be maintained lifelong. Kubota et al. (2008) demonstrate that DNA methylation can be changed in the short term by

some factors such as malnutrition, mental stress, and some drugs as well as methylation supplements. They investigated DNA methylation changes attributed to stress in rodent muscle tissue. DNA methylation in the upstream-regulatory regions of three genes (i.e., MyoD, myogenin, and myostatin) related to muscle differentiation in the soleus (lower limb) muscle tissues in "acute-exercise" (30 min on treadmill, 9 weeks of age) rat group (n=6, control=6) were contrasted to "chronic-disuse" (3 weeks tail-suspension, 18 weeks of age) rat group (n=5, control=5) using bisulfite sequencing and COBRA methods. Percentages of methylated-CpGs in the acute-exercise group were similar to the control group (i.e., 57% and 42% in MyoD, 25% and 35% in Myogenin, 49% and 50% in Myostatin). Percentages of methylated-CpGs in the chronic-disuse group were different from the control group [i.e., 60% and 27% in MyoD, 58% and 37% (24% and 17% {p=0.02} by COBRA) in Myogenin, 70% and 36% in Myostatin]. Those results suggest that chronic muscle disuse stress can change DNA methylation in muscle tissue though not acute muscle exercise activity, thereby indicating that muscle tissue has DNA methylation plasticity.

A final methodological challenge pertains to definitions and *molecular measurements* of stress. Insofar as glucocorticoid and GRE may be principal factors contributing to the activation of EBV, some assessment of glucocorticoid levels may need to be a part of the obstetrician's and gynecologist's management of the pregnant female. This need may be more general – particularly in view of increasing diagnoses of post-traumatic stress disorders (PTSD) associated with returning war veterans and other traumatic situations (e.g., earthquakes and tsunamis). As an example, stresses associated with the extant 'financial meltdown' may pose significant (albeit subtle) public health and epidemiologic risks with *anticipated* increased prevalence rates in EBV-associated autoimmune, psychosomatic and other diseases and syndromes (cf. World Federation for Mental Health, 2008; Smith, 2009a; Smith, 2009b). At the very least, these findings should direct attention to an increased need for scientific and professional vigilance regarding stress and epigenetic (autotoxic and autovirulent) diseases.

Although many methodological and other challenges are cited, LR about the autism spectrum underscores a number of complex and thorny issues regarding stress. Project Ice Storm reports (Laplante et al., 2004; King and Laplante, 2005; Laplante et al., 2007; Laplante et al., 2008; King et al., 2008) reveal a need to distinguish between direct effects of glucocorticoid acting on fetal brain and GRE activating EBV which, in turn, acts on fetal brain. A recent report that rainfall is correlated with the prevalence of autism (Waldman et al., 2008) raises a question of whether stress is a factor in this finding – and especially if the finding has merit (cf. Weiss, 2008). A stress-activated role for EBV in the autism spectrum is strongly supported by the King et al. (2008) observation that prenatal maternal stress from a natural disaster predicts dermatoglyphic asymmetry in humans along with the numerous studies revealing autoimmune findings and/or mutations, rearrangements and copy number variations at various chromosomal or mitochondrial loci (e.g., Todd and Ciaranello, 1985; Singh et al., 1993; Vojdani et al., 2002; Dalton et al., 2003; Singh and Rivas, 2004;

The Autism Genome Project Consortium, 2007; Oliveira et al., 2007; Libbey et al., 2008; Singer et al., 2008; Braunschweig et al., 2008; Martin et al. 2008; Theoharides et al., 2008; Weiss et al. 2008; Marshall et al., 2008; Mefford et al., 2008; cf. Need et al., 2009). Additional support for direct and indirect roles of stress is derived from the report of climate, sun, and culture relationships from an 1810 year Chinese cave record (Zhang et al., 2008; cf. Kerr, 2008).[18]

Autovirulence Can Explain the Autism Spectrum and Schizophrenia

The autism spectrum disorders represent 3 of the known pervasive developmental / neurodevelopmental disorders defined in the Diagnostic and Statistical Manuals of Mental Disorders (DSM-IV and DSM-IV-TR; American Psychiatric Association, 2002; Johnson et al., 2007; Myers et al., 2007). These disorders generally are diagnosed in early childhood – usually between ages 1 and 3 years old. The diagnoses are associated with varying degrees of dysfunctional communication and social skills, and repetitive and stereotypical behaviors.

It now is proposed that EBV, some adenovirus or other *stress- (or trauma-) activated* infectious autovirulent pathogens (i.e., autovirions; Smith, 1983; Smith, 1984; cf. Bauer, 1983; Kupfer and Summers, 1990; Schuster et al. 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Hardwicke and Schaffer, 1997; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000) *in the pregnant female* may be transmitted to her yet unborn offspring *in utero* (i.e., a congenital process; cf. DiPietro, 2004; DiPietro et al., 2006; Gallagher et al., 2008; Laplante et al., 2004; King and Laplante, 2005; Laplante et al., 2007; Laplante et al., 2008; King et al., 2008; Khashan, Abel et al., 2008; Khashan, McNamee et al., 2008). This thesis comports with other reports including autoantibodies against serotonin receptors (Todd and Ciaranello, 1985), autoantibodies against myelin basic protein (Singh et al., 1993; Libbey et al., 2008), autoantibodies against neuron axon and glial filament protein (Singh et al., 1997), aberrant responses to neurotoxins (Edelson and Cantor, 1998; Edelson and Cantor, 2000), neuron-specific antibodies (Vojdani et al., 2002), serum antibodies to caudate nucleus (Singh and Rivas, 2004), aneuploidies and chromosomal rearrangements (The Autism Genome Project Consortium, 2007), maternal antibodies against neuronal tissue (Dalton et al., 2003), maternal antibodies

[18] It should not escape one's attention that the "financial meltdown" in the USA in October and November 2008 reveals a timely and unique opportunity for investigating the effects of large-scale stressful events on public health (Smith, 2009a; Smith, 2009b). These effects could be reflected in blips in prevalence rates of autism, schizophrenia, PTSD, and other indicators. Adding support for this observation are Project Ice Storm findings (Laplante et al., 2004; King and Laplante, 2005; Laplante et al., 2007; Laplante et al., 2008; King et al., 2008), precipitation studies (Waldman et al., 2008), results of an 1810 year Chinese cave record (Zhang et al., 2008), and the effects of wars, trauma and catastrophes on common sense (Smith, 2007; Smith, 2008b). Taken together, LR suggests a need for a dedicated national effort directed at monitoring and assessing phenomenological and existential events likely to have subtle impacts on public health.

against fetal brain proteins (Singer et al., 2008; Braunschweig et al., 2008), transmissibility of maternal IgG from mothers of autistic children to rhesus monkeys (Martin et al. 2008), findings (including stress) associated with mast-cell activation (Theoharides et al., 2008), mitochondrial dysfunction (Oliveira et al., 2007), and, other aneuploidies, microduplications, microdeletions and other copy number variations (Weiss et al. 2008; Marshall et al., 2008; Mefford et al., 2008; Need et al., 2009). Although it is likely that autovirions are transmitted via the umbilical cord, this is not essential. Indeed, it is of interest to determine if autovirions and/or antibodies are detected in amniotic fluid.

Perhaps the most compelling evidence for an autovirulent etiology for the autism spectrum can be stated quite succinctly. Insofar as neuroligin-neurexin interactions appear to be significant factors in synaptic adhesion (Tabuchi et al., 2007; Chen et al., 2008; Kim et al., 2008), *and*, in a recent count, there were 29 candidate genes for autism/autism susceptibility (Sutcliffe, 2008; Stephan, 2008; Lewis, 2009), then the most parsimonious explanation for these findings is an underlying breach in the genetic code processing – by definition an epigenetic phenomenon consistent with autovirulence. This is an empirically testable thesis. One only needs to demonstrate that that stress-activated EBV autovirions effectively and selectively alter normal versus aberrant neuroligin and/or neurexin gene products, and thereby produce aberrant synaptic connections. This would be the functional equivalent of Linus Pauling et al. (1949) using the nascent electrophoresis technology to demonstrate that sickle hemoglobin differs structurally from normal hemoglobin – giving birth to molecular diseases and molecular genetics (Pauling et al., 1949). Just as EBV contributes to the production of structurally and functionally different alpha-interferon and acid-labile alpha-interferon (see Footnote 12), with this providing the basis for formulating the notion of autovirulence, the neuroligin and neurexin issue may be the clincher for autism. The emergent preliophics invention is designed to identify aberrant functional differences possibly in neuroligin and/or neurexin moieties. It will be important to identify if one or both gene products are aberrant. More important, the Tabuchi et al. (2007), Chen et al. (2008) and Kim et al. (2008) neuroligin-neurexin interaction findings provide excellent opportunities for using preliophic moleculation processes (Exhibits A through E; cf. Smith and Shadel, 2008) to model normal versus aberrant molecular functioning. Moreover, if 29 or more genes are implicated in the autism spectrum (cf. Sutcliffe, 2008), preliophics may provide an unique opportunity to discern whether some or all gene products are aberrant, along with the specifics of any aberrations.

Overall, the hypothesis is consistent with a neo-Darwinian and neo-Lamarckian "tripartite theory of evolution" (Smith, 2006a; Smith, 2006c; Smith, 2007). It also is consistent with the Barker Hypothesis concerning long-term consequences of *in utero* fetal experiences (cf. Barker et al., 1989; Barker, 2001; Barker, 2002; Gluckman et al., 2008), recent findings on allergies and asthma risks may be set in the womb (Huebner et al., 2008), stress during pregnancy (DiPietro, 2004; DiPietro et al., 2006; Laplante et al., 2004; King and Laplante, 2005; Laplante et al., 2007; Laplante et al.,

2008; King et al., 2008), and a four-component model of evolution (Jablonka, Lamb and Avital, 1998; Jablonka and Lamb, 2005). Distinguishing among intrauterine umbilical and amniotic possibilities and perinatal experiences (e.g., breastfeeding) also are important.

In the etiology of schizophrenia, the host is older and already may be infected with the offending virus though *not necessarily* from an *in utero* source or transfer.[19] That potentially stress- (or trauma-) activated virus, in turn, may release autovirulent pathogens (cf. Bauer, 1983; Kupfer and Summers, 1990; Schuster et al. 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Hardwicke and Schaffer, 1997; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000). These auto-transmissions and auto-infections of autovirions then can contribute to the panoply of epigenetic byproducts in brain mimicking natural biological products including de novo mutations (Stark et al., 2008; Xu et al., 2008; Walsh et al., 2008), microdeletions associated with chromosome 22q11.2 deletion syndrome (Simon et al., 2008; Stark et al., 2008), "rare" (The International Schizophrenia Consortium, 2008) and "recurrent" deletions (Stefansson et al. 2008), and loci association studies (O'Donovan et al., 2008) associated with schizophrenia, recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes (Mefford et al., 2008), and abnormal miRNA processing in brain (Stark et al., 2008). Indeed, a significant feature of the autovirulence hypothesis is its association with mutations, deletions, rearrangements, copy number variation, transpositions, etc.

Heretofore (and with the exception of autotoxins such as prions), there are few convincing examples revealing the fate of autovirions crossing placental and/or blood-brain barriers – whether in fetal, post-natal or adult brains. It also is a significant feature because one now can envision and anticipate a broad spectrum of outcomes including the autism spectrum *and other undiagnosed, misdiagnosed or unexplained disorders* (e.g., ALS, Guillain-Barre syndrome, post-polio syndrome [PPS] and Tourette's syndrome; cf. Kiessling et al., 1993; Petek et al., 2001; Muhle et al., 2004; Claessen, 2005; Kirkman et al., 2008; Fields, 2008). PPS particularly is interesting because polio virus has not been isolated during this late-stage in disease. Hence, the identification of possible sources of autovirulent cofactors, *if any*, may present significant challenges. *In retrospect, this finding should not be surprising because of the autotoxic examples provided by prions and the broad spectrum of EBV-related disorders* (Table 1; cf. Smith, 2003b).

The emphasis on stress and trauma as activators of EBV or other viruses is not without cause. This investigator finds stress and trauma to be significant contributors to anxiety in disorders of common sense (Smith, 2007). Smith (2007) reports Proposita "D" exhibits extreme forms of generalized anxiety disorder and Propositus "E" reveals evidence of mild, clinically diagnosed autism. DiPietro et al. (2006) report a number of physical

[19] A recent report by Xu et al. (2008) implicating *de novo* mutations in sporadic schizophrenia could contradict, or more likely, add clarity to this matter if those *de novo* mutations arose *in utero* (during pregnancy).

and psychological correlates and associations relating maternal psychological stress during pregnancy to child development at age 2, although there is no evidence that the effects could be attributable to an infectious etiology. Other persons cite stress being among the potential cofactors in chronic fatigue syndrome (cf. Hillenbrand, 2003; Wyller, Eriksen and Malterud, 2009). Still others cite anecdotal evidence that stress was associated with cold-induced urticaria, thyroiditis (both Hashimoto's and Kawasaki's thyroiditis)[20], fibromyalgia, Hodgkin disease, schizophrenia, breast cancer (Peled et al., 2008), et al. (anonymous personal communications). Furthermore, Gallagher et al. (2008) report that stress is a factor in parental caregivers of children with developmental disabilities mounting a poor antibody response to pneumococcal vaccination. The Gallagher study did not consider roles of stress in concert with predispositions to stress-activated viruses prior and during pregnancy. Significantly, stress is known to activate EBV and other herpesviruses (Hardwicke and Schaffer, 1997; cf. Bauer, 1983; Kupfer and Summers, 1990; Schuster et al. 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000).

PTSD in returning male and female battleground veterans should merit special attention because of implications for battlefront medicine and childrearing (Smith, 2007). Indeed, an epidemiologic study of autism associated with maternal PTSD may be informative, as would a separate study of schizophrenia associated with maternal PTSD.

Regarding schizophrenia, it remains to be determined if this paradigm fundamentally is inconsistent with reports that individuals with 22q11.2 microdeletions show behavioral and cognitive deficits and are at high risk of developing schizophrenia (Stark et al., 2008). As noted, *de novo* mutations could affect the germline at some particular point in the past. One example might be the increased polymorphisms in myelin genes associated with white matter lesions and disorders (Fields, 2008). It also remains to be determined if the unknown alteration in the biogenesis of microRNAs (siRNAs and miRNAs) is associated with epigenetic mechanisms (cf. Stark et al., 2008). Finally, it should not escape one's attention that loci on 22q rarely are implicated in autism or only recently were discovered (cf. Auranen et al., 2000; Muhle, 2004).

How Does the Autovirulence Hypothesis Differ from Autoimmune and Other Theories?

Reports of antibodies against serotonin-binding sites (Todd and Ciaranello, 1985), myelin basic proteins (Singh et al., 1993), antineuronal proteins (Kiessling et al., 1993), neuronal and glial filament proteins (Singh et al., 1997), and caudate nucleus (Singh et al., 2004) in persons with autism and Tourette syndrome are among the many reasons an autoimmune hypothesis was put forth to explain aspects of autism and Tourette syndrome

[20] It may not be entirely coincidental that both forms of thyroiditis were discovered in Japan – in EBV-hyperendemic regions bounded by the Tropic of Cancer on the north and Tropic of Capricorn on the south.

(Singh and Rivas, 2004; Libbey et al., 2007; Libbey et al., 2008; Kirkman et al., 2008; Fields, 2008). In autism, there generally is an underlying presumption of a familial source for those antibodies / autoantibodies (Sweeten et al.; 2003) or in the autistic person *per se*. The presence of antibodies also poses an underlying question of whether those antibody findings contribute to cause and/or consequences. Perhaps most significant, autoimmune and other theories provide no basis for hypothesizing about epigenetic mechanisms.

Tabuchi et al. (2007) recently reported a mouse model of autism based on a single mutation in the neuroligin-3 gene. Although the investigators claim their model characterizes many disorders reported for the autism spectrum, it lacks the explanatory power to explain most autoimmune findings. More important, the mouse model is based on a single mutation whereas the autovirulence model can explain the frequent appearance of multiple mutations, *de novo* mutations, polymorphisms and irregularities at multiple chromosomal loci.

Dalton et al. (2003) identified a mother with three children who produced antibodies which bind to rodent Purkinje cells. Her first child is normal, the second is autistic, and the third has a severe specific language disorder. When her antisera was inoculated in pregnant mice during gestation, they found altered exploration and motor coordination and changes in cerebellar magnetic resonance spectroscopy in the mouse offspring, comparing with offspring of mice injected with sera from mothers of healthy children. This evidence supports a role for maternal antibodies in some forms of neurodevelopmental disorder. In a somewhat similar experiment, Martin et al. (2008) induced autism-like symptoms in rhesus monkeys after inoculating antisera in pregnant monkeys and then observed their offspring. The antisera were obtained by pooling samples of antibodies against fetal brain from 21 mothers with autistic children. These experiments come closest to affirming the autovirulent model, although there were no controls for viruses which produce autovirions and those which do not produce autovirions. Nor were there controls for specific autovirions. There also were no attempts to infer possible epigenetic mechanisms underlying the autistic symptoms in the rhesus monkey offspring. In general, experiments of these types only will have relevance if purified autovirions are the known transmissible and infectious agents – regardless of any observations of antibodies or autoantibodies.

The Walsh et al. (2008) and Weiss et al. (2008) reports of significant broadly-based increases in *de novo* mutations in childhood- and adult- onset schizophrenia tend to refocus claims of specific mutations at selected chromosomal loci. The autovirulence model is the only model to-date which can explain these multiple *de novo* mutations, gene polymorphisms, microdeletions, and microduplications, and all associated idiopathic presentations.

Epidemiologic models also add support for the autovirulence model. In a study of perinatal, parental and socioeconomic risk factors, Larsson et al. (2005) report that breech birth, low Apgar scores, gestational age at birth, and parental psychiatric history for schizophrenia-like psychosis and/or

affective disorders were significant risk factors. There was no statistically significant association between autism and weight for gestational age, parity, number of antenatal visits, parental age or socioeconomic status. Once again, even these epidemiologic findings overlook possible autovirulent etiologic factors.

The autovirulence hypothesis posits that the presence of antibodies in persons with autism and some other disorders may derive from maternal sources. Yet, it is important to stress that antibodies are neither necessary nor sufficient to affirm the autovirulence hypothesis. References to beneath-the-radar and hit-and-run possibilities are meant to underscore that the autovirulence hypothesis is far more general, comprehensive and encompassing. This also is a reason that comparisons among presentations in the autism spectrum, schizophrenia, Tourette syndrome, ALS and post-polio syndrome should focus on broad irregularities – such as disturbances in white and gray matter (cf. Fields, 2008; Nacewicz et al., 2006), regardless of antibodies to specific components in white matter.

Grossberg and Seidman (2006) posit a neurodynamic "iSTART" model of autism. Their model is designed to explicate how cognitive, emotional, timing, and motor processes may be integrated with regional characteristics of the autistic brain (including prefrontal and temporal cortex, amgydala, hippocampus, and cerebellum). Like the models cited above, their model also lacks any concrete mechanism which may explain either epigenetic findings (e.g., autoimmune presentations) or the heterogeneity associated with actual clinical presentations.

In summary, the autovirulence hypothesis represents the first comprehensive and parsimonious model of autism, schizophrenia and other disorders. Its features both clarify issues (e.g., Fragile X should not be considered a part of the autism spectrum) and resolve various controversies (e.g., the putative association of MMR vaccines with regressive autism [cf. Singh et al., 1998; Singh et al., 2002; Singh and Jensen, 2003; Libbey et al., 2007] and putative roles of mercury in autism [cf. Libbey et al., 2007]). The theory also can explain seemingly spurious *and controversial* associations (e.g., between celiac disease and autism [cf. Vazirian, 2007; Babb and Stinnett, 2007; Vazirian, 2009; Adams, 2007] and benefits of gluten-free diets in autism [cf. Rudy, 2008]). This should not be surprising because autovirions may be etiologic factors in Crohn's disease, celiac disease, and inflammatory bowel disorders based on the broad presentations of mutations and gene polymorphisms (cf. Smith, 2003b; Rioux et al., 2007; Barrett et al., 2008; Shugart et al., 2008; Ma, 2008; Kaser et al., 2008; Clevers, 2009). Indeed, the shear number of genes (i.e., >30 genes) implicated in Crohn's disease (Barrett et al., 2008), and its idiopathic nature (see Footnote 15), should direct attention to and implicate possible autovirulent factors.

Ubiquity, the Womb, the Bony Cranium and Evolution – a 'Big Picture'

Why are ubiquitous viruses (e.g., EBV and some adenoviruses) associated with a broad spectrum of diseases? How can common viruses be associated with an extraordinarily broad range in uncommon diseases … and not in all infected persons? For example, Smith (2003b) identified more than

90 diseases associated with EBV – many of which are never taught in textbooks, medical schools or reference manuals. This list is updated in Table 1. From this perspective, is it surprising that the autism spectrum and schizophrenia are additional examples of autovirulence?

These questions could be framed differently. To wit, can ubiquitous viruses (capable of autovirulent consequences) be beneficial? I believe the answer is yes (Smith, 1989)! EBV-associated autovirions could be direct or indirect mutagens contributing to the generation of a broad range in hemoglobinopathies that served to disrupt the spread of malaria – even though malaria remains an active selection factor (Smith, 1989; Smith, 2006c). As mutagens, at most *pseudo-randomness* can be claimed of autovirions thereby providing an innovation and refinement to perspectives on Darwinian evolution. Insofar as these mutations may take place *in utero*, this is a further innovation and refinement on Darwin's notion of mating for the survival of the 'fit'. Mating already would have occurred at pregnancy. On the other hand, many mutations could contribute to gene polymorphisms at the germline (in the fetus).

Are autovirions associated with ubiquitous viruses the *sole* causes of the autism spectrum and schizophrenia? An obvious answer to this question is no! It is an etiologic factor, though probably not the sole factor. Diseases such as X-linked lymphoproliferative syndrome (Purtilo, 1991; Purtilo, 1992; Sumegi et al., 2002) teach that autovirulent actions of EBV may interact with genetic factors. Susceptibility to prion diseases also teaches of genetic factors (Mead et al., 2007). The binding of methyl mercury to EBV-associated dUTPases reveals the potential importance of environmental cofactors (Tarbouriech et al., 2005; Tarbouriech et al., 2006). The mercury finding is particularly significant because it contradicts claims that mercury in thiomersal (=Thimerosal) associated with measles, mumps and rubella (MMR) vaccines is an etiologic factor in autism. By the time a child receives the MMR vaccine, a mother's exposure to mercury already would have contributed to the onset of autism.

Even research on persons with disorders in common sense and their offspring (Smith, 1988; Smith, 2004; Smith, 2006a; Smith, 200b; Smith, 2007) suggests that other psychological factors (including nurturance, passive-aggressive tendencies, anxiety and other psychological issues) may be implicated in autism. Severity in condition possibly is correlated with titers of autovirions and/or some specific antigens or antibodies. The common sense findings are particularly important for two reasons. First, dysfunctional common sense is not a recognized disease entity in any clinical profession – despite its profound and disabling consequences on self and others. Despite its "ubiquity," common sense and its disorders remain beneath-the-radar among clinicians. Second, persons with autism and schizophrenia present with unique commonsense issues. Just as mirror neurons (or their use) may be defective in autism, the same can be said for autism. What remains unclear is whether aberrant common sense is a causal or correlative consequence of disease.

As noted above, context (especially *in utero*) also may be important cofactors in discerning causality, just as context and opportunism among

pathogens are crucial in assessing causality in HIV/AIDS. To wit, HIV *and* opportunistic pathogens are causes of AIDS, *not HIV alone.* Relatively common pathogens often are not associated with AIDS *per se* (Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2006c; Smith, 2007; cf. Prusiner, 2002). The latter is taught in applications of sentential logic (i.e., applying Modus Tollendo Tollens in reference to HIV/AIDS, and not applying Modus Ponendo Ponens inappropriately; Smith, 2006c) and in ethological studies (Sigurdsson, 1954a; Sigurdsson, 1954b; Sigurdsson, 1954c; Lerche et al., 1984).

Surprisingly, evolution itself could be a cofactor! As noted earlier, the ubiquity of EBV, and possibly adenoviruses, could have been evolutionarily assured by the autovirulent production of acid-labile α-interferon. Moreover, despite its extraordinary mutagenic potential, EBV seems to benefit from hosts who live long lives – despite the plethora of EBV-associated diseases. Thus, it is arguable that autism and possibly schizophrenia are evolutionary byproducts of autovirulence just as TNR diseases may be evolutionary byproducts of autovirulence.

Ubiquity of selected viruses is not the only issue. A tripartite evolutionary system in mammals posits that a form of evolution *in utero* functions at an important second level and evolution in brain (in a bony cranium) operates at a unique third level (Smith, 2006a; Smith, 2006c).

This report demonstrates that the womb could play a central role in non-Darwinian and non-Lamarckian evolution (Smith, 2006a; Smith, 2006c; also see Footnote 9). Darwinian evolution largely is concerned with mating, reproduction, mutations, selection, survival, extinction and continuity.[21] The womb provides a unique packaging system for isolating and protecting the rapidly developing fetus. Findings in this report suggest that the womb also is a veritable cauldron for context-specific (existential) events associated with autovirulent actions in the developing fetus, with many of those actions having evolutionary consequences. The *in utero* environment serves to concentrate and facilitate evolutionary changes possibly explaining changing rates in evolution (Smith, 2006a; Smith, 2006c), and increased recognition of *de novo* mutations and copy numbers, gene variants, repeat instabilities and TNRs, increased rates of gene polymorphisms, and other idiopathic findings having underlying significance in reports by Auranen et al. (1980), Barker et al. (1989), Barker (2001), Barker (2003), Cleary and Pearson (2003), Eriksson et al. (2003), Goldman et al. (2004), Sweeten et al. (2003), Campbell et al. (2006), Sebat et al. (2007), Walsh et al. (2008), Stark et al. (2008), Xu et al. (2008), Gluckman et al. (2008) and Need et al. (2009).

Most important, the womb is an 'island' which comports with many 'near-axiomatic' features characterizing slowly progressive processes (Smith, 1994). Prevalence rates of conditions associated with autotoxicity and autovirulence often are higher in island environments – whether on physical

[21] For lack of a better term, continuity (including fitness) refers to changes in time. It is not the typical mathematical notion of continuity. Gould and Ethredge (1993) posit some changes in time occur in 'fits and starts'. Mayr (1976; 1996) discusses other forms of evolutionary changes.

islands, on college campuses, in ghettos, in the military, in homosexual communities, in consanguineous relationships, or *in utero*. Islands also magnify titer-dependent actions of many autotoxins and autovirions, with titers often being higher in island environments.

Hemoglobinopathies, cited above, are classic examples of possible consequences of EBV in hyperendemic regions (Henry S. Kaplan, personal communication 1981). Autovirions circulating in vascular and lymphatic compartments provided the natural battleground for autovirulent mutations and gene polymorphisms, along with malaria-related selections. The womb, as an *in utero* ('island') cauldron, serves to concentrate evolutionary changes – passing along changes to the offspring. This is the basis of the earlier assertion that *de novo* and idiopathic findings often provide logistic clues to underlying autotoxicity, autovirulence and context-specificity. The same can be said of 'founder effects'.

The brain, in its bony cranium, points to a third level of non-Darwinian evolution. The 'DNA as LTM' hypothesis posits that DNA changes in selected cells and in selected regions in brain (e.g., in forebrain and cerebellum) represent *a priori* events associated with the formation of LTM, with axon-dendrite formation and connectivity representing *a posteriori* consequences and thus giving rise to neural networks (Smith, 1979; Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007; Smith, 2008; cf. Berezikov et al., 2006). For thermodynamic and syntropic reasons, one can anticipate that DNA changes are made in A*T-rich regions thereby producing G*C-richer regions (Smith, 2003a; Smith, 2006a; Smith, 2006b; Smith, 2006c; Smith, S007). In classic studies of biochemistry and genetics, DNA changes generally occur during replication and are accompanied by cell reproduction or cell division. For brain, it is hypothesized that the evolution of the bony cranium served to ablate the cell reproduction or cell division step while retaining DNA replication mechanisms. This also is a lesson taught is studies of slow viruses which contribute to dementia (in brain) and 'immune dementia' (Smith, 1979).

This model has two significant advantages. First, it is *parsimonious* with DNA changes and dynamics associated with gene rearrangements in the immune system and transpositions in general. In the immune system, clonal expansion (cell reproduction/cell division) and redundancy in information are essential for thorough immune surveillance. In brain, the bony cranium may have served to obviate the evolutionarily deleterious consequences of redundancy (by constraining and/or ablating cell reproduction and cell division) while maximizing information potential. In effect, the formation and development of axons and dendrites (i.e., neural networks) are analogous to the formation and development of immunoglobulins and cell surface markers in lymphocytes – *though without clonal expansion*. It should not escape one's attention that this model also is evolutionarily efficient by minimizing brain size and weight (cf. Berezikov et al., 2006). Not surprisingly, these findings hold true in anatomical studies of brain associated with enrichment experiences (Bennett et al., 1964; Bennett et al., 1969; Diamond et al., 1980). The second advantage of the model is that puts in clearer perspective various different types of evolutionary tools for LTM required at the different

evolutionary levels, *with some of those tools possibly being susceptible to autovirulent actions*.

In brain, if cell reproduction and mutations[22] are eliminated as evolutionary issues (in a Darwinian sense), what triggers DNA changes? When does the brain begin accommodating changes in DNA? Do specific changes in DNA represent measurable units of LTM? Regarding autovirulence, can one identify specific critical points that might be susceptible to Murphy's Law (i.e., if something can go wrong, it will)? If upstream *a priori* events associated with DNA changes are affected by autovirulence, what can be the range in their downstream consequences on *a posteriori* outcomes in neural networking? How can upstream or downstream autovirulent events affect cognition, behavior and social interaction? Finally, if, *in utero*, autovirulence contributes to *de novo* mutations or other changes in the germline, how will those changes manifest themselves in the individual and her/his offspring?

With reference to the autism spectrum and schizophrenia, these are questions which now must propel LR and specific inquiry regarding slowly progressive processes derived from autotoxicity, autovirulence, and context-specificity. These questions also bring us "full circle" to the counterintuitive, enigmatic and seemingly disparate findings which form the basis for this report.

The 'DNA as LTM' hypothesis and mirror neurons provide the basis for a third level in mammalian evolution[23] (Smith, 2006a; Smith, 2006c; Smith, 2007). *In utero* events could have slowly progressive and long-term consequences on memory, cognition, behavior and social interactions. This may be an important lesson learned from the autovirulence hypothesis pertaining to the autism spectrum. To the extent that aberrant translation products contribute to derangements in the fetus, these byproducts could contribute to the production of antibodies against fetal brain in sera of some (*though not necessarily all*) mothers with autistic children (cf. Singer et al., 2008; Braunschweig et al., 2008). Equally important, consequences of autovirulence *in utero* may contribute directly or indirectly to the newborn lacking capabilities to take advantage of imitation thought to be a basis for the mirror neuron system and central to early learning and development (cf. Dapretto et al., 2006; Iacoboni, 2008). Any limitations in the ability to imitate may circumscribe ranges of changes in DNA (i.e., the 'DNA as LTM' hypothesis), thereby contributing to circumscribed cognitive, behavioral and social skills in the affected newborn and developing child. These cascading events and consequences obviously are matters for further explication, and especially in regard to disambiguating whether mirror neurons are direct or indirect targets of autovirulence, and whether an autistic person may have

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[22] For brain, it is important to distinguish between random and pseudorandom *mutations*, on the one hand, and quite precise and encoded *changes* in DNA, on the other hand. The former are consistent with Darwinian evolution, whereas the latter are not.

[23] This author knows of no extant evidence of mirror neurons being present in non-mammalian species, although it logically, logistically and evolutionarily would make sense that mirror neurons would be present across many animal species.

intact mirror neurons though with other lesions obviating the effective use of mirror neurons.

In summary, Darwinian evolution has concerns for mating, reproduction, mutation, selection and survival – along with an overlay of microbiological, pathogenic and environmental cofactors. Evolution *in utero* is concerned with activation (by viruses and sperm!), development transmissibility, infectiousness, pseudorandom (e.g., *de novo*) mutations, titers and "birth" – with an overlay of autotoxic, autovirulent and environmental cofactors. "Evolution" in brain (which includes adaptation and nurturance) is concerned with imitation, encoded DNA changes,[24] local syntropy, and, access and propagation (i.e., transmission) of information (involving nurturance, LTM, learning, sleep, etc.; Smith, 1988; Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007) – with an overlay of social, psychovirus (Smith, 1988), common sense (Smith, 1988; Smith, 2006a; Smith, 2006c; Smith, 2007), cultural and environmental (Palmer, Blanchard and Wood, 2008) cofactors.

Pathogenicity of 'Code' Altering Entities Across Evolutionary Systems

This report began with an observation that three seemingly disparate reports, when considered together, reveal evidence that transmissible and infectious autovirulent factors are implicated in the etiology of the autism spectrum and schizophrenia. A unifying and parsimonious thesis is that autovirulent secondary factors associated with stress-activated viruses (cf. Bauer, 1983; Kupfer and Summers, 1990; Schuster et al. 1991; Schuster, Chasserot-Golaz, Urier et al., 1991; Glaser et al., 1995; Hardwicke and Schaffer, 1997; Schaffer and Hardwicke, 1997; Schaffer and Hardwicke, 2000) could contribute to code altering epigenetic and epigenomic cascading consequences. Because autism and schizophrenia generally are regarded as diseases of brain, and because an initial infectious insult may have occurred in the womb of the pregnant female, it may be important to parse the potential etiology of those cascading events – from germline, to womb, and then to brain. It also was noted that the Henle-Koch postulates may not be an adequate methodological procedure for determining or disambiguating causality in regard to gamma herpesviruses and some adenoviruses. Because of their ubiquity and their association with a plethora of diseases, it virtually is impossible to attribute exact infectious agents with precise diseases,

[24] Even though precise mechanisms remain unknown, LR reveals that there must be one or more schema for encoding DNA changes associated with LTM in forebrain, cerebellum and possibly other brain regions. This is analogous to early predictions of a genetic code, even before it was explicated and elucidated (cf. Watson and Crick, 1953a; Smith, 1953b; Crick, 1958; Crick et al., 1961). For logistic, thermodynamic and syntropic reasons, one can anticipate that those changes will produce *increasing* G*C **::** A*T ratios in selected regions in brain – and especially in forebrain and cerebellum. Those ratios should increase monotonically as a function of age (and indirectly as a function of sleep and experience) in forebrain and asymptotically in cerebellum (Smith, 2003a; Smith, 2006a; Smith, 2006b; Smith, 2006c; Smith, 2007; cf. Pozzoli et al., 2008). How autism and schizophrenia intersect with these changing ratios remains to be explicated.

especially when contexts are existentially unknown or poorly understood. Hence, the intersection of natural evolution with the complex pathogenesis of diseases that may impact that evolution acquires increasing importance.

A further complication is that at least three levels of evolution are implicated in these findings. Germline and Darwinian evolution is well-suited to accommodate diseases of mating, reproduction, mutation, selection and survival caused by environmental, microbiological, and other pathogenic cofactors. In the womb, and even with the same (identical) autovirulent factors, pathogenesis may take on different forms, consequences *and meanings*. Autovirulent actions *in utero* may contribute to auto-infectious and auto-transmissible consequences in the pregnant female and/or infectious and transmissible consequences for the developing fetus. Mating and reproduction no longer are disease-related issues, whereas pseudorandom mutations, selection and survival retain. Causes not only include microbiological and environmental cofactors, autotoxic and autovirulent factors acquire an increasingly important role in morbidity and mortality. With good fortune and timely intervention, consequences of autotoxicity and autovirulence may be reliably predicted and/or circumvented, thereby also creating increased opportunities for 'debugging' cause, consequence and association – even in the absence of the unreliable or irrelevant Henle-Koch postulates. At the very least, many *in utero* byproducts of autotoxicity and autovirulence will produce structural markers (e.g., aberrant translation products, antibodies, autoantibodies, etc.).

Then, there is the brain! Even though not widely understood or appreciated, the use of LR, the invocation of the 'DNA as LTM' hypothesis and the tripartite model of evolution all teach that complex pathogenic consequences of autotoxicity and autovirulence may obtain in the form of upstream *a priori* (i.e., structural and molecular) byproducts and/or downstream *a posteriori* (i.e., structural, and/or neuronal and network) byproducts *and* '*byprocesses*'. This was the basis for contrasting LR with *descriptive-structuralism* methods often used in biological sciences and *heuristic functionalism* methods often used in computer and information sciences (Smith, 1983). Autism and schizophrenia make this lesson even more exciting and challenging! Apart from occasional immune complications which can be anticipated and expected (Smith, 1979), pathogenic consequences in the brain of an autistic or schizophrenic person may be diverse and far-flung. Long- and short-term memory, cognition, consciousness, awareness, reality and behavior all become pathogenic epigenetic and epigenomic targets for byproducts and byprocesses of downstream processes. LI and LR tools are essential if progress is to obtain.

In short, each level in evolution presents unique targets for autovirulence, differences in pathogenicity, and differences in outcomes and consequences. Some pathogens may be autovirions. Other pathogens may be aberrant translation products or autoimmune consequences. Still other pathogens may be aberrant transmissible *information* causing discernible

disturbances in other persons' performance (e.g., psychoviruses[25] and their contributions to aberrant common sense and other disorders; Smith, 1988; Smith, 2004; Smith, 2006a; Smith, 2006c; Smith, 2007; Smith, 2008). In the end, LI and LR may be essential in disambiguating cause, consequence and associations, in reference to the germline, the womb, and, ultimately, the brain and its cognitive and behavioral processes. This pathogenic *transduction* (Smith, 1983) from aberrant molecular events to aberrant information events underscores both the excitement and challenges for debugging the autism spectrum and schizophrenia because fundamentally they represent diseases of aberrant information triggered by aberrant (epigenetic) molecular events.

Intelligence, Logical, Methodological, Logistic, Ethnomethodological and Philosophy of Science Issues

Thus far, the emphasis in this report is placed on general (normal and pathogenic) mechanisms underlying autotoxicity and autovirulence, with the autism spectrum and schizophrenia representing an instructive subset of epigenetic disorders associated with dysfunctional cognition and (personal and social) behavior. The term instructive is used because autism and schizophrenia generally are recognized as being diseases of brain (and not the immune system or other non-central nervous systems), although the co-cited findings reveal antecedent transmissible and infectious *autovirulent* etiologic factors operating at the germline and in the womb underlying those consequences in brain. An analogous situation was found in transmissible dementia. In earlier studies, the actions of slow viruses were thought to be limited to brain; immune and other consequences were overlooked (Smith, 1979). Subsequent analyses of immune findings permitted one to anticipate HIV/AIDS, BSE and other disorders (Smith, 1979; Smith, 1983; Smith, 1984; Smith, 2003c).

The recent deaths of Jesse Gelsinger (Lehrman, 1999; Smaglik, 1999) and Jolee Mohr (Wadman, 2007) could represent other instructive consequences of autovirulence. Their deaths could teach that adenovirus autovirions may complicate gene therapy and genetic engineering – claims to the contrary notwithstanding. Indeed, there is no evidence that proponents of gene therapy are aware of adenovirus autovirulent small RNAs or their possible association with aberrant translation products (cf. McConnell and Imperiale, 2004). In addition to a wrongheaded approach to HIV vaccine

[25] The term psychovirus refers to transmissible and infectious information causing somewhat circumscribed aberrant responses in infected individuals. The term was coined in 1985 to explain a phenomenon of transmissible parental negativism reliably causing aberrant common sense in some offspring (Smith, 1988). Other psychoviruses have been described elsewhere (Smith, 2006c). Psychoviruses have no resemblance to 'memes' (Dawkins, 1976), and are not modeled after genes (Smith, 1988; Smith, 2004; Smith, 2006a; Smith, 200b; Smith, 2007; cf. Dawkins, 1976). This is the reason for using separate nomenclature to distinguish memes from psychoviruses. Indeed, by analogy, the few psychoviruses described to-date comport favorably with slow viruses acting on *non-proteomic* regions of the genome (Smith, 1988; Smith, 2004; Smith, 2006a; Smith, 2006c).

development paradigms,[26] adenovirus autovirions also may have played some role in the doomed Merck HIV STEP vaccine trials (cf. Check, 2003; News in Brief, 2007). Perhaps most important and especially for philosophy of science, the ubiquity of EBV, adenoviruses and vesicular stomatitis virus (all of which produce autovirions) have served to obfuscate disciplined scientific reasoning and inquiry while also presenting a compelling argument favoring LR and interdisciplinary inquiry in biological sciences (cf. Smith, 1983; Smith, 2001; Smith, 2003a; Smith, 2003b; Smith, 2006a; Smith, 2006c; Smith, 2007).

Regarding autotoxicity, autovirulence and context-specificity, LR has an additional advantage. Typically, scientists use Ockham's razor combined with inductive, deductive and/or gestalt reasoning. This then is followed by some form of experimental, phenomenological and/or hermeneutic explication. When using LR, studies of autotoxicity, autovirulence and context-specificity teach that Ockham's razor and experimentation should be the final order of the day. Experimentation certainly does not occupy the esteemed position advocated by many proponents of "scientific methods" (cf. Popper, 1963; Glass and Hall, 2008). To the contrary, good theory and a solid notion of 'scientific common sense' are essential (Smith, 2006a; Smith, 2006c; Smith, 2007) in order to obviate catastrophic consequences such as the Gelsinger-Mohr deaths and the 'mad cow' disease epidemic. Moreover, verisimilitude is far more robust when using LR (cf. Popper, 1963). To paraphrase a tactical rule in USA jurisprudence, one only should ask questions in courts of law for which answers are known. One only should pursue experiments for which virtually all outcomes are known or anticipated. Verisimilitude is best served qualitatively and quantitatively by grounded theory (cf. Braud and Anderson, 1998) … with discoveries through LI and LR serving to inform adequate theory prior to experimentation.

Because autotoxins and autovirions potentially are exceedingly harmful to individuals and *en masse* – possibly requiring the highest biohazard safety precautions – experimentation should be the last resort in carefully secured P4-type research facilities, and only after all logistic, anticipatory and "look ahead" consequences are fully assessed. This was the lesson lost to investigators pursuing adenovirus-associated vectors in gene therapy and vaccines. The lesson also was overlooked by policy-makers in the United Kingdom, thus giving rise to bovine spongiform encephalopathy (i.e., 'mad cow' disease).

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[26] The term 'wrongheaded' is used advisedly because it mathematically and logically is *improbable* that any direct neutralizing vaccine against HIV or other lentivirus can be crafted (Smith, 1989; Smith, 2001; Smith, 2006a; Smith, 2006a; Smith, 2007). Ethological studies (cf. Sigurdsson, 1954a; Sigurdsson, 1954b; Lerche et al., 1984; Smith, 2006c) teach that multivalent, killed vaccines against potential opportunistic (i.e., nascent in contrast to common) pathogens can be effective in circumventing the *trans*-activation of HIV thereby effectively providing a vaccine against AIDS, *though not HIV per se*. Herpesviruses are an exception because they *cis*-activate HIV and lentiviruses (cf. Rosadio, 1984; Smith, 1983; Smith, 1984; Smith, 1989; Smith, 2001; Smith 2006c; Smith, 2007).

LR also teaches that one's choice of a "problem space" (e.g., genome databases for 'mining' data; cf. Wiley, 2008) often can stifle scientific inquiry if those databases do not anticipate DNA dynamics consistent with the 'DNA as LTM' (cf. Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007). To date (and based on the various human genome project reports in *Nature* [Volume 409, 15 February 2001] and *Science* [Volume 291 (5507), 16 February 2001]), most investigators never have considered possible DNA dynamics in brain, immune and other memory systems (cf. Smith, 1979; Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2003a; Smith, 2006a; Smith, 2006c; Smith, 2007; Berezikov et al., 2006; Kawaji et al., 2008; Spencer [1000 Genomes Project], 2008; Grant, 2008a; cf. Pozzoli et al., 2008) – this despite the compelling evidence in the examples of transposons (McClintock, 1950) and immunoglobulin gene rearrangements (Tonegawa et al., 1978; Sakano et al., 1979). Failures in appreciating DNA dynamics effectively circumscribes the range in epigenetic and epigenomic consequences one may envision for brain especially, and may have importance in other aspects of autism and schizophrenia.

Regarding the fourth objective cited in the Introduction, there are several important lessons to be learned. There are challenges in peer review qualitatively and methodologically (Smith, 2001; Smith, 2006c; Smith, 2007; cf. Horrobin, 1982; Glen and Smith, 1982). Peer review and institutional reviews obviously failed *if* the Gelsinger and Mohr deaths *potentially* are attributable to autovirulence. Peer review failed to teach *when and how to 'stop'* pursuing failing approaches directed at producing vaccines against HIV (Smith, 2001; Smith, 2006c; Smith, 2007). Peer review failed in claims that HIV is the sole cause of AIDS (Commentary, 2000; Prusiner, 2002; cf. Smith, 2001; Smith, 2006c; Smith, 2007). *Peer review continues to fail in attempts at producing vaccines against HIV* (cf. Grant, 2008b).

A second lesson concerns co-citations and *rereading* of scientific reports. The present report reveals the seminal importance of having perused three reports simultaneously and contemporaneously. This is not a new lesson. It was taught in early instances of HIV/AIDS when it was crucial to read, *reread* and co-cite three articles by Bjorn Sigurdsson on slowly progressive infections in sheep (Sigurdsson, 1954a; Sigurdsson, 1954b; Sigurdsson, 1954c; cf. Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2006c). Those studies revealed AIDS-like disease in Icelandic sheep between 1933 and 1954; its onset was initiated by the importation of 20 karakul sheep from Halle, Germany. The mædi-visna virus in sheep is equivalent to HIV in humans, Johne's disease is an opportunistic infection, and rida (i.e., scrapie) could be an autotoxic byproduct resulting from some ovine viral action.

Sigurdsson's attempts at producing a vaccine against the Mycobacterium *johnei* (i.e., an ovine equivalent to M. *avium-intracellulare* which is opportunistic in humans with HIV) taught that vaccines against potential opportunistic pathogens can be beneficial. Indeed, Sigurdsson's reports, when combined with ethological findings at the UC Davis Primate Center reported by Roy V. Henrickson et al. (Lerche, 1984; Roy V. Henrickson, personal communications in 1982, 1984 and 1999), point to

clearly 'wrongheaded' approaches to vaccines against HIV (also see Footnote 26), as contrasted to vaccines against AIDS – again, a teaching of Modus Tollendo Tollens (Smith, 1983; Smith, 1984; Smith, 1989; Smith, 2001; Smith, 2006c; Smith, 2007). Those studies also revealed the need to clearly distinguish between nascent and common pathogens in AIDS, with the former contributing to opportunism and AIDS. Moreover, additional reasons could be anticipated and cited to explain the repeated failures in approaches to HIV vaccines.

Rereading and LR also would have revealed various fallacies in assumptions about:

- HIV and its evolution (i.e., lentivirus evolution is titer-dependent; Smith; 1983; Smith, 1984; Smith, 1989);
- use of linear graph-theoretic analyses of lentivirus evolution (i.e., non-linear graph analysis is more appropriate);
- the origin of AIDS and its evolution (i.e., the origin of AIDS can be traced to a complex set of events associated with the onset of the "baby boom" and invention of the birth control pill; Smith, 1989);
- lentiviruses (lentivirus genetics was long known to be far more complex than the *gag*, *env* and *pol* genetics of oncoviruses and little being known about spumavirus genetics; Smith, 1979; Smith, 1983; Smith, 1984; Smith, 1985; Smith, 1989; Smith, 1994; Smith, 2001; Smith, 2006c);
- nascent versus common pathogens in HIV/AIDS (i.e., opportunistic pathogens in AIDS generally are nascent, not common; Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2006c; Smith, 2007);
- AIDS as an acquired immunodeficiency syndrome in contrast to an acquired abnormal tolerance syndrome (AATS; Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2007);
- the Henle-Koch postulates (HKP) having relevance in HIV/AIDS (i.e., the HKP only apply if a pathogen is the *sole* and mutually exclusive cause of a disease,[27] whereas HIV *and it opportunistic pathogens* are causes of AIDS; Smith, 2001; Smith, 2006c);
- other issues of sentential logic in HIV/AIDS (e.g., fallacies about the relevance of *Modus Ponendo Ponens* in HIV/AIDS, whereas it is *Modus Tollendo Tollens* that is relevant; Smith, 2001; Smith, 2006c); and,
- general issues of causality and association (e.g., *cis*- versus *trans*-activation of HIV and other lentiviruses, associations among herpesviruses and lentiviruses, autotoxicity and autovirulence et al.; Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2006c; Smith, 2007; and, Smith unpublished reports).

A third lesson concerns the importance of early detection. If stress and/or trauma activate viruses thereby giving rise to autotoxins and/or autovirions, then the initial 'hit-and-run' and/or 'beneath-the-radar' findings must be pursued when the offending virus *and its associated secondary*

[27] This observation is especially important in regards to autotoxicity and autovirulence. One could attribute cause to a virus whereas it may be autotoxins and autovirions which really are the etiologic factors.

pathogens initially are active and not during any convalescent phases. Logistically, studies of 'first reports' could be crucial (cf. Hillenbrand, 2003; e.g., a 2008 'first episodes' NIMH five-year grant of $9.8 million to Dr. Anil K. Malhotra and the Zucker Hillside Hospital in Manhasset, NY to study people suffering a first episode of schizophrenia). Subsequent inferences, at best, can be based on aberrant translation products, (preferably monoclonal) antibodies against them, and/or accumulating byproducts. Moreover, if there is any lesson to be learned from prion diseases, it is that precautions against extreme biohazards should be the rule rather than the exception. Autovirions and/or their aberrant translation products may have costly and elusive biohazardous consequences.

Another lesson pertains to interdisciplinary, transdisciplinary, metadisciplinary and ethnomethodological issues. How one knows what one knows and 'taken-for-granted' assumptions can be crucial to the discovery and explication of causality. This report reveals additional elements of process and timeliness, thus implicating the importance of existential, phenomenological, *in situ* and *in virtualis*[28] studies (Smith, 2006c; Smith, 2007; Smith, 2008).

Preliophic processes and *in virtualis* studies pose an even more important issue for the sciences. At present, studies in the sciences generally are categorized as being theoretical, experimental and applied. This research, and particularly its emphasis on LI and LR, teaches the value of a fourth scheme for categorizing the sciences; to wit, theoretical, logistic, experimental and applied sciences. *In virtualis* studies would span logistic, experimental and applied sciences, with LR also playing a prominent role in theoretical sciences. Emphasis on large-scale (heuristic) simulation and emulation processes and micro-scale preliophic processes would take on more prominent roles in the '*In Vitro* ↔ *In Virtualis* ↔ *In Vivo*' scheme.

Early examples of appropriate preliophic and *in virtualis* studies should include the assessment of neuroligin and neurexin in autism and schizophrenia to determine instances of if either or both molecular moieties may comprise aberrant translation products (cf. Tabuchi et al., 2007; Kim et al., 2008; Chen et al., 2008). Over the longer term, comparable preliophic and *in virtualis* studies also should assess whether calpain and cortactin can represent aberrant translation products. Insofar as recent studies reveal that calpain and cortactin regulate and control the sprouting of neurons (Mingorance-Le Meur and O'Connor, 2008) – a mechanism known as neural plasticity – a finding of aberrant translation products associated with either of these molecular moieties could have value in identifying and categorizing cognitive dysfunctions and disorders.

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[28] The term *in virtualis* was coined to represent the *process-oriented* intermediate between *in vivo* and *in vitro*. *Preliophic* processes represent one form of *in virtualis* intermediate processes. Insofar as "virtual" is a word taken directly from Medieval Latin term "virtualis" (W. Cawley, personal communication), this can be schematized as: '*In Vitro* ↔ *In Virtualis* ↔ *In Vivo*'. *In virtualis* emphasizes underlying notions of the 'virtual' and 'verity' (Smith, 2006c).

It should not escape one's notice that epigenetic mechanisms can mimic hereditary processes and obscure genetic versus infectious findings in twin studies involving autistic and schizophrenic persons. In monozygotic twins, a crucial clue is whether exposed twins behave in identical ways – and not whether those twins are autistic *per se*. Mere autism without identical behavior could be an important clue supporting autovirulence in contrast to monozygosity. As noted earlier, *maternal* exposure to mercury could mimic *unfounded* and *unsupported* claims of toxic aspects of thiomersal in MMR vaccines administered to persons who later are identified as being autistic (cf. Palmer, Blanchard and Wood, 2008; Tarbouriech et al., 2005; Tarbouriech et al., 2006). Indeed, an association between autism and maternal exposure to mercury (e.g., in dental amalgams, fish products and the environment) should be investigated further (cf. Palmer, Blanchard and Wood, 2008), and claims of associations between MMR vaccines and autism should be dismissed categorically. *This report suggests that autism already exists by the time a child is exposed to MMR vaccines.*

Regarding thiomersal specifically, it usually presents as ethyl mercury, whereas methyl mercury may be a far more significant toxic factor because it binds to monomeric EBV dUTPases (cf. Tarbouriech et al., 2005; Tarbouriech et al., 2006). It remains to be determined if the concentration of mercury is a *cis*-activating or *trans*-activating factor, or another form of cofactor in EBV-related autovirulent processes.

Finally, in terms of classifications of diseases in the autistic spectrum (ASD) and pervasive developmental disorders (PDD), the autovirulence hypothesis clearly distinguishes autovirulence of the form hypothesized in this report as etiologic factors in autism and schizophrenia from possible autovirulence evolutionarily associated with TNR diseases. Fragile X syndrome should be excluded from ASD/PDD classifications because it is a TNR disease (Cleary and Pearson, 2003).

Overall, the autovirulence hypothesis may explain numerous enigmatic epidemiologic findings associated with the autism spectrum related to genetics (Muhle et al., 2004; Yrigollen et al., 2008), gender (male versus female; Matsuishi et al., 1987), parenting (i.e., father versus mother; Daniels et al., 2008), families (Sweeten et al., 2003), diseases (e.g., epilepsy, autoimmune diseases, etc.; Muhle et al., 2004), studies of twins (Bailey et al., 1987; Steffenburg et al., 1989), and, most important, regional differences (Matsuishi et al., 1987; Daniels et al., 2008). Regarding the latter, EBV is quasi-hyperendemic[29] in an Equatorial region roughly bounded by the Tropic of Cancer on the north and the Tropic of Capricorn on the south (Table 2; cf. Adjei et al., 2008; Fombonne, 2003; Newschaffer et al., 2007; Morbidity and Mortality Weekly Report, 2007; Wrong Diagnosis, 2009; World

[29] It may seem contradictory to suggest that EBV can be simultaneously ubiquitous (i.e., present in 95% to 99% of persons over, say, age 18, worldwide) and hyperendemic. The answer requires an appreciation of culture, lifestyle, environmental, pathogenic, developmental, and other activation and selection factors. This goes to the core of the question, how can a ubiquitous virus cause so many uncommon diseases, and in diverse subpopulations? It also teaches an appreciation of LR about subtle epidemiologic issues.

Autism Awareness Day, 2009), a point unnoticed in Jones et al. (2008) and Pennisi (2008). It is associated with a plethora of hemoglobinopathies within this region, with malaria possibly being a selection factor.[30] Within the same region, it also is associated with nasopharyngeal carcinoma, Burkitt's lymphoma, Kaposi's sarcoma, Hodgkin disease, many polyclonal lymphomas, and *de novo* mutations. Using LR, one can anticipate that autism prevalence rates (cf. Table 2; Fombonne, 2003; Newschaffer et al., 2007; Morbidity and Mortality Weekly Report, 2007; Wrong Diagnosis, 2009; World Autism Awareness Day, 2009) and *de novo* mutations will be higher within this Equatorial region (cf. autism odds-ratios for mothers in Table 1 in Daniels et al., 2008; also see <http://www.kintera.org/atf/cf/%7B2DB64348-B833-4322-837C-8DD9E6DF15EE%7D/Brochure_EpidemiologyFAQ.pdf>). The increased prevalence of *de novo* mutations is an obvious consequence of the extraordinary mutagenic potential of autovirions produced by EBV and other viruses.

What is Next?

Several recent findings point to exciting new directions that must be considered. Kuban et al. (2009; cf. Johnson and Marlow, 2009) and Buhimschi et al. (2009) reveal the potential utility of maternal pregnancy records, neonatal records associated with premature births and umbilical cord blood samples in screening for autism and other congenital (in utero) disorders – including cerebral palsy. These data could reveal potential evidence of aberrant translation products and/or autovirions. Findings by Mitchell et al. (2009), when coupled with earlier reports (cf. Kasarskis et al., 1995; McGeer and McGeer, 2002; Ekestern, 2004), reveal the potential for screening cerebral spinal fluid (CSF) using preliophics to discern aberrant functional molecules (Smith and Shadel, 2008) as contrasted to the use of electrophoresis in disambiguating aberrant structural molecules (cf. Pauling et al., 1949).

Because autism and schizophrenia reveal slowly progressive implications for brain and the central nervous system, this report now gives birth to a possibility that the motor neuron disease amyotrophic lateral sclerosis (ALS = Lou Gehrig's disease) should be added to a list of suspected diseases of autovirulence, as should be syringomyelia and post-polio syndrome. Whether EBV and/or adenoviruses should be suspected sources of autovirions remains an open matter. The slowly, progressive nature of ALS, its epidemiology (and especially in an Equatorial belt worldwide [Reed et al., 1987; Kuzuhara & Kokubo, 2006; Spencer et al., 2005], conjugal clusters [Cornblath et al., 1993; Camu, Cadilhac, & Billiard, 1994; Poloni et al., 1997; Rachele et al., 1998; Corcia et al. 2003], military clusters [ALS Association,

[30] Although Stanford Professor Henry S. Kaplan refused to believe that EBV was associated with Hodgkin's lymphoma / disease because of its ubiquity, he marveled that EBV was hyperendemic in the Tropical Equatorial region (Henry S. Kaplan, personal communication in 1981). Stanford Professor Luigi Luca Cavalli-Sforza also affirmed that EBV was hyperendemic in some Tropical regions and in malaria-endemic areas. He was less specific about geographic boundaries (Luigi Luca Cavalli-Sforza, personal communication in 1981).

2008], and sports clusters [Wicks et al., 2005]), CSF biomarker panel for identification of patients with ALS (Mitchell et al., 2009; Wagner, 2009), and its range in immune and cognitive symptoms (###), make it a prime candidate for further analysis (###). Moreover, infectious and environmental etiologies have long been suspected as causal factors (###).Possibly the most salient clues to an autovirulent etiology are recent reports of mutations in the superoxide dismutase 1 (antioxidant) gene on chromosome 21 in familial ALS could be implicated in disease progression (Nishitoh et al., 2008), TARDBP gene (TDP-43) mislocalizations that are suggestive of molecular mimicry (cf. Neumann et al. 2006; Kwong et al., 2007; Mackenzie et al., 2007; Sreedharan et al., 2008; Johnson et al., 2008; Foulds et al., 2008; Turner et al., 2008), and deleterious variants of FIG4 (a phosphoinositide phosphatase; Chow et al., 2009). Mutations in TDP-43, located on chromosome 1p36 in patients with familial ALS, also are reported, although there is little overlap in these two gene mutations suggesting distinct SOD1 and TDP-43 familial patterns (Rutherford et al., 2008; Turner et al., 2008; Sreedharan et al., 2008). Other studies show genetic linkages to a locus on chromosome 9p (Watts et al., 2004; Skibinski et al., 2005; Morita et al., 2006; Vance et al., 2006; Valdmanis et al., 2007). Autovirions may have generated one or more of these mutations at the germline. They also could be implicated in molecular mimicry producing CSF biomarkers (cf. Mitchell et al., 2009) and in sporadic cases of ALS.

Guillain-Barre syndrome and multiple sclerosis are other candidate diseases for analysis of autovirulent etiologic factors (Table 1). Trauma and stress often precede reports of Guillain-Barre, and slowly progressive autoimmune findings are the rule rather than the exception. An emphasis must be placed on first occurrences of any disorders potentially associated with autovirulence if autovirions are to be established as causal factors.

The case for an autovirulent etiology in multiple sclerosis (MS) undoubtedly will be more interesting and challenging. As noted, antibodies to myelin basic protein are found in multiple sclerosis and autism (###). Indeed, MS could bring clarity to a need to distinguish primary infections, their secondary consequences, and other cofactors. MS prevalence rates are high on the Färoe Islands, and along a broad swath of territory along the USA and Canadian borders. What do these observations mean? What is the significance of the 'island' effect on the Färoe Islands (cf. Smith, 1994)? Because other pathogens allegedly are associated with MS, do these indicate primary versus secondary factors, stress-activation, cause versus consequence, *cis*-activation versus *trans*-activation relationships, or mere co-morbidities? Possible *cis*-activation versus t*rans*-activation (co-partnering) relationships are especially intriguing because many herpesviruses *cis*-activate lentiviruses (Rosadio, 1983; Smith, 1983; Smith, 1984; Smith, 2001; Smith, 2006c) thereby presenting another argument against attempts at making vaccines targeting HIV directly. This also was taught in HIV/AIDS, and resulted in high titers of acid-labile ɑ-interferon, Kaposi sarcoma, hairy leukoplakia and the panoply of other EBV-associated presentations. Indeed, viewing HIV/AIDS in this logistically systematic way provides direct insight into the successes of highly a### AIDS-related therapy (HAART). Clinicians

unwittingly combined treatments for both opportunistic and HIV virus components. The term unwitting is used because the same logic obtains in the pursuit of vaccines in HIV/AIDS (see Footnote 26).

Tourette syndrome is included in a list of candidate diseases of autovirulence for several reasons. Nicotine recently is shown to alleviate some symptoms in Tourette (###). Nicotine addiction also has been observed in schizophrenia (###). Logistically, it is important to rule out aberrant functioning at nicotinic receptor sites and/or cravings for nicotine. Genetic and autoimmune factors associated with antineuronal and brain "white matter" also provides clues that an underlying autovirulent mechanism may have an etiologic role in Tourette syndrome (cf. Kiessling et al., 1993; Libbey et al., 2007; Libbey et al., 2008; Kirkman et al., 2008; Fields, 2008).

A third goal must be to sequence both α-interferon and acid-labile α-interferon as a first step in circumscribing the range of aberrant translation products and instances of molecular mimicry. This goal also must include the purification of antigens associated with antibodies against fetal brain in sera of mothers with autistic children (cf. Okarma et al., 1982). Knowledge of these antigens could contribute to some understanding of targets of autovirions, and ranges in their slowly progressive outcomes. Despite more than a quarter of a century of literature on small RNAs, time now is long past due for determining their precise functions as *pathogens*.

Once precise mechanisms are known for underlying autovirulent actions, a long-term goal should include using high-speed computers to identify and simulate autovirulence regarding those genes and gene products that are targets of autovirulent actions. This would find good use as more genomes are sequenced. Equally important, pharmaceutical chemists, vaccinologists and public health teams then may find ways to circumscribe and/or circumvent the horrors of autovirulence.

Another promising approach derives from LR about molecular mimicry. One inference regarding autovirulence and molecular mimicry it is that the products of molecular mimicry have consistent structures *and functions*. For example, α-interferon and acid-labile α-interferon are consistent and do not vary in structure or function (or aberrant function) from one instance to another. Hence, high-speed computer techniques as well as preliophics may be used to categorize many of those consistent functions and aberrant functions. One example would be to circumscribe those aberrant translation products that possess mutagenic potential. This could have value in *anticipating*, treating, circumventing and preventing cancers and other diseases (e.g., TNR diseases). The explication of molecular mimicry vis-à-vis autism, schizophrenia and other mental disorders may have even greater significance. It could lead to approaches for identifying, assessing and resolving signal and noise issues cited earlier in this report that were attributed to the "unnecessary battle" among neuroscientists and geneticists regarding the biology of mental disorders (Editorial, 2008). Perhaps most important, an appreciation of functional products (and properties) of molecular mimicry could have long-term value in elucidating issues such as aberrant "beliefs," "awareness," "realities," and diverse (albeit concrete)

symptoms in neuropsychiatric disorders such as hallucinations, paranoia, coprolalia, tics, delusions, obsessions, compulsions, dissociative behavior, etc. Concretely, analyses of products of molecular mimicry may provide insights into receptors and their agonists and antagonists.

Insofar as this report hypothesizes that *in utero* transfer of autovirulent factors may give rise to a broad spectrum of slowly progressive disorders, an obvious 'next step' is to explore transmission and infectiousness of similar factors during breastfeeding and in breast milk. The neonate is not developing as rapidly as the fetus, yet the range in context-specific possibilities could give rise to other significant slowly progressive disorders of brain and the immune system. Breast milk also may provide clues regarding the half-lives of autovirions and their aberrant translation byproducts.

Semantic and epidemiologic issues surrounding transmissibility and infectiousness should not be overlooked. A compelling case can be made for the *in utero* transmission of maternal autovirions to the unborn fetus or for the transmission of autovirions during breastfeeding. In these instances, the notion of infectiousness also is clear. Auto-transmission and auto-infectiousness of autovirions in schizophrenia and other stress- (or trauma-) induced disorders may be more problematic and challenging, particularly in relation to clinical and laboratory diagnostics pertaining to past (i.e., within the host) hit-and-run and beneath-the-radar occurrences.

As noted earlier, the epidemiology of autism and *de novo* mutations in EBV-hyperendemic regions may have seminal importance. If findings comport with anticipated results, this could lead to discovering other undiagnosed or ill-characterized disorders especially in EBV-hyperendemic region worldwide.

Perhaps most exciting, the examples of autism and schizophrenia reveal novel research opportunities for circumscribing mechanisms associated with belief, awareness, reality and consciousness (cf. Smith, 2007; Smith, 2008), and cognitive, behavioral and social performance. For example, autism is characterized by evidence of restricted awareness and beliefs, late speech, limited language and social skills, occasional hearing impairment, occasional mental retardation and seizures, occasional savant behavior, and sensory deficits including occasional sensitivities to sound, texture, smell, taste and touch – including synesthesia (Baron-Cohen et al., 2007; Asher et al., 2009; cf. Baron-Cohen, Leslie and Frith, 1985; Baron-Cohen and Belmonte, 2005). Schizophrenia is characterized by positive, negative and cognitive symptoms. Positive symptoms can include unusual thoughts or perceptions, including hallucinations, delusions, thought disorders, disorders of movement, confabulations, occasional paranoia, occasional violence, speaking to oneself Negative symptoms in schizophrenia can include flat affect, lack of pleasure, diminished ability to initiate and sustain planned activities, and infrequent speech. Cognitive symptoms in schizophrenia can include problems with attention, memory and executive functions. Schizophrenics are 3 times as likely to have an addiction to nicotine when compared to the general population. ###with multiple personalities being symptoms in Dissociative Identity Disorders, a formidable

challenge will be to identify specific mechanisms possibly underlying these symptoms. To the extent that aberrant translation products may be circumscribed based on their range in autovirulent actions, one *logistically* can foresee establishing concrete markers associating autistic and schizophrenic symptoms with objective molecular (vis-à-vis neural network) aspects of consciousness, cognition, behavior and social interaction. In short, a new and emergent paradigm for explicating (i.e., 'debugging'; Smith, 1979) mainstream psychological issues may derive from 'back-to-front' molecular re-engineering and reverse-engineering studies of downstream aberrant translation products (and antibodies to some of those products) and working backward through neural networks to understand the natural roles of native upstream (non-aberrant) molecules.

Studies of the autism spectrum may provide other opportunities for 'back-to-front' molecular re- and reverse-engineering vis-à-vis the mirror neuron system. For example, fMRI studies reveal subtle mirror neuron dysfunction in high-functioning children with autism when compared to matched controls (Dapretto et al., 2006). If one can establish associations between those dysfunctions, on the one hand, and aberrant translation products and their consequences, on the other hand, then this could provide additional clues for 'debugging' the molecular basis of LTM, cognition and behavior (cf. Smith, 1979; Smith, 2006c).

Research on disorders in common sense also has relevance (Smith, 1988; Smith, 2004; Smith, 2006a; Smith, 2006c; Smith, 2007). Although there are no clinical or professional studies of disorders of common sense anywhere in the world, second-generation data are emerging regarding offspring of persons with dysfunctional common sense (Smith, 2004; Smith, 2007). In Smith (2007), both Proposita A and D have offspring possibly classifiable as persons with mild autism. One of these offspring (Propositus E) was clinically diagnosed with Asperger (###) syndrome. Both Proposita C and E may be regarded as savants of sorts. Proposita A and D both have profound generalized anxiety disorder, with Proposita A being medicated for her disorder, and Proposita D being in total denial of her florid disease.

These observations pose intriguing questions and challenges. Because of their tendencies to generalized anxiety disorder, did Proposita A and D shed autovirions during their pregnancies? What specific autovirions, antigens and/or antibodies are correlated with severity of autism and its place along the autism spectrum … and in what titers? Insofar as antibodies against fetal brain in sera of mothers with autistic children need not be present in autism, what additional downstream markers may have relevance … and especially among persons in second generations of persons with aberrant common sense? What role does nurturance play in any disorders in common sense among offspring of persons with dysfunctional common sense?

Because this author has made a career of studying "the unknowingly needy" (i.e., persons who need help but are unaware of their needs for help) and "the worried well" (i.e., persons who do not need help but believe they need help; Smith, 1974 unpublished; Smith, 1984; Smith, 1989; Smith, 2003b; Smith, 2004; Smith, 2006a; Smith, 2006c; Smith, 2007), an

additional goal must be to identify and characterize syndromes, disorders and diseases associated with autotoxicity, autovirulence and context-specificity. Clearly, the spectrum of beneath-the-radar and hit-and-run processes fall within this goal. A more challenging situation involves pathogens likely to be transduced from aberrant molecular entities to aberrant information entities as may be occurring in autism and schizophrenia.

Finally, time now is ripe for funding theoretical, experimental and methodological research on autotoxicity, autovirulence and context-specificity – particularly in view of implications for microbiology, neurosciences, public health, tropical medicine, etc. Equally important, this report points to a need for a fundamental paradigm shift regarding the obstetric and gynecologic management of autovirulent factors in the pregnant female.

Time also is ripe for establishing a National Stress Surveillance Program (NSSP). This effort should be directed at documenting stress-related direct and viral-mediated illnesses and conditions. A long-term goal must be the prevention of disease and minimization of public health costs. The adage that "an ounce of prevention is worth a pound of cure" should be the watchword of the NSSP.

Conclusions, Implications and Anticipatory (Logistic) Reasoning

The autovirulence hypothesis, when combined with other seemingly disparate findings related to the autism spectrum and schizophrenia (Daniels et al., 2008; Sebat et al., 2007; Singer et al., 2008; Walsh et al., 2008; Campbell et al., 2006; Palmer, Blanchard and Wood, 2008), *and negative evidence in vaccine and gene therapy research* (cf. Lehrman, 1999; Smaglik, 1999; Wadman, 2007; Check, 2003; News in Brief, 2007; McConnell and Imperiale, 2004), now teach obstetricians, gynecologists, pediatricians, geneticists, neurologists, neuroscientists, microbiologists, infectious disease and tropical medicine specialists, epidemiologists, and clinical laboratory scientists to be vigilant in detecting and assessing autotoxic and autovirulent factors as well as their association with epigenetic and epigenomic diseases.

At an epistemological level, there are two main sources for claims that autism without a diagnosable cause is a heritable disorder; to wit, the rate of recurrence in siblings of affected individuals and twin studies (Muhle et al., 2004). Our findings diminish and discount both sources, while revealing a unique opportunity to view infectiousness and evolution through lens analogous to those used in particle physics. To wit, autotoxins and autovirions, *as secondary particles*, are analogous to quarks and other elementary particles in particle physics produced using accelerators and cyclotrons. The cell is the analogue of a bubble chamber, and viruses are analogous to accelerated protons or electrons. Scattering patterns give rise to context-specificity. Some autovirions have "half-lives" that present vexing challenges regarding detection and consequences. The half-lives of aberrant translation products also may have significance – especially if accumulation of those products is the source of disease. These observations provide the basis for the terms 'hit-and-run' and 'beneath-the-radar'.

This analogy and metaphor is apt for another reason. Secondary particles are released from an integral intracellular space or compartment after some traumatic event thereby causing the spillage or extrusion of transmissible and infectious intracellular entities into the extracellular compartment. A high priority should be placed on clinical and laboratory (*early*) identification and diagnoses of these autotoxic and autovirulent secondary particles and their context-specific presentations. Significantly, these findings teach that prions are not the only epigenetic and epigenomic products contributing to slowly progressive diseases of brain. The association of prions with dementia may have clouded the broader picture. That autotoxins and autovirions can reach across the blood-brain barrier – whether directly or indirectly – now represents a potentially important finding consistent with many cognitive and behavioral symptoms in autoimmune and other diseases. <Check out Nicolas Wade NYT science article on 6/10### for possible relevance> Finally, our analyses teach that linkages presumed to have an underlying genetic basis actually may derive from epigenetic and/or epigenomic obfuscation.

At a more general level, our findings point to a potentially significant role for autotoxicity and autovirulence in evolution. Hemoglobinopathies were cited above, particularly in the context of malaria being a selection factor. Although mitochondria are known to use a different "genetic code" from the classic "genetic code," the notion that virus-related autovirulent (secondary) particles can sabotage 'codes' challenges Darwinian views on random mutations and selections (Smith, 1983; Smith, 1989). Moreover, mitochondria should not be ruled out as targets of autovirulent actions thereby further obfuscating an already cloudy picture (see Mitochondria; Item 70 in Table 1). One should not be surprised if new mitochondrial disorders are discovered. Nor should one be surprised if EBV-associated mitochondrial disorders are among undiagnosed diseases affecting the "unknowingly needy" and "worried well" (Smith, 1979; Smith, 1983; Smith, 2006a; Smith, 2006c; Smith, 2007)

Whereas paleontologists work at the level of fossils comprising bones and tissue, there now may be a need to scrutinize archeological and paleontological records for autotoxins and autovirions in order to further appreciate their roles in evolution. Indeed, when taken in the context of recent genomic analyses of "Glennie," the platypus (Warren et al., 2008; Murchison et al., 2008; Schmitz et al., 2008; Veyrunes et al., 2008; Whittington et al., 2008), it now is reasonable to speculate about evolutionary conditions contributing to the montage of avian, reptilian and mammalian traits in the platypus – and why this confluence took place on the Australian continent where there are numerous unique and intriguing birds, monotremes, marsupials, reptiles and other animals not seen elsewhere in the world. Can we learn more about evolution, rates of evolutionary changes and autovirulence by examining differences between eggs, wombs, and pouches? What can we learn about 'DNA as LTM' mechanisms in brain and immune systems by examining differences between birds, reptiles, monotremes, marsupials and placental mammals (cf. Kaiser et al., 2004)?

Are isolation and plate tectonics sole factors in this evolutionary process, or could epigenetics also be a factor?

To some persons, these may appear to be far-fetched and overreaching questions. Other persons will object to the jargon used throughout this report. That said, nomenclatures (e.g., epigenetics, autotoxicity, autovirulence, context-specificity, molecular mimicry) are rigorous, precise, tidy, and appropriately specialized. Still others may characterize this report as being diffuse, facile and discursive. As noted in Footnote 6, a central goal in LR is to see the 'big picture' first – even if that big picture crosses disciplinary boundaries or is at variance with one or more disciplines. Many persons who would subscribe to Ockham's razor still cannot perceive the merits, utility, parsimony *and beauty* underlying a 'DNA as LTM' hypothesis. To the naysayer alleging that LR merely is building a 'house of cards' (Smith, 2006c; Smith, 2007), Popper's notion of verisimilitude never has been breached regarding any research by this author. More to the point, some persons have noted that many autistic persons seem stuck in perpetual "fight" mode (in contrast to "flight" and "fright" modes and "temporary autism"; cf. Gladwell, 2005 –pp. 221-222, 232, 235-236,243; Smith, 2006a; Smith, 2006c; Smith, 2007). Perhaps there is much to learn about autovirulence and the molecular basis of LTM from studies of the diverse (brain) neurophysiology in the animal kingdom 'down under'.

Encapsulation of Findings

Succinctly, this report includes a cornucopia of findings:

1. It no longer is useful to conceive of cells and viruses as sacrosanct entities. By way of an analogy, just as atomic physicists found that by bombarding nuclei in a bubble chamber could produce elementary subatomic particles (e.g., quarks), cellular and viral substituents and secondary particles may play prominent and unique roles as transmissible, infectious, and pathogenic (though not necessarily replicatable) sources of cascading epigenetic and epigenomic consequences. The analogy ends there. This report underscores the extreme importance in distinguishing those autotoxic and autovirulent secondary particles, their aberrant *a priori* and *a posteriori* consequences, and expanded notions of epigenetics and epigenomics of diseases.
2. Stress-activated Epstein-Barr virus (EBV) *secondary* small RNA particles (i.e., autovirions) are transmissible, infectious and pathogenic (Smith, 1983; Smith, 1984; Smith, 2003a; Smith, 2009c). The transmissibility, infectiousness and pathogenicity of other small RNAs and microRNA now must be considered in microbiology, genetics, genomics, microbiology, and in other disciplines (cf. Wang et al., 2009). One also must consider and anticipate a broad array of pathogenic consequences attributable to those autovirulent particles. Most investigators overlook the potential transmissibility and infectiousness of intracellular products. This phenomenon was first described at a philosophy of science conference (Smith, 1983).

3. One can *infer* that pathogenic, "beneath-the-radar," "hit-and-run" autovirions interfere with the genetic code by contributing to the production molecules derived from aberrant translation or transcription. The earliest instance of autovirulence was *inferred* and reported in 1983. Once prodded, a Japanese research team reluctantly revealed that increasing EBV infectious titers in cultured cells were associated with increasing titers of α–interferon and acid-labile α–interferon. This teaches that experimental and laboratory scientists may not fully appreciate the importance of logic, methodology and philosophy of science in contrast to brute force experimentation. It also teaches that scholarship in science requires "reading between the lines."
4. The putative epigenetic mechanism is far more expansive than epigenetics typically reported by geneticists. Geneticists often limit discussions of epigenetics to methylation and imprinting. Their focus often is limited (e.g., histones). Our expanded notion of epigenetics generalizes the both Prusiner prion hypothesis and the Bishop-Varmus oncogene hypothesis. In the former case, the important issue is not proteinaceous infectious particles (i.e., prions) lacking nucleic acids. The general issue is that substituents or secondary particles are transmissible, infectious, and pathogenic – producing epigenetic consequences. Regarding the oncogene hypothesis, the more general issue goes beyond cancers and/or virus and retrovirus contributions. The general concern is about all aberrant products and aberrant functions. A recent report by Kelly et al. (2009) underscores the point beautifully. The investigators overlook possibilities that BHRF1 and the EBV bcl2 homologues in Burkitt's lymphoma may be aberrant translation products associated with EBER-1 and/or EBER-2. Other reports also implicate potential aberrant translation products associated with EBV (Dickerson et al., 2009) and gamma herpesviruses (Sathish, Zhu and Yuan, 2009). Perhaps most important, the putative epigenetic mechanism has profound implications for evolution insofar as the underlying mechanism could represent a significant *generator* of diversity, with selection factors then contributing to actual diversity. These findings teach the importance and limitations of *definitions* (cf. Ennis, 1974). A generalized notion of epigenetics ultimately must be instructive.
5. The putative mechanism can explain the etiologies of the *entire* autism spectrum, schizophrenia and selected other mental illnesses. Although it is uncommon to find a parsimonious explanation with one 'brush stroke', the underlying mechanism may have been missed because the perceived sanctity of the genetic code. 'Disciplined' scholars generally do not challenge 'taken-for-granted' (i.e., ethnomethodological) assumptions. Our findings teach that 'chance favors the prepared mind' (cf. Footnote 6), and especially the "mind" receptive to LR and an expanded version of meta-analysis!
6. The claim that the putative mechanism can explain the etiologies of the *entire* autism spectrum is used advisedly. Our science teaches that Fragile X syndrome should not be considered in the autism spectrum. It

is a trinucleotide repeat (TNR) disease and generally has a different etiologic basis. Our findings also teach that claims are misplaced regarding mercury being implicated in the etiology of autism. Methyl mercury, which binds to the EBV secondary small RNAs, could play a role in autism, but not ethyl mercury in post-natal vaccines. Lastly, controversies surrounding celiac disease and autism, and irritable and inflammatory bowel disorders and autism, may have merit, though only because of the vast array of stress-activated epigenetic aberrant products and/or their consequences contribute broadly to spectra of illnesses (cf. Vazirian, 2007; Babb and Stinnett, 2007). The important "take-home" message is that any symptoms associated with autovirulent actions may be associated with the autism spectrum.

7. Our findings teach that scientists (especially geneticists and "genomicists") should develop tools to screen for aberrant gene products (i.e., "noises" comprising aberrant protein sequences and conformations) and aberrant gene functions, in addition to screening for defective genes (i.e., "signals" indicating genetic diversity).
8. The putative mechanism has profound implications for evolution – and especially the evolution of hemoglobinopathies, selected *de novo* mutations, novel *in utero* (i.e., congenital) evolutionary processes never envisioned by Darwinists, and various idiopathic illnesses. As noted, transmissible and infectious autovirions may have contributed to the non-constant generation of diversity – *especially in an Equatorial region where EBV is hyper-endemic*. As we celebrate Darwin's 200th (February 12th, 1809) birthday, my findings should remind readers that evolution remains an important, active and vibrant topic.
9. In regard to autism, the model posits that (glucocorticoid-mediated) stress-activated EBV leads to the release of autovirions in the pregnant female (i.e., *in utero*). Titers of autovirions (and titers of their aberrant translation products) in the unborn fetus(es) determine the entire autism spectrum. This thesis fundamentally shifts the paradigm about the etiology of autism from some post-natal factor to the pregnant female, and underscores the importance of the medical management of stress during pregnancy. With the financial meltdown contributing to wholesale stresses (associated with losses in jobs, foreclosures, etc.), this finding and logistic reasoning point to the importance of anticipatory sciences – including the potential for anticipating chaos (Smith, 2009a; Smith, 2009b; Smith, 2009c)! This is the basis of the GPS metaphor.
10. The theory rejects the MMR vaccine (thiomersal) hypothesis as a cause of autism. Instead, the theory suggests that maternal exposure to methyl (not ethyl) mercury may contribute to pathogenicity insofar as methyl mercury can bind to autovirions. This finding also teaches the importance in digging deeply into issues of causality. It further teaches that pathology as a discipline must give way to more sophisticated pathogen analyses. By way of an analogy, one often hires a plumber to unplug a drain, though occasionally without exploring reasons underlying the upstream causes of the blockages. In the present context, pathogen analysis would be akin to 'purifying' and

understanding aberrant molecular *functions* (in contrast to aberrant molecular *structures*).

11. Findings in this report pose fundamental ethnomethodological and logical challenges. For example, the transmissibility of autovirions *in utero* can mimic findings in classic studies of monozygotic and dizygotic twins. Autovirulence also can give rise to aneuploidies (especially mosaic aneuploidies), *de novo* mutations and other idiopathic findings. My passing comments about Sarah Palin's child ('Trig') having Down syndrome can be illustrative. Maternal stress in Sarah Palin's role as a neophyte Governor (and not age) could give rise to the Down syndrome aneuploidy – and especially when her daughter Bristol's concurrent infectious mononucleosis was being reported. This is a reminder of possible new ways for interpreting old data.
12. Just as Pauling, Itano, Singer and Wells (in 1949) reported using the then nascent electrophoresis technology for separating molecular *structures* to discover molecular / genetic diseases (e.g., sickle hemoglobin), my preliophic moleculator invention provides a novel molecular vectorial technology for elucidating normal and aberrant molecular *functions*. The latter technology may find utility in explaining which aberrant translation products give rise to aberrant cognitive, social, emotional and other findings in autism, schizophrenia and various mental disorders. As an example *and although yet unproven*, I cite possibilities that aberrant versions of neuroligin and/or neurexin may be critically important in autism and schizophrenia. I anticipate that, in the long-run, preliophics will prove to be central in making connections between aberrant molecules and higher-order neural-network concepts (e.g., aberrations in cognition, consciousness, beliefs, emotions, reality, awareness, attention, and social behavior as might be expected in autism or schizophrenia).
13. Not only are autovirions pathogenic, there is circumstantial evidence that their pathogenicity may have contributed to the deaths of Jesse Gelsinger and Jolee Mohr in ill-advised gene therapy experiments where adeno-associated vectors were used as vehicles for conveying genes. VAI and VAII small RNAs associated with adenoviruses now must be ruled out as etiologic factors in those deaths. More important, the biohazardous features of autovirions point to the importance of highly secure laboratory environments (e.g., P3 facilities or higher). There also are potential national security implications. Our findings may represent the first concrete example in which one may *anticipate* biohazardous consequences.
14. Far-ranging implications include support for a long-standing (albeit little known) model that DNA is the repository of long-term memories (LTM) in brain, the immune system and selected other systems in organisms. The model could help explain the evolution and etiologies of trinucleotide repeat disorders (e.g., Huntington's disease, Fragile-X syndrome et al.). Regarding the evolution of LTM, the examples of platypus and echidna genomes are stark reminders that genome studies of platypus, echidna and other brains could be highly instructive.

15. Other long-range implications include a plethora of other known and 'to-be-discovered' (some of which may be anticipated) stress-activated illnesses, especially surrounding the extant global financial meltdown and the numerous stresses on individuals and families (Smith, 2009b). Indeed, a global stress surveillance program now should be considered by the World Health Organization, the US CDC, and other health agencies and ministries.
16. Philosophy of science implications go beyond Karl Popper's notion of verisimilitude insofar as logic and logistic reasoning (LR) challenge issues of experimentation and general experimental methods. For example, LR may provide guidance regarding which experiments are vacuous, those which may be contraindicated and those experiments that are essential. LR also may provide clarity regarding such diverse phenomena such as the Henle-Koch postulates and Ockham's razor. For example, it often is overlooked that the Henle-Koch postulates have no relevance regarding the issue of causality in HIV/AIDS because those postulates require that the offending pathogen be the sole cause of underlying disease. As for Ockham's razor, this report highlights the seminal failures of simple and disciplined approaches. The etiology of the autism spectrum disorders and schizophrenia would never be inferred under the William of Ockham scholasticism principle of simplification. Rather, parsimony must be the ultimate objective!
17. Ostensibly, this report is about the central role of epigenetics in evolution. Our notions of autotoxicity, autovirulence and context-specificity serve to unify a generalized prion hypothesis, a generalized oncogene hypothesis, and transmissible and infectious secondary particles which contribute to (i.e., generate) rapid, though stable, diversity – with selection factors determined by environmental influences.

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Table 1
Diseases, Symptoms, Conditions and Syndromes Associated with EBV
(Based on a partial PubMed search of 21141 citations)

1. Aberrations in membrane and nuclear proteins
2. Aberrations in teleomeric protein complexes (Wistar study – Molecular Cell, March 29, 2002)
3. Acid-labile α-interferon (Kikuta, Mizuno and Osato study)
4. Acute cerebellar ataxia
5. Antiphospholipid Antibody Syndrome – Cervera, R. and Asherson. R. A. Antiphospholipid syndrome associated with infection: clinical and microbiological characteristics, Immunobiology 2005; 210:735-741.
6. Antiphospholipid Antibody Syndrome and Pregnancy
7. Aplastic Anemia
8. Autoimmune Hepatitis
9. Autonomic neuropathy
10. Babesiosis; Mycoplasma Infections (also see Rasmussen's encephalitis/disease); Hepatitis A; Coxsackieviruses; Herpes Zoster; HIV-1 Associated CNS Complications (Overview); HIV-1 Associated Opportunistic Neoplasms: CNS Lymphoma; Cytomegalovirus
11. Bell's palsy
12. Bone Marrow Transplantation, Long-Term Effects (Two cases of chronic active Epstein-Barr virus infection in which EBV-specific cytotoxic T lymphocyte was induced after allogeneic bone marrow transplantation. Pediatr Transplant. 2008 Feb 6)
13. Brachial plexus neuropathy; Brachial Neuritis; Neonatal Brachial Plexus Palsies
14. Breast Carcinoma [Detection of Epstein-Barr virus in breast carcinoma in Egyptian women, Clin Biochem. 2008 May; 41(7-8):486-92; Detection of Epstein-Barr virus in breast cancers with lymphoid stroma, Ann Biol Clin (Paris). 2008 Jan-Feb; 66(1):59-62]
15. Burkitt's Lymphoma
16. Castleman's disease (HHV8)
17. Childhood Cancer, Epidemiology
18. Chorioretinitis
19. Chronic Fatigue Syndrome; Chronic Fatigue Syndrome
20. Chronic Obstructive Pulmonary Disease (COPD) - High levels of Epstein-Barr virus in COPD. Eur Respir J. 2008 Jun; 31(6):1221-6
21. Cold Agglutinin Disease; Cold Agglutinin Disease
22. Cold-induced urticaria [Ann Allergy 1983 Apr; 50(4):271-274]
23. Coma
24. Common Variable Immunodeficiency
25. Complement Receptor Deficiency
26. Crohn's and other irritable and inflammatory bowel disorders
27. Cryoglobulinemia
28. Cutaneous Manifestations of HIV Disease
29. Ear, Inner and External Ear, Inflammatory Diseases –
30. Early Symptomatic HIV Infection

31. Encephalitis
32. Epiglottitis
33. Erythema Annulare Centrifugum
34. Esophageal Lymphoma
35. Esophagitis
36. Fever of Unknown Origin
37. Fibromyalgia
38. Gastric carcinoma [Cancer Res. 2008 Mar 1;68(5):1427-35; Epstein-Barr virus associated gastric carcinoma: epidemiological and clinicopathological features, Cancer Sci. 2008 Feb;99(2):195-201; A case of Epstein-Barr virus (EBV) associated remnant gastric carcinoma arising 7 years after distal gastrectomy for EBV associated gastric carcinoma, Nippon Shokakibyo Gakkai Zasshi. 2007 Dec; 104(12):1728-32]
39. GI dysfunction secondary to selective cholinergeic dysautonomia
40. Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood)
41. Granuloma Annulare
42. Guillain-Barre Syndrome
43. Hairy Leukoplakia
44. Hashimoto's thyroiditis
45. Head and Neck Cancer: Squamous Cell Carcinoma
46. Hearing loss
47. Heart Transplantation; Heart Transplantation; Heart-Lung Transplantation
48. Hemophagocytic syndromes
49. Hodgkin Disease; Hodgkin Disease; Hodgkin Disease, Thoracic
50. Human Herpesvirus Type 6
51. Hypoglossal nerve palsy
52. Infantile Polyarteritis Nodosa
53. Interstitial Lung Disease in Children
54. Intestinal and Multivisceral Transplantation
55. Kaposi Sarcoma
56. Leukemias
57. Liver Transplantation; History of Pediatric Liver Transplantation
58. Lung Transplantation; Lung Transplantation; Heart-Lung Transplantation
59. Lupus Erythematosus, Acute
60. Lymphoma, Diffuse Large Cell; Lymphoma, Malignant Small Noncleaved; Lymphoma, Mantle Cell
61. Lyomyosarcoma (?###)
62. Lymphoma, Non-Hodgkin
63. Lymphomatoid Granulomatosis
64. Lymphoproliferative Disorders; Lymphadenopathy
65. Lymphoproliferative Syndrome, X-linked
66. Malignant Tumors of the Nasal Cavity
67. Meningoencephalopathy
68. Mesenteric Lymphadenitis

69. Metamorphopsia (Alice in Wonderland Syndrome – Metamorphopsia is a visual illusion that distorts the size, shape, or inclination of objects)
70. Mitochondria-related – Epstein-Barr virus immediate-early protein Zta co-opts mitochondrial single-stranded DNA binding protein to promote viral and inhibit mitochondrial DNA replication (J Virol. 2008 May; 82(9):4647-55)
71. Mononucleosis and Epstein-Barr Virus Infection; Mononucleosis; Infectious Mononucleosis, Infectious mononucleosis due to Epstein-Barr virus with suspected reactivation of human herpesvirus 6 (Kansenshogaku Zasshi. 2008 Jan; 82(1):47-50)
72. Mucocele and Ranula
73. Multiple cranial nerve palsies
74. Multiple Sclerosis; Multiple Sclerosis; Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis, Neurology 2008 Mar 25; 70(13 Pt 2):1113-8; Epstein-Barr virus genotypes in multiple sclerosis, Acta Neurol Scand. 2008 Feb; 117(2):141-4]
75. Myelodysplasia
76. Myelodysplastic Syndrome
77. Myogenic Tumors – Posttransplant Epstein-Barr virus-associated myogenic tumors: case report and review of the literature, Am J Transplant. 2008 Jan; 8(1):253-8
78. Myopericytoma – Multifocal Epstein Barr virus (EBV)-associated myopericytoma in a patient with AIDS, Neuropathol Appl Neurobiol. 2008 Feb; 34(1):115-7
79. Nasopharyngeal Cancer [Expression of Epstein-Barr-virus-encoded small nuclear RNA in nasopharyngeal carcinomas of Aegean Turkish patients, Virchows Arch. 2008 Apr; 452(4):411-4]
80. Neuroendocrine Carcinoma – Small-Cell Neuroendocrine Carcinoma of the Nasopharynx: Report of a Rare Case Lacking Association With Epstein-Barr Virus, *International Journal of Surgical Pathology* 2008 May 28
81. Nonrhabdomyosarcoma Soft Tissue Sarcomas
82. Oculoglandular syndrome associated with reactivated Epstein-Barr-virus infection, British Journal of Ophthalmology 2008; 92(6):740.
83. Normal-tension glaucoma - Anti-Ro/SS-A positivity and heat shock protein antibodies in patients with normal-pressure glaucoma, American journal of ophthalmology 1998; 125(2):145-157; Antiphosphatidylserine antibodies are elevated in normal tension glaucoma, Clinical and Experimental Immunology. 2001; 125(2):211–215.
84. Oral Manifestations of Systemic Diseases; Some Crohn's Disease
85. Periodontitis (Patient with severe periodontitis and subgingival Epstein-Barr virus treated with antiviral therapy, J Clin Virol. 2008 Jun; 42(2):176-8)
86. Periorbital Infections
87. Pharyngitis
88. Pharyngitis, Viral; Pharyngitis
89. Pityriasis Lichenoides

90. Pneumonia, Viral; Lymphocytic Interstitial Pneumonia
91. Posttransplant Lymphoproliferative Disease
92. Pregnancy- and Fetus-related disorders – Fetal exposure to herpesviruses may be associated with pregnancy-induced hypertensive disorders and preterm birth in a Caucasian population, BJOG. 2008 Mar; 115(4):492-500
93. Rasmussen's encephalitis
94. Reye's syndrome
95. Severe Combined Immunodeficiency
96. Sjögren Syndrome; Sjögren Syndrome; Sjögren Syndrome; Sjögren Syndrome
97. Some sarcoidoses
98. Splenomegaly
99. Telogen Effluvium (stress- or trauma-induced premature hair-graying)
100. T-Cell Disorders; Some B-cell lymphomas and other disorders; Non-functional antibodies
101. Tonsillitis and Peritonsillar Abscess
102. Transplants, Renal
103. Transverse myelitis
104. Unilateral laterothoracic exanthem with coincident evidence of Epstein-Barr virus reactivation: exploration of a possible link., Dermatol Online Journal 2008 Jan 15; 14(1):24
105. Unusual neurologic findings in childhood (Journal of Child Neurology 2000; 15:791-796)
106. Upper Respiratory Infection
107. Viral Infections of the Mouth
108. Viral Meningitis; Meningitis; Meningitis, Aseptic
109. Vulvar Ulcerations – Picture of the month quiz case. Vulvar ulcerations resulting from acute Epstein-Barr virus infection, Arch Pediatr Adolesc Med. 2008 Jan;162(1):86-7

Table 2 – Autism Prevalence Rates Around the World (2000-2008)

Continent/Region	Country	Approximate Prevalence Rate
North America	Canada	65/10,000=1/154
	United States	66/10,000=1/152
Caribbean	Haiti, Amer. and Brit. W. Indies, Martinique et al.	Insufficient data
Central America	Mexico, Guatemala, Costa Rica et al.	20/10,000=1/500
South America	Brazil, Venezuela, Chile, Peru et al.	20/10,000=1/500
Northern Europe	Finland	12/10,000=1/833
	Sweden (includes large immigrant population)	53/10,000=1/86
	Denmark	12/10,000=1/833
	Iceland	13/10,000=1/769
	UK and Ireland	116/10,000=1/86
Western Europe	Belgium, Luxemburg and The Netherlands	20/10,000=1/500
	Germany	20/10,000=1/500
	France	20/10,000=1/500
	Spain and Portugal	
	Principalities	
	Austria and Switzerland	
Southern Europe	Italy	20/10,000=1/500
	Greece, Crete, Malta et al.	20/10,000=1/500
Eastern Europe	Russia, Poland, Hungary, Czech and Slovak Republics et al.	Insufficient data
Southeastern Europe	Albania, Bulgaria, Montenegro, Serbia, Croatia, Romania, et al.	
Middle East	Syria, Lebanon, Israel, Saudi Arabia, Iran, Iraq, Qatar et al.	10/10,000=1/100
North Africa	Egypt, Libya, Morocco, Algeria et al.	Insufficient data
Mid-Equatorial Africa	Nigeria,	Insufficient data
Southern Africa	Angola, Botswana, South Africa, Zimbabwe, Zambia, Swaziland	
South-Central Asia	India, Bangladesh, Pakistan	Insufficient data
Eastern Asia	Japan	89/10,000=1/116
	China	Insufficient data
	Korea	Insufficient data
South-East Asia	Taiwan, Singapore, Thailand	Insufficient data
Southwestern Asia	Turkey	
Oceania	Australia	39/10,000=1/256
	New Zealand	20/10,000=1/500
	Papua New Guinea	20/10,000=1/500

Figure 1 – Autotoxicity

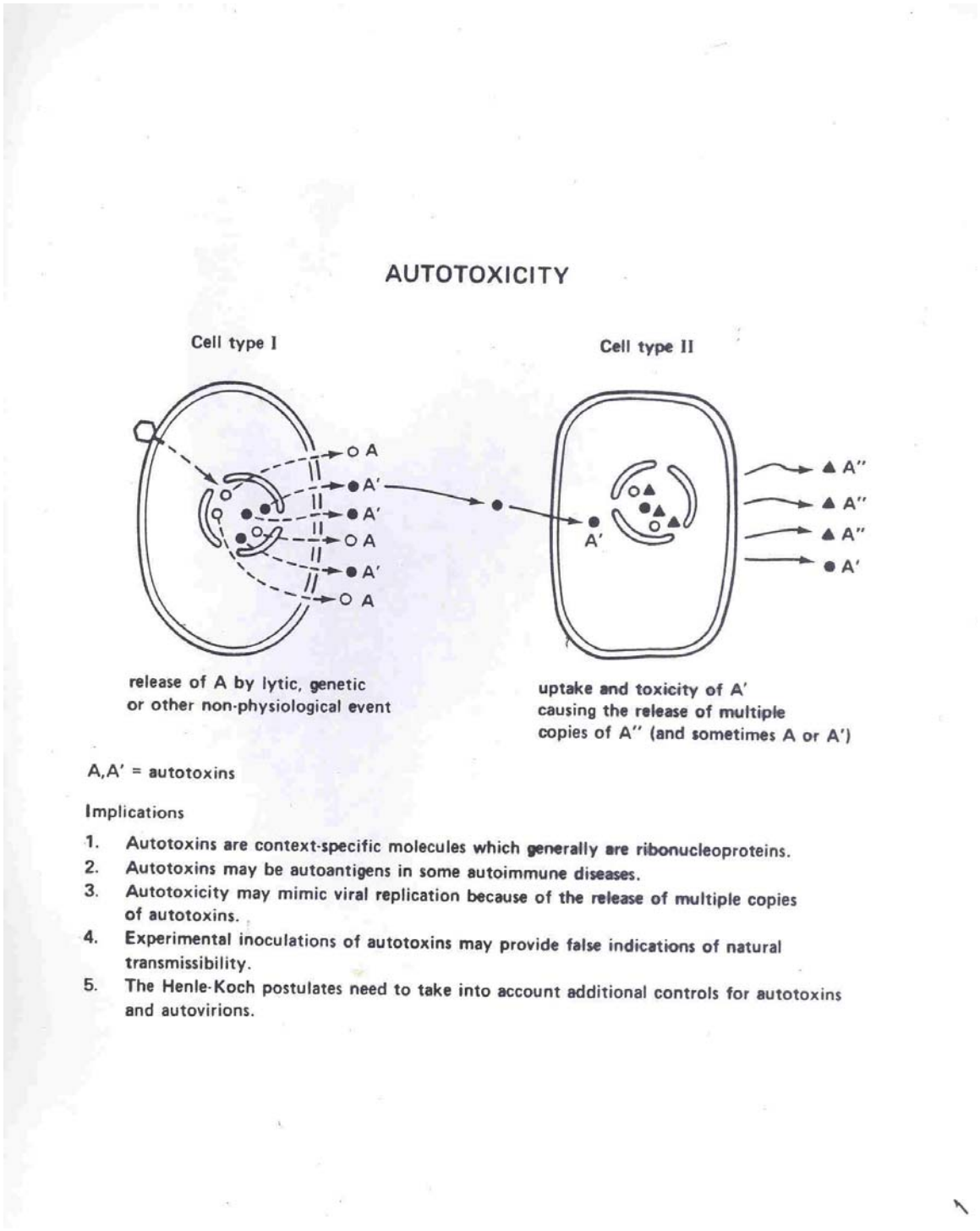
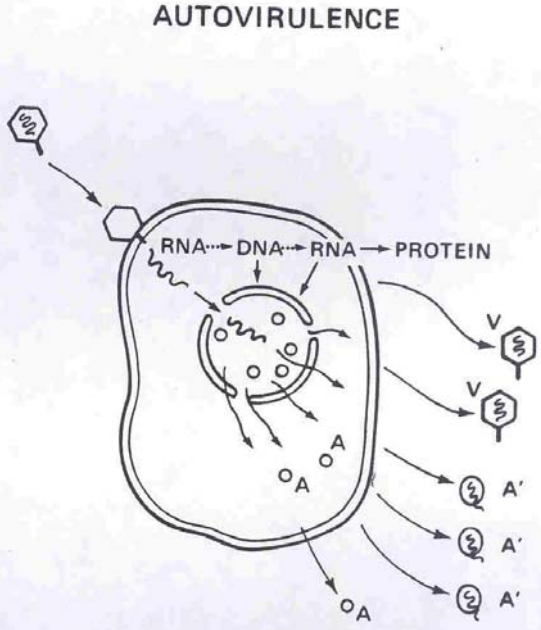


Figure 2 – Autovirulence



V = virus
A = autotoxin
A′ = autovirion

Implications

1. Context-specificity of autovirions generally is based on the source of the small, regulatory RNA contained within them.
2. Autovirions may be associated with some autoimmune diseases.
3. Autovirions may appear to be replicated, although the number of autovirions may depend on the transcription of some viral or other nucleic acid product.
4. Autovirions may mimic viruses both in their transmissibility and their apparent replicability.
5. "Slow viruses" may be autovirions or autotoxins.
6. Adenoviruses and Epstein-Barr viruses can produce autovirions.

Figure 3 – Schematic Representation of Aberrant Transcription and Translation Products

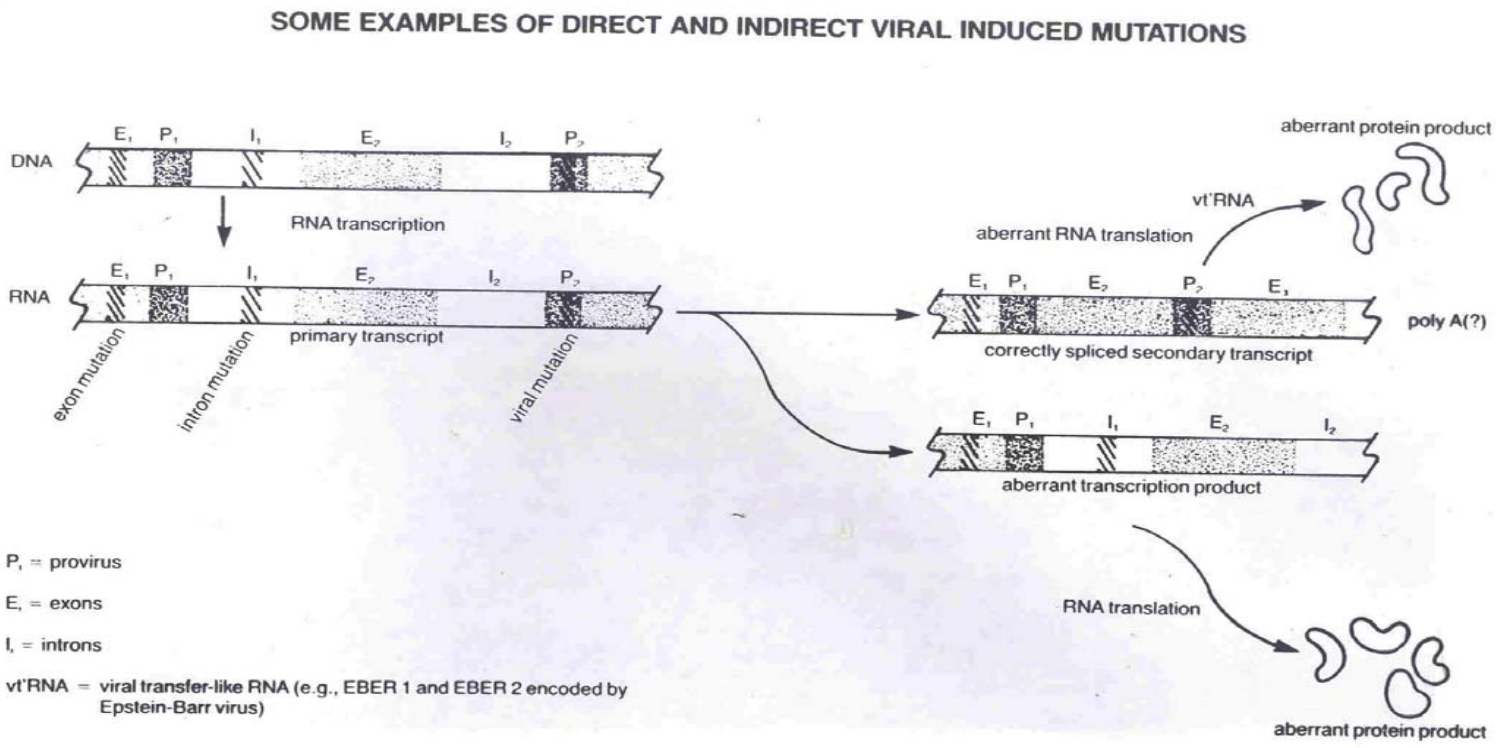


Exhibit A – Schematic Views of Preliophic Moleculator

1/5

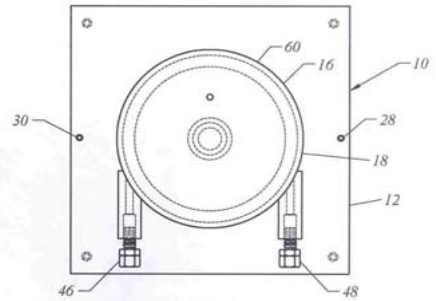


FIG. 1

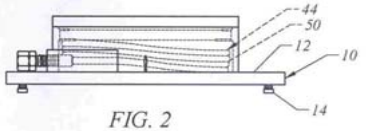


FIG. 2

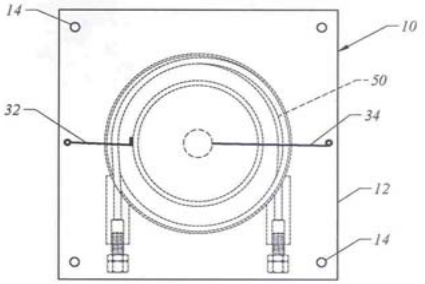


FIG. 3

Exhibit B – Additional Schematic Views of Preliophic Moleculator

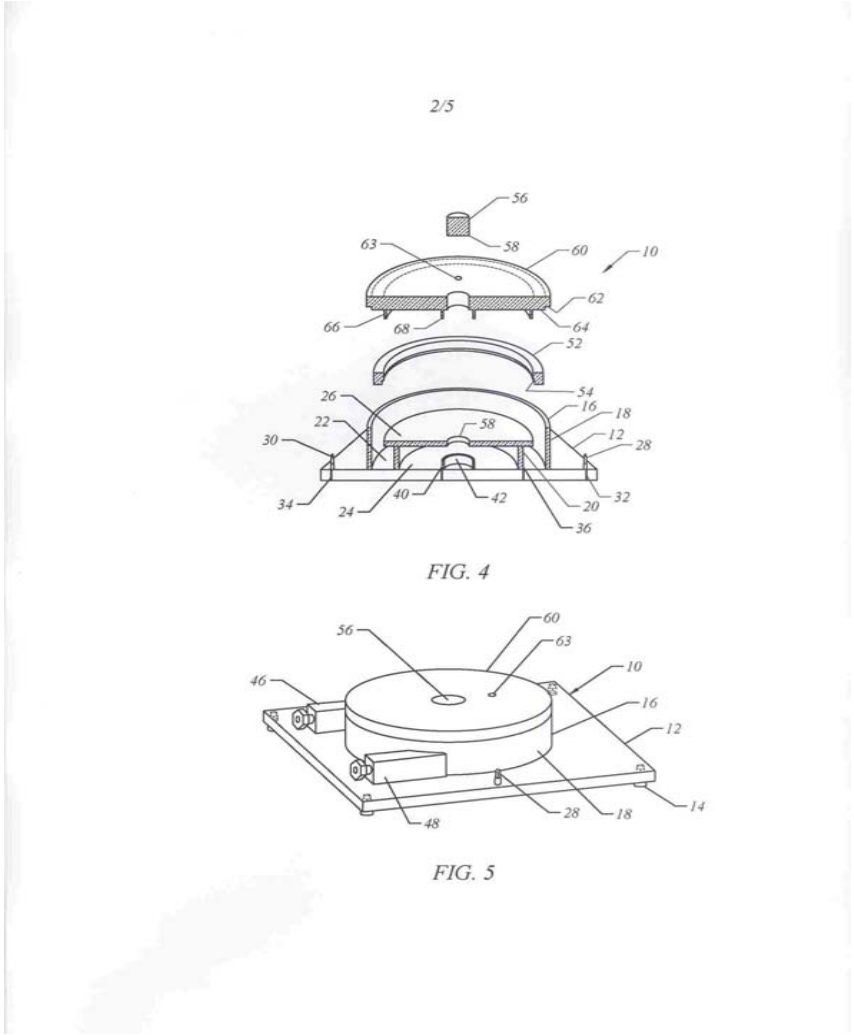
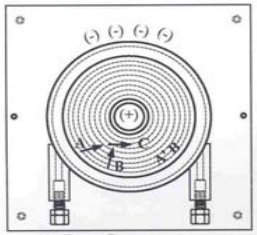


Exhibit C – Schematic Views of Prototypical Preliophic Moleculator Processes

3/5

PRELIOPHIC MOLECULATION PROCESSES

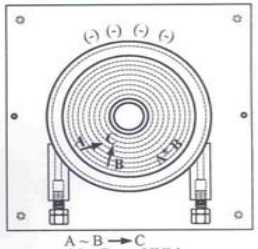
MOLECULAR MIMICRY



A ~ B → C
A' ~ B → NULL
A' IS ABERRANT TRASLATION PRODUCT OF A

FIG. X1

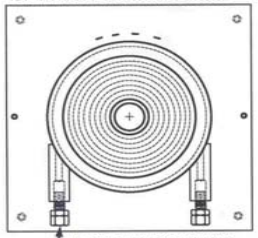
MOLECULAR CHIRALITY



A ~ B → C
A* ~ B → NULL
A* CHIRAL OPPOSITE OF A

FIG. X2

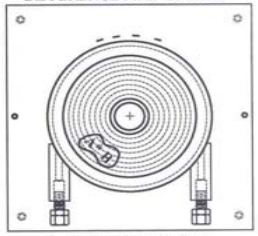
MOLECULAR EMULATION OF WARM AND COLD BLOOD



INPUT TEMPERATURE REGULATED TO BE CONSTANT VERSUS INPUT TEMPERATURE IS COLD OR VARIABLE

FIG. X7

JUST NOTICEABLE DIFFERENCE PHENOMENA



A ~ B ARE REAGENTS WITHIN A "JUST NOTICEABLE" DISTANCE - THE DEVICE AND PROCESS CAPTURE INTERACTIONS AS FUZZY AND ACCURATE PROCESSES

FIG. X8

Exhibit D – Additional Schematic Views of Prototypical Preliophic Moleculator Processes

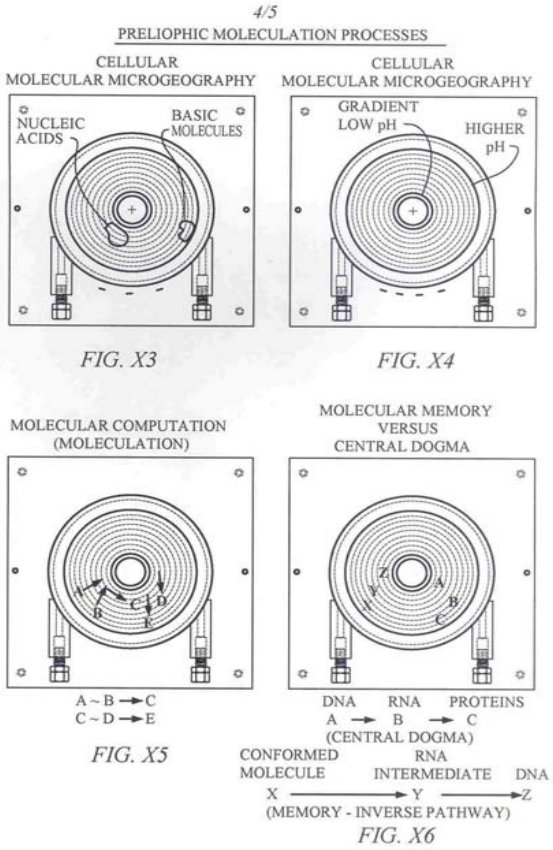


Exhibit E – Additional Schematic Views of Prototypical Preliophic Moleculator Processes