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New Theory of HIV Diversification

Why it may never be possible to make a protective vaccine

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Running Head: *Somatic Ig Hypermutation Diversifies HIV*

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Abstract

Several observations suggest that the mutation rate of the Human Immune Deficiency Virus (HIV), the causative agent of Acquired Immune Deficiency Syndrome (AIDS), is much higher than generally believed. This evidence is briefly reviewed. A new speculative theory for HIV diversification (in development since 2013) is thus proposed whereby the virus co-opts the host's somatic hypermutation (SHM) machinery normally targeted to rearranged immunoglobulin (Ig) variable genes (VDJs) within antigen-activated Germinal Centre B lymphocytes. The pessimistic conclusion - that a conventional vaccine is impossible – is a message not really welcomed in this modern age addicted to only positive scientific results. We argue this should be taken as a spur to approach viral prophylaxis and therapy from entirely new directions. Viruses, particularly HIV and its antecedents, have had billions of years of both cosmic and terrestrial evolution to figure out, by trial and error, how to multiply and infect the next host cell. The implications of our novel and plausible HIV immune evasion strategy is discussed both for the host-parasite relationship and current vaccine research. Because the straight forward and simple idea in this paper has been in preparation for three years it has been found necessary to add a Post Script to this viXra.org submission.

Introduction

It is now 35 years since HIV/AIDS burst unexpectedly on the scene. The pandemic has unleashed a vast research effort and huge strides have been made in understanding the medical biology of pathogenic retroviruses (Boyd 1997; Ryan 2004) and their effects on the immune system (Brumme et al, 2010) and the evolution of the wider genome (Dawkins et al, 1999; McLure et al, 2013; Wickramasinghe 2012; Steele 2014, 2015; Wickramasinghe and Steele 2016). Indeed the literature is vast – almost every relevant topic has been investigated in depth and this literature can be accessed by a simple Google search with a precise question. Since the mid 1990s HAART (highly affective antiretroviral therapy) allows long term survival and much of the urgency has thus subsided in other areas of protective immunotherapy (Palella et al 1998). Nevertheless it is still an unpalatable fact that all efforts to create a truly protective *immunological* neutralizing vaccine have come to naught. The consensus belief is that the high HIV mutation rate – much like the high mutation rates in other RNA viruses such as influenza, and positive-strand RNA flaviviruses (Sanjuan and Domingo-Calap 2016) – mitigates against success. The belief in eventual success however prevails - eventually a new trick or angle will be found allowing the production of a traditional protective viral vaccine, much like the immunological success with the less variable polio virus, small pox virus and, more recently, Ian Frazer's herpes papilloma virus (HPV) where a protective vaccine can be produced against cervical cancer.

So, in the current era of HAART treatment, the urgency really has eased to produce a genuinely protective vaccine. Nevertheless much highly expensive research, funded by literally hundreds of millions of scarce tax-payer dollars, is still devoted to HIV vaccine research each year. The tacit suspicion is *we are digging the same fruitless hole even deeper.* Indeed, we suspect that the field, and Mankind generally, *knows this* and would welcome truly radicle new ideas to

both tackle HIV and better understand the explosive emergence of new virulent viral epidemics (e.g. see such analyses in Wickramasinghe 2012; Wickramasinghe and Steele 2016). It is in this spirit (and see Post Script) we submit a radically different yet speculative molecular model to explain HIV's highly effective immune evasion strategy, and thus the difficulty this poses for all contemporary vaccine development. If our explanation has scientific value it should stimulate efforts to take our novel proposal seriously, or even disprove our proposal by observation and experiment. Our suggestive mechanism is not overly pessimistic as each HIV survivor would have a degree of immunity if exposed to another new retroviral pathogenic variant.

Multifaceted Immune Evasion Strategies

The striking facts about HIV are its multifaceted immune evasion strategies. Many pathogenic viruses share these but HIV seems to have a patent on the process of keeping one step ahead of the immune system. For antibody-mediated immunity the somatic hypermutation (SHM) process of Ig diversification is clearly not fast enough – it seems always a step behind the latest viral mutant. Why is this so?

The current mainstream theory is that HIV infects $CD4^+$ T cells, integrates its provirus in some of them and multiplies thus destroying $CD4^+$ cells and causing ineffective adaptive immunity and then rapidly mutates to further evade the residual ongoing immune response (involving potentially neutralising antibodies produced by B lymphocytes and $CD8^+$ cytotoxic T lymphocytes, CTLs).
The high mutation rate is attributed to the "error prone" reverse transcription (RT) step, advanced by Howard Temin and colleagues estimated at 10^{-4} to 3.4 x 10^{-5} mutations per bp per replication cycle (Dougherty and Temin 1988; Mansky and Temin 1995). For a viral RNA genome of 10 Kb this is about one point mutation per proviral cycle. However all the evidence points to a much higher mutation rate during infection.

Known early mutagenic events after infection include error-prone reverse transcription itself; anti-viral activity of APOBEC3G deaminase (Harris et al 2004; Chiu and Greene 2005; Russell et al 2009; Kim et al 2010; Refsland and Harris 2013) targeting single stranded (ss)DNA (C-to-U in first cDNA strand when ssDNA exposed by the digestive action of RNase H); and ADAR deaminase-mediated A-to-I RNA editing, which if affected before the RT step on double stranded (ds)RNA portions of the viral genome (Doria et al 2009) will result in A-to-G mutations in the proviral DNA. Further, it is well known that in any *in vivo* population of newly minted HIV particles most (> 99.9%) are empty or replication defective virions. Fewer than 1 in 1,000 to 1 in 10,000 peripheral blood mononuclear cells in infected individuals have integrated proviral DNA (Harper et al 1986). The frequency of cells carrying transcriptionally active provirus is an order of magnitude or two lower,10^{-4} to 10^{-5} (Brown 1990). The sensible conclusion, given these facts, is that the *in vivo* mutation rate is much higher than generally believed.

So the highly effective antiretroviral therapy involving three or more different drug targets on the HIV life cycle has been a triumph of clinical medicine (Palella et al 1998). The strategy really has allowed long term survival of HIV-positive patients and their ability to lead productive lives. But this success came at a scientific price - it masked some clear facts that were just emerging in a number of areas, or are emerging now, but are not highlighted as they do not seem relevant under the current explanatory paradigm. Many of these facts are half forgotten but will be revived here in the context of a new model of HIV diversification.

One main early event in HIV infection (as with many other viruses) is sustained polyclonal B cell activation (Lane et al 1983; Schnittman et al 1986). However definitive studies also show that HIV-1 can infect B cells, particularly activated B cells (Gras et al 1993) as well as macrophages and other white cells, not just $CD4^+$ T cells. Indeed HIV-1 can infect and produce provirus and then progeny

virus in activated B cells in an efficient antibody and complement-dependent manner *in vitro* (Gras et al 1993).

The HIV virus has, as mentioned, multiple immune evasion strategies including envelope protein molecular mimicry, the capturing and re-expression of portions of host genes (Ig, TCR, MHC), effects on host MHC Class I and Class II gene expression, amongst others. Veljkovic (2005) has reviewed much of this evidence. However there is one set of captured host sequences, now embedded within the *Env* gene sequence which present a puzzle pregnant with implications. viz. Ig RSS. These are immunoglobulin Recombination Signal Sequences which are targeted by the host's Recombination Activating Genes (RAG 1/2) involved in the V,D,J recombination steps in Ig and T cell receptor (TCR) somatic gene assembly in the ontogeny of development of mature B and T lineage cells. In the case of the Ig DNA V->DJ rearrangement, this is an absolute pre-requisite for the next steps viz. a). targeting of activation-induced cytidine deaminase (AID) to VDJ sequences converting cytosines to uracils (C-to-U); b). these C-to-U lesions then mature to Abasic sites and single stranded DNA nicks thus initiating the processes of targeted somatic hypermutation and class switch recombination (Di Noia and Neuberger 2007; Teng and Papvisilliou 2007). The mechanism of Ig SHM is an RNA/RT-based mechanism (the "Reverse Transcriptase Model" of SHM) which produces strand-biased mutations at A:T and G:C base pairs (Steele 2009; Lindley and Steele 2013). All the SHM molecular data gathered since 1980 supports directly or indirectly this RNA/RT-based mechanism (Steele 2016). This involves error-prone cDNA synthesis via an RNA-dependent DNA polymerase (DNA Polymerase-η) copying the Ig pre-mRNA template and integrating the now error-filled cDNA copy back into the normal chromosomal site. That is, AID induced dC-to-dU lesions and long-tract error-prone cDNA synthesis of the transcribed strand by the SHM specific DNA Polymerase-η acting as a reverse transcriptase (Franklin et al 2004).

Why should HIV carry such sequences for DNA binding proteins in its envelope

protein amino acid sequence? Indeed it is worth quoting Veljkovic in full on these and other curious embedded *Env* sequences:

> "The nucleotide sequence GCTGGTGG, encoding the amino acids QLV of this motif, represents the *Chi* signal promoting generalized recombination in prokayotes ……. Downstream from the putative *Chi* sequence, a heptamer sequence, CAGTCTG, has been identified… Five of the seven bases in this nucleotide sequence match the consensus recombination signal CACTGTG already found to be involved in V-(D)-J recombination of the Ig gene … It is of note that a similar sequence exists at the same position in the gp120 gene of nearly all HIV-1 isolates.. " (Veljkovic 2005).

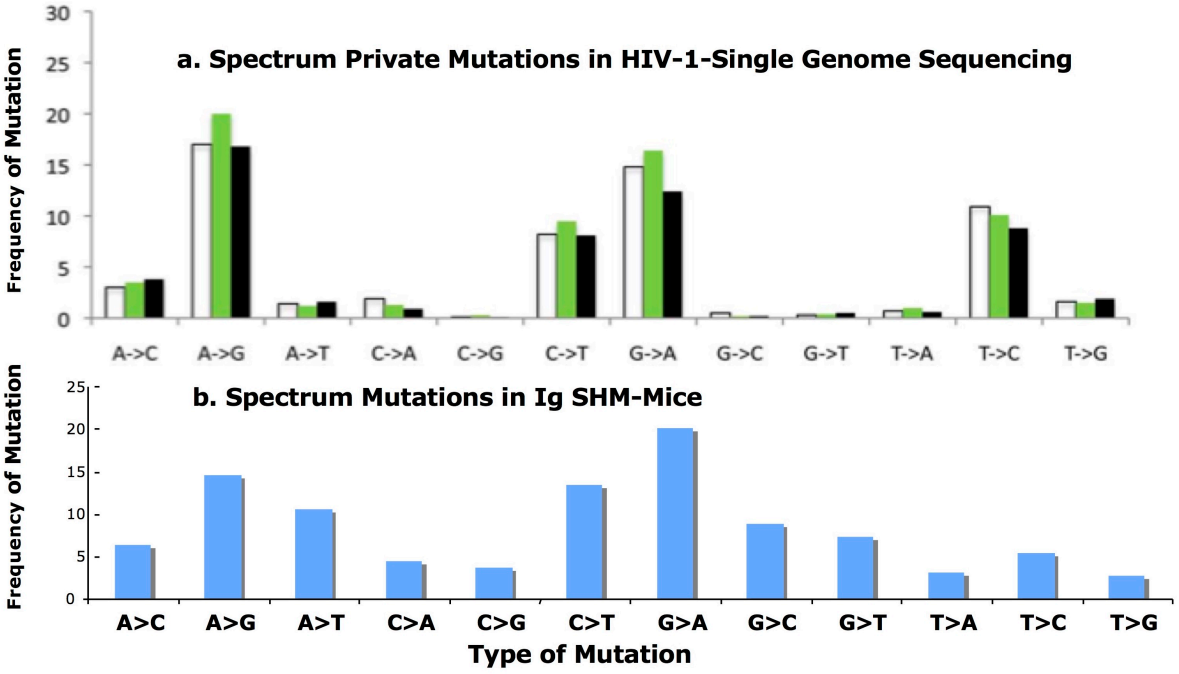

Figure 1 Comparison of the HIV Mutation Spectrum with the Strand Biased Ig SHM Spectrum. *Figure 1a* From control data in Figure 5 in Mullins et al 2011. Specificity of private mutational change over time. Open bars are from day 0, shaded bars are from day 56, and black bars are from day 125 post infection. the Y-axis shows the total number of private mutations in a group of 10 subjects. *Figure 1 b* Adapted from Table 1 Steele 2009 PCR hybrid artefact minimised data.

Another curious fact which is now becoming evident is the spectrum of base

substitutions within HIV genomes. Mullins and co-workers have provided a good example of point mutation spectra from single genome HIV sequencing (Mullins et al 2011). Note the similarities in these HIV-1 mutation spectra and the somatic mutation pattern observed in murine rearranged Ig VDJ genes following somatic hypermutation *in vivo* (Figure 1). However this comparison while suggestive is also quite misleading if corrected for base composition (which is always applied to the Ig mutation data (Steele 2009) but not the HIV data). Thus the base composition of any single HIV-1 genome is in fact *very similar* to the base substitution spectrum shown in Figures 1a suggesting that the basic strand biased pattern of mutations of A exceeding mutations of T (A>>T) and mutations of G exceed mutations of C (G>>C) has been laid down and embedded in human retroviral genome structures over presumably billions of viral life-cycles over potentially millions if not billions of years (Wickramasinghe 2012; Wickramasinghe and Steele 2016). These are the fundamental strand biases noted in the AID-initiated Ig SHM process (Steele 2009) and human cancer genomes (Steele and Lindley 2010; Lindley and Steele 2013; Steele 2016) which are best understood as being generated via based-modified Ig pre-mRNA template intermediates and error–prone cellular reverse transcription. To this point, as far as we are aware, it is not clear how wide spread these patterns are in other biological systems for DNA diversification; although it is emerging as a fundamental somatic mutation pattern in higher vertebrates.

Why should *Env* have embedded V-D-J RSS?

Let us focus more precisely on why HIV-1 should need to have embedded a captured nucleotide sequence such as the RSS involved in immunoglobulin V-D-J recombination. The RSS DNA sequence in this sense is *never expressed* as protein. It is the target site for binding by the RAG1/2 recombinase enzymes that carry out Ig re-arrangement i.e. V-D-J recombination. Somatic Hypermutation of Ig genes targets (*only*) rearranged V-D-J sequences. However embedded heptamers in the 3’ region of V_H regions are known to be involved in V_H

replacement at $V_HD_HJ_H$ sites (Chen et al 1995). Thus it is conceivable that the embedded heptamer is involved in recruiting the somatic hypermutation machinery and now targeting the RNA/RT-based Ig hypermutation mechanism just discussed to the integrated 10 kb provirus DNA sequence. Given that in cancer genomes the RNA/RT-based AID and ADAR deamination signatures are targeted (in a codon-context fashion) to numerous non-Ig genic sites across the cancer genome, this is a not unreasonable assumption (Lindley 2013; Lindley et 2016). Maybe the reason HIV-1 has done this is to target the Ig SHM machinery to the viral envelope *Env* gene in particular to produce protein variants that keep a step ahead of specific antibodies - which are also employing the same mutation mechanism in the same hypermutating B lymphocyte!

HIV diversification – A new theory required

The observations outlined above suggest that a new theory to explain HIV diversification is required. Given that the host already has an efficient somatic hypermutation process targeted to immunoglobulin variable genes (Ig SHM) it seems only logical to explore the possibility that HIV may have found a way to co-opt Ig SHM to enhance its ability to evade the immune response. Indeed, Balin et al (2008) have also suggested this and investigated this possibility in part by showing that the HIV envelope coding sequence when transfected into a B cell line *in vitro* mutates in a manner consistent with the direct action of AID deamination of DNA creating C-to-U mutagenic lesions. By itself this is not convincing as we know that any DNA sequence parked in the VDJ locus of a hypermutating B cell (or any where else in the B cell genome as a V(D)J transgene) will be an AID target and hypermutate (Yelamos et al 1995). However full blown Ig SHM *in vivo* is *much more* than just AID deaminase action (producing the strand biased base substitution pattern in Figure 1b). The data suggest involvement of error-prone DNA polymerase-η (Zeng et al 2001), which is the only known error-prone DNA polymerase involved in physiological SHM *in vivo* (Delbos et al 2007), and DNA polymerase-η happens also to be an efficient

reverse transcriptase *in vitro* (Franklin et al 2004).The signatures of other putative base modifications of RNA (adenosine-to-inosine RNA editing, Steele et al 2006) are also implicated in the generation of the complex set of strand-biased base substitution signatures observed at AID-mediated lesions (Steele 2009; Steele 2016).

We suggest the following model:

• HIV-1 infects many different lymphoid and related white cells - but particularly *activated B cells* in the early phase of infection.

• A fraction of infected activated B cells carry a productive provirus.

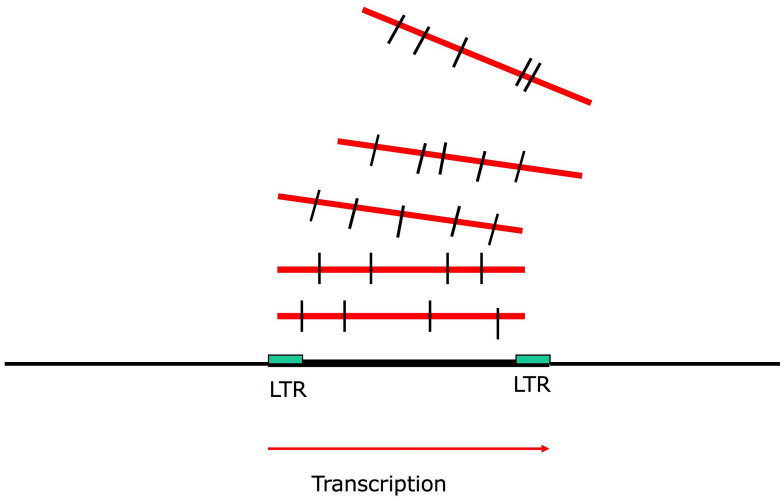

Figure 2 Ig SHM targeted hypermutation at HIV provirus loci. A single provirus bounded by 5' and 3' long terminal repeats (LTR) will produce numerous variant HIV RNA sequences driven by the endogenous Ig SHM process - many of these will integrate back into the proviral site by target site reverse transcription (TSRT, Luan et al 1993; Steele et al 1997; and see, particularly for the mechanistic RT copying and site-specific integration steps, Steele 2009,2016; Lindley and Steele 2013)

• During somatic hypermutation of the HIV-infected B cell in an antigen-activated Germinal Centre (or at other possible non-Germinal Centre sites, Di Niro et al 2015) the SHM machinery involving AID deaminase, Uracil DNA glycosylase, ADAR1 A-to-I RNA editors, RT-Pol-η , subverted mismatch repair MSH-2/MSH-6 (MMR) etc. (Steele 2009; Steele 2016) are recruited and now target the

integrated transcriptionally active HIV-1 provirus (as well as the endogenous Ig V(D)J site).

• The mutant B cell surviving the Germinal Centre reaction will produce a single mutant antibody but also *numerous mutated LTR bounded HIV-1 variants*. The spin-off of mutated HIV-1 RNA genomes is shown schematically in Figure 2.

The implications of this model for HIV vaccine research are two fold:

1. The HIV-1 mutant population will *always* be a step ahead of the somatic antibody variants produced during affinity maturation.
2. It will *never* be possible to produce an effective conventional immunological vaccine for HIV without controlling SHM in B cells.

In this scheme HIV has come up with the ultimate immune evasion strategy. It also has developed a means of diversification, as required or on demand. In this way the virus prepares itself to remain ahead of the host whilst it is also diversifying. Further, the survivors are being exposed to many new retroviral variants. If the explanation is to have any value for vaccine research it may stimulate scientific efforts to take such a possible HIV strategy into account or disprove our proposal.

Postscript *: Retroviruses, Evolution and HIV Immunity*
26th December 2016

The formal argument and critical analyses herein was essentially in place by early 2014. However, it is not surprising, on reflection, that our HIV proposal is at the cross roads of many controversial currents in modern biomedical science and social policy. The multiple controversies that have roiled the globe for 35 years can be encapsulated in a series of questions : Who first discovered the HIV/AIDS virus? Where did the virus come from? Is it just another harmless endogenous-

like retrovirus with the host's misdirected inflammatory immune response the main cause of the collateral damage and immune system collapse? Why has the field of Immunology, and thus Immune Prophylaxis, been blindsided by HAART medicines? Will such an explosive, unexpected and virulent retroviral epidemic happen again targeting the human immune system in a sexually transmissible mode (catching the CDC and Pirbright Institutes flat-footed once again)? Why has a vaccine not been developed?

It is to be expected, on further reflection, that after the expenditure of billions of tax-payer dollars, the rise of numerous powerful biomedical centres, and thus prestigious powerful biomedical careers, the last thing the HIV field wants to hear about is a plausible reason why they have been caught flat-footed and why they have failed to develop an effective protective vaccine. The huge social cost of unemployment within the biomedical-bigpharma-industrial complex is just too painful to confront (we would imagine).

However, the back story to this paper is of broad scientific and social interest – for public health and science policies in particular. It is clear that modern science needs to be both reorganized and returned to its tried and true scientific roots. viz. the search for enduring scientific truths by tried and true objective methods, centred on individuals or small groups of collegial yet competing creative scientists. Such an approach is expected to be far less expensive and more cost effective. It might seem old world in its goals, yet quite frankly, modern science is shredding its credibility at a shockingly high paced rate- and as Alexander Unzicker has presciently forecast (Unzicker and Jones 2013) the day of reckoning is nigh and the "bubble" is about to burst.

It was therefore decided to give the paper a decent burial in an online scientific archive yet with a clarifying Post Script putting the problem in its proper perspective. Indeed there have been significant developments since 2013 which can now also be addressed.

Sir Karl Popper and Modern Science

Both Physicists and Biologists are ultimately in the business of providing rational and plausible explanations for the causes of natural physical and living phenomena (for living systems, from a Physics perspective, also see two important books by Mai-Wan Ho (2008) and Chandra Wickramasinghe (2015a).

The guiding philosophical principle, articulated most clearly and comprehensively (in response to David Hume's problem of induction) has been Sir Karl Popper's *Falsification Criterion*. It was advocated to not only decide factual matters in Science but also for the healthy running of a free and open civilized Society (viz. piece-meal social engineering in response to problems as they arise by trial and error elimination).

He first outlined his theory over 80 years ago in his *Logic of Scientific Discovery*, then in a series of great works including his powerful World War II effort written in New Zealand, *The Open Society and its Enemies*. He lived until 1994 (92 yr) and thus witnessed the crushing defeat of both Hitler's Nazi Germany, Mussolini's Fascist Italy, Hirohito's Imperial Japan and then the Reagan/Thatcher-driven collapse of the Soviet Union. We need more Karl Poppers in the world today because dangers and threats like these to civilized open societies still confront us as manifest in radical Islamic Fascism.

Sadly, there has been a distinct drift away in modern times from the scientific necessity to advance testable theories with clear plans for their refutation. If the process is successful it should confirm that the specific part of a theory tested may be true. But if the theory is refuted by severe tests it implies that the causes of the phenomenon under investigation requires a new testable theory – a clear case of *Unended Quest* as Karl Popper articulated in his famous 1976 autobiography. Thus " ..the method of science is the method of bold conjectures

and severe and ingenious attempts to refute them".

This should be a cold hard law of modern scientific practice. Because if Paul Feyerabend's *Anything Goes* relativism *Against Method* is codified as the acceptable norm of behaviour, it leads to knaves, thieves, mafia types and scoundrels who can game the system gaining wrongful scientific recognition, a phenomenon now blossoming and quite destructive to the credibility of modern Science and the Nobel committee. The scandalous 2011 Nobels in Physiology or Medicine to Bruce Beutler and Jules Hoffman induces incredulity; and, quite frankly, is the final nail in the coffin for the once proud and great Nobel Prizes unless matters are urgently taken to change things fast (Garwood 2011, 2012). Once the indefinable and potentially fragile issue of "credibility" is torn asunder - with both the public and tax-payer, and the scientific community - it is unlikely to be recovered any time soon, if ever. The shattering of the hard won trust in the Nobel tradition must be taken seriously by the committee – such that when the Nobel website invites suggestions it takes submitted suggestions seriously and starts to change the rules for awarding Nobel Prizes. A simple public announcement would do the trick as a 2017 New Year's resolution.

The failure of modern Physics over the last 40 or so years, to adhere to Popper's very sensible advice, is most eloquently illustrated by an important book published in 2013 by the theoretical Physicist, Alexander Unsicker (with Sheilla Jones) entitled *Bankrupting Physics: How Today's Top Scientists are Gambling Away Their Credibility*. Unzicker has gone several important steps further than the previous, and also devastating, critique of "String Theory" by Lee Smolin in his *The Trouble with Physics* (2006); and also Peter Woit in his *Not Even Wrong*. (2006).

Indeed, Alexander Unzicker completely exposes an overt and dangerous delusional tendency in modern Theoretical Physics (the "explanation arm" of Physics charged with providing "rational explanations of natural Physical

phenomena" for public consumption). As Unzicker explains, modern Physics has gone completely feral and disconnected itself from testable and observational physical reality (instance Max Tegmark's very interesting and readable, yet largely untestable, *Our Mathematical Universe*, 2014 – but Max should not be promoted as "Rock God" of Cosmology – what an outrageous marketing campaign). Modern theoretical physicists are advancing theories which no longer are able to be tested by observation and experiment, not even in principle.

Modern science is in deep trouble as the problem identified by Unzicker is not confined to Physics, but also manifest in Biology, particularly its supposed "quantitative" disciplines in the Biomedical Sciences (Molecular and Cellular Biology, Virology, Immunology, Genomics) and Evolutionary Sciences (which would include environmental studies which would take in "Climate Change" phenomena and Ecology).

Cosmic Biology- Fred Hoyle, Chandra Wickramasinghe and Tom Gold

Early 20th Century Physics (till about mid-Century) had a fluid and evolving (revolutionary) series of stages through the work of Planck, Einstein, Rutherford, Bohr, Schrödinger, and Feynman, which was successful through its sheer necessity to completely extend and qualify the limits of Newtonian Physics. A necessary addition now to this Pantheon would be the great Astrophysicists Sir Fred Hoyle, N. Chandra Wickramasinghe and Thomas Gold. The scientific achievements of these three men, separately and together, fully illuminates the great and grand Popperian traditions of Science. Their discoveries and clear explanatory theories have ensured their place in the Pantheon.

Thus the 20th Century achievements in Physics were characterized by the advancing of testable theories – which a cynic would devalue by stating blandly "Yes but it all ended in disaster, culminating in Hiroshima and Nagasaki."

Be that as it may, that does not negate the necessity to demand in science that all propositions, theories and explanations, *must be Popperian*. The potential for refutation of a theory is what separates science form delusion and superstition.

Indeed Modern Biology has been trapped for over 100 years in a dead theory. It is dogmatic closed loop system of Neo-Darwinism and Population Genetics Statistical Theory (based on simple Mendelian ideas). This trap has only been scientifically fruitful up to a limited extent but its ability to explain and predict is in steep decline – and as we have shown here (and below) the very paradigm it represents hampers our efforts to understand HIV emergence, diversification (virulence) and thus its control. Surely these intangibles illuminated by HIV should herald a thorough root-and-branch overhaul of the main guiding scientific theories as they are almost certainly deeply flawed.

Great strides have been made over the past 50-60 years in understanding the full extent of an all pervasive "Cosmic Biology" driving the origins and evolution of life on Earth (Wickramasinghe 2012; and also see the great synthesizing and contemporary work of N. Chandra Wickramasinge . *The Search for Our Cosmic Ancestry* 2015a). Further, there is now a far better understanding of clear non-Darwinian evolutionary mechanisms, shaping both the immune and central nervous systems in particular (e.g. Retroviral and RNA/RT-based Lamarckian Inheritance as well as retroviral/retro-element-driven genomic block structure, see Steele 1979; Steele et al 1998; Steele and Lloyd 2015; Steele 2015; Dawkins 2015; Erwin et al 2016). A clear causal chain of new viruses arriving from space driving evolution on Earth can thus be discerned and rationally understood (Wickramasinghe and Steele 2016). Indeed LINE retro-element transposition (and Alu co-mobility) is a *normal* part of genomic rearrangement during specific neuron commitment, much like the V->DJ rearrangement in specific lymphocyte commitment in the Immune System (Erwin et al 2016).

Retroviral/RT Driven Evolution (Terrestrial and Cosmic)

The authors and their colleagues, have worked separately and together on retrovirus-driven issues, including error-prone reverse transcription (RT) processes, in the evolution of higher vertebrate immune systems (and related genomic structure-function issues) since the 1970s (Steele 1979; Steele et al 1998; Steele et al 2011; Williamson et al 2011; Steele and Lloyd 2015; Dawkins et al 1982; Dawkins et al 1983; Dawkins et al 1999; Steele 2015; Dawkins 2015; Lloyd et al 2015). With respect to HIV and "retroviral evolution" in general, viz the genomic duplicative processes generating the polymorphic block (Ancestral) haplotype structure of the human genome, the key concepts can be traced to what is now known as the "*Retroviral-Induction Model* " (Dawkins et al 1999; Steele 2014; Steele 2015 p.95). Thus when a retrovirus infects a human cell all measure of mutagenic processes are unleashed, including: AID/APOBEC-deaminase induced C-to-U events leading to C-to-T mutations, Abasic sites, and ssDNA nicks, as well as ADAR-deaminase induced A-to-I RNA editing events. Both of these DNA and RNA deaminations are now identified as codon-context Targeted Somatic Mutations (TSM) in the human cancer exome. As well as these we have LINE/Alu–retro-element mutagenic mobility (Harris et al 2004; Refsland and Harris 2013; Chiu and Greene 2005; Muotri et al 2008; Doria et al 2009; Jones et al 2013; Lindley 2013; Lindley and Steele 2013; Lindley et al 2016). So as discussed already LINE/Alu retro-mobility now appears as a normal part of specific synaptic neuronal Brain development (Erwin et al 2016). Thus retroviruses and other viruses liberated in Cometary debris trails both add new DNA sequences to terrestrial genomes but also drive further mutagenic change within somatic and germline genomes.

ASI/ICB

For almost 45 years EJ Steele has been a member of the *Australian Society for Immunology (ASI)* and has published often in the Society's journal *Immunology &*

Cell Biology (*ICB*, now a *Nature Publishing Group (NPG*) journal but previously *The Australian Journal Experimental Biology and Medical Science,* which was edited and run by Professors Derrick Rowley and Ieva Kotlaski of The Department of Microbiology at the University Adelaide where EJS completed his PhD under Derrick Rowley on Secretory IgA Antibodies in Intestinal Immunity to Cholera , 1971-1976). The office for the "Australian" journal, as it was affectionately and colloquially known, was then re-located to The John Curtin School of Medical Research, *JCSMR,* during much of the 1990s and 2000s (under Professor Christopher Parish) but has now re-located to the Walter and Eliza Hall Institute for Medical Research (*WEHI*) in Melbourne (Professors Philip D Hodgkin, Gabrielle Belz and other senior Australian Immunologists in the *ASI* run the journal). With respect to the *JCSMR,* EJS was both a *JCSMR* Post Doc (1976-1977; 1981-1985) and a *JCSMR* Visiting Fellow (to Professors Gordon L Ada and Robert V Blanden 1985-2003). Thus EJS has always considered the *ASI*, *ICB* and the *JCSMR* his *alma maters* or his primary "home" in Australian Immunology and Biomedical Science.

The core mechanistic thesis in the present paper, which was developed through much of 2013 into 2014, was submitted to the *ICB* Editorial Office at *WEHI* on 27th April 2014. As indicated EJ Steele had previously published a number of speculative (yet testable) theoretical papers like this (and other more wet-lab experimental papers) in *ICB*. The expectation on submission was collegial "give and take", or a modified MS exchange to and fro, in the traditional way of science and scientific research.

Acknowledgement of receipt of the paper by a journal assistant was swift. Thus on 29th April 2014 :

From: <icb.office@wehi.edu.au>
Reply-To: <icb.office@wehi.edu.au>
Date: Tuesday, 29 April 2014 7:36 am
To: <ejsteele@cyo.edu.au>
Subject: ICB-14-TA-0123V1 Receipt of New Paper by Immunology and Cell Biology
Dear Dr. Steele
On 28th Apr 2014, I received your manuscript entitled "New Theory of HIV Diversification: Why it

may never be possible to make a protective vaccine" by Edward Steele and Roger Dawkins.
Your manuscript has been assigned the Paper #: ICB-14-TA-0123V1.
You may check on the status of this manuscript by selecting the "Check Manuscript Status" link under the following URL:
http://mts-icb.nature.com/cgi-bin/main.plex?el=A2Bq1BKb3A7Fnq7F1A9RRYtvlWJ3ycqLP4Bp42AZ

However a little while later, on the same day, when the email system was checked there was a message from an *ICB* Editor in Leuven, Belgium (!! ??). The following email was received:

From: <icb.office@wehi.edu.au>
Reply-To: <icb.office@wehi.edu.au>
Date: Tuesday, 29 April 2014 7:39 am To: <ejsteele@cyo.edu.au>

Subject: Decision on Manuscript ICB-14-TA-0123V1
Dear Dr Steele
Thank you for the submission of your research manuscript to our editorial office.
The Editorial Board has examined your manuscript and has, unfortunately, deemed it unsuitable for publication in Immunology and Cell Biology. An alternative journal may be more appropriate.
Thus, I regret to advise that we are unable to consider your manuscript for publication in ICB.
I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.
Yours sincerely

So effectively we were informed almost instantly that the paper was unsuitable as soon as it arrived at *ICB*. Immediate contact was made by EJS with the journal in Melbourne to inquire why the rejection was so swift (as that had never happened before). The contact was Professor Phillip D Hodgkin, Professor of Immunology at *WEHI*. He was an old colleague of EJS (a scientific generation younger than EJS) from The John Curtin School of Medical Research (*JCSMR*) and Hodgkin was now both a senior officer (or officer emeritus) in the *ASI* and very familiar with the practices of the society's *ICB* journal – he is now one of Australia's most senior immunologists. The following email was sent:

From: Ted Steele <e.j.steele@bigpond.com>
Date: Tuesday, 29 April 2014 at 1:54 PM
To: <Hodgkin@wehi.edu.au>
Subject: Current editorial policy at ICB?

Dear Phil:

How are you? It has been sometime since we have been in touch. But I am curious to know what the current Immunol Cell Biol publication policy is, particularly with respect to ASI members and those who have published in the Australian journal over many years.

I have written, I thought, a considered (well within my expertise) Theoretical article " to challenge and provoke discussion in the international scientific community" and just submitted it Sunday night to ICB. Today within 3 mins apart I receive an email with assignment of a MS number. Then 3 minutes later I received notification it had been rejected! (see below)

Not only do I think this is strange but unjustified – is a new form of censorship now transposed to science?

I attach the paper and associated submission details – I named you, FN Papvassiliou, GW Both, AJ Hapel, and PJ Gearhart as senior scientists suitable as reviewers.

I have tried to contact Simone Farrer but to no avail thus far.

I am sorry to bring this matter up with you like this but if this is general ICB editorial policy sooner or later it will destroy the journal.

I will try and ring you about this.

Ted
--
Edward J Steele PhD
CYO Honorary Research Fellow
CY O'Connor ERADE Village Foundation

Phil Hodgkin then replied:

From: Phil Hodgkin <hodgkin@wehi.EDU.AU>
Date: Wednesday, 30 April 2014 at 1:54 PM
To: Ted Steele <e.j.steele@bigpond.com>
Subject: Re: Current editorial policy at ICB?

Hi Ted,

Thanks for your message. I agree something is amiss - I'm investigating and will get back to you. I don't think there is any policy change.

All the best,

Phil

The next day the Editor-in-Chief of *ICB* at WEHI Professor Gabriel Belz made contact:

On 1/05/2014, 8:45 AM, "Gabrielle Belz" <belz@wehi.EDU.AU> wrote:

Dear Ted,
I have been looking into the decision that was made on your manuscript recently. I did not handle this manuscript but am looking into it and believe the editor was not completely aware of our Theoretical Article category and how these are normally handled (since I do usually do these but was away).

I expect we will reinstate the submission and be able to send the work for review in the next few

days. I do however, as a courtesy, need to discuss this with the deputy editor who did handle the work in my absence.

I also appreciate that the emails you received suggested that any decisions that were made were done within 3 mins - this is not actually the case, at least as recorded on the Nature site, so it is unfortunate that the acknowledgement and decision emails arrived to you with this type of message.

In any case, I hope that I will be able to convey positive news in the next day or so and thank you for your patience.
Best regards,
Gabrielle

Gabrielle Belz BVBiol, BVSc, PhD, DVSc
Division of Molecular Immunology,
Walter and Eliza Hall Institute of Medical Research,

Within 24 hours we had a stock rejection response which EJS considered quite shocking.

On 2/05/2014, 6:12 AM, "Gabrielle Belz" <belz@wehi.EDU.AU> wrote:

Dear Ted,

The manuscript has been considered at some length. The work is on an interesting topic but one that is perhaps more suited to a specialist clinical journal as it is a little outside the scope of ICB. The manuscript poses some big questions, but the arguments are unfortunately is not well supported in the manuscript by the large base of data in the research area. Thus, we do not feel that the topic is dealt with in sufficient depth to draw the conclusions of the work.

It would be possible to send the manuscript for review. I could not provide any guarantee that the comments would be more positive though.

I appreciate this is perhaps not the feedback you would have liked.

Regards,
Gabrielle

Then a response from Professor Phil D Hodgkin:

On 2/05/2014, 12:21 PM, "Phil Hodgkin" <hodgkin@wehi.EDU.AU> wrote:

Dear Ted,

Sorry that the paper was not reviewed but, of course, Gabrielle and Adrian have to make a lot of decisions and stand by them, and I can't really intervene more than I have. For the record I haven't seen your paper and can't comment on the decision itself, although of course I understand your disappointment.

I presume you copied to me as I also have a fondness for theory and would like to see such papers supported in ICB, which is true. I will do my best to engender more sympathy in future amongst the executive editors. However, it is regrettably true that the term 'theory' does not have the impact or resonance amongst the up and coming generations it did for us.

Do theoretical papers have to be shocking and clash with accepted wisdom to have any value? While I agree your position has an element of truth, it is an extreme view. An idea can be right or wrong and either could be shocking, with the former a lot more valuable than the latter. Also a valuable theoretical paper might simply point out deficiencies in current thinking without offering an alternative (ie. pointing out the need to find an alternative). A well reasoned paper in that vein may not be shocking at all while being very valuable.

All the best,

Phil

This story of rejection, so familiar to many scientists no doubt, is recounted in detail for a reason. I believe it reveals deep changes that are underway in the normal Popperian practice of modern science. It also reveals potentially other destructive under-currents now overt and manifest in "academic science" and the small mindedness and petty behavior of the current generation of many institutional scientists either running, or enveloped within, "big science" and "big institute" environments. There seems to be in play the inbuilt mental censor " to not rock the boat" – straight out of Soviet Russia and other 20th and 21st Century Communist Totalitarian societies.

Dare it also be said there are other destructive human emotions are at play here, which would take too long to recount the full cause-and-effect chain in detail, such as: virulent destructive envy (Gillman 1998; Schoeck 1966), over weening pride and conceit, and an arrogance associated with the absolute control of new scientific information, and, dare it be said, a *genuine fear* based on a colleague's desire to not break ranks and thus keep "Running with the Herd" where it is far safer scientifically and academically for one's career (Gold 1989).

But the rejection by *ICB* necessitated the above EJS response in 2014 because the decision from his "*alma mater*" journal was totally uncharacteristic. The editor was contacted again and then Professor Phil Hodgkin was contacted (not shown).

On 2/05/2014, 8:18 AM, "Ted Steele" <e.j.steele@bigpond.com> wrote:

Dear Gabrielle:

Thank you for taking the time to review the decision.

However, as I indicated to Phil Hodgkin theoretical papers are a different category entirely – they are a different scientific beast. To be of any value they must to be shocking and clash with excepted wisdom – that is their role. A theoretical paper supported by current mainstream data in the field has no value at all as a theory paper.

A specialist clinical journal would be outside the scope of this paper - as clinicians have no track record at all in developing viable immunological theory (if MacFarlane Burnet can be a considered a clinician he was a clear exception - they don't mint them like that anymore in the current era, in my view).

The paper was not written lightly. I have indeed spent a lot of time reviewing all the relevant data in the HIV field over the past 30 years pertinent to the issues raised in the paper. The new model is in fact not inconsistent with all current data. The biggest thing I found in reviewing the field is that few if anyone was or is looking critically and directly at B cells – except that French group of Gras et al in the early 1990s. So the additional data discussed in the theory remains to be discovered.

Thanks again

Ted
--
Edward J Steele PhD

CYO Honorary Research Fellow
CY O'Connor ERADE Village Foundation

None of the correspondences were of any avail, the Editor-in-Chief of *ICB* still rejected it – on the flimsiest of grounds. Plausible theoretical papers clearly are a *different category* entirely now – to be of any value they must conform to existing norms and paradigms, they must address and support popular positions, they certainly cannot be potentially shocking and clash with excepted wisdom. Their new role at *ASI/ICB*, despite the positive promos at the ICB website (check it out), is they *must consolidate the existing dogma*.

A theoretical article supported completely by immediate and extant data in a given field has no real value at all as a theory paper, which hopes to predict (and be tested by) new phenomena. Theory must go beyond its immediate data domain and make surprising or interesting predictions in the Popperian spirit. This was at one time always understood in Physics but it has not been part of the

development of modern in Biology (the caveat now is this approach would be: "at least it *was* understood in modern Physics").

The entire HIV field was carefully reviewed by the authors over a number of years – the paper was not written flippantly or lightly. The new model is in fact not inconsistent with current data, however it goes much further than the current data. The important aspect in reviewing the HIV field was that few investigators, *if any*, were looking critically at B cells – except the French group Gras et al in the early 1990s (Gras et al 1993).

Group Think and *Running with the Herd* are powerful forces in modern scientific research (Gold 1989).

EJ Steele's faith in Physics has also been shaken over the past few years. The seminal work discussed above, of Fred Hoyle and N. Chandra Wickramasinge (H-W) on Cosmic Biology and Panspermia is shockingly avoided or *under cited* by mainstream Physics particularly scientists at NASA and other space agencies (extensive references can be found in Wickramasinghe 2012; Wickramasinghe and Steele 2016). Why is this?

From the biological perspective all the assembled H-W data since the 1970s (or earlier) in books and papers is coherent, specific, multifactorial and Popperian in all relevant details viz. all the Cosmic Biology predictions (which have been confirmed) were all potentially falsifiable *in advance* of the testing (see Wickramasinghe 2015a and the compendium of H-W papers in Wickramasinghe 2015b). It is clear to EJ Steele, who has read many of the H-W books and critically evaluated the key primary published data, that the Solar System (via its ubiquitous Comets acting as "cosmic incubators") and the wider Universe is teeming with living systems (e.g. microorganisms, viruses etc) implying proliferating cellular reservoirs (to allow viral replication) on a Cosmic scale. The spherical Oort Cloud, the source of long period Comets, around our solar system

is the dead give away here. Possibly the majority of these billions of comets *did not* originate from our Solar System accretion plane – they have most likely arisen by capture of Comets by our Sun's gravity from other passing Solar Systems (see Hal Levison 2010 - https://science.nasa.gov/science-news/science-at-nasa/2010/23nov_aliencomets). The Oort Cloud then is the interface exchange connecting Life in our Solar System with Life in other parts of our Galaxy and the wider Universe.

The dramatic revelations of Tom Gold on the existence of terrestrial life to about 10 Km inside the Earth's crust confirms a clear fact : if microbial life can thrive at such great depths (Gold 1992,1999) it can also thrive on Solar System bodies (Planets, Moons, Comets, etc) and thus throughout the Universe. The Hoyle-Wickramasinghe best guess is that cellular Life emerged at least by 12-13 Billion years ago, in the early stages of the present observable Universe.

That Fred Hoyle did not share the Nobel with Willy Fowler in 1984 for his theoretical work, with the Hoyle predictions confirmed by Fowler on nucleosynthesis in the Sun, was truly shocking. This fact shock EJS to his core as well as his faith in Physics – which to EJS has been his anchoring guide and *exemplar* of the objectivity of the scientific enterprise. And it added to his already deep skepticism about the Nobel nomination process (above and below).

That skepticism has been engendered by watching the awarding of recent Nobel Prizes up close in modern Immunology. Some are beyond dispute – Sir McFarlane Burnet's contribution to modern immunology via the Clonal Selection Theory is a monumental achievement, as is Sir Peter Medawar's experiments on neonatal tolerance in Transplant Rejection studies of the ontogeny of The Self-NonSelf Discrimination. Susumu Tonegawa fully deserved his 1987 Nobel for discovering the V->DJ rearrangement process, as well as molecular (DNA) evidence confirming previous amino acid sequencing data that somatic hypermutation was

a fact during immune responses. The latter Vλ myeloma protein sequence data was provided by the group of Melvin Cohn and Martin Weigert in a famous *Nature* paper in 1970, four years before Tonegawa's observations at the DNA level. So Tonegawa should have shared the prize with Melvin Cohn and Martin Weigert.

However, it must now be said publically and very clearly (and unequivocally) - Professor Robert V Blanden should have shared the 1996 Nobel on MHC-Viral Restriction with Rolf Zinkernagel (his PhD student) and Peter Doherty (a Post Doc at the time in the laboratory next door to Blanden's in the Department of Microbiology at the *JCSMR*).

Unzicker and Jones' *Bankrupting Physics* should be required reading in undergraduate science degrees. The analyses and dissections in the book are also a *must read* for all contemporary scientists. The corrupting influence of big science, big data, and nationalistic big government tax-payer funding, big corporations is laid out clearly. The associated clear shift in the upper echelons of Physics (the fundamental arenas of Theoretical Physics) is striking. It is a clear move away from Popper's *Falsification Criterion* on a massive scale. Paul Feyerabend's advocacy of base and uncivilized human behavior has triumphed. This is all clearly outlined by Unzicker and Jones. The shift really is, to call a spade-a-spade, to delusion and fantasy. All budding young Physicists have been warned by the Unzicker diagnosis. (The upside is that Unzicker reveals so many potentially rich fields in modern Physics ripe for exploration by young enthusiastic creative scientists).

There is a parallel in Biomedical Science in this Whole Genome Sequencing era. Indeed critical analyses of data, deep and nuanced historical analyses and reflection of the data and concepts in a given field, insights into novel molecular mechanisms etc. have been sidelined by big data, big groups, big institutes, research by large committees and multi-institute teams, with papers of > 20 co-authors not uncommon (much like sub-atomic particle Physics!) . The

opportunities for knaves, sharp operators, game players, dare we say "criminal scientists" to pervert Science are all pervasive (Garwood 2011,2012). This is now coupled to a blind adherence to the outdated, and very limited, Neo-Darwinian-Population Genetics Paradigm in Biology (Wickramasinghe and Steele 2016).

As a consequence Biomedical Science is riddled with fundamental contradictions in data analyses and interpretations in both genetics, genome structure and evolution (Steele 2014; Steele 2015; Wickramasinghe and Steele 2016). Fraudulent and highly dubious publications are now rampant, published in the high impact journals.

EJS has a rule to not look at *Nature* and *Science* until an excitable colleague emails him and urges him to pay attention to it and sends him the PDF.

However so few in *Nature* and *Science* are worthy of serious consideration any more. The last really important papers in *Nature* on, for example, Ig SHM appeared 2001-2003, led by Patricia J Gearhart's ground breaking paper on DNA Polymerase-η as the A:T mutator in 2001 (Zeng et al 2001), the key work of Igor B Rogozin and Thomas A Kunkel defining W<u>A</u> hotspots for DNA Polymerase-η action (W = A or T; Rogozin et al 2001); and then the revolutionary papers on AID-mediated DNA deamination by the Cambridge group of Michael S Neuberger, Reuben S Harris, Svend Petersen-Mahrt, and Javier Di Noia (reviewed in Harris et al 2003;Di Noia and Neuberger 2007;Teng and Papavisiliou 2007; see also Steele 2009, 2016). The follow up work reporting AID-deaminase action on ssDNA substrates at Transcription Bubbles should also be noted from the laboratories of Myron F Goodman (Pham et al 2003) and Frederick W Alt (Chaudhuri et al 2003, 2004). However the really big multi-author and multi-centre combines (> 20 coauthors) publishing in *Nature* , *Science* and *Cell*, on somatic mutation investigations make seriously big mistakes, particularly in cancer research (e.g. Welcome Trust Sanger Institute papers, and see critiques in Lindley and Steele 2013; Steele 2016).

The Nobel Prize

This tragic conclusion now applies to the Nobel Prize which has now become a totally bankrupt annual farce. The clear rule with the Nobel should be this: a discovery should be coupled to, and absolutely related to, the *character* and intelligence of the scientist who *made* the discovery.

But why "Character"? The question is "Surely you can have a really great scientific discovery in Science without looking at the scientist's "Character"?

Not so, and there is complete agreement here with Alexander Unzicker who has been devastating, and quite unrelenting, on this very crucial point (read the book and also check out the interview at (https://www.youtube.com/watch?v=OtHWw0bwm4w). We must look at the real record of those in the Pantheon i.e. whom all serious objective observers agree "should be in the Pantheon".

There have always been great scientific discoveries, but the "Character" of the person making the discovery has been the key in all cases – the uniqueness of the discovery relates to the individual analytical mind that "*first made the connection*". This is the key. Why? In such an answer we run the risk of spelling it out in kindergarten terms and thus alienating the reader. However, genuine dedicated scientists know exactly what is meant here.

And why should the Nobel be awarded every year? "…Because it has to be awarded each year". What if there is nothing worthy that has been discovered? "We award it any way – it is in the Will".

And this is the problem. The Nobel has become a "bureaucratic exercise" – it must be awarded each year. Think about that for a minute – the inevitable result

is the dumbing down of the prize. This is coupled to the fact that previous winners have a say in the nomination! Because many undeserving non-entities have now received the Nobel Prize this means the awarding of future prizes will be dumbed down further by the nomination process. Clearly it is time for the Nobel committee, dare it be said, to use Donald J Trump's very apt conclusion to "Drain the Swamp."

So, since about 1980 the provenance of many Nobel awards is suspect. There are clearly well deserved ones as well. But it is the rising incidence of 2nd order awards that is destroying the credibility of the Nobel as an institution. This is a tragic development for young scientists who grew up in the 20th Century.

Surely only the truly great scientists should be allowed entry to the Pantheon? There is clearly only one solution. The Nobel Committee must now make a decision to award the Prizes *occasionally* – and on real Pantheon entry merit criteria. Many Nobels over the past 30 years or so need careful expert scrutiny, many do not make the grade. What a tragedy for Mankind!

The "Occasional Nobel Award" will restore the credibility of the Nobel Prize, otherwise the Prize and its prestige will go extinct. The Nobel must be for highly original work and discoveries at the very highest level of human achievement, and that involves a human factor – "Character". Because it is clear to the authors that only men and women of real character make *enduring* discoveries.

So this leads to a key issue "Why have the extensive and voluminous data and logical analyses published by Hoyle and Wickramasinghe not been *completely* accepted by the wider Physics and Biology communities? It is really quite outrageous for anyone that has examined and evaluated the data.

So it seems really deep emotional factors are at play here affecting scientific judgement. That is the only conclusion that can be reached. The requirement that

an objective scientist "must confront the data before reaching a conclusion" seems to be abandoned when it comes to the data showing that the Cosmos is teeming with life and organisms (microbial in the main, and viruses) which are falling to Earth from Comet debris trails each day. The cost to monitor this in-fall is a fraction of the cost to build and maintain, for example, the Large Hadron Collider run by CERN near Geneva. Balloon collection surveys of the stratosphere, carefully controlled, are, by comparison, very cheap to run and are already yielding interesting results with many novel microorganisms and viral clusters (Combe et al 2015) identified coming in vertically, and at great cosmic speed, from Space (Wainwright et al 2014; Wainwright et al 2015a, 2015b).

Individual Human Brains – The Real Integrative Super Computer

We should not underestimate the great creative and analytical power of the individual human Brain. It is the individual Brain confronting the data that makes scientific breakthroughs. That has always been the case - and all true scientists know that this claim is a true statement. It far exceeds the power of the "Big Research Committee" or "the Big Institute", or the individual "Brain" directing such a "Big" enterprise (because, obviously, the enterprise in an authoritarian structure will bend its will to the "Director" who is usually in the game for "Power" *only* – the outcome depends thus on the quality of the "Director's" Brain – which is a huge risk and waste of tax-payer funds given that "Power" *per se* is being rewarded here, not the creative scientific work of responsible individual scientists.

Thus it must go to "Character", that really is the bottom line, otherwise science and Nobel awards descend into corruption and chaos (Garwood 2011.2012).

"Big Data" pipelines suffer from the same problem. We must assert that the analytical power of an individual Brain far exceeds the power of the Algorithm, and the Big Data, multi-author publications currently in vogue.

Robyn A Lindley and Targeted Somatic Mutation (TSM)

A contemporary and real-time unfolding example is the discovery of Targeted Somatic Mutation (TSM) mutation signatures in cancer genomes which are clearly in "Codon-Context" in genome–wide exome DNA sequence data (Lindley 2013; Lindley et al 2016). This creative process has been observed up close. The discovery was not made by a "Pipeline" or a by "Committee" or by a " Multi-Centre" Research conglomerate, nor was it achieved under the protective umbrella of a cosy academic institution. It was made under difficult working conditions, with scarce funds under great physical hardship by an individual analytical "Brain" curating and analyzing the data manually (Lindley RA 2017 *Targeted Somatic Mutation (TSM) Signatures: A Review*. Submitted). Thus to the genuine relief of all true scientists, it is still the "individual scientific Brain" which is the "Super Computer" of the 21st Century.

Peter A Bretscher, HIV Immunity and Overdue Scientific Recognition

We close this extended Post Script by drawing attention to the great scientific contribution (over almost 55 years) of Peter A Bretscher a remarkable Physicist who moved into Cellular Immunology in the early 1960s mentored by Francis Crick. Together with the brilliant Melvin Cohn, Peter published (1970) the *Two Signal Model of the Self- Non Self Discrimination*, which, along with Sir MacFarlane Burnet's *Clonal Selection Theory of Acquired Immunity*, is now recognized as a bedrock principle of modern Immunology. Peter, quite unabashedly, is in the genius class, as that description is traditionally understood. He is already in the Pantheon.

His work is summarized in extensive lucid detail in his first great book published in Canada earlier this year (Bretscher 2016). To cut to just one of his numerous basic insights and predictions with respect to HIV Immunity: the key in Immune Class Regulation is to induce Cell Mediated Immunity (CMI) against HIV virus

infected cells (whether they be T cells, Macrophages, Dendritic cells, or B cells) by *Low Dose vaccination* strategies. Or,manoeuvres to ensure T lymphocyte subset ratios are flipped (e.g. Th1/Th2 (IgG2/IgG1) >1) ensuring a CMI response, rather than antibodies, against HIV infected cells. In such a situation curative HIV immunity is predicted to be delivered, and the same strategy can be applied to Cancer immunotherapies. Needless to say Peter's book documents the very Popperian struggle (over 55 years) he and his associates endured to publish extensive experimental data to consolidate his theory of Immune Class Regulation. Clinical Immunologists, Oncologists and Vaccine developers are urged to become familiar with Bretscher's discoveries and testable theories.

Why submit to viAra.org?

The viAra.org site was found by reading Unzicker and Jones (p.245) and that is why this new model of HIV immune diversification, and thus immune evasion, has now been archived and published at this website. The viAra.org website gives all the reasons why other scientists felt such a site was necessary in modern times. Our paper will be widely cited in future publications and books, and circulated as a PDF reprint to colleagues.

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Conflict of Interest

The authors have no commercial conflicts of interest that would compromise the objectivity of this paper.

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