MULTIPLE SCLEROSIS UNRAVELLED

Abstract

Multiple Sclerosis (MS) is a complicated confluence of genetic (SNPs) and environmental (Western life style) influences.

The gut microbiome plays a central role in MS where Single Nucleotide Polymorphisms (SNPs) control microbiome compositional patterns. Dysfunction of the complex network of gut bacteria, where also other factors like diet play a role, weakens epigenetic control on host cells and associates with the disease.

If epigenetic regulation of gene expression fails and viral genes are no longer silenced, we see an interaction in the viral repertoire. At that point, herpes viruses including the Varicella Zoster Virus (VZV) and the Epstein-Barr Virus (EBV) may trigger large scale HERV activation in a triangular arrangement with the genome. Transgenic cells change phenotype, there is breach of tolerance and autoimmune problems start. Human Endogenous Retroviral sequences (HERVs) are mobile subcellular structures that span the divide between "self" and "foreign".

MS is a specific disease pattern within this new autoimmunity paradigm. Relapse Remitting (RR) and progressive MS are caused by two different underlying mechanisms; a double peak is seen in the graph of age of onset. Low immunity of the naso-pharynx with spill-over of viral activity into the Central Nervous System (CNS) and spinal column is suspect. Hypoperfusion (CCSVI), gut dysfunction and low vitamin D cause low immunity.

In the early phase (RR), VZV/HERV activation with a VZV-initiated evasion of T-cell immunity, possibly combined with toxins from a leaky gut and/or adjuvants, causes microbleedings and the white matter lesions. At the later stage (progressive phase), EBV/HERV stimulation of B-cell growth causes progression in the grey matter. For the protection against the virus, structures similar to lymph nodes are found in the brain’s meninges of MS patients.

The B cells cause huge oxidative stress which leads to mitochondrial failure. Gradually, less energy is supplied to the ion pump, the equilibrium of charging can no longer be maintained, cells become electrically dormant and motor functions fail. A herpetic neuralgia of peripheral nerve and muscle cells may add to the problems. The MS symptoms experienced are the aggregation of the problems.

As regards therapeutic options, the VZV/EBV should be killed by chemo or suppressed by monoclonal antibodies or High Active Anti-Retroviral Therapy (HAART). The HERV should be silenced through manipulation of the gut microbiome. This will stop progression and achieve a reversal of inflammation. Anti-oxidants will then need to clean up the cells. Activating muscles will activate the neuroplasticity in the CNS, and should accelerate and strengthen recovery.

Contents

Critical need for an open debate for solving the MS puzzle

In most chronic autoimmune diseases there is a symptomatic inclination to look at symptoms rather than causes. Symptoms have always been treated; protocols were designed to suppress or modulate the immune system. In the MS picture, there is a massive confusion of cause, effect and secondary effect.

The medical world looked at chronic diseases as a black box where they modulate the input a bit to see how the output would change. Real causes have never been treated. For that, a thorough in-depth understanding of the disease mechanisms will be necessary. We need to start looking inside the black box and try to understand what happens in there. This represents a complete shift away from current thinking and practice.

People normally follow logical laws; our minds works linear and have greatest difficulty to deal with non-linear models or complex elements along a disease process. But linearity does not apply in medicine, and most certainly not in the case of MS. There are very many facets, a large variety of influences, different underlying mechanisms, feed-forwards and feed-backs, and convolved vicious loops that lead to MS. What comes first and what follows, what is coupled and how, is not always obvious. This explains the erratic course of the disease, and the large variety of symptoms and disease progression seen in MS patients.

MS is a subtle highly complex non-linear disease process that goes down as deep into our microcosm as the genetic rearrangement of DNA fragments at the micro-cellular level. If you apply only causal thinking, you won't be able to unravel and nail down the disease. Old concepts will need to be revisited.

Why will a progressive MS patient, when walking and his gait becomes more difficult and then he stands still for a while, go much better again immediately after. This is difficult to explain by the static concept of demyelination. Or the concept of immune suppression. This concept looks like an oversimplification where it would be more appropriate to talk about an immune system that calms down because more favourable micro-cellular conditions were created. Or the concept of inflammation of fatty acids. Could it be that Ω3 is just non-inflammatory but that it looks anti-inflammatory as it distinguishes from other fatty acids? Old concepts will need to be revisited.

Change will not come easy. In our modern world, significant systemic problems are pervasive and that hampers a course toward profoundly and expeditiously changing the paradigm. There are a lot of detractors for everything new that happens. There is always a lot of skepticism about anything new, especially when it seems to have a 'holistic' aspect.

Issues will be subject to interpretation, factual mistakes or flawed concepts may be re-introduced. While it may be tempting to block or build new walls around anything new, the challenge will be to keep open the discussion without any strong preconceptions and foster an open exchange of ideas.

This paper is an attempt to launch such discussion, proposing new ideas and concepts on this complicated subject. Diversity helps. Further proof-of-concept studies will need to follow.

[names]

Introduction

Chronic disease begins in the mitochondria. Mitochondria dysfunction and early death are common pathways in all those illnesses.

24 million people in the US have an autoimmune diagnosis, but another 50 million do not feel well and have autoantibodies but do not yet have enough antibodies to make a diagnosis. So, that means about 75 million have autoimmune problems. That's extremely significant, and it is a sign that our lifestyles have led us down a very dangerous path. Even more disturbing, more and more children are being diagnosed with an autoimmune problem as children.

[statistics Europe]

Despite the increase in longevity which may be attributed to new medical techniques, drugs and technology, we are as a society progressively less well. Why is this happening to us? What has given rise to the single largest epidemic of chronic disease in human history? Have our genes gone bad or have we adopted a lifestyle that could explain the current scourge of autoimmune diseases?

Since the weight of genetic changes is insignificant in just such a short period of a few generations, we will need to search the causes at the environmental level. Has our modern Western lifestyle over the last 20 - 50 years broken with the evolutionary path of the last many millions of years.

In a study of gut bacteria of children in Burkina Faso (in Africa), Prevotella made up 53% of the gut bacteria, but were absent in age-matched European children. Studies also indicate that long-term diet is strongly associated with the gut microbiome composition—those who eat plenty of protein and animal fats typical of Western diet have predominantly Bacteroides bacteria, while for those who consume more carbohydrates, especially fibre, the Prevotella species dominate. Other studies revealed that people with a modern Western lifestyle have around 1000 different gut species where the hunter-gatherers have around 1500. It is the adaptive potential of the gut microbiome that is optimizing itself for the best nutitional digestions and absoption.

But if overstretched, it could go wrong. A long chain of events follows that, in the case of MS, eventually leads to high oxidative stress and mitochondrial dysfunction and death in the CNS and the spinal column. We are talking here disruptions in the grey matter, the axons and dendrites and synapses that transfer signals between nerves. Over time, the equilibirum of the ion pump becomes more difficult to maintain which explains the motor dysfunction.

This thesis examines the underlying processes that eventually lead to MS and - when it becomes clear what happens inside the black-box - provides directions for therapy.

Multiple Sclerosis Appears to Originate in Different Part of Brain than Long Believed

http://news.rutgers.edu/research-news/multiple-sclerosis-appears-originate-different-part-brain-long-believed/20130910#.Voo7ubbhDs1

Minding My Mitochondria: How I overcame secondary progressive multiple sclerosis (MS) and got out of my wheelchair, Terry Wahls

http://www.amazon.com/Minding-Mitochondria-2nd-progressive-wheelchair/dp/0982175086/ref=sr_1_1?s=books&ie=UTF8&qid=1453278410&sr=1-1&keywords=minding+my+mitochondria

A Conversation with Terry Wahls, M.D., Author of "The Wahls Protocol"

http://www.drfranklipman.com/a-conversation-with-terry-wahls-md/

Dr. Terry Wahls: Presentation on the Wahls protocol

https://www.youtube.com/watch?v=oW6njb4ZVpA&list=UUFeOdDfq-nePMzokX8-ROHg

Dr. Perlmutter: Brain Maker, Fecal Transplants, and How to Heal Your Gut with Real Food

https://www.youtube.com/watch?v=baJqlQVK-9E

The Exploding Autoimmune Epidemic - Dr. Tent - It's Not Autoimmune, you have Viruses

https://www.youtube.com/watch?v=r8FCJ_VPyns

From genes to gut microbiome to epigenetic response

The evolutionary aspects of human development

Eukaryotic cells have probably been exposed to retroelements since their early beginning. More than half of the human genome has probably undergone reverse transcription before incorporation. Thus many defence mechanisms against damage from newly acquired retroelements must exist, among them methylation, histone modification and inhibitory RNA.

Retroelements provide genetic flexibility which gives certain positive selection value to them. Therefore, the pathogenicity of early retro viral infections will be eliminated and contribute in several ways to genetic diversity.

In an evolutionay sense, disease equates negative selection. The persistence of Endogeneous Retroviruses (ERVs) stretches over several hundred million years and has led - over time- to a stable host – viral sequence interaction, with a minimum of negative selection, that is disease.

The genetic material of the human being consists of approximately 8% of human endogenous retroviruses (HERV's). These are viruses that through inheritance stay in the genes for many generations. These viruses are often not or hardly expressed, but some viruses may occur in certain diseases. This means that certain proteins are created under the influence of such a virus. These proteins are present in the blood.

In the blood and in the cerebrospinal fluid of MS patients, we find elevated substances such as HERV-env and HERV-polymerase. The presence of these substances could have a predictive value for the course of MS over the longer term.

Viral infections left (H)ERV sequences behind along our evolutionary path in our cells. These are remnant of earlier infections that were silenced and pacified over time and positive selection. Also in the whole animal kindom and plants they often are the dominating genetic components. While this has provided us with a great evolutionary resilience and resistance, as we shall see, we also pay a price for that flexibility.

Over the last 10-30 million years, the EBV virus has arisen and is almost ubiquitous among the human population. Under certain conditions, an interplay may develop between the genome and its foreign HERV sequences and the herpes virus.

Treatment against human endogenous retrovirus: a possible personalized medicine approach for multiple sclerosis.

http://www.ncbi.nlm.nih.gov/pubmed/26376649

Evolutionary Aspects of Human Endogenous Retroviral Sequences (HERVs) and Disease

http://www.ncbi.nlm.nih.gov/books/NBK6235/

Endogenous retroviruses and multiple sclerosis–new pieces to the puzzle

http://www.biomedcentral.com/1471-2377/13/111

The role of the gut microbiome in health and disease

Molecular mechanisms mediate epigenetic phenomena. The term 'epigenetics' literally means 'outside conventional genetics' and is used to describe the study of stable alterations in gene expression potential that arise during development and cell proliferation. Epigenetic mechanism guard against viral genomes that would otherwise hijack cellular functions for their own ends.

The main mechanisms that exist in epigenetic regulation are DNA methylation and histone modification. Diseases occur when the regulation is pertubated. External influences on epigenetic processes are seen in the effect of diet on long –term diseases.

How does the genome adapt to developmental and environmental cues? There is a rapidly growing understanding of the key role of the gut microbiome in epigenetic regulation.

The microbiome co-evolved with the genome. The microbiome – genome relationship has developed over 1 Billion years of evolution. Hence, as could be expected, the two communicate closely together. The microbiome – genome relationship 'regulates' the expression of Endogeneous Retroviral (ERV) sequences left behind in our cells, silencing them where possible through epigenetic regulation.

Human associated microorganisms are present in numbers exceeding the quantities of human cells by at least 10 fold. The microbiome directly influences health and provides an extra means of adaptive potential to different life styles.

Metagenomic sequencing increased our knowedge of the role of the microbiome in health and disease. It is becoming apparent that the microbiome compositional patterns associate with specific diseases and contain certain prognostic value. The pattern for different microbial genomes contains a single trough and a single peak, the latter coinciding with the bacterial origin of replication. For several bacterial species, peak-to-trough coverage ratios (PTRs) correlate with the manifestation of specific disease.

Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals

http://www.nature.com/ng/journal/v33/n3s/full/ng1089.html

The role of microbiome in central nervous system disorders

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4062078/

Growth dynamics of gut microbiota in health and disease inferred from single metagenomic samples

http://www.sciencemag.org/content/349/6252/1101.abstract

The MS Microbiome Consortium (MSMC): an academic multi-disciplinary collaborative effort to elucidate the role of the gut microbiota in MS

http://www.neurology.org/content/84/14_Supplement/P2.205

Host genetic variation controls the structure of the microbiome

As we have seen, the microbiome plays a critical role in the epigenetic regulation of gene expression. The microbiome is central in MS and autoimmunity. Differences in gut bacteria may change epigenetic control on the host cells. But there is more to it.

While microbial communities are influenced by environmental factors (diet, metabolic factors, stress), there is also a degree of genetic influence of the host on the microbiome configuration. Hence, the host ancestral genome structures its microbiome.

In particular single nucleotide polymorphisms (SNPs) [in or around HERV-loci] have shown an association with the microbiome configuration and susceptibility to several diseases including MS and other auto-inflammatory disorders.

Host genetic variation impacts microbiome composition across human body sites

http://www.genomebiology.com/2015/16/1/191

mtDNA haplogroup and single nucleotide polymorphisms structure human microbiome communities

http://www.biomedcentral.com/1471-2164/15/257/

HERV-W polymorphism in chromosome X is associated with multiple sclerosis risk and with differential expression of MSRV

http://www.retrovirology.com/content/11/1/2

Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with a Striking Depletion of Species Belonging to Clostridia XIVa and IV Clusters

http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0137429

Researchers find strong correlations between the composition of the human microbiome and genetic variation in immune-related pathways

http://www.the-scientist.com/?articles.view/articleNo/37982/title/It-s-in-the-Genes/

Silencing the Human Endogenous Retrovirus

The genome is full of viruses, generally they are silent which means they are methylated. Organisms have a major interest in silencing viral genes that get into the genome. Otherwise they would screw up the genome. It is an evolutionary conserved mechanism to silence these transportable elements, these viruses. This is most important in ealry embryonic lineage, which gives rise to germ cells. These early embryonic cells express several methyltransferases. It only serves to maintain methylation once methylation has already been established by a different enzyme. It propagates the methylation signal from one cell division to the next. It does not establish new methylation on its own.

Only embryonic cells express de novo methyltransferase, later they are not expressed. And this explains why if a virus gets into a cell later, it is not methylated.

Biochemical evidence indicates that DNA methylation is just one component of a wider epigenetic program that includes other post synthesis modifications of chromatin.

A key issue of any therapeutic strategy that attempts to remedy the abnormal epigenetic state is that of specificity. Interfering with the factors that modify the chromatin state is likely to affect the expression of unwanted genes such as endogeneous retroviruses [Jeanisch 2003]

The genetic information of an organism is differentially expressed in both time and space through mechanisms that we are finally beginning to understand. Epigenetic mechanisms constrain expression by adapting regions of the genome to maintain either gene silencing or gene activity. This is achieved through direct chemical modification of the DNA region itself and by modification of proteins that are closely associated with the locus. The targeting of specific genetic loci ensures that these effects are local. The triggers for this differential marking of the genome are largely mysterious, but are finally yielding to intense study. What needs to be explained is the variety of stimuli that can bring about epigenetic changes, ranging from developmental progression and aging to viral infection and diet.

The “pacification” of a retroviral gene is not straightforward. Retroviruses carry with them a number of cis- and trans-acting mechanisms optimized to suit a free-living exogenous virus, making them potentially dangerous to the host even after eons when the integrated viral gene (“provirus” or “virogene”) has been severely damaged.

The future will see intense study of the chains of signaling that are responsible for epigenetic programming. As a result, we will be able to understand, and perhaps manipulate, the ways in which the genome learns from its experiences.

Precursors to MS

The Human Endogeneous Retrovirus and MS

Evidence was found of endogenous retrovirus gene activation in MS. Endogenous retroviruses are viruses captured by and scattered among the human genome. Some are more recent than others. So far they have not been very well characterised or implicated in human diseases.

It is suspected that they are activated by something else, some sort of mutation or genetic rearrangement that goes on with the herpes virus.

The Marek disease herpesvirus of turkeys (MDV) can transduce avian leukosis virus (ALV). Such recombinant MDV is more lymphomagenic than MDV which does not contain ALV. This is an example of herpesvirus pathology enhanced by a retrovirus.

Herpesviruses are highly prevalent in many species. In humans, human herpesvirus 7 (HHV7), Epstein-Barr Virus (EBV), human herpesvirus 6 (HHV6), Varicella-Zoster Virus (VZV) and Herpes Simplex type 1 (HSV1) are the most prevalent. They infect over 60% of the population and can then remain latent for a lifetime. In this respect the herpesviruses are almost as "endogenous" as HERVs which often are present in 99-100% of the population. As we saw, it is not unlikely that these viruses may utilize each other. The love and hate relationship between the human organism and a HERV then becomes a triangle drama.

The MDV - ALV interaction may not be the only herpes-retrovirus interaction. It was recently found that the immediate early protein ICP0 of herpes simplex can transactivate the LTR (Long Terminal Repeat sequences) of HERV-K(HML-2). In an intriguing series of experiments, Thorley-Lawson's group got evidence for a HERV-K(HML-2) env superantigen mediated stimulation of T cells after EBV infection. The growth stimulation was abrogated in the presence of anti-HERV-K(HML-2) antibodies.

The suggested chain of effects is reminiscent of that of MMTV (the Mouse Mammary Tumor virus), which also activates a T cell to secrete B cell growth factors via a viral superantigen in order to stimulate growth of its host cell, the B cell. In this case, the benefactor allegedly is EBV. These findings need confirmation, but they emphasize the potential of interactions between highly prevalent selfish genes/retroviruses and ubiquitous exogenous viruses like the herpesviruses.

EBV is considered a major cause of lymphomas. The putative involvement of the HERV protein in EBV-related growth stimulation of B cells raises the possibility that immunization against the HERV protein, or prevention of its expression via transduction of anti-sense constructs, might inhibit EBV lymphomagenesis. This would be a logical consequence of the results of Sutkowski et all.

If epigenetic regulation of gene expression fails and viral genes are no longer silenced, we see an interaction in the viral repertoire. Human endogenous retroviruses (HERVs) are mobile subcellular structures that span the divide between "self" and "foreign". Where (late infection with) EBV or other herpes viruses may trigger HERV activation. Furthermore toxic substances as ε-toxin from the gut or mycotoxins are suspect. At that point, cells change phenotype, there is a breach of tolerance, and autoimmune problems start.

MS is in fact a retroviral disease, not an exogenous retroviral disease as HIV, but an endogenous retroviral disease within a bared immune response. This brings together the viral concept of MS and folds in the concept that MS is an autoimmune disease.

Human Endogenous Retroviruses and Multiple Sclerosis

https://www.youtube.com/watch?v=xecaTyxmd2o

Virology: an update of the Charcot project

https://www.youtube.com/watch?v=Ss5alRN9voA

Evolutionary Aspects of Human Endogenous Retroviral Sequences (HERV) and Disease

http://www.ncbi.nlm.nih.gov/books/NBK6235/

Endogenous retroviruses and multiple sclerosis–new pieces to the puzzle

http://www.biomedcentral.com/1471-2377/13/111

HERV-W polymorphism in chromosome X is associated with multiple sclerosis risk and with differential expression of MSRV

http://www.retrovirology.com/content/11/1/2

The connection between brain and bowel

Whereas the brain is protected to a significant degree by the existence of the blood brain barrier, over recent years it has become clear that it is not the immune-privileged organ that was considered in the past. Indeed peripheral infections have been known for many years to impact on neuronal function and the CNS effects of sickness behaviour have been well rehearsed.

Peripheral administration of lipopolysaccharide increases inflammatory and oxidative stress in brain, and glial activation in the hippocampus, to a greater extent in aged, compared with young, rats. Consistently, age is associated with increased vulnerability to infections, while infections have been shown to accelerate progression of diseases such as Alzheimer's disease and MS.

These findings support the notion that a communication network between the CNS and the periphery exists. This communication network is consolidated by the association between psychiatric conditions, like anxiety, and the inflammatory changes in the gastrointestinal tract that typify inflammatory bowel disease.

A reciprocal interaction exists between the gut microbiota and CNS function. For example, it has been shown that the stress associated with neonatal maternal separation induces cognitive dysfunction and impacts on composition of gut microbiota.

Modulation of Intestinal Microbiota by the Probiotic VSL#3 Resets Brain Gene Expression and Ameliorates the Age-Related Deficit in LTP

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159266/

Modulation of Gut Microbiota–Brain Axis by Probiotics, Prebiotics, and Diet

http://pubs.acs.org/doi/abs/10.1021/acs.jafc.5b02404?journalCode=jafcau

A direct link between brain and immune system

The recent discovery of the Brain Lymphatic System causes a revolution in the thinking about the immunity of the brain. The vessels discovered are actual, real lymph vessels with enclosing vessel walls. These vessels line the meningeal layer and drain alongside cerebral veins. The mouse and human brains both contain actual vessels--and as inferred, probably all mammalian brains have lymph vessels in the meningeal layer.

The interaction between the CSF, blood, lymphatic and immune system in the brain is complex. The lymph cleansing system discovered does not involve vessels inside cerebral brain tissue. It is a free-flowing wash of CSF and lymph fluid, facilitated by glial cells (thus the "glymphatic" name) and sleep. However, the theory is that these newly discovered vessels are used for drainage of this interstitial cleansing fluid. This theory needs further research.

Dr. Schwartz has been publishing for 15 years on the fact that those circulating T reg cells are there for a purpose: to facilitate cognition, neuroplasticity and healing in the brain.

Scientists at the University of Toronto say they have found another clue in understanding the cause of what drives multiple sclerosis. Normally, immune responses are triggered in lymph nodes and other lymphoid organs to provide protection a virus or pathogen. However, scientists have observed that lymphocytes can sometimes congregate into so-called "tertiary lymphoid tissues (TLTs)" in the brain of MS patients. These structures are similar to lymph nodes, but are found within the brain's meninges. They often coincide with the appearance of tell-tale brain inflammation associated with progressive MS.

The discovery of the brain lymphatic system, Paolo Zamboni

http://www.pagepressjournals.org/index.php/vl/article/view/5360

Two new studies suggest a potential game-changer in how scientists understand of the brain, which could advance research on MS and Alzheimer's, Anne Kingston

http://www.macleans.ca/society/science/are-we-on-the-cusp-of-a-revolution-on-how-we-understand-the-brain/

Researchers at the University of Toronto have found another clue in understanding the cause of what drives Multiple Sclerosis (MS) disease

http://www.sciencedaily.com/releases/2015/12/151215160628.htmIntegration of Th17- and Lymphotoxin-Derived Signals Initiates Meningeal-Resident Stromal Cell Remodeling to Propagate Neuroinflammation

http://www.cell.com/immunity/abstract/S1074-7613(15)00462-8?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1074761315004628%3Fshowall%3Dtrue

Besides the white matter, the grey matter is involved with widespread synaptic loss

The proteins in the CSF of the new MS patients suggested physiological disruptions not only in the white matter of the brain where the myelin damage eventually shows up. They also pointed to substantial disruptions in the grey matter, a different part of the brain that contains the axons and dendrites and synapses that transfer signals between nerves.

Several scientists had in fact hypothesised that there might be grey matter involvement in early MS, but the technology needed to test their theories did not yet exist. Schutzer's analysis, which Coyle calls "exquisitely sensitive," provides the solid physical evidence for the very first time. It includes a finding that nine specific proteins associated with grey matter were far more abundant in patients who had just suffered their first attack than in longer term MS patients or in the healthy controls. "This evidence indicates grey matter may be the critical initial target in MS rather than white matter," says Coyle. "We may have been looking in the wrong area."

Multiple Sclerosis Appears to Originate in Different Part of Brain than Long Believed

http://news.rutgers.edu/research-news/multiple-sclerosis-appears-originate-different-part-brain-long-believed/20130910#.VouIwrbhDs0

It has been estimated that the human brain comprises 8.6 × 1011 neurons that are connected by ∼1014 synapses. These synapses decline in number during ageing and show accelerated loss in neurodegenerative diseases. Recent imaging techniques shed light on synaptic pathology in multiple sclerosis, and conclude that such pathology is widespread and occurs without coincident demyelination or axonal degeneration.

While multiple sclerosis was initially considered to be a chronic inflammatory disease that mainly affects white matter, it is now clear that grey matter pathology such as neuronal and axonal loss is equally widespread. Demyelinated areas in the hippocampi of multiple sclerosis brains show a consistent reduction in synaptic density. Grey matter demyelination and accompanying neuronal demise contribute to permanent neurological disability in multiple sclerosis as revealed by their correlation with disease progression. Similarly, cognitive dysfunction is found in over 50% of patients with multiple sclerosis and can be attributed to grey matter pathology.

Widespread synaptic loss in multiple sclerosis

http://brain.oxfordjournals.org/content/139/1/2

A central role for the naso pharynx

Chronic Cerebro Spinal Venous Insufficiency (CCSVI) or blocked internal jugular veins may be a factor here causing hypoperfusion of CNS and nasopharynx, lower AMP and Adonesine, and with that a reduced control of infection by cellular immunity, e.g. infection and proliferation of herpes, in particular VZV and EBV from the nasopharynx. Evidence accumulates of vein irregulaties and the incidence of MS in the vicinity of the heavy metal industry.

Investigation into the possible cause of the cluster of Multiple Sclerosis in East Boston, and Winthrop, MA

http://www.areco.org/ms.pdf

El Paso Multiple Sclerosis (MS) Study

http://www.dshs.state.tx.us/epitox/elpasostudy.shtm

Taking into account the current epidemiological data, the autoptic findings, and the relationship between CCSVI and both hypoperfusion and cerebrospinal fluid flow, CCSVI can be inserted in the list of multiple factors involved in MS pathogenesis.

CCSVI is associated with multiple sclerosis

http://www.ncbi.nlm.nih.gov/pubmed/22971467

The viral replication starts in the naso pharynx due to a weakened immunity that may be caused by CCSVI/hypoperfusion, poor diet, low sunshine/Vit D, and other factors. It will spill over into the lymphatic system in the neck and into the CNS via meninges and Virchow-Robin perivascular spaces.

[I had a stiff neck and spots in the neck prior to diagnosis which is an indication of VZV; I also suffered from severe pain in the naso pharynx during several years before diagnosis, always in Spring when immunity is low. I also suffered fom a bad gut which probably was leaky where toxic materials from the gut (epsilon toxin) may have combined with VZV/bleedings, leading to inflammation. My family lived in the shadow of the heavy metal industry causing vein abnormalities]

It has been suggested for decades that micro organisms contribute to the pathogenesis of MS and that there is a link with the lymphatic system. The article from 2007 already noted "Data is reviewed which shows that the CSF and extra-cellular fluid circulation is bi-directionally linked to the lymphatic drainage channels of the nasopharyngeal mucosa. While this provides a facility by which the CNS may mount immunological responses to antigenic challenges from within, it is also a route by which products of nasopharyngeal infection may drain into the CNS and be processed by the immune cells of the meninges and Virchow-Robin perivascular spaces." [Gay]

Virchow–Robin spaces (VRS), also known as perivascular spaces, are the immunological spaces between the arteries and veins (not capillaries) and pia mater that can be expanded by leukocytes. The spaces are formed when large vessels take the pia mater with them when they dive deep into the brain. The pia mater is reflected from the surface of the brain onto the surface of blood vessels in the subarachnoid space. Perivascular cuffsare regions of leukocyte aggregation in VRS, usually found in patients with viral encephalitis.

VRS are extremely small and can usually only be seen on MR images when dilated. While many normal brains will show a few dilated VRS, an increase in dilated VRS has been shown to correlate with the incidence of several neurodegenerative diseases, making the spaces a popular topic of research.

Epstein–Barr virus and multiple sclerosis: potential opportunities for immunotherapy, Michael Pender

http://www.nature.com/cti/journal/v3/n10/full/cti201425a.html

Bacterial toxins and Multiple Sclerosis, Gay F, Journal of the neurological sciences 262:1-2 2007 Nov 15 pg 105-12

http://www.unboundmedicine.com/medline/citation/17707408/Bacterial_toxins_and_Multiple_Sclerosis_

Virchow-Robin space, Perivascular cuffsare regions of leukocyte aggregation in VRS, usually found in patients with viral encephalitis. (encephalitis = accuyte inflammation of the brain)

https://en.wikipedia.org/wiki/Perivascular_space

MS as an evasion of immunity

Different mechanisms underly MS

The MS timeline shows a double peak in the graph of age of onset where a first peak appears around the age of mid 20's and a second peak in the early 40's. Of course we know about RR and the progressive phase, but this fact provides an indication that a two stage process is at work with different underlying mechanisms. One mechanism wanes with time, the other increases with time.

When at mid age, any new acute problems occur, this will result in more severe symptoms because the second process that causes the steady progression in the background has advanced further and if one has not already been diagnosed during the RR phase because symptoms were relatively mild, one gets diagnosed at this stage.

A detailed inspection of disability progression charts would also suggest that two largely independent mechanisms are underlying. And they may work at different places.

In the beginning, the herpes virus including herpes simplex, Varicella Zoster Virus (VZV) and Epstein-Barr Virus (EBV) spreads through the Virchow-Robin spaces in meningeal follicles, the lymphatic system and stem cells including OPCs and bone marrow.

In the RR phase, VZV/HERV in combination with toxins and/or "adjuvants" causes vasculopathies, microbleedings, endothelial inflammation, and lesion in the white matter. VZV also evades T-cell immunity but over time the immune system learns and RR wanes. VZV is believe to cause the inflammation in RR; immunologists know that VZV is an inflammatory virus. Demyelination is seen as collateral damage.

In the second phase – the progressive phase – a different mechanism is at work. An unbridled diffusion of EBV infected and immortalised B cells is seen which cause high oxidative stress. It is believed that this is a EBV/HERV related stimulation of B-cell growth and that this is a natural and healthy reaction of the immune system to prevent neoplasia/cancer. EBV would be the beneficiary. Immunologist know that EBV is an onco virus. Because of changes in innate immunity above 60 years of age, B-cell growth stops above 60 and no new cases of MS are reported but more cancers.

As we shall see in the next sections, this picture of VZV involvement in RR MS and EBV involvement in progressive MS is confirmed by epidemiological analysis. Epidemiological studies don't lie. If framed within right boundaries, they just tell us what we see in the population and that can't be wrong.

MS is thus a loss of epi-genetic control on HERV with VZV possibly in combination with toxins triggering cellular inflammation with an initial VZV evasion of T-cell immunity (RR), and; with EBV stimulating B-cells growth leading to huge oxidative stress and progressive mitochondrial failure. In other words, MS is caused by HERV/VZV with a herpes evasion of T-cell immunity and a deficient humoral immunity (B-cells).

Both mechanisms may assail the body in different places including the brains with white matter lesions in the first phase as well as grey matter loss including in the spinal column in the second

phase. In addition, a herpetic neuralgia may cause muscles to loose weight and sensitivity [PHN]. The effect on our mobility is then the result of a degrading serial pathway from brains to muscle cells and sensors.

Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2814602/

Antivirus immune activity in multiple sclerosis correlates with MRI activity

http://www.ncbi.nlm.nih.gov/pubmed/25939660

Evolutionary Aspects of Human Endogenous Retroviral Sequences (HERVs) and Disease

http://www.ncbi.nlm.nih.gov/books/NBK6235/

Varicella Zoster Virus and Relapsing Remitting Multiple Sclerosis

http://www.hindawi.com/journals/msi/2011/214763/

Pathogenesis and Current Approaches to Control of Varicella-Zoster Virus Infections

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3811230/

Human immune response to herpes viruses

The multiple layers of the human immune response present a challenge to viruses, which must survive and multiply within a host for a sufficient period of time to allow successful transmission to susceptible individuals. Given the large proteomes and comparatively low polymerase error rate of human herpesviruses, antiviral immunity at first glance appear to have the upper hand. Nonetheless, herpesviruses manage prolonged incubation periods following initial infection, with systemic dissemination and prolonged secretion, often from multiple sites. In contrast to the similarly large poxviruses, the ability to subsequently establish persistent infection is a hallmark of the human herpesviruses. To enable this lifestyle, the herpesviruses devote a significant proportion of their genome coding capacity to the expression of immuno-evasins, a collection of molecules that disrupt

normal immune physiology. Each human herpesvirus studied has evolved elegant cell biological solutions to problems posed by the immune response.

Innate immunity, an evolutionarily conserved and relatively non-specific system of pattern recognition molecules hardwired in the genome, cytokines such as interferons, phagocytes and natural killer (NK) cells, represents the first line deployed against microbial invaders, including herpesviruses. The clonal expansion of B- and T- lymphocytes that bear antigen-specific receptors for viral epitopes underlies the adaptive antiviral immune response, laying the groundwork for a highly pathogen-specific defense. Such specificity comes at a price – lymphocyte proliferation requires time to unfold, and innate immunity, in particular NK-cell activity, limits the initial herpesvirus spread. Indeed, NK cell immune deficiencies result in dramatic infection by several herpesviruses. There is significant cross-talk between the innate and adaptive systems, and preliminary pathogen recognition by the innate immune system directly contributes to the development of adaptive immunity. Further, the eventual adaptive response utilizes branches of the innate system for crucial effector function.

Innate and adaptive immunity act in concert to allow recovery from acute herpesvirus infection. Adaptive immunity then allows for lifelong immunological memory, affording both control of persistent herpesvirus infection and protection against reinfection. Once present, virus-specific CD4+ T-lymphocytes then coordinate the adaptive antiviral response, directing the production of virus-specific immunoglobulin by B-lymphocytes, the antiviral activity of CD8+ T-lymphocytes and NK cells, and further stimulating the activity of phagocytic cells.

Through millennia of coevolution, herpesviruses have largely reached a state of equilibrium with their human hosts. At the cost of a large proportion of their coding capacity, herpesviruses perturb adaptive immunity to achieve persistent infection, in general with remarkably little collateral damage to their hosts. However, lapses in T-cell immunity, such as by immunosuppressive agents or by coinfection with other pathogens such as Human Immunodeficiency Virus, can lead to significant herpesvirus-associated pathology.

Human herpesvirus genome size and polymerase fidelity place constraints on epitope mutation, and generally do not allow for antigenic variation as a means to avoid T-cell immunity. Herpesviruses therefore, have devised a range of mechanisms to subvert adaptive immunity. Generalized T-cell immuno-evasion strategies shared by herpesviruses include latency, restriction of viral gene expression to immunoprivileged sites such as the CNS, interference with complement, cytokines, NK-cell function, and apoptosis.

Herpesvirus evasion of T-cell immunity

http://www.ncbi.nlm.nih.gov/books/NBK47418/

Relapse-Remitting MS: Varicella-Zoster Virus and cell mediated immunity

The acute nature of RR relapses suggests that the effects of the VZV virus may block the cell machinery leading to mitochondrial malnutrition that provide insufficient energy to maintain the

charge of the ion pump. Eventually, the sitation will be dramatic and the immune system, initially evaded by VZV, will correct the cells that are in crisis. One possible mechanism is through intra-cellular viral control by interferon γ (IFNγ) by T cells (arrival of CD4+ T lymphocytes, CD8+ cytotoxic T cells produce IFNγ). IFN's are a group of proteins known primarily for their role in inhibiting viral infections. As cells recover, remittance is seen of MS symptoms.

The high load of autoreactive T- and B-cells will pass the Central Nervous System (CNS) and cross-react with the transgenes/HERVs in the OPCs. Due to this cross-reaction, many OPCs will die which leads to a diminishing number of OPCs, of dendrocytes and a reduced myelination of neurons. During this cross-reaction, many mediators will be released by the infiltrating T-cells. This will increase angiogenesis and cause hyperproliferation of surrounding tissue cells in the CNS which in turn causes the pathological lesions (sclerotic plaques) typical for MS.

A well functioning intestine with sufficient production of IFN's is essential. A distorted gut microbiota, gut leakage and compromised cell lining caused by a "Western" diet with high fat and polysacharide may interfere with the production of IFNγ, leak toxins such as epsilon toxin into the circulation and may skew us towards getting sick.

In particular VZV which is an "inflammatory virus" is suspect at this stage. DNA from VZV was found in the CSF from 100% of MS patients studied during relapse. In contrast VZV was not found in CSF from controls. Results from other herpes viruses tested were similar in MS patients and in controls.

The participation of varicella zoster virus in relapses of multiple sclerosis

http://www.ncbi.nlm.nih.gov/pubmed/24635924

Varicella Zoster Virus and Relapsing Remitting Multiple Sclerosis

http://www.hindawi.com/journals/msi/2011/214763/

Interestingly, the presence of large quantities of DNA from VZV in subarachnoid space is almost restricted to the periods of exacerbations. Steady diminution and eventual disappearance from clinical relapse to clinical remission constitute strong evidence to support the participation of VZV in the pathogenesis of RR MS.

Varicella-zoster virus in cerebrospinal fluid at relapses of multiple sclerosis

http://www.ncbi.nlm.nih.gov/pubmed/18306233

This view is further supported by epidemiological observations [Kang]. Epidemiological studies don't lie and if well conducted they are always right. Kang et al analysed a database of 349,477 patients who had VZV as a risk factor for MS in a region of the world historically considered low risk for MS. In the analysis, the data was compared with a randomly selected control group of participants who did not have herpes zoster that was 3 times as large as the patient sample (n = 1,262,200). The results

show that the herpes zoster group has a 3.96 times greater risk of developing MS than did the control group.

The study highlights the time elapsed from the event of shingles until the ocurrance of MS, as approximately 100 days. In addition, evidence suggests that up to 30% of relapses among MS patients are associated with an infectious process. A possible explanation is the reactivation of latent herpes viruses by other infectious agents, and a cross-recognition of common viral antigens with antigens found in the myeline sheath. The time lag could be explained by a series of procresses required by the immune systems of genetically susceptible individuals to reach a “threshold” and start the disease process. The threshold may also explain, in part, the observation that some patients have higher recurrence rates of MS around a certain month of the year.

Other epidemiological studies from geographical areas, where the incidence of MS has increased in recent decades, pointed out a high frequency of varicella and zoster in the clinical antecedents of MS patients while laboratory investigations have found large quantities of DNA from VZV in leucocytes and CSF of MS patients. Again, these were restricted to the ephemeral period of MS relapses, followed by a disappearance of the virus during remission.

The above observations and the peculiar features for VZV, mainly characterised by its neurotropism and long periods of latency followed by viral reactivation, support the idea on the participation of VZV in the etiology of RR MS.

Herpes Zoster and Multiple Sclerosis

http://jid.oxfordjournals.org/content/204/2/177.full

Varicella zoster virus contributes to relapse in patients with multiple sclerosis

http://www.nature.com/nrneurol/journal/v4/n6/full/ncpneuro0798.html

Varicella Zoster Virus and Relapsing Remitting Multiple Sclerosis

http://www.hindawi.com/journals/msi/2011/214763/

Varicella-zoster virus particles have been found in CSF of patients during relapses, but this particles are virtually absent during remissions.

https://en.wikipedia.org/wiki/Pathophysiology_of_multiple_sclerosis

The endothelial inflammation and microbleedings and MS

Varicella zoster virus (VZV) infects >95 % of the world population. Typically, varicella (chickenpox) results from primary infection. The virus then becomes latent in ganglionic neurons along the entire

neuraxis. In immunocompromised individuals, VZV reactivates and causes herpes zoster (shingles), pain, and rash in 1-2 dermatomes. Multiple case reports showed a link between stroke and zoster, and recent studies have emerged which reveal that VZV infection of the cerebral arteries directly causes pathological vascular remodeling and stroke (VZV vasculopathy). In the past few years, several large epidemiological studies in Taiwan, Denmark, and the U.K. demonstrated that zoster is a risk factor for stroke and that antiviral therapy may reduce this risk. Herein, the history, clinical features, and putative mechanisms of VZV vasculopathy, as well as recent epidemiological studies demonstrating that zoster increases the risk of stroke, are discussed.

Endothelial cells lining the vessel wall are connected by adherens, tight and gap junctions. These junctional complexes are related to those found at epithelial junctions but with notable changes in terms of specific molecules and organization. Endothelial junctional proteins play important roles in tissue integrity but also in vascular permeability, leukocyte extravasation and angiogenesis. In this review, we will focus on specific mechanisms of endothelial tight and adherens junctions.

The endothelium connects the vascular and immune systems. It allows for permeability in the blood brain barrier, the gut and all 60,000 miles of blood and lymph vessels. The endothelial tight junctions line the vascularity and intestines.

The relationship between herpes zoster and stroke, Maria Nagel
http://www.ncbi.nlm.nih.gov/pubmed/25712420

7T MRI: New Vision of Microvascular Abnormalities in Multiple Sclerosis

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2579786/

Endothelial adherens and tight junctions in vascular homeostasis, inflammation and angiogenesis

http://www.sciencedirect.com/science/article/pii/S000527360700346X

Toxins and MS: Genetic rearrangement of transgenic cells

In MS, we see many patients with a leaky gut [leaky gut, ceuliacie, engrainisation…]. There is possibly a role for epsilon toxin from the gut bacteria Clostridium Perfringens. Bad gut bacteria produce for instance the ε-toxin that leak into the circulation and apparently home in on [dendric] cells that are virus infected. These are typically the OPCs because they help divide the viral genes. Other toxic substances from fungi are also suspect. Frederic Gay in his article speculates about a 50 kDa particle.

Bacterial toxins and Multiple Sclerosis, Gay F, Journal of the neurological sciences 262:1-2 2007 Nov 15 pg 105-12

http://www.unboundmedicine.com/medline/citation/17707408/Bacterial_toxins_and_Multiple_Sclerosis_

The bacteria Bordetella pertussis and its secreted toxin have been extensively used within the last 50 years to vaccinate against whooping cough. In the study, the bacteria appeared to induce neuropathology in experimental autoimmune encephalomyelitis, the key animal model for human MS.

Researchers say the bacteria can behave as a neuropathogen causing MS. Evidence supporting the hypothesis was the MS epidemic in the Faroe Islands during and immediately after World War II. According to the article, authors who studied the outbreak noted that “MS is the rare late outcome of a specific but unknown infectious disease of adolescence and young adulthood.”

Epidemiologic evidence for multiple sclerosis as an infection

http://www.ncbi.nlm.nih.gov/pubmed/8269393

Clostridium perfringens Epsilon Toxin Causes Selective Death of Mature Oligodendrocytes and Central Nervous System Demyelination

http://mbio.asm.org/content/6/3/e02513-14

Why do ε-toxin home in on OPCs? In fact, they may home in on all cells but in OPCs the "fertile" ground is found to do the genetic rearrangement. Which then shows up as microbleedings and white matter lesions. The herpes virus including VZV infect in particular OPCs and bone marrow because these cells divide.

It is postulated that ε-toxin, but perhaps other bacterial cell molecules and transportable proteins as well e.g. from the naso pharynx and/or from the gut, trigger transgene herpes/VZV primed cells to activate intra-cellular events e.g. through sharing segments of DNA. This would lead to the release of pro-inflammatory lipid mediators, enzymatic activities and modified cell signaling events.

Also mycotoxins such as black mold (stachybotrys) may trigger MS. The environment of Scotland and Seattle are extremely similar in many ways: they are on almost the same latitude, they are both maritime climates with average temperatures between 40's-60's Fahrenheit with 100% humidity. Both places rarely get strong heat or clear strong sun or enough UV rays to dry out moldy houses, cars, etc and dry out or kill spores in the air, nor does either place get much of a hard freeze to arrest mold growth and dry out air. With the advent of air conditioning, places that are normally very dry and sunny like Kuwait, are seeing an explosion in MS.

In other words, 'synergetic effects' of virus and bacterial and myco-toxins working together that Buhner talks about in his book Healing Lyme disease coinfections cause havoc in the cell’s genetic arrangement, shedding cytokines and chemokines and leading to inflammation and microcellular bleedings.

Clostridium perfringens Epsilon Toxin Causes Selective Death of Mature Oligodendrocytes and Central Nervous System Demyelination

http://mbio.asm.org/content/6/3/e02513-14

Healing Lyme Disease Coinfections: Complementary and Holistic Treatments for Bartonella and Mycoplasma

http://www.amazon.com/Healing-Lyme-Disease-Coinfections-Complementary-ebook/dp/B00CWD7W2C/ref=sr_1_2?ie=UTF8&qid=1439115670&sr=8-2&keywords=buhner+lyme+disease

The role of the gut on cell mediated immunity (epigenetic control):

Our "Western" diet causes an effect on IFNγ and IL17 production which in turn causes an effect on cell-mediated immunity with T-cell (IFNγ) mediation. During periods of low immunity, periodic reactivation from latent viral reservoirs results in viral subclinical shedding and the associated inflammation with continued neurological and developmental issues.

When a representative model of the human gut eco-system was established in mice, switching from low-fat, plant polysaccharide-rich diet to a high fat, high sugar "Western" diet shifted the structure of the microbiota of these "humanized" mice in a single day and changed the metabolic pathways in the micro biome and its gene expression.

The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice

http://stm.sciencemag.org/content/1/6/6ra14

Interferon Gamma (IFN-g)

http://www.bio.davidson.edu/courses/immunology/students/spring2006/v_alvarez/ifn-gamma.html

Germ free mice induced for EAE produced lower levels of proinflammatory cytokines, IFNγ and IL17 in both the intestine and the spinal cord and displayed reciprocal increase of CD4 T cells.

http://www.pnas.org/content/108/Supplement_1/4615/F4.expansion.html

Some microbe families from the gut microbiota however promote the inflammatory cascade in the CNS. The strongest here being the unculturable Clostridium family of which the Segmented Filamentous Bacteria is the most active and have a key role in the coordinated maturation of gut helper T cell responses.

The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses

http://www.ncbi.nlm.nih.gov/pubmed/19833089

This observation coincides with the recent finding on ε-toxin: Clostridium perfringens Epsilon Toxin Causes Selective Death of Mature Oligodendrocytes and Central Nervous System Demyelination. It would thus occur that cell mutation is incited by both a lack of IFN γ combined with a toxic microcellular environment.

Clostridium perfringens Epsilon Toxin Causes Selective Death of Mature Oligodendrocytes and Central Nervous System Demyelination

http://mbio.asm.org/content/6/3/e02513-14

Impaired transport from Golgi apparatus results in evasion of T-cell immunity

Abendroth et al (2001) sought to examine the effects of varicella-zoster virus (VZV) infection on the expression of major histocompatibility complex class I (MHC I) molecules by human fibroblasts and T lymphocytes. They found that VZV downregulates MHC I expression by impairing the transport of MHC I molecules from the Golgi compartment to the cell surface. This effect may enable the virus to evade CD8+ T-cell immune recognition during VZV pathogenesis, including the critical phase of T-lymphocyte-associated viremia.

Varicella-zoster virus retains major histocompatibility complex class I proteins in the Golgi compartment of infected cells

http://www.ncbi.nlm.nih.gov/pubmed/11312359

High anti-golgi autoantibody levels: an early sign of autoimmune disease?

http://www.ncbi.nlm.nih.gov/pubmed/10468179

Antibodies from patients with autoimmune disease react with a cytoplasmic antigen in the Golgi apparatus

http://www.ncbi.nlm.nih.gov/pubmed/6373921

The Golgi complex is an organelle involved in terminal processing, sorting and transporting of proteins to their final destinations.

Anti golgi antibodies and cryoglobulins

http://medind.nic.in/iac/t12/i1/iact12i1p16.pdf

Cell surface expression of class I molecules is reduced upon VZV infection, an effect that has been observed in both human T-cells in the SCID-hu thymus/liver mouse model and in skin biopsy specimens. Microscopic and biochemical experiments demonstrate the accumulation of class I MHC molecules in the Golgi compartment in VZV-infected cells.

The ORF66 gene-product is expressed during the early period of virus infection and serves to retain class I molecules in the Golgi complex. Cellular transfectants that express ORF66 demonstrate reduced cell surface expression of class I MHC. The molecular mechanism by which VZV halts class I in the Golgi has yet to be fully elucidated. The UL49.5 gene-product of several varicelloviruses including bovine herpesvirus I, pseudorabies virus, and equine herpesvirus 1, though not of varicella zoster, blocks the TAP peptide transporter through conformational arrest and subsequent proteasomal degradation.

Dendritic cells (DCs) are professional antigen-presenting cells that play a crucial role in stimulation of adaptive T-cell responses. Multiple members of the human herpesvirus family decrease the capacity of DC to stimulate T-cells.

Infection of DCs by other herpes viruses can even facilitate VZV dissemination and support infection of T-cells themselves. VZV-infected T-lymphocytes play an important role in supporting persistent viremia.

VZV also interferes with Jak/STAT signaling, apparently by the inhibition of Jak/STAT2 protein synthesis.

Herpesvirus evasion of T-cell immunity

http://www.ncbi.nlm.nih.gov/books/NBK47418/

Progressive MS: Epstein-Barr Virus and deficient humoral immunity

Many observations implicate Epstein–Barr virus (EBV) in the pathogenesis of MS, namely universal EBV seropositivity, high anti-EBV antibody levels, alterations in EBV-specific CD8+ T-cell immunity, increased spontaneous EBV-induced transformation of peripheral blood B cells, increased shedding of EBV from saliva and accumulation of EBV-infected B cells and plasma cells in the brain.

Several mechanisms have been postulated to explain the role of EBV in the development of MS including cross-reactivity between EBV and CNS antigens, bystander damage to the CNS by EBV-specific CD8+ T cells, activation of innate immunity by EBV-encoded small RNA molecules in the CNS, expression of αB-crystallin in EBV-infected B cells leading to a CD4+ T-cell response against oligodendrocyte-derived αB-crystallin and EBV infection of autoreactive B cells, which produce

pathogenic autoantibodies and provide costimulatory survival signals to autoreactive T cells in the CNS.

The rapidly accumulating evidence for a pathogenic role of EBV in MS provides ground for optimism that it might be possible to prevent and cure MS by effectively controlling EBV infection through vaccination, antiviral drugs or treatment with EBV-specific cytotoxic CD8+ T cells. Adoptive immunotherapy with in vitro-expanded autologous EBV-specific CD8+ T cells directed against viral latent proteins was recently used to treat a patient with secondary progressive MS. Following the therapy, there was clinicall improvement, decreased disease activity on magnetic resonance imaging and reduced intrathecal immunoglobulin production.

Epstein–Barr virus and multiple sclerosis: potential opportunities for immunotherapy

http://www.nature.com/cti/journal/v3/n10/full/cti201425a.html

The B-cell mechanism that occurs as of mid-age but that is probably underway much longer is a different mechanism all together than the VZV mechanism underling RR MS. EBV infected B-cells cause immune subversion and disease progression. With the virtual non-existence of MS in EBV seronegative people (still 5 - 10 % of population), epidemiological analysis would seem to confirm the very strong relationship of EBV with MS.

Universal EBV seropositivity, high EBV antibody levels and alterations in EBV-specific CD8+ T-cell immunity are commonly observed and likely to be an important contributing factor to MS rather than the result of MS.

The EBV virus has spread so far that increasingly B-cells get infected with a lack of sufficient T-cell control function to contain an unbridled B-cell replication. In fact, HERV may help T-cells to stimulate B-cell growth factors via a viral superantigen in order to stimulate growth of its host cell, the B-cell. EBV is the beneficiary; otherwise EBV infected cells might develop into cancers and that would be the end of story.

Disruption of the highly evolved balance (after many millions of years of co-evolution) between the EBV lytic and latent life cycles and host immune control results in a range of EBV-associated diseases involving B-cells, epithelial cells, T-cells, natural killer (NK) cells and muscle cells.

Here a weak [epigenetic] control may activate HERV virus and contribute to a spreading of the disease in meningal follicles. Staphylococcal immune complexes and myelinolytic toxin in early acute MS lesions connects the matter to EBV proliferation from the pharyngeal cells.

Viruses as an endothelial disrupters

The association between EBV infection and CCSVI has not yet been explored; however, it could be hypothesized that venous stasis in the superior saggital sinus due to extracranial outflow impairment could affect the drainage of bridging veins that pass through the subarachnoid space (near the meninges and EBV-infected B-cell follicles) and contribute to EBV activation. The venous stasis

hypothesis in the SSS may contribute to understanding why so many different viruses and bacteria have been linked to increased MS susceptibility risk over the last 50 years.

http://ccsviinms.blogspot.be/2011/08/bnac-review-venous-stasis-and-ebv.html

MS and B cell depletion:

A new study has uncovered a type of B cell that may fuel inflammation in patients with multiple sclerosis. The findings help explain the long-standing question of why an experimental therapy that removes these immune cells from the body is effective against the disease. Selectively eliminating the pool of rogue B cells, while sparing healthy B cells, may offer a more targeted approach for treating multiple sclerosis and potentially other autoimmune disorders. Some [B cells] may be bad in MS and some may actually be beneficial. The subset of pro-inflammatory B cells may also serve as a potential marker of disease relapse and patients' response to treatment.

Multiple sclerosis is traditionally viewed as a T cell-driven disease. In this autoimmune disorder, the immune system, primarily T cells as well as immune cells called myeloid cells, are thought to destroy myelin, a fatty substance that insulates and protects nerve fibres. [This is RR]

B cell depletion therapy, which removes B cells from the blood, can keep relapses at bay in multiple sclerosis patients. The success of this treatment in clinical trials has put the spotlight on B cells as key players in the disease. B cells are best known for their ability to make antibodies, and abnormal antibodies are common in multiple sclerosis patients.

However, the B cell depletion treatment has little effect on the abnormal antibodies found in these patients. This "striking and surprising observation" led Bar-Or and colleagues to suspect functions for B cells beyond antibody production, he said. B cells fulfil other important roles, including secretion of cytokines, small signalling proteins that can either quench or promote inflammation.

Analysing B cells in blood samples from multiple sclerosis patients and healthy individuals, and studying patients' immune responses before and after B cell depletion therapy, Bar-Or's team identified a subpopulation of B cells that releases a powerful pro-inflammatory cytokine called GM-CSF, which is known to drive inflammation in the brain.

Compared to healthy individuals, untreated multiple sclerosis patients had abnormally abundant and more readily activated GM-CSF-producing B cells. These B cells stimulated myeloid cells in a dish to secrete pro-inflammatory cytokines, which in turn can activate pro-inflammatory T cells.

After undergoing B cell depletion therapy, multiple sclerosis patients experienced fewer flare-ups of their symptoms and showed reduced inflammation in their blood. The results suggest that by partially eliminating the rogue B cell pool, the therapy may have blunted inflammation triggered by myeloid cells and T cells. These benefits persisted for months after treatment and even as patients formed new B cells.

While B cell depletion therapy has proven highly effective in advanced clinical trials, its long-term

safety remains to be seen. The therapy "may be taking some of the good with the bad, so by getting a better sense of who the bad guys are, we can hopefully develop treatments that are as effective and potentially even safer," said Bar-Or.

Rogue B Cells May Drive Inflammation in Multiple Sclerosis, American association for the advancement of science, 27/10/15

http://www.aaas.org/news/rogue-b-cells-may-drive-inflammation-multiple-sclerosis-0

Oxidative stress leads to mitochondrial failure and disease progression

EBV infected B cells cause a huge oxidative stress on the mitochondrial membranes with insufficient protective cellular feeding and antioxidant mechanisms (such as astrocytes). As a consequence, mitochondria will fail one by one up to the point where the ion pump cannot maintain the equilibrium of charging to perform normal motor operation. This occurs first because the ion pump needs most energy, in fact more than the muscle cells. At this point, cells may not have died but have become 'electrically' dormant. The neurological path is weakened.

Characterization of the superoxide-generating system in human peripheral lymphocytes and lymphoid cell lines

http://www.ncbi.nlm.nih.gov/pubmed/7592536

Peroxynitrite: biochemistry, pathophysiology and development of therapeutics, Csaba Szabó

http://www.enzim.hu/~lbarna/articles/17667957.pdf

Oxidative stress has been strongly implicated in both the inflammatory and neurodegenerative pathological mechanisms in MS. In response to oxidative stress, cells increase and activate their cellular antioxidant mechanisms. Glutathione (GSH) is the major antioxidant in the brain, and as such plays a pivotal role in the detoxification of reactive oxidants. Previous research has shown that GSH homeostasis is altered in MS.

Glutathione in multiple sclerosis: more than just an antioxidant?

http://www.ncbi.nlm.nih.gov/pubmed/24842957

Oxidative stress is often seen in papers about SNP, epigenetics and the gut microbiome. There, it is often argued that oxidative stress follows when it has all gone wrong. But it might be different where oxidative stress contributes to the cause, where oxidative stress puts in motion a vicious cycle. This would also explains why the massive use of antioxidants may start to make a difference, after some

period of time. [Terry Wahls had her metabolism flooded with supplements for quite a while before she started the diet and recovered from MS.]

If identical twins get separated at young age but before adolescence, the person that moves further South has less risk to develop MS at a later date. That person will have more sun exposure and therefore a higher vitamin D level in the circulation during adolescence when the body goes through a main phase of cellular growth. When the cells are formed, they take vitamin D directly from the circulation where the vitamin D level determines the number of mitochondria per cell (1500-3000; the heart up to 5000, Sinatra). And when the cells have more mitochondria, they will be more resilient. And one is better protected against MS or rheuma arthritis.

Mitochondria May Play a Role in MS Development and Progression

http://multiplesclerosisnewstoday.com/2015/07/08/mitochondria-may-play-a-role-in-ms-development-and-progression/

Besides a cross-reaction with transgenic OPCs (cause collateral damage on myelin and endothelial inflmmation), the autoreactive B-cells have substantial super-oxygen generating capability (the mechanism to prevent recurrent infections). The superoxide reacts with the nitric oxide (NO) in the cell membranes and produces excess peroxynitrite which is by far the worst free radical. Peroxynitrite is the cyclic culprit of immune system apoptosis and responsible for the damage in MS. [Scaby]

Peroxynitrite-induced membrane lipid peroxidation: the cytotoxic potential of superoxide and nitric oxide
http://www.ncbi.nlm.nih.gov/m/pubmed/1654835

Results indicate that the oligodendrocyte loss and demyelination observed in MS and spinal cord injury may be due to the toxic effects of Peroxynitrite on oligodendrocytes.

http://www.sciencedirect.com/science/ar ... 2898000782

Peroxynitrite, generated by the reaction of nitric oxide (NO) with superoxide at sites of inflammation, is a strong oxidant capable of damaging tissues and cells. Detection of nitrotyrosine (NT) at inflammatory sites serves as a biochemical marker for peroxynitrite-mediated damage. In this study, NT was detected immunohistochemically within autopsied CNS tissues from six of nine multiple sclerosis (MS) patients, and in most of the MS sections displaying inflammation. Nitrite and nitrate, the stable oxidation products of NO and peroxynitrite, respectively, were measured in cerebrospinal fluid samples obtained from MS patients and controls. Levels of nitrate were elevated significantly during clinical relapses of MS. These data suggest that peroxynitrite formation is a major consequence of NO produced in MS-affected CNS and implicate a role for this powerful oxidant in the pathogenesis of MS.

Peroxynitrite is highly destructive causing Apoptosis, Programmed Cell Death, Oxidative stress, ROS, RNS, DNA oxidation and nitration, Lipid oxidation, peroxidation and nitration, Protein oxidation.

DNA strand alterations and breakdown, Mitochondrial dysfunction.

Reduced cortical microvascular oxygenation in multiple sclerosis: a blinded, case-controlled study using a novel quantitative near-infrared spectroscopy method
http://www.nature.com/articles/srep16477

Although the peroxynitrite may inhibit viral replication, it disables glyceraldehyde 3 phosphate which impacts the sodium/potassium pump and cell viability. Over time the vitality of the cell declines as ATP levels decline and the loss of some AMP leads to a fall in Adenosine (endogenous inhibitor of arachidonic acid) and a loss of purine from Adenosine loss.

Ultimately energy levels decline and uric acid levels fall. The loss of Adenosine and cellular IFNγ will lower the ability to control inflammation and indeed the suppression of the transfer of EBV from latently infected cells to other cells. And the endothelium inflammates leading to an endothelial dysfunction.

As regards the anti-inflammatory properties of Adonesine (the A in ATP), Adenosine is a purine. The last step in the metabolism of purines is Uric acid. As Uric acid is low in MS, it is likely the recycling is faulty. Probably cells convert 2 ADP into 1 ATP and 1 AMP. The AMP washes out of the cell and the ATP is spent to become ADP and then combines with another ADP to become ATP and AMP again but the purine gets gradually lost to the cell until it is unviable. Uric acid also is a scavenger of peroxynitrite so the cycle worsens over time.

The huge oxidative stress jams mitochondria of the cells, causes effects on the mitochondrial electron transport chain and ion pump inactivation, inhibits ADP to ATP conversion and depletes energy in the form of ATP resulting in a mitochondrial energy failure.

As the ion pumps already run on their edge where a number of mitochondria in the cell have failed, the equilibrium can not be easily maintained. When cell gates close with increasing temperature (either from the outside or fever induced; cooler weather or high air pressure have the reverse effect), the conduction of the nerve path runs down. Here the ion pumps are the most important energy consumers that require the biggest amount of cellular energy.

Metabolic Cardiology, Steven Sinatra

http://www.amazon.com/Sinatra-Solution-Metabolic-Cardiology-ebook/dp/B00AU6V0VC/ref=sr_1_1?s=books&ie=UTF8&qid=1439137297&sr=1-1&keywords=steven+sinatra

Electrochemical gradient

https://en.wikipedia.org/wiki/Electrochemical_gradient

Energy transduction: uses of ATP

http://biochem-vivek.tripod.com/id55.html

Cellular respiration

https://sites.google.com/site/accessrevision/biology/cell-form-and-function/cellular-respiration

As the number of active gates/mitochondria per cell decreases, we see an increasingly big temperature effect in patients with MS and a loss of muscle strength and sensitivity in the periphery. As cells shrink in size because gates/mitochondria successively fail, it causes whole brain atrophy.

Hence, the typical fatigue, weakening of muscles and whole-brain atrophy observed in MS patients is partly caused by the EBV infected B cells but with a completely different underlying mechanism than the demyelinating plaques in the brains. And the typical MS motor dysfunction will be caused by a combination of factors.

If the health of the mitochondria runs down, the heat effect - a natural protective mechanism of the cells that closes the gates or slows down the cells - will become more pronounced. If it gets colder, the mitochondria will work faster. And the pump charges better, and even progression may slow down.

Strictly speaking, it is not the ion channels themselves that are impaired. It is the supply of energy to the ion channels that declines. The availability of energy to the ion channel, which is ATP dependent, and thus the formation of ATP in the mitochondria. That in turn is dependent on fats and nucleic acids from the glycolysis side and the functioning of the electron transport chain on the other. Then it depends on the permeability of the membrane for ADP and ATP which is carnitine dependent. The carnitine would need a fatty acyl CoA enzyme (also ATP dependent) to become acetyl-L-carnitine.

(Short term) stressors initiate cases of multisystem illnesses by stimulating nitric oxide synthase (NOS) activity and consequently produce increased levels of NO and its oxidant product peroxynitrite. The immune system will be triggered by the biochemical cycle mechanism with NF-κB a first responder to the harmful cellular stimuli. The increased NF-κB activity will lead to increased iNOS activity by stimulating through the inflammatory cytokines the activity of the iNOS gene itself.

NO synthase is influenced by sex hormones, is higher in women which explains the gender bias in autoimmunity. Further, the study below supports the hypothesis of a direct involvement of HERV-W/MSRV in MS pathogenesis, identifying a genetic marker on chromosome X that could be one of the causes underlying the gender differences in MS. The gender bias may therefore be a combination of hormonal and genetic factors.

HERV-W polymorphism in chromosome X is associated with multiple sclerosis risk and with differential expression of MSRV

http://www.retrovirology.com/content/11/1/2

In the chain of events leading to MS, at some point the HPA axis may also get affected with consequences for cortisol production and with that gut functioning resulting in yet another vicious cycle.

http://www.amazon.com/Explaining-Unexplained-Illnesses-Fibromyalgia-Post-Traumatic/dp/078902389X/ref=sr_1_1?s=books&ie=UTF8&qid=1439193153&sr=1-1&keywords=martin+pall

Nitric Oxide and health:

NO is one molecule of nitrogen and one of oxygen. It is a gas and when formed naturally in the body is a signalling agent. It is critical for good health and is responsible for vasodilation and is integral to prevention of hypertension, limiting arterial plaques, modulating cholesterol, controlling bacterial infection, bone density and managing inflammation. It is in every cell, tissue and organ in your body. Nitric oxide diffuses out of the endothelium into the smooth muscle of the artery.

The production of NO is triggered three enzymes known as Nitric Oxide synthases. They are either constitutive such as endothelial (eNOS) and neuronal (nNOS) or inducible (iNOS). The various forms of NOS oxidize L-arginine to produce NO.

The Truth About L-Arginine

https://www.youtube.com/watch?v=IPd2NB9mjaM

Peroxynitrite is the product formed by the interaction of NO and Superoxide. Normal oxygen gas in the body is O2 which is two molecules of oxygen. Superoxide is two molecules of oxygen with an extra electron. It has a negative charge and is what we call a free radical.

Combining NO and superoxide creates another free radical called peroxynitrite. This is a particularly troublesome product as it can disable the enzyme Glyceraldehyde-3-phosphate dehydrogenase. This is an acidic protein that acts as the major link between carbohydrate metabolism and lipid metabolism and is key in the breakdown of sugars when converting glucose to pryruvate. The energy released in that process forms ATP and that is required to drive the citric acid cycle.

A lack of ATP will prevent the correct exchange of sodium and potassium through the cell resulting in cells that are sodium clogged. That overload of sodium will also trigger the release of calcium into the cell from the sarcoplasmic reticulum signalling muscles to contract. The protein strands in the contracted muscles require ATP to signal them to release. As it is in short supply our muscles stay tight. If this process arises during a major inflammatory attack then it may be associated with a reperfusion injury which will result in some cells becoming denatured and some ion channels may be jammed open or shut.

The 1998 Nobel prize was awarded to three US researchers only six years after they published for their work on the role of Nitric Oxide. The gas was named the molecule of the century. NO is a major messenger in talk between cells.

Louis Ignarro “Nitric Oxide: Biology and Pathobiology”

http://www.amazon.com/Nitric-Oxide-Second-Biology-Pathobiology/dp/0123738660/ref=sr_1_1?s=books&ie=UTF8&qid=1454064624&sr=1-1&keywords=Nitric+Oxide%3A+Biology+and+Pathobiology

On the need to rethink autoimmunity risk factors

Industrialized foods increase the likelihood of developing autoimmune disease

Israeli and German researchers maintain that industrialized food additives may raise the risk of developing autoimmune diseases, a finding that comes soon after the World Health Organization's announcement that eating excessive amounts of processed foods raises the risk of cancer. The scientists argue that processed foods weaken the intestine's resistance to bacteria, toxins and other hostile nutritional and non-nutritional elements.

This increases the likelihood of developing autoimmune diseases, in which the body's immune system attacks cells, tissues or organs as if they were foreign bodies. The researchers examined the effects of processed food on the intestines and on the development of autoimmune diseases – more than 100 of which have been identified, including type 1 diabetes, celiac disease, lupus erythematosus, multiple sclerosis, autoimmune hepatitis, Crohn's disease, scleroderma and myesthenia gravis.

Researchers argued that patients with a family background of autoimmune diseases should consider avoiding processed foods [genetic dimension]

In their study, the researchers focused on the significant increase in the use of industrial food additives aimed at improving qualities such as taste, smell, texture and shelf life, and found a "significant circumstantial connection between the increased use of processed foods and the increase in the incidence of autoimmune diseases."

Many autoimmune diseases result from damage to the functioning of the "tight junctions" that protect the intestinal mucosa, the researchers said. When functioning normally, tight junctions serve as a barrier against bacteria, toxins, allergens and carcinogens, protecting the immune system from them. Damage to the tight junctions (also known as "leaky gut") leads to the development of autoimmune diseases.

The researchers found that at least seven common food additives weaken the tight-junctions – glucose (sugars), sodium (salt), fat solvents (emulsifiers), organic acids, gluten, microbial transglutaminase (a special enzyme that serves as food protein "glue") and nanometric particles.

"We hope this study and similar studies increase awareness about the dangers inherent in industrial food additives and raise awareness about the need for control over them."

Israeli, German researchers find link between industrialized foods and autoimmune diseases

http://www.jpost.com/Business-and-Innovation/Health-and-Science/Israeli-German-researchers-find-link-between-industrialized-foods-and-autoimmune-diseases-439296

Adjuvants may trigger autoimmune diseases and lymphoma

The emerging epidemic of Hodgkin and non-Hodgkin lymphomas worldwide continues to defy our understanding and forces the search for the causative factors. Adjuvants are known to act as triggers of immune and inflammatory responses. Animal experiments have demonstrated that long-term inflammation is related to aggravation of the immune network resulting in cellular and humoral responses leading to autoimmunity and lymphoma development. Chronic stimulation of the immune system is thought to be the key mechanism through which infectious diseases as well as autoimmune diseases can lead to lymphomagenesis. Many adjuvants can act similarly perturbing immune system's function, inducing a state of prolonged immune activation related to chronic lymphatic drainage. Several mechanisms were proposed by which adjuvants induce inflammation, and they are discussed herein. Some of them are triggering inflammasome; others bind DNA, lipid moieties in cells, induce uric acid production or act as lipophilic and/or hydrophobic substances. The sustained inflammation increases the risk of genetic aberrations, where the initial polyclonal activation ends in monoclonality. The latter is the hallmark of malignant lymphoma. Thus, chronic adjuvant stimulation may lead to lymphoma.

Adjuvants and lymphoma risk as part of the ASIA spectrum

http://www.ncbi.nlm.nih.gov/pubmed/25582758

Adjuvants as a main cause of autoimmune diseases and lymphoma

http://autoimmunity.kenes.com/scientific-information/scientific-program-highlights#.VmawX794Pq0

Vaccination, adjuvants and MS

While there may be no longer-term association of vaccines with MS or any other acquired central nervous system demyelinating syndromes which argues against a causal association, the short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. In the short term vaccinations may in fact increase risk by triggering events that lead to the onset.

Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases

http://www.ncbi.nlm.nih.gov/pubmed/25329096

The consequences of vaccination in combination with many other predisposing factors may be become alarming. For instance, Crohn's disease - another autoimmune disease - is uniquely linked to measles that through interaction with HERV transgenic cells sets off autoimmunity.

This French study suggests statistical data show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later.

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination

http://www.ncbi.nlm.nih.gov/pubmed/25395338

The Norwegian supreme court recently found that in some very rare cases the vaccine could trigger MS.

[role of adjuvants needs to be clarified]

Beyond MS - towards a new paradigm for autoimmunity

In our current system, we see a very large number of overlapping autoimmune diseases with different names. Every expression of a neurological set of symptoms got its own name, based on several types of observations. And we see various signs and symptoms that are overlapping.

But in fact, a bigger common scheme is underlying. A scheme that encompasses the wide variety of observations, their patterns of case initiation, their chronic nature and many of their shared and unique symptoms and signs of the chronic phase of the disease. A scheme that explains many unexplained observations and the multiple similarities of these illnesses by a simple conceptual framework.

Traditional major disease paradigms should be complemented by a new model based on the health of the mitochondria, a new virological consciousness and the biochemical cycle mechanism.

Therapeutic options

This thesis presents a coherent and consistent picture of the many facets that play a role in MS. That logic adds greatly to its plausibility. The precise concepts and mechanisms of what makes up MS will now need to be identified and confirmed in further proof-of-concept studies along the lines of this thesis.

Notwithstanding, as we know the main elements of the new theory, we may advance on a possible treatment strategy and already now define critical steps towards recovery. In fact, Terry Wahls defeated her MS and came out of the wheel chair following exactly these steps.

An effective cure for MS would seem to comprise the following steps:

Kill or suppress the virus

by chemo (Endoxan/cyclophosphamide of Mitoxantrone/Novantrone)

Endoxan/cyclophosphamide is a rather toxic anti-cancer drug. In MS, it is used in low dose. Cyclophosphamidehas mostly been used for the chronic progressive form. It appears safe and its use for MS has recently revived.

[Unfortunately this cyclophosphamide MS treatment has major side effects, both short and long term. In the longer term, it can cause a variety of cancers in its own right. These side effects limit its usefulness for people with MS.]

[What is crucial here is the working mechanism by which B cells decrease. Is it the drug that attacks the EBV/viral component and then the B cells wane, or does it work more directly on the depleting B cells and not the virus?]

Terry Wahls had two sessions with Novantrone in the years prior to her recovery.

by monoclonal anti bodies (Rituximab which is an FDA approved anti-EBV treatment)

The monoclonal antibodies are relatively large and hence treatment needs intrathecal injections to be effective. Cyclophosphamide are very samll particles, much smaller than mabs, so one can do without.

or by High Active Anti-Retroviral Treatment (HAART treatment as used in anti-HIV)

Isentress anti-viral drug
Julian Gold trial https://www.youtube.com/watch?v=Ss5alRN9voA

Strengthen the epigenetic control via the gut microbiome.

Through manipulation of the gut microbiome, a reversal of inflammation can be achieved and progression be stopped.

The manipulation of bacterial composition is done through lots of fibre intake and vegetable diet. Low consumption of wheat products (gluten), sugar and (trans)fats could be beneficial. This is essentially the Wahls diet or a hunterer-gatherer diet.

The only hunter-gatherers left in the world have 1500 different gut species, where the rest of the world averages only 1000. The big differences in their diet being: the low consumption of meat vs the rest, and the very high consumption of fiber.

There is a relatively simple test on metabolites in urine which may provide an indication of a leaky gut.

For the future, we may be able to identify active “driver”and “modulator” species and distinguish them from bystander commensal species, and pinpoint disease-causing or disease-modulating microbes that contribute to MS whose activities may be masked by other bacteria and assess therapeutic responsiveness of pathogenic and probiotic species introduced into the microbiome.

U.S. Patent No. 9,005,603 generally relates to a bacterial therapy containing Prevotella histicola for treatment of autoimmune diseases such as arthritis and multiple sclerosis. This species reduces inflammation, a hallmark of autoimmune disease.
http://www.patentdocs.org/2015/08/guest-post-the-emergent-microbiome-a-revolution-for-the-life-sciences-part-ii-2015-patent-trends.html

A Novel Probiotic Mixture Exerts a Therapeutic Effect on Experimental Autoimmune Encephalomyelitis Mediated by IL-10 Producing Regulatory T Cells
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0009009

Modulation of Intestinal Microbiota by the Probiotic VSL#3 Resets Brain Gene Expression and Ameliorates the Age-Related Deficit in LTP
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0106503

Gut Bacteria Role in Multiple Sclerosis Treatment?
http://www.emaxhealth.com/1275/gut-bacteria-role-multiple-sclerosis-treatment

VSL#3 administration modulated the expression of a large group of genes in brain tissue as assessed by whole gene expression, with evidence of a change in genes that impact on inflammatory and neuronal plasticity processes.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159266/

Flood the metabolism with anti-oxidants

Our nerve cells have not died but have fallen asleep. The mitochondria provide insufficient energy to recharge or maintain the equilibrium and cells become electrically dormant. Anti-oxidants will need to clean up the cells and increase the energy supplied by the ATP cycle.

A vegetable /fibre diet with lots of phytonutritients will induce powerful antioxidants in the body. This is again the Wahls diet. Additional supplementation with CoQ10, L-Arginine, D-Ribose, Magnesium, Vitamin B etc may be useful as well as methotraxate -a medication used in combination with Rituximab in combating RA- may help to strengthen mitochondrial working.

Stimulate the muscles

Activating the muscles will stimulates the CNS and vice versa. The term neuroplasticity gained prominence in the latter half of the 20th century, when new research showed many aspects of the brain remain changeable (or "plastic") even into adulthood.

https://en.wikipedia.org/wiki/Neuroplasticity

Neuro Muscular Electric Stimulation (NMES) may help and seems an effective modern therapy against herpes and it was extensively used by Terry Wahls.

Annex I: Specific features of MS explained in this context

The case of identical twins

If identical twins get separated at young age but before adolescence, the person that moves further South has less risk to develop MS at a later date. That person will have more sun exposure and therefore a higher vitamin D level in the circulation during adolescence when the body goes through a main phase of cellular growth. When the cells are formed, they take vitamin D directly from the circulation where the vitamin D level determines the number of mitochondria per cell (1500-3000; the heart up to 5000, Sinatra). And when the cells have more mitochondria, they will be more resilient. Extending that line of thinking, all players of the national Canadian ice hockey team – a physically very demanding sports - were born in February. The foetus went through the main phase of cellular growth during the end of Summer early Autumn when the vitamin D level in the circulation of their mother must have peaked.

The double peak in the graph of age of onset

This provides an indication for a two stage process with different underlying mechanisms. In particular the Varicella Zoster virus (VZV) which is an inflammatory virus is suspect in the RR phase. As of mid age, a HERV/ EBV virus stimulated B-cells growth causes huge oxidative stress. At this point the progressive mechanism is already well underway.

The extinction of new cases above the age of 60

An typical feature of the MS is the extinction of the disease above 60 years of age, with no new cases reported after 60. Immunosenescence results in a natural decline in humoral immunity above 60 caused by a reduction in the population of antibody producing B-cells. Where apparently the immune system unable to get under control - after millions of years of coevolution with the virus – switches back one gear or changes to avoid further damage is done. This is why cancers occur more at later age.

Chronic Cerebro Spinal Venous Insufficiency (CCSVI)

CCSVI or blocked internal jugular veins may be a factor here causing hypoperfusion, lower AMP and Adonesine, and with that a reduced control of infection by cellular immunity, e.g. infection and proliferation of VZV/EBV from the nasopharynx. Evidence accumulates of vein irregulaties and the incidence of MS in the vicinity of the heavy metal industry (Boston and Texas studies).

CCSVI may be a factor here again because the pharynx/tonsil drain through the Internal Jugular Veins where hypoperfusion may result in low pharynx/tonsil immunity with subsequent spreading of infection into the CNS.

The story of Dr. Zamboni is almost anecdotal. As a young doctor, while he was stationed on the island of Sardinia, he diagnosed many young people with venous insufficiencies in the neck. Many years

later, he was longst back on the Italian mainland, his wife developed MS. He went back to Sardinia and found that over 90% of the young people that he had diagnosed with vascular problems in the neck had developed MS. In a later study of almost epidemiological size (1600 subjects), Dr. Zivadinov et al (Bufallo, US) found a strong correlation between vascular narrowings in the neck and MS.

The pharynx and tonsils

An interesting feature is that in childhood, the tonsil is relatively large compared to the nasopharinx. Possibly, here we may find an explanation why EBV infection of young children gives a different (less viral load) but stronger (age) protective immune response than in late-infected adolescents or adults. [Hudnall speculates on the link to pharyngual epithelium and the tonsil in his chapter on Epstein-Barr Virus: Pathogenesis and Host Immune Response]

In Rheuma Arthritis, a disease with common roots to MS, there is a suspicion that the pharynx/tonsils are a causal factor. Patients who get their tonsils removed (from Waldeyer's tonsillar ring with a key role in our immunity) show a clear and lasting improvement.

EBV universal positivity

With the negative argument, that is the virtual non-existence of MS in EBV seronegative people (still 5 - 10 % of population), epidemiological analysis would seem to confirm a strong relationship of EBV with MS.

VZV epidemilogical results

Epidemiological studies provide a clear indication that VZV contributes to RR MS.

Gender bias

NO synthase is influenced by sex hormones, is higher in women which explains the gender bias in autoimmunity and MS. There is also the possibility of a direct involvement of HERV-W/MSRV in MS pathogenesis, identifying a genetic marker on chromosome X that could be one of the causes underlying the gender differences in MS.

Blood pressure

There are a couple of threads in the CCSVI forum pronouncing low blood pressure as a common symptom in MS patients. http://www.thisisms.com/forum/general-discussion-f1/topic9665.html

This could be a sign of a high NO synthase relaxing the vessels but at the same time elevating the oxidative stress.

Low fat diet – Swank

Saturated fats block the anti-viral properties of ApoA1. ApoA1 has anti-sense RNA which may explain its anti-viral properties.

Gut flora transplantation

Patients recovered from MS after a gut flora transplantation / Borody.

HIV patients

HIV patients recovered from MS after they started with highly active anti-viral therapy (HAART).

Strong temperature effect

Gradually, as the MS progresses and increasingly mitochondria fail and cells become electrically dormant, rising temperature and closing cellular gates (a natural protective mechanism) will have more profound effect on patients with MS.

Periods of immune deficiency

Patients with MS may experience periods of immune deficiency. One sign of such period is dry eyes.

The role of Vitamin D

Vitamin D has many roles in the built of the cells. After adolescence, Vitamin D blocks EBNA and with that the proliferation of the EBV.

http://www.abstractstosubmit.com/ectrims2015/pupload/documents/0_917.pdf

Besides the links mentioned in the above thesis, literally hundreds of other links to the medical literature can be found on this thread: http://www.thisisms.com/forum/general-discussion-f1/topic15188-720.html

Annex II: Alternative concepts for subversion of the immune response by EBV

Primary lytic replication of EBV in pharyngeal mocusal epithelium precedes long-lived latent infection of resting memory B-cells. During primary infection, EBV infects autoreactive naïve B-cells in the tonsil, driving them to enter germinal centres where they proliferate intensely and differentiate into latently infected autoreactive memory B cells (Step 1), which then exit from the tonsil and circulate in the blood (Step 2).

http://www.nature.com/nsmb/journal/v19/n9/pdf/nsmb.2367.pdf

http://www.nature.com/cti/journal/v3/n10/full/cti201425a.html

The number of EBV-infected B cells is normally controlled by EBV-specific cytotoxic CD8+ T cells, which kill proliferating and lytically infected B cells, but not if there is a defect in the defense mechanism.

One concept postulates the EBV secretes lytic-cycle early protein BARF1 which is a binding protein for the hematopoietic cytokine hCSF-1, evading and subverting key host signaling pathways. BARF1 also inhibits the secretion of antiviral IFN-α. This impedes the primary response via CD8+ cytotoxic T-cells and natural killer cells to clear EBV-infected cells, in line with T-cell mediated adaptive immunity against EBV.

Another concept suggests EBV is masked by a protein p47phox which is required to make superoxide to prevent recurrent infections. Here, the idea is that these transformed B cells are not perceived as foreign and thus not as a serious infection by the immune system.

Surviving EBV-infected autoreactive memory B cells enter the CNS where they take up residence and produce oligoclonal IgG and pathogenic autoantibodies, which attack myelin and other components of the CNS (Step 3).

Autoreactive T cells that have been activated in peripheral lymphoid organs by common systemic infections circulate in the blood and enter the CNS where they are reactivated by EBV-infected autoreactive B cells presenting CNS peptides (Cp) bound to major histocompatibility complex (MHC) molecules (Step 4). These EBV-infected B cells provide costimulatory survival signals (B7) to the CD28 receptor on the autoreactive T cells and thereby inhibit the activation-induced T-cell apoptosis, which normally occurs when autoreactive T cells enter the CNS and interact with non-professional antigen-presenting cells such as astrocytes and microglia, which do not express B7 costimulatory molecules (Step 5).

After the autoreactive T cells have been reactivated by EBV-infected autoreactive B cells, they produce chemokines and cytokines such as interleukin-2 (IL2), IFNγ and tumour necrosis factor (TNFβ) and orchestrate an autoimmune attack on the CNS with resultant oligodendrocyte and myelin destruction (Step 6).

A further concept is described by David Hudnal in his chapter Epstein-Barr Virus: Pathogenesis and Host Immune Response. Following initial exposure to infectious saliva, EBV likely undergoes a brief period of lytic replication in oral and nasal epithelium. Subsequent infection of naïve B cells within subjacent tonsillar lymphoid tissues leads to a brief “pre-latent” period of lytic and latent gene expression prior to epigenetic repression of viral genes. This brief pre-latent period is marked by limited expression of a small set of lytic genes with regulatory function, excluding lytic genes essential for DNA replication and virion assembly. It is likely that by promoting cell growth and inhibiting apoptosis, pre-latent lytic gene products, including BART miRNA, viral BCL-2 homologs, and BZLF1, contribute to the early survival of EBV-infected B cells.

Following epigenetic repression of the full complement of lytic genes and a subset of latent gene promoters, rapid growth of latent-infected B cells is induced by expression of the full growth-promoting complement of latency genes, i.e., the latency III program. Expression of the full complement of lytic and latent antigens by infected epithelial cells and B cells triggers a vigorous humoral and cellular immune response that leads to suppression of viral replication.

Latent-infected B cells persist by switching from the highly immunogenic latency III program to the less immunogenic latency II program, with virus gene expression restricted to three proteins, EBNA-1, LMP-1, and LMP-2A. EBNA-1 maintains the viral genome, while LMP-1 and LMP-2A maintain cell growth while preventing apoptosis. The absence of EBNA-2-mediated transactivation allows for latency II B cells to adopt a germinal center B-cell phenotype and, in so doing, survive germinal center and/or extrafollicular proliferation and maturation into EBV-infected memory B cells. EBV-infected memory B cells persist by switching from the latency II program to the latency 0 program, with near- complete absence of viral gene expression, with only intermittent LMP-2a expression.

An interesting feature is that in childhood, the tonsil is relatively large compared to the nasopharinx. Possibly, here we may find an explanation why EBV infection of young children gives a different (less viral load) but stronger (age) protective immune response than in late-infected adolescents or adults. [Hudnall speculates on the link to pharyngual epithelium and the tonsil in his chapter on Epstein-Barr Virus: Pathogenesis and Host Immune Response- see also Annex II]

Annex III: Author's personal timeline and VZV/EBV trail in his family

1956	**born in August, by normal delivery, no breast feeding, mother's vitamin D level during main phase of cellular growth in Winter time, family lived for generations in the shadow of the heavy metal industry**
1963 (+7)	
1970 (+7)	**lost control of left hand, gut was stable, fully recovered after 2 weeks (first lesion?)**
1978/79 (+8)	**dry eyes in Spring (Sjogren's syndrome autoimmune condition), wrong Plantar reflex, right leg weaker and thinner than left leg**
1984	'strange gait' after 10 km beach run, situation would recover to normal within minutes
1986 (+8)	**limping right leg and knee, recovered in a few weeks time (second lesion?)**
1994 (+8)	**inflammation of eye nerves, recovered in a few weeks time**
1998 onwards	bad gut, periods of numbness around right knee
1998/99	moments of leg muscle weakness when hiking, rapid exhaust after downhill skying, strange gait after 1 day mountain climbing and decent
2002	diagnosed with Irritatable Bowel Syndrome (and leaky gut?)
2002 (+8)	**numbness on hands, left side of left hand most affected**
2002-2004	painful 'pressure' on nasopharynx, always in Spring
2003	physiotherapy for painful and stiff neck , heavy VZV spots in the neck in particular after shaving
2004	diagnosed with RR-MS, two new active lesions, two old lesions, after stressful period, massive chocolate consumption, vaccinations Hepatitis-B and yellow fever (caused painful intestine), bad gut, painful pharynx
2009	diagnosed CCSVI Pattern C by prof. Zamboni, R-IJV truncated in lower neck (probably a birth defect), L-IJV dominant system but >90% obstructed behind the left ear
2011	IJVs liberated, first left, then right, noise in the head significantly down (first in left ear and later in right ear)

2012	extensive blood test reveals perfectly normal blood values, with the exception of high herpes simplex and EBV immune complexes 20X above max
2015	MRI of CNS largely the same as 2008 MRI, VZV down, neck is 'clean'

1963	grandfarther died from a naso pharyngeal carcinoma (EBV related) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151957/
~1986	farther's gait affected, problems 'evaporated' a few years later when above 60 years of age (he never had MS), he is 88 years old now and in good health
~2004	uncle died from coronary artery aneurism, a far-uncle died from the same cause (EBV/VZV related)
~2010	youngest brother diagnosed with mitochondrial energy failure (born in June)
~2011	after stressful period , farther had 3 attacks of what looked like Meniere
2013	the son of youngest brother diagnosed with Hodgkin (EBV related)
2015	another brother also born in August affected by arthritis, a bit of arthritis seen on my mother's side of the family but only in my own generation, mother is 87 years old and in good health, other brothers born in late Autumn/Winter time are in good health

Addendum to thesis MS Unravelled

The thesis will need one further iteration:

- to argue that the immune system does what it should do. this follows the thinking of Michal Schwartz. the fact that MS patients have an overall reduced cancer risk is indicative of the fact that we have an immune system that tries to correct where it can. this would be in the virus' own interest (because if a cancer would develop, that would be end of story for the patient and the virus)

and not - and this is very important - that it is an overactive immune system that causes the autoimmunity. that autoimmunity does not come from the immune system itself but from the cellular conditions, the interplay of the HERV and the VZV/EBV and possibly toxins/adjuvants.

the effects of interferons then are primarily antiviral, this 'silences' the cells, and with that the immune system calms down. so the understanding of immune suppression of interferons is based on a completely wrong understanding;

- the role of toxins and adjuvants needs to be clarified. a Harvard study questions why epsilon toxin zooms in on the OPCs. I think that it works differently. the toxins are everywhere (they are very small 50 kDalton particles), but in the OPCs, the fertile ground is found for the genetic interaction, these cells that then get in crisis etc. why is this happening? because the virus - after millions of years of evolution - has learned to home in on fast-dividing cells like OPCs. because it is precisely these fast-dividing cells that help with the spreading of the virus. and this again is in the virus' own interest.

- the 100 days effect in the VZV inflammatory phase needs some further stipulation. the low immunity, the VZV spreading, the microbleeding come first. the immune system corrects 100 days later. in my own case, the low immunity and the gut leakage were there in the early Spring, the flare-up with MS diagnosis followed mid-Summer.

- the inflammatory phase vs the progressive phase, concentrated respectively in CNS and in spinal column. there are increasingly indications for this such as this article:http://www.hcplive.com/conference-cover ... -sclerosis

- the membranes, transmembrane interaction of HERV/VZV, the oxLDL, the effects of simvastin on progression, the effect of living in coastal areas and fish consumption (with apoa1 anti-sense RNA which is antiviral) needs also some further thought and elaboration.

Most of these issues are already in the thesis now but they could be more pronounced.