Introduction

In a previous article published in the Townsend Letter I described an innovative multifactorial model for the development of autoimmune disease.¹ The implications of this model in terms of selecting herbal treatments were also discussed. The model, which can be described as a dual signal hypothesis, proposes two basic simultaneous requirements for the development of autoimmune disease. These are the primary lesion (the driver behind the attack on self which determines the site of the autoimmune reaction) and a state of immune dysregulation (an abnormal responsiveness of the immune system in some compartments). In particular, the role of micro-organisms in the onset and progression of autoimmune disease was stressed.

An essential feature of this model is that the capacity for self-recognition is a normal immune function. In other words, immune cells which could cause autoimmune disease exist in every normal individual. The capacity for self-recognition, and indeed autoimmune response, may serve a useful function when controlled by appropriate regulatory factors, for example dead tissue clearance and stimulation of healing. This has certainly been proposed in the context of multiple sclerosis (MS).²

The following quotation is from a review article entitled “Tolerance and Autoimmunity” which was published in the New England Journal of Medicine in 2001:³ “Since immunization of normal animals with certain self-antigens in an adjuvant induces autoimmune diseases, it follows that autoreactive T cells must be present in normal animals. Indeed, B cells and T cells that recognize insulin or myelin basic protein can be isolated from persons without diabetes or multiple sclerosis, respectively...”

“Considerable evidence implicates infection as a cause of autoimmune diseases, such as multiple sclerosis and type 1 diabetes. Mechanisms that could lead from infection to autoimmunity include the release of sequestered autoantigens through tissue damage, the activation of a large fraction of the T-cell population by superantigens, and the induction of inflammatory cytokines and costimulatory molecules by microbial products. In mice, so-called bystander activation of this type can precipitate autoimmune diabetes.

“Alternatively, a structural similarity between microbial and self-antigens (“molecular mimicry”) could have a key role in activating autoreactive T cells. Indeed, some T cells can recognize both a microbial peptide and a self-peptide with a similar amino acid sequence.”

With the proposed model, many event sequences are possible. The simplest example is that the same microorganism acts as both the primary lesion and the source of immune dysregulation. This may be the case for the autoimmune destruction which can occur with HIV-1 infection. In another scenario, a person might already be in a state of immune dysregulation and then react inappropriately to an infection. The infection passes, but the state of immune dysregulation persists and, because of the influence of the infection, develops into a self-sustaining autoimmune process. In this instance, best results will be achieved by concentrating treatment on the immune dysregulation and the self-sustaining inflammatory processes.

Another possible event sequence is that there is a chronic presence of a micro-organism to which the immune system is responding in a normal way. However due to molecular mimicry the micro-organism is also inducing a cross-reaction with self tissue. But this cross-reaction only occurs to a mild, non-damaging degree because the immune system is behaving normally. (This could also include a potentially pathogenic organism in the bowel flora.) Other events then trigger a state of immune dysregulation and the immune system begins to aggressively cross-react and destroy self tissue. In this instance, both the primary lesion (the micro-organism presence) and the cause of immune dysregulation require equal attention.

Another variation is possible which could be relevant to the development of MS. Here, at a certain age, a viral infection creates a clone of T lymphocytes which are capable of cross-reacting with self tissue. However, because there is no immune dysregulation, no damaging cross-reaction occurs, but these cells persist as memory cells after the virus has gone. They are then reactivated by exposure to the same virus, or one that is antigenically similar. If this event coincides with a state of immune dysregulation, autoimmune disease may develop. In this example the best approach to treatment is to (1) prevent the potential triggering effect of the second viral exposure or infection and (2) decrease the immune dysregulation and self-sustaining inflammatory processes.

The involvement of micro-organisms in the development of autoimmune disease is a controversial and confusing issue. Because an autoimmune disease is not an infection, but rather might be an abnormal response to micro-organisms under particular circumstances, it would be unreasonable to expect a single species of micro-organism only to be implicated in each autoimmune disease. This makes an “infectious” etiology difficult to prove, particularly if the implicated micro-
organisms vary from region to region and from person to person. As might be expected from the model, studies in the current scientific literature have implicated the association of several microorganisms with each autoimmune disease. These can provide useful information and will be reviewed below in the context of MS.

Immune system dysregulation may be caused by several factors acting together. For example the adverse effects of infection, food intolerance and stress may combine to create a state of immune dysregulation. Each contributing factor should be identified and addressed in the treatment protocol. The type of microorganism responsible and the sequence of events leading to the disease must be determined for each patient. Often this determination will not be possible, but a careful case history and an up-to-date knowledge of the particular disease label will greatly assist this process.

In the context of MS, a dual signal hypothesis similar to the one proposed above has been afforded some credibility in the scientific literature. For example, a recent report suggested the following: "We report evidence that a 'local' inflammatory process occurring in the CNS along with a concomitant, but possibly unrelated, peripheral inflammatory event may trigger a CNS-specific autoimmune reaction cascade sustaining the MS pathogenesis." Cytokines were suggested as key mediators of both events.

Experimental Models and Current Theories of MS

There are two main animal models of MS: Tsunoda I, Fujinami RS. Two models for multiple sclerosis: experimental allergic encephalomyelitis and experimental allergic encephalomyelitis, which is an autoimmune disease caused by the concomitant injection of myelin basic protein and complete Freund's adjuvant, and Theiler's murine encephalomyelitis virus disease, which is a demyelinating viral disease.

Corresponding to these are theories behind the cause of MS. The first is that MS is an autoimmune disease possibly triggered by cross-reactivity (molecular mimicry) to a viral infection (the Hit-Run Theory). The second is that MS is a demyelinating viral infection of the brain. Different viruses may be implicated in different patients (Hit-Hit Theory). A third basic theory has been proposed: MS is a progressive inflammatory disease of the brain of unknown origin.

In this context it is interesting to note the results of a recent histopathological study on the brains of MS patients. In a collaborative study involving centers in the US, Germany, and Austria, neuropathology was defined comparatively in biopsy and autopsy materials from 83 patients with firm diagnoses of MS. All patient samples studied included one or more lesions in active stages of demyelination, and patients from whom samples were chosen included individuals with detailed clinical histories and well-documented remitting—relapsing or progressive disease. Importantly, this landmark study determined that among the patient materials studied, four distinct patterns of demyelination were present. Two of these patterns (designated I and II) showed similar features and were consistent with a T cell- or T cell plus antibody-mediated process of demyelination.... Pattern III lesions included a clear inflammatory infiltrate, primarily made up of T lymphocytes, with some macrophages and activated microglia.... Pattern IV samples showed oligodendrocyte death in areas of demyelination, but no evidence of apoptosis was identified;...Among the samples studied, pattern II proved to be the most common, followed by III, I, and IV in decreasing order of prevalence. Patterns II and III were identified with frequency in patients with acute MS, while pattern III was rare in individuals with established disease. Within any given patient the pattern of neuropathology was consistent, and regardless of pattern, all patients from whom samples were studied developed clinically definable MS.

"From these observations, the authors concluded that patterns I and II are consistent with demyelination via autoimmune-mediated mechanisms, while patterns III and IV are more consistent with demyelination via toxin-, virus- (or perhaps other microbially-) mediated mechanisms."

As a result of this significant study, it can be theorized that MS is not a single disease entity and that all the above theories of the cause of MS might be relevant. However, it should be emphasized that the majority of patients exhibiting chronic MS exhibited a neuropathology consistent with autoimmune attack.

Differing etiologies might also be behind the different clinical pictures of MS. Although individuals with MS can display wide variations in clinical course, the disease usually occurs in two general forms, remitting-relapsing and chronic progressive, with the former being more common. Most patients with remitting-relapsing disease eventually progress to the latter form (secondary progressive), with consequent increase in motor dysfunction.

Risk Factors of MS

A study of the various risk factors which have been linked to the incidence or progression of MS can yield insights into its possible causes. Although such studies do not prove cause and effect, and indeed in many cases have yielded inconclusive results, they can provide valuable clues for therapeutic intervention with herbal treatments.

Genetic Factors

Genetic factors play some role, but there is no simple pattern of inheritance. The only genetic region that has been clearly demonstrated to contribute to MS risk is the HLA (MHC) system. But again this is complex. The prevalence of MS in twins is relatively low.

Vaccination

Despite some single case reports, studies have consistently failed to show any detrimental link with vaccination.

Infection

Typical infections occurring later than normal in childhood comes through consistently as a risk factor. However, tonsillitis and other infections (and allergies) in early childhood are also identified risks (perhaps indicating poor immunity). There is a strong connection with a history of infectious mononucleosis (relative risk factor, odds ratio, of 13.5).
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Latitude
The risk of MS increases with latitude, although this association is not as clear as was once thought. This risk is determined in the first 15 years of life. Various explanations have been proposed including:
- Latitude is linked to infections later in childhood.
- UV light is immune suppressing or acts by some other means.
- MS is linked to a vitamin D deficiency.
- Pineal gland involvement.

Stress
Is a potential trigger, according to one review. In an interesting prospective study a Dutch research team surveyed 73 people between the ages of 18 and 55 who had relapsing-remitting MS. They were followed up for an average of 18 months, during which time they kept a diary of stressful events in their lives. The severity of their MS symptoms were also closely followed over the same time period. It was found that a stressful life event which was unrelated to their MS doubled the risk of worsening of MS symptoms, usually within 4 weeks. Interestingly, infection increased the risk of an exacerbation by a factor of three but this was independent to the effect of stress.

Cigarette Smoking
Smoking is a clear risk factor according to a recent study. Results from the large US Nurses' Health Studies indicate a link between MS and current smoking and also a progressively increasing risk with cumulative exposure to tobacco smoke.

Animal Exposure
Animal exposure linked to increased MS risk is mainly for dogs and birds, although cats have been implicated.

Trauma
Studies do not support a link with head or other physical trauma and are difficult to undertake.

Solvents
There is clear evidence of a link to solvent exposure. In one study solvent exposure was found to double the risk of developing MS.

Mercury from Dental Amalgam
This is controversial, but there is suggestive evidence. Two case-control studies showed a trend which was not statistically significant. Benefit or changes after amalgam removal have been shown in MS patients.

Dietary Factors
Early studies found links with animal and dairy product consumption. For example, a relationship between MS prevalence and dairy product consumption was found in a survey of 27 countries. The strongest correlation was for milk consumption. Evidence for a link between neurological disease (including MS) and gluten sensitivity or celiac disease is suggested by some, but is not strong. Vitamin B12 deficiency has been linked to MS.

Chronic Sinusitis
A British study published in the Lancet in 1986 found a high incidence of chronic sinusitis in MS patients. Moreover, the sinusitis was generally present before the MS developed. This was refuted in a later study using radiological diagnosis. However, a more recent study (1997) again confirmed that the incidence of chronic sinus disease (53%) was much higher in MS than in the general population.

Does an Infective Agent Trigger MS?
The proposition that infectious agents play an etiologic or co-factorial role in the pathogenesis of MS, both at the onset of the disease and in the occurrence of acute episodes, is one of the more enduring notions of etiology of this disease. Strong interest in an infectious etiology has repeatedly emerged in the last century, since Pierre Marie in 1884 expressed his seminal hypothesis: "I was struck by the coincidental occurrence of sclérose en plaques with infectious illnesses, and by the close relationship that, from a theoretical point of view, unites these diseases. Therefore, I made an effort to renew my idea that sclérose en plaques often starts as an infectious process."

The Case of the Faroe Islands.
These are islands at a high latitude which are part of Denmark and very isolated. Despite the high latitude, there were few recorded cases of MS up to the early 1940s. The first cases for native Faroese occurred in 1943 with an epidemic cluster of 21 cases. This correlated with their occupation by British troops during World War II and was followed by three successive epidemics of 10, 10 and 13 cases at 13-year intervals. It must be noted that this interpretation has been challenged by other researchers. One group of Danish experts have implicated Epstein-Barr Virus (EBV) as the causative factor behind the Faroe MS cases. They proposed that it is a well-known phenomenon that soldiers excrete high doses of EBV which may have been transmitted horizontally to the adult native population, who may in turn have been previously EBV seronegative.

Clusters
The Faroe Islands cases of MS are the best-known example of a cluster. Clusters can be defined as geographically bounded groups of occurrence of sufficient size and concentration to have been unlikely to have been caused by chance. It can be proven that MS does indeed occur in clusters, then an infectious agent is the most likely cause. The following two paragraphs were offered by the Danish team mentioned above:
"Clusters of MS outside families are considered with skepticism by epidemiologists, but a recent study in Norway showed that MS patients within the same birth cohort had lived significantly closer to each other than would be expected during ages 13-20 years, with peak clustering at age 18 years (P=0.002). The agent thought to be involved in the clustering is EBV." Our group has searched for clusters of people who lived together around puberty and who later developed MS. Besides a great number of couples, we found six such clusters in which three or more people have had close contact and later
developed MS. The most interesting was seven people with MS who originated from a small community called Fjelsø, with 200-300 inhabitants. During an 11-year period, each of them had attended the same elementary school with 70-80 pupils for seven years, which during this 11-years period had a total of 127 pupils. Besides they had been scouts together with the older ones being scoutmasters for the younger ones, and some of the older had also been children's nurse for the younger."

**Infectious Agents Implicated in MS**

The difficulties associated with implicating specific viruses or other infecting agents in MS have been elegantly outlined as follows: If MS is induced and/or exacerbated by transient virus infection, there are several corollaries that may explain the equivocal results obtained for the association of viruses with MS. Firstly, it would not be possible in most cases to detect virus in autopsy tissue from MS patients, or in biopsy samples taken after the initial triggering phase. Secondly, virus infections need not be specific, and it is possible that a range of viruses with common properties could be involved in either the triggering or maintenance phases. Thirdly, it is probable that, if viruses are involved in triggering and/or maintaining MS, that these are common viruses that only have this effect in a minority of genetically susceptible individuals.

**Epstein-Barr Virus (EBV)**

There is a strong relationship with EBV infection and the development of MS. One hundred percent of MS sufferers were seropositive to EBV and the lack of evidence of current EBV infection suggests its role as a persistent latent virus. EBV may play an indirect role as an activator of the underlying disease process. A single sub-type of EBV was found in members of an MS cluster and in MS relapses EBV DNA in peripheral blood is an early event.

The Danish team cited above have extensively reviewed the role of EBV in MS and have suggested the following (which is highly relevant to the context of this article): "Since 1988 our group has searched for a retrovirus as the cause of MS. Although we found signs of retrovirus in cells from a patient with MS in 1990 and later established cell lines from MS patients producing retrovirus, we have realized, through epidemiological studies in families, that a retrovirus with behavior like the known human retroviruses cannot itself be the environmental agent causing MS even in genetically susceptible people. Similar conclusions have also been reached by other groups. We suggested that one or more viruses in addition to retrovirus were involved and put forward a dual infection hypothesis, suggesting that infection with an MS retrovirus is a prerequisite for development of multiple sclerosis."
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MS, but MS develops only or especially in genetically susceptible persons, who around puberty or later in life are infected with EBV. They also add: "An extensive historical prospective study was performed by our group. Everyone in Denmark, who had a diagnosed late EBV infection during a 9-year period, were searched in the nationwide Danish MS Registry. A 2.8 times higher risk for development of MS was found after late infection with EBV. MS developed 2-22 years after a diagnosed EBV infection."

Endogenous Retroviruses

Endogenous retroviruses (coming from the host's own DNA) have been identified in MS plasma samples and not in controls and elevated antibodies towards these have been found. They could be involved in the pathogenesis since positive MS patients showed a progressive course. Their expression could be triggered by other viruses (see below). As stated above, it has been proposed that infection with both a retrovirus and EBV may lead to MS. But it could be that the retrovirus is endogenous and is activated by the other (EBV or another virus) viral infection.

Human Herpes Virus 6 (HHV-6)

A multitude of studies have investigated the prevalence of HHV-6 in tissues from MS patients compared to normal controls. This is an ubiquitous virus, so an association has been difficult to prove, with many positive and negative studies. Recent reviews concluded that no definite link can be drawn from current evidence. HHV-6 in MS may be an effect, rather than a cause. However, HHV-6 could be a factor in a subset of MS patients, one estimate was 15%. Also it could be that particular varieties of HHV-6 may be pathogenic in MS.

Other Viruses

Coronaviruses are controversial in the context of MS and so are canine distemper virus and measles virus. There is an apparent connection between MS in males and shingles. Herpes simplex virus (HSV) has been found in MS lesions. A treatment study of relapsing-remitting MS patients with acyclovir (at doses active against HSV) found a 30% reduction in the relapse rate. Bird viruses have also been suggested.

Chlamydia

Like HHV-6, the role of the respiratory bacterium of Chlamydia pneumoniae in MS is controversial and no conclusive link has been established. However a recent study found a positive association between Chlamydia infection and progressive MS. Detection errors for Chlamydia and large variations in laboratory techniques appear to have a confounding effect on results. Like HHV-6, it is possibly a relevant pathogenic factor for a subset of MS patients.

The spirochaete Borrelia burgdorferi, which causes Lyme disease has been implicated in some MS patients on the basis of serological findings, but the results are conflicting.

Infection and MS Exacerbation

This phenomenon has already been mentioned previously. It suggests that, at the very least, phytotherapy for MS should be targeted at reducing the frequency of infections. There is considerable evidence to support the exacerbating role of infections in triggering relapses and worsening progression in MS patients. Some of these studies are listed below.

HHV-6 reactivation was linked to disease activity. Exacerbations by systemic infection lead to more sustained damage than other exacerbations. Influenza vaccination aggravated 5% of MS patients, but influenza illness aggravated 33%. Upper respiratory infection and adenovirus antibodies were correlated with relapse in one group of MS patients.

Mechanisms of Infection-induced Autoimmunity in MS

Several hypotheses have been proposed in the literature to explain the possible mechanisms behind a viral-driven autoimmune response in MS. These include altered self, mistaken self, superstition and bystander activation. But, while the most popular theory is molecular mimicry, it is still highly controversial.

Theories as to how molecular mimicry might trigger MS (and autoimmune diseases in general) have become more sophisticated (and complex). One reason behind this is that our understanding of the immunological cross-reactivity for T-cells has expanded considerably in the past few years. While it holds true that sequence homology (an identical consecutive sequence of at least six amino acids) is a prerequisite for B-cell cross-reactivity between two different proteins, this is not the case for T cells. T-cell responses are dependent on antigen-presenting cells (macrophages) which process antigens into relatively small peptide fragments before offering them in conjunction with self-MHC antigens. As a result of this, sequence homology is not essential for T-cell immunological cross-reactivity. In this context T cell responses are said to be "degenerate." Based on this knowledge one research group proposed: "A very important implication is that the potential for autoreactivity is very high, and any concept about autoimmunity must explain not only how autoactivity is initiated, but also why it is rare. A model for how cross-recognition of foreign and self-peptides could initiate autoimmune responses is proposed, based on two fundamental requirements, the activation of cross-reactive T cells in the periphery, and the recognition of myelin antigens in the CNS." This is highly consistent with the dual signal hypothesis proposed as a working model for phytotherapy.

In terms of the temporal relationship between viral infection and disease development in MS, a number of mechanisms have been proposed. Two such examples are provided as Figure 1 and Figure 2.

Persistent viral infection

Figure 1. Hypothetical relationship between MS and viral infections.
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As mentioned previously, retroviruses may play a role in establishing colonies of primed autoreactive T-cells which are then reactivated to such destructive effect on subsequent viral infections.53

Weaving the Threads Together

The pathogenic and risk factors identified thus far for MS can be incorporated into the proposed model to arrive at a rational therapeutic strategy.

- The primary lesion probably involves a viral infection in most cases (EBV, HHV-6 or other viruses, maybe an exogenous retrovirus: almost all enveloped viruses), but could be bacterial (Chlamydia) in others as described above. It may require more than one viral infection to activate the autoimmune process.
  - Key factors in immune dysregulation are probably:
  - Chronic sinus disease
  - Activation of endogenous retroviruses
  - Exposure to solvents or Hg
  - Antigenic factors in diet, especially cow’s milk
  - General poor immunity
  - Vitamin D and B12 deficiency
  - Cigarette smoking
  - Stress
  - Possibly bowel flora dysbiosis

Figure 2. Diagram of postulated mechanisms of generation of anti-myelin autoimmunity, triggered and/or exacerbated by transient virus infections. A central feature of this hypothesis is the peripheral stimulation of anti-myelin immunity within the CNS. This peripheral stimulation could occur by cytokine secretion in response to a heterologous antigen, or by molecular mimicry.56

Health Care Practitioners require a compounding pharmacy that:

- Accommodates and is easy to use
- Provides up-to-date information & research
- Continually trains pharmaceutical staff
- Possess the broadest range of capabilities
- Understands the needs of patients

and most important, is...

...Always available to serve YOU!
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There is also a need to provide ongoing protection against infections because of their role in exacerbating MS.

Therapeutic Strategy
- There is a clear role for immune support because of the role of pathogenic organisms and the exacerbating effect of recurrent infections. Echinacea is the key herb.
- Antiviral herbs, especially St-John’s wort (active against enveloped viruses), have an important role.
- Anti-inflammatory herbs to quieten the pathological progression including Rehmannia, Hemidesmus and Bupleurum.
- Antioxidant herbs can be valuable, especially those that access the brain such as Ginkgo.
- Chronic sinus disease (if present) must be addressed with herbs such as Eyebright and Golden Seal.
- Tonic, adaptogenic and adrenal tonic herbs such as Korean Ginseng, Ashwaganda and Rehmannia to help support the stress response.
- A low antigenic diet (dairy-free and preferably gluten-free) rich in fish.
- Other appropriate strategies directed against the factors involved in immune dysregulation.
- Address bowel flora dysbiosis if the patient does not progress.

Case History
A female patient aged 33 sought help with a history of aggressive MS. Diagnosis was 4 years ago. Symptoms included (on and off) optic neuritis, numb legs and hands (mainly at night) and poor memory. Previous drug medications included oral corticosteroids and interferon-beta injections. She reacted badly to both these treatments. Current medication was daily injections of copolymer-1.

Her history revealed infection with Epstein-Barr virus (mononucleosis) at age 22 and severe head trauma 4-1/2 years ago when she fell off a cliff and temporarily lost her sight.

Since the EBV infection she has suffered from low energy. She has a chronic sinus problem which began at least 10 years ago.

Treatment
a) Echinacea angustifolia/purpurea root 1:2 35 mL
Eyebright 1:2 20 mL
Ginkgo standardised extract 2:1 20 mL
St John’s Wort 1:2 25 mL
Dose: 8 mL twice a day

b) Herbal tablets containing: Eyebright, Golden Rod, Echinacea, Golden Seal and Cayenne (3 per day); Grape Seed extract, Green Tea, Turmeric and Rosemary (2 per day)

c) Tylophora 1:5, 10 drops a day for 2 weeks of each month

Outcomes
This patient has received herbal therapy since February 2003. She is no longer taking copolymer-1 (Copaxone) and has reported substantial improvements in energy and wellbeing since beginning her herbs. MS symptoms have been completely absent for at least 2 months and were considerably improved after just 1 month of herbs. Her chronic sinusitis is markedly better. Treatment is ongoing.

References
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