

BROCHURE MS MODEL

Linda Anchell
(lindafrd@pcug.org.au)

<http://members.ozemail.com.au/~lindafrd/index.html>

1999 some changes in Nov 2003

This "model of MS" is a development of ideas that I had heard and read between 1995 and 2001. I am very grateful to the speakers and authors for their inspiration.

I have no medical or scientific qualifications other than having MS and an enquiring mind. However, I put these ideas together because they were a way that I found helpful to think about MS. I hope that you might also.

Linda Anchell (All Saint's Day, 1st Nov 2003)
in Australia
lindafrd@pcug.org.au

Rex Simmons' AGM Address (9/10/95) to the MS Society of the ACT [A Report]

Last year Rex enlightened us with a new way of looking at MS. He told us the history of the description of MS and outlined the various ways that it shows itself. Then came the statement which had stirred participants at the John Curtin School of Medical Research seminar on MS in September.

MS is not primarily an auto immune disease.

There are difficulties with the idea of MS being primarily an auto immune disease.

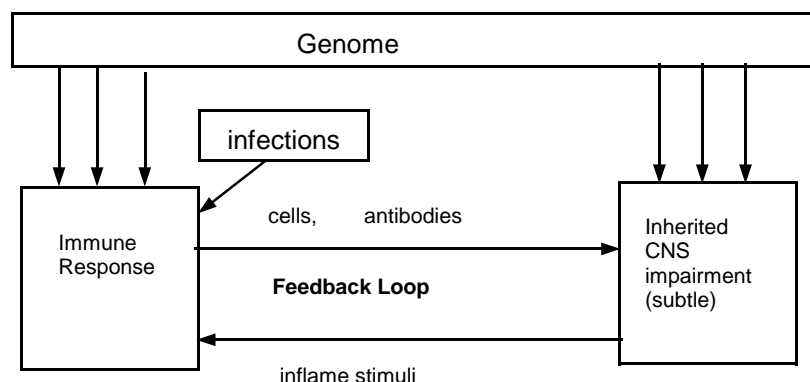
1. It is not like other autoimmune diseases.
2. there is a missing autoantigen. (If it existed it would have been found by now.)
3. the non-specific inflammatory profile of the lesion. **see c. below.
4. Immunotherapy is only marginally effective.
5. There is a wide clinical spectrum. (MS shows itself in many different ways, but it is still the same disease.)
6. Immunogenetic alleles are missing.

Rex asked many questions, and made certain points. Among them were:

- b. There are multiple auto antigens, so, **why is MS organ specific?**
- c. Biochemically, the inflammation of MS plaques looks like any other chronic inflammation. "No adhesion or cytokine molecule [unique to MS] was apparent."
- d. If auto immunity is the only event going on in MS then we should be able to cure it.
- e. The association of MS with genes controlling the immune system (HLA) is weaker than expected for an auto immune disease. (and, if MS is only genetically determined then we should see more connection. For example, for identical twins, if one twin has MS then there is a 38% chance that the other twin will also have MS. Genetics are involved but there is obviously some environmental influence.)

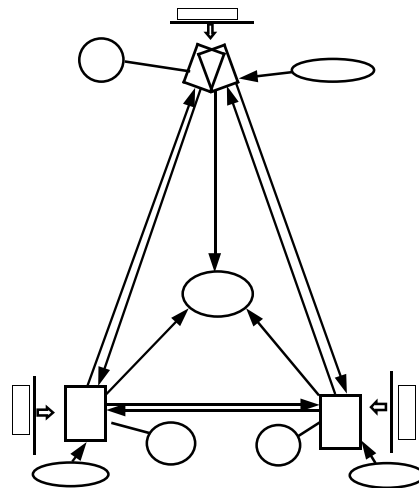
The conclusion that Rex reached was that a **Bifactor system** was operating in MS. The two factors were (i)the immune response and (ii)the inherited Central Nervous System impairment. He suggested a polygenetic inheritance of impairment/susceptibility (?) in both the immune system and the Central Nervous System. The genetic inheritance (?) could be weak or strong. Something (perhaps infection) triggered an immune response which then triggered the impairment in the CNS. This produced the pathology (or symptoms) of MS and by inflaming stimuli, a feedback loop to the immune system was started.

It looked like this:



A Response to Rex.

Rex's diagram, and the feedback loop between the immune system and the Central Nervous System intrigued me. At the AGM, Richard Foster asked Rex "what about triggers on the CNS, as well as the immune triggers?" So I changed an idea that I had been brewing on for a few months. If you look at the CNS as being both the neural network (this is where the demyelination happens), and also the chemical side of brain activity (really the neuroendocrine system) *then* triggers to the CNS start popping up all over the place. So I put Rex's diagram on its side and split CNS into two parts - neural and neuroendocrine (or chemical).



Triggers and therapies could operate on all three boxes - immune system, neuro endocrine and neural systems. There may be genetic susceptibility operating on all three. (*polygenetic* ?) And, they all (?) contribute to the symptoms (pathology) of MS.

There are two interesting consequences to modelling MS like this: 1. The Feedback Loop and 2. The Role of the Neuro Endocrine system.

- 1 The Feedback Loop: This might simply go around the circle (in either direction) or there could be a feedback between only two of the systems. Perhaps looking at it like this exposes a possible complexity of MS. Therapies can (and do) interrupt this feedback. (sometimes).
- 2 The Role of the Neuro Endocrine system. There are lots of triggers and therapies and symptoms involved here.

I think there are very real advantages for those of us who have MS to see the condition in these terms.

Demyelination (neural) and autoimmunity (Immune) are what define MS. We see the condition with these spectacles on. But, in support groups, we talk about bladders, memory, fatigue and pain. The medicines we take affect the neuro endocrine system. (After all, chemicals do change chemicals.) Even when we know that a symptom is caused by demyelination a drug can change things. I am not alone in taking a drug for one symptom (e.g. fatigue) and finding that a lot of other things improved as well (e.g. bladder).

Again, we talk of stress, trauma and grief as triggers for exacerbations.

These have their effect on the neuroendocrine system in most people. There is some evidence in the scientific literature for MS starting from these. [Not much, but some.]

Our neuroendocrine system can be changed by our own efforts, not only by drugs. It is this system that Norman Cousins changed when he belly laughed his way through a night of British comedy, and cured his illness. Laughter is the best medicine. Endorphins (the natural morphine, or runner's high) are released by exercise. [We can't always cure ourselves. A positive attitude does help. But we can't always just "snap out of it." Depression and fatigue are very real.]

Thanks to Rex who has changed the way that I think about MS.

For definitions of terms, I recommend Paul's glossary at <http://www.mult-sclerosis.org/chooseglossary.html>

CIRCULATION IN THE MODEL

Notes:

1. The Chemical (Neuroendocrine) and Neural (Central Nervous) systems overlap. (*Neuro = Neural*) They are separated in the model to show up some distinctly different triggers, pathologies and therapies. Separating them also enables questions to be asked.

2. Connections between the Chemical (Neuroendocrine) and immune system are not unique to MS. Multiple Sclerosis is only indicated in the model when the neural (CNS) System is involved.

1 Immune to Neural (CNS)

This connection is well documented

2 Neural (CNS) to Chemical (Neuroendocrine)

Demyelination, especially in the brainstem, cervical medulla and hypothalamus, affect the neuroendocrine system. (Brainstem inflammation affects the neurotransmitters, especially e.g. Serotonin in the Raphe Nuclei and Noradrenalin. [Damasio's discussion in ch 5 of *Descartes' Error* (pp94,5) makes this a more global phenomenon, affecting more than brainstem activity.]

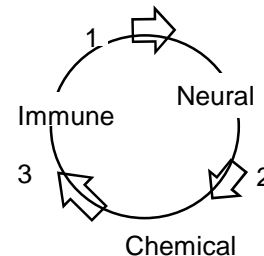
3. Chemical (Neuroendocrine) to Immune system.

This is well documented. (See Blalock and Chelmicka-Schorr)

CIRCULATION IN THE MODEL

Notes:

1. The Chemical (Neuroendocrine) and Neural (Central Nervous) systems overlap. (*Neuro = Neural*) They are separated in the model to show up some distinctly different triggers, pathologies and therapies. Separating them also enables questions to be asked.
2. Connections between the Chemical (Neuroendocrine) and immune system are not unique to MS. Multiple Sclerosis is only indicated in the model when the neural (CNS) System is involved.



1 Immune to Neural (CNS)

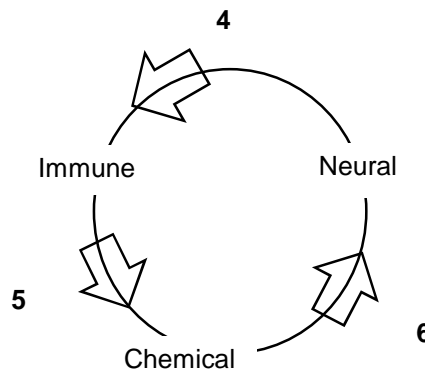
This connection is well documented

2 Neural (CNS) to Chemical (Neuroendocrine)

Demyelination, especially in the brainstem, cervical medulla and hypothalamus, affect the neuroendocrine system. (Brainstem inflammation affects the neurotransmitters, especially e.g. Serotonin in the Raphe Nuclei and Noradrenalin. [Damasio's discussion in ch 5 of *Descartes' Error* (pp94,5) makes this a more global phenomenon, affecting more than brainstem activity.]

3. Chemical (Neuroendocrine) to Immune system.

This is well documented. (See Blalock and Chelmicka-Schorr)



4. Neural (CNS) to Immune:

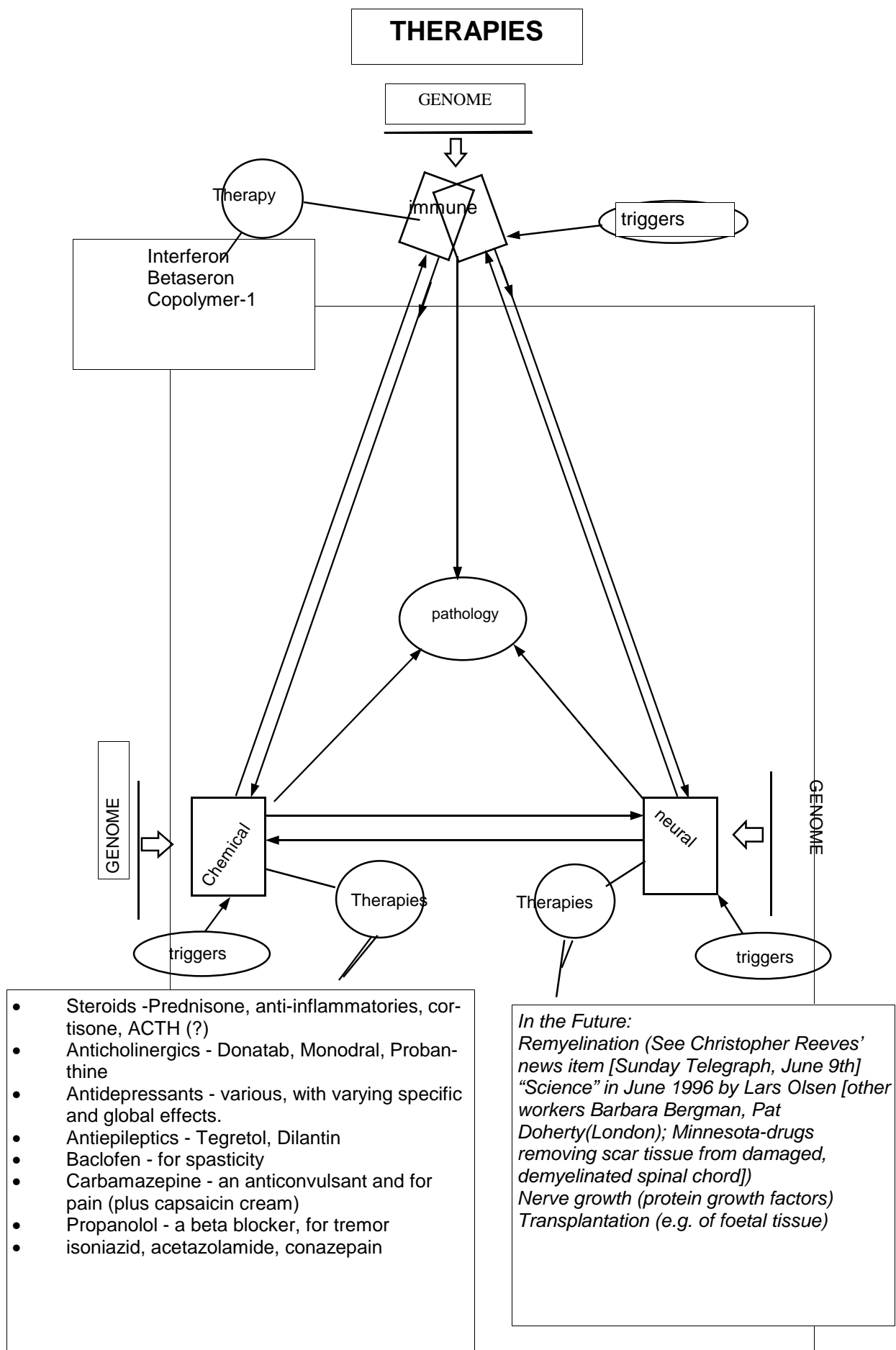
[Inflamed stimuli. .*Rex's term*]

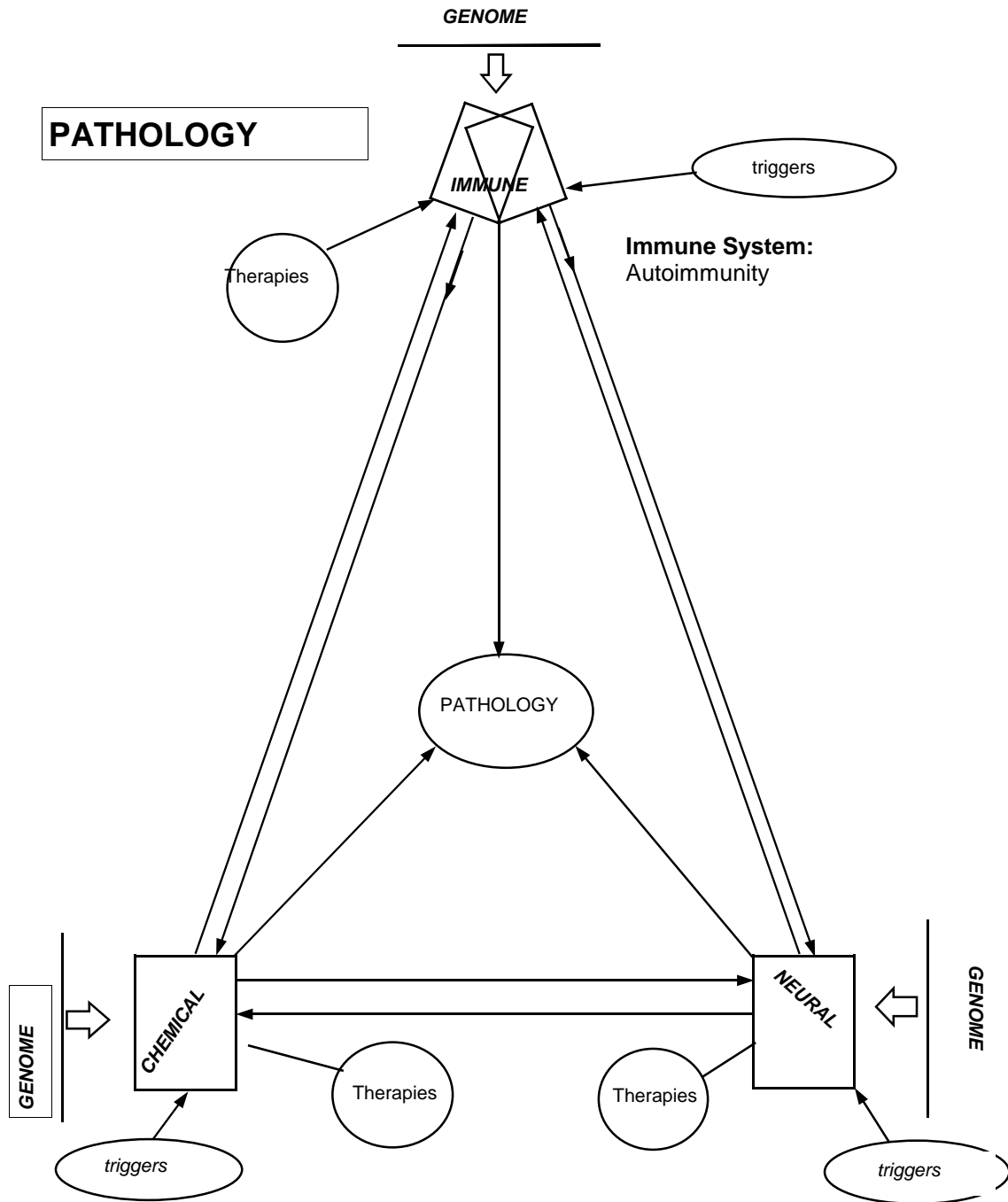
5. Immune to Chemical (Neuroendocrine)

[See Blalock, *Immunol. Today* 1994; 115(11) 504] e.g. *Interleukin-1 to Hypothalamus*

6. Chemical (Neuroendocrine) to Neural (CNS)

A question to consider. It may be worth noting that some neurotransmitters (e.g. Acetylcholine and GABA) have chemical similarities to Myelin. (??)



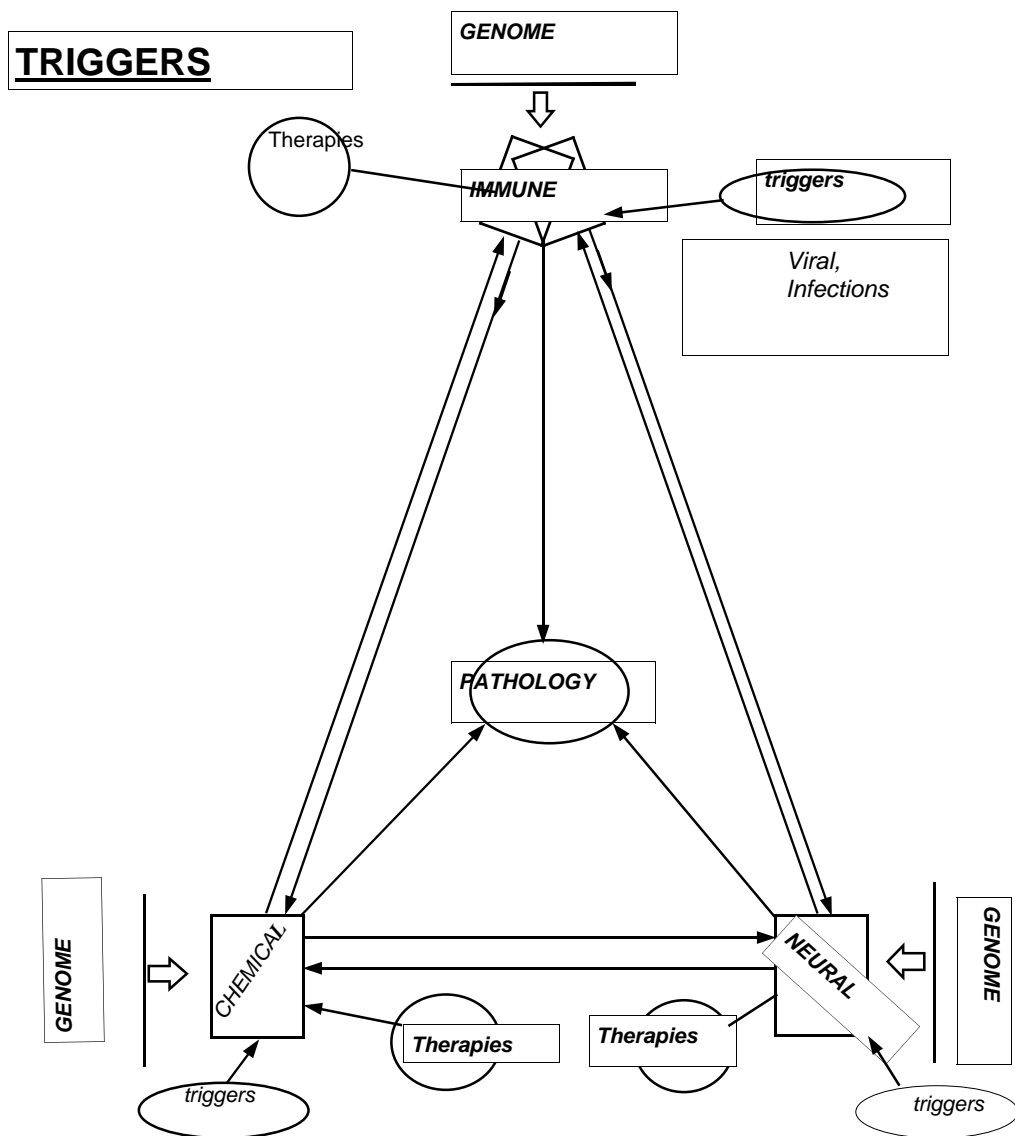


Chemical/Neuroendocrine:

- | Fatigue
- | Depression, Euphoria,
- | Bladder/Bowel, Sexual problems
- | Cognitive, Memory, Emotional (lability, irritability)
- | Temperature Regulation, Cardiac, Circulation
- | Bipolar Affective disorder
- | Autonomic disorders with motor and sensory symptoms.
- | Sweating response, blurred vision, pupil size, noise sensitivity(?)

Neural:

- | Demyelination,
- | Inflammation and plaques leading to consequent pathologies.



- Depression (Bipolar and Unipolar Affective disorders)* (Hutchinson, 1993)
- Emotional Stress (e.g. grief)
- Stress (particularly chronic)
- Chronic Fatigue syndrome (M.E.) (This is initially triggered from the immune system. But if it triggers [develops into] MS then it would work from the neuroendocrine/chemical system)
- Toxins (e.g. physotstigmine and piperazine)
- Drugs (perhaps antihistamines, marijuana?)
- Lifestyle (Diet/Exercise etc.)

[Richard Fisher's question:
Is there a Central Nervous system trigger?
(ACT MS Society)]
 [e.g. does Adrenoleukodystrophy require a trigger?] Age?
 e.g. Puberty (acting on the neuro-endocrine (chemical) system).
 e.g. calcification of the Pineal gland

Could Landry-Barre syndrome be a trigger? (Itself started by a virus or infection or "various systemic and toxic disorders." [Gould's]) Or, other disorders, like Horner's Syndrome, Shy-Drager etc.?

BIBLIOGRAPHY

Blalock, J E (1994) The Syntax of immune-neuroendocrine communication
Immunology Today (1994) **15**(11),504-511
see: <http://www.ozemail.com.au/~lindafrd/page13.html>

Chelmicka-Schorr, E and Arnason, B G (1994) Nervous System - Immune System Interactions and their role in Multiple Sclerosis Annals of Neurology **36** (Supplement) s29-s32
see: <http://www.ozemail.com.au/~lindafrd/page15.html>

Hutchinson, M; Stack, J and Buckley, P (1993) Bipolar affective disorder prior to the onset of Multiple Sclerosis. Acta Neurologica Scandinavica **88**;388-393

Michelson, D Stone, L & Galliven, E et al (1994) Multiple Sclerosis is associated with alterations in the Hypothalamic-pituitary-adrenal axis function. Journal of Clinical-Endocrinological-Metabolism **79**(3)848-853

Moutschen, M; Triffaux, J-M; Demonty, J et al (1994) Pathogenic Tracks in Fatigue Syndromes. Acta Clinica Belgica **49**(6)274-289

Damasio, Antonio, R (1995) Descartes' Error *Emotion, Reason and the Human Brain* Picador, London. see especially, chapter 5 pages 94 & 95. and note 4, p.246 on neural and neuronal theories of integrated models of the mind. Including Edelman(1987) Neural Darwinism chapter 7 fig 7-1, p132, p 137, pp139-142 for Damasio see: <http://www.ozemail.com.au/~lindafrd/page5.html>

Merola, B Longobardi, S Colao, A et al (1994) Hypothalamic-Pituitary-Adrenal Axis in Neuropsychiatric Disorders. Annals New York Academy of Sciences 1994 Nov 25;**741**:263-70

and a new addition

On January 13th 2001 I was alerted to a paper in the Pharmacological Review
<http://pharmrev.aspetjournals.org/cgi/content/abstract/52/4/595>

Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES The sympathetic nerve-An integrative interface between two supersystems: the brain and the immune system.
Pharmacol Rev 2000 Dec;**52**(4):595-638

see:

http://www.ozemail.com.au/~lindafrd/ImmuneSystem_and_SympatheticSystem.htm