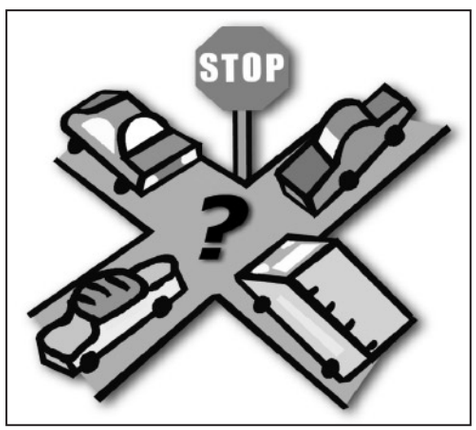
The Four-Way Stop Dilemma:
A Hypothesis of Immune System Entanglement in Chronic Illness

Chronic illnesses are, by their very definition, difficult to resolve. They often resist a skilled practitioner's best efforts at therapy. And all too frequently, when healing shifts do take place, they trigger severe reactions that may be even more stressful for patients than their original, underlying condition.

These *Herxheimer* reactions are often attributed to inflammatory cascades triggered by the die-off of pathogenic microbes and degraded endogenous cells. While there is no doubt that microbial die-off can play an important role, I suspect that other factors may be involved. In particular, thinking about the "cytokine storm" – a powerful over-stimulation of the immune system associated with avian influenza – has prompted me to form a new hypothesis about the relationship between complex chronic infections and Herxheimer reactions.



I refer to this new hypothesis as the "Four-Way Stop Dilemma" since it resembles what happens when four cars simultaneously arrive at a traffic intersection. The hypothesis is a work-in-progress and my hope is that an active exploration of these speculative ideas will stimulate dialogue about new and better clinical approaches.

I'm sure that most of us have experienced the four-way stop dilemma. Who has the right of way? Who should go first? We wait and wait to see what will happen until someone finally makes a move. Just then, another car lunges into the intersection and everyone locks up again – accompanied by blaring horns.

I suspect that something similar happens in the immune system and that by learning to recognize the Four-Way Stop Dilemma pattern we can find better ways to break through the fixation of chronic illness and offer therapeutic relief with less healing stress.

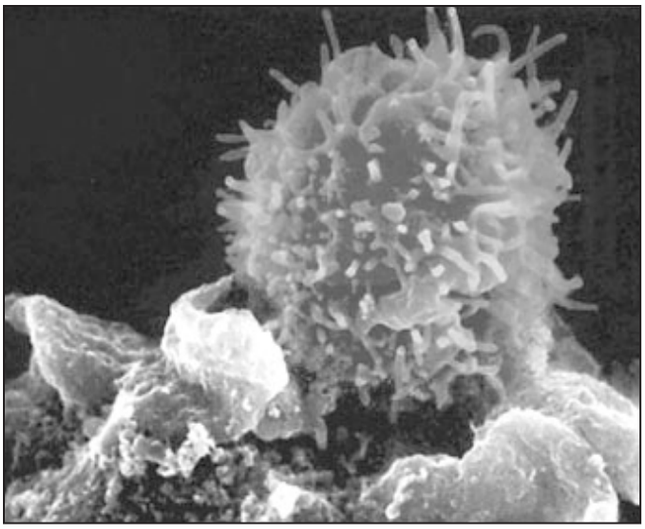
Dynamic Opposition Creates Balance

Many physical features of the body are organized into opposing pairs. We have one set of muscles that contract a joint and an opposing set that expands it again. We have hormones, like insulin, that lower blood glucose and others, like glucagon, that raise it. The healthy body is a symphony of systems that are regulated by the fluid interaction of dynamically opposed potentials.

From this perspective, one useful abstraction about our immune system is the division of labor between a pair of complementary responses referred to as Th1 and Th2.

Briefly, the immune system begins with a population of naïve, undifferentiated T-helper lymphocytes referred to as ThP or "T-helper Primary" cells. In response to an immune threat, some of these cells differentiate into Th0 cells that possess the potential to further differentiate into more specialized forms.

Under ideal conditions, a viral or intracellular bacterial infection will cause some of these Th0 cells respond to chemical messages, primarily initiated by Interleukin-12, and differentiate into natural killer and cytotoxic T cells.



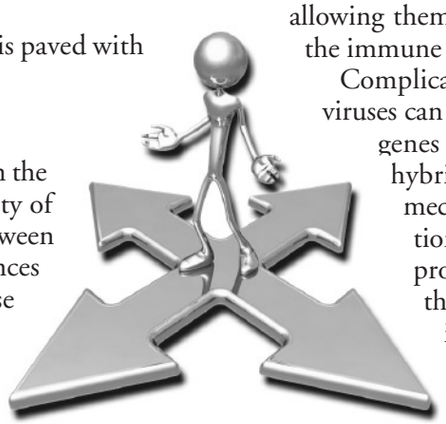
Scanning electron microscope image of human lymphocyte. Image courtesy of Lawrence Berkeley Laboratory

Conversely, in the presence of extracellular bacteria, toxins and allergens, Th0 cells respond to a different set of messages, primarily initiated by Interleukin-10, and differentiate to mount a targeted humoral response including the upregulation of eosinophils, neutrophils and antibody secreting cells.

So far so good. But the road to health is paved with complications.

When Fluidity Becomes Fixation

First of all, the immune system relies on the fluidity of these two responses – the ability of the body to rapidly and clearly shift between the Th1 and Th2 pathways as circumstances require. But many conditions can cause a shift from a system characterized by fluidity to one in which either arm of the system becomes chronically dominant, rigidly fixated in one mode or the other.



Environmental illness and multiple chemical sensitivity may be expressions of a rigid Th2 dominance. In this state, a person becomes chronically hyper-responsive to non-self substances, even when they are harmless or present at otherwise inconsequential levels. In the "distributed computing network" of the immune system, generating a false positive is usually preferable to missing or misidentifying a serious threat.

The other side of the coin is Th1 rigidity, a condition in which the inflammatory characteristics of cytotoxic immune responses become fixated. Th1 rigidity is associated with autoimmune and degenerative conditions since the immune system is in a constant mode of cellular attack.

It would be natural to think that Th1 rigidity is caused by chronic viral infections and Th2 rigidity is caused by chronic bacterial problems or high levels of environmental or metabolic toxins. But it's not that simple.

Although ideally the body would seek a Th1 response to a viral infection, some viruses have evolved the ability to mislead the immune system, triggering the production of peptides that mimic IL-10, the primary initiator of a Th2 response. Conversely, although the body would ordinarily seek a Th2 response to a bacterial infection, some bacteria have the ability to trigger the production of peptides that mimic IL-12, the initiator of a Th1 response.

What results may be a thorny, 4-way tangle of genuine and misdirected immune responses. And like four cars waiting at the 4 corners of an intersection, it can be difficult to know who should go first. In the immune system, it seems plausible that when one response or the other starts to break out of the jam, it may not only inhibit the opposing process but also may trigger a set of false responses that further congest and derail the flow of effective immune system messages.

Flying Below the Radar – Stealth Adaptation and Immunological Complexity

I suspect that in today's extremely toxic world, many people harbor both chronic viral and bacterial infections. This has become all the more likely in light of the fact that both viruses and bacteria have become *stealth adapted*, allowing them to "fly below the radar" of many of the immune system's detection capabilities.

Complicating matters further is that fact that viruses can infect bacteria and integrate bacterial genes into their own structure. These hybrids, called *viteria*, can then use viral mechanisms to deliver bacterial information – such as the genetic instructions to produce a potent cellular toxin – into the host cells they later infect, amplifying the effects of illness and further derailing an already confused set of immune responses.

Should the immune system initiate a Th1 response to attack the virally infected cell? Or should it upregulate Th2 to act against the toxin? Does it attempt to initiate apoptosis to cause the infected, toxin producing cell to self-destruct before it does any more harm? Or is apoptosis blocked by the originally protective inflammatory processes induced by the immune system itself?

Bacterial Trickery – A Legacy of Stealth

The next profound complication is that many bacteria readily shed their cell walls, and therefore the antigenic markers used by the immune system to track them, in response to challenges from the immune system. This transforms them into cell wall deficient variants of the original bacterium (sometimes called CWDs, L-forms or pleomorphic variants) capable of evading the immune system. Some bacteria may even, like viruses, take up residence inside of cells.

Borrelia burgerdorfi, the spirochetal bacterium associated with Lyme disease, can rapidly shift to become a small, spherical, intracellular parasite referred to by some researchers as *Borrelia myelophora* because of its affinity for the fatty myelin sheaths surrounding nerves. *Borrelia* also plays a number of other tricks including presenting and then withdrawing surface antigens similar to endogenous antigens in our own cells, such as LFA-1 (Lymphocyte function associated molecule-1).

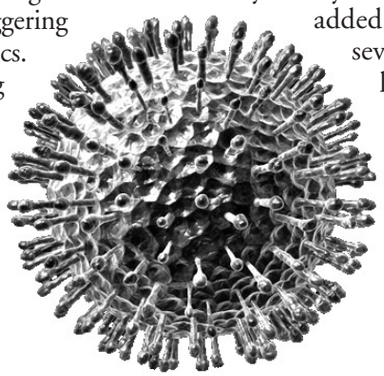
Having set in motion an antibody-mediated immune response which no longer has a bacterial target, the system responds by targeting and attacking the similar antigens on our own cells. This effect, which has been compared to a bullfighter using his cape to attract a bull and then artfully withdrawing it, is thought to be responsible for much of the inflammatory sequelae seen in the progression of Lyme disease.

Another source of intracellular CWD stress can come from *mycoplasma*, the pleomorphic stealth variants of the *mycobacteria* associated with tuberculosis and paratubercular disorders. Although the medical community has only started paying serious attention to mycoplasma in the last 10 years or so, their association with rheumatoid arthritis has been known since 1939 when they were first isolated from the synovial fluid of RA sufferers.

Chlamydia pneumoniae is another bacterium that readily invades cells and evades targeted immune detection. In particular, when *Chlamydia* infects arterial cells, the immune system responds by mounting an inflammatory reaction mediated by C-reactive protein (CRP). As the stealth *Chlamydia* infection persists, the sustained inflammatory immune response can create lesions in the arterial walls, leading to the deposit of plaque and in time, calcification of the lesion contributing to the development of atherosclerosis.

HHV-6 – A Sleeping Viral Giant

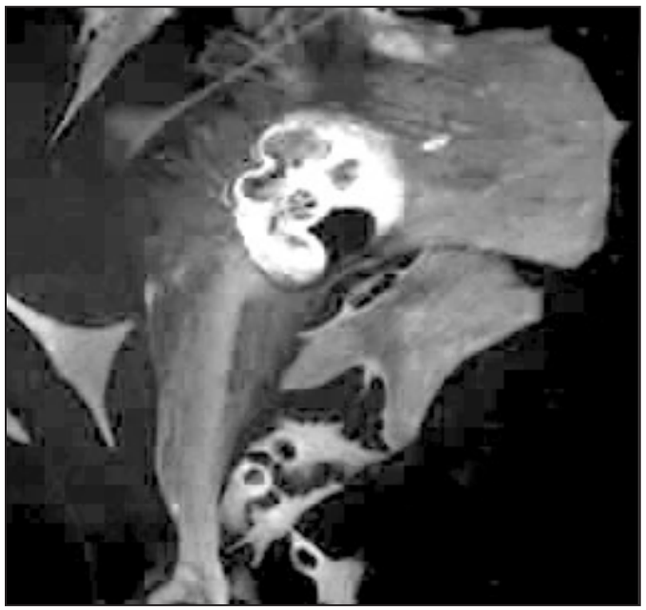
Human herpes virus 6 (HHV-6) is among the viruses that misdirect the immune system by triggering the release of Th2 initiating cytokine mimics. By fooling the immune system into believing it's under serious bacterial attack, attention is shifted away from the Th1 mechanisms that would, in an otherwise healthy person with optimal, fluid immune response, control the virus and eliminate the infection.



Computer simulation of herpes virus, courtesy of *3DScience.com*

Mainstream medical practice essentially ignores HHV-6 for a very simple reason: about 95% of the general population shows IGg antibodies against it. The rationale for discounting it is that if HHV-6 is so common, it can't possibly be doing anything bad. Still, even if all HHV-6 did was to trick the immune system into ignoring other viruses (not to mention, dysplastic and malignant cells), setting the stage for chronic infection and misguided Th2 responses, it would be bad enough.

But HHV-6 is potentially much worse. Researchers have noted that certain conditions, such as prior infections with HHV-4 (the Epstein-Barr virus that causes infectious mononucleosis and Burkett's Lymphoma), HHV-5 (cytomegalovirus) and extreme toxic insults, may change the body's relationship with HHV-6, allowing it to progress into a more pathogenic relationship.



HHV-6A virus infecting human glial cell. Image courtesy of Dr. S. Jacobsen, NINDS, NIH

Consider the fact that in approximately 70% of MS patients examined, their inflamed, demyelinated neurons showed infection with HHV-6 while adjacent, healthy neurons showed no signs of the virus.

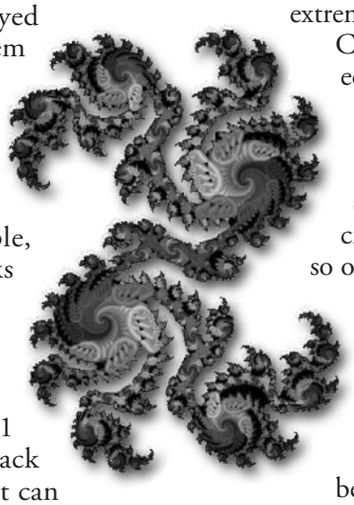
Further, lymph node biopsies of individuals who have died from AIDS related conditions tend to show high levels of HHV-6 and little, if any HIV. The same thing is observed in CD-4 cultures. When HIV is added, it is only slowly adsorbed into the cells but when HHV-6 is added, the virus is rapidly adsorbed leading to severe cytopathic damage. This observation has prompted a number of researchers to speculate that, at the very least, HHV-6 is an important cofactor in AIDS pathogenesis and may be the primary cause of cellular destruction in AIDS related illnesses.

Moreover, when a sophisticated diagnostic tool called nested PCR is used to carefully discriminate active HHV-6 infections from inactive IGg memory of exposure, a significant proportion of chronic fatigue sufferers test positive. Interestingly, in many of these cases the level of active infection is cyclical, going up and down over time. Clinically, this suggests that HHV-6 levels should be tracked over a period of time and correlated with symptoms. But there may also be a deeper implication.

Cycle of the Shifting Tides

In terms of the Four-Way Stop hypothesis, this cyclical activity – which is seen in other severe immune challenges including chronic Lyme disease – may actually represent a rhythmic "tidal shift" between Th1 and Th2 dominance patterns. Rather than being related to the life cycle of the infecting organism as is often suggested, I suspect it may have more to do with how the immune system reacts over time to the complex terrain of the infection.

As soon as one arm of the system has succeeded in achieving dominance, the factors arrayed to oppose it may begin to pull the system in the opposite direction – eventually establishing primacy and becoming the new dominant pattern. This, of course, causes the system to shift yet again in the opposite direction, in an endlessly vicious circle. For example, if a Th1 response eventually breaks through and begins to mount an assault against a viral pathogen like HHV-6, the virus may counter by eliciting the production of IL-10 like peptides, thrusting the system away from the Th1 response it finds so challenging and back toward the Th2 dominance in which it can continue to hide.



The loser, of course, is the infected individual, who is constantly tossed back and forth between a set of opposing "emergency responses," neither of which was ever intended to remain active for long periods of time. While the immune system is essential to life, it's very, very expensive to operate at this level.

Immune responses can cause cell damaging inflammation which may be experienced as a host of autoimmune and degenerative diseases. They can produce reactive oxygen species that promote electron depletion and oxidative stress, a physiological manifestation of "depleted ch'i" and free radical damage. And through the sustained action of critical immune supporting chemicals like RNase-L (an enzyme that prevents viruses from replicating), it can profoundly interfere with normal cellular activities like the essential conversion of nutrients into cellular energy. Many researchers have associated the hyper-activation of RNase-L with the debilitating effects of chronic fatigue syndrome.

Chaordic Harmony vs. Chaotic Confusion

One of the greatest scientific achievements of the 20th Century, along with the landmark theories of Relativity and Quantum Mechanics, was the development of Chaos Theory. Before Chaos Theory, there was a general assumption that complex phenomena – things like aerodynamic turbulence, the behavior of the stock market and almost *everything* in the biological world – had a correspondingly complex cause.

But Chaos Theory shows us that complex natural systems possess a vast and underlying elegance. In fact, most naturally complex phenomena emerge from a simple pattern that is repeatedly mixed back on itself until it appears arbitrarily complex.

For example, imagine two mounds of taffy – one blue and the other white. Each time the two blobs are pulled together and twisted, they mix and form swirls. After only a very few pulls, the swirls will appear incredibly complex but in fact, the mixing process that produced them is extremely simple.

Chaos Theory has shown that the mathematical equivalent of a taffy pull can generate objects of literally infinite complexity, like the Mandelbrot Set shown here. Although it is generated from an extremely simple equation, every crinkle can be expanded to reveal more crinkles, each of which can be expended, and so on, *ad infinitum*. This would be nothing more than a mathematical parlor trick, except for the fact that the mathematics of fractals – objects like the Mandelbrot set – maps directly onto the organization of neurons in the brain, the interaction of hormones in the endocrine system, the communication between cells in the beating heart and in all likelihood, the complex coordination of messages within the immune system.

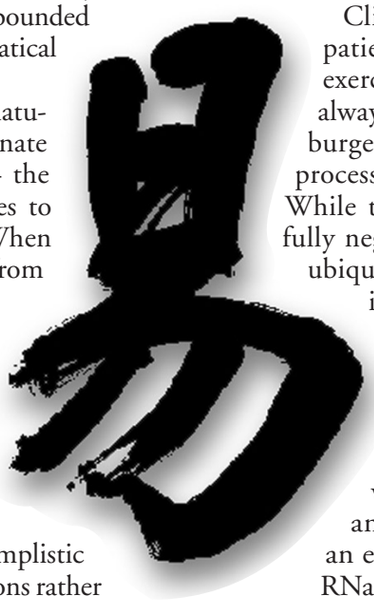
In the healthy body, the apparent simplicity of wellness *emerges,* almost magically from the complex but dynamically regulated interaction of countless physiological phenomena.

The concept of "emergent order" is not new. In 1776, in his pioneering economic treatise "The Wealth of Nations," Adam Smith observed that a well ordered marketplace manages to automatically determine the fair price of goods without any kind of central, governing authority. Although he didn't have the mathematics of fractals and Chaos Theory at his disposal, Smith realized that the natural, chaotic interplay of supply and demand seemed to guide merchants as if *"…by an invisible hand to promote an end which was no part of his intention... "*

It is precisely the freedom to chaotically interact without interference or fixation that allows physical functions to adapt and adjust to infinitely changeable conditions. This emergence of order out of apparent chaos is sometimes called the *chaordic principle* and is an essential aspect of all natural systems. In fact, long before Adam Smith the ancient Chinese understood this extremely well.

The ideogram, or word picture for the Taoist Book of Changes, the *I Ching*, consists of two parts. The upper part represents the sun moving through the sky as a symbol of regular, predictable change. The lower part derives from a cluster of banners rippling in the wind. For the banners, each individual change is chaotic and infinitely unpredictable. But because the banners are attached to a post, their

movements are ultimately bound within a finite range. The juxtaposition of regular, cyclical variation and infinitely variable but finitely bounded change was the Taoist's perfect symbol for how the natural world works. It's just the same in Chaos Theory with its notions of bounded chaotic interaction defined by mathematical functions called "strange attractors."

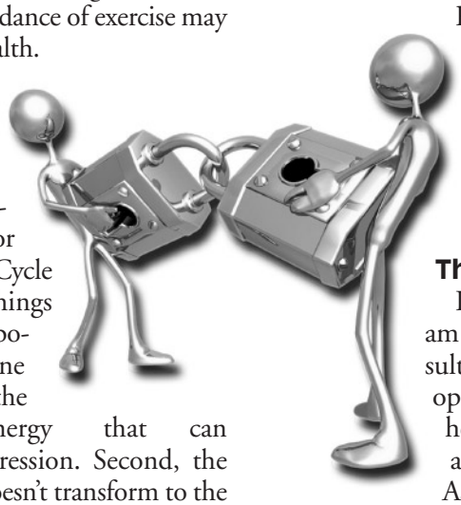


Fixation – the unnatural blockage of naturally chaotic movement – inhibits the innate chaordic property of a natural system – the miraculous "invisible hand" that emerges to create healing and maintain wellness. When fluidity is lost, a system can easily shift from the chaordic emergence of balance to a genuinely chaotic state that cannot maintain harmony. Alternately, it can shift into an "inorganic oscillation" – exactly the kind of "tug of war" between opposing poles described above as the endless tidal shift between Th1 and Th2 dominance. Practitioners with sensitive palpatory skills often associate rigid, simplistic rhythms in the body with inorganic functions rather than healthy dynamics.

Clinical Considerations

It's important to note when dealing with complex chronic infections that almost any symptomatic picture can present. Several types of infection, including Lyme disease, have been referred to as "Great Imitators" since the repertoire of disturbances they cause is almost endless in its variation. The longer a complex chronic infection has been active, the more diverse, varied and confusing the symptoms are likely to be.

Some pathogens, including HHV-6, are cardiotropic, meaning that they have a natural affinity for the heart. In an infected individual exercising to improve his or her health, the accelerated blood flow through the heart can actually increase the intensity of viral activity, resulting in extreme exercise intolerance. The resulting avoidance of exercise may in turn, lead to a general decline in health.



Chronic infection patterns frequently derail critical metabolic functions through disturbance of endocrine functions, blockage of enzyme pathways and the accumulation of microbial and cellular toxins. For example, when any stage of the TCA Cycle is inhibited, at least three negative things can happen. First, fewer reduced metabolites are produced leading to a decline in ATP production. Consequently, the individual experiences diminished energy that can manifest as fatigue, lethargy or depression. Second, the blocked intermediate – the one that doesn't transform to the next stage – piles up inside the cells and becomes a burden that has to be cleared. And third, since the continuity of the cycle is broken, input of new substrates is constantly required since the blocked pathway never completes. The original molecules are not recycled so there is a constant demand for new material. This demand may be experienced as hunger.

Clinically, what does this sound like? A patient who is always tired, can't tolerate exercise, and gains weight because they're always hungry? We have taken to blaming the burgeoning obesity epidemic on McDonalds, processed foods, TV and a sedentary lifestyle. While these lifestyle choices contribute powerfully negative effects, I strongly suspect that the ubiquitous spread of chronic, stealth infection is also a major contributing factor.

As we've discussed, chronic viral infections may misdirect the immune system into ignoring them by sending out misleading Th2 signals. If that's the case, what prevents the viruses from overrunning our bodies and destroying us? Part of the answer is an enzyme called RNase-L.

RNase-L inhibits viral replication by attacking and breaking down its RNA. In a healthy, fluid terrain, a small amount of RNase-L is produced, switched on by binding with an activator molecule (2'-5' Oligo-adenylate synthetase), does its job, and is rapidly switched off by undocking the activator. Switching off is important because if the RNase-L remains activated, it will start to attack and destroy the normal cellular RNA used in countless essential processes, including the generation of cellular energy.

In chronic viral infections, RNase-L can remain stuck in the "on" position. This situation has been described as a forest fire within the body that endlessly consumes ATP, burning up cellular energy as fast as it's created. Worse still, in these chronically disturbed states, an alternate, low molecular weight variant of RNase-L can appear that basically lacks a responsive "off switch." This 37kiloDalton molecule (as opposed to the normal, 80kDa version) has been used by some researchers as a marker for the organic basis of certain instances of chronic fatigue.

Therapeutic Options

I preface this discussion by offering that I am not a clinician. I conduct research, consult with individuals about unconventional options and teach innovative methods to healthcare practitioners, but I do not assume responsibility for medical care. As such, the following suggestions should be considered points of departure for clinical exploration, rather than treatment guidelines or established protocols.

That said, what does all this speculation and theorizing about immune pathway activation tell us? How can we use this information to function more effectively at a clinical level?

First of all, it tells us that we have to work to *simplify* the proliferation of confusing and potentially contradictory messages activating within the immune systems. In the kind of mixed chronic infections I believe are becoming more common, it may not be enough to work on the viral part of the picture and then move on to the bacterial part, or vice versa. The problem is that interleukin mimicry couples the two types of chronic infections into a single, self-maintaining system.

It's as though the gas pedal and brake of my car are locked together. When I need to stop, pushing the brake also unexpectedly revs up the engine and tries to make me go faster. When I try to accelerate, pushing the gas pedal also engages the brake. The system therefore tends towards stasis – the very meaning of a chronic condition that cannot find resolution – while simultaneously consuming a great deal of energy.

The only way out of the bind is to weaken and eventually eliminate the coupling between the two systems.

I don't have any pat answers – every case is different and the subject needs serious exploration. A large part of my motivation for writing this article is to stimulate conversation about these ideas so that we can compare notes and try new methods. But there are several approaches that may each contribute important elements to the goal of simplifying the immunological terrain and uncoupling linked infections.

These approaches include both familiar and novel applications of:

1. *Immune Regulation/Receptor Blocker Therapies*
2. *Anti-Inflammatory Therapies*
3. *Isopathic and Biological Therapies*
4. *Complex Anti-Microbial Strategies*
5. *Optimal/Alternative Metabolic Pathways*
6. *Biological Terrain Adjustment*
7. *Energetic Therapies*

Each of these approaches could be the subject of an entire article – some of them, an entire book. In the following sections I'd like to outline each of these methods as food for thought. Hopefully, practitioners who are experienced in these and other therapies will offer their perspectives.

1. Immune Regulation/Receptor Blocker Therapies work to improve the body's ability to accurately discriminate between different immune system pathways and responses. It's relatively easy to pump new signals into the immune system using herbs, mushrooms, drugs, supplements – even lifestyle modifications. It's significantly more difficult to address coupled or fixated response patterns, and some of these therapies work by selectively blocking immune responses.

Glutathione/NAC supplementation is an approach to immune regulation that provides a host of benefits across a variety of pathways and systems. NAC (N-acetyl-cysteine) is a highly bioavailable precursor of glutathione (which may also be taken in the form of reduced glutathione or synthesized from precursors naturally present in pristine, undenatured dairy whey). NAC is mildly antiviral but more importantly, by restoring proper levels of intracellular glutathione it can have a profound impact on appropriate immune pathway activation.

Low Dose Naltrexone (LDN) is a therapy that uses a small dose of the drug naltrexone – usually 4.5 mg once a day – rather than the usual 50 mg or more per day used to desensitize opiate addiction. Naltrexone blocks opiate receptors associated with many types of immune system cells and helps to restore proper endorphin and enkephalin levels. By resetting immune sensitivity in this way, important shifts can occur including clearer determination of immune pathway activation. See ***www.lowdosenaltrexone.org*** for more information about this therapy.

The Marshall Protocol (MP) uses Benicar, an angiotensin receptor blocker (also known as an ACE inhibitor) in conjunction with pulsed antibiotic therapy to break down Th1 rigidity. It's used to activate suppressed immune responses from the chronic intracellular bacterial infections associated with sarcoidosis, including atypical presentations involving pleomorphic, cell wall deficient forms. See ***www.marshallprotocol.com*** for more information.

Isoprinosine is a drug that is valued not only for its antiviral action and low toxicity but also for also for its ability to help disentangle Th1/Th2 pathway activation. However, Isoprinosine primarily acts as a Th1 activator so it should be used with caution in cases of Th1 rigidity.

One potential limitation is that some therapies, such as the Marshall Protocol, are considered complete solutions that should not be modified. I suspect, however, that some of the extreme Herxheimer reactions associated with these types of therapy may at least in part be due to the influence of comorbid viral and bacterial infections, which can produce the Four-Way Stop Dilemma. For example, if Th1 is downregulated in response to therapy, RNase-L can be upregulated, or bacteria may express IL-12 mimics that push the Th1 response back up again, slowing the healing process and subjecting the patient to increased biological stress.

2. Anti-Inflammatory Therapies: Many symptoms of chronic infection are associated with persistent inflammation. In addition to pain and connective tissue damage, chronic inflammation can also suppress the beneficial expression of apoptosis – a process by which intracellularly infected and malignant cells self-destruct to limit the damage they can cause. Inflammation can also profoundly interfere with the coordination of endocrine signals and neurotransmitter functions leading to an almost endless cascade of stressful symptoms.

EFA supplementation is a well known dietary approach with anti-inflammatory benefits. Boosting the consumption of healthy omega-3 essential fatty acids and balancing their ratio with other lipids, particularly omega-6s helps regulate the eicosanoid hormone system leading to a reduction of proinflammatory type 2 prostaglandins.

Selective COX-2 (cyclooxygenase-2) enzyme inhibitors provide another way to reduce proinflammatory responses. Synthetic COX-2 drugs like Vioxx have been taken off the market because they were not sufficiently selective and also inhibited critical COX-1 mediated processes. Naturally selective COX-2 enzyme inhibitors include curcuminoids, a class of compounds found in turmeric, and resveratrol, a well known compound extracted from grape skins. Interestingly, ViraWall, the highly antiviral phycocyanin protein complex I described in the March 2006 (Volume 15, Numver 3) issue of *Explore! for the Professional* not only inhibits influenza infection but also a very potent COX-2 inhibitor.

NF-κB ("nuclear transcription factor kappa binding") is a potent cell signaling molecule whose activation stimulates the production of COX-2 and its associated inflammatory responses. NF-κB is activated by many of the cytokines we've been discussing as well as free radicals resulting from oxidative stress. It's easy to see how the chronic but ineffective immune hyperstimulation of the Four-Way Stop Dilemma can upregulate NF-κB and COX-2 and therefore a set of chronic inflammatory processes. Many of the same substances that act as selective COX-2 inhibitors such as curcumin and phycocyanin also work further up the chain to regulate NF-κB.

Antioxidants are obviously good candidates to function as anti-inflammatory synergists since free radicals stimulate the proinflammatory pathways described earlier. In addition to elevated cytokine levels, protracted immune responses are also major generators of free radicals. Some excellent antioxidants include lipoic acid (including the more potent R-lipoic acid form), green tea polyphenols, resveratrol, vitamins C and E, curcumin, glutathione and its precursors and synergists including NAC, undenatured dairy whey and co-Q10.

3. Isopathic and Biological Therapies: Readers of *Explore* Magazine are probably the practitioners best able to understand and appreciate the role that Enderlein Remedies and other biological modulators can play in untangling a complex immunological terrain. An intelligent combination of fungal isopathic formulas, bacterial immunomodulators and hapten antigen analogs (the Pleo San and Polysan remedies) can help clean up a chronically burdened terrain, lowering the interference generated by complex immune signals. See ***www.pleosanum.com*** for additional information.

I have used these remedies extensively for nearly 15 years with results that are often nothing short of miraculous. More than a decade ago I developed an advanced method of live blood analysis I call "Differential Isopathic Assessment in Darkfield" or just DIAD Microscopy for short. See ***http://www.exobiotics.com/DIAD*** for more information.

DIAD uses standardized concentrations of isopathic solutions as "biological developers," adding them to the blood to generate a complex set of differential reactions. While the reactions on each slide (there are usually 8 to 12 of them in a full screening) are individually significant, it is the complete set of reactions taken as a whole that provides detailed insight into the individual's unique immunological situation – what I call the "EcoBiotic Terrain." This advanced method has been described as a "CAT scan of the immune system" and is the most accurate method I know for charting and adjusting the course of biological therapy. I teach professional seminars in the theory and practice of EcoBiotic Therapy and DIAD Microscopy several times each year. See ***http://www.ibeamhealth.htm*** for more information.

4. Complex Anti-microbial Therapies: Proponents of natural medicine are justifiably reluctant to use antimicrobial therapies such as pharmaceutical antibacterial and antiviral drugs. Applied indiscriminately, these drugs not only destroy symbiotic flora and damage cells but also can push pathogens deeper into the body by encouraging their conversion to stealth forms such as CWDs and other pleomorphic variants.

The body's natural antiviral mechanisms can be extremely toxic which is one reason why chronic viral infections can be so draining. We've already discussed the chronic activation of RNase-L, especially the poorly downregulated 37kDa variant, and how it can destroy essential cellular RNA. We've also noted the chronic inflammatory action of NF-κB and COX-2 that are activated in the presence of protracted cytokine and oxidative stress states. The fact that viruses are usually hidden inside cells means that the immune system is usually directed to attack the whole cell – a set-up for autoimmune and degenerative conditions. Pharmaceutical antivirals also tend to be very toxic.

However, within the context of the Four-Way Stop Dilemma, intelligent application of pharmaceutical and natural antimicrobial compounds may be essential. Remember that working on one side of the chronic infection may prompt the challenged pathogen to shift dominance back toward the other side, forcing a return to the status quo. The patient may have gotten little for their effort aside from an additional dose of Herxheimer stress.

Complex chronic infections may require simultaneous therapeutic pressure from several directions at once so that no one pathogen has a chance manipulate its preferred immune response (the course that challenges it least) back into dominance. This possibility occurred to me while working with ViraWall, the antiviral protein compound I've already mentioned. (See ***www.virawall.com*** for more information.)

In a chronic viral infection, there is an uneasy equilibrium struck between immune regulation and the replication of new virons. Infected cells either swell and burst, releasing new copies of the virus through a process called lysogenization, or they continuously "bud" new copies through their cell walls in a reversal of the endocytosis through which the virus originally entered and infected the cell.

ViraWall blocks these newly replicated virons from entering additional cells, in essence putting up a "firewall" against the propagation of the infection. Clearly, this viral firewall effect can be highly protective against new infections, which is why we're so interested in ViraWall's remarkable ability to block influenza viruses.

In chronic infections, when cells are able to protect themselves by locking out new copies of the virus, the immune system may finally have an opportunity to get ahead of the infection and resolve it. But for a period of time, while the previously intracellular virons are stuck in the humoral compartment looking for a new home, a couple of things can happen.

First, depending upon the particular virus, there can be a shift in immune system signals. In my experience, these shifts tend toward inflammatory reactions which may be addressed with NAC and the anti-inflammatory compounds discussed earlier. But this is also a time when the virus may be more vulnerable to the action of virucidal compounds, either pharmaceutical agents or natural substances such as chaparral, elderberry and skullcap.

We are currently exploring combined protocols that use ViraWall to decouple viruses from cells, virucides to inactivate them, anti-bacterials and isopathics to simultaneously control the bacterial and mycotic dimensions and anti-inflammatory compounds to protect the system from the effects of switching between different immune system modes.

5. Optimal/Alternative Metabolic Pathways: When primary metabolic pathways are blocked, it may be helpful to supply the body with the nutrients it's best able to utilize, including substances that produce energy by atypical means. We've already identified the potential blockage of the TCA Cycle (also known as the Krebs or Citric Acid Cycle) by chronic immune hyperstimulation. Interferences may occur at many other stages in the system, from the upstream catabolism of nutrients, to glycolysis, beta-oxidation and carbon chain reorganization of lipids, cell wall and mitochondrial membrane transport, enzyme cofactors, lectin sensitivities and a seemingly endless array of other challenges.

D-Ribose is a sugar that is metabolized through the pentose phosphate pathway, an anaerobic process that can generate substantial quantities of ATP when normal, aerobic functions are blocked and degraded.

A Metabolically appropriate diet may help to optimize an individual's most functional pathways by providing an abundance of the nutrients s/he best utilizes. There are many theories and approaches, each with its proponents and detractors. I've studied the work of George Watson (fast vs. slow oxidizers), William Donald Kelly (sympathetic vs. parasympathetic metabolizers), William Wolcott (oxidative vs. autonomic dominance), Peter D'Adamo (blood type diets and lectin avoidance), Barry Sears (macronutrient ratios) and others. They can't *all* be the last word on nutrition. Unfortunately, what I tend to see is that people with chronic complex infections have no ideal diet. The best approach is to find a variety of wholesome foods that are well tolerated and pay more attention, at least at first, to anti-inflammatory and anti-oxidant needs than hard and fast nutritional rules.

Vitamin D reduction: Chronic intracellular bacterial infections such as those involved in sarcoidosis may be associated with very high levels of activated vitamin D. Food sources of vitamin D are biologically inactive and are converted into the hormone calcitriol or 1-alpha, 25-dihydrovitamin D (or 1,25-D for short). In addition to its well-known action as a calcium metabolism regulator, 1,25-D is also a powerful immune system modulator and can participate in the fixation of Th1 inflammatory responses and the corresponding downregulation of Th2 responses. Along with angiotensin receptor blocking and pulsed antibiotics, avoidance of vitamin D and the sunlight that converts inactive D vitamins into 1,25-D are important aspects of the Marshall Protocol described earlier. (See ***www.marshallprotocol.com/forum2/2572.html*** for additional information.)

6. Biological Terrain Adjustment: We usually think of Biological Terrain adjustment as a matter of pH and redox values that have something very general to do with nutrition and optimal energy production. But bioterrain therapies go straight to the core of key issues such as oxidative stress, cellular energy production, energy flow and both chemical and electrical signal handling throughout the body, including gross and subtle facets of immune system regulation.

Though fairly "low tech," using diet, electrolytes, EFAs and other natural means to balance the biological terrain may help open the communications channels the immune system needs to function properly.

7. Energetic Therapies: This is an almost limitless area, from very esoteric speculations such as the electrical transduction of gene expression codes pulsing within the DNA molecule to more traditional approaches like the use of acupuncture and pulsed magnetic field therapies to help restore blocked energy pathways in the body. With the modern discovery of the physiology of the ch'i meridians described by traditional Chinese medicine by Becker, Nördenstrom and others, we are beginning to develop a rational way to integrate the use of structured energy in medicine. See ***www.ibeamhealth.com*** for more information.

Another interesting aspect is the direct use of electromagnetic energy (photons) to target malignant and infected cells or to directly influence biochemical reactions with energy through so-called "alternative cellular energy" pathways. See ***http://www.s3support.com/members/scientific/publications/index.com*** for more information.

An Invitation to Join in an Exchange of Ideas

The ideas and speculations offered in this article are just the tip of the iceberg. A group of colleagues and I are in the process of creating a new, non-commercial website to host conversations, blogs, links and other communications about the complexities of health, illness and natural approaches to medicine. We call it "Club Immune" and by the time you read this it should be available on the web at ***www.clubimmune.com.***

I look forward to developing an ongoing dialog about these complex and important issues. In the meantime, please feel free to contact me at ***dilemma@clubimmune.com.***