Intracellular Bacteria Cause Inflammatory Diseases

In April 1997, the National Institutes of Health published this statement: "A considerable body of experimental and clinical evidence supports the concept that difficult-to-culture and dormant bacteria are involved in latency of infection and that these persistent bacteria may be pathogenic."

See Bacterial persistence and expression of disease.

In July 2006, the Centers for Disease Control and Prevention published this statement: "Evidence now confirms that noncommunicable chronic diseases can stem from infectious agents."

See Emerging Infectious Determinants of Chronic Diseases.

Variant bacteria

We believe the Th1/Th17 (T-helper) inflammatory response occurs in reaction to the invasion of cells by extremely tiny variant bacteria. These parasitic, ‘stealth’ bacteria are also called pleomorphic (many shapes), L-form (named for the Lister Institute where they were discovered), Cell Wall Deficient (CWD), cell wall divergent, cell-wall defective, large bodies, cryptic bacteria, nanobacteria or spores. Coccoid (spherical) is a term that refers to these elemental forms. Cysts or colonies of these tiny L-forms can be enclosed within a protein shell. See Immune System and Intracellular Bacterial Disease Process.

Size

These bacteria are about 0.01 microns in diameter, smaller than any known viral or fungal particle. They are the smallest identified bacterial forms and are too small to be seen with normal optical microscopes.

Species

There are at least 53 identified species of L-form bacteria. A wide variety of these bacteria is illustrated in Dr. Lida Mattman's slides in the textbook “Cell Wall Deficient Forms: Stealth Pathogens”, Third Edition 2001, CRC Press.

Sources of exposure

Humans are exposed to L-form pathogens in food/milk (they're not killed by pasteurization), water (they're not killed by chlorination), intimate contact (spouses are
at higher risk of communication), before birth (via sperm), at birth (mother to child transmission) and biologic (injectible) medicines (they are too small to be filtered during the 'purification' processes used in pharmaceutical manufacturing procedures). They have even been cultured from dry soil. L-forms of Bacillus anthracis (Anthrax) are known to survive in dry soil indefinitely.

**Detecting L-form bacteria**

It's difficult to identify the presence of intracellular bacterial species. A few researchers are using dark field microscopy to detect L-form bacteria in the bloodstream. These intracellular (within the cell walls) bacteria will not necessarily show up in lab cultures because they are very difficult to grow. They will not show up in antibody testing because they are hidden inside the cells of the immune system which has been unable to detect them and kill them so antibodies have not formed. **Polymerase Chain Reaction (PCR)** tests may only show small (almost undetectable) quantities of the bacterial 16S RNA because the lifetime of the phagocytes is long (intracellular bacteria use biochemical mechanisms to delay apoptosis) so they don't die and expose their interior to the bloodstream very often. Biopsy testing doesn't usually work because the bacteria are destroyed when taken out of the body as their homeostasis is destroyed and the lysosomes in the immune system kill them.

The inability of most research labs to be able to culture CWD forms has been a big obstacle, but this is not the prime reason for the stasis in research; that may be as much political as anything else. It would be career destroying for a scientist to say that the CDC and the Infectious Disease Society have been negligent in ignoring the pleomorphic and persistent nature of bacteria in compromised humans.

"The cell wall is an essential structure for virtually all bacteria, forming a tough outer shell that protects the cell from damage and osmotic lysis. It is the target of our best antibiotics. L-form strains are wall-deficient derivatives of common bacteria that have been studied for decades. However, they are difficult to generate and typically require growth for many generations on osmotically protective media with antibiotics or enzymes that kill walled forms. Despite their potential importance for understanding antibiotic resistance and pathogenesis, little is known about their basic cell biology or their means of propagation. We have developed a controllable system for generating L-forms in the highly tractable model bacterium Bacillus subtilis. Here, using genome sequencing, we identify a single point mutation that predisposes cells to grow without a wall. We show that propagation of L-forms does not require the normal FtsZ-dependent division machine but occurs by a remarkable extrusion-resolution mechanism. This novel form of propagation provides insights into how early forms of cellular life may have proliferated."

**Life without a wall or division machine in Bacillus subtilis**

**Koch's postulates**
Koch’s Postulates have caused physicians to rely almost totally on a response to antibiotics in a Petri dish (in-vitro) rather than in-vivo to select an appropriate antibiotic. But some pathogens have to be grown on special substrates (e.g., Treponema (syphilis) and Helicobacter) and physicians should be aware that there are also other pathogens (especially intracellular) that do not show up in standard lab cultures. Th1/Th17 inflammatory diseases are a chronic intracellular, polymicrobial infection, in which the DNA is is believed to be horizontally mobile between pathogen and host and, therefore, the postulates of Koch are no longer relevant.

Intracellular bacteria control the action of the immune system
Bacteria have developed the ability to morph into a tiny form with reduced cell walls in order to evade the immune system and survive the antibiotics that kill bacteria by inhibiting cell wall formation. These variant forms of the original parent bacteria have learned how to live within the cells, including the cells of the immune system (phagocytes) that are supposed to kill them.

β-Lactam Resistance in Staphylococcus aureus Cells That Do Not Require a Cell Wall for Integrity
"Originally called L-forms, cell wall-defective (CWD) bacteria were first described in Streptobacillus moniliformis. We now know that many bacteria can become cell wall defective in the presence of various agents, including cell wall-active antibiotics, and can be propagated indefinitely on suitable media. CWD bacteria have been reported under a number of conditions, including burn site infections, sarcoidosis, and culture-negative febrile episodes in bone marrow transplant patients. Indeed, the clinical importance of CWD bacteria may be underestimated, as they do not grow on routine bacteriological media and are resistant to antibiotics that act on the cell wall. Moreover, cell wall-defective variants of Staphylococcus aureus were shown to be ingested by rat peritoneal macrophages, without phago-lysosomal fusion and digestion, and should therefore be expected to evade the immune system by intracellular refuge."

It is theorized that intracellular bacteria control the actions of the immune system by releasing proteins that act on the kinases within the phagocytic cells to release Th1/Th17 cytokines (small secreted proteins which mediate and regulate immunity).

Recently, Japanese researchers have discovered that Anaplasma phagocytophilum (Ap) secrete a protein which binds with another protein produced by white blood cells; and that connection creates compartments that siphon host-cell nutrients to feed the bacteria, enabling their growth inside the white blood cells.

Autophagosomes induced by a bacterial Beclin 1 binding protein facilitate obligatory intracellular infection
Their report states: "All of this activity allows the bacteria to remain hidden from the immune system because the induction of autophagy is considered a normal cell function and it does not produce any inflammation, which would recruit infection-
fighters to the scene. Instead, the Ap bacteria set themselves up comfortably inside granulocytes and steadily grow for a few days until they rupture their host cells and generate a strong immune response -- which makes an infected person sick."

The ability of one intracellular bacterial species to subvert natural processes and evade detection by the immune system lends credence to the theory that intracellular bacteria may have discovered other ways of thwarting the immune system (e.g., secretion of substances to down-regulate the VDR). Further study is needed.

**Successive infection**
The disease state a person acquires is thought to depend on the sequence, symbiosis and type of chronic pathogens which infect the body, not one causative species. This is called 'successive infection' or 'infectious cascade' and it’s only indirectly related to defective human genes or genetic predisposition.
The process of cell mutation and changed expression of genes is probably due to the bacterial, viral and bacteriophage infections acquired during a lifetime. For example, if the DNA of a cell has been altered by a previous pathogen, the changes caused by an L-form pathogen will be different than if the DNA had not been already altered.
The disease that develops (e.g., CFS, FM, arthritis, Parkinson’s, MS, dementia, sarcoidosis, atherosclerosis, etc.), and how quickly it develops, is determined by factors such as:

- Exposure (i.e., some intracellular species are acquired before birth along the maternal line and L-forms are found everywhere in the environment including sperm)
- Route of transmission (e.g., healthcare workers have a higher incidence of sarcoidosis)
- The species of Cell Wall Deficient (CWD) bacteria
- Virulence of the species
- Horizontal transfer of DNA between species of chronic pathogens
- External stimuli (e.g., high 1,25-D, beta-lactam antibiotics).

An acquired (not genetic) predisposition to inflammatory (‘autoimmune’) diseases explains why there are no specific genetic susceptibility alleles being isolated, despite intensive genomic studies. A few dominant (successful) genetic adaptations shared among species probably account for the predominance of some diseases among a wide variety of diseases and syndromes.

**A spectrum of symptoms which gradually accumulate**
Th1/Th17 inflammatory diseases appear to be a spectrum of symptoms which gradually accumulate into a recognizable condition. Although patients usually identify a date as the point at which the disease became manifest, they haven’t recognized the insidious progression of disease symptoms.

**Dysregulated vitamin D metabolism**
Vitamin D metabolism dysregulation is thought to be a mechanism that intracellular bacteria use to hide from the immune system and defeat the action of antibiotics alone,
allowing them to multiply safely sequestered within the cells. We theorize that Vitamin D Receptors are blocked by bacterial proteins causing the inflamed tissues to produce an excess of the secosteroid 1,25-dihydroxyvitamin-D in an attempt to activate Vitamin D Receptor (VDR) transcription. The blocked VDR allows the bacteria to colonize the phagocytes, avoiding the lysosomal phagocytosis.

Inflammation Therapy (IT) uses Benicar to control 1,25-dihydroxyvitamin-D and angiotensin II. Benicar seems to competitively up-regulate the VDR to produce anti-microbial peptides that can then weaken and kill the CWD forms. At high doses, Benicar also blocks key cytokine cascades, thus providing an anti-inflammatory effect and helping the patient feel better. See Benicar.

The correct antibiotic regime also weakens these antibiotic-resistant bacteria so the immune system can more effectively kill them.

**Gene transfer**

The main problem in Th1/Th17 diseases is that the VDR, which controls much of the innate immune system, seems to be blocked by bacterial ligands. There are many types of bacterial species at work that can transfer genes horizontally, and focusing on just one is an error.

The L-form bacteria enter the cell via endocytosis or some other means. We think they have a way to block the vitamin D nuclear receptor (VDR) ligand with a protein antagonist (perhaps capnine). The problem is that the phagocytes, while successfully engulfing the bacteria, are unable to kill them.

Transcription for specific genes occurs when the correct promoters and enhancers are provided by the activated VDR to separate the DNA double helix at the correct gene location and make the complement mRNA coded for a protein. The mRNA then returns to the cytoplasm to be translated into protein by the cell ribosomes.

However, when an antagonist is attached to the VDR ligand, the VDR is not in the correct physical shape to enter the nucleus through the nuclear membrane pores to access DNA where it would normally transcribe 900+ genes into mRNA. Many of these proteins are critical to the function of the immune system.

One researcher, using computer molecular modeling and affinity calculations, has determined that Benicar is a VDR agonist (activates the VDR), and in high enough concentrations will dislodge the bacterial antagonist (which inhibit VDR function). Over time, Inflammation Therapy will allow the hormone 1,25-D to regain homeostasis with the VDR and reactivate the immune system on its own.

**Genetic mutations**

Variations in the DNA sequences of humans can affect how humans develop diseases and respond to pathogens, chemicals, drugs, vaccines, and other agents. A single-
nucleotide polymorphism (SNP, pronounced snip) is a DNA sequence variation occurring when a single nucleotide (A, T, C or G) in the genome differs between members of a biological species or paired chromosomes in a human.

For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTTA, contain a difference in a single nucleotide. In this case we say that there are two alleles. Almost all common SNPs have only two alleles. The genomic distribution of SNPs is not homogenous; SNPs usually occur in non-coding regions more frequently than in coding regions or, in general, where natural selection is acting and fixating the allele of the SNP that constitutes the most favorable genetic adaptation. Besides natural selection other factors like genetic recombination and mutation rate can also determine SNP density.

Even bacteria can have gene SNPs.

**Insights into the Molecular Basis of L-Form Formation and Survival in Escherichia coli**

Intracellular bacteria which have invaded nucleated cells are believed to be able to influence DNA transcription and repair. Chronic damage to the human body occurs when the pathogens evade phagocytosis in the phagocytes where the genes for most of the body's immune functions are being transcribed, modified, and translated. The association between genetic changes and disease is associative, not causal. It is estimated that in a single human being there are 25,000 human genes and over a million bacterial and viral genes. Of the total number of cells in the human body, about 10% are estimated to be human cells, and about 90% are bacterial cells.

It is the ability of the genomes to interact which is key to chronic disease. Genetic mutations or defects are thought to be due to the chronic Th1/Th17 pathogen infection.

Bacteria are capable of mutating and changing genetic expression of cells. The evident communicable nature of these diseases and the fact that up to 25% of the population seem susceptible to Th1/Th17 diseases also argues against DNA mutation (genetic defect).

**Beta-lactam antibiotics**

The beta-lactam antibiotics (cephalosporins and penicillins) that attack cell walls are deadly to blood-borne bacteria but ineffective against CWD bacteria. In fact, beta-lactam antibiotics are used in-vitro (in a test tube) to promote the formation of L-form bacteria. Studies show that beta-lactam antibiotics actually cause CWD bacteria to form from blood-borne bacteria.

**Bacteriostatic antibiotics**

Sequencing of the human genome has enabled scientists to identify exactly how antibiotics work at the molecular level. Inflammation Therapy uses bacteriostatic antibiotics known as "Protein Synthesis Inhibitors" (PSI) to inhibit bacterial growth and assist the immune system in eliminating intracellular bacteria.
Minocycline

The tetracyclines are all different at the molecular level and Minocycline is the tetracycline of choice.

Intracellular bacteria are thought to have only one known resistance mechanism 30S ribosomal sub-unit, a single SNP, making Minocycline a suitable first-line antibiotic. Minocycline (one of the widest spectrum antibiotics available), stops bacterial protein synthesis by binding to the 30S Ribosomal sub-unit in the region of the helix which advances to 'read' the mRNA. It reportedly also binds to the 16S RNA at five other positions in the 30S sub-unit, but its hindering of the helix advance is believed to result in its primary functional inhibition of protein synthesis. One molecule of Minocycline inhibits one 70S bacterial Ribosome from manufacturing proteins.

Antibiotics inhibit bacterial protein synthesis

A website (www.riboworld.com) put together by two scientists from the Max Planck Institute in Germany, collates the knowledge about how antibiotics inhibit bacterial protein synthesis. The molecular models are taken from a variety of scientific papers, and provide a clear insight into exactly how each antibiotic works. Minocycline can also inhibit mammalian protein synthesis to a small degree, which is undesirable because this can suppress the immune system and other important functions. The goal is to use just enough Minocycline to block the bacterial pathogens’ ability to synthesize proteins without significantly inhibiting the body’s own ability to synthesize proteins. Therefore, Minocycline is used in low, pulsed doses in IT. It then has more of an effect on bacterial protein synthesis than on mammalian protein synthesis. Thus, the immune system enhancement by Benicar and the unique antibiotic regimen significantly tilts the advantage in favor of the immune system which is actually the most effective ‘antibiotic’.

This paper explains the interactions between antibacterial agents and phagocytes.

Synergistic antibiotic combinations

All bacteria need to manufacture a variety of proteins in order to survive and Inflammation Therapy is designed to make that task progressively harder. For that reason, therapy progresses from pulsed, low-dose Minocycline monotherapy to a synergistic, dual-therapy with an azolide antibiotic that forms a unique double bond in the 23S RNA. This totally unique azolide binds into the key pockets of the 50S bacterial ribosomal sub-unit where there are actually two molecules which obstruct each ribosome. None of the other 50S inhibitors do this. The key difference is that this unique antibiotic has superior tissue penetration for the first 5 days after administration, resulting in a greater concentration of the drug in the tissue that then circulates in the plasma compartment.

There are likely to be many different species of bacteria involved in causing the Th1 disease in any individual. Killing the bacteria causing these chronic diseases is a very
difficult task, and that is why Inflammation Therapy is not just a simple "take these pills for 5 days" treatment. Eventually therapy progresses to various three-antibiotic combinations, one of which binds to a different region of the 50S Ribosomal sub-unit and is therefore able to kill even more resistant intracellular species.

**Antibiotic resistance**
Statistically, the chance that bacteria will evolve that cannot be killed by IT is apt to be very small. The combination of an angiotensin receptor blockade with safe, wide-spectrum, symbiotic antibiotics seems to effectively eliminate all strains of antibiotic-resistant bacteria.

**Differences in antibiotic effectiveness**
There is definitely a variation in the effectiveness of various antibiotics in patients. The factors seem to be:
1. Patient's prior exposure to the antibiotics
2. Strength (or weakness) of the patient's own immune system
3. Species of bacteria present
4. Concomitant health problems (e.g., kidney failure)
5. Concomitant infections (e.g., fungal, viral)
6. Medications being taken by the patient

**Nucleated cells**
Phagocytes are a class of cells which include the monocytes, macrophages, lymphocytes, neutrophils, dendritic cells, and polymorphonuclear cells. They are loosely termed "white blood cells." Phagocytes have the ability to engulf and ingest, and therefore destroy, foreign matter or organisms. This process is called phagocytosis.
The infected phagocytes circulate in blood and tissues. In the extreme case of sarcoidosis they clump together and form granuloma, clusters of phagocytes without the normal supporting structure. They are also capable of accumulating in regions of inflammation such as joints.
As distinct from normal white blood cells, these phagocytes have differentiated (formed) with a nucleus, mitochondria, and other structures useful in performing their function - to kill and digest old tissue and pathogens.
When a phagocyte becomes infected, intracellular bacteria can manufacture a lot more proteins, cytokines and toxins than they could if they had infected a red cell, as the cell nucleus and mitochondria allow them access to human mRNA transcription, and human nutrients.

**Cytokines**
The bacteria cause the phagocytes to emit Th1 cytokines, apparently giving the bacteria extra protection or nourishment. These cytokines are what cause long term damage to the tissues and to the well-being of the human host. For example, angiotensin II is known to accelerate the deposition of collagen into tissue and long-term deposition of collagen leads to fibrosis.

**Cell life and apoptosis**
Several studies have noted that the infectious agents (bacteria) prolong the life of cells
by delaying maturity and apoptosis (cell death), A macrophage is one of the cells suffering the least apoptosis, typically accepted to have about a 45 day life. By comparison, a neutrophil suffers apoptosis in 24 hours, so they make poor homes for chronic pathogens.

Co-infections
When the body is weakened by chronic, inflammatory disease, opportunistic co-infections are common, because the immune system is overwhelmed dealing with the intracellular bacteria. Sometimes bacteria are detectable in the bloodstream by routine methods (co-infections), but these are not the bacteria that usually make people chronically ill.

Co-infections that have been resistant to treatment will likely be eliminated by the immune system as its proper function is restored with Inflammation Therapy. See Co-infections.

The potential for healing
Intracellular bacteria primarily cause genetic changes in the nucleus of infected cells. Because these cells don’t live forever (apoptosis), the effect of the pathogens should become less important as the immune system eliminates them. Although there are signs of permanent damage (fibrosis, collagen, scarring, nerve damage), the body seems to have a remarkable ability to heal.

Documentation of compromised white blood cells by intracellular pathogens

Alan Cantwell, MD, was able to image pathogens in white cells.

Dr. Emil Wirostko photographed images of coccoids within a monocyte in the vitreous humor of the eye.

Compromised white blood cells in these diseases have been reported by Dr Andrew Wright, who uses dark field imaging to see them in the blood from a pin-prick.
Microbiologist Lida H. Mattman, M.S., Ph.D., former Director of the Nelson Medical Research Institute in Warren, Michigan, author of “Cell Wall Deficient Forms - Stealth Pathogens”, isolated many L-forms in pure culture using blood samples.

See also:

History of Research into Cell Wall Deficient Bacteria (L-forms).

CWD bacteria - studies

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Note: This document contains statements which represent scientific theories supported by the medical literature and molecular modeling by an independent researcher, but not yet generally accepted by the scientific community. These theories and research fit the medical model of Inflammation Therapy which has provided considerable supporting anecdotal evidence. CIR makes no claim as to the accuracy of these statements and they will be updated whenever new information becomes available.