The Case for Mycoplasma's Role
as a Cause of Autoimmune Rheumatoid Diseases

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2000

Harold Clark, Ph.D. Mycoplasma Research Institute, Florida, was associated with Thomas McPherson Brown, M.D., who postulated and conducted experiments seeming to demonstrate a relationship between mycoplasmas and Rheumatoid Diseases (RD) in both animals and humans. In a letter to the The Arthritis Trust of America, Dr. Clark says,

"They may be an associated cause, but how do mycoplasmas cause Chronic Fatigue Syndrome (CFS) and Rheumatoid Arthritis (RA), etc?

"I have pondered this question for many years, since 1952 when Dr. Brown, et. al. first postulated an antigen-antibody mechanism controlled by cortisone or tetracyclines. Since that time many of the pieces to this complex puzzle have been identified, but very few have been pursued.

"In the enclosed article I have tried to fit some of the pieces together in a not too technical picture, a road map for other investigators to follow.

"If Rheumatoid Disease and Chronic Fatigue Syndrome are immune complex disorders as many suspect, why hasn't the mycoplasma antigen complex been pursued? If they are also autoimmune disorders, why haven't other investigators demonstrated a mechanism for mycoplasma's role?

"After all these years we still seem to have more questions than answers. Hopefully the results on the doxycycline trial will provide more answers.

"'A maverick is one who can read the road signs before they are printed.'"

The pathogenic mechanisms of mycoplasmas have eluded investigators for centuries.

In 1984 the National Arthritis Advisory Board reported "Because we know mycoplasmas can cause arthritis in many animals, and because we know that they do cause acute and chronic diseases in humans (lungs & genitourinary tract) we must take seriously the possibility that they (mycoplasmas) cause arthritis in humans".

Today mycoplasma arthritis in humans is now one of the many accepted forms of arthritis. (16)

But How do Mycoplasmas Cause Arthritis and the Chronic Rheumatoid Diseases?

To answer this question you should know about mycoplasmas's unique properties that contribute to its host reaction.(8,17) Unlike viruses and bacteria mycoplasmas are the smallest free-living and self-duplicating microorganisms, as they don't require living cells to replicate their DNA and growth. More complex than viruses mycoplasmas utilize RNA for replication making them succeptable to the nucleophilic growth inhibiting antibiotics. This antibiotic sensitivity was a clue used in the identification of the filtrable viral-like Eaton Agent as a mycoplasma (*M. pneumoniae*) the cause of atypical pneumonia. This respiratory strain is also a suspected cause of arthritis, neurological and other localized disorders. The ring and hexadic growth cycle morphology observed by electron microphotography in some mycoplasma strain indicates the need to further examine other strains to determine their true morphology, growth cycle, and minimum reproductive units.(1,2) Their size and shape would effect their growth rate and intracellular pathogenicity. Support for a hexadic division and not just the simple binary division was the report that genomes of two sequenced mycoplasma subdivided into six equal segments. In another report was finding [that] the helicase enzyme that splits DNA was composed of six functional sites.(5,6)

Figure 1

Figure 1 shows a ceramic model of a mycoplasma hexadic growth phase (1,000,000 X). Support for a hexadic budding and not just the simple binary division was the report that genomes of two sequenced mycoplasmas subdivided into six equal segments. In another report was finding the helicase enzyme that splits DNA was composed of six functional sites.

Mycoplasma's tiny viral-like size and pleomorphism would facilitate their cell penetration but limit their synthetic capacity thus requiring preformed macro molecules for growth and reproduction. These include basic peptides or protein fragments from enzyme digested tissues and constant cell replacement. Also required are nucleotides, nucleic acid fragments, cholesterol and fatty acids in the form of nucleoproteins and lipoproteins. Cultures of whole tissue homogenates and biopsies can be inhibitory for mycoplasma isolation and growth. Mycoplasmas can live intra and extracellular as saprophytes utilizing the fragments from dead or dying cells. Their double layer lipoprotein membrane controls the intracellular flow of nutrients and provides a highly unstable osmolar microbe difficult to isolate and visualize.

Mycoplasma's fastidious growth requirements have been extensively studied in attempts to prepare a completely synthetic culture media as used in tissue cell cultures. Although mycoplasmas can be cultured in the broth digest of most human tissues their antigenic composition and properties vary among the tissues. (2,3) In early investigations gastric mucin was added to the culture media because of mycoplasma's attraction to the mucoidal synovial membranes. The highly variable composition of mycoplasmas has been studied in vitro and found to mimic their culture media. It could be assumed that their composition and properties would also mimic and vary among the in-vivo cultures of host tissues and fluids. For example the cholesterol concentration in the host's mycoplasmas would depend on the host's cholesterol levels in blood and tissues. The wide variation in mycoplasma's composition of lipid, nucleic

acid, and protein produced in a test tube culture may be more variable in the hosts. Mycoplasma's composition and pathogenicity in a living host would also be dependent on other concurrent microbial infections requiring multiple antibiotics as well as their health. In the aging process when cells are dying faster than being synthesized and replaced, more host components for mycoplasma growth become available. Perhaps that is why some progressive chronic diseases, such as Alzheimers and rheumatoid arthritis, appear more frequently with age or lay dormant in sensitized hosts until stressed. Senior succeptability would also depend on an adequate blood circulation. Perhaps we should be looking for rheumatoid brain and neurological diseases, such as multiple sclerosis (MS) with disfunction and autoantibodies.

Mycoplasmas are species specific. Many animals; rodents, birds, pigs, cows and others are frequently infected with their own strains that are known to cause arthritis, respiratory, neurologic, reproductive and other disorders. Because of their specificity the mycoplasmas initiate and transmit pathology only in related species that are genetically succeptable. Sequencing their entire genomes may indicate why the mycoplasma animal strains are species specific and seem more pathogenic, without the human immune system. The human strains have been found in the related great apes, particularly the gorillas, known to develop the chronic and systemic symptoms of rheumatoid arthritis. Exposed to many animals the captive circus and zoo elephants cultured and serologically tested were found to be infected with several of their own specific mycoplasma strains frequently associated with arthritis. Like humans elephants testing positive for mycoplasmas did not all develop arthritis symptoms.

The ubiquitous mycoplasmas frequently colonize the nasal pharyngeal and genitourinary tracts of both animals and humans. They have been found associated in over 50% of the normal population and primarily in females who have a four fold greater incidence than males which happens to be the distribution of rheumatoid diseases. Mycoplasma's affinity for the G.U. tract would indicate their in-utero transmission with symptoms developing later in life.

The low cytotoxicity of mycoplasmas contaminating tissue cell cultures continues to be a problem indicating the difficulty to eliminate and control with antibiotics or vaccines, when protected by their intracellular location.(4) Their affinity to synovium joint tissues is the result of both vasculization and mucosal membrane adherence factors. Mycoplasma's unilateral localization supports both migratory as well as fixed symptoms with one or several tissues affected. The systemic rheumatoid arthritis is considered to be both an immune complex (IC) and an autoimmune disorder.(7) It is also considered to be a classical example of a hypersensitivity reaction where the mycoplasma antigens have been found to cause a delayed-type intradermal inflammation as in tuberculosis positive patients and in the "Graft vs. Host" rejection. The closely related Lupus is a collagen vascular, also a mixed connective and a classical immune complex disorder with an autoimmunity to the basic nucleoproteins.

The activation of immune cells by the foreign or mitogenic mycoplasmas play a key role in the development of rheumatoid arthritis in the antibody deficient agamma patients. The antibody free patients require booster shots of hyper globulin to help sustain their immune system.

The frequently associated Jarisch Herxheimer flare reaction indicates the release of excessive mycoplasma antigens into the sensitized host tissues following antimycoplasma therapy. It is an example of a delayed-type hypersensitivity reaction that may persist for several days until the antigen (Ag) and antibody (Ab) levels are decreased. The flare results from the formation of the irritating Immune Complex (Ag+Ab) with the activation of host's T-lymphocytes to release inflammatory enzymes, such as the Cox 2, and hormones. (See "The Herxheimer Effect," http://www.arthritistrust.org. Ed.) As chelating agents the tetracyclines have multiple actions including antioxidants (electron scavenger) and antiinflammatory. As immunosuppressives the tetracycline antibiotics, like cortisone, suppress the Immune Complex (IC) formation that causes activation of the destructive complement proteolysis.(7) As chelating agents tetracyclines oral and/or intravenous administration could influence their effectiveness on mycoplasma.

The direct identification of mycoplasma antigens in the immune complex fraction from the synovial fluid of rheumatoid arthritis patients provides tangible support of mycoplasma's role in pathogenesis.(9) This is further supported by the rise and fall of complement and circulating Immune Complex (IC) levels. When combined with the mycoplasma antigens to form an IC the attached IgG antibody is conformed or altered and as such activates the proteolytic complement system.(11,12) In the mycoplasma complement fixation test (MCF) the patient's sera is positive if it reacts with the mycoplasma test antigens and fixes or neutralizes complement and prevents cell destruction. The mycoplasma antigen preparations and the patient's sera must be tested for non-specific complement fixation. In further support of mycoplasma's pathogenicity in rheumatoid disorders is the marked increase in mycoplasma antibody titers following a spontaneous flare reaction as in acute and convalescent infections.(13,14)

Mycoplasma growing in whole serum enriched broth specifically incorporates basic proteins, such as IgG gamma globulin. By altering the attached protein structure makes them both foreign and autoantigenic to the host. When attached to the lipophilic mycoplasma cells as an adjuvant carrier the altered basic tissue proteins are now autoantigenic to the host tissue causing the formation of the tissue autoantibodies characteristic of the so-called rheumatoid factor and other autoantibodies. Rheumatoid arthritis developing after *M. pneumoniae* infection is host dependent resulting in both IC and autoantibody activities.

To test this autoimmune mechanism, in the absence of human volunteers, *M. pneumoniae* was cultured in a rabbit muscle digest broth enriched with rabbit serum and used to immunize rabbits. The resulting rabbit antisera was positive to both *M. pneumoniae* and IgG an auto antibody to its altered self.(10) Although not required for growth the mycoplasma incorporated various amounts of the basic IgG protein from the serum enriched culture. Injection of rabbits with their own native sera containing IgG, as in humans, does not elicit antibody to the native IgG unless given with an adjuvant carrier, such as with the available mycoplasma lipoprotein membrane. The production of experimental autoimmunity requires the antigen such as basic myelin protein to be given with some artificial adjuvant carrier,

The final conclusive tests will come when mycoplasmas are cultured in human tissues; lymphocyte, erythrocytes, myelin, pancreas and other tissues associated with specific autoantigens. Like the IgG, mycoplasmas can attach to and thus alter other specific basic proteins in the cell membranes. Mycoplasma's adhesiveness could attach irreversibly to specific basic protein membrane sites in nerves, blood vessels, and even dental, whereby their accumulation and elevated cholesterol, would lead to specific (arterial and myloid) plaque formation. To verify mycoplasma's role in the plaque and tissue pathogenesis the deposits should be tested for their antigens and/or DNA.(16)

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