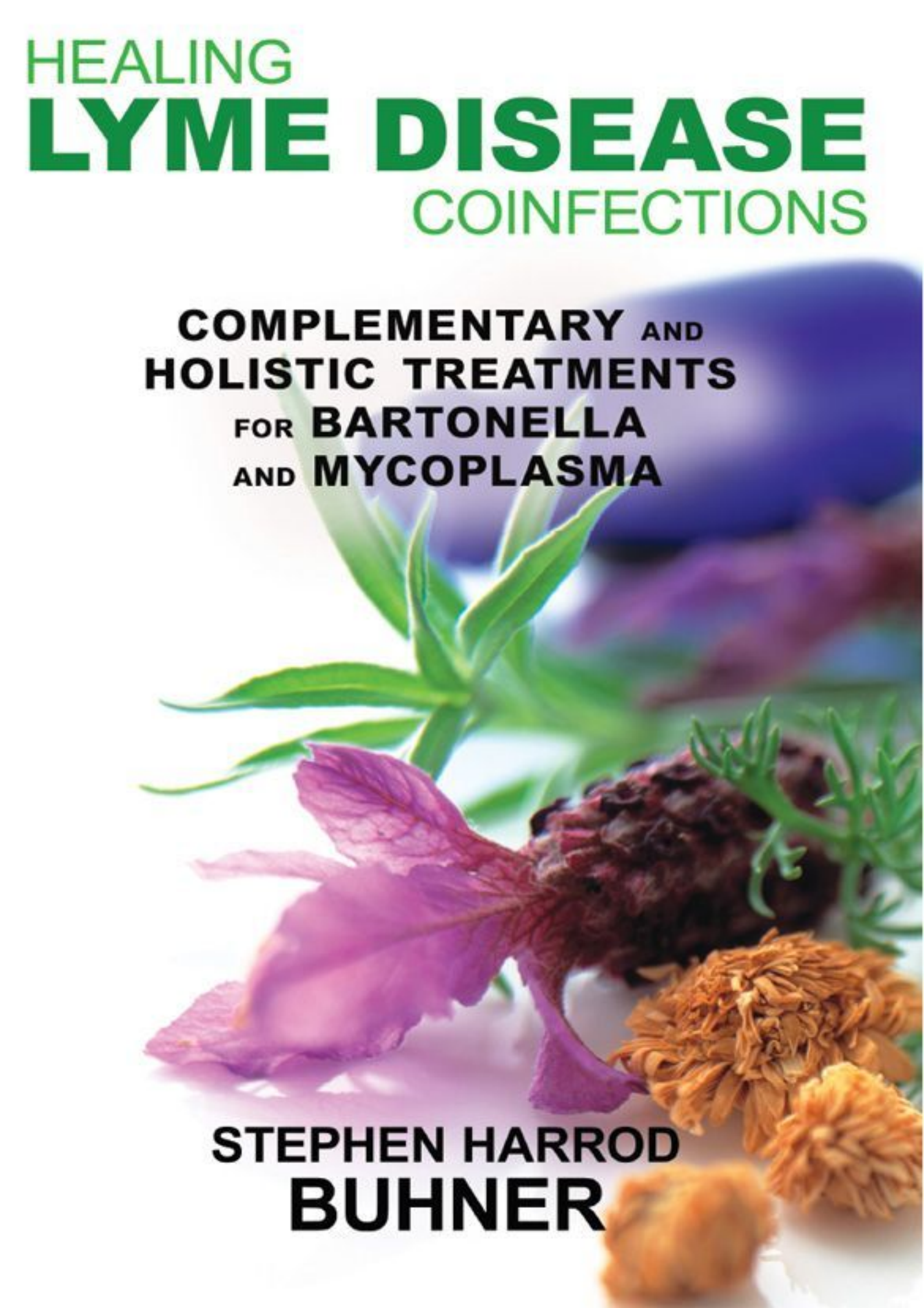
HEALING LYME DISEASE COINFECTIONS

COMPLEMENTARY AND HOLISTIC TREATMENTS FOR BARTONELLA AND MYCOPLASMA



STEPHEN HARROD BUHNER

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Healing Arts Press
Rochester, Vermont • Toronto, Canada

For Julie McIntyre,
whose caring for and dedication to her patients
is a constant inspiration to me.
And for everyone who has struggled with
either of these diseases—
there is hope,
don't give up.

HEALING LYME DISEASE COINFECTIONS

"Bacteria outnumber us, outthink us, cooperate better than we do, and inhabit a far wider range of ecological niches. Without them we would be dead, yet many of them are lethal. For the past one hundred years we have waged war on them, and we are losing. Stephen Harrod Buhner is not afraid. He is paving a path into a future where we use simple tools to nourish cooperative health. If you or anyone you love has ever had an infection, you need this book. At times technical, at others dryly lyrical, it is sure to become a gleaming guidepost to many who have resigned themselves to a lifetime of distress and a trusted reference for health professionals wishing to assist those with resistant and chronic infections."

SUSUN S. WEED, AUTHOR OF *HEALING WISE* AND *MENOPAUSAL YEARS THE WISE WOMAN WAY*

"Packed with information never before presented, *Healing Lyme Disease Coinfections* is a not-to-be-missed treasure on the topic of Lyme disease. While exploring numerous new therapeutic interventions, Buhner's pure intent and deep wisdom unfold before the reader, while his humorous style lightens the journey. This book is a masterpiece that provides its readers with life-changing information and is poised to become the reference book for the ages."

SCOTT FORSGREN, EDITOR AND FOUNDER OF BETTERHEALTHGUY.COM

"Well rooted in the scientific literature and benefitting from a deeply cultivated knowledge of herbalism, this exceptionally well-written book is an empowering resource for those suffering from Lyme disease coinfections and an essential reference for their clinicians."

LAURIE REGAN, PH.D., N.D., DEAN OF CLASSICAL CHINESE MEDICINE AT NATIONAL COLLEGE OF NATURAL MEDICINE

AND COHOST OF TRUE NATURE RADIO

Contents

How to use this Book and Who it is for

This book is meant for two groups of people: 1) those who are suffering from a difficult-to-treat bartonella or mycoplasma infection, and 2) clinicians who themselves treat people with bartonella or mycoplasma.

IF YOU HAVE BARTONELLA OR MYCOPLASMA

This book is designed to help you understand the disease itself and as well to understand some of the approaches that can be used to treat the disease and the symptoms it causes.

Please understand that some of the book is fairly technical. That is for the clinicians (or for you if you want to delve that deeply into it). You can skip the really technical bits if you want. They are not necessary to understand in order to treat either of these conditions effectively. In general, I think you will find the overview chapters on both bartonellas and mycoplasmas useful. The deeper technical look at the cytokine cascade and the minutiae of what the organisms do in the body are not really necessary if you just want a good overview of the bacteria.

The book also explores just how widespread these kinds of infections are. And, as usual, the real figures are very different than what the Centers for Disease Control (CDC) indicate—by a factor of anywhere from 100 to 1,000. Both bartonellas and mycoplasmas are *very* common and there are many millions of people in the United States, between one-tenth and one-third of the population, who are asymptomatically infected. Treatment is often difficult and many physicians don't understand *how* to treat or diagnose these bacteria very well, so this book also examines which antibiotics (and tests) research has found useful (and which ones are not).

The book also contains an extensive look at the natural protocols that are effective for each of the diseases. Please note: *these protocols are designed to be able to be used along with antibiotics.* I don't think you necessarily have to give up

either pharmaceuticals *or* natural medicines to find health. However, if you have tried antibiotics and they have failed to help you, the protocols in this book can be used all by themselves to treat both bartonellas and mycoplasmas.

Also, a note: *the herbs and supplements in this book are **not** the only ones in the world that will help.* Please use the protocols outlined herein *only* as a starting place, a guideline. Add anything that you feel will help you and delete anything that you feel is not useful. Bacteria, when they enter a human body, find a unique ecosystem in that particular person. Thus the disease is always slightly different in every person. That means that a pharmaceutical or herb that works for one person may not work or work as well for another. *There is no one-size-fits-all treatment for these particular organisms.*

As well: if you have a very healthy immune system, you will probably need to use smaller doses; if your immune system is severely depleted, you may need to use larger doses. If you are *very* sensitive to outside substances, as some people with Lyme, bartonella, and mycoplasma can be, then you might need to use very tiny doses, that is, from one to five drops of tincture at a time. (This is true for about 1 percent of the people with these infections.)

Please be conscious of how you respond to the medicines you take inside you. If something disagrees with you, if you feel something is not right in how you are responding to a medicine, **stop taking it.** Remember: you will always know yourself better than any outside physician.

IF YOU ARE A CLINICIAN

I have gone into a lot of depth on both bartonella and mycoplasma organisms so that you can begin to understand just how complex their actions in the body are. It is my hope that Western herbal medicine can begin to emerge as a highly sophisticated form of healing. To that end I have introduced the idea of thinking about the synergies that exist between coinfections as well as the concept of examining the kind of cytokine cascades bacteria create during infection. Each stealth pathogen decreases the activity of certain parts of the human immune system and activates others. So while some parts of

the immune system become less functional, others become overactive. The overactivity comes from the initiation of unique cytokine cascades. Each stealth pathogen creates a different kind, that is, they stimulate certain kinds of inflammation in the body, using the body's own immune response for their own ends. This is important to understand when designing any kind of elegant, interventive treatment strategy. If you *know* what is happening in the body, you don't have to guess what to do—you *know* what to do.

And while I don't go into it in any depth in this book, the idea of the complex synergies that exist between herbal medicines is crucial, as is an understanding of herbal synergists. These concepts are developed in detail in the revised and expanded second edition of my book *Herbal Antibiotics* (Storey Publishing, 2012). If you wish to look deeper into plant synergists and herbal synergies, I think you will find that book useful. As well, time and space limitations made the inclusion of *in-depth* monographs on many of these herbs impossible to include in this volume. I have done in-depth monographs on many of these herbs elsewhere; if you would like to see them they can be found in three other books: *Healing Lyme* (Raven Press, 2005), *Herbal Antibiotics* (second edition), and *Herbal Antivirals* (Storey Publishing, 2013).

HOW I ARRIVED AT THE HERBAL PROTOCOLS IN THIS BOOK

The protocols in this book were developed by exploring the dynamics of the diseases themselves, their impacts in people, the experience of clinicians treating them, the protocols those with the diseases have used, many hundreds of journal papers, a look at the plants' history of usage around the world for treating these and similar conditions, and my own experience with plant medicines over a 25-year period. But please note …

The plants herein are just guidelines. The protocols themselves are just guidelines. The dosages are just guidelines. There is *no* one-size-fits-all way to treat these diseases. The intent of this book is to give those who wish one an understanding of the diseases so that they can be treated more effectively and with greater sophistication. This is just a

beginning, a starting place so we no longer have to grope along in the dark.

Feel free to alter, add, delete, innovate, think outside the box, argue, insist, and never settle for less than being healthy in the way that you understand it.

And remember: *all* plants are useful as medicinals. Again, ALL plants are useful as medicinals. The secret, as always, is in the dose, the timing, and the combination that is used. Just because a plant is not mentioned in this book does not mean it is not useful.

One of the things I have learned from the ill people I have worked with since 1986 (especially those in the Lyme community) is that when a lot of people with a lot of motivation begin looking around themselves, searching for answers, they come up with some truly amazing things. If you lock people in a room with only four ways out, someone will find a fifth way out. *Always*.

Trust yourself, and remember, only *you* know what health is for you.

1

Emerging Diseases and Coinfections

The New Epidemics

> *Hosts that are coinfected by multiple parasite species seem to be the rule rather than the exception in natural systems.*
>
> *Coinfections could, thus, increase vulnerability to the emergence of new parasites by facilitating species jumps, if the coinfected portion of a population provides favourable conditions for an emerging parasite to adapt to a new host species.*
>
> ANDREA GRAHAM ET AL.,
> "TRANSMISSION CONSEQUENCES OF COINFECTION:
> CYTOKINES WRIT LARGE?"

I first became interested in bacterial diseases in the early 1990s after reading about the emergence of resistant bacteria in hospitals. Having studied mathematics, I well understood what an exponential growth curve meant. I could see as well as anyone that we had only a short period of time in which to begin to address the problem.

As I studied more deeply, I began to be aware not only of resistant bacteria, the majority of which have flowed from hospital settings into the general community, but also of diseases emerging in the human population due to overpopulation and the environmental disruption it causes. Lyme was among the emerging diseases that caught my attention and, as time went on, the coinfections that often accompany Lyme infection did as well.

It became clear, the more I learned, that many of these emerging diseases were difficult to treat with conventional technological medicine, that the diagnostic tests were often

unreliable, and that many of the organisms did not respond well to antibiotics. As well, and most regrettably, it slowly became obvious that many physicians had little knowledge of, or much interest in, these diseases.

I have been deeply immersed in the study of emerging and resistant bacteria for over two decades now. It is clear that while technological medicine still has a role to play, sometimes an important one, evolutionary changes are occurring that make many of our assumptions about such diseases and their treatment obsolete.

I was born in 1952 into an extended family that included many physicians, among them a surgeon general of the United States. For my family, "modern" medicine was *the* way to approach disease—the *only* way. Penicillin had become widely available in 1946, just after World War II, and new antibiotics were being discovered (seemingly) every day. Vaccines, too, were making history. The year I was born there were 58,000 new cases of polio, more than 3,000 of those infected died, and many of the others were permanently disabled—some terribly so. The next year, Jonas Salk announced the successful testing of his vaccine against polio. Then, in 1962, Albert Sabin introduced his oral vaccine, something that made mass vaccination easily possible. I still remember that long walk to the lunch room in elementary school, the long wait in line, and the sugar cube in the tiny white paper cup.

The excitement of those days is now very hard to explain to newer generations, but for people then, it seemed as if infectious diseases were going to be permanently eradicated. In fact, many researchers and physicians in the late 1950s and early 1960s, including my great-uncle Lee Burney, then surgeon general of the United States, and my grandfather David Cox, president of the Kentucky Medical Association, went so far as to loudly proclaim the end of all infectious disease was just around the corner. A 1963 statement by the Australian physician Sir F. Macfarlane Burnet, a Nobel laureate, is typical. By the end of the twentieth century, he said, humanity would see the "virtual elimination of infectious disease as a significant factor in societal life" (Levy 1992, 3). And in 1970, one of my great-uncle's successors, Surgeon

General William Stewart, testified to Congress that "it was time to close the book on infectious diseases" (Levy 1992, 3). With satisfaction the physician David Moreau observed in a 1976 article in *Vogue* magazine that "the chemotherapeutic revolution has reduced nearly all non-viral disease to the significance of a bad cold" (Griggs 1991, 261).

They were wrong, of course, the victims of their own hubris and a deep lack of understanding of the natural world, most especially of bacteria. By the time David Moreau's comments appeared resistant bacterial diseases were already on the rise. A short 30 years later, with infectious diseases from resistant bacterial strains become rampant, the world came to face the specter of epidemic disease outbreaks more dangerous than any known in history. As bacterial resistance researcher and physician David Livermore recently put it, "It is naive to think we can win" (Bosley 2010).

There are two factors that have stimulated the emergence of potent bacterial disease organisms. The first is the tremendous overuse of antibiotics over the past 70 years. The second is the extreme ecological disruption that increasing human population density is causing.

In an extremely short period of geologic time the Earth has been saturated with hundreds of millions of tons of nonbiodegradable, often biologically unique pharmaceuticals designed to kill bacteria. Many antibiotics (whose name literally means "against life") do not discriminate in their activity but kill broad groups of diverse bacteria whenever they are used. The worldwide environmental dumping, over the past 65 years, of huge quantities of synthetic antibiotics has initiated the most pervasive impacts on the Earth's bacterial underpinnings since oxygen-generating bacteria supplanted methanogens 2.5 billion years ago. It has, according to medical researcher and physician Stuart Levy, "stimulated evolutionary changes that are unparalleled in recorded biologic history" (Levy 1992, 75). Bacteria *had* to evolve resistance. If not, due to their crucial role in the ecological functioning of this planet (and our own bodies), all life, including the human species, would already have been killed off by those very same antibiotics.

Ecological disruption has also played an extensive role. Increasing damage to wild landscapes, intrusions into forest ecosystems, the cutting of those same forests to make way for suburbs, damage to plant diversity and its crucial homeodynamic functions by suburban and agricultural intrusions, the reduction of wild predator populations, and the increases in deer, mice, and insect populations as a result, have also put tremendous pressure on bacterial populations. As fewer and fewer wild animal populations are available as hosts for the bacterial diseases that once were (mostly) limited to those populations, the bacteria have no choice; they have to jump species—they have to find new hosts. Because human beings now live in the habitat formerly occupied by those animals, many of the bacteria are now learning to live in human beings.

Unfortunately, both bacterial resistance and ecological disruption can't help but intersect—with, of course, terrible ramifications. Many of the primary coinfections of Lyme are closely related to some of the most potent resistant bacterial organisms known. They are all members of the Proteobacteria phylum, a large and genomically close group of bacteria.

One branch of the Proteobacteria includes bartonella (*Bartonella* spp.), and another includes *Ehrlichia* spp., *Anaplasma* spp., Rocky Mountain spotted fever, and the other rickettsias—all of which are coinfections of Lyme. A different but closely related branch includes *Klebsiella* spp., *E. coli*, cholera organisms, *Pseudomonas* spp., *Salmonella* spp. (including *Salmonella enterica*, the cause of typhoid fever), and *Shigella* spp.—all now resistant to many antibiotics. It also includes *Yersinia* spp., the organism responsible for the plague, a bacteria transmitted by fleas much as bartonella is. Still another branch includes the bacteria responsible for gonorrhea infections (also resistant) and another includes both *Helicobacter* and *Campylobacter* organisms.

There is strong evidence that both resistance and virulence factors are being shared among all members of this phylum. In other words, the various bacteria are teaching each other how to resist antibiotics and how to more easily infect people, thus making them sicker. They do this, usually, through sharing

segments of DNA that have within them resistance and virulence information. Bartonella organisms are often coinfective with many of the bacteria in this phylum and, in many instances, these kinds of multiple infections show a remarkable synergy during the disease process. In other words, the bacteria work together to reduce the effectiveness of the immune response and thus enable long-term infection.

In practical terms what all this means is that a great many more diseases are emerging out of the ecological matrix of the planet and infecting human beings. And many of them possess, or soon acquire, resistance to many or most of the antibiotics that people use to treat bacterial diseases. And what they do together in the body is a great deal more complex than what any one of them does alone. All this can make them very difficult to treat.

One of the most important understandings now facing us is accepting the limits of pharmaceuticals in the treatment of many of these diseases. While antibiotics do still have a role, sometimes a very important one, they can no longer be relied on to provide the *sole* response to these kinds of diseases. We have to approach treatment with a more sophisticated eye.

There are two important aspects to this. The first is realizing that single-treatment approaches, most of which were developed out of an inaccurate nineteenth- and early-twentieth-century bacterial paradigm and are based on identifying the bacterial pathogen involved and killing it, i.e., monotherapy, are going to have to be abandoned as the primary method of treating these kinds of diseases. (Something that newer generations of physicians, especially in countries other than the U.S., are beginning to understand.) The second is coming to understand just *what* the bacteria do in the body and then designing a treatment protocol that is *specific* in counteracting what the organisms do—exactly. In essence this means designing treatment protocols that address bacterial cytokine cascades, the particular health or nonhealth of the person's immune system, and the specific symptom picture that is reducing the quality of the person's life. Combined with antibacterials, of whatever sort, this creates the most sophisticated basic approach to the treatment of bacterial

diseases. (If you add to that approach sophisticated human-to-human interactions oriented around deep caring and personal presence, something most physicians do not understand, you have the core of the most elegant and potent paradigm of healing disease that can occur.)

Some additional sophistications can occur, among them the synergy that occurs among the healing agents that are used *and* the synergy that exists between the different bacteria. That is, we must learn to look at what happens when there are multiple infectious bacteria, all coming into the body from, say, a tick bite. Studies on the complex interactions that occur between coinfectious bacteria are uncommon but, when combined with the experience of clinicians, they are revealing.

COINFECTION DYNAMICS

Coinfective bacteria interact both in the vector that spreads them (for example a flea or tick) and then in the host they are transferred to. One of the better articles on this is "Transmission consequences of coinfection: Cytokines writ large?" by Andrea Graham et al. (2007). The authors propose a unique approach to understanding the dynamics of coinfections. Instead of focusing on the organisms themselves, they suggest focusing on the cytokine cascades that the organisms produce in the body. They comment, "When the taxonomic identities of parasites are replaced with their cytokine signatures, for example, it becomes possible to predict the within-host consequences of coinfection for micro-parasite replication" as well as symptom picture, treatment approaches, and treatment outcomes.

Cytokines are small cell-signaling molecules released by the immune system, and the glial cells of the nervous system, that are important in intercellular communications in the body. In practical terms, when a bacteria touches a cell, the cell gives off a signal, a cytokine, that tells the immune system what is happening and what that cell needs. Each type of infectious bacteria initiates a particular kind of cytokine cascade, that is, an initial and very powerful cytokine is released into the body, that initial cytokine stimulates the production of others, and those still others—all of which have potent impacts on the

body. It is these cytokines, in fact, that create most of the symptoms that people experience when they are ill. What I explore in the more technical material on what these coinfections do when someone is infected is their cytokine cascades. This determines many of the most effective approaches to treat the conditions they cause—which I go into in the protocol section. And, of course, the impact of the vector of transmission plays a crucial part in this as well.

Bacteria have learned to work synergistically together or, for instance, to take advantage of the biologically active components in tick saliva in order to facilitate avoidance of the immune system—tick saliva itself begins a cytokine cascade that Lyme bacteria take advantage of in order to more successfully infect a new host. Although little research has occurred on louse and flea feces, two main routes of infection for bartonella, researchers comment that a similar dynamic might be playing out here as well: "It is also quite likely that under natural conditions components of the flea feces other than *B. henselae* may enhance the development of *Bartonella*-induced lympoadenopathy and thus enable the onset of disease at a lower dose of infection in humans" (Kunz et al. 2008). Given the very long evolutionary relationship between ticks and Lyme or fleas and bartonella, it is not surprising that the bacteria have learned to utilize both to assist their infection of new hosts.

Bartonella species, like many infectious bacteria, utilize the immune system of whatever mammal they infect as part of their infection strategy. They essentially use our own body's response to them to promote their agenda. As Graham et al. (2007) note: "The influence of cytokines on effector responses is so powerful that many parasites manipulate host-cytokine pathways for their own benefit," as is indeed the case with bartonellas and mycoplasmas. Most crucially, the authors continue, "The magnitude and type of cytokine response influence host susceptibility and infectiousness. Susceptibility to a given parasite will be affected by cytokine responses that are ongoing at the time of exposure, including responses to pre-existing infections." In other words, the bacteria use the inflammatory processes already occurring in the body (e.g., if

you have preexisting arthritis) to facilitate successful infection. This is more pronounced if infection occurs by more than one organism. Graham's research confirmed that, as the researchers put it, "Coinfection increases the reproductive number for the incoming parasite species and facilitates its transmission through the host population." In other words, while the immune system is often compromised by the cytokine dynamics initiated by one type of bacteria, multiple, simultaneously initiated cascades are more potent in their impacts—infection is much more easily accomplished. In addition, you begin to get assaults on multiple body systems. If bartonella is a coinfection with Lyme, for example, what you then get is assault on and resultant degradation of the collagen systems of the body by the Lyme spirochetes while a simultaneous assault on red blood cells occurs with continual subversion and abnormalization of endothelial cells and their functions. So, the infected person is battling not only Lyme arthritis or neurological Lyme (both caused by collagen degradation) but a red blood cell infection (with potential anemia and lowered oxygen availability in the blood) and abnormal endothelial cell growth in the blood vessels themselves.

But the bartonella bacteria also use what the Lyme bacteria are doing for their own purposes. Once Lyme spirochetes damage collagen tissues, for instance in the joints of the knee, the body sends CD34+ cells to that site to help repair the damage. This is a normal part of the healing process when collagen is damaged. But bartonellas typically invade CD34+ cells, so some of those CD34+ cells will be infected and the bartonellas will take advantage of the local inflammation to establish a colony of their own in that location. The existing inflammation actually facilitates their growth. Once established, they will begin their own cytokine cascade, which will itself contribute to even more collagen degradation at that location.

Were the infected person already suffering a preexisting inflammation in that joint location (as is common in the aged), the process is even easier for the bacteria. The inflammation

would, by itself, stimulate the movement of infectious bacteria to that location.

If you add other coinfectious bacteria to the mix, the picture becomes even more complicated. For example, if *Babesia* bacteria are present then, once bartonella bacteria enter the body, the red blood cells are going to have two organisms infecting them, thus increasing the negative impacts on red blood cells. This is, as Graham et al. (2007) comment, more common than otherwise: "Hosts that are coinfected by multiple parasite species seem to be the rule rather than the exception in natural systems and some of the most devastating human diseases are associated with coinfections that challenge immune response efficacy."

The foundations of this phenomenon are ecological more than anything else. As Graham et al. (2007) observe, "Coinfections could, thus, increase vulnerability to the emergence of new parasites by facilitating species jumps if the coinfected portion of a population provides favorable conditions for an emerging parasite to adapt to a new host species."

Another very fine paper on this subject, by S. Telfer et al. (2010), echoes Graham et al. when its authors note, "In natural populations 'concomitant' or 'mixed' infections by more than one parasite species or genotype are common. Consequently, interactions between different parasite genotypes or species frequently occur. These interactions may be synergistic or antagonistic with potential fitness implications for both the host (morbidity and/or mortality) and parasite (transmission potential)." In other words, if you want to successfully treat someone who is infected with a vector-borne infection you need to realize up front that it is usually the case that coinfection has occurred and you have to look at the interactive picture, not merely single infectious agents—we can no longer assume that bacterial organisms exist in a vacuum. They can't be studied in isolation.

But equally important is the *immune health* of the infected person. Telfer et al. (2010) comment that "there is mounting evidence from experimental studies that the outcome of

interactions during co-infections (for either the host or the parasite) is context dependent, potentially varying with different host or parasite genotypes or environmental conditions. Perhaps most critically, outcome can depend on the timing and sequence of infections… . Susceptibility is a property of an individual host at a given time… . The ability of a parasite to establish an infection successfully will depend on the initial immune response of the exposed host. On entry into the host, a parasite will experience an 'immunoenvironment' potentially determined by both previous and current infections, as well as intrinsic factors such as sex, age, nutritional status and genotype. The immediate immuno-effectors in a naive host will be dominated by cells and molecules that comprise the innate immune response, and thus the efficiency of this arm of host immunity at reducing and clearing an infection will be influential in determining susceptibility."

S. Resto-Ruiz, A. Burgess, and B. F. Anderson (2003) emphasize this as well, as do so many other researchers: "Patients with intact immune function who become infected with *B. henselae* usually [do not experience severe symptoms. However,] the reduced ability of the host's immune response to control bacterial infection apparently results in a bacteremia of longer duration." In other words, the immune status of someone with coinfections *must be* addressed as part of any treatment protocol. Due to the synergistic nature of coinfections an inescapable truth exists: the weaker or more compromised the immune system, the more likely someone is to become infected and the more likely they are to have a debilitating course of illness. Improving the immune status of those with chronic bartonellosis allows the immune system, refined over very long evolutionary time, to do what it does best, which is to use very elegant mechanisms to control and clear infection. Eventually, the healthy immune system begins to identify the outer membrane proteins of the bacteria and create antibodies to them. Due to the sophistication of the bacteria's subversion of the host immune system during coinfections, this can take anywhere from four to eight months. In those whose immune systems are very compromised it may take longer; how long is directly proportional to the health of the immune system. Once the

immune system creates the proper antigens, the bacteria are then eliminated fairly rapidly from the body. Reinfection is difficult as the antibodies remain in the body for some time.

Focus on the immune status of the individual is a crucial element in addressing the treatment of coinfections and it is one that technological medicine is generally unable to address. It is most definitely *not* a subject in which most physicians are trained. Addressing this competently is also made more difficult because the synergy of the coinfections' impacts on immune function also has to be addressed. As Telfer et al. (2010) comment, "Attempts by the immune system to simultaneously counter the multiple parasite species involved in a co-infection can lead to immunopathological disease and pathology that are more than the simple additive pathogenic effects of the different parasite species." This is a crucial point. *The impact of multiple coinfectious organisms is* ***not*** *additive.* They are synergistic. They create effects that are more than the sum of the parts.

For example, infections with both babesia and bartonella are synergistically impactful on red blood cells and can reduce red blood cell counts up to 25 percent, leading to anemia, fatigue, breathlessness, and general weakness. In the immune-competent, neither bacteria will normally create this severe an impact by themselves. (One positive note: because both bacteria are competing for red blood cells, longer studies have found that the babesia bacteria, over time, tend to clear the bartonella infection by outcompeting them. In the initial stages, however, the impact on red blood cells is immense.) Babesias are thought to sequester themselves in the capillary networks of the spleen and liver. Bartonella species sequester themselves in the endothelial cells of the capillary networks of the spleen and liver. Both then seed the bloodstream from those locations at regular intervals. The impacts of infection with both parasites on the spleen and liver are much greater than either alone and this has to be taken into account in any treatment approach. In other words, you have to design spleen- and liver-supportive interventions that are extremely focused on normalizing functioning in those organs. This protects them

from cytokine damage *and* begins to reduce habitat for the bacteria, thus reducing bacterial load and presence in the body.

Telfer et al.'s (2010) research also found that infection with *Anaplasma* (for example) made subsequent infection by *Babesia* much easier—in fact, twice as likely. Reversing the order of infection found the same rate of increase—each organism paves the road for the other. Telfer et al. also found that animals infected with one bartonella species who were also infected by other bartonella species were much more likely to have long-term infections, that is, a chronic illness. As well, an *Ehrlichia* infection, when combined with bartonella (or babesia or a hemoplasma), is often much more severe in the disease impacts than would be expected by looking at either alone. In this situation, both white and red blood cells are infected. Specifically, *Ehrlichia* bacteria infect neutrophils, the most abundant form of white blood cell in the body and an essential element of the innate immune system. Thus the immune system is fighting not only bacteria in the red blood cells and vascular tissues but bacteria inside its own immune cells. To make it worse, the bacteria cross-talk and engage in mutual support of each other, actually enhancing each other's impacts on the host and their resistance to antibiotics.

TREATMENT DYNAMICS

During coinfection with both mycoplasma and bartonella, there are going to be severe effects on the endothelial cells, the red blood cells, and the brain and central nervous system that are out of proportion to infection by either organism alone. Thus the cytokine impacts on those areas of the body are going to be stronger, synergistic, and more debilitating. Thus treatment regimens must be designed to reverse much stronger effects than would occur by either alone. This often calls for larger doses, longer treatment duration, and more sophisticated intervention for symptom management. As only one example, such a double infection *may* cause both a form of regular epileptic seizures *and* periodic bouts of homicidal rage. Herbs that reduce the cytokine cascades involved *and* are specific for these types of seizures *and* are particularly calming to the

nervous system, thus reducing extreme rage events, need to be used and the doses need to be largish, continual, and very focused. (Chinese skullcap is a specific example and it tends to be synergistic with several others such as motherwort and pasque flower that are also specific for these kinds of conditions, though in slightly different ways.)

In my experience, the technological medical community tends to downplay both the impact and occurrence of coinfections in the people they see while the natural medicine community tends to exaggerate it. Oddly, in spite of their training, most physicians don't really understand bacterial organisms very well, nor how to treat them. They tend to look in textbooks (or drug company brochures) for a pharmaceutical that is active for the bacteria in question and apply it, a fairly superficial approach that is increasingly failing in practice. If they have not definitively *identified* the bacterial cause of the condition they will generally prescribe a broad-spectrum antibiotic that will, as often as it helps, do more harm than good (the literature is full of such blunders). They are also very poor at developing a broad, synergistic, and human view of the people they treat, the disease conditions that occur, and the pharmaceutical interventions they commonly use. Most of them stopped *reasoning* a long time ago and simply act as if the worldview they were trained in, in school, really is an accurate map of the world around them—even when current events and research are clearly showing it is not.

The natural medicine community, on the other hand, often tends to be somewhat hysterical about resistant or emerging infections, commonly fails at rigor of analysis, and too often lacks the focus, and courage, needed to confront deadly or life-debilitating infections. Both make too much money off people's suffering—though, in fairness, most (not all) of the alternative community tends to make much less—I just don't see that many herbalists with their own private airplanes. (Nevertheless, overall, the natural medicine community is much safer, irrespective of their level of training—they very rarely kill their patients. *Properly* prescribed pharmaceuticals are the fourth leading cause of death in the United States.)

When approaching the treatment of coinfections, the approach should be depth based with rigor of analysis. The bacterial infections need to be identified (and no, muscle testing is not reliable enough, and no, ELISA is not either—neither should be relied upon as diagnostically definitive).

Once a diagnosis is achieved, a treatment protocol should be initiated. This seems obvious but in the actual world, not the theoretical one in people's heads or in books, most people are not diagnosed competently, or accurately. Many physicians and herbalists (including most naturopaths) simply look at the symptoms and *guess* at what the underlying condition is. In acute conditions where something must be done immediately this is a legitimate approach but *at the same time,* in the background, there needs to be a concerted effort to correctly diagnose. Physicians, counterintuitively, are often not very good at this—as a number of the case studies in this volume make clear. For many of them the problem lies in their internalized paradigms about disease, the structure of their practice, and, frankly, tremendous hubris. Those of us concerned with Lyme and its coinfections have heard scores of stories about physicians insisting that Lyme could not be the cause of a person's symptoms simply because Lyme isn't endemic in that location (so the physician refused to test for it), or that the person had already used antibiotics and the disease was cured so that all the symptoms must now be in their head, or that they just did not have time for the kind of neediness that the Lyme-infected often present. Most physicians are not in the healing business but the pharmaceutical dispensing business—these are not the same things.

Still, it is clear that in some cases antibiotics are very effective and with diseases as debilitating as Lyme and its coinfections they should be considered. However, if that kind of superficial approach fails, then an in-depth understanding of the cytokine cascades and the likely interactions between the coinfections should be developed and a treatment protocol initiated that addresses all that in depth. The most important thing in treating coinfections is to reduce the inflammatory processes the bacteria initiate, basically by counteracting the

cytokine cascade they initiate. That stops pretty much all the symptoms right there especially if treatment protocols are also begun that are designed to protect the areas of the body that are affected. And again, the immune system must be strengthened. As Telfer et al. (2010) observe, "An immune response that effectively cleared the infection from endothelial cells would therefore ultimately control an infection [by bartonella]." Importantly, this observation applies as well to *any* intervention that will protect endothelial tissue from the bacteria, not just immune response. So if you use Japanese knotweed (*Polygonum cuspidatum*) or epigallocatechin gallate (EGCG) as an interventive, abnormal endothelial cell inflammation would cease. The bacteria *can't* survive if they are not able to initiate their particular form of inflammation in the body; it is how they make habitat and scavenge food. If you enhance immune function along with this, the body is then able to deal with the infection on its own. The addition of protocols to reduce acute symptoms and help restore quality of life are also very helpful. Not only does this help support the body's health at that particular location but the quality of life of the infected person is enhanced. The importance of this on outcomes cannot be stressed enough.

And finally, the *human* response of the healer toward the patient is essential. People who are ill *need* deep, caring contact with another human being. It is an essential aspect of healing. Physicians (and herbalists, including naturopaths) who don't take the time for this are, in my opinion, engaging in malpractice of the most egregious sort and, in effect, betraying their duty to their patients. I have continually seen, and numerous studies have found, that this one thing, in and of itself, contributes significantly to the successful resolution of illness. Genuine caring *is* medicine and it is time, more than time, that we, as a culture, recognize that. We absolutely *have to abandon* the paradigm that insists we not touch our patients, that we not love them, that we not spend time with them, that we not act as guides for them on their journey through illness. We must abandon the training, and the teacher, that tells us that we should *not* care, that somehow, as healers, we must keep our emotional distance from those who come to us.

Antibacterials *can* help but comprehensive treatment protocols must be more complex than that simple, monotherapeutic approach. Relying on a "kill the invaders" approach is becoming increasingly ineffective. Soon, if the world's major epidemiologists and researchers are to be believed, it won't work at all.

The bacteria are *evolving.* We should, too.

2

Mycoplasma

An Overview

Mycoplasmas are most unusual self-replicating bacteria, possessing very small genomes, lacking cell wall components, requiring cholesterol for membrane function and growth, using UGS codon for tryptophan, passing through " bacterial-retaining" filters, and displaying genetic economy that requires a strict dependence on the host for nutrients and refuge. In addition, many of the mycoplasmas pathogenic for humans and animals possess extraordinary specialized tip organelles that mediate their intimate interaction with eucaryotic cells. This host-adapted survival is achieved through surface parasitism of target cells, acquisition of essential biosynthetic precursors, and in some cases, subsequent entry and survival intracellularly. Misconceptions concerning the role of mycoplasmas in disease pathogenesis can be directly attributed to their biological subtleties and to fundamental deficits in understanding their virulence capabilities.

JOEL BASEMAN AND JOSEPH TULLY,
"MYCOPLASMAS: SOPHISTICATED, REEMERGING,
AND BURDENED BY THEIR NOTORIETY"

The mycoplasmas enter an appropriate host in which they multiply and survive for long periods of time. These microorganisms have evolved molecular mechanisms needed to deal with the host immune response and the transfer and colonization in a new host. These mechanisms include mimicry of host antigens, survival within phagocytic and nonphagocytic cells, and generation of phenotypic plasticity.

Mycoplasmas are Gram-positive bacteria and they are *tiny*. In fact, some of them approach in size the smallest genome that has been calculated to be theoretically possible. Such is the case with *Mycoplasma genitalium,* a common pathogen of human beings. It is the smallest bacterium known.

To get an idea of just how small: 4,000 mycoplasma bacteria can fit inside one red blood cell; in comparison, only about 12 bartonella bacteria can. And red blood cells are tiny themselves, only about six to eight micrometers in width (a micrometer is a millionth of a meter). Just pretend a red blood cell is the size of the point of a pin (it is actually smaller), then imagine 4,000 bacteria inside that point. That's how small mycoplasmas are.

Mycoplasma Terminology

The common name *mycoplasma* covers the Mycoplasma genus as well as some closely related bacteria in other genera such as *Solobacterium moorei, Spiroplasma mirum,* and *Ureaplasma* spp.

Besides their tiny nature, the mycoplasmas also have some other differences when compared to other bacteria. Bacteria, similarly to us and our skin, have a membrane that covers their interior. This is called the *cytoplasmic membrane*. Most bacteria, over time, learned that that was not enough to protect them, so they created what is called a cell wall to surround them, similar in some respects to our clothes, or more accurately, a latex glove (or even more accurately, a castle wall). Gram-negative bacteria expanded on this innovation and created a double cell wall. This provides even more protection, making Gram-negative bacteria harder to treat. Mycoplasma organisms are unique in that they have *only* a cytoplasmic membrane. In a sort of reverse engineering, they split off from their nearest Gram-positive relatives a very long time ago and began reducing the size of their genome and, in consequence, their physical form. This included getting rid of the cell wall entirely, creating a rather unique form of parasitic organism.

And while Gram staining leads to identification of bacteria because of how the cell wall stains (or doesn't), mycoplasmas are considered to be Gram-positive organisms in spite of not having a cell wall because their DNA makeup shows them to be closely related still to their ancient Gram-positive relatives.

Because mycoplasmas do not possess cell walls they are more flexible physically and can take on a variety of shapes. They can be round, pear shaped, flask shaped, helical, and often possess extended filaments of various lengths. Some of them have complex tip structures that they use to attach to cells, others do not. Some of them can crawl or glide on glass (or on our interior cells) and possess a great deal of motility.

There are over 200 different mycoplasma organisms, but like most coinfectious bacteria, they have only recently begun to be understood. Their incredibly small size, their lack of cell wall, and their very stringent habitat requirements made any research on them very difficult until the past several decades. (They don't like to be grown in captivity.) They are difficult to grow, in part, because of their unique nutritional requirements and tiny genome size. None of the hemoplasmas (a form of mycoplasma) have been grown in captivity as yet and only a tiny minority of all the mycoplasmas have been. None of the plant-specific mycoplasmas have been grown in labs either.

> *Even with mounting evidence of their pervasive and pathogenic potential, mycoplasmas still evoke the image of a group of obscure or impotent organisms. Yet they are evolutionarily advanced procaryotes, and their elite status as "next generation" bacterial pathogens necessitates new paradigms in fully understanding their disease potential.*
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> JOEL BASEMAN AND JOSEPH TULLY, "MYCOPLASMAS: SOPHISTICATED, REEMERGING, AND BURDENED BY THEIR NOTORIETY"

The first mycoplasma was isolated in 1937. In 1950 a bovine (cow) mycoplasma was found. In 1954 the first ureaplasmas were identified. In the 1960s there was enough evidence that these various organisms were finally understood to be unique bacterial forms and were put in their own family. But their role in human disease was still very poorly understood. In the 1970s it was first discovered that certain mycoplasmas had adverse effects in pregnancy. Then in 1980

mycoplasmas that caused male urinary tract infections were found.

It was only in the 1990s that researchers finally learned enough to begin to grow some of them in labs. Then in the 2000s extensive DNA research began to reveal their deeper natures. (This heightened research only occurred because it was accidently discovered that nearly all in vitro culture studies of most pathogenic bacteria had for decades been infected with mycoplasmas, invalidating a lot of research.) As with Lyme and bartonella only in the decade around the millennium did the ability to really work with mycoplasmas begin to take off and produce some deeper understandings of the organisms. (In spite of their relative newness to human understanding, there are already over 20,000 research papers on mycoplasma organisms at PubMed, the free Internet research database. These chapters can only give an overview.)

Because of the growth of DNA analysis, many bacteria that lack cell walls, most considered to be unrelated in the past, are now being included among the mycoplasmas. In fact, they now have their own class—the Mollicutes—and their own family, Mycoplasmataceae.

Mollicute means "soft skin" and refers to the lack of a cell wall while *mycoplasma* itself, oddly, means "fungus formed." An early researcher (1950s) thought the organism he was working with most resembled a fungus (*myco*) and his name for it has, unfortunately, stuck. This often leads to some confusion among the general public; some people believe that the mycoplasmas are fungoid in nature, not bacterial. Others confuse the mycoplasma with another group of bacteria, the mycobacteria, among which is *Mycobacterium tuberculosis*. The mycoplasmas and the mycobacteria are not related.

There are now five orders in the Mollicute class, seven families, fourteen genera, and more than 200 different species. Most of the Mollicutes that cause human disease, with a few exceptions, are either *Mycoplasma* or *Ureaplasma* species. (The exceptions are *Solobacterium moorei* and *Spiroplasma mirum*.)

Mycoplasmas are widely present throughout nature, infecting mammals, reptiles, fish, arthropods, and plants. There are a great many more than the 200 that have currently been identified. As Razin, Yogev, and Naot (1998, 1097) comment, the numbers of "mollicutes that have already been characterized and taxonomically defined constitute only a part, apparently a minor one, of the mollicutes living in nature." All mycoplasmas, irrespective of host, whether animal or plant, cause similar diseases. All of them are commonly (though not always) transmitted by insects.

Of the 200-plus currently known mycoplasmas (more are being discovered all the time) 29 have been found to infect human beings; at this point 23 of those are known to cause human illness. However, these numbers, as with the number of mycoplasma species, are increasing rapidly. As research tools (and researchers) become more sophisticated, mycoplasmas are being found to be common sources of disease, much more so than previously thought.

Formerly, mycoplasmas were thought to primarily infect the respiratory and the genitourinary tract. And it is true that they have a predisposition for those locations. But it is becoming increasingly clear that systemic infections are much more common than formerly thought. Ultimately, mycoplasmas can infect *any* organ of the body and it is becoming widely recognized, among researchers at any rate, that these bacteria are at the root of many chronic diseases whose origins have been confusing, for example rheumatoid arthritis and certain forms of cancer.

Too, the action of mycoplasmas inside the body is much more complex than originally thought. It was formerly speculated that the mycoplasmas infected *only* the surface of cells, however it is now known that most (and probably all) mycoplasmas also exist intracellularly where they easily reproduce and are more effectively protected from host immune responses and antibiotics. And they are common: they can be transmitted through insect bites, open wounds (however tiny), inhalation, ingestion, and sex.

The primary mycoplasmas that cause human disease that have been studied in some depth are (in descending order) *Mycoplasma pneumoniae, M. genitalium, M. hominis, M. fermentans, Ureaplasma urealyticum, U. parvum,* and *M. penetrans*. These are considered to be the primary human-disease-causing mycoplasmas.

Other mycoplasmas that cause human disease but are less common (at least in researchers' opinions) as primary human-disease agents are *Mycoplasma pirum, M. salivarium, M. haemofelis, M. ovis, M. haemohominis, M. suis, M. arginini, M. arthritidis, M. edwardii, M. pulmonis, M. orale, M. faucium, M. hyorhinis, M. amphoriforme, Solobacterium moorei*, and *Spiroplasma mirum*.

Other mycoplasmas are known to infect humans but are not yet known to cause disease. They are *Mycoplasma primatum, M. spermatophilum, M. laidlawii, M. buccale, M. lipophilum,* and *M. oculi* (a.k.a. *M. bovoculi* and *Acholeplasma oculi*). In fact, most mycoplasmas were, at one time, thought to be commensal bacterial organisms. That is, bacteria that infect us but that are benevolent and cause no harm. Given the historical ignorance of mycoplasma involvement in human disease, the infectious and disease-causing nature of this last group of mycoplasmas can't be ruled out. For instance, though not yet implicated in specific disease conditions itself, *Mycoplasma laidlawii* has been found to bind to the HIV virus and accelerate its entry into human cells. This finding is suggestive in that it is very similar to some of the early research on other mycoplasmas that are now known to be disease agents in humans. As well, *M. spermatophilum* has been found in the gastric mucosa of people suffering from chronic gastritis though it has not been linked to that disease. It is a common bacteria on sperm (hence its name) and the surface of the cervix and quite likely it is involved in diseases in those locations as many other mycoplasmas are. *M. oculi* has been found to possess procoagulant activity, which could mean it is involved in the kinds of coagulant vascular disorders many mycoplasmas cause. Most of this last group of mycoplasmas, should they prove to be virulent, can be treated much as the other mycoplasmas in this book are.

Erysipelothrix rhusiopathiae was, for a while, included in the mycoplasma grouping (it was somewhere else before that) but has now been moved, once more, to a different family. (Why have taxonomy anyway?) It can cause a variety of diseases such as erysipelas and sometimes septicemia, endocarditis, pneumonia, acute meningitis, peritonitis, septic arthritis, granulomatous cheilitis, Baker-Rosenbach erysipeloid, intra-abdominal abscess, erythematous-violaceous lesions, severe aortic regurgitation, and so on. It has been commonly believed to be a disease organism limited to pigs but like so many other medical bacterial beliefs that is now known to be incorrect. *E. rhusiopathiae* can be found in over 50 different animals including humans. It is *not only* transmitted through contact with farm animals. It can be treated much as the mycoplasmas in this book are but I won't go into depth on it as it is not now considered to be a mycoplasma. (If they move it back again, I will have angry feelings and update the book.)

What is true is that the numbers of mycoplasma species that do cause human infection are much greater than has been historically realized. As understanding of this group of bacteria grows such awareness is unavoidable—they are significant agents of human disease. And the diseases they cause cross a wide spectrum from mild respiratory infections to cancer. While many mycoplasma infections are mild and self-limiting, some exist as low-grade chronic conditions for decades. Research is finding that the longer such a chronic mycoplasma infection lasts, the worse the impact on the health of the person. A few examples: long-term chronic mycoplasma infection is now known to stimulate the formation of particular forms of cancer (including Hodgkin's disease), mycoplasma infection is now known to be one of the primary causes of rheumatoid arthritis, and chronic mycoplasma infection is a common cause of infertility in men and women.

THE DISEASES MYCOPLASMAS CAUSE

Here is an overview of the mycoplasmas that are known to cause diseases in people.

Mycoplasma pneumoniae

Although *M. pneumoniae* can infect *any* part of the body, its primary colonization site is the ororespiratory tract. The disease it most commonly causes is pneumonia (hence its name).

Up to 40 percent of all non-hospital-acquired pneumonias are caused by the organism. Twenty percent of those admitted to hospitals with pneumonia suffer from it. *M. pneumoniae* causes 50 percent of all pneumonias in school-age children; it is the primary cause of what is called "walking pneumonia"; it is most severe in children under five years of age—they experience a 67 percent hospitalization rate. *M. pneumoniae* is a common coinfectious agent in many of the pneumonias caused by other bacterial and viral organisms. (And when it is, it acts synergistically, making the illness worse and treatment more difficult.)

The incubation rate can take anywhere from a few days to three weeks. It is primarily transmitted through close contact with people who are infected, usually through coughing. Epidemics of *M. pneumoniae* tend to be cyclical (no one knows why) and occur every four to seven years, often from May through July. (No one knows why that happens either.)

M. pneumoniae can affect both the upper and lower respiratory tract. Symptoms can persist for months. The early signs are usually pharyngitis (sore, inflamed throat) and hoarseness—typical of most colds and flus. But an intractable cough, occurring day and night, soon begins. And that is just the start. Once the disease really sets in, the symptom list gets longer: fever, cough, malaise, headache, intractable sore throat, chills, earache, coryza (nasal and sinus mucous membrane inflammation), diarrhea, nausea/vomiting, chest pain, lymphadenopathy, skin rash, conjunctivitis, and otitis media/myringitis.

Fever, cough, malaise, and headache are the most common symptoms and occur in nearly every case of infection. Fifty percent of those infected will have upper respiratory tract manifestations including pharyngitis and tracheobronchitis. One-third will present with symptoms in the ear: otitis externa, otitis media, and myringitis.

Infection outside the ororespiratory tract is unfortunately common. Up to 25 percent of those with a *Mycoplasma pneumoniae* infection will experience extrapulmonary complications. In fact, it is often the case that someone will clear the respiratory infection and then, seemingly unrelatedly, will begin experiencing a quite different set of symptoms in other parts of the body. Some people who are infected will experience systemic infections with no pulmonary involvement at all. Here is a list of the nonpulmonary complications that are known to occur.

Ocular (eye) infection, most often in children: Conjunctivitis, anterior uveitis, optic neuropathy, retinitis, retinal hemorrhages, iritis, ocular myasthenia gravis, and optic disk swelling. There can sometimes be permanent damage to the vision.

Ear involvement: Sudden hearing loss, tinnitus.

Cardiac complications: These occur in up to 10 percent of those infected and include heart failure, myocarditis, pericarditis, pericardial effusion, cardiac thrombus, Kawasaki's disease, temporal arteritis, and acute myocardial infarction.

Neurological problems: About 7 percent of people who are infected with this particular organism get neurological problems, and up to 80 percent of those have had *no* (or very mild) pulmonary involvement. The central nervous system (CNS) is often directly infected, oftentimes quite severely. Demyelination of the nerve sheaths is common.

Common neurological symptoms are chronic fatigue, encephalitis, aseptic meningitis, meningoencephalitis, cerebellar ataxia, severe hemorrhagic leukoencephalitis, polyradiculitis, transverse myelitis, Guillain-Barré syndrome, cranial and peripheral neuropathies, optic neuritis, diplopia, stroke, striatal necrosis, psychological disorders, facial nerve palsy, mental confusion, acute psychosis, and coma. The organism has been linked to Tourette's syndrome; over half of those with Tourette's have been found to be infected.

Infection of the CNS can be fatal in up to 10 percent of

cases and 25 percent experience chronic problems in mental and motor function even after the infection is resolved. Recurrent seizures, similar to epilepsy, can sometimes occur. If there is CNS involvement during infection with *Mycoplasma pneumoniae* there is a seven times greater chance of death or permanent disability when compared to other types of CNS infections (such as Lyme or bartonella). It is very common in those with ALS (amyotrophic lateral sclerosis) and there is speculation that it may be a primary cause of that disease.

> *The consistency with which* Mycoplasma pneumoniae *has been implicated as a cause of encephalitis, and the increased incidence of central nervous system (CNS) disease observed during M.* pneumoniae *outbreaks, support the role of* M. pneumoniae *as a CNS pathogen.*
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> A. BITNUN AND S. E. RICHARDSON, "MYCOPLASMA PNEUMONIAE: INNOCENT BYSTANDER OR A TRUE CAUSE OF CENTRAL NERVOUS SYSTEM DISEASE?"

Hematological (blood) symptoms: Hemolytic anemia, intravascular coagulation, aplastic anemia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, arterial thrombosis, Raynaud's syndrome, and splenic infarct. Vasculitis is common. The organism has severe impacts on the vascular system and is a major cause of vasculitic disorders.

Gastrointestinal symptoms: These occur in about 25 percent of those infected and can include nausea, vomiting, abdominal pain, diarrhea, loss of appetite, cholestatic hepatitis, and pancreatitis.

Renal (kidney) symptoms: Glomerulonephritis (usually membranoproliferative). This is when the part of the kidneys that is supposed to filter waste and fluids is damaged. In essence, there is damage to the cellular structure of the kidneys caused by inflammation and intrusion of immune complexes and bacteria deep into the cellular tissue.

Bone, joint, and muscular symptoms: Mycoplasma pneumoniae is one of the main causes of rheumatoid

arthritis. It is also one of the primary causes of adult-onset Still's disease (a kind of inflammatory arthritis). Successful treatment of the bacteria can result in complete remission of both conditions. In both situations, there is a breakdown of the synovial tissues in the joints and a lot of pain.

Myalgia, arthralgia, and polyarthropathy occur in about 15 percent of those infected. Rhabdomyolysis has also been reported, which is a breakdown of muscle fibers that leads to the release of muscle fibers into the blood. This often contributes kidney damage.

Dermatological symptoms: These are very common, about 25 percent of people get them. Normally they are self-limiting. Rash, urticaria (hives), and pityriasis rosea are fairly common. This bacteria is the main cause of rashes (erythema) that occur during pneumonia (in up to 84 percent of cases). It is the main infectious cause of Stevens-Johnson syndrome (a rather nasty condition also called toxic epidermal necrolysis that usually occurs from taking pharmaceuticals). In the immune-compromised, dermatological symptoms are often much worse.

Mycoplasma hominis, M. genitalium, Ureaplasma urealyticum,* and *U. parvum

All four of these organisms, with some differences as noted below, tend to produce similar disease pictures. they can infect any part of the body but their primary colonization site is the urogenital tract. they have been implicated in up to 20 percent of men and women with urethritis and 20 percent of women with cervicitis. they often cause male urethritis, prostatis, epididymitis, urinary calculi, pyelonephritis, bacterial vaginosis, cervicitis, pelvic inflammatory disease, infertility, chorioamnionitis, intrauterine growth retardation, spontaneous abortion, postpartum/postabortion fever, and extragenital disease. in infants they can cause meningitis, encephalitis, pericarditis, chronic lung disease, prematurity/low birth weight, and brain abscesses.

Additional specifics on each of them are provided below.

The natural habitats of human and animal mycoplasmas are the mucous surfaces of the respiratory and urogenital tracts, the eyes, alimentary canal, mammary glands, and joints.

S. RAZIN, D. YOGEV, AND Y. NAOT, "MOLECULAR BIOLOGY AND PATHOGENICITY OF MYCOPLASMAS"

Mycoplasma hominis

M. hominis has been found present in about 10 percent of women with pelvic inflammatory disease, usually accompanying chlamydial or gonococcal infections (with which it is synergistic). It is common in at least 10 percent of women with postpartum or postabortal fever. It is very common in women that experience premature labor, spontaneous abortion, and severe chorioamnionitis—that is, a bacteria-caused inflammation of the fetal membrane. It can cause scalp abscesses in newborns. It is the cause of two-thirds of all cases of bacterial vaginosis. It is the cause of at least 5 percent of all cases of pyelonephritis—that is, bacterial infections in the urinary tract that ultimately reach, and infect, the kidneys.

Besides the common urogenital problems it causes, when *M. hominis* becomes systemic it has also been found to cause septicemia, wound infections, central nervous system infections, brain abscess, parapharyngeal abscess, meningitis, joint infections, septic arthritis, prosthetic joint infections, rheumatoid arthritis, upper and lower respiratory tract infections, pneumonia, chronic fatigue, and endocarditis. It is very common in those with ALS (amyotrophic lateral sclerosis) and there is speculation that it may be a primary cause of that disease.

The organism, asymptomatically, is common in about 3 percent of the population and in about 15 percent of people who have engaged in orogenital sex. It has been found in about 10 percent of people with respiratory complaints.

M. genitalium

M. genitalium has been found in about 1 percent of all women and is considered to be one of the newest of the emerging sexually transmitted diseases. The bacteria can adhere to sperm and travel into women during sexual intercourse, subsequently infecting them; it can travel from the woman into the man during intercourse as well, moving up the penis, deeper into the system. It can also be transmitted during oral sex. About 5 percent of men who have chronic prostatitis are infected. And it has been found to be a possible cause of

epididymo-orchitis—an inflammation of the testicles and the epididymis (this is the cluster of tubes attached to the testicles inside the scrotum). It has been linked to various reproductive cancers. It can also cause rheumatoid arthritis. Common symptoms are urethritis, discharge, burning on urination, vaginal itching, and pain during intercourse.

Ureaplasma urealyticum* and *U. parvum

The ureaplasmas are the most common bacteria in the urogenital tract. Fifty percent of all men carry them, 5 percent of children, 40 percent of sexually *inactive* women, 67 percent of sexually active women, and 25 percent of postmenopausal women. During pregnancy up to 82 percent of women have been found to be infected.

Infertile couples have twice the infection rate as fertile couples. Women who receive pregnancy care in hospitals are at extreme risk of systemic infection from the bacteria—it is commonly spread on hospital equipment, especially on catheters, surgical instruments, and hands. Any break in the skin will let it deeper into the system. The organism has been found in 62 percent of women with laparotomy incisions. It is a significant predictor of postpartum endometritis; the risk for infection is threefold in those who are delivered by caesarean and eightfold in those who experience a spontaneous birth (that is, not planned). It has been found in newborns in the auditory canal, nasopharynx, trachea, stomach, vagina, anus, blood, and cerebrospinal fluid. Premature infants are most at risk for problems such as intraventricular hemorrhages, respiratory distress syndrome, bronchopulmonary dysplasia, and long-term illness.

The bacteria strongly affects the sperm membrane and reduces sperm motility and sperm count. It is common in men with orchitis, epididymitis, spermatocystitis, prostatis, and urethritis.

Ureaplasmas can cause the formation of struvite kidney stones because of their ability to metabolize urea. This increases the amount of ammonia in the urine and urinary tract and stimulates the precipitation of magnesium ammonium phosphate, i.e., struvite kidney stones.

It has also been found in joint inflammations and is linked, like many of the mycoplasmas, to rheumatoid arthritis.

M. fermentans

There are a number of different strains of this organism. *All* cause human infection and there is really not that much difference between the strains. The *incognitus* strain however is the most commonly discussed, the most studied, and the most commonly thought to be a primary human pathogen.

This mycoplasma has been found in the upper and lower genital tracts, the upper and lower respiratory tracts, the bone marrow, synovial fluid, and amniotic fluid. It can cause pneumonia, rheumatoid arthritis, temporomandibular joint damage, chorioamnionitis, cancer, leukemia, chronic fatigue, periodic fevers, fibromyalgia, memory loss, headaches, diarrhea, depression, irritability, chronic bronchitis, abdominal bloating, chronic gastritis, skin rashes, and in AIDS patients necrotizing lesions on multiple internal organs. Fulminant infection in non-immunecompromised people has been reported. It is very common in those with ALS (amyotrophic lateral sclerosis) and there is speculation that it may be a primary cause of that disease. The organism has been found to facilitate the HIV virus in both penetration and activation. It has been linked to mycoplasmal cancer, especially in gastric tissues.

Roughly half of all U.S. soldiers in the first Iraq war tested positive for the organism; it has been strongly linked to Gulf War syndrome.

M. penetrans

This organism was first identified in men with HIV. Its major distinction among the mycoplasmas is that it has been commonly found *inside* human cells where it is relatively safe from both the immune system and antibiotics. (Hence its name.) This particular mycoplasma, because of its movement inside host cells, stimulated a closer look at the mycoplasmas. It has since been discovered that most if not all the mycoplasmas also penetrate human cells and exist intracellularly.

M. penetrans is most commonly found in those with HIV, however it has been found in the non-HIV population where it is being increasingly recognized as a common disease pathogen. It causes a hypercoagulable state (primary antiphospholipid syndrome) that provokes blood clots in arteries and veins. It can cause anemia, primary antiphospholipid syndrome, urethritis, respiratory disease, severe respiratory distress, rheumatoid arthritis, and bacteremia. It has commonly been found in the blood of those with severe chronic fatigue and is suspected as one of the major causes of that condition. It is very common in those with ALS and it may be a primary cause of that disease (along with just about every other mycoplasma). The organism has been found to facilitate the HIV virus in both penetration and activation (along with numerous other mycoplasmas).

It has a major impact on the sexual health of both women and men. It can cause stillbirth, miscarriage, preterm delivery, or severe preeclampsia in women. It is a cause of vulvovaginitis in prepubertal girls and has been found in 6 percent of women tested in Nigeria—apparently a not uncommon percentage in all populations. It attaches to semen and is thought to have a role in low sperm counts. While generally thought of as something that accompanies AIDS, the organism is commonly present in urogenital testing in both women and men. It is apparently a pretty common STD.

Mycoplasma penetrans may occupy an intermediary state between the hemoplasmas (hemotropic mycoplasmas) and the nonhemotropic mycoplasmas. It *can* be both a hemotropic mycoplasma and a nonhemotropic mycoplasma. It does have an affinity for red blood cells and can cause anemia and lysis of red blood cells, usually within two to three days of infection.

Solobacterium moorei

This is a common bacteria of the mouth and one of the causes of bad breath (halitosis). However, it has been found to be a bacterial cause of peridontitis, root canal infections, infection in dental implants, osteonecrosis of the jaw, wound infections, septicemia, bacteremia, proctitis, and thrombophlebitis.

M. salivarium

Like *Solobacterium moorei* this is a common bacteria in the mouth (hence its name). It can cause diseases in that location such as disorders of the temporomandibular joints (anterior disk displacement, pain), gingivitis, peridontitis, and jaw (submasseteric) abscesses but it can also go systemic. It has been found to cause pleural space infections (empyema), cancer (including ovarian), brain abscesses, arthritis (rheumatoid and non-), and chronic gastritis. It has been found in occluded biliary stents as a primary pathogen.

M. orale

Again, this is a common bacteria in the mouth. It disrupts both calcium and potassium ion currents in the salivary glands resulting in hyposecretion of saliva. It may infect the synovial fluid in the temporomandibular joint (TMJ) causing reactive arthritis in the TMJ either by itself or synergistically with other bacteria. It has been found in the synovial fluid of those with rheumatoid arthritis. It can cause abscesses, destructive bone disease (it has been found in the bone marrow), and chronic gastritis.

Spiroplasma mirum

This organism can cause cataracts, neurological damage, and certain encephalopathies similar to mad cow disease. It is emerging as a rather serious pathogen.

Mycoplasma pirum

This organism is common in AIDS patients but also causes urogenital infections, respiratory infections, and chronic fatigue in the non-immune-compromised.

M. faucium

This has been found to cause cerebral abscesses and chronic gastritis.

M. amphoriforme

This organism was first isolated from an AIDS patient with chronic bronchopneumonia in 2003 and subsequently cultured from three other AIDS patients with bronchial symptoms,

including chronic bronchitis. It was eventually found in the non-immune-compromised as well—two adults and one child with respiratory infections in 2009—and is suspected to be the primary infectious agent in one case of respiratory infection with sepsis. It is not known at this point whether or not it causes systemic infections (it probably does) but its respiratory picture is similar to that of *M. pneumoniae,* with which it is closely related.

M. arginini

The first human infection by this mycoplasma (which is normally found in sheep, cattle, goats, and cats) was found in an employee of a slaughterhouse who was experiencing bacteremia and multiple organ and tissue infection. He was immune-compromised (hypogammaglobulinemic) and had advanced Hodgkin's lymphoma, which made him particularly susceptible.

M. arginini is also common in chronic gastritis, is closely associated with ovarian cancer, and has also caused severe eosinophilic fasciitis. In the latter case, it was accompanied by skin lesions, progressively worsening over 19 months, and by recurrent fevers and urethritis in a previously healthy 23-year-old man. He was infected with multiple mycoplasma organisms. Urethra cultures were positive for *M. arginini* and *Ureaplasma urealyticum*. He had serum antibodies to *M. pneumoniae*, and *M. arginini* was isolated in blood samples and in skin lesions.

M. edwardii

This mycoplasma was identified as the cause of septicemia in an advanced AIDS patient.

M. hyorhinis

This is normally a mycoplasma species found in pigs; however, four different studies have found it present, and implicated, in cancer in people. It has been found in gastric, ovarian, prostate, and colorectal cancer tissues, and in cervical condyloma tissue. Laboratory study has confirmed that is stimulates cancer formation in these kinds of cells. This

species has also been found to be relatively common in those with peptic ulcers.

M. arthritidis

Normally this organism infects mice and rodents, in whom it causes chronic joint inflammations and infection of ocular ciliary body cells, but it has been found upon occasion in people with rheumatoid arthritis. It has been isolated from the human genital tract, synovial fluid, bone marrow, and lymph nodes.

M. pulmonis

This organism normally infects rats and mice but it has been found in people who have a lot of contact with rats and mice (lab technicians). It generally causes pulmonary symptoms (hence it name) similar to *M. pneumoniae*.

The Hemoplasmas

There are three groups of these particular mycoplasmas: those previously considered to be *Haemobartonella* species, those once considered to be *Eperythrozoon* species, and the newly discovered that were put in the mycoplasma grouping from the day they were found. As with the mycoplasmas in general, there are more being discovered all the time. There is as yet some degree of unclarity about how these bacteria should be named. For example, sometimes they are denoted with a *haemo-* prefix in front of the species name (e.g., *Mycoplasma haemofelis*). Other times the prefix is left off (e.g., *Mycoplasma felis*).

The main ones appear to be *Mycoplasma haemofelis* (formerly *Haemobartonella felis*—infects cats), *M. haemomuris* (formerly *Haemobartonella muris*—infects rodents), *M. haemocanis* (formerly *Haemobartonella canis*—infects dogs), *M. haematoparvum* (for merly *Eperythrozoon parvum*—infects pigs), *M. coccoides* (formerly *Eperythrozoon coccoides*—infects mice), *M. suis* (formerly *Eperythrozoon suis*—infects pigs), *M. wenyonii* (formerly *Eperythrozoon wenyonii*—infects cattle), *Mycoplasma haemobovis* (a.k.a. *M. haemobos*—cattle), *Mycoplasma bovis* (cattle), *Mycoplasma teganodes* (a.k.a. *Eperythrozoon teganodes*—cattle), *Mycoplasma tumoii* (a.k.a. *Eperythrozoon tumoii*— cattle), *Mycoplasma ovis* (sheep and goats), *Mycoplasma haemominutum* (cats), *Mycoplasma turicensis* (cats), *Mycoplasma haemodidelphidis* (opossums), *Mycoplasma mariboi* (a.k.a. *Eperythrozoon mariboi*—flying foxes), *Mycoplasma kahaneii* (primates), *Mycoplasma haemolamae* (alpacas and llamas), and *Mycoplasma haemohominus* (people).

They are generally thought of as belonging to two different largish groupings, the *haemofelis* group and the *haemominutum* group. Not

all of them have been found to infect people but enough have to indicate that they can easily jump species (as most mycoplasmas do). Nearly all of these infect animals in close contact with people; there is significant evidence that there is common transference from the primary animal host to people.

Wild populations of animals unrelated to people have not been examined in any depth as yet. There is every reason to suspect that the hemoplasmas are widespread in the animal world; their numbers are bound to increase substantially.

All of them are hemotropic, that is, attracted to red blood cells. They latch onto erythrocytes to gather nutrients, damage the red blood cells in the process, and cause anemia, jaundice, fatigue, breathlessness, and sometimes death. Infection is often asymptomatic unless the animal has low immune function or the organisms jump into a different host species. The bacteria tend to sequester in large quantities in the spleen and have been found in the lymph system, including the nodes, and in bone marrow. They periodically move from those locations into the blood to scavenge more red blood cells. They were once, as usual, believed to rarely enter inside the blood cells themselves but it is now recognized that they also exist intracellularly. Studies with porcine hemoplasmas have found them to be, as is the case with other mycoplasmas, sequestered in large numbers inside erythrocytes, where they are protected from host immune responses.

They often cause lysis or the breaking apart of the red blood cells as they scavenge nutrients, but the host immune system has also been implicated in this if the numbers of hemoplasmas are high on the surface of blood cells. Cold agglutinins, a type of antibody, can be stimulated during surface infection of the red blood cells, and those antibodies can begin to actively destroy red blood cells to combat the disease, causing anemia and sometimes death. *If the spleen is removed or damaged in those asymptomatically infected, the infection becomes acute very rapidly.* They are spread by arthropod vectors such as ticks, fleas, biting flies, and so on. They are extremely hard if not impossible to cultivate in laboratories.

Only four of the hemoplasmas have been found to infect humans so far: *M. haemohominus, M. ovis, M. haemofelis,* and *M. suis*. This number is almost certainly going to increase substantially over time.

M. haemohominus

This hemoplasma was discovered in 2011. Little is known about it as yet. It was found in a woman in England who presented symptoms of chronic moderate neutropenia (abnormally low white blood cell counts), acute hemolysis (rupture of red blood cells), anemia, enlarged liver and spleen, thrombocytopenia (with resulting bruising and easy bleeding), fever, abdominal pain, joint pain, night sweats, and weight loss.

The hospital treatment was poor; the mycoplasma infection was not identified. Hepatic arterial bleeding occurred during liver biopsy (which necessitated laparotomy), renal failure soon occurred, then pneumonia. The woman was treated with piperacillin-tazobactam, doxycycline, and prednisolone for five days; symptoms resolved and she was discharged. Twenty-one days later she readmitted with lightheadedness, nausea, petechiae on the legs, anemia, thrombocytopenia, and fever. Transfusions were necessary as no pharmaceutical treatment helped. Eventually doxycycline was again used (100 mg 2x daily, oral) and again symptoms began to resolve. Bone marrow samples were taken and found to be infected with a novel mycoplasma species. Using veterinary guidelines (as this mycoplasma was genetically similar to several common to veterinary practice) doxycycline was continued for three weeks. Seventeen days after stopping the doxycycline symptoms returned: nausea, vomiting, sweats, hemolysis, anemia, fever, and liver/spleen enlargement. Doxycycline was again prescribed and improvement was seen within 24 hours. After eight weeks of doxycycline the blood still showed the presence of a unique mycoplasma so moxifloxacin was added (400 mg once daily). The patient took this combination for another six months before becoming negative for mycoplasma. One year later she was still free of the organism but had lingering polyarthralgia (multiple locations of joint pain) and a low white blood count. The woman, it turns out, had had a history of low immune function as determined by chronic low white blood cell count tests.

This is a good example of how focused treatment has to be when working with mycoplasmas in general and hemoplasmas in particular. Unfortunately, this exact progression (and regression) in hemoplasma treatment occurs fairly frequently in hospital settings. It can be laid to two problems: 1) failure to correctly diagnose, often due to incorrect information about the common nature of mycoplasmas, and 2) ineffective treatment approach, specifically failure to understand the necessity for long-term treatment.

M. ovis

Though it is normally found in sheep, a veterinarian in Texas was found to be infected with two strains of this bacteria as well as coinfected with bartonella. *M. ovis,* especially with a concomitant bartonella infection, can cause acute or chronic anemia, jaundice, and fatigue. It has strong impacts on pregnancy.

M. haemofelis

Though *M. haemofelis* was once thought to be limited to cats and their fleas, it is now known that, similarly to bartonella, cats, fleas, and flea feces can transmit it to people. Not a lot of study has occurred on this species but it has been found to cause soft tissue cellulitis in cat owners through bites. Septic arthritis transmitted through a cat bite has also been reported in a person that was immune-compromised (hypogammaglobulinemic).

Mycoplasma suis

This mycoplasma normally infects pigs but is being routinely found in swine-farm workers in China. Nearly half of all swine-farm workers tested (32 of 65) were found to be positive for the organism. The most common symptoms are easy bleeding, fever, and anemia. It is most probably somewhat common in the rest of the world, especially in hog farms and their workers. Few people have been tested for it.

NUTRIENT SCAVENGING AND HOST SPECIFICITY

As with Lyme and bartonella, much of what has been assumed to be true about the mycoplasmas is not.

Mycoplasmas, because they have so significantly reduced their genome, lack many of the metabolic pathways necessary to synthesize crucial cell components and generate energy. They are dependent on nutrients that they scavenge from their hosts. Again, as with Lyme and bartonella, mycoplasmas use highly sophisticated strategies, developed over long evolutionary time, to scavenge what they need from their hosts. (This is explored in depth in the next chapter.)

The different species of mycoplasma have tended to pick hosts that they prefer. In other words, they adapted themselves

to most easily infect and scavenge what they needed from specific host species. This led scientists to definitively state that mycoplasmas are host specific (as they did with bartonella). Unfortunately this is just not true. Mycoplasmas are highly adaptable and can rather easily jump species and rearrange their genome structure to accommodate life in the new host. While most people focus on the jump of mycoplasmas from animals closely associated with people (dogs, cats, cows, sheep, and so on) some research has shown the possibility of a jump from plant mycoplasmas (phytoplasmas) to humans, which, it is important to remember, already occurred long ago. The plant mycoplasmas are the oldest of the genera, the animal mycoplasmas came much later.

> *The mollicute chromosome is a genetically dynamic structure that undergoes frequent rearrangements, insertions, deletions, and inversions of genes or entire genome segments.*
>
> S. Razin, D. Yogev, and Y. Naot, "Molecular biology and pathogenicity of mycoplasmas"

Usually, mycoplasmas and their hosts are fairly well adapted to each other. It makes no sense for a parasitic organism to kill off the host it needs to survive. It appears that mycoplasmas and their hosts are, like many other bacteria in and on our bodies, mutualistic organisms. In other words, they each give something to the other. This occurs most often within our bodies but it can also occur in the larger ecosystem itself.

Some research on mycoplasmas and their hosts (which include a large range of both animals and plants) has found that this relationship lends a tremendous stability to both organisms. Mycoplasmas have been found to provide protection for their host species from other, competing species. For instance, when other animals enter the ecorange of their main host species, disrupting their balanced presence in that area, some of the mycoplasma organisms will jump into the competing species. Once they do, they tend to cause severe illness, killing off the competing species, thus helping to eliminate a species that may be a danger to their host group.

The mycoplasmas tend to affect, irrespective of mycoplasma species, the ability of the competing organisms to reproduce, to breathe, or to walk. All species are highly effective in reducing the numbers of competing organisms.

Mycoplasmas, as already mentioned, tend to jump in large numbers into new species when the ecological habitat they formerly inhabited in relative peace has been significantly disrupted—in this case, through forest clearing, overbuilding, and increasing human presence.

The mycoplasmas tend to cause disease in their preferred host species only when an individual's immune system is malfunctioning. In an ecological sense, the bacteria reduce the numbers of less fit members of the species much like wolves hunting and catching the sicker members of a deer herd.

In general, if the immune system is kept healthy, the organisms, which are present in most people, live in a relatively disease-free balance with their hosts.

MYCOPLASMA AWARENESS: CONTAMINATION OF CELL LINES AND HIV

Public assumptions about the nature of bacteria are still very misguided and they have come from the unfortunately simplistic paradigms of medical scientists of the mid-twentieth century. Buckminster Fuller once commented, correctly, that the information taught students in the U.S. school system, on average, runs 50 to 100 years out of date. Most people, and many physicians, still think that bacteria are unintelligent, that they are very well understood by science, and that "modern" medicine is in a superior position when it comes to dealing with them. This is not very accurate.

Most people do not realize that there are hundreds to millions of different kinds of bacteria that have not yet been discovered, that many of the ones that are known have never been examined for their role in human disease, that common medical substances such as the cell lines used for research or blood stocks are never tested for the presence of scores of bacteria or viruses (it has just been assumed they are not

present), or that antibiotics are increasingly useless against many bacteria.

Mycoplasmas possess some unique behaviors. One is that they can (and have) found ways to grow in many of the cell cultures used by scientists during routine research. Up to 87 percent of cell cultures have been found to be infected. In consequence researchers have spent years doing research on hundreds of different projects unaware that their results were contaminated and that, as a result, the results were skewed, often considerably. Mycoplasmas in cellular cultures do not cause turbid growth as most other bacteria do, so they remain relatively invisible to the eye. As well, their impacts on the cells themselves tend to be subtle. They cause alterations in the cells that are so subtle in fact that they do not appear to be from bacterial contamination—often the alterations have been attributed to the research itself.

Once someone discovered mycoplasma contamination in a cell culture being used for research, and as knowledge of it spread, examination of cell cultures for mycoplasmas was conducted in some depth. Such contamination was found to be very common. Because of the impacts this had on decades of research (making much of it useless) mycoplasma research itself was begun in earnest. Researchers had to understand how to test for mycoplasmas, identify the species found, and learn how to decontaminate cell cultures. This led to tremendous growth in mycoplasma knowledge.

The second major stimulus for mycoplasma understanding came, as it has with so many other diseases, from AIDS.

AIDS has changed medicine, and the medical paradigm, in a number of significant ways. Perhaps the major one is that it has significantly increased understanding of the importance of the immune system and its relation to disease onset. As with bartonella and Lyme, mycoplasma infections have been found to be highly responsive to the health of the individual's immune system. In other words, if immune health is high, then either the mycoplasma organisms will be prevented from causing infection entirely or else the disease itself will be mild. The more depleted the immune system, the worse the disease

that develops. As researcher Mark Lappé (1986, xviii) has commented, "It is the *body* which ultimately controls infections, not chemicals. Without underlying immunity, drugs are meaningless."

Many of the disease-causing mycoplasmas were only discovered because the diseases they caused were so virulent in those with AIDS. The physicians knew something was causing the problem even if they could not find it. Because of the huge investment in AIDS research, they took the time and eventually found the organisms that were responsible. They then began to look at milder versions of those same diseases in non-AIDS populations to see if the organisms were present there as well. And what do you know? They found them.

AIDS taught physicians that no matter what they did, no matter what drugs they used, if the body itself could not mount an immune response, then the disease could not be either controlled or eradicated. When treating any mycoplasma infection working with immune health is essential.

INCIDENCE OF INFECTION AND DURABILITY OF THE ORGANISMS

Mycoplasmas are asymptomatically present in anywhere from 15 to 75 percent of the healthy U.S. population, that is, 50 to 275 million people. This percentage range is common throughout the world.

Chinese researchers randomly chose 1,600 people from Inner Mongolia from 1994 to 1996. Blood tests found that 35 percent were infected with mycoplasma organisms, as were 57 percent of pregnant mothers, and 100 percent of the children born to those mothers. Between 1994 and 2007 about 13,000 people in China were found to be infected by hemotropic mycoplasmas. (This does not include other mycoplasma infections.)

Studies have found a much higher incidence of hemotropic mycoplasma infection in farm workers and veterinary doctors than others. This is not surprising; the mycoplasmas are not species specific (just species preferent) and they can jump into other species with which they have close contact.

From 25 to 60 percent of all house cats in the U.S. are infected (25 to 60 million) and from 50 to 80 percent of all feral cats (35 to 60 million). From 40 to 65 percent of all cat fleas are infected with mycoplasmas. Stray and flea-infested cats are much more likely to be infected. At least 10 percent of dogs are infected (about 8 million total).

At least 15 percent of all pigs are infected with *Mycoplasma suis;* it is endemic in over 40 percent of all large pig farms. This kind of infection rate in farm animals is, unfortunately, rather common. In France 40 percent of all herds of beef cattle are infected with *Mycoplasma bovis,* and the average infection rate of individual cattle in those herds runs from 10 to 20 percent. Mycoplasmas also survive easily in horse sera. The organisms can be found in stored, unheated horse sera for nearly a year after infection. Mycoplasmas are common in chicken stocks as well and can be transmitted by chickens to their eggs. (The infection survives refrigeration.) They are also commonly found in food vegetables such as endive, broccoli, and kale. More seriously, food animals infected with mycoplasmas, when harvested for consumption, will still contain viable mycoplasma organisms.

Mycoplasma bacteria are common in bulk milk tanks since they commonly infect the mammary glands of all infected animals and are transmitted through milk into nursing calves. (Yes, this is true in humans as well.) Up to half of all dairies have tested positive for mycoplasma and up to 63 percent of bulk milk samples have been found to be infected with from one to five different mycoplasmas. Mycoplasmas are found at high levels as well in goat milk and exist quite happily in goat cheese. Pasteurization failures are commonly reported in cow milk; mycoplasmas are fairly resistant to heat. Usually, pasteurization heats milk to 161 degrees (Fahrenheit) for 15 to 20 seconds. However, *Mycoplasma canadense* can take 158 degrees for three minutes and *M. bovis* for one minute. Transmission from infected bulk milk supplies, even after heating, has been documented on many dairy farms.

Mycoplasmas are also often expressed through urine and feces and can be found in agricultural bedding sand and are

still viable up to eight months later. Transmission to new herds has occurred through this mechanism.

Mycoplasmas can survive starvation and low temperatures for long periods, even being frozen for up to six months. Food has to be cooked at temperatures higher than 160 degrees (F) for more than three minutes—at least—to inactivate the bacteria.

Blood supplies are not routinely screened for mycoplasma bacteria and transmission through that route is relatively common. The bacteria will often produce an asymptomatic condition but if the immune status of the person falls, the organisms will often bloom and initiate a disease process in the person who has received infected blood.

MYCOPLASMA TRANSMISSION BY INSECTS AND COMPANION ANIMALS

Mycoplasmas have been found in ticks, fleas, scabies and other mites, mosquitoes, lice, flies (including dragonflies), biting flies, and midges. All have been found to transmit the organisms to new hosts. Ticks do transmit mycoplasmas to people. Mosquitoes have been found to easily transmit hemoplasmas between pigs; they almost certainly do so between all other species they bite, including humans. Biting flies are common transmitters in cattle and other farm animals. Mycoplasmas are strongly present in wild cat and wild cat flea populations; they transmit by fleas fairly easily. The organisms are present in the flea, its eggs, and its feces. Scratching skin where eggs or feces are present or ingesting either can transmit mycoplasmas.

Mycoplasma organisms tend to concentrate themselves in the salivary glands, and saliva, of both animals and insects. Tests of the arthropod vectors of mycoplasmas show that the salivary glands (and gut and hemocele) contain large numbers of the bacteria, which are then transmitted when the insects seek a blood meal. Mycoplasma organisms also invade the salivary glands of every *host* they enter, including people. They are strongly present in cat saliva and glands, for instance, and can be transmitted to new hosts through cat bite. This can

be the cat's owner as well as other cats—any animal the cat bites.

The organisms are also present in feces and urine, arthropod or animal. This allows them to be transmitted through both these mechanisms as well.

Mycoplasma organisms have a highly adaptable capacity to live in organisms whose body temperature is that of the outside air and then to enter mammals, for example, where the temperature is self-regulated at a much higher degree. Additionally, the immune system in the vector is much different than in the animal host. Mycoplasma organisms analyze the blood to determine the kind of animal they are entering and modify their physiology to allow them to survive in the new host. They are very adaptable, being able to respond to widely different immune systems, body heats, and chemical environments.

There is a lot of horizontal gene transfer among the various mycoplasmas, especially during coinfections. That is, they exchange genetic information with each other and use the information gained to alter their form to better evade the immune system. They have also been found to exchange genetic data with other bacterial groups, such as *E. coli,* in order to acquire resistance information, helping them to better avoid antibiotics. The mycoplasmas are highly adaptable and are able to jump species and engage in gene rearrangement quite capably. This makes transmission of unique mycoplasma species into the human population and their companion and agricultural animals very easy.

DIAGNOSIS

Diagnosis of the mycoplasmas has been, as with many Lyme coinfections, problematic.

The primary diagnosis medium that should be used is polymerase chain reaction, a.k.a. PCR. Some studies show that it runs from 90 to 100 percent accurate with from 95 to 100 percent sensitivity (if hybridization techniques are used), but if it is combined with enzyme immunoassay (ELISA) the accuracy tends to run around 95 percent *on average*. PCR

appears to be the best single diagnostic tool, ELISA second. These two diagnostic procedures can be performed and the results obtained within hours, which is essential for acute episodes. In spite of the higher cost of these approaches they should be used in all suspected cases of mycoplasma infection.

DNA probe runs from 90 to 100 percent sensitive and 89 to 98 percent accurate. It can, as well, take only hours to perform. Its cost is comparable to PCR.

Nanorod array-surface-enhanced spectroscopy has shown very good results, with a 97 percent accuracy. It is very quick and can be performed at the point of care but is not commonly available.

Other diagnostic approaches, i.e., cold agglutinins, culture, serology, passive agglutination, take much longer, from one to six weeks, and are not nearly as sensitive or accurate.

Because mycoplasma symptoms can cover such a wide range, differential diagnosis is difficult. However, in every situation where Lyme disease symptoms are present, mycoplasma infection should be suspected and tested for. If there are respiratory symptoms, rheumatoid arthritis, or urogenital infection, especially with low sperm counts or infertility, mycoplasma should be suspected. Subtler symptoms are possible and should be considered as indicating a test for mycoplasma: calcification in the brain with or without lesions, leaky vessel walls with purpuras, coagulation problems, mitochondrial malfunction, and/or anemia—especially in people with Lyme or bartonella that is proving difficult to resolve.

PHARMACEUTICAL TREATMENT

Macrolide antibiotics (azithromycin, telithromycin, erythromycin, clindamycin), the tetracyclines (doxycycline, tetracycline), and the fluoroquinolones (gemifloxacin, moxifloxacin, levofloxacin, as well as investigational fluoroquinolones such as ABT-492 and garenoxacin) are the most effective general-practice antibiotics against the mycoplasmas.

The newer ketolide antibiotics are showing a lot of promise in treating mycoplasmas. A relatively new ketolide antibiotic, CEM-101, has shown extremely good results at low dosages against 36 isolates of *M. pneumoniae,* 13 of *M. hominis,* 15 of *M. fermentans,* 5 of *M. genitalium,* and 20 of *Ureaplasma urealyticum,* including resistant strains. Other new ketolides (ABT-773 [cethromycin]) are showing promise as well against both resistant and nonresistant strains.

Penicillins, beta-lactams, cephalosporins, vancomycin, sulfonamides, trimethoprim, and rifampin, which act on the cell wall of bacteria, are *not* effective as these bacteria lack cell walls.

In general, doxycycline appears to be the best initial antibiotic to use in treating nonurogenital mycoplasmas. It will usually reduce the symptoms *but,* as the case study of the woman infected with *Mycoplasma haemohominus* makes clear, the drug may not clear the organism from the body. Moxifloxacin was a necessary addition (both were used for six months of treatment) to clear the infection. Nevertheless, in cases of recalcitrant or chronic infection doxycycline shows the most consistent results.

For urogenital mycoplasmas azithromycin shows much better outcomes than doxycycline (87 versus 45 percent cure rates). However, the best outcomes (97 percent) are generated by an extended five-day course of azithromycin, 500 mg on day one, 250 mg from days two through five. Single-dose treatments of azithromycin have a higher relapse rate and reduce the ability of subsequent five-day treatment regimens to cure the infection. Single-dose treatment is contraindicated as it leads to higher relapse and the emergence of resistant strains.

Prophylactic treatment with azithromycin during *M. pneumoniae* outbreaks in hospitals has shown good success in limiting the outbreak but has raised concerns that it may stimulate resistance to the drug.

Because mycoplasmas almost always initiate inflammation it is common during most medical treatment, at least of serious infections, to use pharmaceutical corticosteroid anti-

inflammatories such as prednisone. This will indeed reduce the cytokine inflammations but the drugs are highly dangerous when used long term. For short-term reduction of acute conditions, they are strongly indicated in all mycoplasma infections.

ANTIBIOTIC RESISTANCE

Antibiotic resistance is a significant problem among all disease-causing bacteria. It is only going to get worse as bacterial learning curves increase. The ketolides, because they are relatively new, show the least resistance so far but that is unlikely to remain true as they enter common practice.

Macrolide resistance is being reported fairly commonly now. This is due to the two most common overuse (and misuse) problems: in agricultural animals (especially chickens) and in hospitals. Seventy-two percent of mycoplasma strains isolated from chickens are now resistant to most macrolides. Macrolide resistance by *M. pneumoniae* infections in people has reached 90 percent in China, Korea, and Japan, leading to severe outbreaks of resistant pneumonia in hospitals and the general community. Resistance rates in the West are lower but have reached 30 percent in Israel. Studies in Denmark have found overuse of the macrolides is common in hospital settings. Resistance rates are exponential in every study that has been conducted. For instance, in France in 2005 there were no macrolide-resistant strains of *M. pneumoniae,* but by 2007 10 percent of hospital-tested *M. pneumoniae* were resistant. Resistance to macrolides has also been documented in Sweden, Norway, New Zealand, and Australia.

M. genitalium (and most likely *M. pneumoniae*) has picked up macrolide resistance factors from *E. coli* (confirmed by DNA analysis).

Mycoplasma hominis and *Ureaplama urealyticum* have also developed strong resistance. In China studies have found that the two organisms were most sensitive to josamycin (90 percent resistant) but were strongly resistant to erythromycin, azithromycin, ciprofloxacin, ofloxacin, clarithromycin, and acetylspiramycin (80 to 92 percent resistant). Similar but lower resistance rates were found in studies in Hungary.

Tetracycline resistance is becoming fairly common and can run as high as 40 percent in some populations of mycoplasmas. DNA analysis has found that the resistance transposons were picked up from staphylococcal bacteria. Doxycycline resistance is regrettably becoming common. Resistant strains of *M. hominis, Ureaplasma parvum,* and *Ureaplasma urealyticum* have been reported.

NONMONOTHERAPY INTERVENTIONS

It is possible to design highly sophisticated protocols for the treatment of mycoplasma *if* the cytokine cascades of these organisms are understood. This kind of approach reduces the likelihood of resistance, reduces the amount and length of time that antibiotics are used, reduces the symptom picture considerably, reduces long-term physiological impacts, and is much more effective than simple monotherapies. But first, the cytokine cascade has to be understood.

3

A Technical Look at Mycoplasma and Its Cytokine Cascade

> *Mycoplasmas may be the only procaryotes which can "symbiotically" grow in the eucaryotic host and have a close interaction with mammalian cells for long periods. Intimate interactions of the mycoplasmas with the host cell surface may trigger a cascade of signals transduced from the cell membrane to the nuclei, altering the function of many genes. Furthermore, mycoplasmas are known to induce a variety of cytokines, which may effectively mediate a wide range of biological actions on cell proliferation and differentiation.*
>
> *Intracellular residence, which sequesters mycoplasmas, promotes the establishment of latent or chronic infection states and circumvents mycoplasmacidal immune mechanisms and selective drug therapies.*
>
> S. RAZIN, D. YOGEV, AND Y. NAOT,
> "MOLECULAR BIOLOGY AND
> PATHOGENICITY OF MYCOPLASMAS"

Understanding mycoplasma cytokine cascades is a bit more difficult than understanding those of Lyme, bartonella, or any of the other Lyme coinfections because, unlike those bacteria, the mycoplasmas have to scavenge nearly every substance they need from their hosts. (They are also much less well understood than most other bacteria; the research on them is *very* new and some of them are still impossible to grow in a laboratory.) Because the mycoplasmas have to scavenge so many nutrients, this means they work to break down multiple parts of the host body through a wide variation of cytokine cascades—often in different body systems. It can get complicated.

Over time, to make it more so, different mycoplasma species have come to specialize in certain systems or certain processes to accomplish nutrient scavenging. So researchers have grouped them, roughly, into three types of mycoplasma organisms: fermenting, nonfermenting, and hemotropic. Unfortunately, as better research is occurring, this categorization is becoming less useful. It turns out that the mycoplasmas are pretty good at altering their genome and many, if not all, can ultimately utilize *any* of those niches.

I think, then, that the best way to think of the mycoplasmas, if you are wanting a rough grouping, is through their route of transmission. While not perfect, it presents, perhaps, a more functional way to understand the organisms. In general (though not always) the different mycoplasmas tend to primarily infect the system that they are transmitted into—at least at first. The main routes of transmission are through the air via inhalation (e.g., *Mycoplasma pneumoniae*), through sex (e.g., *Ureaplasma urealyticum*), blood transmission by biting insects (e.g., the hemoplasmas), and through ingestion (e.g., *M. salivarium*).

The mycoplasmas that are inhaled tend to cause pulmonary infections. Those transmitted through sex tend to cause urogenital infections, those through blood transmission infections of the red blood cells, and those through ingestion diseases of the mouth (gums and jaw) and gastric mucosa. However, while they have a *preference* for certain locations it is not absolute. *Any* of these site-preferent organisms can infect *any* of the other sites that different mycoplasmas infect and they utilize pretty much the same infection processes to do so. As well, *any* of these site-preferent mycoplasmas can also infect *any* organ in the body should they go systemic. And many of them do, for most of the mycoplasmas have a strong tropism for joint tissues so many of them infect synovia and cartilage regardless of their initial infection site. To also keep in mind: the mycoplasmas that enter a new host species tend to be less site specific; they tend to go systemic more often than not.

However, the most concise way to think about the mycoplasmas (barring perhaps the hemoplasmas) is that they

are bacteria that specialize in infecting cilia and ciliary-like bodies in the host. They have a tropism for these kinds of tissues. They seek them out no matter where they are in the body, they attach to them and begin breaking down the cilia and the surrounding tissues. Wherever they break them down is where symptoms occur. Since cilia, in one form or another, occur throughout the body, the mycoplasmas have a lot of choices.

MYCOPLASMAL INTERACTIONS WITH HOST CELLS

The Mollicutes as a group possess such a tiny genome that they have a significantly reduced ability to engage in the range of metabolic activities available to organisms with more complex genomes. Their genome is reduced so much in fact that most of the genome is concerned with mechanisms for scavenging what they need from their hosts. Here is a look at their major scavenging activities.

Energy Scavenging

Sources of energy are among the most important. These include adenosine triphosphate (ATP), adenosine diphosphate (ADP), L-arginine, L-lactate, pyruvate, 2-oxobutyrate, and various sugars such as glucose, fructose, mannose, maltose, ribose, glycogen, starch (a converted, protected sugar), and ethanol and glycerol (converted sugars). Many of the sugars they scavenge are commonly present in cell walls, proteins, nucleic acids, and the flavins such as riboflavin (vitamin B2). These types of sugars are strongly present in all the polysaccharide cellular structures that make up the mucous membranes in the respiratory system, urogenital system, gastric system, and collagenous tissues such as cartilage.

Amino Acid Scavenging

The mycoplasmas cannot synthesize many of the basic nutrients they need to live so they scavenge those substances from their host's tissues. This includes most if not all the amino acids, including alanine, arginine, asparagine, cysteine, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. *All* mycoplasmas scavenge

asparagine, glutamine, threonine, histidine, and tryptophan. Nearly all scavenge proline, phenylalanine, methionine, lysine, serine, tyrosine, glycine, valine, isoleucine, and alanine. About half scavenge arginine. Leucine and cysteine scavenging has been observed but is uncommon.

The amino acids are scavenged from peptide strands in the body (i.e., peptides, polypeptides, and proteins). This includes things such as substance P (a neuropeptide), calcitonin (produced in the thyroid), and amyloid precursor proteins (present in many tissues but concentrated in the synapses of neurons).

Nucleobase Scavenging

Mycoplasmas also scavenge a number of nucleobases needed for DNA/ RNA synthesis (essential for reproduction and repair). These include hypoxanthine, adenine, guanine, uracil, thymine, cytidine monophosphate (CMP), and the sugar ribose. Adenine is scavenged (produced) from the adenosine in ATP and ADP and ribose from ADP (sometimes written ADP-ribose).

Essential Vitamin and Mineral Scavenging

Mycoplasmas also scavenge a number of essential vitamins and minerals. The B-complex vitamins (riboflavin, thiamine, niacin, pantothenic acid, pyridoxine, folic acid, biotin, cyanocobalamin, choline) are deeply scavenged as well as minerals such as zinc, phosphorus, magnesium, selenium, calcium, and copper. (Zinc, selenium, and copper, for example, are scavenged from sperm by genital mycoplasmas to such an extent that sperm quality can be significantly decreased and fertility severely compromised. In fact, all zinc-dependent processes in the body can be affected.) Some other substances essential to the mycoplasmas are spermine, lipoic acid (created from fatty acid synthesis), and coenzyme A.

Bacterial infection with mycoplasmas also reduces the amounts of vitamin A in the body, primarily from the impacts of the potent oxidants it generates and its depletion of zinc—which is needed for vitamin A transport and its conversion into retinol, which is necessary for proper eye function.

Interestingly, vitamin A supplementation has been found to decrease the levels of mycoplasmas in the host. Vitamin E levels are also severely reduced by the bacteria as it directly counteracts the oxidation dynamics stimulated by the bacteria.

Lipid Scavenging

Mycoplasmas are either partially or totally incapable of lipid synthesis, so they are dependent on scavenging fats from their hosts. Scavenged lipids include fatty acids, triglycerides, and cholesterol. Unlike most bacteria, mycoplasmal membranes contain sterol, which they must acquire by scavenging cholesterol.

Mycoplasmas also scavenge linoleic, palmitic (a.k.a. hexadecanoic), linolenic, oleic, and myristic acids from host tissues in significant quantities. They get many of these by breaking down cells in the host body as all these substances are present in cellular walls. For example, many, if not most, mycoplasmas (not just the hemoplasmas) scavenge red blood cells and stimulate lysis or the breakdown of those cells. The red blood cells not only contain ATP (which is intently scavenged) but their membranes are composed of cholesterol and a number of phospholipids such as phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphoinositol, and phosphatidylserine. Mycoplasmas break down phosphatidylcholine into needed nutrients such as choline and palmitic acids.

Sphingomyelin, a major focus of scavenging for the mycoplasmas, is one of the four primary phospholipids in the plasma membrane of cells. Whenever cell death occurs, sphingomyelin is liberated from the cell. Mycoplasma species stimulate the production and distribution of sphingomyelinase (ASM), the particular enzyme that breaks down spingomyelin, wherever they congregate. ASM activity generates palmitic acid, choline, phosphates, and serine. But sphingomyelin is not only found in red blood cells; rather crucially, it is also strongly present in the myelin sheaths that surround nerve cell axons. When it is broken down from the nerve sheaths, it causes many of the neurological symptoms that accompany mycoplasma infection.

Phosphatidylserine, also scavenged, is most abundant in red blood cells, the brain, liver, and kidneys—all primary sites of mycoplasma infection. This has damaging impacts on memory, brain function, mood, speed of recovery from injury, muscle soreness, stress levels, and general well-being.

Many cells in the human body contain these phospholipids and every cell that mycoplasmas enter (macrophages, lymphocytes, endothelial and epithelial cells) is scavenged for these kinds of nutrients. Once the mycoplasmas attach to the cell membranes, there is a slow dissolution of the lipid layer from the host cell with an accompanying influx of nutrients into the mycoplasma cell.

Many mycoplasmas also scavenge other lipids, most especially phosphatidylglycerols, among which is cardiolipin. (Some of the mycoplasmas, e.g., *Mycoplasma orale,* are able to synthesize phosphatidylglycerol.) The breakdown of phosphatidylglycerols produces high levels of glycerol (a type of alcohol, i.e., a converted sugar), docosahexaenoic acid, and simple lipids such as palmitic acid. Cardiolipin is a primary component of mitochondrial membranes. Once mycoplasmas enter a cell or cause its lysis, they have direct access to the cardiolipin in the mitochondria, which they then begin to degrade. This causes many of the typical symptoms of mycoplasma infection such as extreme fatigue and neurological disorders that are somewhat similar to Parkinson's and Alzheimer's disease. (It is also connected to a particular kind of autoimmune condition that the mycoplasma can create.) Mycoplasmas, especially *M. pneumoniae,* are well able to metabolize glycerol and the body's phosphatidylglycerols are their main source. The mycoplasmas use several enzymes, including glycerol kinase, to metabolize glycerol to produce energy. One of the metabolic by-products of this is hydrogen peroxide, which is cytotoxic to the host's cellular functioning.

Phosphate Scavenging

Mycoplasmas also use the phosphates they liberate when breaking down phospholipids in a process called phosphorylation. This is one of the most important

mycoplasma actions. Phosphorylation occurs when a phosphate molecule is added to a protein or other organic molecule. Its function is to activate or deactivate protein enzymes. Enzymes (called kinases, and denoted by the suffix -*ase*) are a special kind of protein that catalyze (activate or increase) chemical reactions in living tissues. Collagenase, for example, when activated, breaks down collagen tissues. (This is useful when old, worn-out cartilage is broken down so it can be replaced by new tissue.) Another way to look at this is that enzymes act on different molecules to convert them into other molecules. Most chemical reactions in cells need enzymes to occur. Enzymes tend to be specific, that is, there is one for collagen (collagenase), another for hyaluronic acid (hyaluronidase), and so on. Important among the mycoplasmas are the protein kinases such as tyrosine kinase (and there are others for other amino acids such as serine and threonine). The protein kinases transfer phosphate groups from ATP to a protein in a cell. They act as an on or off switch for cellular functions. A long-term problem occurs if a protein kinase gets stuck in the on position (or is too often activated). This can cause unregulated growth of the cell, which can lead to cancer, a common problem with decades-long mycoplasma infections.

Whenever a phosphate group is transferred from high-energy donor molecules (such as ATP) to another molecule you get phosphorylation. Whenever a phosphate group is removed (through the use of phosphatases) you get dephosphorylation. Phosphorylation is one of the main ways that mycoplasmas get nutrients. (It is also the primary way they generate energy for themselves.) The enzymes they create break down molecules to liberate their underlying substances, which they then use to live and reproduce. The breakdown of collagen by collagenase, which is common during mycoplasma infection, results in, among other things, rheumatoid arthritis.

Mycoplasmal Mechanisms for Adaptation to Host Cells

The mycoplasmas also generate a wide range of chemoattractants that they use to facilitate their contact with tissues containing the compounds they need. They also have

the ability to move, or glide, on surfaces as they seek out tissues containing these nutrients. In other words they have ways to pull the tissues to themselves or to move toward them if necessary.

Besides the use of enzymes, mycoplasmas also stimulate a wide range of immune responses in the host immune system to liberate nutrients. These immune responses, generally various forms of inflammation, also break down host tissues. At the same time they undermine the natural structures of the body, for example making the endothelial lining of blood vessels more porous, so that the mycoplasmas can move through them to gain direct access to tissues that are underneath, tissues that are rich in substances they need.

The mycoplasmas also possess a large number of transporter genes that facilitate the transport of the substances they are harvesting into their cells. They also use these transporter processes to transfer themselves and mycoplasmal substances *into* host cellular tissues.

Mycoplasma genomes, while possessing some variation, are remarkably similar. *All* the mycoplasmas contain very large genome segments that focus on energy generation, phosphorylation (used for enzyme production, replication, antigenic rearrangements of the genome and mycoplasmal cellular surface), chemoattraction, cellular adhesion, cytokine stimulation, and transport of nutrients.

Because the mycoplasmas do not have a cell wall, their cytoplasmic membranes actually touch whichever cells they come into contact with. This facilitates fusion with the host cells, significantly enhancing the transfer and exchange of membrane components into host cells. Mycoplasma species also have a habit of engaging in fusion with each other (made easier by their lack of cell wall), which leads to the formation of both interspecific and intergeneric hybrids (i.e., hybrids from different species and hybrids from different genera).

Proteins make up over two-thirds of the mycoplasma bacteria's external membranes (a great deal more than other bacteria), the rest being membrane lipids, primarily sterol. The large number of proteins and a very flexible genome support

complex cellular rearrangements in the mycoplasmal cell wall. It also makes for a tremendously flexible cellular membrane. Mycoplasmas are pleomorphic—that is, they are able to take many shapes: round, elongated, rod-shaped, pear-shaped, with or without tip organelles, and even filamentous. They are extremely adaptable, able to alter their genome and thus their cellular membrane rapidly in order to facilitate host infection and avoidance of the immune system. As researchers Razin, Yogev, and Naot comment (1998, 1121), there are "rather frequent and significant chromosomal rearrangements taking place in the mycoplasmas" continually. These rearrangements are stimulated by the conditions that face the organisms. If the environment changes, so do they. Razin, Yogev, and Naot put it perfectly:

> All microorganisms are faced with the perpetual challenge of living in diverse and changing environments. To meet this challenge, microorganism populations as a whole must possess mechanisms and strategies allowing them to sense environmental changes and to rapidly respond and adapt to the new surroundings. In the case of pathogenic bacteria, their adaptive potential is challenged by the host defense mechanisms. Only microorganisms able to exhibit environmentally responsive and adaptive molecular traits, enabling them to enter, adhere to, and replicate with the host will survive. Thus, successful bacterial pathogens are those which have evolved molecular mechanisms to deal with the rigors of the host immune response and the need to be transferred and reestablished in a new host. Such mechanisms include mimicry of host antigens, survival within professional phagocytes, and generation of phenotypic plasticity.

> Phenotypic plasticity has been defined as the ability of a single genotype to produce more than one alternative form of morphology, physiological state, and/or behavior in response to environmental conditions. One of the most common ways for phenotypic plasticity is antigenic variation. The term "antigenic variation" or, as it is also named, "phenotypic switching" refers to the ability of a microbial species to alter the antigenic character of its

> surface components including flagella, pili, outer membrane proteins, and capsules that enhance the colonization of host tissues and evade phagocytosis. (Razin, Yogev, and Naot 1998, 1125)

In other words, the mycoplasmas are highly variable in their genetic structures; they can alter them at will and do so depending on the nature of the ecological system in which they find themselves (i.e., what kind of host) and the immune responses of that ecological system. This is crucial to understand in the treatment of mycoplasma or of Lyme and any of its coinfections—all these organisms are always in the process of intelligently adapting.

Nutrient Depletion in Host Cells

Mycoplasmas scavenge so many nutrients from host tissues that those tissues often become depleted of those essential nutrients (and energy reserves). This is especially true if immune function, general health, or daily nutrient intake is low. As Razin, Yogev, and Naot note (1998, 1118), "The demonstrated energy-yielding pathways of mollicutes produce low ATP yields and relatively large quantities of metabolic end products, in some cases depleting host tissues of the specific substrate metabolized." This depletion of host tissues is another main cause of the symptoms that occur during both acute and chronic mycoplasma infection. For instance, L-arginine depletion (which occurs when arginine-utilizing mycoplasmas use it for energy production) can result in erectile dysfunction, neurological impairment, dementia, growth retardation, encephalopathy, and hyperammonemia—an excessive buildup of ammonia in the blood. Hyperammonemia has a number of highly negative impacts. Among them are severe alterations in the neurotransmitter system in the brain. Both arginine- *and* urea-depleting mycoplasmas can cause this condition.

MYCOPLASMA GROUPING AND ENERGY PRODUCTION

Although not my favorite way of thinking about them, the mycoplasmas have been traditionally grouped into two (now three) main groups: fermenting (those that use glucose for

energy), nonfermenting (those that primarily use arginine), and hemotropic (those that colonize red blood cells and utilize them for energy). Fermenting mycoplasmas include *M. pneumoniae, M. fermentans, M. genitalium,* and *M. pulmonis*. Nonfermenting include *M. arthritidis, M. hominis,* and the ureaplasmas.

It should be clearly understood that this rough grouping of the mycoplasmas into three categories is *entirely artificial;* I doubt it will withstand the deeper understandings of the organisms that are now emerging. *All* of the mycoplasmas have the ability to generate energy through any or all of these mechanisms. In fact, some mycoplasmas use two, some all three, of the mechanisms to one extent or another. *M. pneumoniae,* for instance, uses glycolysis *and* blood cell scavenging, and its genome still possesses the structure necessary to engage in arginine scavenging. And, despite these rough categories, some mycoplasmas use none of them.

Rather technically: *M. bovis, M. agalactiae,* and *M. bovigenitalium* use neither sugars nor arginine but rather organic acids such as lactate and pyruvate. Acetyl coenzyme A (acetyl CoA) is then produced through the oxidative phosphorylation of pyruvate. Acetyl phosphate is then generated from acetyl CoA and adenosine diphosphate (ADP) using the enzyme acetate kinase. ADP is stored in blood platelets and is used, essentially, by the body to store ATP in a reduced but savable form for future use. (ADP also has other important functions, including the stimulation of platelet aggregation at wound sites.) This process can be used by both fermenting and nonfermenting mycoplasmas *if they choose to*. In fact, during glycolysis glucose is turned into pyruvate and then the same metabolic pathways are used to produce energy. The fermenting mycoplasmas, if enough glucose is not available, will simply turn to organic acids such as lactate instead.

The ureaplasmas use neither glycolysis nor arginine dihydrolase-ATP nor acetate kinase-ATP-generating pathways. They possess instead a very potent urea enzyme termed urease. This particular urease is stronger than any known enzyme by a factor of 100. (Urease inhibitors, by the way, can significantly

inhibit ureaplasma growth.) The ureaplasmas engage in urea hydrolysis to generate energy. (In the process there is an intracellular accumulation of ammonia/ammonium ions.)

The arginine-utilizing (nonfermenting) mycoplasmas depend on arginine to produce their energy by breaking it apart into its constituent parts, one of which they use to produce ATP. The initial breakdown comes through the use of an arginase enzyme called arginine deiminase, which splits arginine into citrulline and ammonia. Another enzyme, ornithine carbamoyl transferase, then splits apart citrulline into ornithine and carbamoyl phosphate. Finally, the carbamoyl phosphate is used to phosphorylate ADP by carbamate kinase, producing one ATP molecule, carbon dioxide, and more ammonia. This tends to increase the pH of the body and bloodstream.

The fermenting mycoplasmas use carbohydrates, e.g., glucose, and produce acids while doing so, which decreases body and blood pH. *M. genitalium* and *M. pneumoniae* carry all the enzymes of the Embden-Meyerhof pathway for metabolizing glucose but not the full pentose phosphate pathway, which is incomplete in the genome. Pyruvate is the end product of glycolysis and the beginning point for gluconeogenesis. It can be converted either to lactate by lactate dehydrogenase or to acetyl-CoA by pyruvate dehydrogenase. Pyruvate kinases are present in the red blood cell membranes and are used by the red blood cells to produce ATP; they are also scavenged and used by the mycoplasmas.

The mitochondria in cells use these exact same kinds of metabolic processes to make ATP for use as an energy source. Mycoplasma infection competes with the mitochondria and, as well, infects the cells containing mitochondria *and* the mitochondria themselves. The bacteria damage the mitochondria and essentially take ATP and ATP constituents from them. Mycoplasmas also degrade the mitochondria into usable nutrients. This causes a tremendous drop in energy in the host body. In fact, lethargic wasting is a common symptom of infection in both people and animals.

About ATP and ADP
and Their Scavenging by Mycoplasmas

In some senses mycoplasma organisms can be thought of as dormant seeds when they enter a human body. Like seeds, once they find the proper soil and soil conditions, they begin to sprout. And like seeds, they possess the minimal supplies to foster settling into their new soil and beginning growth. But they also, like seeds, need a fairly immediate supply of energy once they do in order to continue to grow. For seed plants this comes from sunlight touching the newly emerging leaves of the young sprout. For mycoplasmas that means the extraction of energy substances, especially ATP and its precursors, from the host cells among which they have settled.

ATP (a.k.a. adenosine triphosphate) is considered to be, in living systems, the molecular unit of currency. It transports chemical energy within cells, allowing them to do the things they need to do to live. ATP is used for energy production, cell signaling, and control of metabolic pathways in the body and is incorporated into nucleic acids when organisms are replicating or repairing DNA.

ATP molecules are made from a purine base (e.g., adenine), a pentose sugar (ribose), and three phosphate group molecules. All these are scavenged by the mycoplasma when the ATP is broken apart into its underlying constituents. Whenever ATP is broken apart, energy is released.

We make ATP in our bodies by using energy, derived from food intake, and through the use of an enzyme, ATP synthase. In essence caloric energy is turned into usable form as ATP by the human body. ATP is commonly found bound to magnesium in cellular tissues and is stored for future use as another, related compound, ADP—adenosine diphosphate (and sometimes as AMP—adenosine monophosphate).

ATP is continually being made and broken apart. In fact, the human body recycles its weight in ATP every day. Most mycoplasmas scavenge ATP from host cells *and* make it through the use of ATP synthase.

ATP has a number of functions other than producing energy. It is intimately involved in the assembly and disassembly of the cytoskeleton in cells. Mycoplasmas also utilize ATP during their extensive rearrangement of host cells during their invasion and encapsulation within cellular tissues.

During extracellular signaling, ATP is used by host cells, most crucially, in the central and peripheral nervous system. Release of ATP from synapses, axons, and glia activates receptors crucial to healthy functioning. During mycoplasma scavenging of ATP from the central and peripheral nervous system, function is lessened, sometimes considerably.

ATP is one of the four primary molecules incorporated into RNA and, in a slightly different form (dNTP, or deoxyribonucleotide triphosphate), is incorporated into DNA. If ATP is scavenged in large quantities from the body both RNA and DNA synthesis is negatively affected. Further, alterations in dNTP levels and their balance can produce poor repair of DNA and RNA or stimulate cancer formation.

Mycoplasmal organisms seek out ATP in the locations where it occurs in the largest quantities—the mitochondria and red blood cells. Still, they can, and do, scavenge it anywhere it exists. Mycoplasmas, for example, also release ATP from chondrocytes in the synovial fluid. They stimulate ATP release from all these cells through a variety of processes, some mechanical, some chemical.

The lipoproteins on the mycoplasmal cytoplasmic membranes help stimulate ATP release in order to make scavenging it easier. These lipoproteins also cause a major increase in plasma membrane permeability—this increase helps the ATP move out of red blood cells, lymphocytes, and monocytes. ATP itself, when released, stimulates the formation of plasma membrane pores in cells, allowing the influx and efflux of larger molecules. In essence, free ATP molecules make a more porous membrane that allows the uptake of scavenged nutrients from host cells, thus reinforcing the action of the mycoplasmal lipoproteins.

Once extracted, ATP increases in the extracellular environment in free form. The ATP is then used (much like

plants use sunlight) as an energy source and to produce growth. The growth *and* the degree of cytotoxicity of the mycoplasmas increase substantially once ATP release is accomplished.

All the free ATP that circulates begins creating numerous physiological impacts. ATP increases microvascular permeability (something the mycoplasmas utilize to move deeper into the system), induces vasodilation, increases nitric oxide production by enhancing the impact of interferon-gamma nitric oxide synthase activity in microglial cells, and is deeply involved in the immune response (it functions as a sort of cytokine in and of itself).

During bacterial infections, host cells die and ATP is released into the bloodstream. ATP then begins to activate P2X(7) receptors on immunocytes and mast cells. This leads to an increase in intracellular calcium activity and the maturation and release of interleukin-1 beta (IL-1β). This activation of P2X(7) is common in arthritis, for example, and has deleterious impacts on the nervous system, including the generation of chronic pain. Prolonged exposure of (any) P2X receptors to ATP results in cell death, leading to the type of tiny foci of necrosis often seen in mycoplasma infections in the brain.

ATP (and ADP, a.k.a. adenosine diphosphate) scavenging stimulates the release of calcium. This may be why calcium deposits in the brain and other locations occur so often during mycoplasma infection. The mobilization of intracellular calcium makes a significant contribution to cell growth and differentiation. ATP also potentiates the prostaglandin E2 release caused by IL-1β and TNF-α, two of the primary cytokines stimulated by mycoplasma infection. ATP regulates the eicosanoid production in organ systems (including in synovial fluid), among which are COX-2 expression and prostaglandin E2 release in astrocytes. This is part of how the mycoplasmas stimulate inflammation in cells.

Mycoplasmas contain a form of ATPase on their cellular surfaces. ATPases are enzymes that stimulate the breakdown of ATP into constituent parts. This is essentially a form of

dephosphorylation. When a mycoplasma membrane touches a host cell, the ATPase stimulates ATP release from the cell. ATP itself, when freed from cells, stimulates more ATP release, especially by the endothelium and brain astrocytes. The cytokine interleukin-1β, one of the major cytokines produced during mycoplasma infection, is a strong stimulant for ATP release as well. The ATP release stimulates hydrolysis of the cell walls, freeing up lipids. The mycoplasmas requires either calcium or magnesium for this activity, which they scavenge from the cells.

Mycoplasmas also scavenge ADP, a form of ATP that the body creates to store ATP in a more stable form. (They also scavenge AMP; see "Impacts on the Synovial Tissue" later in this chapter.) The mycoplasma ATPases can also bind to and stimulate the release of ADP, which, like ATP, is broken down into its constituent parts for use. Many mycoplasmas produce an ADP-ribosyltransferase enzyme that helps them process ADP and also promotes vacuolization inside host cells.

While ATP is found in the largest amounts in mitochondria and red blood cells, ADP is very high in blood platelets. It is not surprising, then, that mycoplasmas stimulate the congregation of blood platelets at locations where they have formed colonies. The mycoplasmas also stimulate the production of blood platelets by stem cells to increase the supply. (See "The Cytokine Cascade" for more on the impacts of this.)

MYCOPLASMA ENTRY INTO THE BODY: MECHANISMS OF INFECTION

Excepting the blood-specific species, mycoplasmas have a tremendous affinity for mucous membranes and cells and cellular structures that are ciliated (including those that possess stereocilia and microvilli). These locations are often the first to be infected by mycoplasmas as they tend to be places where the outside world touches the inside of the body most directly. They are also high in the very compounds that mycoplasmas need to survive.

Mucus is very high in glycoproteins (sugar and amino acids) and water. It is produced to protect epithelial cells in the

respiratory, gastrointestinal (GI), and urogenital tracts and in the visual and auditory systems. Many of the mucous systems in the body contain different forms of cilia (whose name means “eyelash” in Latin—from my junk-yard of semi-useless facts). They are protuberances, like eyelashes, that are extruded from some types of cells. There are two types, motile and primary/nonmotile.

In micrographs (photographs through microscopes) motile cilia look most like waving sheets of grass covering the surface of the cells. These cilia move in coordinated waves to move mucus up and out of the body (e.g., the well-known and famous, among pulmonary physicians, mucociliary escalator). This serves to remove dust and dirt particles from the respiratory system. In the fallopian tubes the motile cilia move the egg from the ovary to the uterus.

Most cells in the body have at least one primary cilium that does not move. These types of cilia, usually one per cell, extend outward from the cell into the lumen, which is the inside space of body structures such as the blood vessels, GI tract, bronchi in the lungs, renal tubules and urinary connecting ducts, and the female genital tract. They essentially act as sensors. They also exist inside cells and protrude into the inner membrane space of a variety of cells, most importantly for mycoplasma infection, the mitochondria. (The flagellum of sperm, by the way, is a modified cilium, again a relatively useless fact I picked up someplace.)

There are also closely related cilia-like structures that exist in the body that are nonmotile as well (and heretically, I will just consider them all cilia). There are two types, stereocilia and microvilli; they each tend to locate in different parts of the body. They are very similar; some people even say they are the same thing (intense arguments are common). They are frequently misunderstood.

These structures were once (like the appendix—an important part of the lymph system) considered to be vestigial organs (remnants from our less evolved ancestors) but, of course, are not (the belief came from mechanocentric projections by vestigial scientists). Once vestigial thinking was

abandoned, their function was thought to be a simple expansion of the surface area of the cells they are attached to. And in fact, the microvilli in the small intestine do serve to increase surface area some thirty- to sixtyfold. But these structures, like "real" cilia, also do a great many other things. And they do move, though somewhat differently than the "real" cilia. They engage in a kind of rhythmic and rapid "beating" or vibrating to help move substances along wherever they are located through a process called mechanotransduction. The microvilli in the small intestine also act to absorb digested nutrients (e.g., sugars and amino acids) and pass them into the blood vessels to which they are also connected. They carry a large number of enzymes on their surface to aid in digestion. There are other microvilli in the small intestine (villus lacteals) that collect lipoproteins composed of trigylcerides, cholesterol, and proteins. All these substances are crucial for mycoplasmal survival so it is not surprising to find that the mycoplasmas infect all forms of cilia as soon as they enter the body. (And their damage to these bodies causes many of the symptoms of infection, including severe wasting from GI tract damage.)

Initial Sites of Mycoplasma Adhesion— Cilia and Mucous Membranes

There are four primary mucous membrane systems that are associated with formal ciliary structures: 1) the vagina, fallopian tubes, oviduct, and uterus; 2) the entire respiratory system including the nasal passages, sinuses, and bronchial tubes; 3) the vesicles of the brain that serve to circulate cerebrospinal fluid and, also a part of that system, the cilia of the eyes' photoreceptors; and 4) the synovial tissues in the joints.

Of the informal ciliary structures, microvilli are located primarily in the small intestine, the plasma surface of eggs (where they help anchor sperm to the egg), white blood cells (a.k.a. leukocytes: lymphocytes, monocytes, macrophages, neutrophils, basophils, and eosinophils), and the kidney proximal tubules. They are very high in actin filaments, which help give them their shape.

The stereocilia are located primarily in the epididymis (the coiled tubes on the back of the testes), the vas deferens (which transports sperm from the epididymis), and the cochlea of the inner ear. Seminal vesicle secretions, by the way, are high in fructose (a sugar), prostaglandins (fatty acids), and proteins (amino acids).

One of the major locations of primary cilia is the synovial tissues in the joints. The synovium is a thin connective tissue that lines the joint spaces that exist to allow us to move and rotate our arms, legs, and so on. This location is extremely high in tumor necrosis factor (TNF) receptors, making it especially susceptible to mycoplasmal cytokine actions.

All these areas are also high in glycocalyx (whose name means “sugar cup” or “sugar coat”), a polysaccharide matrix excreted by epithelial cells that forms a coat on the surface of epithelial tissues. (The slime on fish, for example, is kind of glycocalyx.) This compound is especially present anywhere in the body mucous membranes are present. It is strongly present in the respiratory system, urogenital system, brain, and cartilage and consists of membrane glycolipids and glycoproteins. It coats endothelial cells in blood vessels, prevents leukocytes from rolling/binding on cells (inflammation destroys its integrity), guides embryonic cells to their destinations in the body, enables sperm to recognize and bind to eggs, protects against cancer, and protects the plasma membrane from chemical injury.

All these sites are primary for mycoplasmal attachment just after the bacteria enter the body. In many respects, the easiest way to think of mycoplasmal bacteria is as cilia-specific bacteria. Many, if not most, of their primary symptoms come from their infection and damage of cilia. This, then, should be the primary orientation to understanding mycoplasmas and the range of problems they cause in the body. As they move deeper into the body, they continue to seek out cilial tissues, including within the cells themselves, allowing them access to the mitochondria.

To reach those deeper cilia, they have to loosen the tight cellular bonds that hold tissues together. The tight attachment

of the epithelial cells to each other and the basement membrane underneath them is broken during the mycoplasmal inflammation process that follows initial attachment, making spaces between the cells. Once the mycoplasmas make the epithelial and endothelial structures more porous, they can move past those barriers deeper into the body, allowing the bacteria access to the basement membranes underneath.

One of their targets is the extracellular matrix that surrounds cells where they can access the primary cilia of the chondrocytes, for example in cartilage. The extracellular matrix is made up of two primary biochemicals: polysaccharides (chains of sugar molecules) and glycoproteins (a protein molecule joined to a sugar molecule), both of which the mycoplasmas can utilize. Fibronectin, a glycoprotein, is an important component of the extracellular matrix and is a substance for which the mycoplasmas have a strong affinity. Proteoglycans, very viscid glycoproteins, are even deeper in the system. They are present in connective tissues and consist of a protein attached to a glycosaminoglycan chain. Glycosaminoglycans (also known as mucopolysaccharides) are long, unbranched sugar molecules. Heparin (an anticoagulant), hyaluronan (in the synovial fluid that lubricates body joints), and chondroitins (in connective tissues, cartilage, and tendons) are all glycosaminoglycans. Collagen, a major component in connective tissues, is formed from amino acids. It is high in proline (which makes up 17 percent of collagen) and glycine (33 percent), as well as hydroxyproline and hydroxylysine—modifications of proline and lysine.

All these locations and substances contain the essential nutrients that the mycoplasmas need to survive and they are very good at finding and infecting them.

The Moment of Infection

Mycoplasmas have a very strong affinity for cilia and cilia-like bodies and the mucous membranes in which they are typically embedded, thus they have specialized in gaining access to those parts of the body that are high in them.

During sex, they travel on men’s sperm into the vagina (or into the penis from the woman’s mucosal membranes). From

there they rapidly move farther into the system, seeking out the cilia deeper in the reproductive tract. They first colonize the cervix, and within three days, postinfection, mycoplasma bacteria can be found in the fallopian tubes, oviducts, and uterus. By three weeks, they can reproduce so much that they begin to occlude the fallopian tubes. This can cause infertility, spontaneous abortion, and birth defects. Mycoplasmas can also adhere to cilia in the developing fetus, causing developmental problems. During female-to-male infection, they move up the penis, deep into the urogenital tract, invading the testes, vas, prostate, and kidneys, all of which contain cilia or cilia-like bodies. This includes the epididymis, vas, and kidneys in particular. They are exchanged similarly during anal sex, generally moving deeper into the GI tract and attaching to the cilia bodies there.

They are inhaled into the respiratory system by anyone breathing the same air as someone who is ill with a respiratory mycoplasma and at first colonize the upper respiratory system and its cilia. Then, as always, they move deeper.

They are ingested in and on food, from fingers that have touched infected cellular tissue, and through oral sex. Once they get inside the body, they begin adhering to cilia and mucous membranes within just a few minutes.

All mycoplasma bacteria have what are called adhesion proteins located on their cellular surfaces and these are designed to attach to receptor sites on their host's epithelial cells. Upon initial entry into the body the mycoplasmas use these adhesions to adhere to cilia and the mucous membranes at their site of intake. As Razin, Yogev, and Naot comment (1998, 1124), "Most human and animal mycoplasmas adhere tenaciously to the epithelial linings of the respiratory or urogenital tract … hence they may be considered surface parasites."

As soon as the mycoplasmas attach to a host cell, mycoplasmal lipoproteins begin to stimulate an inflammatory response in the cell. Many of the lipoproteins on the surface of the bacteria are toxic to the cells they touch and produce immediate effects. For example, the choline-containing lipids

in the mycoplasma cytoplasmic membrane are strongly involved in its adhesion to the host cell, stimulate fusion with host cells, and induce the release of very specific cytokines such as tumor necrosis factor alpha (TNF-α) by the host cell. (Each of the mycoplasmas is slightly different with different composition to its cytoplasmic membrane, so that each stimulates a slightly different cascade.) This begins an inflammatory process that immediately starts degrading the cells, releasing the cellular contents in a form the mycoplasmas can utilize.

The bacteria begin excreting peroxide and superoxide radicals that also damage the host cells through their potent oxidation of the cell surfaces. (High levels of arachidonic acid are also released and the urea-plasma species can generate ammonia, which has system-wide effects.) This also produces an inflammatory process in the cell, causing alterations in the cellular membrane. (It also begins to call cells from the immune system to that location.) As the cell wall becomes weakened by the inflammatory cascade, the mycoplasmas begin hydrolysis of host cell membrane phospholipids by generating and releasing specific enzymes. In other words, they actively begin breaking down the cellular membranes of the host cells in order to get the lipids they need.

Almost immediately they also initiate processes to stop the cells from dying, that is, they inhibit apoptosis. In this way, they keep the source of their food alive, even if in a degraded form, so it keeps producing substances the mycoplasmas need for as long as possible. One of the ways they do this is to stimulate (upregulate) the production of calpastatin in host cells. Calpastatin, when present, inhibits the production of another substance called calpain. Calpain, of which there are several forms, is a protease that is highly active in cell cycles, including cellular death. In other words, it, along with a number of other substances that are also regulated by the mycoplasmas, is one of the modulators of death for bacteria-invaded cells. Calpains are also involved in the long-term potentiation of neurons and memory, in blood clotting, and in increasing and decreasing the diameter of blood vessels. As a

consequence of mycoplasmas inhibiting calpains neurons and memory are also deeply affected during infection.

The mycoplasmas also reduce apoptosis by interfering with TNF-α-induced cell death, reducing it by up to 60 percent. Caspase-8 (a protein that is central to apoptosis) is reduced similarly. Mitochondrial transmembrane potential is inhibited by up to 75 percent, thus stopping another mechanism involved in apoptosis. All these actions, in essence, immortalize cells, which, over time (decades), can create various forms of cancer, a common problem in long-term mycoplasma infection.

Cells are highly responsive to the movement of ions, that is, electrically charged molecules of substances such as calcium (Ca+) and potassium (K+). The mycoplasmas interfere with these ions, most especially Ca+ and K+, and this is another mechanism that has wide-ranging effects on cellular functioning and health. The bacteria create an immediate loss of Ca2+-activated K+ channels in all tissues they infect. In bronchial tissues, for example, this directly affects the cilia by depolarizing the cell membranes. This and other factors cause the cilia to become swollen, some “fall off ” the cell, and they lose their ability to move, resulting in ciliostasis. This has a number of repercussions among which is a significant buildup of mucus in those tissues. In other words, glycoproteins composed of sugar and amino acids begin to build up rather than move out of the system. This creates a perfect growth medium for the mycoplasmas, one in which they can scavenge some of their most crucial nutrients.

This is, in essence, what pneumonia is. The cilia no longer work, there is tremendous fluid buildup in the lungs, creating a warm, moist medium on which the bacteria grow unimpeded, and the person eventually drowns from the buildup in the lungs. *Mycoplasma pneumoniae* is the species that most specializes in this particular process (though others can do so as well).

THE CYTOKINE CASCADE

As the initial inflammatory process becomes established a unique cytokine cascade is initiated that contributes further to

the mycoplasmal penetration into the body and its cells. As Shlomo Rottem comments (2003, 426), "The induced cytokines have a wide range of effects on the eukaryotic host cell and are recognized as important mediators of tissue pathology in infectious diseases." Cytokine cascades not only break down the cells to which the mycoplasmas are attached, they are also an essential part of the immune response to infection. Cytokines are in many respects messenger molecules that are released by infected cells; they tell the immune system what is going on and what the cells need. This begins calling immune cells to that location. To facilitate this further, the mycoplasmas begin releasing chemoattractants that also call specific cells to that exact location. Several things occur from this. The cytokines themselves cause cellular breakdown and a loosening of the tight bonds that exist between cells. The immune cells that come to the location also contribute to cellular breakdown and that loosening. And finally, the mycoplasmas really like certain immune cells—they infect them too. Immune cells will often act to engulf bacteria, sequestering them inside themselves, where the immune system can kill them. Mycoplasmas are especially good at evading engulfment and rather than being engulfed, they begin attacking the immune cells themselves, breaking them down as well. The immune cells become not the predator but the prey. Once attached to the immune cells, the mycoplasmas initiate cytokine cascades in them, creating even more crucial messenger molecules. As Rottem continues (2003, 426), "It appears that although mycoplasmas circumvent phagocytosis, they interact with mononuclear and polymorphonuclear phagocytes stimulating the synthesis of cytokines with proinflammatory action. These immunomodulatory influences depend on both the immune cells and the *Mycoplasma* spp. involved." And to add insult to injury, they also hitch a ride on the immune cells to get to other locations they particularly like, most especially the spleen.

> *Mycoplasmas interact … [with a broad range of host cells, including] peritoneal and alveolar macrophages, synovial cells, polymorphonuclear granulocytes, brain astrocytes, blood monocytes,*

> *interdigitating and follicular dendritic cells, and different monocytic cell lines.*
>
> S. RAZIN, D. YOGEV, AND Y. NAOT, "MOLECULAR BIOLOGY AND PATHOGENICITY OF MYCOPLASMAS"

The primary cytokines produced by mycoplasma-infected cells at the point of initial infection are ATP (which acts as a cytokine when in its free state in the body), nuclear factor kappa-B (NF-κB), tumor necrosis factor alpha and beta (TNF-α, TNF-β), interleukin-8 (IL-8), IL-6, and IL-1β. These cytokines can be generated at very high levels by mycoplasmas; for instance, mycoplasma infection can increase the levels of TNF-α from 200 to 500 times. All these cytokines have a variety of effects on the body; for example, ATP release stimulates the activity of P2X(7) receptors that are common on cells in many locations, including the brain and spleen. And this, again, starts other processes—the essence of a "cascade."

P2X(7) activation stimulates the exposure of phosphatidylserine, a lipid that is usually concealed inside lipid layers in cell membranes. It also causes the shedding of L-selectin, an adhesion molecule carried on leukocytes. It can also cause cell death.

Phosphatidylserine, which is only exposed during damage to a cell, stimulates macrophages to attack the cell showing it, in essence bringing immune cells to that location where they can be accessed by the mycoplasmas. This kind of phosphatidylserine/macrophage interaction is particularly dynamic in the spleen, which is why spleen enlargement is common in many mycoplasma infections.

L-selectin shedding acts as a homing receptor for leukocytes, stimulating them to enter the endothelial venules of the lymph nodes and other endothelial cells. This produces, among other things, enlargements of the lymph nodes and a proliferation of mycoplasmas in the nodes.

But by far the most serious effects of P2X(7) activation are in the brain. (See "Impacts on the Brain and Central Nervous System" later in this chapter, for more.) Inhibition of P2X(7) can counteract these impacts and should be considered in any mycroplasma protocol.

Once the initial cytokine cascade is initiated, it begins to stimulate the production of beta-chemokines (a group of small cytokines). Prominent among them are monocyte/macrophage chemoattractant protein-1 (MCP-1), monocyte/macrophage chemoattractant protein-2 (MCP-2, a.k.a. CC chemokine ligand 8 or CCL8), and macrophage inflammatory protein-1 alpha and beta (MIP-1α and β). These chemokines are chemotactic (attractive) for both lymphocytes and macrophages—that is, they call them to that location. Cyclooxygenase-2 (COX-2), an inflammatory enzyme, is also released; prostaglandin E2 (PGE2) production is strongly stimulated; catalase is inhibited.

Cyclooxygenases are a group of enzymes that are initiators for the formation of a number of important biological chemicals including prostaglandins, prostacyclin, and thromboxane. (COX enzymes are still sometimes called prostaglandin synthases.) They are strongly involved in inflammation and pain. COX-2 specifically stimulates PGE2.

Prostaglandins are lipid compounds derived from fatty acids. They can be generated at any location in the body by specific cytokines. Once the mycoplasmas initiate prostaglandin production this gives them a source of location-generated lipids, from which they can scavenge nutrients they need. (They are also strongly present in seminal fluid, another reason why the mycoplasmas infect the prostate and sperm.) However, prostaglandins are also messenger molecules and they cause a variety of physiological effects. PGE2 is deeply involved in bronchodilation and constriction, GI tract muscle constriction and relaxation, vasodilation, gastric acid secretion, uterus contraction, the stimulation of autonomic neurotransmitter function, the stimulation of platelet responses, the generation of fever, and hyperalgesia—a hypersensitivity to pain. But for mycoplasmas, one of PGE2's main uses, besides its content of lipids, is that it stimulates mucous secretion in both the lungs and gastric mucosa. (In some circumstances PGE2 reduces mucous secretion in the lungs, but during mycoplasma infection it increases it.) PGE2 is also a fairly potent abortifacient, another reason why mycoplasma infection can cause spontaneous abortion.

Mycoplasmas stimulate a 2.5- to 4.5fold increase in the body's levels of PGE2 during infection.

Catalase is an enzyme that living organisms use to decompose hydrogen peroxide into oxygen and water. Mycoplasmal organisms decrease catalase production and activity by a minimum of two-thirds in host tissues, thus increasing hydrogen peroxide levels. Hydrogen peroxide is a potent oxidant. When its levels increase, this increases inflammation and cellular breakdown. Catalase inhibition has a number of effects, including significantly increasing the chance of preterm labor or premature rupture of membranes. This is another one of the reasons for the organisms' impacts on pregnancy.

Deeper Specifics on the Cytokines

Mycoplasmas stimulate epithelial cells to begin producing fibroblasts to which they also adhere. Once attached they cause the fibroblasts to produce IL-6, IL-8, CXC chemokine ligand 8 (CXCL8), CXCL1, MCP-1, and CC chemokine ligand 2 (CCL2). Importantly, mycoplasmas, in the presence of TNF-α (the levels of which are very high during infection), as researchers note, "release more IL-6, CXCL8, and CXCL1 than predicted by the responses to either stimuli alone" (Fabisiak et al. 2006, L781). This is a perfect example of the kind of cytokine synergy that is possible with coinfectious bacteria, especially when they are stimulating cytokine release.

IL-6 is a particularly active cytokine during mycoplasma infection. Like COX-2, IL-6 is strongly involved in the generation of PGE2, especially in the brain and hypothalamus (something that contributes to the generation of fever during infection). The mitogen-activated protein kinases (MAPKs) p38 and JNK (c-Jun N-terminal kinase, a type of stress-activated MAPK), both upregulated by mycoplasmas, are integral to IL-6 release. Both are enzymes that use phosphorylation to generate cellular activity, in this instance the production of IL-6.

As the immune system responds to the initial inflammation that the mycoplasmas cause, monocytes (part of the innate immune system) begin swarming to the area of infection. They

then begin differentiation into macrophages and dendritic cells. Lymphocytes (of the adaptive immune system) are also stimulated to respond, and T cells, B cells, and natural killer (NK) cells also begin moving to the site of infection.

Mycoplasmas affect the differentiation of hematopoietic stem cells into dendritic cells (DC). They generate a unique DC form that has a markedly reduced expression of DC-SIGN and stimulates a downregulation of CD11c, HLA-DR, and CD1a and an upregulation of CD123, HLA-ABC, CD80, CD40, CD86, CD54, CD83, CD25, and CCR7. This creates a much reduced phagocytosis by the cells, one of the ways that the mycoplasmas avoid the immune response and engulfment.

The mycoplasmas then begin infecting the different elements of the immune system and start inducing cytokine release by them. They cause the polyclonal stimulation of T cells and B cells and activation of the cytolytic activity of macrophages, NK cells, and cytotoxic T cells. They stimulate the production of NF-κB, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, interferon-alpha (IFN-α), IFN-β, IFN-γ, monocyte/macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), granulocyte-monocyte colony stimulating factor (GM-CSF), major histocompatibility complex (MHC) expression, activator protein-1 (AP-1), c-Fos, and numerous prostaglandins and nitric oxide. The contact between mycoplasma cellular proteins and macrophages results in significant activation of mitogen-activated protein kinases (MAPKs), including extracelluar-signal-regulated kinase 1 and 2 (ERK-1 and -2), JNK, and p38. CD4+ lymphocytes are downregulated, one of the reasons mycoplasmas are synergistic with the AIDS virus.

The mycoplasmas stimulate nitric oxide production through the use of iNOS (inducible nitric oxide synthase). This enzyme catalyzes the production of nitric oxide from L-arginine. It is potently cytotoxic to cells, especially in the brain. NF-κB is an upstream signaling cytokine for this process.

Mycoplasma strains that cause arthritis have high levels of NT5E (a.k.a. ecto-5′-nucleotidase) activity. This is an enzyme involved in the conversion of purine mononucleotides to

nucleosides. Nucleosides are a nucleobase (amino acid) bound to a ribose (sugar) molecule. NT5E activity is significantly increased on synovial cells in joints suffering from mycoplasma infection. This liberates ATP from the synovial cells (such as chondrocytes) for use by the bacteria. Blood platelet counts in the synovial fluid are also high—giving the mycoplasma a source of ADP for further ATP generation. IL-1β and TNF-α levels are high in the synovial fluid, which also stimulates prostaglandin release. ATP synergistically potentiates IL-1β- and TNF-α-stimulated prostaglandin release.

One mycoplasma, *M. arthritidis,* is unique in that it possesses what is called a superantigen, denoted MAM. Normally, during bacterial infection, when T cells are activated the response uses only about 0.001 percent of the body's T cells. MAM can activate up to 20 percent of the T cells, causing a tremendous over-response. These overactivated T cells then produce a massive cytokine cascade of their own, including large amounts of TNF-α. Toll-like receptors 2 and 4 are also strongly stimulated. Levels of IL-1β, IL-6, IL-8, IL-17, and hepcidin, an iron regulator peptide hormone, increase. Spleen cells infected with MAM showed a significant reduction of their ability to generate IL-2 while IL-4 and IL-6 both increased, apparently indicating a shift from Th1 to Th2 immune function.

PLATELET STIMULATION AND EFFECTS ON THE BODY

Blood platelets (also called thrombocytes) are formed in bone marrow and are highly stimulated by the mycoplasmas, in both their production and congregation.

Upon receiving signals from the body that more are needed, the hematopoietic stem cells begin producing megakaryocytes. These are then transformed into platelets. (Each megakaryocyte can produce from 2,000 to 5,000 platelets.) Cascade cytokines, especially IL-6 and granulocyte colony-stimulating factor (G-CSF), significantly stimulate platelet production. (Cytokines such as CXCL5, CXCL7, and CXCL4 can inhibit platelet production and are downregulated by the

bacteria.) Once the platelets are stimulated, the mycoplasmas cause them to congregate at specific locations in the body. They do this through adhering to and damaging (or stimulating inflammation at) epithelial cellular surfaces, which are extensive throughout the body.

The endothelial cells that line blood vessels are a specialized form of epithelial cell and mycoplasmas have a proclivity for them. Biopsies of brain tissue, for instance, have found clusters of *M. pneumoniae* on the surface of endothelial cells in the brain *and* intracellularly *within* endothelial cells. They have not been found *in* nerve cells (parenchymal) but neurovascular invasion and attachment are somewhat common. (The symptoms accompanying this are generally encephalopathy, ataxia, and neuropathy.)

Mycoplasma adherence to and stimulation of inflammation in epithelial (or endothelial) cells causes the cells to get "leaky," that is, for spaces to form between them. It stimulates endothelial cells to release substances such as von Willebrand factor (vWF), platelet-activating factor, and collagen into the bloodstream. This causes the congregation and activation of platelets at that location. Once the platelets are activated, they alter their shape, becoming more spherical, and they begin to extrude a number of contents, normally stored in granules inside themselves, into the surrounding medium. These include ADP, calcium, serotonin, transforming growth factor beta 1, platelet-derived growth factor, fibronectin, beta-thromboglobulin, vWF, fibrinogen, and coagulation factors V and XIII. As the platelets clump together they use the fibrinogen and vWF as a kind of glue to hold them together. This forms a kind of platelet plug (or scab) over the wounded cells. The platelets secrete chemicals that promote the invasion of fibroblasts from surrounding connective tissues into the damaged tissues. This is, in part, why the cells become "leaky." The fibroblasts begin restructuring the tissues, using the fibronectin, along with other substances, to begin healing the wound. The ADP that is released stimulates more platelet aggregation, which stimulates more ADP release and so on. The mycoplasma organisms use the ADP to help them produce energy.

Altering the healthy ecology of the platelets in the blood can cause a great many problems. Excessive bleeding occurs if platelet numbers are too low or excessive clotting if they are too high. In essence certain vascular disorders develop. This is a common problem during mycoplasma infection.

Mycoplasmas should be considered to be primary thrombocytopathic agents. They can cause low platelet counts (thrombocytopenia), decreased function in platelets (thromboasthenia), and increases in platelets (thrombocytosis). Petechiae (purpuras), small red or purple spots on the body caused by tiny hemorrhages, are a common symptom in mycoplasma infections and come from thrombocytopenia.

Vascular lesions form, the endothelial cells swell, the nuclei are abnormal, there is a proliferation of endothelial cells that may occlude the blood vessel. Chronic vasculitis can occur in the brain (causing stroke), blood vessels, heart, spleen, and liver. Vessel wall destruction is begun. Vascular changes including coagulopathy are common.

The mycoplasmas stimulate leakiness in blood vessels so they can penetrate into the layers underneath them, allowing them access to deeper cellular structures. They stimulate the coagulation of blood at sites of infection in order to scavenge red blood cells. In this instance, they call red blood cells to them rather than infecting them freely in the bloodstream—which they can also do.

Blood platelets, as mentioned, release a number of substances once activated. These include platelet-derived growth factor (PDGF), transforming growth factor beta 1, 2, and 3 (TGF-β group), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), platelet-derived epidermal growth factor (EGF), and vascular endothelial growth factor. The mycoplasma organisms utilize many of these as part of their modulation of the host immune response.

INTRACELLULAR SEQUESTERING

While mycoplamas tend to congregate on the surface of cells they have also been found to exist intracellularly much more frequently than previously thought. (They are not just surface

parasites.) The bacteria binds to the host cell, a depression is created in the cell, then a “dramatic rearrangement of microtubule and microfilament proteins” occurs (Razin, Yogev, and Naot 1998, 1099). The mycoplasmas begin degrading the host cell walls, then use transporter processes to transport mycoplasmal substances into the host cell. Many of these substances are designed to rearrange the cytoskeleton of the cell and permit cellular entry and vacuolization by the bacteria.

As soon as two hours postinfection, researchers found, mycoplasmal bacteria could be found “invaginated in the cell membrane or internalized in the cytoplasm, free or inside vesicles. Adherence triggered a signal that promoted cytoskeletal changes, namely, aggregation of tubulin and α-acetinin and condensation of phosphorylated proteins” (Razin, Yogev, and Naot 1998, 1098). Normally, they create a vacuole inside which they live, keeping them protected from the cell they are now inside of. This penetration of the cell, at least to begin with, does little damage to the cell. Eventually, mycoplasmas may replicate beyond the ability of the cell to hold them, causing cell death, which releases multiple mycoplasma organisms into the blood. (Some hemoplasmas will produce up to 4,000 new bacteria inside a blood cell.)

The binding of mycoplasmas to the cellular surface, the fibronectinbinding proteins on the cellular surface, and the fibronectin that mycoplasmas bind (discussed below) begin to induce cytoskeletal changes in the host cells. Tubulin aggregation occurs at the sites of bacterial clustering, as do α-actinin and phosphorylated proteins. The mycoplasmas create tendrils, tubes really, that allow them entry into the cells they are infecting, while at the same time stimulating the cells themselves to create and open channels into their interior. This reorganization of the cells promotes mycoplasma uptake into the cells; in essence it stimulates a form of phagocytosis in nonphagocytotic cells. This gives them entry into the host cells, where they are relatively protected from host immune responses. (They have this same kind of effect on fibroblast, epithelial, endothelial, and lymphocytic cells.)

Mycoplasmas can gain intracellular residence in *any* cells they attach to: red blood cells, endothelial cells, epithelial cells, immune cells, and so on. At least 10 percent of all mycoplasmal cells are held intracellularly during infection. This protects this subpopulation from immune assault (and antibiotics) and allows regular seeding of the host from the protected niches. *Mycoplasma penetrans,* for example, moves quite rapidly into the urothelium soon after infection. The bacteria not only infect the urinary tract, renal pelvis, ureters, bladder, and urethra (all a part of the urothelium) but can be found intracellularly, happily replicating, for months or years after infection. Direct biopsy has found the organisms up to six months (the end of this particular study) after infection, and urine specimens show their presence in this system for a year after infection.

Once inside, the bacteria tend to congregate in the cytoplasm and perinuclear regions of cells. This also puts them in close contact with the mitochondria, one of the main organs they scavenge for nutrients—another reason for internalization.

Vacuolization quickly results in mitochondrial swelling as inflammation is stimulated in that organ of the cell, and chromatin—the combination of DNA and proteins (histones) that make up the nucleus of the cell—moves from deep inside the cell to the periphery where its contents can be more easily accessed by mycoplasma organisms. The histones are translocated across the cellular membranes and into the mycoplasma bacteria clustered on the cellular surface.

This destruction of the mitochondria, as they are scavenged for nutrients, causes tremendous fatigue. If this is accompanied by high-level scavenging of red blood cells, the oxygen levels available to the cells falls, sometimes severely. So, both the cells that create energy by burning oxygen *and* the cells that carry oxygen to them are damaged.

Human and animal mycoplasmas also have the capacity to move into and exist inside of immune cells. Once the mycoplasmas enter immune cells, blood platelets, or red blood cells, they are circulated throughout the body via the

bloodstream. During this process they begin infecting sites much deeper in the body, including the spleen, bone marrow, lymph, and liver.

PLASMINOGEN AND FIBRONECTIN BINDING DURING INFECTION

Plasmin is produced in the liver and released into circulation in the bloodstream as an inactive enzyme precursor called plasminogen. Many mycoplasmas, such as *M. hypopneumoniae* (a pig pathogen, closely related to *M. synoviae, M. pulmonis,* and *M. penetrans*) and *M. fermentans,* bind plasminogen to their cell surfaces in substantial quantities. When plasminogen comes into contact with the endothelial cells that line the blood vessels (for example), this stimulates the release of the tissue plasminogen activator (TPA) normally found on the endothelial cells. Tissue plasminogen activator turns plasminogen into plasmin. Plasmin has a number of functions, among them the breakdown of blood clots. It also activates collagenase, an enzyme that breaks down collagen. Plasmin also breaks down or degrades proteins, including some that are mediators of the complement system, and weakens the wall of the Graafian follicle. The mycoplasmas utilize this breakdown process in their scavenging of nutrients.

The Graafian follicle is a type of ovarian follicle that occurs during the maturation of the ovarian follicle, a form of somatic cell that contains immature eggs. The impact on the Graafian follicle is another one of the reasons that infertility, spontaneous abortion of the fetus, and abnormalities in newborns occur during mycoplasma infection.

Plasminogen can also be activated by a number of other substances, including urokinase (found in the kidneys, urine, bloodstream, and extracellular matrix) and kallikrein (found in the blood and throughout the body). Thus, wherever mycoplasma organisms congregate they can find a substance to activate plasminogen.

A number of the symptoms that mycoplasma infections cause come from the organism’s ability to bind plasminogen to its cell surface and the subsequent activation of enzymes to

turn plasminogen into plasmin. Once plasminogen begins to congregate on the surface of the cell it stimulates the release of TPA by the endothelial cells, thus activating the plasminogen by turning it into plasmin. This is, in part, what causes symptoms such as thrombotic thrombocytopenic purpura, excessive bruising, and so on.

The breakdown of collagen by collagenase, which is activated by plasmin, is where many of the arthritic symptoms of mycoplasma infection come from.

Mycoplasmas also use plasminogen to facilitate their entry into host cells. They bind plasminogen to their surface, in essence covering their membrane with plasminogen and making them appear to be a normal part of the host. They are then able to attach themselves to plasminogen receptors on the surface of epithelial and endothelial cells. As plasminogen is converted to plasmin, they are able to penetrate into the cell, facilitating vacuolization.

Oddly enough, many mycoplasma organisms also bind fibronectin. Once mycoplasmas bind to epithelial or endothelial cell surfaces, the cells begin to increase their production of fibronectin. (Fibronectin is also a common component of blood plasma.) Mycoplasma cellular surfaces contain powerful fibronectin-binding proteins (FnBP). The binding proteins induce an inflammation that, in part, stimulates the cells to produce more fibronectin, which then binds to the receptors at the same time that plasma fibronectin is also attaching to the mycoplasma cellular surface. Fibronectin is intimately bound up in the ability of mycoplasmal organisms to invade cells.

FnBP promotes attachment of mycoplasmas to both endothelial and epithelial cells, triggering uptake of the organisms by the cells. As with plasminogen, the fibronectin covers the surface of the cell, attaches to fibronectin binding sites on the host cells, and triggers host cell uptake of the mycoplasmas via a host-cell drive process involving actin remodeling and microtubule generation. The fibronectin on the mycoplasma induces capillary endothelial cell growth, i.e., angiogenesis, and can result in vascular disorders such as

extensive coagulation, inflammation of the endothelial cells, and blockage of blood vessels. (Fibronectin is deposited at the sites of injury in blood vessels, causing a blood clot.) Fibronectin also plays a major role in cell growth, migration, and differentiation. It is critically important in embryonic development.

Altered fibronectin dynamics are associated with a number of pathologies, including cancer.

> *[Mycoplasma] virulence determinants are undeniably complex, and their unique biological properties likely challenge the host differently than typical bacterial pathogens.*
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> JOEL BASEMAN AND JOSEPH TULLY, "MYCOPLASMAS: SOPHISTICATED, REEMERGING, AND BURDENED BY THEIR NOTORIETY"

IMPACTS ON THE SYNOVIAL TISSUE

Most mycoplasmas invade synovial tissues in the body because they are very high in the nutrients the mycoplasmas need. As usual, inflammatory processes are initiated and the synovia is degraded—in essence turning into a kind of mush. This causes an influx of protein-rich fluids into the joints—an edema or swelling around the joint results. The fluid is turbid and includes fibrin flakes 1 to 2 mm in diameter. There is considerable inflammation and cartilage erosion in the bones and joints. The lymph nodes draining arthritic joints tend to enlarge. Lesions in the subsynovial layer contain an exudation of the protein-rich fluid, neutrophils, histiocytes, lymphocytes, and plasma cells. The edema or swelling is sometimes severe, and very common. Extensive necrosis can occur, again, most likely from the continual high levels of TNF-α and IL-1β.

The synovial lining of the tendon sheaths is damaged as are the points of muscle attachment. Mitochondrial swelling in all the cells is common. Fibrin and intracellular debris fill the intercellular spaces. Platelet aggregation occurs. Cartilage lysis is present. Bone resorption is common in long-standing infections (in part as a result of PGE2 levels—PGE2 is highly involved in bone resorption). Levels of ecto5′-nucleotidase (NT5E, a.k.a. CD73) in the synovial fluid are high, much higher than in serum, showing that it is being generated in the joints.

During mycoplasma-initiated rheumatoid arthritis the synovial lining is stimulated to produce NT5E in large quantities. Mycoplasma organisms have now been found in over 90 percent of those with rheumatoid arthritis. (PGE2 stimulates the production of NT5E threefold.) NT5E is an enzyme that is used to scavenge and break down AMP (adenosine monophosphate). AMP is another form of ATP that can be used to generate energy. PGE2 stimulates AMP production particularly easily in synovial tissues and the NT5E is used to break it apart into usable constituents. In essence, the mycoplasmas overstimulate the synovial tissues, leading to a continual inflammation in the synovia.

M. fermentans, like many of the mycoplasmas, irrespective of its route of infection is specifically drawn to the joints in whatever host it infects. Within seven days it begins infecting the synovial tissues in the joints, causing severe inflammation and a chronic arthritis. The infections are characterized by the infiltration of neutrophils and the substitution of adipose tissue for connective tissue.

IMPACTS ON THE REPRODUCTIVE SYSTEM DURING MYCOPLASMA INFECTION

Mycoplasmas that infect the reproductive tract cause a large number of problems. Once the mycoplasmas enter the genital tract, the structure of the mucous membranes begins to alter, inducing a different microbial environment. The system then becomes more susceptible to infections by other microorganisms. Bacterial vaginosis is common.

For females in all mammalian host species, the vagina and cervix are the initial sites of colonization. Within two hours postinfection, mycoplasmas are attached to vaginal and cervical epithelial cells. By three hours they invade the cells themselves and can be found intracellularly. Ninety-five percent of the cells are infected, and half contain mycoplasma-enveloped vacuoles. Sixty percent of the vacuoles are adjacent to the nucleus of the cells. (This causes, among other things, cervical abscesses.) Within three days the uterus and fallopian tubes are also infected. (Classic pelvic inflammatory disease.) The epithelium of the fallopian tubes is colonized and the cilia

are damaged, sometimes permanently. This causes difficulty in the egg moving from the ovaries to the uterus, inhibiting pregnancy. The fallopian tubes can sometimes be completely occluded, blocking the passage of the egg completely.

As soon as the mycoplasmas adhere to the vaginal cells and the cervix, cytokines begin to be released in significant quantities: IL-1β, TNF-α, IL-6, IL-8, G-CSF, IFN-γ, MCP-1, and RANTES (CCL5). This begins drawing immune cells to the location and the same pattern of immune-cell cytokine induction and invasion begins.

Vaginal cells contain high levels of toll-like receptor 2 (TLR2), which is a signaling protein that calls cells of the immune system to that location. Mycoplasmal bacteria activate TLR2 (along with caspases) and use it to induce cellular death in both lymphocytes and monocytes, allowing scavenging of those immune cells.

Mycoplasmas can infect not only the ovaries but also the eggs. Eggs, irrespective of species, contain numerous nutrients the bacteria like. (Mycoplasmas cause severe damage to chicken egg production.) The eggs themselves are scavenged for nutrients, their cellular integrity severely diminished. This, again, severely affects fertility.

When mycoplasmas infect the uterus, they cause inflammation in the endometrium (a condition called endometritis), which interferes with egg implantation. Should pregnancy occur in spite of all this (or if infection occurs postpregnancy), the bacteria can also infect the fetus. The amniotic fluid will show increased levels of cytokines, specifically IL-1β and IL-6.

Mycoplasmas infect the cilia in the fetus as well as every tissue they have an affinity for. This can cause severe problems in development, especially if they are scavenging glycoproteins from developing tissues such as the extracellular matrix, bones, and joints. Low birth weight is common. Chorioamnionitis, an infection of the fetal membrane, can occur as well. Placental lesions occur. Preterm rupture of the membranes is common. Vasculitis of the umbilical vessels can

occur, abscesses may form, and fetal membrane necrosis may occur.

Mycoplasmas also have a strong affinity for mammary glands. And in fact they infect the mammary glands of all animals that have them. The bacteria are a common cause of mastitis and regularly infect milk supplies in agricultural animals, and the organisms are passed to offspring in milk.

Female infection by mycoplasmas is enhanced by the use of hormone replacement therapy. The arginine-dominant mycoplasmas (*M. hominis, M. fermentans,* the ureaplasmas) generally use estradiol, while the glucose-utilizing (*M. pneumoniae, M. pulmonis, M. genitalium*) prefer progesterone. Exogenous estradiol and progesterone, as numerous studies have found, actually increase the likelihood of infection considerably while normal, body-produced estrogens do not.

Again, within three days, postinfection, mycoplasma bacteria can be found in the fallopian tubes, oviducts, and uterus. This same time frame is present if the colonization is moving the other way, from the woman into the man. Within a short period of time, the mycoplasmas have traveled up the penis and located themselves in the epididymis and the vas deferens, and begun attaching themselves to sperm. In both instances, fertility begins to drop, the more so the longer the infection. They also infect the prostate (and are a factor in the development of prostate disease), altering the gene expression of prostate cells. These altered gene expressions last long term.

Sperm, again, are modified cilial organisms. Once mycoplasma attach to sperm, a variety of problems occur. Sperm DNA is fragmented; zinc, selenium, and copper levels severely decrease; sperm density, motility, and vitality all decrease. Testosterone levels drop. (Increasing testosterone levels has been found to increase the cellular immunity to mysoplasma infections.)

In short, all the reproductive organs, male or female, are severely affected by mycoplasma infection. The health of the organs decreases and cellular structure can be permanently damaged.

IMPACTS ON THE BRAIN AND CENTRAL NERVOUS SYSTEM

Mycoplasmas, again, have an affinity for the cilia-containing areas of the brain and central nervous system (CNS) as well as the blood vessels in the brain. Once there they begin altering the cilia, the mucosa, and the endothelial tissues. Brain alterations immediately occur. Cytokine production by the brain's astrocytes is stimulated; reactive oxygen species (ROS) are produced. Glial production of TNF-α and PGE2 production increases, and IL-6 increases are, as researchers have noted, "massive." All three are apparently stimulated by macrophage-activating lipopeptide-1.

Levels of nitric oxide go up 15- to 20-fold. IL-1β and TNF-α levels increase throughout the brain, including in the hypothalamus, cortex, amygdala, and hippocampus. There are strong impacts on the hypothalamo-pituitary-adrenal axis. There is a significant depletion of corticotropin-releasing hormone and an elevation of both serum adrenocorticotropic hormone and corticosterone. The cytokine impacts on brain cells stimulate ATP release, which immediately begins altering function in axons, glia, and synapses. P2X(7) receptors are strongly stimulated.

Extreme ATP signaling is severely deleterious to the oligodendrocytes that form the myelin sheaths for axons in the brain and spinal cord. (Schwann cells perform the same function in the peripheral nervous system as oligodendrocytes do in the brain.) ATP also impairs white-matter function in the brain. ATP functions as an excitatory neurotransmitter in the brain, spinal cord, and peripheral nerve terminals; it's a potent transmitter of astrocytic calcium signaling, as a mediator of axo-oligodendroglial communication, and is a potent immunomodulator affecting microglia recruitment and activation. ATP signaling is a major factor in neuroinflammation. Excess ATP release results in neurodegeneration—in severe cases even to the destruction of the spinal cord.

ATP stimulates P2X(7) receptors, which, over time, produce neuronal excitotoxicity. Excessive stimulation of P2X(7)

receptors in oligodendrocytes is toxic to those cells. This causes oligodendrocyte death, myelin damage, and axon dysfunction. Excess ATP production also leads to white-matter ischemia. This can cause loss of motor and sensory function, neurobehavioral problems, and cognitive impairments.

There is an abundance of P2X(7) receptors on both myelin and oligodendrocyte cells. The oligodendrocytes and the myelin are both high in the glycolipids that the mycoplasmas need, especially galactosylceramides (galactocerebrosides). These are carried on the surface of mature oligodendrocytes and are released when those cells die. The mycoplasmas also scavenge and activate an enzyme, glutamine synthetase, from the oligodendrocytes. They use this to convert glutamate to one of the amino acids they need, glutamine, in the presence of ATP and ammonia.

The cellular damage the mycoplasmas cause stimulates significant ATP release from the damaged cell cytoplasm into the extracellular environment. This quickly activates P2X(7) receptors on all cells in the brain, including astrocytes. A dramatic increase in intracellular calcium levels begins, mediated by the P2X(7) receptors, which begins to cause significant damage in the CNS and brain. Levels of ATP (a neuroexcitant) continue to increase and levels of adenosine (a neuroprotectant) to decrease.

P2X(7) receptors are highly expressed in microglial cells in the white matter of the brain, on all myelin sheaths, and on oligodendrocytes. High levels of ATP immediately cause myelin destruction, oligodendrocyte cell death, and death of the microglia in the white matter, leading to small foci of necrosis throughout the white matter.

Preventing P2X(7) receptor activation has been shown to reduce or even eliminate this. Direct inhibition is possible with a number of herbs, ERK inhibition will also reduce P2X(7) activation, and a number of herbs and supplements will also help reduce ERK. I think P2X(7) reduction is one of the most important things to address when treating mycoplasmal CNS infections. Importantly, P2X activation (of any sort) has been found to be a primary source of the difficult nerve pain that

sometimes accompanies mycoplasma infection. Reducing P2X receptor activation is the best way to counteract it.

Ectonucleotidases also play a role in the CNS problems that mycoplasmas can cause. Ecto-5′-nucleotidase, which the mycoplasmas commonly either stimulate or carry on their plasma membrane, has profound effects, not only in the synovial tissues, but also in the brain. Seven different kinds have been discovered so far, five in the cytosol, one in the mitochondrial matrix, and one in the outer plasma membrane. Ecto-5′ hydrolyzes AMP, among other things, and is particularly active within the synaptic clefts during development and regeneration (as well as in the mature retina). The synaptic layers of the hippocampus, cortex, and cerebellum contain particularly large and active amounts of ecto-5′.

With extensive or long-term mycoplasma infection of the CNS, tiny calcifications with atrophy of the cerebrum, pons, and midbrain are present, cerebral atrophy is common, and multifocal white-matter lesions may occur throughout the brain, including striatum, midbrain, and pontine tegmentum. Optic nerve involvement is common. (This nerve is very high in P2X[7] receptors.) There are widely disseminated, millimiter-size gray lesions in the cerebral white matter; the anatomic markings of the basis pontis are obscured. The capillaries experience stimulation of endothelial tissue that builds up and can obscure the vessels, leading to stroke. The endothelial cells enlarge and the nuclei are severely damaged as they are scavenged for nutrients. The endothelial abnormalities are common in the white-matter lesions; there is vacuolization of the bacteria, demyelination of the nerve sheaths, spheroids, necrosis, vascular fibrosis, and mineralization (calcification). This tends to be most severe in the basis pontis.

Inflammation throughout the brain and CNS can occur with sometimes severe immune infiltrates. COX-2 expression and PGE2 release in astrocytes occur. There may be necrosis and severe edema. The longer the infection occurs, the deeper the invasion of mycoplasmas into the brain. Mycoplasmas

increase PGE2 levels in hypothalamic, hippocampal, and cortical tissues.

In later stages, multiple hemorrhagic foci (to 2 mm) can occur within the white matter of the cerebral and cerebellar hemispheres, brain stem, cortex, and basal ganglia. The foci consist primarily of fibrinoid necrosis of the walls of the small veins, surrounded by hemorrhagic parenchymal necrosis and dense annular infiltrate of neutrophils and macrophages. These are primarily caused by long-term presence of TNF-α and IL-1β at those sites. These cytokines are stimulated by ATP in ATP-activated glial cells. Demyelinization is apparently an intermediate stage caused by cytokine-initiated inflammation earlier in the infection. Many mycoplasmas colonize defined areas of the cell, which results in microcolony formation and the development of microlesions and small foci of necrosis throughout the CNS.

Meningoencephalitis, epilepsy (relatively common), ataxia, polyradiculoneuropathy, confusion, brain fog, severe neurobehavioral disturbances, psychosis, severe headaches, eye problems, coma, and death, in short, the typical range of symptoms associated with brain infection by inflammatory bacteria, are common.

During chronic epileptic states the levels of ATP are commonly higher in the brain as are the actions of enzymes designed to break it down (especially after a seizure). These enzymes release adenosine (a neuroprotectant) into the system in an attempt to reduce seizures and heal the brain. However, during mycoplasma infection of the CNS, the released adenosine is scavenged. This leads to constant high levels of ATP and continuing damage to the brain synapses. The interruption of the normal levels of ATP and ATPase enzymes is a primary cause of mycoplasma-induced epilepsy.

The increased levels of ATP in the hypothalamus have a potent effect on the regulatory roles the hypothalamus plays in body temperature, food intake, hormone secretion, cardiovascular activity, and sleep. This, along with damage to the GI tract cilia and intense nutrient scavenging, can lead to the wasting that may accompany mycoplasma infection.

Alternating low-grade fever and feelings of coldness and sleep disruption also occur from this disruption of the hypothalamus. ATP impacts in the hippocampus interfere with normal emotional processing and can stimulate extreme emotional states including psychosis.

Mycoplasma species have been found to stimulate amyloidosis at sites of infection, primarily in joint tissues (amyloid arthropathy) but also in the brain (Alzheimer's). Amyloidosis can occur in many places in the body but is always characterized by amyloid deposits. Amyloid is a dense, insoluble waxy substance that is extracellularly deposited and disrupts the functioning and structure of organs such as the brain, kidneys, liver, spleen, and joints. Amyloid deposits are common in rheumatoid arthritis. The amyloid deposits are made up of fibrils composed of polypeptide chains. Cytokines such as TNF-α, IL-1β, IL-6, IL-8, and MIP-1α and β are all known contributors to this process.

The amyloid fibrils' polypeptide chains primarily consist of glycosaminoglycans, apolipoprotein E, and serum amyloid P component. The deposits are formed by the aggregation of misfolded proteins. The proteins are either expressed or precipitated by the cells where the cytokine production is strongest. Abnormal activity of the chondrocytes and macrophages, induced by the cytokines, plays a major role in their production. Amyloid deposits have been found in mycoplasma-infected animals in the kidneys, liver, spleen, and joints. Calcitonin, which is upregulated by mycoplasma infection, is another of the generators (amyloidogenics) of amyloid deposits, being found as extracellular deposits in systemic and peripheral amyloidosis. Beta-amyloid, central to the pathogenesis of Alzheimer's disease, is toxic to cells, increasing cell death due to increased levels of calpain. However, mycoplasmas stop cellular death and inhibit calpain through the generation of calpastatin.

The mycoplasmas apparently generate the formation of amyloid deposits so they can scavenge the glycosaminoglycans of which they are mostly composed. They apparently interfere with the cellular death that amyloid

deposits can cause in order to keep their habitat producing food.

The long-term presence of mycoplasmas in the brain is beginning to be linked to the generation of Alzheimer's disease, and some mycoplasmas such as *Spiroplasma mirum* are being linked by some people to the misfolding of proteins in the brain that causes spongiform encephalopathy. Antiserum to scrapie-associated fibril proteins cross-reacts with those of *Spiroplasma mirum,* lending some credence to the hypothesis. Further, the cytadherence-related proteins, proline rich, in the mycoplasmas have marked impacts on protein folding and binding.

AVOIDING IMMUNE RESPONSE—ANTIGENIC VARIATION

Surface proteins on bacterial cells are one of the ways that the host immune system comes to identify the bacteria. Once it does so, it begins generating antibodies that will target those proteins wherever it finds them. So the bacteria have specific mechanisms in place to engage in recombination of their genome in order to create variations of those proteins. This allows the bacteria to still have attachment proteins but in new forms, forms not recognized by the host immune system, thus allowing chronic infection.

The mycoplasmas are very good at this. Neyrolles et al. (1999, 1569) comment that *M. penetrans,* for example, "undergoes spontaneous and reversible phase variation at high frequency, leading to heterogenous populations of mycoplasmas, even when derived from a clonal lineage." Razin, Yogev, and Naot note:

> The discovery that the minute mycoplasmas possess an impressive capability of maintaining a surface architecture that is antigenically and functionally versatile has placed the mycoplasmas in the "elite" group of bacterial pathogens and parasites distinguished by remarkable antigenic variability. (1998, 1126)

In fact, the mycoplasmas dedicate a considerable portion of their genome to this ability. They are able to alter their form as

well as their cytoplasm membrane components extremely rapidly in order to avoid the host immune response. Razin, Yogev, and Naot (1998, 1126) comment, “Despite their very limited genetic information, the number of genes in mycoplasmas involved in diversifying the antigenic nature of their cell surface is unexpectedly large.” The mycoplasmas in fact engage in a kind of rapid shuffling of their genomes, an oscillation, like shuffling a deck of cards, in order to produce the widest range of variations in the shortest amount of time. They begin this the moment they enter a new host.

In consequence, the bacteria will, in a short period of time, produce a large number of genetic variants in the host and these variants continually create even more variants, keeping the bacteria one step ahead of the immune response.

The mycoplasmas are extremely fast-evolving bacteria. Multiple mycoplasma infections, which are very common, result in a high level of communication between the different species. In fact, if a mycoplasma species jumps into a new host species, any mycoplasmas already in the host will exchange genetic data with the new mycoplasmas, enabling them to more effectively parasitize the host. This process, as it develops over time, allows tremendous niche specialization for the mycoplasmas. Nevertheless, this specialization, again, is not absolute. The mycoplasmas can jump and adapt to new species easily, primarily due to the smallness of their genome and their dependence on extremes of antigenic variation for adaptation.

Again, the lower the immune function in the host, the more effective this strategy is and the longer and more chronic the condition becomes. With extremely low immune function, the symptom picture becomes worse.

CANCER STIMULATION

Long-term mycoplasma infections are increasingly being linked to the development of cancer. This is especially true in those with asymptomatic infections.

Numerous studies have found that the incidence of mycoplasma organisms in cancer tissues is high; at least half

of those tested show tissues infected with mycoplasma organisms. They have been found associated with ovarian, lung, prostate, breast, cervix, renal, gastrointestinal (including colon, esophagus, stomach), and glial (brain, CNS) cancers. Tests of cancerous prostate tissues found that mycoplasma presence is three times that of those with benign prostatic hyperplasia. Strikingly, *no* mycoplasmas have been found in those men who were lesion free. Prostate cancer patients are twice as likely to have antigens to mycoplasmas in serum. And in vitro studies have shown that mycoplasma infection causes the malignant transformation of benign human prostate cells. Prostate-specific antigen (PSA) levels in prostate cancer are higher in those with mycoplasma infection.

There are various reasons that the mycoplasmas can cause cancer formation. The potent nucleases on the Mollicutes, along with superoxide radicals, enter host cell cytoplasm and produce, among other things, clastogenic effects, that is, the breakage of DNA. The mycoplasmas interfere with normal host cell DNA repair. Mycoplasma infection regularly causes chromosomal aberrations, altered morphology, and cell transformation.

The bacteria also inhibit apoptosis, in other words they make cells “immortal” in order to keep feeding off them, thus interrupting the body’s normal method of dealing with cancer cell development. The mycoplasmas have been found to stimulate oncogenes and they inhibit known tumor suppressors as well. Many of the cytokines and growth factors they stimulate promote the growth of tumor cells. And all this happens over a very long time period, decades, usually in the asymptomatic. The mycoplasmas exist in close proximity to host cells, inducing alterations in them for years, ultimately leading to cancer.

Mycoplasmas are one of the strongest inducers of bone morphogenetic protein 2 (BMP-2). BMP-2 RNA is especially high in those with lung tumors and the compound has been found to stimulate lung tumor growth in mice. Mycoplasma-infected cancer cells tend to migrate much more readily than the noninfected; lymph node metastasis is enhanced considerably.

Mycoplasma hyorhinis, which has been implicated in numerous cancers (gastric, ovarian, prostate, and colorectal), contains a lipoprotein, p37, on its membrane that has been found to promote malignant changes in mammalian cells and to enhance invasiveness of tumors. p37 makes cancer cells smaller, more spherical, and easier to detach from each other. Their adhesion to the underlying matrix they are growing on is lessened as well, leading to increased metastases. *M. hyorhinis* also produces a compound, thymidine phosphorylase, that counteracts cytostatic compounds (including those produced by the body) designed to kill cancer cells. p37 increases the activity of matrix metalloproteinase-2 (MMP-2) and stimulates the production of TNF-α from human mononuclear cells; both of these have been found to aid in cancer development by the bacteria.

All the urogenital mycoplasmas have been linked to cancers of the reproductive system and to cervical dysplasia. *M. pneumoniae* has been linked to the development of tumor-like formation in the lungs. *M. fermentans* to gastric cancer and leukemia. *M. hominis* to prostate cancer.

THE HEMOPLASMAS

The hemoplasmas, as yet, can't be grown in a laboratory and they are very newly understood to *be* mycoplasmas, and in consequence less is known about them than the rest of the family. Nevertheless, the analysis of their genome shows virtually the same general structure as all mycoplasmas. In other words, they need and scavenge the same things using the same processes as their relatives. The hemoplasmas scavenge ATP, adenosine, hypoxanthine, diphosphoglycerate, NADH (a B-vitamin-containing nucleotide that is a reduced form of nicotinamide dinucleotide), lipids, sugars, vitamins, and amino acids.

Purines, for example, are incredibly important substances for life on this planet but the mycoplasmas cannot synthesize them. Two of the four bases in nucleic acids (which are needed for DNA synthesis and repair as well as cellular replication) are made from the purines adenine and guanine. The hemoplasmas, like the other mycoplasmas, get their adenine

from the adenosine phosphates (ATP, ADP, AMP) that they break down.

Blood parasites, such as the hemoplasmas and the plasmodium protists that cause malaria, also need a purine derivative, hypoxanthine, for nucleotide production. Hypoxanthine is a metabolite produced from red blood cell nucleotide metabolism and it is scavenged by the hemoplasmas from the breakdown of red blood cells.

Both red blood cells and many mycoplasma bacteria use the same processes to create ATP from precursors, that is, the Embden-Meyerhof pathway. Since red blood cells do not store glycogen they must continually catabolize glucose from the bloodstream as a source of energy, much in the same way glucose-utilizing mycoplasmas do. The Embden-Meyerhof glycolytic pathway also produces an intermediary compound, diphosphoglycerate, that is used by red blood cells in processing oxygen. In most cells this compound is only a trace element but in red blood cells it accounts for two-thirds of the cell's phosphorus. Hemoplasmas are particularly drawn to this compound and scavenge it for its constituent elements. Red blood cells also generate NADH. Mycoplasmas are particularly fond of it.

Red blood cells are filled with ATP. The red blood cells can release their ATP when they are broken apart (lysis) but they can also release it when their structure is compressed or "sheared." Red blood cells, like the mycoplasmas, can alter their cellular shape in order to facilitate their movement through even the tiniest blood vessels. The compression that occurs during that process stimulates the release of ATP. The cell deformation caused by mycoplasmal cytoskeleton rearrangements (when they enter red blood cells) also stimulates the release of ATP. And when cholesterol is scavenged from red blood cells it reduces the cholesterol content of the cell membranes, which increases deformability and stimulates ATP release even more.

Red blood cells are also scavenged for lipids, sugars, vitamins, and amino acids. The red blood cell membrane is composed of three layers: the glycocalyx on the exterior

(which is heavily scavenged for its sugars), the lipid bilayer (which also contains transmembrane proteins), and the membrane skeleton made up of structural proteins. Half the membrane mass is proteins, the other half is lipids. In fact, red blood cells contain more than 50 known membrane proteins. All of these are scavenged by hemoplasmas.

The lipid bilayer contains cholesterol and a number of phospholipids such as phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylinsitol, and phosphatidylserine. Although levels are low, red blood cells also contain phosphatidylglycerols, which are also scavenged. From these the hemoplasmas get sterols, choline, palmitic acid, phosphates, serine, glycerol, and docosahexaenoic acid. During mycoplasmal attachment to the red blood cell exterior membranes, substances are released that slowly degrade and pull these lipids out of the cell membranes for mycoplasmal use.

Red blood cells are also intimately involved in the transport of essential amino acids throughout the body. The hemoplasmas use this to their advantage as it allows them to scavenge all the amino acids from one location. The proteins in the red blood cell membranes are also broken apart into their constituent amino acids.

In addition the B vitamins are intimately involved in red blood cell production and exist in quantity in those cells, from which they are scavenged. The blood plasma also transports nutrients throughout the body, which allows the hemoplasmas to access what they need when they need it. Hemoplasma infection has been found to result in lower blood glucose levels; the bacteria have been found to scavenge it directly from the blood.

Once attached to the erythrocytes, the lipid proteins in the mycoplasmal membrane begin alterations in the red blood cells. Hemoplasmal membrane cytoplasm contains attachment organelles that facilitate exterior bonding to red blood cells. The organisms form clusters in indentations on the red blood cells, and fibril intrusions soon occur, reaching deeper into the cells.

Most hemoplasmas remain on the surface of the cell but some use the same process of intracellular sequestering as the other mycoplasmas do. Once inside the cells, the mycoplasmas may exist either in a vacuole or free in the cytoplasm. Here they are protected from the host immune system and most antibiotics and can happily reproduce; up to 4,000 mycoplasmas can live inside a single red blood cell. They are also widely circulated around the body, to every organ and location, a process they utilize to spread. Red blood cell infection can reach 100 percent during some hemoplasma infections.

During these infections, blood cells are not only parasitized and intracellularly invaded, many of them are killed outright. The extreme reproduction of the hemoplasmas inside the cells can burst them open. Others, severely scavenged for nutrients, simply die. In addition there is sometimes an autoimmune response that contributes to red blood cell death. Agglutinins (both cold and warm), a type of antibody, can be stimulated enough during surface infection of the red blood cells that those antibodies can begin to actively destroy red blood cells to combat the disease.

Red blood cell death, a.k.a. eryptosis, is increased by a number of factors. Ca+ activity increases, which stimulates red blood cell membrane scrambling and activates an enzyme that degrades the cytoskeletal proteins. Ceramide, which is one of the component lipids that makes up sphingomyelin, will, when released, enhance Ca+ and cell membrane scrambling, thus increasing eryptosis. ATP depletion and the presence of oxidative compounds such as nitric oxide will also increase eryptosis. (Resveratrol, thymol, and urea, among other substances, inhibit eryptosis.)

This combination of factors begins producing the kinds of anemia seen in hemoplasma infections. This leads to a number of problems such as weakness, fatigue, and breathlessness (and in extreme circumstances, death) but it also begins significant immune response processes (besides the generation of agglutinins).

At the onset of anemia, the host body immediately begins to release red blood cell precursors, normoblasts and reticulocytes, into the bloodstream. Unfortunately, the hemoplasmas can also infect these cells. Carried to the bone marrow in the blood, the hemoplasmas have been found to infect the marrow, where they can enter into red blood cell precursors at the site of their production.

Red blood cells, when lysed by pathogenic bacteria, make and release nitric oxide as a mechanism of killing invading bacteria. However, the hemoplasmas contain potent antioxidants they use to protect themselves from red blood cell oxidants. And while they remain unaffected the release of large quantities of nitric oxide has highly negative effects on the host body and cellular structure. It is part of an inflammatory response that the hemoplasmas, like all mycoplasmas, use to break down host tissues.

Macrophages are also called to the site of red blood cell breakdown. Phosphatidylserine, which is normally sequestered in the cell bilayer, is exposed during red blood cell breakdown. This immediately stimulates the migration of macrophages to the compound, where the macrophages begin working to phagocytose the red blood cells expressing that lipid. This process is particularly strong in the spleen, which accounts in part for spleen enlargement during hemoplasma infections. Phosphatidylserine exposure on the exterior of the cell also potentiates the adhesion of red blood cells to vascular endothelial cells, something that occurs during *M. pneumoniae* infection, for example. This is one of the causes of the coagulation problems that can occur during mycoplasma infection.

During many mycoplasma infections, including hemoplasmal, the erythrocyte sedimentation rate (ESR) increases. ESR is the rate at which red blood cells sediment, or fall to the bottom of a test tube in one hour. It is a common measure of inflammation. Fibrinogen in the blood, stimulated by all the mycoplasmas, causes red blood cells to stick together, making them heavier and thus fall faster.

Studies have found that CD35 (complement receptor type 1) is significantly elevated in erythrocytes infected by *M. ovis*. During red blood cell death phosphatidylserine is exposed on the outer membrane of the cell, where it is immediately scavenged. Infection by *M. ovis* causes increased hemorrhagic tendency, intravascular coagulation, and consumption coagulopathy.

Besides the marrow, the hemoplasmas have been found in large quantities in the spleen, the lymph system (including the nodes), the liver, lungs, and joints. Similarly to bartonella, the hemoplasmas, because there is a cycle of increased and decreased presence in the red blood cells, are assumed to invade a particular niche in the body from which they are seeded into the bloodstream at regular intervals. (Since they are spread through blood-sucking vectors, they would need to maintain a presence in the bloodstream for transmission.) However, such a niche, if it exists, has not yet been definitively determined. There is some speculation that there are two sites, the bone marrow and the spleen. Specifically: *if the spleen is removed or damaged in those who are asymptomatically infected, the infection becomes acute very rapidly and can quickly lead to death.* Thus, the spleen is significant in the control of mycoplasma infection and any treatment plan must include supporting its healthy function.

In animals, where the most research has occurred with the hemoplasmas (the hemoplasmas have a long record of infection in farm animals), the symptoms of infection are anemia, weakness, lethargy, fever, poor growth, anorexia, depression, estrus problems (decrease, delay, or absence), embryonic deaths and spontaneous abortions, scrotal edema, mastitis, and lymphadenopathy.

Death can occur if the anemia is pronounced enough. Based on the chronic infection picture in animals veterinarians feel the hemoplasmas can infect reproductive tissues and produce impacts similar to those of the urogenital mycoplasmas. The early reports of human infections indicate that the hemoplasmas do, in fact, generate similar symptom pictures in people.

M. haemohominus causes chronic moderate neutropenia (abnormally low white blood cell counts), acute hemolysis (rupture of red blood cells), anemia, enlarged liver and spleen, thrombocytopenia (with resulting bruising and easy bleeding), petechiae, fever, abdominal pain, nausea, joint pain, night sweats, and weight loss. *M. ovis* causes acute or chronic anemia, jaundice, and fatigue (and seems to be a fairly common infectious agent in China). *M. haemofelis* causes soft tissue cellulitis and septic arthritis. *M. suis* causes easy bleeding, fever, and anemia. The hemoplasmas have been linked in at least two studies to the development of lupus.

However, as the mycoplasmas as a group are better understood, it is becoming clear that most if not all the mycoplasmas are hemotropic. *M. bovis, M. gallisepticum,* and *M. pneumoniae* can all invade erythrocytes. Like the hemoplasmas, they utilize the red blood cells not only for scavenging nutrients but also for safe transport throughout the body, protected from immune responses and antibacterial substances. A number of these have been found to be transmitted by ticks, indicating a regular presence in the bloodstream.

AUTOIMMUNITY PROBLEMS DURING MYCOPLASMA INFECTION

There are a number of autoimmune conditions that have been linked to mycoplasma infection. Mainly these are: 1) attacks on the red blood cells, 2) attacks on mitochondrial bodies, and 3) attacks on galactocerebrosides.

Immune cells have been known to target erythrocytes infected with *M. pneumoniae* and some of the hemoplasmas as well. The infection of red blood cells causes the production of autoimmune hemolytic anemia (AIHA) antibodies, which results in the body attacking its own cells—specifically the red blood cells. The cytoskeleton protein components, such as actin, that are normally inside the red blood cells are exposed during mycoplasma infection of red blood cells and this begins to stimulate an antibody response to them. There are two forms of anti-red-blood-cell antibodies that lead to two forms of AIHA: warm agglutinin disease, which is marked by the

production of IgG antibodies, and cold agglutinin disease, which is marked by the generation of IgM antibodies. In the first, the antibodies bind the red blood cells at body temperature or higher. In the second, body temperature has to fall below normal (probably due to mycoplasmal dysregulation of the hypothalamus) before the antibodies bind the red blood cells. In this way, in addition to the lysis of red blood cells by mycoplasmas, the body's own immune responses can kill the red blood cells. In some instances the attack is so severe as to cause death, especially if transfusion is attempted to counteract the anemia.

During mitochondrial autoimmunity the mitochondria of cells are attacked. Mycoplasmas use a pyruvate kinase (pyruvate dehydrogenase) as part of their metabolic processes —in part to generate ATP. However, red blood cells do so as well and they keep their pyruvate kinase deep inside the lipid layers of the red blood cells. But during red blood cell lysis, it is exposed to the blood plasma. The autoimmunity responses that occur in response produce antimitochondrial antibodies that can begin attacking mitochondria throughout the body. This produces severe fatigue but has also been linked to the development of primary biliary cirrhosis.

Some of the most research on autoimmunity during mycoplasma infection has occurred with studies on antigalactocerebroside antibodies. Galactocerebroside (GalC) is a type of glycosphingolipid. Glycosphingolipids, including galactocerebroside, are crucial components in nerve cell membranes. They are present in all nervous tissues and make up to 2 percent of the gray matter of the brain and up to 12 percent of the white. They are also present in the spleen and red blood cells. They are major constituents of oligodendrocytes, a type of brain cell, a variety of neuroglia. Their main function is the insulation of axons in the brain and spinal cord. GalC is a major glycolipid of the myelin sheaths and the cell membrane of the myelin-forming cells (oligodendrocytes and Schwann cells).

GalC is heavily scavenged by mycoplasmas in the CNS. The compound is liberated from tissues so the mycoplasmas can meet nutrient needs; however as the process continues, the

body begins making antibodies to the compound. It does so because there is a compound in mycoplasma cellular membranes that is structurally identical to GalC. This can create tremendous neurological problems as the body itself begins degrading the insulation of the axons in the brain and spinal cord. Guillain-Barré syndrome is one of the main diseases that results, and encephalitis, bulbar paralysis, encephalomyelitis, coma, and quadriplegia from destruction of the spinal cord are also possible.

Similar cerebrosides, specifically fast-migrating cerebrosides that are derivatives of galactosylceramide (GalCer), have also been found to cross-react with mycoplasma antibodies. GalCer is the principal glycosphingolipid in brain tissue and is present in all nervous tissues. Similarly to GalC, it is found in the spleen and red blood cells and is a major component of myelin nerve sheaths and is broken down by mycoplasmas and incorporated into mycoplasmal cells. Antibodies to GalCer form and then attack host tissues in the brain and spinal cord. These particular antibodies are present in a substantial number of people with multiple sclerosis.

TREATMENT

The mycoplasmas are the most complex of the Lyme coinfections and their range of actions in the body is very broad. Because they scavenge so many substances there is a lot more involved in their treatment than with simpler bacteria such as the bartonella. Nevertheless, mycoplasma infection can be treated effectively. The next two chapters explore just what it takes to treat it.

4

The Mycoplasma Protocol

A Very Simple Overview

The full discussion of the mycoplasma protocol is fairly complex. This chapter presents a very simple overview of what it looks like in its most basic form. Please be aware that there is considerably more depth in the full discussion in the next chapter. And, if you would, please look at the contraindications for the suggested herbs and supplements (if any) before you use them. And also be aware that while nearly all herbs and supplements are very safe, individual reactions *not included in the literature* can occur. ***If you begin taking any of these herbs or supplements and experience side effects that just don't seem right, stop taking them.*** Remember: you are the best person to determine whether something works for you or not.

Please bear in mind as well that while this chapter presents an easier way to get an idea of the mycoplasma protocol, the protocol can be varied considerably. This protocol is ***not*** the only way to address a mycoplasma infection. All herbs are useful in some ways; these are just the ones that I think most beneficial. Add whatever else seems to work for you (and subtract whatever does not).

The treatment of coinfections, especially mycoplasma, is not, and cannot be, a one-size-fits-all process. There is no one, right way to treat these kinds of infections; the bacteria are too diverse and people's bodies and immune profiles are too varied. Each treatment plan should be individually designed. This is just a starting point from which to begin.

Also: To counteract the inflammation in the body, the quantities of herbs and supplements you are taking need to be highish and constant. In other words, the body needs to be bathed in counteractants to the mycoplasmal cytokines and

membrane proteins for a considerable amount of time to 1) turn the physiological condition around and 2) make the environment unpleasant enough that the mycoplasmal population significantly drops.

And again, yes, this protocol can be taken along with antibiotics (please see the next chapter for any listings of herb/drug or supplement/drug interactions; there are some).

And yes, all the tinctures can be combined with water or juice (I would highly recommend pomegranate) and taken together. (And yes, some of them do taste dreadful.)

THE BASIC PROTOCOL

Cordyceps: Tincture, ¼ teaspoon 3x daily; or powder, 1 tablespoon 3x daily; or capsules, 2,000 mg 3x daily.

Chinese skullcap: Tincture, ¼ teaspoon 3x daily; or powder, 1 teaspoon 3x daily; or capsules, 1,000 mg 3x daily.

Isatis: Tincture (two-thirds root, one-third leaves, if possible), ½ teaspoon 3x daily.

Houttuynia: Tincture, ¼ teaspoon 3x daily.

Sida acuta: Tincture, 30 drops (one dropperful) 3x daily.

N-acetylcysteine: 2,000 mg in the morning, 2,000 mg just before bed.

Vitamin E (alpha-tocopherol): 200 IU or 150 mg daily.

Olive oil (infused with olive leaf is best): 1 ounce in the morning, 1 ounce in the evening just before bed. And, yes, since you are asking, drink it down, or else add it liberally to your food.

Immune formulation: Tincture combination of schisandra, eleutherococcus, and rhodiola, ½ teaspoon 3x daily.

Nutrient replacement as food: Daily intake of eggs, calf or beef liver, oysters, one Brazil nut, sesame seeds (or tahini), avocados, chlorella/spirulina/seaweed green drink (¼ cup of the mixed powders in juice—pomengranate is best—or water), pomegranate juice throughout the day.

And, if you can afford it, fermented wheat germ extract daily for 6 months.

ADD TO THE BASIC PROTOCOL, BASED ON SYMPTOMS

If you have a systemic mycoplasma infection …

With urinary tract infection, use:

1. Uva ursi and phellodendron (or other berberine plant) tincture mix (two-thirds uva ursi, one-third berberine plant), ¼ teaspoon 3x daily for 30 days, plus …
2. Bidens tincture, ¼ teaspoon 3x daily for 30 days.

With cervix/vaginal infection, use:

1. Berberine plant or tea tree oil or uva ursi douche for 3–7 days.

With cervical dysplasia:

1. *Echinacea angustifolia* suppository for 14 nights, plus …
2. Berberine plant or tea tree oil or uva ursi douche for 3–7 days.

With lung infection, use:

1. Bidens tincture, ¼ teaspoon 3–6x daily until infection resolves, plus …
2. Tincture mix of equal parts pleurisy root, licorice root, elecampane root, yerba santa leaf, and lomatium, ¼–½ teaspoon 6x daily until infection clears.

With *severe* anemia or red blood cell lysis, use:

1. *Sida acuta* tincture, increase dosage to ½ teaspoon 3–6x daily until condition resolves, plus …
2. N-acetylcysteine, increase dosage to 4,000 mg 2x daily until condition resolves, plus …
3. Bidens tincture, ½ teaspoon 6x daily until condition resolves.

With hemoplasma or intracellular red blood cell mycoplasma infection, use:

1. *Sida acuta* tincture, increase dosage to ½ teaspoon 3–6x daily, and/or
2. Cryptolepis tincture, ½ teaspoon 3–6x daily, and/or
3. Alchornea tincture, ½ teaspoon 3–6x daily, and/or
4. Bidens tincture, ½ teaspoon 3–6x daily.

With severe brain/CNS involvement, use:

1. Motherwort tincture, ¼–½ teaspoon up to 6x daily, plus …
2. Greater celandine tincture, ¼ teaspoon 3x daily, plus …
3. Kudzu root tincture, ¼ teaspoon 3–4x daily.

With nerve destruction, use nerve growth factor stimulants:

1. Chinese senega root tincture, 30 drops 3x daily for 30 days, plus …
2. Lion's mane (*Hericium erinaceus*), 3–8 grams per day; or 1 teaspoon tincture 2x daily.

With neural pain, use:

1. Greater celandine tincture, ¼ teaspoon 3x daily, plus …
2. Kudzu root tincture, ½ teaspoon 3–4x daily.
3. Theramine may also be of use.

With anxiety, use:

1. Pasque flower tincture, 10 drops each hour for as long as necessary, and/or …
2. Motherwort tincture, ¼–½ teaspoon up to 6x daily, and/or …
3. Coral root tincture, 30 drops (full dropper) up to 6x daily.

With sleep disturbance, use:

1. Melatonin liquid, taken according to the manufacturer's directions, 1 hour before bed, and/or …
2. Ashwagandha tincture, ½ teaspoon 1 hour before bed; or powder or capsules, 1 gram 1 hour before bed, and/or …
3. Motherwort tincture, ¼ *ounce* (yes, that is right) in liquid just before bed (if the melatonin does not help).

With severe fatigue, use the following for 6 months:

1. Eleutherococcus tincture (Herb Pharm formulation), ¼ teaspoon every morning, plus …
2. Rhodiola tincture, ¼ teaspoon 3x daily, plus …
3. Schisandra tincture, ¼ teaspoon 3x daily, plus …
4. Motherwort tincture, ¼ teaspoon 3x daily, plus …
5. Fermented wheat germ extract, if you can afford it.

With joint involvement/rheumatoid arthritis, use:

1. Greater celandine, olive leaf, the berberine plants, ashwagandha, and green tea (which contains EGCG) can all help this condition; however you can also add …
2. Chondroitin/glucosamine sulfate combination that gives you 1,500 mg of glucosamine and 1,200 mg of chondroitin daily
   (***note:*** do not use with CNS complications), and/or …
3. Teasel root tincture, ¼ teaspoon 3–6x daily.

With wasting (i.e., severe weight loss), use:

1. Fermented wheat germ, 9 grams daily (best choice), and/or …
2. Shiitake mushroom, powdered or as food, 6–16 grams per day (it can be mixed in with the chlorella green drink mix). A pure extract of lentinan can also be used, at 1–3 grams per day.

5

Natural Healing of Mycoplasma

In Depth

Data indicated that pathogenic mycoplasmas reside and replicate intracellularly over extended periods in human cells, consistent with the ability of mycoplasmas to circumvent antibiotic therapy and immune surveillance and establish chronic infections.

S. F. DALLO AND J. B. BASEMAN, "INTRACELLULAR DNA REPLICATION AND LONG-TERM SURVIVAL OF PATHOGENIC MYCOPLASMAS"

Their streamlined genome size, which illustrates extreme biological gene economy, imposes complex nutritional requirements, such as dependence on external supplies of biosynthetic precursors, including amino acids, nucleotides, fatty acids, and sterols. This limited coding capacity dictates for mycoplasmas a parasitic way of life that few pathogenic microorganisms can claim.

JOEL BASEMAN AND JOSEPH TULLY, "MYCOPLASMAS: SOPHISTICATED, REEMERGING, AND BURDENED BY THEIR NOTORIETY"

The first and most important thing to understand about the mycoplasmas is that they are very old. The ancestral mycoplasmas split off from the *Streptococcus* branch of bacteria some 600 million years ago. The phytoplasmas that infect plants began to specialize some 500 million years ago, diversifying considerably upon the emergence of flowering plants 140 million years ago. The mycoplasmas that cause human disease, that in fact specialize in the infection of mammals, began to develop along with the emergence of mammals themselves some 220 million years ago. Primates

emerged around 100 million years ago, apes 28 million years ago. The earliest human ancestors showed up about 8 million years ago, Neanderthals 2 million years ago, and modern humans 200,000 years ago. In all that time, the mycoplasmas have been specializing in infecting host species very similar to us. And they have gotten very good at it.

In contrast pharmaceutical antibiotics were discovered in 1928 and only commercially produced in 1942. The first isolation of a human-infectious mycoplasma in a lab took place only in 1937. By the 1990s researchers learned enough about these bacteria to grow (some of) them in labs. Only in the few decades since have the organisms begun to be studied in any depth. We've got maybe 80 years of experience with the mycoplasmas, science-wise; they have millions of years of experience with life-forms very similar to us. So, the first and most important thing to understand about the mycoplasmas is that they are very old, very experienced, very adaptable. We are babies in comparison and, if you have looked at just how adaptable the mycoplasmas are, not very smart babies at that.

In order to successfully treat organisms as complex and as highly intelligent as the mycoplasmas, it is important to, first, get rid of all sense you may have of superiority to "stupid" bacteria due to our "superior" intelligence. We can't see what we assume is not there, in this case, sophisticated intelligence and adaptability in a bacterial species. Second, it is crucial to understand what they do and why they do it—*and to begin to intervene in that process in a sophisticated way.* That is, for us to adapt our own behaviors to theirs. In other words, to be like Ginger Rogers in relation to Fred Astaire—doing everything he did but in high heels and backward. And, with respect for their capacities, to begin to intervene in what they do at the subtlest levels possible.

In this process, it is also crucially important to support our most intelligent ally—the human body. Health, irrespective of what medical science does, cannot be restored if the human body does not also participate. This is one of the deepest teachings of AIDS. For, like the mycoplasmas, the human body has come out of a long history of complex development on this planet and it has its own long-developed mechanisms

for dealing with infections. Thus, supporting immune function as well as organ health is important.

If you know the type of mycoplasma infection involved, that is, the particular species, *and* if you have a comprehensive symptom list it is much easier to design a protocol for a mycoplasma infection. However, it is possible to develop a general protocol that can be applied to all mycoplasma species. One caveat: *this is a general protocol. The best protocols will be designed for the individual person and the specific species of mycoplasma, and will be adjusted as needed during treatment.*

THE SEVEN THINGS TO KEEP IN MIND

There are seven things to keep in mind when designing a mycoplasma treatment protocol.

1. Replace the nutrients that are scavenged by the mycoplasmas. This must be done to avoid nutrient depletion in the body and the problems it can cause. ***Note:*** *this will* ***not*** *" feed" the mycoplasmas.* They are doing just fine feeding themselves—from your body's own tissues. Supplementation keeps ***your*** body from experiencing nutrient depletion as they do so. Crucially: ***all*** research has found that replacing scavenged nutrients is essential to restore normal cellular and organism functioning. I repeat … all research has found … (that's good, repeat it as often as you can).
2. Reduce the cytokine cascade that the bacteria initiate. This will go a long way toward relieving the symptoms that mycoplasma infection causes and, importantly, since the mycoplasmas use the cytokine cascade to break down tissues to acquire nutrients, this will begin to starve them, reducing their numbers.
3. Use specific antibacterials to kill the mycoplasmal organisms or at least severely restrict their numbers. Herbs, supplements, and antibiotics are all useful and highly synergetic for this. ***Note:*** *unless, specifically noted otherwise, antibiotics can be used along with* ***all*** *the herbs and supplements in this book.*

4. Support and protect the organs and systems that the mycoplasmas affect. This will also relieve many mycoplasmal symptoms; it will also reduce the organisms' nutrient intake since they gain many nutrients by breaking down parts of various organs and systems. Some of the most important are red blood cells; endothelial tissues; mucous membrane systems; the brain, spinal cord, and peripheral nerves; collagen, cartilage, and synovial tissues; the spleen and lymph system; and the immune system. Also: in essence, mycoplasmas are first and foremost bacteria that infect the ciliary structures of the body. The more you protect such structures, the better your protocol will work.
5. Enhance immune function. The stronger the immune system, the less severe the course of the disease.
6. Address specific symptoms not addressed otherwise. This will reduce the symptom picture and increase the quality of life.
7. *The most elegant interventions will act in three or more of these categories.* That is, if you find an herb that a) replaces nutrients, b) reduces cytokine cascade, c) protects specific organ systems, and d) enhances immune function or is antibacterial or addresses specific symptoms (or every one of those things)—*that* is what an elegant intervention looks like. It is a way of identifying the most specific herb or supplement for treating a mycoplasma infection. (Two of the best herbal examples of this are cordyceps and houttuynia.)

It is important to keep in mind that mycoplasma infections, especially of long duration, are first and foremost nutrient deficiency diseases. Second, long-term infection results in specific kinds of damage to certain areas of the body, especially the cilia, parts of the CNS, the reproductive system, the immune system, and the synovia. Correcting all this takes time. To repeat: *this takes time*. The greater the degree of nutrient deficiency (and the longer it has lasted), the longer it will take. The greater the damage to the bodily systems, the longer it will take to reverse the conditions and restore the body to health. Keep in mind: *it can be reversed*. It just takes

time and focus. In the beginning, progress is infinitesimal; it builds incrementally each day. In long-term chronic conditions you should expect a minimum of a year to turn the condition around, two years if the damage is serious.

A good way to visualize this is to think of treatment as the process of bathing the body in cytokine inhibitors for an extended period of time. This will, over time, stop the inflammation that has been occurring. Once that has occurred, the immune modulators you use will bring immune function to the place where it can deal with infection itself. Antibacterial herbs will reduce the numbers of mycoplasmal bacteria, reducing cytokine presence through that process. And specific organ support will begin healing the damage that has occurred in the various parts of the body. It is pretty straightforward, it just takes time.

REPLACING NUTRIENTS

One of the difficulties with mycoplasma treatment is that the bacteria utilize so many nutrients from the body that a full list of the supplements needed to replace them is, frankly, daunting. It leads to the "maracas syndrome," that is, the condition of taking so many pills that you rattle when you walk. Additionally, it makes breakfast a trial; nobody wants to down 50 capsules and tablets first thing, much less three times a day. There are ways to minimize this problem, especially if you design your diet to replace the majority of the nutrients the bacteria are scavenging. Additionally, some of the herbs will actually replace nutrients while adding immune support or antibacterial actions, e.g., cordyceps and houttuynia.

And replacing the nutrients really is important. The cellular changes that occur upon mycoplasma infection, Shlomo Rottem (2003, 425) comments, "are similar to those caused by nutritional effects such as the depletion of amino acids, sugars, or nucleic acid precursors."

> Mycoplasmas … depend on the host microenvironment to supply the full spectrum of biochemical precursors required for the biosynthesis of macromolecules.

> Competition for these biosynthetic precursors by mycoplasmas may disrupt host cell integrity and alter host cell function. Nonfermenting Mycoplasma spp. utilize the arginine dihydrolase pathway for generating ATP and rapidly deplete the host's arginine reserves affecting protein synthesis, host cell division, and growth… . M. fermentans infection of rat astrocytes has been shown recently to result in a choline-deficient environment… . Choline is an essential dietary component that ensures the structural integrity and signaling functions of the cell membranes; it is a major source of methyl groups in the diet, and it directly affects cholinergic neurotransmission, transmembrane signaling, and lipid transport and metabolism. (Rottem 2003, 424)

All the scavenged nutrients must be replaced regularly in the diet or by supplementation. As Rottem continues (and numerous researchers have affirmed), "These morphological effects can be reversed … by replenishing the medium with fresh nutrients" (2003, 425). So, addressing the nutrient depletion is essential and, again, it can be done more easily by a combination of diet, herbs, and supplements. Tastes better, too.

To reiterate: A number of websites that discuss the treatment of mycoplasmas insist that such things as arginine and fatty acids should not be taken in the diet as these "feed the bacteria." Again, this will only result in a worsening of the illness—the mycoplasmas need these substances and they are going to get them from your body one way or another; they are very good at doing so. If you don't replace what they take, as the host cells are depleted of these nutrients, a plethora of symptoms will occur, most of them extremely annoying.

Also: Those on cholesterol-lowering drugs should be cautious if they also have a mycoplasma infection because of the heavy dependence of the bacteria on cholesterol. The combination of mycoplasmas and cholesterol-lowering drugs can cause a significant decrease in cholesterol in the body, especially if the diet is also low in cholesterol. Cholesterol is an essential nutrient, crucial for cellular health, and also necessary as a substrate for steroid production in the body.

Reductions below a certain point can cause significant problems.

There are two ways to address the nutrient depletion caused by mycoplasmas: the first is direct supplementation, the second is a very good diet—I mean *very good*. And by *very good* I don't mean what you think I mean. It has nothing to do with food fascism. It means designing meals that will replace as many nutrients as possible. This, unfortunately, takes a lot of planning and focus; it can also be fun and very tasty. Also: in replacing nutrients that are deficient due to mycoplasmal scavenging meat proteins are essential. ***Let me repeat:*** meat proteins are essential.

Diet alteration is one of the most difficult things to accomplish successfully because of the multitude of cultural and psychological meanings associated with it (food *is* love for many people) but in this instance it is tremendously helpful. In this section I will list the foods that are specifically good for nutrient replacement.

In terms of diet, if you want to replace the nutrients scavenged by the mycoplasmas, here is what you should eat at least every other day (altering it with other things on the lists on the off days) until you are well: eggs, calf or beef liver, oysters, one Brazil nut, sesame seeds (or tahini), avocados, chlorella/spirulina/seaweed green drink (which is basically chlorella, spirulina, and seaweed powders in water or juice).

With the addition of an RNA/DNA complex (or ¼ cup of chlorella in juice) and the use of olive oil (as described later in the antibacterial section) this will replace everything you are losing. If you are suffering severe weight loss, the use of fermented wheat germ and the chlorella/ spirulina/seaweed green drink is essential if you want to reverse it.

THE NUTRIENTS TO REPLACE

B Vitamins

All the mycoplasmas scavenge these very deeply; they must be replaced daily. A good B-vitamin complex is essential. I would recommend the use of something similar to Source Naturals Coenzymate B Complex. The dosage should be adjusted for

the degree of impairment the mycoplasma is causing. In general, dosing should be 2x the recommendation on the bottle and increased as necessary depending on symptoms.

Food sources: The B vitamins are found in the highest amounts in wheat germ, dark green leafy vegetables (asparagus, spinach, turnip greens, and so on), oysters, clams, mussels, crabs, lobsters, beef, liver, pork, ham, chicken, turkey, fish, eggs, whole grains, rice, peas, beans, lentils, nuts, avocados.

Choline

Choline is usually grouped among the B vitamins and is often contained in B supplements. Nevertheless, I mention it here because it is essential to replace. During mycoplasma infection it is heavily scavenged—in fact, *M. fermentans* (for example) depletes this nutrient almost completely from host tissues. The amount contained in B-complex formulations is generally sufficient.

In general, the recommended dosage is 500 mg daily.

Food sources: Choline is found in the highest quantities in egg yolks (which is why nearly all mycoplasmas so strongly scavenge eggs from their hosts), caviar (fish eggs), organ meats (liver, kidneys, brain, and so on), beef, pork, poultry, fish, soy, whole grains, wheat germ, cocoa and dark chocolate, milk, tea (green and black), shellfish, peanuts.

Three ounces of egg yolk contains about 680 mg of choline (the same amount of egg whites contains about 1 mg), three ounces of beef liver has about 400 mg, one medium oyster has around 9 mg, three ounces of wheat germ contributes 150 mg.

Zinc

Zinc plays essential roles in most cell and organism function and is second only to iron in its concentration in the body. It is crucial for immune function, cell division, cell growth, wound healing, and reproductive system health. It is a potent antioxidant, especially in the brain. Zinc levels are high in the CNS and the brain tissue; it is heavily scavenged by

mycoplasmas and its reduction leads to damage in all these systems. It is crucial to replace during a mycoplasma infection.

Dose recommendations are 25–50 mg daily, depending on the level of impairment.

Food sources: Zinc is found in the highest amounts (in descending order) in oysters, wheat germ, liver, seeds (highest in sesame seeds, tahini, pumpkin and squash seeds, and watermelon seeds), roast beef, dark chocolate and cocoa, lamb, peanuts, garlic, chickpeas.

To give you an idea of levels: oysters concentrate zinc (and copper as well). One medium oyster contains about 13 mg of zinc, three ounces of wheat germ contains 17 mg, calf liver has about 12 mg per three ounces, sesame seeds contain about 8 mg per three ounces, and so on.

Copper

Copper is crucial in reducing tissue damage caused by free radicals and oxidants, for maintaining the health of bones and connective tissues, to preserve the myelin sheaths that surround nerves, to keep the thyroid gland healthy, and to prevent easy rupture of blood vessels. Mycoplasmas affect all these things, so supplementation one way or another is crucial.

The dosage recommendation for copper is normally 2–5 mg daily. I would not go much higher than this with a supplement. If you are taking copper in food, the body can deal with the higher levels because of the form it comes in.

Food sources: Copper is found in the highest amounts (in descending order) in liver, oysters, seeds (especially sesame seeds and tahini, sunflower seeds, and pumpkin and squash seeds), cocoa and chocolate, nuts (cashews have the most followed by hazelnuts, Brazil nuts, walnuts, pistachios, pine nuts, peanuts, pecans, and almonds), calamari and lobster, tomatoes (especially sun-dried), legumes (beans, peas, alfalfa, and clover have the most), lamb chops, cherries, whole grains, artichokes, avocados, radishes, garlic, mushrooms, potatoes, bananas, soy.

To give you an idea of amounts: calf liver supplies a bit more than 4 mg of copper per ounce, a medium oyster contains about 0.66 mg of copper, ¼ cup of sesame seeds 1.5 mg, a cup of cooked turnip greens 0.33 mg.

Selenium

Selenium is also crucial. It is incorporated into proteins in the formation of antioxidant enzymes in order to protect the body from free radicals, which the mycoplasmas create in abundance. Antioxidant enzymes are essential to immune function and for a healthy thyroid. Mycoplasmas reduce this mineral to very low levels.

The daily dosage in mycoplasma infection is 200 mcg daily (repeat: *micrograms*).

Food sources: Selenium is found in the highest amounts (in descending order) in Brazil nuts, fish (tuna, cod, halibut, sardines, flounder, salmon), poultry (chicken and turkey), sunflower seeds, shellfish (oysters, mussels, shrimp, clams, scallops), meat (liver, beef, lamb, pork), eggs, mushrooms, whole grains, wheat germ, onions, garlic, asparagus, broccoli, tomatoes.

One ounce of Brazil nuts (usually just called “nuts” in Brazil) will supply 544 mcg of selenium—you don’t need many; one Brazil nut can supply a whole day’s supply of selenium. To give a comparison, tuna fish contains 68 mcg per ounce, cod 32 mcg per ounce, turkey 27 mcg, sunflower seeds 23, oysters 22, and so on.

Amino Acids

The most important to replace are L-arginine, L-tryptophan, L-threonine, and L-serine, though all need to be supplemented, especially the eight essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Even though only about half of the mycoplasmas scavenge L-arginine (thus depleting body supplies) that particular amino acid is somewhat antibacterial for the others. L-tryptophan is another that is heavily scavenged by all mycoplasmas. Additionally, if vitamin B3 levels fall, as they do because of mycoplasma scavenging, tryptophan is used to

make more, at about a 60:1 ratio. Thus what happens is that a whole lot of tryptophan is used to make up the loss in B vitamins. The combination of scavenging and conversion will reduce levels severely, very fast.

The recommended daily dose (for someone weighing 150 pounds) for the eight essential amino acids established by the World Health Organization is isoleucine 1,400 mg, leucine 2,700 mg, lysine 2,100 mg, methionine 700 mg, phenylalanine 1,500 mg, threonine 1,000 mg, tryptophan 300 mg, valine 1,800 mg.

Dosage for L-tryptophan: Irrespective of the WHO guidelines, most sources cite the normal trytophan supplementation dosage range as being 1–3 grams daily. During mycoplasma infection that should be increased to 3–6 grams daily. **Food sources:** Foods high in tryptophan are seaweed, spirulina, chlorella, spinach, soy, eggs, halibut, lobsters, shrimp, crabs, poultry, red meat, dairy, seeds (walnuts, sesame seeds, tahini, sunflower seeds, pumpkin seeds), whole grains (especially raw oat bran and wheat germ). Seaweed, spirulina, and chlorella contain about 1,000 mg (i.e., 1 gram) of tryptophan per three ounces, mozzarella cheese has about 500 mg per three ounces, red meats contain about 400 mg per three ounces, halibut about 300, peanuts about 230.

Dosage for L-threonine: This should run 7–15 mg per kilogram (2.2 pounds) of body weight. For someone weighing 150 pounds that would be 500–1,000 mg daily. During mycoplasma infection that should double. **Food sources:** Foods high in L-threonine are (in descending order) beans, lentils, nuts, and seeds (soybeans contain 1,600 mg per four ounces, lentils 1,000 mg, cowpeas 900 mg, peanuts 880 mg, flaxseed 770 mg, sesame seeds or tahini 740 mg, chickpeas 720 mg, almonds 680 mg, and walnuts 600 mg); meat, poultry, and fish (salami, beef, salmon, chicken, shrimp, pork); dairy products and eggs (eggs and egg yolks, milk, cheese).

Dosage for L-serine: There aren’t any established daily recommendations for serine, however serine is crucial for myelin sheath formation and is important in the CNS, and its replacement is essential during mycoplasma infection. It can

be gained from a standard amino acid supplement mix or from the use of phosphatidyl serine powders (with the dosage as recommended on the product label). **Food sources:** Serine can also be found (in descending order) in soybeans, eggs and egg yolk, lentils, peanuts, cowpeas, almonds, chickpeas, sesame seeds and tahini, flaxseed, walnuts, salami, beef, salmon, shrimp, chicken, pork, milk, asparagus, beans. The suggested mycoplasma diet will replace what you need just fine.

Dosage range for L-arginine: L-arginine is a critical amino acid to utilize. The addition of L-arginine to cells infected with *M. salivarium* (and other arginine-utilizing mycoplasmas) in vitro has been found to normalize damaged cellular structures. In addition to the benefits of replacing the L-arginine scavenged by mycoplasmal organisms, this amino acid is somewhat toxic to those that do not scavenge it, and importantly it acts to remove ammonia from the body. Ammonia buildup is common with many species of mycoplasma and can cause severe problems in the CNS. The normal dosage range for L-arginine during mycoplasma infection should be 2–4 grams daily. **Food sources:** Foods that are high in L-arginine are (in descending order) red meats (especially liver and kidneys), nuts (peanuts, almonds, walnuts, hazelnuts, cashews), spinach, lentils, whole grains (especially wheat), soy, seafoods (crabs, shrimp, lobsters, tuna, salmon), eggs.

Fatty Acids

Mycoplasmas scavenge particular fatty acids, in specific oleic (the most), linoleic, palmitic (a.k.a. hexadecanoic), linolenic, and myristic acids. The best overall source for these is olive oil (though it does not contain myristic acid). Olive oil is 55 to 83 percent oleic acid (an omega-9), 3.5 to 21 percent linoleic acid (an omega-6), 7.5 to 20 percent palmitic acid (saturated fatty acid), 0.5 to 5 percent stearic acid (saturated), and about 1.5 percent linolenic acid (omega-3). (Cordyceps is also particularly high in oleic acid.)

Coconut oil is a good source for myristic acid. Myristic acid makes up 16 to 21 percent of coconut oil; palmitic acid, 7.5 to

10 percent; and oleic acid, 5 to 10 percent. Myristic acid is also in milk fats including cheeses.

Because olive oil contains three substances that are potently antimycoplasmal (see the antibacterial section) as well as the fatty acids most scavenged by the mycoplasma organisms I recommend that virgin olive oil be added to the diet.

Food sources: Eat lots of olives as well. Note: Olive leaf, often touted as an antibacterial, is not as effective in this instance as the oil. See the olive oil section in the antibacterials section for a discussion.

RNA/DNA Complex

RNA/DNA complexes are used in hospital nutrition formulas to reduce the time of recovery after surgery, to boost the immune system, and to improve health in severe disease situations. RNA/DNA combinations boost memory and mental sharpness, counteract damage to the brain, improve depression, increase energy, and counteract long-term deficits in chronic disease conditions.

Typical dosages run from 500 mg to 1,500 mg daily. During mycoplasma infection, if the infection is serious, that should run from 1,000 mg to 3,000 mg daily in three divided doses—the higher doses for those severely affected. Tablets are available that contain from 100 mg to 250 mg.

Food sources: Chlorella, at least ¼ cup daily. (Note: Ordering it in bulk one-pound lots wholesale is much cheaper than all those ridiculous capsules.) Cordyceps is very high in the nucleobases that are used to make up RNA/DNA. If you are using chlorella and cordyceps, you won't need to supplement with an RNA/DNA complex.

CYTOKINE CASCADE REDUCTION

The mycoplasmas, although they do stimulate a variety of cytokines, tend to be dependent on the same initial cytokines —which then stimulate others. When researchers talk about cytokine cascades, they often speak of upstream and downstream events. What they mean is that there are certain

cytokines that are stimulated first and these then stimulate the production of others. Research has found, over and over again, that if you interrupt the cascade upstream, the downstream events don't occur. In treating mycoplasma infection the research shows that the most important cytokines to disrupt are, in this order, TNF-α, NK-κB, IL-1 (especially IL-1β), IL-6, IL-8, ERK-1 and ERK-2, JNK, p38, and Rho kinase. Inhibition of the MAPKs will inhibit many of these cytokines. Inhibiting nitric oxide is also crucial as it is one of the things the bacteria use to initially stimulate the other cytokines.

It is also especially helpful to reduce P2X(7) receptor activation and reduce the impacts of so much free ATP in the CNS and brain. Nitric oxide and the reactive oxygen species (peroxides, superoxides, and hydroxyl radicals) must also be reduced as they have tremendous impacts on cellular function, especially in the brain. Antioxidants that address these, especially those reducing nitric oxide, are essential. PGE2 is another chemically active substance with wide-ranging effects that the mycoplasmas generate in high quantities. It is crucial as well to inhibit its production. In sum, P2X(7) receptors, nitric oxide, and PGE2 must all be inhibited.

PRIMARY CYTOKINE CASCADE INHIBITORS

These are the herbs and supplements that will be the strongest and most reliable in reducing the mycoplasmal cytokine cascade. The most important are cordyceps, Chinese skullcap, and N-acetylcysteine.

Cordyceps

Cordyceps sinensis is almost always the main species used though *C. militaris* is considered interchangeable. There are a lot of different species in the genus; many of them are usable medicinals but these two species are where I would focus the most for mycoplasma.

Cordyceps is a unique kind of mushroom that grows, mostly, on insects of one sort or another—though, of course, it kills the host in the process. In the past, the whole thing was used to make medicine, and these days the mushroom is either

grown on grain or else the mycelium is grown in a vat through a fermentation process, much like penicillin.

There is some speculation, but there is little research on it as yet, that the fruiting mushrooms grown on grain have different medicinal actions and chemistry than those found wild and this is true of the vat-grown mycelium as well.

Studies of the gross constituents show a high similarity between the grown and wild species and, when tested, the grown varieties do have very similar impacts in the body. The one in-depth study I have seen does show a variation in chemistry—the same compounds are in both but in differing quantities, the grown having much more of some, less of a few others. One other analysis found that there were some particular compounds in the insect-host-grown cordyceps that were not in the vat-grown. Those compounds tend to be named after the insect host itself, e.g., cicada peptins. And those compounds do have medicinal actions themselves. Nevertheless, most studies have been with the grown varieties not the wild and they do have a very close range of action to those of the wild species.

Cordyceps really is a very potent and very good medicinal with a wide range of actions. And, as you will see, it is very specific for many of the problems that mycoplasmal organisms cause.

It is an immunomodulator and immunoadaptogen, mitochondrial adaptogen (increases oxygen utilization in the mitochondria, stimulates ATP production by the mitochondria, protects mitochondria from adverse events), anti-inflammatory, antioxidant, neuroprotective, antitumor, antimetastic, hepatoprotective (autoimmune protection, reduces fibrosis, reduces and inhibits cirrhosis, anti-hepatitis B), renoprotective (protects from toxicity, inhibits renal failure, reverses glomerulonephritis), cardiotonic (hypotensive, strengthens heartbeat, antiarrhythmic, improves myocardial ischemia), nerve sedative, sleep regulator, anticonvulsant, antitussive, antiasthmatic, expectorant, bronchial regulator, antipyretic, adrenogenic, steroidogenic, hypolipidemic, hypoglycemic, antibacterial, animicrobial, insecticidal.

Cordyceps is a rather potent immunoadaptogen. If immune activity is high, it reduces it, if low, it enhances it. When taken regularly, if the immune system is stressed by, say, a bacterial organism, the herb will stimulate the immune system in just the right way to respond to the stressor while lowering the levels of or inhibiting entirely the bacterial-induced cytokines that are generated.

Cordyceps is not primarily an antibacterial but is rather a systemic tonic and adaptogen, but still it does have some antimicrobial actions. It is active against *Mycobacterium tuberculosis, Plasmodium* spp., *Clostridium* spp., herpes simplex virus 1, HIV-1 protease, hepatitis B, and various cancers (breast, thyroid, kidney, bladder, prostate, lung, Leydig tumor cells, melanoma).

The herb, while not generally active against bacteria, is, however, highly protective of the human body when bacterial infections occur. For example, in one study, mice were fed either phosphate buffered saline (PBS) or *Cordyceps sinensis* (CS) mycelium for three days and then infected with *Streptococcus pyogenes*. The PBS group showed bacterial dissemination throughout their bodies, those in the CS group did not. Only 40 percent of the PBS group survived until day eight, at day ten 70 percent of the CS group were still alive. In addition the PBS group showed extensive skin necrosis, none in the CS group did.

Survival was significantly increased *if* the CS group received more CS every other day. In fact, *all* of the CS-treated group then survived while ALT and AST levels remained normal. Use of the extract, in vitro, against the same bacterial strain showed *no* direct antibacterial activity at all.

The herb is specific for fatigue and weakness, especially after long illness or in chronic infections, poor mitochondrial function, chronic wasting, unproductive cough from no known cause, general inflammation in brain or joints, mental fog and confusion, low libido, lung infections, kidney infections, thick mucus in the lungs that will not move, immune dysregulation, dizziness, tinnitus, nocturia, cancer. It is especially effective for mycoplasma infections. ***Note:*** dosages need to be rather

large; the usual tepid American doses of 500–1,000 mg daily are ineffective for active disease conditions.

Cordyceps has a unique chemistry and, when considering mycoplasma infections, this includes a number of the nutrients that the mycoplasmas scavenge, especially oleic acid, adenosine, DNA/RNA nucleotides, amino acids, sterols, minerals, and B vitamins. It will also stop the exact cytokine cascade the bacteria initiate *and* restore immune function, while also protecting a number of organs and their functioning. It is perhaps the most specific herb on the planet for mycoplasma infections.

There are three constituents that are, at present, considered to be the major active chemicals in cordyceps: cordycepin (a.k.a. 3′-deoxyadenosine, a purine alkaloid and a derivative of adenosine), cordycepic acid (a.k.a. D-mannitol), and cordyceps polysaccharide. Some commercial formulations are standardized for cordycepic acid (usually 10 percent), others for 7 percent cordycepin or 0.1 percent adenosine (sort of the same thing). Most are made from cordyceps mycelium and will state as much on the label.

Vat-fermented cordyceps mycelium contains a lot more cordycepin than the wild mushrooms, 40 micrograms per gram versus 5 mcg/g. Cordycepic acid varies in wild populations, comprising anywhere from 7 to 29 percent by weight depending on time of year, location, and so on. The fruiting bodies contain from 30 to 85 milligrams per gram of cordycepic acid; the mycelial content is much higher (which is part of the reason the whole caterpillar is harvested for medicine, not just the club mushroom itself).

Cordyceps, like most mushrooms, has a very high polysaccharide content. The main one is considered to be cordyceps polysaccharide and is primarily composed of D-mannose and D-galactose in a ratio of 3:5. It runs from 3 to 8 percent by weight of the harvested fungus. Most of the rest of the polysaccharides in the herb are simply labeled by identifiers such as P70-1, CPS-1, and so on. As with many mushrooms, there are a lot of them, 36 so far.

The fungus is very high in nucleotides, the molecular components of the nucleic acids RNA and DNA. The main ones are guanosine, adenosine, and uridine in that order. The nucleotides tend to be higher, often much more so, in cordyceps vat-grown mycelium than in the wild fungus.

There are various sterols. Ergosterol is a primary one, a precursor of vitamin D2. It is much higher in the fruiting body itself (10 mg/g) than in the mycelium (1.5 mg/g). Others are sitosterol, daucosterol, and campesterol.

Cordyceps is very high in 18 different amino acids. The mycelial powders have the highest content. Glutamate, arginine, and aspartic acid are the highest.

The mushroom is also very high in fatty acids, in this order: linoleic acid, oleic acid, palmitic acid, and other octadeca acids.

It also contains substantial quantities of 13 different minerals (and traces of seven more), in this order: potassium, phosphorus, magnesium, calcium, sodium, iron, aluminum, zinc, manganese, silicon, boron, copper, selenium.

And, of course, vitamins: E, K, B_1, B_2, B_{12}.

There are a few other compounds in the fungus including cordymin, various aminophenols, some unusual cyclic dipeptides, various dihydroisocoumarins, cordypyridones A and B, various diphenyl ethers, myriocin, various polyamines (cadaverine, spermidine, spermine, putrescine, and so on).

The constituents of *C. militaris* are very similar.

Cordyceps was first recorded in Tibet in the fifteenth century in the medical text *Mennag chewa rinsel* by Zurkhar Namnyi Dorje but it isn't used much by the Tibetans (or the Indians either). It is, however, a primary herb in traditional Chinese medicine.

In traditional Chinese medicine, cordyceps is described variously as having a neutral property and sweet taste or as being sweet/acrid with a warm property. It acts on the lung and kidney channels, is lung-nourishing, kidney-vital-essence- and vital-energy-tonifying, hemostatic, and phlegm resolvent, that

is, a mucolytic. It is generally prescribed for overall debility after sickness and for the aged. It is considered to be one of the three primary invigorating medicinals in Chinese medicine along with Asian ginseng and deer antler.

It is specific for tonifying the lungs, arresting bronchial bleeding, dispelling phlegm, chronic cough, asthma, wasting, and tonifying the kidneys. It is also used for impotence, low libido, poor seminal emissions, and aching of loins and knees, and as a tonic for spontaneous sweating, aversion to cold, tinnitus, chronic nephritis, general weakness, and sexual hypofunction.

Most of the scientific studies have occurred since 1995, which is when the world began to notice the herb. There were four studies published in 1995, by 2011 there were 80. And those are just the ones accessible through PubMed, the National Library of Medicine's online database of research in the life sciences and biomedical fields; there are scores more in the Chinese, Japanese, and Korean databases, most not translated into English. Here is an overview.

In Vitro Studies

Cordyceps downregulates a number of inflammatory cytokines and upregulates others such as IL-10, TGF-β, and IL-1ra that are specific for controlling overactive inflammation responses in the body. In underactive immune systems, it will upregulate cytokines to help the body deal with disease. In overactive immune circumstances it will downregulate them.

It downregulates or inhibits NF-κB, TNF-α, IL-1β, IL-12, nitric oxide, iNOS, SOD (superoxide dismutase), elastase, luceriferase, ERK, PI3K (phosphoinositide 3-kinase), JAK-2 (Janus kinase-2), JNK, p38, PGE2, Syk (spleen tyrosine kinase), STAT-1 (signal transducer and activator of transcription-1), AP-1, MMP-3, MMP-9, and H_2O_2 hemolysis, and it scavenges hydroxyl radicals.

When cells are challenged by bacterial membrane proteins it strongly downregulates TNF-α, IL-12, and nitric oxide. In lipopolysaccharide-activated macrophages it inhibits NF-κB, nitric oxide, TNF-α, IL-1β, IL-6, IL-12, IFN-γ, AP-1, COX-2,

and the phosphorylation of p38 MAPK and Akt, as well as inhibiting PGE2 levels and suppressing Syk/NF-κB, IKKÎμ/IRF-3 (IkappaB kinase epsilon/interferon regulatory factor-3), and p38/AP-1 pathways.

Treatment with cordyceps or the cordyceps constituent cordycepin, or adenosine, causes lipopolysaccharide-stimulated macrophages to return to their original inactivated shape. This dynamic is dose dependent and needs relatively high levels of the herb.

Cordycepin suppresses TNF-α and MMP-9 expression in human bladder cancer cells, inactivates the PI3K pathway in LNCaP cells, and increases levels of TIMP-1 and TIMP-2 (tissue inhibitor of metalloproteinase) and thus downregulates MMP-3 and MMP-9 in prostate cancer cells.

Cordyceps possesses a potent sphingomyelinase inhibitor that inhibits the breakdown of sphingomyelin in the body, especially in the brain, making it specific for mycoplasma. It strongly inhibits hydrogen peroxide oxidation and activity against cells and actively protects the mitochondria (reducing oxidative stress and mitochondrial depolarization). It acts as an intracellular antioxidant and is a strong hydroxyl radical scavenger. All these actions are dose dependent.

Cordyceps stimulates ATP generation by mitochondria and antioxidant activity, and it modulates immune responses intracellularly. It protects mitochondria from ROS and enhances the mitochondrial antioxidant defenses. The effects are dose dependent.

Cordycepin strongly inhibits lipopolysaccharide-activated inflammation in microglia cells. It significantly inhibits the production of nitric oxide, PGE2, and proinflammatory cytokines in the microglia. It suppresses NF-κB translocation by blocking IκB-α degradation and inhibits phosphorylation of Akt, ERK-1 and ERK-2, JNK, and p38 kinases. A compound of cordyceps, coptidis rhizoma, and Chinese skullcap also has been shown to have powerful neuroprotective effects on lipopolysaccharide-activated microglial cells. It inhibited nitric oxide, iNOS, COX-2, PGE2, gp91-phox, iROS (intracellular reactive oxygen species), TNF-α, IL-1β, and IκB-α

degradation. It upregulated heme oxygenase-1 and increased cell viability and mitochondrial membrane potential. The three-herb compound was found to strongly protect neural cells from toxicity.

Cordyceps is strongly modulatory on immune cells. In vitro it acts as an activator and maturation stimulant to immature dendritic cells by stimulating the expression of costimulatory molecules and proinflammatory cytokines, enhancing dendritic-cell-induced allogeneic T cell proliferation and reducing the endocytotic ability of dendritic cells. *However,* during lipopolysaccharide stimulation cordyceps suppresses the proinflammatory cytokines involved. It suppresses the lipopolysaccharide-induced, dendritic-cell-elicited allogeneic T cell proliferation and shifts the immune response from a potent Th1 to a Th2 dynamic. In the absence of infection, it potentiates Th1 immune activity. During active infection, it actively modulates the extreme upregulation of lipopolysaccharide cytokines and balances the overreactivity of the Th1 response.

Cordyceps has a lot of effects on airway epithelial cells. It acts to normalize cellular function in airway epithelia by normalizing ion transport. It blocks airway inflammation by blocking NF-κB production in airway epithelial cells. It significantly reduces EGF-stimulated mucous hypersecretion in lung mucoepidermoid cells by downregulating COX-2, MMP-9, and MUC5AC gene expression through blocking NF-κB and the p38/ERK MAPK pathways. Cordyceps strongly affects the inflammation that can occur in the entire bronchial tree. After application of cordyceps, the cell proliferation found in bronchoalveolar lavage fluids is significantly reduced. The herb downregulates IL-1β, IL-6, IL-8, and TNF-α. It is strongly protective of cilia.

In rheumatoid arthritis synovial fibroblasts it inhibits IL-1βinduced MMP-1 and MMP-3 expression. MMP-1 degrades fibrillar collagens, MMP-3 the extracellular matrix. It also inhibits MAPK activation, specifically p38 and JNK. It is a fairly potent inhibitor of p38 phosphorylation.

Cordyceps is highly protective of renal tubular epithelial cells in vitro. It is antiadipogenic. It is antiatherogenic by blocking MAPK, specifically ERK, JNK, and p38. It suppresses the expression of diabetes-regulating genes. It reduces platelet aggregation.

In Vivo Studies

In rats, cordycepin attenuates neointima formation (a thickened layer of arterial tissue) in vascular smooth-tissue muscle cells by inhibiting ROS. Cordymin, a constituent of cordyceps, is strongly anti-inflammatory in induced gastric inflammation in mice by inhibiting IL-1β, TNF-α, and total oxidant levels. It has also been found to be strongly analgesic. Cordyceps (*militaris*) extract suppresses induced acute colitis in mice and significantly reduces the production of inflammatory cytokines from macrophages and mast cells. Nitric oxide, iNOS, and TNF-α are strongly inhibited. Cordyceps extract inhibits airway inflammation in rats by blocking NF-κB. It significantly inhibits ovalbumin-induced airway inflammation in sensitized guinea pigs and rats that mimics the human condition of asthma.

Lipopolysaccharide-injected mice, experiencing induced inflammation, show a remarkable reduction of IL-1β, TNF-α, iNOS, COX-2, and PGE2 when given an extract of *Cordyceps pruinosa.*

Cordyceps extract increases CD4+ and CD8+ lymphocytes, IL-4, and IL-10 in mice, especially in mesenteric lymph node lymphocytes.

Regular daily doses of cordyceps extract prevent disuse-induced osteoporosis in rats.

It increases glutathione levels, reduces oxidants, and lowers blood glucose levels in streptozotocin-induced diabetic rats.

Cordyceps extract significantly improves learning and reduces memory impairment in mice. *Cordyceps militaris* extract (and cordycepin) protects hippocampal neurons in gerbils from ischemic injury. Cordycepin is strongly protective of neurons against cerebral ischemia-reperfusion. It considerably lowers levels of MMP-3 in the brain, increases

SOD, and decreases malondialdehyde, significantly reducing oxidation. In one study, *Cordyceps sinensis* mycelium strongly protected rat neurons from ischemic injury by inhibiting NF-κB, PMNs (polymorphonuclear neutrophils), IL-1β, iNOS, TNF-α, ICAM-1 (intercellular adhesion molecule-1), and COX-2. A cordymin extract pretty much did the same thing in another study. And in still another study cordyceps extract protected the brain from injury after middle cerebral artery occlusion-induced cerebral ischemia in rats. Cordycepin was found to prevent postischemic neuronal degeneration in mice.

Cordyceps sinensis extract significantly reduces renal ishcemiareperfusion injury in rats. Various forms of renal injury in rats have been ameliorated by the use of several types of *Cordyceps cicadae* extracts.

Corcycepin is strongly steroidogenic. It stimulates testosterone production in mouse Leydig cells. Serum testosterone and sperm count and motility are strongly increased in rats after supplementation with *Cordyceps militaris*.

Human Clinical Studies and Trials

Cordyceps extract inhibits the proliferation and differentiation of Th2 cells and reduces the expression of related cytokines by downregulating GST-3 mRNA and upregulating FOXP3 mRNA and relieves chronic allergic inflammation by increasing IL-10 in the blood of children with chronic asthma.

In one study, 60 asthmatic patients were split into two groups. Thirty used an inhaler, the rest used cordyceps capsules. IgE, soluble ICAM-1, IL-4, and MMP-9 were all lowered in the cordyceps group (though not as much as in those using an inhaler). Another study at the Beijing Medical University with 50 asthma patients found that the symptoms in the group treated with cordyceps were reduced by 81 percent in five days versus 61 percent over nine days in the pharmaceutical group.

There have been a number of other trials of the herb in the treatment of chronic obstructive pulmonary disease (COPD), asthma, and bronchitis that have not been translated into

English. The herb was effective for all these conditions; it is especially indicated for COPD.

Sixty-five renal dialysis patients were split into two groups. The 33 in the second group took cordyceps (330 mg) and ginkgo (230 mg) 3x daily for 3 months. At the end of that period microinflammation, a problem in renal hemodialysis, was significantly lowered in the herb group. Levels of hs-CRP (high-sensitivity C-reactive protein), IL-6, and TNF-α were all much lower.

In one study with 51 patients suffering chronic renal failure, the use of 3–5 grams/day of cordyceps significantly improved renal function and increased immune function. Another study with 57 people suffering gentamicin-induced renal damage split the subjects into two groups, one receiving cordyceps, the other conventional pharmaceuticals. After six days those in the cordyceps group had recovered 89 percent of their kidney function versus 45 percent in the other group.

Sixty-one people with lupus nephritis were split into two groups. One received 2–4 grams of cordyceps (before meals) and 600 mg of artemisinin (after meals) 3x daily for 3 years. They were observed for an additional five years after treatment. Twenty-six had no recurrence, four had mild, and for one the herbs did not work.

A randomized trial of cordyceps in the treatment of 21 aged patients (divided into two groups) found that cordyceps ameliorated aminoglycoside nephrotoxicity.

Cordyceps sinensis was used in the long-term treatment of renal transplant patients. Long-term survival was no different in the treated and untreated groups, however the incidence of complication was significantly lower in the cordyceps group. The cordyceps group needed much lower doses of cyclosporine A and serum levels of IL-10 in the cordyceps group were much higher. Another renal transplant study with 200 transplant patients showed the same outcomes.

Three separate studies with a combined patient population of 756 men and women who were experiencing reduced sex drive found that after 40 days 65 percent of those on cordyceps

reported improved libido and performance versus 24 percent of those taking a placebo. In another study with elderly patients complaining of decreased libido, impotence, and other sexual malfunctions 3 grams/day of cordyceps was administered for 40 days. Increased sperm survival time, increased sperm count, and decreased numbers of malformed sperm were all found in the majority of males. Improvements in hypoleukorrhagia, menoxenia, and sex drive were reported in a majority of the women.

There have been a number of clinical studies of the herb in cancer treatment, along with chemo and radiation. In one study of 50 patients, tumors reduced in 23. In another, after two months, most patients taking cordyceps reported improved subjective symptoms. White blood cell counts stayed at 3,000/mm^3 or higher. The use of cordyceps during radiation and chemo has been found to counteract the negative immune effects of those procedures.

There have been a number of Chinese studies on using the herb for treating heart conditions, liver problems, hypercholesterolemia, and male/female sexual dysfunction but few of them have been translated into English. There have also been a few studying exercise tolerance and improvement, e.g., 20 adults aged 50 to 75, in a double-blind, placebo-controlled trial showed improved exercise performance. However, the main studies in the U.S. have been on exercise tolerance with young athletes and they all showed no improvement. The dosages were extremely low.

The best overall look at the herb, its history, and its medical uses is probably John Holliday and Matt Cleaver, *On the Trail of the Yak: Ancient Cordyceps in the Modern World* (June 2004). I have only found it online and downloaded it from the website of Earthpulse Press (www.earthpulse.com).

Important: To be effective for anything, cordyceps *must* be dosed appropriately. That means a minimum dose of 3 grams daily but the best results occur with 6 grams daily as the baseline, especially in acute conditions. The renal studies usually used from 3 to 4.5 grams. This dose range can also work for lung problems, except in truly acute conditions when

it should be 6 to 9 grams. In mycoplasma treatment it should be 6 to 9 grams per day as well.

Important note: There is a ridiculous herban (or is it urban?) legend that if a person has a candida infection (or any kind of yeast or fungal infection or overgrowth, e.g., thrush) they can't take any kind of mushroom (IT'S A FUNGUS!) as it will cause the yeast/fungal infection to grow out of control. This is totally and completely untrue. It is akin to saying that I have an allergy to eggplant, so I can't eat any other plants. Some people do have allergic reactions to fungi, and if you do, don't use this one. But it will NOT, absolutely NOT, cause candida or any other kind of intestinal or systemic yeast or fungal infection to "bloom."

Preparation and Dosage

Cordyceps needs to be viewed as a medicinal *food,* not a raw drug to be taken in minute doses. Again, the Chinese tonic dosages are normally rather large, 3–9 grams per day and during acute disease conditions they can go as high as 50 grams, nearly two ounces, per day.

If you think of the herb as a food, then eating two ounces, say, as you do of asparagus or potatoes, doesn't seem like all that much. In China, cordyceps is often added to soups and stews (just as astragalus is) as a food ingredient for chronic illness. Sometimes the Chinese decoct it in water and drink it as a tea, however traditional healers for millennia in Tibet and India (and in parts of China) used the herb only after soaking it in an alcohol/water combination, usually the local alcoholic drink. And in fact a number of the constituents are only extractable in alcohol.

The best way to use the herb is either as a powder preparation, taken directly by mouth (allowing the stomach acids and bile, etc., to extract for you), or as a tincture.

For mycoplasma I would recommend you buy the powder in bulk from someone such as 1stChineseHerbs.com and then use 3–4 tablespoons of the powder blended in water or juice 3x daily.

The tepid U.S. dosages, 500–1,000 milligrams daily, are useless for any active disease condition. I repeat: *useless.*

Since you will probably not be using the wild-crafted mushroom, make sure you get a Chinese-produced cordyceps that is the vat-grown mycelium. This mycelial culture is from Tibetan wild-harvested cordyceps. The U.S. version, while a similar starter, is normally grown on rice or some other grain. It may be great but I prefer the vat-grown.

Capsules: The Chinese brands, if you buy capsules, run around 900–1,000 mg per capsule and the suggested dose is 6,000 milligrams (6 grams) per day—just for a tonic dose. If you want to use the capsules for mycoplasma I would double that.

Tincture dosages: Tonic—¼–½ teaspoon 3x daily; active infection—½–1 teaspoon 3–6x daily.

Some sources recommend taking cordyceps with vitamin C to help assimilation. There isn't anything in the scientific literature on this and the Asians used the herb (and noted its beneficial effects) for thousands of years before vitamin C was discovered, so … not sure where that urban legend came from.

Side Effects and Contraindications

There are no side effects noted in the literature. Up to 5 grams per kilogram of body weight per day have been used in rats long term with no side effects. That would be 350 grams—i.e., about 12 ounces or ¾ pound—in a person weighing 150 pounds. Double that dose was used with rabbits for three months with no side effects.

The only reported side effects I can find are occasional reports of dry mouth, nausea, and diarrhea. One case of an allergic reaction (a general allergy to fungi) that subsided when the herb was discontinued.

Herb/Drug and Herb/Herb Interactions

Cordyceps sinensis is synergistic with cyclosporine A and the amount of the drug needed is lessened if cordyceps is taken. The hypoglycemic actions of the herb also reduce the dosage needs for those on antidiabetic medications. There is some

concern as well that cordyceps might be synergistic or additive with anitretroviral drugs, thus affecting dosage requirements, but nothing has yet been reported in the literature.

Vitamin C is reputed to help assimilation and may, *if this is true,* increase the impact of the herb in the body.

Finding It

You can get bulk powder and capsules from 1stChineseHerbs.com (www.1stchineseherbs.com) as well as many other online purveyors. If you want to spend enormous amounts of money, you can also buy the wild-crafted mushroom itself. Or … you can join the local mycological society (find a fun one, usually it *won't* include guys with mathematically shaven beards) and learn to find it in the wild; in the U.S. this will almost always be *Cordyceps militaris,* but again, this is interchangeable with *Cordyceps sinensis.*

Chinese Skullcap

Scutellaria baicalensis is the primary species used in China and the one meant when Chinese skullcap is talked about. It most definitely ***does not*** mean the American skullcap, *Scutellaria lateriflora*—or any of the other American species. For reasons I will discuss in this section I strongly suggest you ***do not use*** *S. lateriflora* as a substitute for treating mycoplasma or viral infections.

With the Chinese skullcap *the root and the root only is used* — generally just from plants three years or older. There is reason to believe that the increase in pharmacological action of Chinese skullcap over the usual American species used as medicinals is due to the difference between using the root in Chinese practice and the leaf in American practice. As far as I know there has been virtually no examination of the use as a medicinal of the root or its constituent strength in any other species besides the Chinese. The U.S. researchers and herbalists just ignore the use of the root of the American species, probably due to an overreliance on the experiences and herbal uses of the Eclectic botanical physicians.

There are, as well, no substantive studies on the difference between roots and leaves of any species of skullcap as regards

their chemical compounds. The few I have seen that touch on it do show substantial differences in how much is in the leaf and the root and these really do need to be explored, especially if American herbalists are insisting that the American skullcaps are interchangeable with the Chinese. Song and Wang (2010) comment, “The results showed that the components and relative contents of the essential oils among flowers, stem, leaves, roots, and seeds have significant differences.” Which is, of course, true of nearly all plants on Earth and one of the most basic understandings of herbal medicine.

Chinese skullcap has a wide range of actions. It is antiviral, anti-inflammatory, antioxidant, nervine, neuroprotective, anodyne, mildly sedative, anticonvulsant, hepatoprotective, antihypertensive, anticholesterolemic, cholagogue, antianaphylactic, antispasmodic, astringent, expectorant, hemostatic, antioxidant, antiangiogenic, antitumor, antimetastic, antibacterial, antifungal, antidiarrheal, antidysenteric, febrifuge, diuretic.

In terms of antimicrobial effects the plant is primarily a strong antiviral. It has actions against influenza A (H1N1, H3N2), influenza B, Sendai virus (parainfluenza), respiratory syncytial virus, vesicular stomatitis virus, HIV-1, hepatitis A, hepatitis B (resistant and non), hepatitis C, and coliphage MS2. It does have a fairly wide range of action against bacteria and some other microbes but the effects are variable. The strongest seem to be against staph.

It has shown action against some other microbes: *Bacillus subtilis, Bacteroides melaninogenicus, Candida albicans, Chlamydia trachomatis, Corynebacterium xerosis, E. coli, Enterococcus faecalis, Helicobacter pylori, Klebsiella pneumoniae, Kytococcus sedentarius, Lactobacillus plantarum, Microsporum audouinii, Microsporum canis, Mycobacterium smegma-tis, Mycobacterium tuberculosis, Neisseria meningitidis, Proteus vulgaris, Pseudomonas fluorescens, Salmonella* spp.*, Salmonella paratyphi, Salmonella typhi, Shigella dysenteriae, Shigella flexneri, Staphylococcus aureus* (resistant and nonresistant strains), *Staphylococcus epidermidis, Staphylococcus hominis,*

Streptococcus hemolyticus, Streptococcus pneumoniae, Toxoplasma gondii, Trichophyton violaceum, Vibrio cholerae, But, again, these antibacterial actions are apparently fairly mild in most cases. As an antimicrobial, Chinese skullcap is primarily an antiviral herb.

When looking at mycoplasma or other coinfections, the herb has a number of specific actions and uses. It is really a top-notch herb for respiratory infections, pneumonia, infections that affect the central nervous system (meningitis, encephalitis, mycoplasma, Lyme, and so forth), impaired brain function, fevers, intermittent fevers, GI tract disorders with accompanying inflammation, diarrhea and dysentery, liver and kidney inflammation, urinary tract infections, nervous irritability, epileptic seizures, convulsions, sleep disruptions, and as supportive therapy in cancer. It is also a fairly potent synergist with pharmaceuticals, herbs, and supplements, helping increase the presence of those compounds in the body by getting them past the GI tract and brain barriers.

The plant chemistry is rather complex, more than 781 different compounds have been found in *S. baicalensis* so far, including 27 different antimicrobial compounds. The six most important are presumed to be baicalein, wogonin, oroxylin A, baicalin, wogonoside, and oroxylin A-7-glucuronide. All are strongly anti-inflammatory, antiviral, and antitumor in action. Some of the other important compounds are considered to be scutellarin, naringenin, apigenin, luteolin, melatonin, and serotonin. All are strongly biologically active.

Until relatively recently it was (wrongly) supposed that melatonin was not present in plants, only animals. A number of plants are now known to produce melatonin (and serotonin). Chinese skullcap has some of the highest levels (7 mcg/g) so far discovered. Studies have found that the melatonin in plants is highly bioavailable and is strongly present in the plasma of animals that ingest them. Plant melatonin does bind to melatonin-binding sites in the human brain, creating specific effects. (One being helping with sleep cycle normalization.)

Melatonin is highly active in the brain; it detoxifies hydroxy radicals, hydrogen peroxide, nitric oxide, peroxynitrite anion,

peroxynitrous acid, and hypochlorous acid. Melatonin is an upstream antioxidant; many of its metabolites, created when it detoxifies those compounds, are also potent antioxidants. It is also synergistic with a number of antioxidant enzymes as well as vitamin C, vitamin E, and glutathione. Melatonin is active at both the micro and macro levels, exerting antioxidative effects at the level of cells, tissues, organs, and organisms. It is a unique substance, much different than other antioxidants. Not only does it work to repair other biomolecules but under in vivo conditions it is four times more potent than vitamins C and E in protecting tissues.

Melatonin is intimately involved in the regulation of circadian rhythms in people, including their healthy sleep cycle. Part of the reason that the sleep cycle is interrupted as people age (and during inflammatory infections in the CNS) is that the oxidative events in the brain are higher and the levels of melatonin (and its regulatory effects) are much lower. Using plants high in melatonin (which is more effective than using melatonin supplements) can normalize the circadian rhythms, including the sleep cycle, and reduce inflammation in the brain and CNS.

The constituents of Chinese skullcap do enter the plasma in substantial amounts; baicalein is strongly concentrated in the lungs, brain, and hippocampus, and wogonin in the liver, kidneys, and lungs. Baicalin concentrates in the brain, specifically in the striatum, thalamus, and hippocampus. Many of their metabolites are strongly present in those locations as well.

This means that the herb and its constituents are specific for many of the problems that mycoplasma causes, especially because of the high levels of melatonin. The root of this plant is extremely specific for protecting the brain and CNS as well as a number of other organ systems that are affected by mycoplasma.

This species of *Scutellaria* is one of the 50 fundamental herbs of Chinese medicine and has been used in traditional Chinese medicine for over 2,000 years. It is one of the most widely used herbs in Chinese medicine.

It is considered bitter and cold, to dispel heat (fever reducer, antiinflammatory), to expel damp heat (e.g., lung infections), to be a detoxicant, to stop bleeding, and to prevent abnormal fetal movements. It is specific for fever, cough, pneumonia, hemoptysis, jaundice, hepatitis, dysentery, diarrhea, bloody stool, vexation, insomnia, headache, enteritis, acute conjunctivitis, uterine bleeding, abnormal fetal movements, hypertension, carbuncle, and furuncle.

Most of the scientific studies on the plant have been conducted in China.

In the West, the Europeans tended to use *S. galericulata,* the American Eclectics *S. lateriflora,* and it is probably from the Europeans that the Americans got their use of the plant. Both were used similarly, primarily as tonics, nervines, and antispasmodics. The Eclectics considered skullcap specific for chorea, convulsions, tremors, intermittent fever, neuralgia, to help sleep, and for nervous afflictions such as delirium tremens and hysteria with involuntary muscle movements. It was used in all cases of nervous excitability, restlessness, and wakefulness, especially after acute or chronic illness. It was considered to be cerebrospinal specific. The usual dose was half an ounce of the recently dried herb in one-half pint of boiling water. The herb was considered to lose its effectiveness if kept too long in the dried state.

The English use was similar with the addition of uses for nervous headaches, headaches from coughing, St. Vitus' dance, hiccups, and tertian ague.

This is in fact the usage range still used by American herbalists and very few of them, unless using the Chinese skullcap, use the root. In current American practice it is considered to be a mild, soothing, and reliable nervine, less stimulating than pasque flower and without the druggy feeling that accompanies valerian if used for sleep.

There are a lot of scientific studies on Chinese skullcap, in vitro, in vivo, and human and clinical trials and studies. The compounds in the root are, not surprisingly, synergistic with each other. All of them that have been studied are potently antiviral, anti-inflammatory, antioxidative, and free radical

scavenging. Wogonin is the most potent nitric oxide inhibitor; oroxylin is the most potent in inhibiting lipid peroxidation. Together they produce effects beyond the individual constituents.

The herb has strong cytokine impacts, reducing nitric oxide, iNOS, IL-3, IL-6, IL-17, COX-2, PGE2, NF-κB, IκB-α, IL-1β, IL-2, IL-12, TNF-α, and VEGF (vascular endothelial growth factor), and it tends to upregulate IL-10. It inhibits the production of IgE, thus suppressing the expression of histamine. It has especially strong impacts in the spleen. It attenuates the activity of c-Raf-1/MEK-1 and -2, ERK-1 and -2, p38, and JNK MAPKs.

In Vitro Studies

Flavones from the root are strongly neuroprotective. Baicalein strongly inhibits the aggregation of neuronal amyloidogenic proteins and induces dissolution of amyloid deposits. Wogonin stimulates brain tissue regeneration, including differentiation of neuronal precursor cells.

Baicalin promotes neuronal differentiation of neural stem/progenitor cells by modulating p-STAT-3 and bHLH (basic helix-loop-helix) protein expression.

Wagonin is neuroprotective against cerebral ischemic insult, and at tiny micromolar concentrations completely suppresses the activity of NF-κB and inhibits the migration of microglial cells to ischemic lesions, thus reducing inflammation at the site of injury. It inhibits the movement of the cells in response to the chemokine MCP-1.

Baicalein attenuates the induced-cell death of brain microglia in mouse microglial cells and rat primary microglia cultures by strongly inhibiting nitric oxide through the suppression of iNOS. The compound inhibits NF-κB activity in the cells as well.

Four compounds in the root inhibit prostate cancer cell proliferation.

Baicalin suppresses IL-1β-induced RANKL (receptor activator of NFκ-B ligand) and COX-2 production at a

concentration of 0.01 mcg/ ml. The longer the constituent is applied the stronger the effect. Used on human peridontal ligament cells it shows highly protective effects.

Baicalein inhibits IL-1β and TNF-α-induced inflammatory cytokine production from human mast cells via regulation of the NF-κB pathway. It inhibits NF-κB and IκB-α phosphorylation.

Baicalin promotes repair of DNA single-strand breakage caused by hydrogen peroxide in cultured fibroblasts.

The plant inhibits aromatase, thus reducing the conversion of androgens into estrogens.

There are scores of other in vitro studies such as these, all showing potent anti-inflammatory and cytokine-modulating actions of the herb and its constituents.

In Vivo Studies

In rats, oroxylin A markedly enhances cognitive and mnestic function in animal models of aging brains and neurodegeneration. Baicalein is anticonvulsive, anxiolytic, and sedative in rats.

Flavonoids from the stems and leaves of *Scutellaria baicalensis* improve memory dysfunction and reduce neuronal damage and levels of abnormal free radicals induced by permanent cerebral ischemia in rats. Other studies have found that the compounds can enhance and improve learning and memory abilities and reduce neuronal pathological alterations induced by a variety of chemicals in mice.

The plant reduces symptoms associated with chronic cerebral hypoperfusion (and chronic lipopolysaccharide infusion), including spatial memory impairments, hippocampal MAPK signaling, and microglial activation.

Baicalein protects mice hippocampal neuronal cells against damage caused by thapsigargin and brefeldin A (BFA). The constituent reduces thapsigargin- and BFA-induced apoptosis of hippocampal cells, reduces the induced expression of endoplasmic reticulum stress-associated proteins, and strongly reduces the levels of MAPKs such as p38, JNK, and ERK. It

reduces ROS accumulation and levels of MMPs. It strongly protects the mitochondria from oxidative damage.

S. baicalensis (in combination with bupleurum) is strongly neuroprotective of iron-reduced neurodegeneration in the nigrostriatal dopaminergic system in rat brains, showing it to be useful for treating CNS neurodegeneration.

Mice, subjected to transient global brain ischemia for 20 minutes, were treated with baicalein (200 mg/kg once daily). Neuronal damage was minimal compared to controls, and MMP-9 activity in the hippocampus was inhibited. Pretreatment with baicalein was, in addition, found to be preventative.

Wogonin is also strongly protective in the brain. Rats were damaged by either four-vessel occlusion or excitotoxic injury (systemic kainate injection). Wogonin conferred protection by attenuating the death of hippocampal neurons. It inhibited the inflammatory activation of the microglia by inhibiting iNOS, TNF-α, nitric oxide, IL-1β, and NF-κB. In vitro studies at the same time found that lipopolysaccharide-activated macrophages were protected similarly.

An ethanol extract of *S. baicalensis* prevented oxidative damage and neuroinflammation and memory impairments in artificial senescence mice. The hippocampus and the mitochondria were strongly protected and neuroinflammation sharply reduced. Expressions of COX-2, iNOS, nitric oxide, PGE2, Bax, and cleaved caspase-3 protein were all reduced. Bcl-2 was increased. The effects were dose dependent and were most effective at 100 mg/kg (that would be 7 grams for a 150-pound person, just in the dosage range usually used in China).

Baicalin reduces the severity of relapsing-remitting experimental autoimmune encephalomyelitis induced by proteolipid protein in a mouse model of multiple sclerosis. All the histopathological findings decrease in the mice given the extract.

Baicalein has been found to be antidepressant in animal models of depression. It reverses the reduction of extracellular

ERK phosphorylation and the level of BDNF (brain-derived neurotrophic factor) expression in the hippocampus of CMS (chronic mild stress) rat models.

Oral administration of baicalein in mice infected with Sendai virus results in a significant reduction of viral titers in the lungs and reduced death rates.

Oral administration of baicalein in mice infected with influenza A virus shows significant effects in preventing death, increasing life span, inhibiting lung consolidation, and reducing lung virus titer in a dose-dependent manner. Amounts as low as 1.2 mcg/ml of baicalin (the metabolite of baicalein) result in significant inhibition of the virus. (***Note:*** plasma levels of baicalin from the ingestion of skullcap root are significantly higher than this after dosing with 3–9 grams per day.)

Baicalin, administered to mice infected with influenza virus, increases survival time, eliminates virus from the lungs, reduces hemagglutination titer and infectivity in the lungs, and reverses pneumonic pathological changes.

In mice infected with hepatitis C virus and treated with *S. baicalensis,* the virus load of the mice decreases after treatment with the herb.

Baicalein and wogonin inhibit irradiation-induced skin damage by suppressing increases in MMP-9 and VEGF through the suppression of COX-2 and NF-κB.

S.baicalensis treatment inhibits passive cutaneous anaphylaxis and reduces histamine release in rats receiving intradermal injections of anti-DNP (dinitrophenol) IgE.

Baicalin, given to pregnant rats, increases the lung surfactant phospholipids in the fetus and accelerates fetal lung maturation.

S. baicalensis is effective in reducing IL-6 and TNF-α in mouse models of pelvic inflammatory disease. The herb is both anti-inflammatory and antinociceptive.

The herb extract stimulates the formation of red blood cells and their precursors under conditions of cyclostatic

myelosuppression and sleep deprivation.

There are many more studies than these, this just gives a very good overview of the range of actions of the plant and its constituents.

Human Clinical Studies and Trials

The root decoction has been used in a number of clinical treatment situations in China to effectively treat scarlet fever, chronic bronchitis, and epidemic cerebrospinal meningitis. (Details are unfortunately sketchy.) The herb is almost always used in combination, so individual studies are few. But there are a few:

Sixty patients with pulmonary infection were treated with either piperacillin sodium or injection of an extract of *S. baicalensis*. Before treatment there was no difference in clinical data. Treatment outcomes were similar in both groups.

In 63 children with upper respiratory infections (51 upper acute, 11 acute bronchitis, 1 tonsillitis) 51 benefited from using the decoction of the root; temperature normalized in three days.

A decoction of *S. barbata* was used with 14 women with metastatic breast cancer in a trial at the Memorial Cancer Institute in Hollywood, Florida, as supportive therapy to normal chemo and radiation. The study authors commented that the herb was safe, well tolerated, and showed promising clinical evidence of anticancer activity.

A 12-week randomized trial of *S. baicalensis* and *Acacia catechu* in Alabama in the dietary management of knee osteoarthritis found that the placebo group had a much higher incidence of respiratory infections than the herbal group. (No mention is made in the study abstract of the herbal compound's effects on osteoarthritis.) However, another study in Arizona, in a randomized, short-term, double-blind event, found that the same mixture (code-named flavocoxid) was as effective as naproxen in controlling signs and symptoms of osteoarthritis of the knee. There was, again, a higher incidence of other effects in the nonherbal group, more edema and muscoskeletal discomfort.

Russian studies with the root found that it increased the relative number of T lymphocytes in lung cancer patients receiving antineoplastic chemotherapy. Another Russian study with 88 lung cancer patients taking a powdered extract of *S baicalensis* root found that ingestion was accompanied by increased hemopoiesis and an increase in immune markers.

There have been a number of combination therapies using *S. baicalensis* in China in the treatment of minimal brain dysfunction, bacillary dysentery, eye infections, and leptospirosis. All showed good outcomes.

Baicalin has been used effectively in treating infectious hepatitis, hepatitis B, and acute biliary tract infections.

The tincture of *S. baicalensis* was used effectively in treating 51 cases of hypertension. Blood pressure levels dropped with accompanying symptom improvement.

Dosages

Again, use the root of Chinese skullcap *and please do not attempt to substitute the American skullcap for this one*.

The Chinese dosages are large, as usual, generally 3–9 grams at a time. Most of the clinical studies and trials used similar dosing. If you are using capsules this is the dosage range you should be exploring, divided into three equal doses every four hours or so.

The herb reaches peak in the plasma and body organs in about one hour and only lasts in the body for about four hours, so you really do need to dose about every three to four hours.

Tincture dosage: ¼–½ teaspoon 3x daily. In acute conditions, double that.

As a wash: The fresh juice of the plant can be used as an eye wash for eye infections, as can the cooled infusion or decoction.

For sleep: The plant and root are high in melatonin, so they can help with sleep. If you are using it for that, take just before bed, ½ teaspoon tincture.

Side Effects and Contraindications

Side effects from *Scutellaria* are rare, mostly gastric discomfort and diarrhea. It should not be used during pregnancy. Caution should be exercised if you are taking pharmaceuticals as it can increase the bioavailability of the drugs, thus increasing their impacts. It may interact additively with blood-pressure-lowering drugs. Type 1 diabetics should exercise strong caution with the herb as it can affect insulin and blood sugar levels.

Herb/Drug and Herb/Herb Interactions

Lots. Chinese skullcap is a synergist, perhaps as efficacious as licorice, ginger, and piperine, and should probably be added to that category of herbs. Among other things it inhibits the NorA efflux pump, which inactivates some forms of antibiotic resistance. Like the other synergists I know of, it is also a strong antiviral, which is beginning to stimulate speculation. Nevertheless, the herb strongly effects pharmaceuticals and herbs taken along with it.

Baicalein, one of the major compounds in *S. baicalensis,* is synergistic with ribavirin, albendazole, ciprofloxacin, amphotericin B.

S. baicalensis is strongly inhibitive of CYP3A4, a member of the cytochrome oxidase system. It is a type of enzyme, strongly present in the liver, and is responsible for catalyzing reactions involved in drug metabolism. Many of the pharmaceuticals that are ingested are metabolized by the CYP3A4 system, meaning that some portion of the drug is inactivated. In some instances it is the metabolites created by CYP3A4 that are active as medicinals. Since the herb inhibits the CYP3A4 system, dose dependently, it can enhance the presence of a number of drugs in the system, specifically acetaminophen, codeine, cyclosporine, diazepam, erythromycin, and so on. It does affect the degree of antibiotics that enter the system.

One of the herb's constituents, oroxylin A, is a strong P-glycoprotein inhibitor. P-glycoprotein is strongly present in the blood-brain barrier, the lining of the GI tract, renal tubular cells, capillary endothelial cells, and the blood-testes barrier. It stops substances from crossing over those barriers.

Additionally, cancer cells use P-glycoprotein as a form of efflux pump in order to eject drugs designed to kill them from the cancer cells. P-glycoprotein inhibitors allow more of a substance to cross over barriers high in P-glycoprotein. That means that oral ingestion of a substance will produce more of it in the bloodstream if it is also taken with a P-glycoprotein inhibitor. This means that Chinese skullcap will act through two mechanisms to increase drug and herb uptake in the body.

It will also increase the effectiveness of anticancer drugs by inhibiting P-glycoprotein-mediated cellular efflux. Paclitaxel uptake, for example, was increased over twofold when administered with oroxylin A.

The herb ameliorates irinotecan-induced gastrointestinal toxicity in cancer patients.

The herb will also increase the uptake of herbal medicines similarly, again by inhibiting the CYP3A4 system and P-glycoprotein.

Finding It

The best tinctures come from Elk Mountain Herbs (www.elkmountainherbs.com), whole herb can be purchased from 1stChinese Herbs.com (www.1stchineseherbs.com), and you can get really good seed from Horizon Herbs (www.horizonherbs.com).

N-acetylcysteine (NAC)

Researchers, studying the cytokine impact of *M. pneumoniae,* found that significant elements of that cascade, specifically intracellular levels of ROS (reactive oxygen species) in epithelial cells, phosphorylation of JAK-2 and STAT-3, STAT-2 DNA-binding activity, and IL-8 expression caused by the bacterial membrane constituents, were inhibited by NAC *in a dose-dependent manner*. In other words, the higher the dose the greater the reduction that occurred. NAC is a precursor of the potent antioxidant glutathione. During mycoplasma infection of the lungs the ROS it stimulates within the cells also cause DNA double-strand breaks. Researchers found that by stopping the ROS increases the DNA strands remained whole.

NAC also strongly inhibits hydrogen peroxide, a common problem in mycoplasma infections. Other studies have noted that NAC inhibits the production of TNF-α, PI3K, p38 MAPK, JNK, IL-6, IL-1β, and MMP-9.

NAC is also strongly mucolytic, meaning it thins, loosens, and clears mucus from the lungs and airways. It is strongly protective of the cilia. NAC is also helpful in septic shock—an overwhelming infection that causes a resultant severe drop in blood pressure. Studies of the supplement in treating septic shock—and endotoxin shock—have found it can reverse those conditions, even if taken postshock.

More interestingly, the levels of glutathione in red blood cells are significantly increased by NAC, thus protecting them from bacterial oxidation and lysis. TNF-α levels are decreased. (NAC is synergistic with pharmaceuticals and herbs in the protection of red blood cells from oxidative death.) NAC has a strongly protective effect on red blood cells, protecting them from oxidative events. This type of protection also occurs in synovial tissues, where it reduces inflammatory cytokines and inhibits collagenase, which breaks down collagen. And, it is also protective throughout the reproductive systems, male and female.

NAC has strong protective effects against neurotoxicity throughout the CNS and can correct neurotoxic effects in the brain, especially in the hippocampus. It protects brain mitochondria from oxidative effects, eliminating membrane depolarization, keeping the mitochondria from swelling, bursting, and releasing ATP. It inhibits brain edema and as well acts throughout the entire peripheral nervous system to inhibit inflammation. It has also been found to protect the fetus during development from the impacts of inflammation induced by bacterial membrane lipids. NAC also inhibits biofilm formation by bacteria, reducing that particular form of protection that many bacteria use.

NAC is a very good systemic; it is widely dispersed in the body within one hour and reaches peak at four hours. Levels remain high for 12 hours. It is predominantly concentrated in the liver, kidneys, skin, thymus, spleen, eyes, brain, and serum.

These actions of NAC are consistent whether in vitro, in vivo, or in human studies. Because NAC has actions in every system that mycoplasma bacteria infect, I think it a crucial supplement to use during mycoplasma infection.

Dosage

The usual dose in most studies on rats has been 20 mg/kg day. That would translate to 1,400 mg daily for a 150-pound person. However, a University of Florida study with people found that a better dose for adults is 4–6 grams per day—for children 60 mg/kg. The best dose for mycoplasma infection, based on this, would be 2,000 mg in the morning and 2,000 mg in the evening just before bed.

Vitamin E

Studies have shown that supplementation with vitamin E will 1) reduce the mycoplasmal inhibition of catalase by at least half, 2) lower the levels of malondialdehyde (an indicator of membrane lipid peroxidation that occurs when the mycoplasmas are lysing cellular membranes) by anywhere from 60 to 75 percent, and 3) increase the levels of lactate dehydrogenase by 20 to 40 percent. In other words it acts as a fairly good antioxidant in protecting cells from oxidative damage by mycoplasmas. Protecting vigorous catalase activity is essential during mycoplasma infection.

Other studies have shown that vitamin E protects the microvilli and the mitochondria in the ovarian surface epithelium from damage. Vitamin E is an essential fat-soluble vitamin that includes eight naturally occurring compounds in two classes: tocopherols and tocotrienols. Tocopherols have been found to stop the vacuolization of *M. penetrans* into host cells.

Dosage

The preferred form of vitamin E is alpha-tocopherol (skip the d-alpha and the dl-alpha forms). In general, use no more than 200 IU per day. In milligrams that would be approximately 150 mg daily.

SECONDARY CYTOKINE CASCADE INHIBITORS

These are inhibitors that are effective but either they are less potent or else they have a problem or two that make them more difficult to use (e.g., EGCG). Japanese knotweed is excellent but I prefer its use, in the context of this book, for bartonella infection, to protect endothelial integrity, or to help reduce brain inflammation. As a strict cytokine cascade reducer for mycoplasma, those in the initial section ("Primary Cytokine Cascade Inhibitors,") are what I suggest as a primary approach.

Bidens (*Bidens pilosa*)

Bidens is a potent systemic antibacterial and anti-inflammatory. I think it specific for mycoplasma infections that are affecting the mucous membranes, whether respiratory or urogenital. It is strongly protective of the cilia. It powerfully inhibits NF-κB, PGE2, iNOS, COX-2, 5-lipoxygenase, and ROS. It is significantly antiangiogenic, modulating blood vessel formation. In vitro and in vivo studies have found it highly effective in protecting erythrocytes from oxidative damage. Bidens is a very strong prostaglandin synthesis inhibitor and a significant free-radical scavenger, comparable to alpha-tocopherol. It also inhibits histamine release.

I suggest its use in mycoplasma primarily as an organ support herb; see "Support and Protect Organ Systems" for more about it.

Chinese Senega Root (*Polygala tenuifolia*)

This is one of the 50 fundamental herbs of Chinese medicine and is known there as *yuan zhi*. It is used in China primarily as an expectorant and to help lung inflammations. But it also has strong impacts on cognitive function, enhancing memory, alleviating neurotoxicity, and producing positive impacts in the treatment of Alzheimer's, dementia, depression, and degenerative diseases. It is a very good anti-inflammatory and inhibits NF-κB, nitric oxide, iNOS, COX-2, PGE2, TNF-α, and IL-1β in microglial cells. One of the more important activities of the herb is that it enhances the secretion of nerve growth factor (NGF) in the brain, spinal cord, and peripheral nervous systems. NGF is a small protein that is crucial for the growth, maintenance, and survival of neurons. When neuronal

damage occurs, higher levels of NGF are essential in stimulating axonal regeneration. This is perhaps the best plant for stimulation of NGF.

Dosage

The dosage is 30 drops of the tincture 3x daily for 30 days. It is contraindicated in those with ulcers or gastritis.

Green Tea/Epigallocatechin-3-gallate

Green tea (*Camellia sinensis*) contains a number of catechins (which are polyphenols), the primary ones being epigallocatechin-3-gallate (EGCG), epicatechin, and epicatechin gallate. It also contains some important flavonoids: kaempferol, quercetin, and myricetin. Its myricetin content is higher than that of nearly all other plants. And of course, caffeine. Most of the research has occurred with EGCG but the other constituents are important and should not be neglected. If possible the best approach is to use a product that contains both the polyphenols *and* the flavonoids. (No, I don't know of one to recommend.)

Although not commonly thought of as an antibacterial, the catechins in both green and black tea have antimicrobial activity against a number of bacteria, including various mycoplasmas—especially *M. pneumoniae* and *M. orale*. They are also strongly reductive of the cytokine cascades the mycoplasmas initiate.

EGCG inhibits a wide range of cytokines, including TNF-α, NF-κB, IL-1β, IL-6, IL-8, ERK, CCL2, MMP-2, MMP-9, EGF, VEGF, PI3K, and p38 MAPK. EGCG also reduces peroxynitrite levels, reduces excess uric acid, reduces proteinuria, and protects rats, in vivo, from ischemia-reperfusion caused by bacterial lipopolysaccharides.

EGCG has been found to, in vivo, suppress induced autoimmune encephalomyelitis. It reduces clinical severity by limiting (and preventing) inflammation and reducing neuronal damage. It stops ROS production throughout the CNS. It reduces cerebral amyloidosis and modulates cleavage of the amyloid precursor protein. Studies have shown that it reduces age-related memory impairment in mice. EGCG apparently

modulates the intracellular levels of free calcium in brain neurons (one of the causes of neuronal problems) and the hippocampus caused in such diseases as Alzheimer's and mycoplasma infection.

EGCG also has some good protection for mitochondria. Besides the anti-inflammatory actions it also increases the accumulation of zinc in the mitochondria and cytosol.

EGCG helps with arthritic inflammation, attenuates the overexpression of proinflammatory cartilage cytokines, and modulates the antioxidant status in arthritic rats. It reduces edema in arthritis, suppresses lipid peroxidation, and increases levels and activity of superoxide dismutase, glutathione, and catalase in cells. It is strongly inhibitive of acetylcholinesterase.

EGCG reduces lesions generated by inflammatory cytokines in peridontitis and colitis. It inhibits angiogenesis and has been found to have a strong impact on cancers cells, inhibiting inflammation and metastasis.

Green tea and EGCG are both synergistic with some herbs and supplements. EGCG, resveratrol, and gamma-tocotrienol (a form of vitamin E) are more effective against breast cancer cells when combined than when separated. The same is true for prostate cancer cells when EGCG is combined with quercetin and genistein. Effectiveness is enhanced against osteosarcoma cells when it is combined with lysine, proline, arginine, and ascorbic acid.

EGCG is synergistic with tetracycline against staph bacteria; it inhibits the efflux pump the bacteria use against the antibiotic. It potentiates beta-lactam antibiotics against resistant bacterial species. And does the same with carbapenems and ampicillins against MRSA (methicillin-resistant *Staphylococcus aureus*). It is synergistic with doxycycline.

EGCG has shown a lot of promise against cancer and there has been extensive testing, mostly in vitro, along those lines.

EGCG and green tea in general have a number of actions that are directly useful during mycoplasma infection but there

are a number of problems in the use of EGCG as a supplement, essentially its bioavailability. (It also can increase nitric oxide production, a potential problem in some cases.)

Unfortunately only about 40 percent of the EGCG taken will get through the GI tract membranes. Most of the EGCG absorption takes place in the small intestine but fairly substantial amounts remain in the GI tract. Once it reaches the colon it is metabolized by the microflora in the gut. (Epicatechin gallate levels, if all the catechins are ingested, are much higher in the blood than EGCG.) The EGCG that does get into the blood undergoes extensive methylation, glucuronidation, and sulfation in the liver, where it is broken down into much less effective metabolites.

Plasma levels of EGCG are highest if it is taken on an empty stomach just after rising in the morning. Peak plasma concentrations are reached in one to two hours; they remain high for about three hours then begin to decline, reaching zero by the next morning. (So, you have to take them every three to four hours.)

The amount of EGCG, and the other tea catechins, that gets into the blood and does remain active depends on a number of factors, few of which are usually taken into consideration when using it as a supplement.

1. Serum albumin levels need to be highish. Human serum albumin contributes to transport and stabilization of EGCG and the other catechins. If it is low, bioavailable levels of EGCG are low.
2. EGCG and the catechins degrade in humidity and hot air temperatures. They have to be stored in a cool, dry location to remain active (think “refrigerator”).
3. Since EGCG is a potent antioxidant, exposing it to the air over any length of time will activate its oxidative actions, causing auto-oxidation and rendering it relatively useless once you ingest it.
4. Taking EGCG with hard water affects its absorption into the body. The harder the water, the less that can be absorbed into the body. Soft water is essential.
5. Ingesting it with milk will inactivate it.

The bioavailability of green tea and EGCG can be significantly enhanced, however, if you take it with certain other substances. Quercetin (1,200 mg daily) or 200 mg ascorbic acid or 1,000 mg omega-3 fatty acids (for instance) will all increase its availability. Quercetin increases bioavailability of the green tea catechins and decreases their methylation, in vitro and in vivo. Quercetin is, itself, a very good supplement for treating cytokine cascade problems. It inhibits NF-κB, TNF-α, IL-1β, EGF, iNOS, nitric oxide, and JNK. I would highly suggest, at minimum, a quercetin/EGCG combination (and no, nobody sells one, so buy them separately). EGCG is also much more effective if combined with resveratrol (knotweed), vitamin E, and/or N-acetylcysteine.

And … there is evidence, as usual, that the whole herb, the green tea itself, is and remains much more bioavailable than the isolated constituents.

Because of the bioavailability problems with EGCG, I am not putting this supplement as a major component of a mycoplasma protocol (though I do include it as one for bartonella). If you do wish to use it, it is really good, but bear all the necessary restrictions on EGCG treatment in mind *and* combine it with other things, most especially quercetin.

Dosage

Try to get a supplement with at least 80 percent total catechins, at least that amount of polyphenols, and 50 percent or so of EGCG. A supplement with the natural green tea flavonoids would be even better. Dosage range is 400–800 mg daily. For greater effectiveness in treating bartonella-generated endothelial cell damage, take it with 1,200 mg quercetin daily —both at the same time, in the morning.

Note: There is about 100 mg EGCG in a cup of green tea. I would imagine that drinking green tea itself throughout the day would be a good approach to get it all and at a better degree of bioavailability.

Comment: EGCG is a very good supplement to use to normalize endothelial cells that are being targeted for

inflammation, especially during bartonella infection. I would highly suggest you use EGCG with resveratrol (knotweed) and quercetin as combination therapy in the treatment of bartonella-initiated angiogenesis in order to increase EGCG's actions along these lines. If you wish to use it for mycoplasma, again, take it along with quercetin, vitamin E, and NAC.

Kudzu Root (*Pueraria lobata*)

Though originally native to Japan, kudzu is an invasive vine in the southern U.S. It is particularly impressive, being able to grow 12 inches per day and up to 100 feet per year. It can't be stopped, it can't be reasoned with, nothing will kill it, and it knows where you live. It is the root that is medicinally used.

Kudzu has long been used in both China and Japan as medicine and food. It increases blood circulation, relieves tension in the face and neck, is somewhat antiviral, lowers blood pressure, and is anti-inflammatory. It can help the headaches that occur from encephalitis, will reduce Bell's palsy, and reduces inflammatory cytokine cascades. Kudzu root has very strong antifever actions as well and will reduce severe fevers fairly quickly; the effects last about eight hours.

Kudzu root and its major constituents (puerarin and kakkalide and irisolidone—a metabolite of kakkalide produced by intestinal microflora that is more potent than kakkalide) inhibit TNF-α, IL-1β, NF-κB, ERK, iNOS, PGE2, COX-2, AP-1, ICAM-1, VCAM-1 (vascular adhesion molecule-1), E-selectin, C-reactive protein (CRP), and the phosphorylation of 1kB-a. It has targeted and potent effects on cytokine-activated microglial cells and will reduce damage by cytokines in the CNS.

Kudzu (and puerarin) are strongly protective of the brain and CNS, especially in ischemia-reperfusion injury. They have a strong protective effect against beta-amyloid-induced neurotoxicity in hippocampal neurons, protect mitochondria from ROS, and stimulate peripheral nerve regeneration. Neuron pain receptors P2X(3) and P2X(2/3), similar to P2X(7), in the brain are inhibited by puerarin, making this a very good companion herb to use with greater celandine (discussed later). The root is, in fact, strongly anti-

inflammatory in the brain and CNS. It significantly inhibits neutrophil respiratory bursts, reducing autoimmune dynamics in the brain. Similarly to motherwort (also discussed later), it modulates Bax/Bcl-2 actions in the mitochondria in the brain and inhibits caspase-3 and iNOS expressions. It is strongly neuroprotective during inflammation disturbances in the brain and CNS.

It is a good herb for these types of cytokine cascades, especially so since it is invasive and there is no dearth of supply. *Anywhere* encephalitis occurs and kudzu grows, use kudzu.

Dosage

In traditional Chinese medicine the usual dose is 6–12 grams per day of the powdered root. Dosing in the West is usually 1 gram per day. Tincture dosage in mycoplasma infection: ½ teaspoon 3–4x daily.

Luteolin

Luteolin, a flavonoid common in plants, is a strong anti-inflammatory and antioxidant that also possesses some antimicrobial and anticancer actions. It inhibits angiogenesis, induces apoptosis, and sensitizes cancer cells to killing agents. It inhibits the cytokine cascade initiated by bacterial membrane constituents: iNOS, NF-κB, TNF-α, IL-6, p38 MAPK, ERK-1 and ERK-2, COX-2. It can be found in celery, thyme, dandelion, clover blossom, sage, green pepper, carrots, olive oil, peppermint, rosemary, oranges, oregano.

Studies have found it protects rat brains from the exact type of damage that mycoplasma causes. Luteolin reduces the immunoexcitotoxicity that causes neurodegeneration in the brain during bacterial infections and promotes CNS repair of damaged cells. It protects cells from ischemia-reperfusion, protects mitochondria from damage, and inhibits hydrogen peroxide damage. A particularly active form of luteolin, luteolin-7-O-glucoside, that is common in *Ailanthus altissima* (tree of heaven) is particularly active as an anti-inflammatory, especially against PGE2 induction. Tree of heaven is an

invasive and is specific for lung inflammations. A tincture will be effective as an anti-inflammatory for mycoplasma infection.

I think that the main luteolin supplements are a bit expensive, hence luteolin's presence in this section, nevertheless:

Dosage

100 mg daily.

ANTIBACTERIALS

There hasn't been a huge amount of testing of herbs against mycoplasma but there has been some. As usual, such antibacterials fall into two groups, systemic and localized. Systemic antibacterials are those that are widely distributed in the blood; localized are those, such as uva ursi, that tend to be excreted in the urine (for example) rather than going systemic. Localized antibacterials are specific for such things as bacterial infections of the urinary tracts while systemics are good for the whole system.

PRIMARY ANTIBACTERIALS FOR MYCOPLASMA

The main systemics for mycoplasma are isatis, houttuynia, and olive oil (and most likely sida and bidens). The primary localized antibacterials are uva ursi and berberine-containing plants such as phellodendron. *Angelica dahurica,* rhubarb, and *Kochia scoparia* fruit are also active.

Note: a couple of important comments here …

1. Fermented wheat germ extract *is* active against mycoplasma bacteria and it does strongly counter a number of their side effects. I think it a major substance to add to any mycoplasma protocol, *however* its cost is generally prohibitive for most people. The best-known brands run around $150 per month, though there is a competitor that is about half that now on the market. I still think it obscene. Nevertheless, it is a remarkably important substance and if you can afford it I think it

worth using. For more about it see the longer analysis fermented wheat germ extract.

2. Although they have not been tested against mycoplasmas, based on what I know about the herbs, their range of action, and their antibacterial capacities, I believe that *Sida acuta* and *Bidens pilosa* are both active against mycoplasmas. Sida is essential anyway to protect red blood cell integrity and bidens is crucial if there is lung or urogenital/reproductive system involvement. So both should be used in mycoplasma infections anyway. *Cryptolepis sanguinolenta* and *Alchornea cordifolia* are probably antibacterial for mycoplasmas as well.
3. There are some other good herbal antibacterials—but they are not available in the U.S. A prime example is *Anogeissus leiocarpus*, an African plant that is listed in the discussion of secondary antibacterials. If it were available in the U.S., I would list it as a primary antimycoplasmal systemic.
4. And finally, pomegranate. Pomegranate is an unusual herb but it is beginning to appear that there is much more to it than anyone has previously suspected. I have included it in the primary antibacterials even though its antibacterial actions against mycoplasma are moderate. I think the juice should be a primary part of any mycoplasma protocol.

Isatis

There are somewhere between 30 and 80 species in this genus. Nobody seems to really know. (I am not sure why I read *anything* by taxonomists.) The most common species in medicine is *Isatis tinctoria* (worldwide) but *Isatis indigotica* is fairly prominently used in China (as is *tinctoria*), *Isatis costata* is used in Pakistan, *Isatis cappadocica* in Iran, and still others here and there. All the species seem to contain similar chemistry. The root and leaves are what are used for medicine, each has slightly different actions.

The plant is an insistent invasive everywhere it goes—yet another invasive medicinal for emerging infections. Like many of the potent antimicrobials effective for resistant and

emerging infections, this one is growing all around us, insisting we notice it. Nevertheless, as an invasive, it has been targeted as a plant to be terminated with extreme prejudice. One thing … if you hear of a plant that is going to destroy the country, ask yourself immediately, "What medicinal qualities does it have?" You will probably find that it is specific for something that "modern" medicine is having trouble treating and, no doubt, for something you are struggling with yourself.

The leaves contain a number of important chemical precursors when they are harvested fresh; they need to be dried with heat (usually in the sun) for the chemicals to convert to their final form. The most important end-product chemicals are tryptanthrin and indirubin. Tryptanthrin is a potent anti-inflammatory compound that strongly inhibits prostaglandin and leukotriene synthesis—it is also potently antiparasitic against toxoplasmal, malarial, and leishmanial parasites. It is much higher in dried leaves than fresh. Indirubin is potently anti-inflammatory as well, although in different ways. It is strongly cytotoxic to leukemia cells and is very virucidal. Indirubin is three to five times higher in the dried leaf than the fresh.

Isatis is a potent antiviral plant. It is directly virucidal as well as inhibiting viral replication, inhibiting virus-cell attachment, and inhibiting viral neuroaminidase similarly to Tamiflu in potency. It potentiates the effectiveness of viral vaccines and is an immune stimulant, anti-inflammatory, antipyretic, antinociceptive, antiallergenic, tyrosinase inhibitor, antioxidant, antifungal, antibacterial, antiparasitic, antileukemic, antitumor, potent urease inhibitor, potent cross-class serine protease inhibitor, butyrylcholinesterase inhibitor, lipoxygenase inhibitor, antiendotoxin, dioxin antagonist (including against TCDD, the most potent).

Isatis has a broad antimicrobial action, including (and importantly) actions against *Mycoplasma hominis, M. pneumoniae,* the ureaplasmas (and, I believe, others as well—I would use it for any mycoplasma infection), influenza viruses, SARS coronavirus, swine pseudorabies virus, Coxsackie virus (B2, B3, B4), rubella virus, avian infectious bronchitis virus, respiratory syncytial virus, human adenovirus type 3, measles,

mumps, chicken pox, Epstein-Barr virus, herpes simplex virus 1, cytomegalovirus, *Staphylococcus aureus, Toxoplasma gondii, Plasmodium falciparum, Leishmania* spp., *Pseudomonas aeruginosa, Trichophyton schoenleinii, Trichophyton simii, Aspergillus niger, Candida albicans, Macrophomina phaseolina, Sporosarcina pasteurii,* leukemic and liver cancer cells, and possibly other cancers. Alcohol/water extracts of *Isatis microcarpa* (dried) leaves are active (in vitro) against *Bacillus subtilis, B. sphaericus, Staphylococcus aureus, Pseudomonas* spp., *E. coli. Salmonella* spp., *Aspergillus niger, A. flavus, Fusarium oxysporum, Alternaria tenuis, Microsporum fulvum.* Water extracts of the root are active against *Staphylococcus* spp., *Bacillus subtilis, E. coli, Salmonella typhi, Streptococcus* spp., and *Haemophilus influenzae.*

Note: The root is the most strongly antibacterial, the leaf the most antiviral. In the treatment of viral diseases I would use a tincture made of one-third root, two-thirds leaf. For mycoplasma infections I would use two-thirds root, one-third leaf—nevertheless, if all you can find is the root, use that. It will work, especially since it is the root that was found to be a mycoplasmal antibacterial.

The plant is specific for the onset symptoms of *M. pneumoniae*, especially those accompanied by maculopapular rashes, sore throat, laryngitis, and tonsillitis. It is specific for all mycoplasmal respiratory infections, will act on red blood cell infections, and protect from endotoxins in the blood. It is specific for the CNS problems attendant to mycoplasma infection: eye complications, encephalitis, meningitis, and CNS inflammations in general. The herb is systemically spread and will reach all parts of the body.

Isatis has been used for millennia in Asia as a medicinal and has been cultivated since neolithic times elsewhere for its use in textiles, body paints, inks, and medicine. It has been traditionally used in Ayurvedic practice but I can find little on it, basically as a digestive tonic and for GI tract problems. Its longest history of use as medicine, however, is in traditional Chinese medicine.

Isatis has been used for thousands of years in China. The leaf of the plant is referred to in traditional Chinese medicine as *daqingye,* the root as *banlan'gen;* they are considered to be close but somewhat different medicinals with slightly different actions. The leaf (*daqingye*) is used as a bitter, cold herb, fever reducing, anti-inflammatory, detoxicant, and for removing heat from the blood. It is considered specific for fever, colds and flu, maculae, papulae, pharyngolaryngitis, parotitis, encephalomeningitis, encephalitis B, erysipelas, carbuncle. It is considered good for headache and sore throat. The root is considered to be bitter, cold, with latent-heat-clearing properties, antipyretic, detoxicant, and anti-inflammatory, and for clearing heat from the blood. It is used for erysipelas, macular eruption due to pathogenic heat, loss of consciousness, hemoptysis, pharyngitis, mumps, conjunctivitis.

There have been a number of good clinical trials in China on the use of the herb for various things. This is just a sampling of those that are related to mycoplasma-type infections and their symptoms.

Isatis tinctoria leaf was used to treat patients with encephalitis B. Headache and other symptoms were sharply reduced, mortality rate was decreased in both mild and serious cases—in critical patients, Western intervention was needed along with the herb in order to prevent death.

Twenty healthy people experienced induced contact dermatitis; they were then treated with a variety of isatis extracts as well as pure tryptanthrin. The isatis extracts were more effective than the tryptanthrin in resolving the dermatitis.

A randomized, double-blind, parallel study was conducted with 200 people suffering from bacterial conjunctivitis. Isatis root eye drops were used (vs. levofloxacin) to treat them. The drops were administered six times daily; 90 percent were cured.

Twenty patients with head or neck cancer were split into two groups in order to test isatis root for the treatment of radiation-induced mucositis. The first group received normal saline, the second gargled, then swallowed an isatis root

decoction. Those receiving the decoction had significantly reduced severity of mucositis and anorexia and less swallowing difficulty. This study echoes other reports that the root decoction heals ulceration in and regenerates mucous membranes.

Purified extracts from isatis—indirubin and meisoindigo (an indirubin metabolite)—were used to successfully treat chronic myelogenous leukemia.

In vivo trials with isatis leaf in rats found that the herb was highly effective in treating chronic pseudomonas lung infection (similar in its dynamics to cystic fibrosis). The herb reduced the incidence of lung abscesses, decreased the severity of macroscopic pathology in lung tissue, and altered the inflammatory response in the lungs from an acute inflammation dominated by polymorphonuclear neutrophils (PMNs) to a less-intense chronic-type inflammation dominated by mononuclear leukocytes.

The herb is antiarthritic, reducing inflammation in the joints. It also will stop lesions, tiny abscesses, in not only the lungs, but the gastric mucosa and presumably the brain as well.

Extracts of isatis leaf reduced induced inflammation in mice. Both topical treatment and oral ingestion were effective; purified tryptanthrin extracts were not effective. (Unusual extracts were tested: supercritical CO2 and dichloromethane.) An in vivo study with mice found that dichloromethane extracts of isatis leaf were effective as an anti-inflammatory in the treatment of arthritis. Extracts of isatis leaf inhibited allergen-induced airway inflammation and hyperreactivity in mice—making it perfect for *M. pneumoniae* and other mycoplasmal respiratory infections.

Isatis root extracts were found to be highly protective of mice after total-body irradiation, modulating inflammation and reducing tissue damage. The root was shown to significantly reduce serum levels of TNF-α, IL-1β, IL-8, and IL-6 and protect hematopoietic stem cells. The leaf inhibited IL-4, IL-5, RANTES, COX-2, and 5-LOX (lipoxygenase) expression.

Endotoxins from Gram-negative bacteria were injected into rabbits: administration of an extract from isatis root (o-aminobenzoic acid) reduced fever and destroyed 84 percent of the endotoxins. Deaths dropped from 70 percent to 20 percent.

Several compounds in the plant have been found to be potent urease inhibitors. Urease is an enzyme found in many bacteria, yeast, and fungi. A urease inhibitor is, in essence, an antimicrobial against microbes that need that enzyme to function. This is what, in part, makes the plant active against the ureaplasmas that cause urogenital infections.

Tryptanthrin (especially), gamma-linolenic acid, and an indolin2-one derivative are highly anti-inflammatory, inhibiting COX-2, 5-LOX, the expression of iNOS, human neutrophil elastase, and the release of histamine from mast cells. Indirubin is a potent inhibitor of cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase 3β, and inflammatory reactions in delayed-type hypersensitivity.

Dosage

Root or leaf tincture, or combination thereof (tastes terrible) …

As preventive: 30 drops up to 6x daily.

For acute conditions: 1 teaspoon up to 10 times daily.

In chronic, recalcitrant mycoplasma: ½ teaspoon 3x daily for 3 weeks, take a break of a week, resume, and so forth.

Side Effects and Contraindications

Leaf: Occasionally nausea, rarely vomiting. Root: Rarely allergic reactions, urticaria, cyanosis of the face, dyspnea—but these were from intramuscular injections, there is no evidence of this from oral ingestion.

However caution should be exercised in long-term use. Normally, you would not take isatis for longer than three weeks. This should be sufficient to deal with anything you have, especially if you have combined the herb with any of the others in this book. You can, if you wish, take a break, then begin again after a week or ten days off.

You should avoid using the herb as a single medicinal if you are presenting with a subjective feeling of cold without fever. The herb can induce a deep chill with overuse (longer than three weeks). It should not be used by people on dialysis or those experiencing renal failure—high doses or long-term use may negatively affect the kidneys. You can use it for mycoplasma infections that are affecting the kidneys—just not if the kidneys are beginning to fail.

Herb/Drug and Herb/Herb Interactions

Synergist with antibiotics and viral vaccines, increasing the activity of both. The herb may interfere with tests for measuring total bilirubin content.

Finding It

You can get bulk isatis root, powder, cut and sifted, or concentrated from 1stChineseHerbs.com (www.1stchineseherbs.com). They carry the leaf as well. You can also get a very nice tincture of the root from Sage Woman Herbs (www.sagewomanherbs.com).

Houttuynia

First up: it is pronounced "hoo-TY-nee-ah," big fella, and, yes, you may say that loudly at square dances.

Houttuynia cordata is the primary species used; some people think there is only one in the genus, others two. (Pistols at dawn.) There is a lot of speculation that there are significant *sub*species (or chemotypes) of *H. cordata,* mostly determined by their taste. Whatever it is, there is definitely something going on that the tongue is noticing even if the brain is not. This does have an impact as the herb is reportedly hard to ingest for a number of people—all because of the taste.

The Chinese/Vietnamese chemotype is reported to possess a taste/ smell similar to coriander; the Japanese chemotype, according to one anonymous reporter, has "a strange lemon or orange odour that is often compared with ginger." To others, however, the taste of the plant, irrespective of chemotype, is apparently very close to rotten fish. This plant may be the

herbal equivalent of cilantro. Some people love it but for those that do not, *hate* is the closest word to describe their reaction.

I have tasted it, and just to be biologically contrary, I experience it in none of those ways. It's not a lot of fun, but then, I've had worse. (Saw palmetto tincture—fetid soap.)

There are a lot of cultivars of this plant; it is common in gardens everywhere, so you get a lot of names for the thing: heart-leaved houttuynia, lizard tail, Chinese lizard tail, chameleon plant (as opposed to the specific variety called "Chameleon"), heartleaf, fishwort, fish-mint, bishop's weed, doku-dami (Japan), and yu xing cao (China). The Chinese name literally means "fishy-smell herb" because, well, it smells like fish—to someone, someplace, I guess. (My favorite synonym is *Houttuynia foetida*.) Generally, the aerial parts are used for medicine, rarely the roots. The Chinese consider the fresh plant the strongest form of the herb. If you are making tinctures use the fresh plant picked just at flowering.

The herb has a wide range of actions. It is antiviral, antibacterial, antifungal, antimicrobial, anthelmintic, larvacidal, anti-inflammatory, antioxidant, anticancer, immunomodulatory, astringent, diuretic, emmenagogue, febrifuge, hypoglycemic, laxative, depuritive, analgesic, hemostatic, antitussive, antileukemic, and ophthalmic.

It is strongly active against *Mycoplasma hominis* (30 strains), herpes simplex virus 1, herpes simplex virus 2, influenza virus A (H1N1 strains), HIV-1, SARS-related coronavirus (FFM1, FFM2), dengue virus serotype 2, cytomegalovirus, avian infectious bronchitis virus (a coronavirus), enterovirus 71, porcine epidemic diarrhea virus, pseudorabies herpesvirus, ECHO virus, *Staphylococcus aureus, S. albus, Streptococcus hemolyticus, Salmonella* spp., *Streptococcus pneumonia, Moraxella catarrhalis, Corynebacterium diphtheriae, Proteus vulgaris, Shigella shigae, S. schmitzii, S. flexneri, S. sonnei, Salmonella enteritidis, Vibrio cholerae, Mycobacterium tuberculosis, Leptospira* spp., *Haemophilus influenzae, Candida albicans, Aspergillus* spp., *Cryptococcus neoformans, Sporotrichum* spp., chromomycosis fungus, *Epidermophyton rubrum, Tinea*

imbricata, Microsporum gypseum, M. ferrugineum, Sarcina ureae, Hymenolepis diminuta, Colletotrichum capsici, Fusarium oxysporum, Malassezia pachydermatis, and *Aedes aegypti* larvae.

There are a number of Internet sites insisting that the herb is active against trichophyton and gonococci but intensive searching has failed to turn up any relevant documents supporting it. Every site I can find simply repeats the same thing—all apparently from the same initial site, wherever that is. It is reported that James Schaller, M.D., found the herb effective, in vitro and in vivo, against bartonella species but I can't find any actual data on that to support it.

The herb is specific for respiratory and intestinal infections, mycoplasma infections, any serious infections in the lungs especially with abscesses, infections in the urinary passages and kidneys, genital infections, dysentery and any bacterial diarrheal conditions, various diseases of the eye (fresh juice or tea applied topically), skin infections with pus or boils. It is especially indicated if any of these conditions are accompanied by foul-smelling discharge.

The herb is effective in long-term traditional and historical practice against a number of disease conditions that mycoplasma does cause, i.e., respiratory infections including pneumonia, urinary and kidney infections, genital infections, eye problems, and skin eruptions.

There is a fairly broad chemistry to the plant: houttuynoside A, various houttuynoids (A through E), houttuynin, houttuynine, lauryl aldehyde, caprylic aldehyde, quercetin 3-rhamnoside, quercetin 7-rhamnoside, capric acid, cordarine, quercitrin, isoquercitrin, alpha-pinene, beta-pinene, linalool, camphene, myricene, limonene, caryophellene, afzerin, hyperin, chlorogenic acid, beta-sitosterol, stearic acid, oleic acid, linoleic acid, myrcene, 2-undecanone, hyperoside, p-cymene, eucalyptol, beta-ocimene, nonanal, fenchyl alcohol, menthol, trans-pinocarveol, verbenol, camphor, beta-terpineol, pinocarvone, isoborneol, pelargol, terpinen-4-ol, myrtenal, alpha-terpineol, verbenone, trans-carveol, piperitone, isopulegol acetate, bornyl acetate, isobornyl acetate, benzyl

isobutyrate, hendecanal, alpha-terpinyl formate, dihydrocarvyl acetate, neryl acetate, undecyl alcohol, geranyl acetate, 4-acetamido-1-hexanol, beta-caryophyllene, betafarnesene, lauryl alcohol, beta-chamigrene, valencene, methyl undecyl ketone, alpha-bulnesene, dodecanoic acid, nerolidol, spathulenol, caryophyllene oxide, viridiflorol, camphor, phytone, heptadecanol, phytol, phytol acetate, a variety of aristolactams, piperolactam, aporphine, splendidine, lysicamine, 4,5-dioxoaporphines, norcepharadione B, noraritolodione, various amides, and so on. The herb is reportedly high in potassium, magnesium, and sodium.

A significant number of these compounds possess antiviral and/or antibacterial actions. The whole herb was found to be more effective than any of the isolated constituents, showing a profound synergism in its chemical actions.

There is a lot of indigenous and local use of the plant throughout its native ranges, both for food and medicine, but the most extensive use of the plant, historically, has been by, no surprise, the Chinese.

In traditional Chinese medicine the herb is considered to be slightly cold, pungent, and specific for the lung channel. It has traditionally been used for removing toxic heat, eliminating toxins, reducing swelling, discharging pus, and relieving stagnation. It is specific for promoting drainage of pus, lung abscess with purulent expectoration, heat in the lung with cough, dyspnea, carbuncles and sores, relieving dysuria, acute dysentery, and acute urinary infections. It is considered latent-heat clearing, antipyretic, detoxicant, anti-inflammatory, and diuretic. It has been traditionally used for virulent carbuncle, lung abscesses, cough with thick sputum, leukorrhea, and edema. The fresh juice for snakebite and skin infections. Common medicinal use in China is for chronic nephritis, inflamed pelvis or cervix (pelvic inflammatory disease), gonorrhea, rheumatism, prolapse, hemorrhoids, inflamed respiratory tract (including pneumonia and bronchitis with or without edema), prevention of postoperative infections, inflammation and pus in the middle ear, measles, tonsillitis, chronic sinusitis, nasal polyps, inhibiting anaphylactic reactions, and various cancers.

Most of the scientific studies have occurred in China, often with injectable forms of the herb. Numerous others have been conducted in India and Thailand. Few have occurred in the U.S. (The herb tastes funny.) In general, the studies found that the effects were dose dependent, in other words, the more they gave, the better the outcome. Since the herb has shown no toxicity from oral ingestion (up to 16 grams per kilogram in mice, a huge dose), that would indicate that largish doses can be used very effectively.

In vitro studies found that the herb (water extract) significantly increases IL-2 and IL-10 cytokines. IL-10 is also known as cytokine synthesis inhibitory factor; it is an anti-inflammatory cytokine. It essentially downregulates other cytokines and blocks NF-κB activity. It is specific for counteracting the effects of mast-cell-initiated allergic reactions, which is why the herb is good for stings and bites and anaphylactic reactions. The herb also stimulates the production of CD4+ lymphocytes. It is especially active in the spleen.

Herpes simplex virus (HSV) 1 and 2 depend on NF-κB activation for replication. In vitro studies found that houttuynia suppressed HSV infection by inhibiting NF-κB activation. The herb's inhibition of NF-κB was also found to significantly reduce chemotaxis during infection, reducing cellular migration. The herb also inhibited hydrogen peroxide impacts on cells. The herb also inhibited lipid peroxidation by 80 percent.

In vitro research found the herb to be active against 21 staph aureus strains (but not very active in stopping biofilm formation in that organism).

In vitro the herb inhibited the production of lipopolysaccharide-induced COX-2 and PGE2 in mouse macrophages.

The herb reduced Th2 cytokines, specifically IL-4 and IL-5. It inhibited HMC-1 cell migration. It also inhibited DNA topoisomerase 1 activity.

Houttuynia liquid extract protected and restored white blood cell counts in mice x-rayed and administered cyclophosphamide. It normalized connective tissue growth factor and increased levels of adiponectin in streptozotocin-induced diabetes in rats.

Water extracts of the herb significantly reduced NO levels in *Salmonella*-infected macrophages and extended life spans of *Salmonella*-infected mice given a lethal dose of the bacteria from 7 days (no herb) to 23 days. The effects were dose dependent.

The herb (water extract) was used to treat bleomycin-induced pulmonary fibrosis in rats. The herb significantly decreased SOD, malondialdehyde, hydroxyproline, interferon-gamma, and TNF-α. The morphological appearance of the lung was markedly improved.

A number of studies found that the herb strongly inhibited induced-oxidation events in rats. It specifically inhibited NF-κB, TNF-α, nitric oxide, COX-2, and PGE2. Houttuynia inhibited IgE-mediated systemic PCA, reduced antigen-induced release of IL-4 and TNF-α, reduced NF-κB, inhibited degradation of IκB-α. It specifically inhibited antigen-induced phosphorylation of Syk, Lyn, LAT, Gab2, and PLC gamma-2. Further downstream it also inhibited Akt and MAP kinases ERK-1, ERK-2, JNK-1, and JNK-2 but not p38.

Extracts of the herb protected rat kidneys when rats were injected with streptozotocin. TGF-β1 (transforming growth factor-beta 1) and collagen levels in renal tissues decreased, BMP-7 increased.

Cows with bovine mastitis were treated with a form of houttuynin, a compound from houttuynia. In acute mastitis 88 percent were cured and 53 percent showed microbiological clearance. In cows treated with combination penicillin/streptomycin the rates were 90 and 55 percent respectively. In subacute conditions the houttuynin results were 94 and 48 percent. In the pharmaceutical group they were 94 and 44 percent. (This finding is significant because of the degree of mycoplamal infection in dairy herds, a major cause of bovine mastitis.)

A modified form of houttuynin both protected mice from and corrected induced membranous glomerulonephritis in mice. It inhibited the expression of NF-κB and MCP-1.

A water extract of the herb protected rat primary cortical cells from beta-amyloid-induced neurotoxicity, specifically through modulating calcium influx and protection of mitochondria.

Researchers in Korea are interested in a class of food herbs they are calling phytobiotics, among which is houttuynia. In one study, researchers found that adding it to chicken feed instead of antibiotics has similar effects on weight, disease reduction, and health as pharmaceuticals without the negative side effects. Lipid oxidation in the meat was significantly reduced.

In another study, the mortality of chicks challenged by *Salmonella* was significantly reduced when the herb was included in their feed. PGE2 synthesis decreased, CD4+ lymphocytes increased, the CD4+:CD8+ ratio balanced, immune function in all chicks was enhanced.

Many of the human studies with the herb used an injectable form and found it highly effective for treating bronchopulmonary complaints including pneumonia. Oral dosing of a compound formula that included *Platycodon grandiflorum* was also effective. Both oral and injectable forms were found prophylactic for leptospira infections. Used alone or in combination with *Artemisia annua* the herb was an effective treatment for leptospirosis.

Cotton impregnated with the water extract (or oral tablets) was used in treating chronic cervicitis with lesions. Applied once every day for five days (243 people participating) the cure rate was 81 percent.

Of 100 cases of chronic suppurative otitis media treated with ear drops of the distillate of the herb, 95 were cured. Thirty-one of 33 cases of atrophic rhinitis benefited from nose drops of the solution.

Irrigation with the extract was effective in treating chronic maxillary sinusitis. And in other studies houttuynia (water

extract) was used to irrigate nasal passages after endoscopic sinus surgery for those with chronic sinusitis and/or nasal polyps. The herbal extract was better than two other irrigants used.

A clinical trial in China in the treatment of chronic-relapsing ulcerative colitis found that the herb cured 20 of 21 and gave improvement in the other. Stool normalization, cessation of diarrhea, reduction of blood in stool, and abdominal pain disappearance all were faster in the herbal group than in those being treated with pharmaceuticals. (Again this is an important study as this kind of condition is relatively common in chronic mycoplasma infection.)

The herb's constituents move fairly rapidly into the bloodstream and maintain a high presence. The absorption half-life after oral ingestion is 3.5 hours. The herb's constituents are present in the highest amounts in the lungs, heart, liver, kidneys, and serum in that order. Elimination of constituents, metabolized or not, in the urine and feces is very low, the main route of excretion is the lungs (breath). Radioactively labeled houttuynine was found in rat tissues for up to 48 hours. The highest levels were in the bronchi (especially at one and four hours postinjection) and in descending order in the gallbladder, liver, ovary, intestine, spleen, kidneys, and lungs. Oral dosing found the highest levels in the bronchi after 24 hours.

Dosage

The tincture of the fresh leaves is the most potent form of the plant as medicine.

For viral infections: ¼–½ teaspoon up to 6x daily.

For mycoplasma: ½ teaspoon 3x daily, the same for bartonella.

I would not use a dried plant tincture unless that is all you can find.

Traditionally the herb (sometimes the root) is used, either dried or fresh, to make a decoction. For dried, 15 to 30 grams (about ½ to 1 ounce) of the dried plant is decocted (that is,

briefly boiled), allowed to cool, then consumed. Fresh, 30 to 50 grams of the fresh herb is decocted similarly. Examination of the decocted herb has, however, revealed that it loses much of its antibacterial/antiviral actions upon boiling (which is why the Chinese tend to boil it really, really briefly). If decocted intensively, the plant works well to stop diarrhea but is relatively inactive antimicrobially. Apparently the Chinese boil it at all simply to alter the taste; the fishy taste is significantly reduced if even boiled briefly.

The fresh plant is much more antibacterial/antiviral (as is the tincture) and is traditionally pounded to make juice for oral administration internally, on wounds, or as eye drops. The remaining mashed plant can be used as a paste applied topically to wounds and bites; the decoction (allowed to cool) can be used for an external wash. The Japanese use a tea, taken regularly, as a tonic medicine.

Again: It can taste nasty, very fishy to some, so put it in something with a strong taste to cover it (fish soup?). Otherwise it can be hard to get it down.

There are a few companies selling the tincture for absurd prices, which, given that the plant is an invasive and very easy to grow, I find obscene. You can also find the powder, sometimes concentrated at 5:1, sometimes just the regular old powdered herb, from some Chinese herb companies. You can encapsulate the powder if you cannot take the taste of the tincture. I have been unable to locate any pre-encapsulated forms on the market. The herb really isn't that popular at this point.

If you do encapsulate it yourself, use 00 capsules. I would begin with 2 capsules 3x daily and see how it goes, adjusting the dose depending on how it works for you. I have never been sure of how to dose the 5:1 concentrated powders that the Chinese often make; presumably you would take one-fifth the dose of the nonconcentrated form.

Side Effects and Contraindications

Fishy-smelling breath (maybe). The taste can be terrible to the point of gagging (some say). Other than the nausea from the

taste there are no reported side effects in the literature from oral ingestion of the plant.

It does have emmenagogue actions (though oddly enough the herb is not traditionally used for starting menstruation) so it should not be used in pregnancy. However, a few individual reports from China say it can, very rarely, cause congestion in the vagina (but I can't really tell what that means).

The Chinese sometimes use it as an injectible and there have been some severe anaphylactic reactions to that. So … don't inject it.

Herb/Drug and Herb/Herb Interactions

None have been noted in the literature or in any anecdotal reports that I can find.

Finding It

If you want a very good fresh tincture at a decent price try Woodland Essence (www.woodlandessence.com). The dried herb (in both powder and cut form) is available from 1stChineseHerbs.com (www.1stchineseherbs.com).

Olive (*Olea europaea*)

Olive oil (and olive leaf) do have some important actions that make them very useful in treating mycoplasma infections. I don't consider them to be *primary* antibacterials but rather to be supportive antibacterials, for reasons that I think will be clear as you read further.

There is a lot of hype about olive *leaf* in the herb world and on the Internet and I am asked about it often. I haven't tended to recommend it as a primary herbal antibacterial in a general sense for a number of reasons. First, there is just not enough data that I can find showing that the plant is broadly active against a wide range of antibiotic-resistant bacteria, which is where my focus has been when looking at systemic antibiotic herbs. Further, there are a lot of questions as to just how systemic the herb's constituents are. A certain percentage of the constituents are systemic but there are some problems in the amounts that are circulated, especially if you are using the leaf, which is taken in much smaller quantities than the oil. A

few ounces of oil just has more of the active compounds—and they are better assimilated in the body. And in this instance, i.e., mycoplasma infection, the oleic acid in the olive oil (something not present in the leaf in any substantial amounts if at all) itself is essential and does, itself, possess a number of important actions in the body. As well, there just has not been much testing of the leaf in human trial, and even historical ethnomedicinal treatment against systemic bacterial diseases is pretty slim for the leaf (though not so the oil).

Historically, the leaf has been used throughout the Mediterranean region for fevers, gout, and diabetes and as an astringent and a surface antiseptic. The oil has been used as a nutritive tonic; for relieving pruritis, stings, and burns; for skin, muscular, joint, kidney, and chest disease conditions; for abdominal chills, typhoid fever, scarlet fever, plague, and heart conditions with edema; to stimulate bile flow; and as a laxative.

However, both the oil and the leaf do contain what are considered to be the two primary antibacterial constituents of the olive plant: oleuropein and hydroxytyrosol.

Oleuropein, the major constituent of both the leaves (6 to 9 percent) and oil (14 percent), and the one for which olive leaf is usually standardized, has been found to be active, in vitro, against *Mycoplasma* spp., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, P. fluorescens, Enterococcus faecalis, Listeria monocytogenes, Staphylococcus aureus,* and mildly against *Salmonella typhi, Vibrio parahaemolyticus, V. cholerae,* and *V. alginolyticus*. It was not found active against various *Bacillus* species (though it does stop spore development), *Aspergillus* spp., *Lactobacillus* spp., *Moraxella catarrhalis,* and *Haemophilus influenzae.*

Hydroxytyrosol, present in much smaller amounts in the oil and in even tinier amounts in the leaves, is much more potent. It is active against all the species listed above, strongly so.

The whole herb (olive leaf) when tested has not shown that broad a range of activity. In vitro, it is active against resistant staph, *Campylobacter jejuni,* and *Helicobacter pylori*. But in

this particular study, the main one I have located, it was not active against 14 other bacteria (species not listed in the abstract unfortunately). The authors remarked, “In conclusion, olive leaf extract was not broad-spectrum in action” (Sudjana et al. 2009, abstract). Nevertheless, one other study found the leaf active against *Bacillus* spp., *Candida* spp., and *Cryptococcus neoformans*. Another found leaf activity against *Aspergillus* organisms. Still another found it active against *Streptococcus pyogenes* and two staph species (but not effective against *Pseudomonas* and *Candida*). Another study found the leaves active against protoscolices of hydatid cysts.

The most interesting study tested oleuropein, intravenous, against both resistant and nonresistant *Pseudomonas aeruginosa*–initiated acute pyelonephritis (sepsis) in rabbits. The constituent did not stop the infection but it did increase survival times from three days to six when tested against the multidrug-resistant strain and from one day to five against the resistant strain. When combined with a relatively ineffective antibiotic (amikacin) against the resistant strain, survival increased again, from six days to ten. In the oleuropein groups the levels of TNFα, IL-6, and bacterial counts all dropped. This makes the leaf and oil, both of which contain that compound, excellent as *supportive* antibacterials in the treatment of systemic *Pseudomonas* bacterial infections. Optimal dosing ran about 8 mg/kg per day of oleuropein in studies, which would be about 560 mg per day for a 150-pound person.

Still, if you compare this kind of research against something like *Sida acuta* you can easily see the difference in range of action, history of ethnomedicinal use, and in vivo and human studies. And in the case of olive leaf, there just has not been as much testing of its systemic antibacterial actions in vivo or in human study—unlike cryptolepis or bidens or alchornea or sida or even licorice. However, the olive oil itself has undergone a lot of study: in vitro, in vivo, and in human trial. It also has a very deep ethnomedicinal and historical use as a medicine.

Olive oil: Studies and Trials

The oil really is a specific for the treatment of mycoplasma. Two of its constituents, hydroxytyrosol and oleuropein, have been found to be, in vitro, active against a number of mycoplasmas (sometimes potently so, depending on species): *M. fermentans, M. hominis, M. pneumoniae,* and *M. pirum*. *M. hominis* and *M. fermentans* are the most responsive to the compounds. In vitro, oleuropein has been found to be antimycoplasmal at 160 mg per liter to *M. pneumoniae,* 320 mg/l against *M. pirum,* 20 mg/l against *M. hominis,* and 20 mg/l against *M. fermentans*.

As well, alpha-tocopherol, a form of vitamin E, which is present in significant quantities in olive oil, has been shown to stop vacuolization by *M. penetrans*. And then there are the oil's anti-inflammatory and antioxidant actions. These come from a variety of its constituents including hydroxytyrosol, oleuropein, luteolin, and alpha-tocopherol. And finally, the oil is rich in those particular fatty acids, most especially oleic acid (which makes up an average of 72 percent of the oil), that the mycoplasma bacteria scavenge, making it a specific nutrient to use for replacing those fatty acids. Thus the oil, as a medicinal herb, hits in four major areas of mycoplasma medicinal activity: specific antibacterial, anti-inflammatory, antioxidant, and nutrient replacement. Here is a look at it in a bit more depth. (Probably the best look at the biological activities of olive oil is Cicerale, Lucas, and Keast 2010. The next best is probably Waterman and Lockwood 2007.)

There are a considerable number of studies on olive oil in the literature—importantly, extra-virgin olive oil is the most effective, refined olive oil is relatively inactive in comparison. (Olive oil infused with the leaf constituents is even better.) The in-depth work on the oil has been stimulated by recognition of the benefits of the "Mediterranean diet" on the health of peoples in that region. Most of those benefits have been attributed to the regular ingestion of large amounts of olive oil.

In vitro studies on the oil have found a wide range of actions: it is highly protective of red blood cells against oxidative damage (perfect for mycoplasma), protects human peripheral mononuclear cells from hydrogen-peroxide-induced damage, inhibits endothelial-cell activation by bacterial

membrane molecules and their cytokine expression thus stopping angiogenesis processes, is proapoptotic, antiproliferative, anti-inflammatory, and antimicrobial. It downregulates a number of inflammatory compounds including COX-2 and Bcl-2.

In vivo studies (mostly rats, mice, rabbits) have found the oil's constituents to be widely distributed throughout the body; the oil's constituents reach the corneas and the oils's fatty acids are incorporated into the cornea itself. Oleic acid in the oil has been found to be potently antioxidative, the mitochondria are protected, and caveolin-1 expression is modified. The oleic acid is particularly inhibitive of TNF-α.

Olive oil inhibits platelet-activating factor (PAF) and PAF-induced aggregation, and it exhibits antithrombotic and antiatherosclerotic actions. It reduces glutathione oxidation and increases antioxidant activity in blood plasma, protects the liver and pancreatic cells from oxidation, and stimulates the expression of antioxidant enzymes. It reduces arachidonic acid metabolism in mucous membranes and inhibits PGE2 synthesis—thus protecting the cilia. It increases the blood-brain barrier's permeability, reduces brain edema, and inhibits brain injury in rats subjected to ischemia-reperfusion. In other words, it stops swelling in the brain, is cerebroprotective, and enhances neurologic functioning. Olive oil protects the heart from myocardial oxidative events and increases plasma and eye lutein levels (this strongly protects the eyes from oxidative events). Olive oil given to mice with an induced colitis reduces the condition and stops the damage from developing into severe chronic inflammation.

There are a significant number of human studies with olive oil. The intake of the oil resulted in a decreased urinary excretion of 8-iso-prostaglandin F (2alpha), a marker of oxidative stress, and three months of a high-olive-oil diet significantly reduced lipoprotein oxidation. A different three-month study found significantly reduced oxidative and inflammatory activity in those taking olive oil. A single dose of the oil in the morning repressed expression of proinflammatory genes, switching activity of peripheral mononuclear cells to a less inflammatory profile. NF-

κB/MAPK and AP-1 pathways were downregulated. ERK, IL-1β, and p38 MAPK release was inhibited, and arachidonic acid production decreased.

Oleic acid itself, a major component of olive oil, has important impacts on inflammation and bacterial infection. It reduces the proliferation of spleen lymphocytes during infection and in fact all lymphocyte levels are affected. Both oleic acid and olive oil have strong impacts on adhesion molecules. They significantly decrease the surface expression of vascular adhesion molecule-1 (VCAM-1). In healthy, middle-aged men two months of regular olive oil intake decreased the expression of intercellular adhesion molecule (ICAM-1); the effect was attributed to oleic acid. ICAM-1 is strongly expressed in the mononuclear cells that infiltrate the inflamed synovium in those with rheumatoid arthritis. Monocyte adhesion to endothelial cells was found to be severely reduced in those with a large intake of olive oil. Again this alteration was attributed to the effects of oleic acid. Monocyte chemotaxis in those who regularly ingest olive oil (Greeks) is much lower than in those who do not (Americans). The difference was positively attributed to oleic acid in the diet. A number of studies have found that people who consume large amounts of olive oil have a significantly reduced level of rheumatoid arthritis in their population. These kinds of outcomes have also occurred in numerous studies with rats. In essence, oleic acid significantly reduces a number of inflammatory immune markers that can occur during bacterial infection.

There do seem to be some bioavailability problems—but much less so with the oil than the leaf or isolated constituents. Studies with oleuropein found that only about half of it makes it past the gut and into the blood. However, it turns out that the bioavailability of oleuropein is much higher if the oil is taken (up to 76 percent). It is primarily absorbed in the small intestine and it appears that the bile is responsible for the oil's constituent transmission in higher quantities than either purified oleuropein or that from leaf intake (or from a water extract). And it appears that intake of any of the constituents, the oil, or the leaf is enhanced by taking it *after* (or during)

eating rather than before—most likely because the bile is already activated at that point. The half-life of oleuropein, for example, is only three hours when taken in a fasting state but is 12 hours after eating.

People taking 100 grams of olive oil (about 3.5 ounces) just after eating showed high levels of tyrosol (another constituent) in plasma peaking between 60 and 120 minutes (other constituents move more quickly into the bloodstream, e.g., hydroxytyrosol). Antioxidant activity significantly increased once plasma tyrosol levels peaked.

Between 55 and 66 percent of the phenols in olive oil are absorbed into the bloodstream after oral ingestion. Studies of the ingestion of one ounce of the oil found that hydroxytyrosol and tyrosol were both absorbed in a dose-dependent manner and that glutathione peroxidase activity significantly decreased after intake. Ingestion of two ounces of olive oil showed similar outcomes. Both tyrosol and hydroxytyrosol are excreted in the urine and serve as markers of uptake by the system. In general, most of those compounds are uptaken and about 20 percent of them are excreted. It also appears that about 15 percent of the oleuropein that goes into the body is converted into hydroxytyrosol in the body and is then excreted through the kidneys. This makes the oil specific for urinary tract and kidney infections due to mycoplasma. Tinier amounts pass the blood-brain barrier and circulate in the CNS.

Besides its antibacterial actions, oleuropein is strongly protective of cells from bacterial membrane constituents. It protects endothelial tissues from inflammation, stops angiogenesis, reduces monocytoid cell adhesion to cytokine-stimulated endothelial cells, inhibits VCAM-1, and inhibits NF-κB. (Hydroxytyrosol behaves similarly.) Oleuropein inhibits nitric oxide, IL-1β, IL-6, TNF-α, iNOS, COX-2, and MMP-9. Interestingly, oleuropein stops the development of morphine antinociceptive tolerance. Over time, as people take opiates for pain, even with years between doses, the receptors in the brain that react to morphine stop doing so. The more you take, even if it is for a week for back pain and then five years later for a broken bone, and so on, the less responsive the

brain receptors become. Then later, if you get cancer, the morphine does nothing. Oleuropein stops this process.

Oleuropein is hepatoprotective in mice. It is antiproliferative for prostate cancer in vitro. It is significantly protective in spinal cord injury (mice), downregulating NF-κB, TNF-α, IL-1β, IL-6, iNOS, MAPK, caspase-3, Bax, and Bcl-2 expression and reducing histological damage, neutrophil infiltration, and glial cell damage. Oleuropein is effective in induced pleurisy in mice, reducing TNF-α, IL-1β, nitric oxide, lipid per-oxidation, and neutrophil infiltration.

There has been a lot of study on hydroxytyrosol, which, it appears, is the most active antibacterial and anti-inflammatory in the olive plant. Hydroxytyrosol is present in olive oil in anywhere from 10 to 300 ppm (parts per million). It is highest in virgin olive oil. The amounts needed to produce effects are equally tiny—50 to 100 micrograms is active enough to significantly inhibit NF-κB, nitric oxide, and ROS in bacterial lipopolysaccharide-stimulated cells and stop the reduction of glutathione that lipopolysaccharides initiate. The ingestion of 25 milliliters of olive oil will produce plasma levels in people of 25 micrograms (thousandths of a gram) per liter of hydroxytyrosol within 30 minutes, which will slowly taper off over the next six hours. In vitro studies have found that hydroxtyrosol inhibits mycoplasmal organisms in a range of 0.03 mcg/ml (*M. hominis*) to 0.25 mcg/ml (*M. fermentans*) to 0.5 mcg/ml (*M. pneumoniae*). Translated to common units that is 30 to 250 to 500 micrograms per liter. For *M. hominis* that would mean the ingestion of one ounce of olive oil, for *M. fermentans* it would be 8 ounces, and for *M. pneumoniae* it would mean the ingestion of about 17 ounces of olive oil to get the active doses of hydroxytyrosol in the blood, assuming that one milliliter of oil produces one microgram of hydroxytyrosol in plasma. This is of course a problem—no one wants to take, or should, 17 ounces of olive oil. For one thing it is a potent laxative. (Just an FYI on that one.) Nevertheless, the oil also contains oleuropein, present in much larger quantities (up to 14 percent of the oil), which is active against the mycoplasmas as well. Fifteen percent of the oleuropein that is ingested is converted to hydroxytyrosol in

the body, thus raising hydroxytyrosol levels in the body. These two compounds, as well as a number of others in the oil, are synergistic with each other, compounding their effects as antimicrobials. (So, the actual dosage range should be 2 to 3 ounces per day of the oil.)

Importantly, hydroxytyrosol does make it, although in tiny amounts, into the brain where it is potently anti-inflammatory. Again, the amounts are tiny, about 92 nanograms (billionth of a gram) per liter. (Tyrosol is present in the CNS at about 74 ng/l.)

Concentrations of hydroxytyrosol occur in the brain, kidneys, heart, and testes.

Hydroxytyrosol inhibits ROS, NF-κB, IL-1β, IL-6, TNF-α, ERK-1 and ERK-2, MMP-2, MMP-9, PGE2, iNOS, nitric oxide, IL-1α, IL-12, CXCL10, CCL2. It strongly protects the retina and organs of the eye from oxidative damage, protects renal tubular cells against hydrogenperoxide-induced oxidative damage and peripheral blood mononuclear cells against oxidative damage, protects the skin from UV damage, stimulates glutathione production in endothelial cells, and is strongly protective of the mitochondria against oxidative stress.

Again, hydroxytyrosol and tyrosol and oleuropein are all much more bioavailable when olive oil itself is ingested than if the pure constituents, or the leaf, or a tea (water extract) is taken. Some 99 percent of the hydroxytyrosol is absorbed when taken in olive oil and 98 percent of the tyrosol. Hydroxytyrosol reaches its peak in 30 minutes, 25 percent is excreted by one hour, 50 percent at hour two, 65 percent at hour three, 70 percent at hour four, 84 percent at hour eight, and 95 percent at hour 24. This is almost identical to the kinetics if hydroxytyrosol is injected. Levels of hydroxytyrosol are highest in the kidneys due to its excretion through that route.

Olive Leaf: Studies and Trials

There are beginning to be many more studies on olive leaf, probably due to its increasing popularity, most of them since

2007.

The three major constituents of the leaves are oleuropein, luteolin, and a form of apigenin. Luteolin itself is indicated in mycoplasma infections as it is highly anti-inflammatory and also possesses some antimicrobial actions. In general, the leaf extracts reduce or inhibit IFN-gamma, TNF-α, IL-17, MMP-2, MMP-9, MMP-13, ROS, hydrogen peroxide, IL-1β, COX-2, and the Bax:Bcl2 ratio. I think the leaf 's most potent effect is as an anti-inflammatory, especially in treating brain and joint inflammations. It may ultimately have a potent place in pain treatment due to its impacts in diabetic neuropathy and its effects on opiate sensors.

In vitro studies found that olive leaf is a potent antioxidant, comparable to milk thistle and green tea. The weakness of the study is that it used ethyl acetate (think "nail polish"), methanol (think "rubbing alcohol"), or a combination methanol/water mix to extract the leaf constituents for testing. The methanol/water combination was strongest. None of these are suitable for human ingestion—well, not if you want to live.

Extracts of the leaf, oil, and pure oleuropein were studied to see their impacts on cytokine-induced B-cell toxicity. Both the leaf and oil (but less so the oleuropein) kept more cells alive and decreased ROS, IL-1β, IFN-gamma, and TNF-α while increasing superoxide dismutase (SOD) and glutathione levels. Insulin secretion was almost totally protected by the leaf extract, much less so the oil and oleuropein, bearing out the leaf 's traditional use for diabetes. The action probably occurs through the leaf 's ability to strongly stimulate glucagon-like peptide-1, an intestinal hormone that lowers glucose levels in the blood.

A water extract of olive leaf significantly reduced (but did not eliminate) the level of salmonella bacteria in infected lettuce leaves.

Levels beginning at 100 mg/l of olive leaf ethanol extract (OLE) increased the total antioxidant activity in human lymphocytes stressed by permethrin. The leaf has shown some anticarcinogenesis effects.

OLE inhibits xanthine oxidase, an enzyme that generates ROS. It can also catalyze the oxidation of xanthine to uric acid and is active in the catabolism of purines. Inhibiting it does reduce gout, bearing out the traditional uses of olive leaf for gout.

OLE, given to rats for 14 days, decreased serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels in the blood. In diabetic rats it also increased the amount of serum insulin available.

Another in vivo study found that dry olive leaf extract, given once a day through intragastric intubation to rats, ameliorated experimental autoimmune encephalomyelitis (EAE). EAE parameters decreased, including cumulative disease index, maximal clinical score, and disease duration. It decreased the cellularity of the draining lymph nodes and the production of IFN-gamma and IL-17 in the cells infiltrating the spinal cord.

Leaf extracts (dose not stated) were found to be highly protective of the brain, CNS, and hippocampus in gerbils during induced transient global cerebral ischemia-reperfusion. ROS, nitric oxide, and lipid peroxidation levels were all decreased. The hippocampus was strongly protected from neural damage.

Treatment of rats with lead-induced neurotoxicity found that olive leaf protected the frontal cortex from lead neurotoxicity, reducing p38 MAPK production, eliminating caspase-3 activity, and preventing DNA fragmentation. Glutathione levels increased.

During induced arthritis, olive leaf extracts protected the joints from inflammation and reduced lipopolysaccharide-induced TNF-α production. They also protected gentamicin-induced nephrotoxicity and modulated permethrin-induced genetic and oxidative damage in rats. Dosing in rats of 50 to 200 mg/kg provided an analgesic action; at the higher level it suppressed morphine hyperalgesia. The water extract of the leaves showed wound-healing activity in rats. The leaves also decreased levels of a particularly difficult kind of pain to treat,

neuropathic pain, that is common in diabetes, something that opiates are useless against. Dosages of both 300 mg/kg and 500 mg/kg per day were effective.

Rabbits given 500 mg/kg of olive leaf extract per day showed increased healing of induced cartilaginous injuries. It reduced inflammation in the joints and stimulated cartilage repair and regeneration.

Olive leaf extract was found to reduce the toxic effects of carbendazim on rats, normalize liver enzymes and protect the liver in others, to be antigenotoxic, to prevent UV damage and carcinogenesis in mice, and ameliorate islet-directed autoimmunity in the pancreas in mice.

Effective dosages of the leaf in most in vivo studies ran from 100 mg/kg to 1,000 mg/kg daily. Translated for a 150-pound person that would mean a dosage range of 7,000 to 70,000 mg daily (7 to 70 grams daily; 70 grams is nearing three ounces). Fifty mg/kg doses also were somewhat effective, around 3,500 mg (3.5 grams) per day for a human of 150 pounds.

I can find only two human studies with olive leaf (in contrast to about 20 with the oil). In a double-blind, randomized, parallel, controlled trial 500 mg twice daily of olive leaf extract was effective in treating stage 1 hypertension as compared with captopril. In the second study, a randomized, single-blind trial, an olive leaf liquid extract did *not* affect anti-inflammatory markers in people. (A couple of other in vivo studies also showed this kind of inactivity.)

Note: The best effects for mycoplasma will be with a combination of the oil and the leaf. The oil will provide the oleic acid, anti-inflammatory actions, and the most potent antibacterial actions; the leaf will provide, mostly, anti-inflammatory and cerebral-protective activity.

Preparation as Medicine

There are a number of ways to approach using the oil, leaf, and isolated constituents as medicines.

1. Virgin olive oil as a supplement

2. Standardized leaf extract (normally standardized for oleuropein content) as capsules
3. Virgin olive oil infused with the leaf
4. The oil regularly in the diet

Some important points:

1. I would not use an alcohol tincture extract of the leaf for mycoplasma. You won't get enough of the active constituents.
2. The capsules should be taken after eating and will be better absorbed if you ingested fats during the meal.
3. High heating of the olive oil will reduce its effectiveness. Low or minimal heating is apparently fine.
4. You might consider making your own leaf-oil infusion.

A number of researchers have been infusing leaf constituents into the olive oil (and other vegetable oils) to strengthen their anti-inflammatory, antioxidant, and lasting qualities. In general it takes the extraction of about 2.2 pounds of leaves and the infusion of that extract into anywhere from 50 to 320 liters of ***refined*** oil (depending on variety of refined oil) to create the same effects in the refined olive oil as virgin olive oil itself normally has. *Leaf-enriched virgin olive oil has itself been found to have better effects in people, increasing the levels of oleuropein, hydroxytyrosol, and so on in the plasma.*

You can make your own leaf-oil infusion two ways: 1) you can put the herb in a jar of olive oil and let it sit in a warm place for several weeks (think "sunny window"), or 2) you can put the herb and oil in the oven and let it heat overnight at the lowest heat possible, at about 150 degrees F. This won't inhibit the oil's actions or damage the oil. But remember: *use **only** cold-pressed virgin olive oil*.

To make: Place one ounce of the leaves in a jar or ovenproof baking dish and add enough oil to soak it through and just cover it slightly. When it is done warming, press out the oil, squeezing out as much as you can by hand or by herb press, and take as a supplement.

Dosages

The easiest approach will be to take one ounce of olive oil in the morning just after breakfast and one ounce in the evening just after dinner. Take three capsules of standardized olive leaf extract with each ounce of oil. (For example Nature's Way contains 250 mg of oleuropein and 250 mg of olive leaf. This will give you 1,500 daily of oleuropein and 1,500 of the whole leaf.)

You can also take one ounce of the leaf-infused oil morning and evening instead of the capsules and oil.

You can also just eat a salad morning and evening at your meal and put one ounce of olive oil on that along with vinegar and whatever else you want. (Take the capsules as well.)

Side Effects and Contraindications

The main side effect with the oil is its laxative actions. If you take it just after eating, that should not be a problem. If it is, split the amounts being taken into three and take with all three meals.

The leaf does lower blood pressure and may cause light-headedness if you stand too quickly. (So stand s l o w l y.)

Herb/Drug and Herb/Herb Interactions

None noted with the oil (well, I would not take it with laxatives). The leaf should not be used with blood pressure medications. The leaf has effects on blood glucose levels. It should not be taken with diabetic medications. Caution should be exercised if you are taking blood thinners.

The Berberine-Containing Plants

Both berberine and the berberine-containing plant phellodendron have been found strongly effective against numerous mycoplasmas. Berberine is strongly antibacterial against *M. salivarium, M. hominis, Ureaplasma urealyticum,* and *M. orale* with a lesser effect on *M. arginini*.

Generally, my preference is for the use of phellodendron, since it is an invasive plant, but you can use any strong berberine plant to treat urogenital mycoplasma infections. Of especial note are goldenseal, barberry, and mahonia. The tincture can be used internally and as a douche; it will be effective for both the urinary and the vaginal passages.

Berberine is absolutely *not* a systemic constituent in plants. Most stays in the bowel, where it does have potent effects. A tiny bit does get circulated but most of it is excreted in the urine or metabolized by the liver. This is what gives the plant its actions on those systems. An even tinier amount does get circulated in the blood and thus will have a tonic-like effect on the lungs, over time. It does have *some* systemic effects,

generally on mucous membrane and cartilage systems in the body. It does help protect and regenerate the cilia during lung infections.

Its strength in treating mycoplasmas is in its excretion through the kidneys and urinary passages. This will bring the constituent into strong contact with those mucous membranes, protecting the kidneys and urinary passages from mycoplasma infection. Berberine-containing plants can also be used as a douche to bring the herb in contact with the cervix and vaginal mucous membranes. This will help cure mycoplasma infections in those cellular locations—it's very good for that. It can be used, if wished, as an adjunct in helping treat mycoplasmal effects on the joints and lungs. It will bring a *tiny* amount of antibacterial activity to those locations. And no, high doses won't get any more of it to those locations though it may cause you some problems in your lungs if you try. The body just doesn't like a lot of berberine in the system (which considers it a toxin); that is why it tends to excrete or metabolize most of it.

The berberine plants have a good range of actions, including antibacterial, antifungal, antiseptic, antiamoebic, astringent, febrifuge, antidiarrheal, antidysenteric, antisecretory, anticholeric, expectorant, diaphoretic, mucosal anti-inflammatory, mucosal stimulant, mucosal tonic, antitumor, anti-inflammatory, and analgesic.

Berberine interferes with the adherence of bacteria such as *Streptococcus* spp. to mucous membranes by stimulating the release of lipoteichoic acid from bacteria or by stopping the formation of complexes between the microbial surface and host cells. It inhibits the intestinal hypersecretion (by about 70 percent) induced by *Vibrio cholerae, E. coli,* and other intestinal disease organisms. Berberine targets the assembly of *E. coli* cell division protein FtsZ. Basically, it is an FtsZ inhibitor, stopping replication of the bacteria.

Berberine-containing plants are active against a wide range of microorganisms. Berberine has been the most intensively tested of the alkaloids though a number of others such as hydrastine, jatrorrhizine, and palmatine have undergone a fair

amount of study themselves. The various antimicrobial alkaloids in the berberine plants tend to be active against different organisms and are highly synergistic with each other and additionally benefit from other compounds in the plants whose only known functions are to disable antibiotic-resistance mechanisms in microbial organisms. Thus, whole plant extracts, rather than isolated constituents, tend to have a greater range of action and, in my opinion, are much more effective.

Berberine plants are active against *Mycoplasma* spp., *Vibrio cholerae, Staphylococcus aureus, S. epidermis, Streptococcus pyogenes, S. mutans, S. sanguis, Fusobacterium nucleatum, Shigella* spp., *Helicobacter pylori, Escherichia coli, Klebsiella pneumoniae, Salmonella typhimurium, S. paratyphi, Corynebacterium diphtheriae, Mycobacterium tuberculosis, Blastocystis hominis, Microdochium nivale, Propionbacterium acnes, Erwinia carotovora, Enterobacter aerogenes, Xanthomonas citri, Bacillus cereus, Cryptococcus neoformans, Trichophyton* spp., *Trypanosoma cruzi, Entamoeba histolytica, Leishmania* spp., *Trichoderma viride* (green strain and brown mutant), *Giardia lamblia, Candida* spp., *Microsporum* spp., *Epidermophyton floccosum, Chlamydia* spp. (including *C. trachomatis*), *Malassezia* spp., *Zoogloea ramigera, Aureobasidium pullulans* (black and white strains), *Bacillus subtilis, Aspergillus* spp., *Pseudomonas aeruginosa,* human cytomegalovirus, herpes simplex virus 1 and 2, hepatitis B, West Nile virus, dengue virus, yellow fever virus, and *Trichomonas vaginalis*.

Many of the berberine-containing plants have been found to contain multidrug-resistance (MDR) reversal activity, usually inhibiting efflux pumps in resistant bacteria. *Berberis* spp. and *Hydrastis canadensis* contain 5′-methoxyhydnocarpin-D (5′-MHC) and pheophorbide A, which inhibit the NorA pump in *Staphylococcus aureus*. This is part of what makes the plants so effective in treating resistant organisms, especially MRSA. There are numerous other compounds in the berberine plants that show this kind of MDR inhibition.

The MDR inhibitors in the berberine plants have been found to be synergistic with the alkaloids in the plants. They have

also been found to be synergistic with pharmaceuticals, increasing their activity and effectiveness in treating resistant organisms and lowering the necessary dose for antibacterial, antifungal, and antiamoebic action.

In this section I am only going to look in any depth at phellodendron since that is my preferred berberine plant (though I will throw in a few others as well here and there). As you will see, it does have effects that are specific for mycoplasmal-induced cytokine and system damage in addition to its antibacterial effects.

An in vivo trial using phellodendron in the treatment of both acute and chronic induced inflammation using an ethanol extract of phellodendron and coptis (in a 2:1 ratio) found the tincture to be as potent in its effects as delecoxib and dexamethasone in reducing inflammation. In vitro studies on human osteoarthritis cartilage found that the plant significantly inhibited collagen and chondrocyte destruction by inhibiting proteoglycan release and type II cartilage degradation, downregulating aggrecanases, MMP activity, phosphorylated ERK-1 and ERK-2, JNK, and p38 MAPK signaling, and upregulating TIMP-1 activity. Another study found potent antioxidant activity by the plant. Berberine also inhibited VEGF and EGF.

Eighty people (45 completing) were enrolled in an eight-week, placebo-controlled, randomized, double-blind study comparing the effects of a *Phellodendron amurense* bark and *Citrus sinensis* peel combination capsule (740 mg 2x daily) on primary osteoarthritis of the knee between overweight and normal-weight persons. Overweight participants lost an average of 5 percent of body weight, and lipid levels, blood pressure, and fasting blood glucose levels normalized. There was significantly less inflammation and fewer symptoms of osteoarthritis in all those who used the herb combination. It was also found effective in treating periodontal disease.

Extracts of phellodendron (Nexrutine) fed to TRAMP mice for 20 weeks significantly inhibited prostate cancer cell proliferation and progression. A number of studies found similar antitumor activity of the plant for the prostate. Strongly

active on the prostate gland in vitro, inhibiting contractility. Dietary berberine and dietary phellodendron extract were found to inhibit cell cycle progression and lung tumorigenesis in mice.

In vivo studies with hyperuricemic mice found a decrease in uric acid levels in mice ingesting a high-dose phellodendron extract. Other studies found that the plant constituent phellodendrine suppresses autoimmune responses in mice and guinea pigs. Unlike prednisone and cyclophosphamide, the extract did not affect antibody production.

Phellodendron extracts prevent ethanol-, aspirin-, stress-, and pylorus-ligation-induced ulcers in mice. Extracts of *P. wilsonii* were highly protective of mouse liver in CCl4-induced hepatotoxicity. Other species provided only moderate protection.

During in vitro studies phellodendron has shown antioxidant, antitumor, anti-inflammatory, antimicrobial (plaque), anti-herpes simplex 1, and antibacterial actions against a wide range of bacteria.

A trial using tablets prepared from *Berberis poirettii* decoction was used in the treatment of 228 cases of chronic bronchitis. Of those, 12.3 percent experienced cure, 39 percent marked effects, 38 percent improved. (A tincture would have worked better.)

An in vivo trial with goldenseal found that the plant was helpful in treating liver cancer in rats. The plant's constituents do possess some antitumor actions and their concentration in the liver was found to be useful in the treatment of liver cancer, primarily as a supportive therapy.

Berberis vulgaris, when used instead of antibiotics in chicken feed, substantially increased their weight, just as antibiotics do.

Palmatine was used to treat 1,042 cases of gynecological infection, upper respiratory infection, surgical infection, tonsillitis, enteritis, and bacillary dysentery with good effect. In the treatment of 200 cases of vulvovaginal candidiasis, 171 were cured, 24 improved.

Numerous in vivo studies have found berberine to be tonically antitumor for a number of different kinds of cancers, from breast to bladder to gastric to liver. It downregulates MMP-1, MMP-2, and MMP-9 and is a potent COX-2 inhibitor.

It has also been found to be immunomodulatory (rather than stimulatory). It does increase IgA antibodies in mucosal tissue but it also reduced the overactivity of various aspects of the immune system. In other words if the immune system is ramped up by an autoimmune dynamic or hyperactivated by something like phytohemagglutinin or phorbol dibutyrate plus ionomycin, berberine modulates the response, suppressing the overactivity.

Dosages

As a douche: Add ⅓ounce of tincture to a pint of water and douche once or twice daily for 3–7 days.

As a tincture: 20–50 drops up to 4x daily. (***Note:*** this dosage is fine for all berberine plants in the treatment of mycoplasma infection of the urinary passages.)

Side Effects and Contraindications

Caution is advised in pregnancy. If you take a lot of a berberine plant over time, it will cause severe dryness in the mucous membranes, especially the lungs.

Herb/Drug and Herb/Herb Interactions

The berberines are synergistic (or additive) with a number of pharmaceuticals such as fluconazole, ampicillin, oxacillin. Repeated use of berberine *may* reduce the GI tract absorption of P-glycoprotein substrates including chemotherapeutic agents such as daunomycin. Berberine intake will *increase* the absorption of cyclosporine A if it is taken after long-term berberine use. Three mg/kg of berberine in human volunteers taken twice daily for 10 days increased the bioavailability of cyclosporine A by 19 percent. A randomized, clinical trial of 52 renal transplant patients for three months found that constant berberine intake significantly increased the amount of cyclosporine A in blood plasma.

Uva Ursi (*Arctostaphylos uva-ursi*)

Uva ursi is a creeping, oval-leaved, kind of leathery-feeling, groundcoverish plant. One of its major chemical constituents is arbutin, present at levels of up to 10 percent in the plant leaves. Once ingested arbutin is metabolized to the fairly strong antibacterial hydroquinone and is excreted from the body through the urinary passages. Hydroquinone has a fairly broad activity against pathogenic bacteria, including the mycoplasmas that cause urogenital infections, especially *M. hominis* and the ureaplasmas.

Arbutin and its metabolite hydroquinone have also been found to have some broader effects in the body. They inhibit bladder cancer cell proliferation, protect sperm from cryodamage, are strongly antioxidative, and inhibit tyrosinase.

Arbutin can also be found in lingonberries, pipsissewa, strawberry tree, damiana, fermented wheat germ, pear skins, and is extremely high in *Bergenia crassifolia* roots—between 20 and 30 percent by weight. Of the foliage plants, uva ursi is the highest, containing 120,000 ppm. It is the primary specific for mycoplasma-caused urinary tract infection (UTI).

Dosage

Tincture: ½ teaspoon 3x daily for 30 days.

Side Effects and Contraindications

Extreme long-term use (three years daily) can produce bull's-eye maculopathy, a depigmentation of the retina, with resultant visual acuity problems. This occurs due to the herb's inhibition of melanin synthesis. Generally, though, the herb has few or no side effects, other than perhaps slight nausea or ringing in the ears. It is a very safe herb.

Pomegranate (*Punica granatum*)

Pomegranate has been used in the Middle East and Asia as a potent medicine for millennia and has been showing up with greater frequency on my radar in the past few years. Both the rind and juice possess a range of antibacterial actions, some strong enough to potentially make the plant a major systemic herbal antibacterial. Due to its actions against mycoplasma

and the need for a juice in which to put tinctures and herbs for this protocol, I think that pomegranate juice is the best choice.

Pomegranate juice is in fact an antibacterial that is effective against some mycoplasmas. It was tested, in vitro, against 32 isolates of mycoplasma species, including *Mycoplasma mycoides, M. capricolum,* and *M. putrefaciens*. It *is* an antibacterial for the mycoplasmas, it's just not as strong as some other things (e.g., *Artemisia herba-alba,* which is not available in the U.S.). Pomegranate has some antiviral, anthelmintic, and antifungal properties. It also possesses antibacterial actions against a number of other bacteria (and yes, the rind is stronger than the juice). Both pomegranate rind and juice have been found to possess antibacterial actions against *Helicobacter, Staphylococcus, Pseudomonas, E. coli* (including O157:H7 strains), *Klebsiella, Salmonella, Streptococcus, Bacillus, Shigella, Listeria, Candida, Vibrio cholerae, Trichophyton,* and *Aspergillus*. Pomegranate juice is also active against a number of mouth bacteria that cause periodontal disease, and it completely blocks the swarming motility of *Pseudomonas* bacteria and is apparently most active against this bacteria. Pomegranate juice inhibits enterotoxins from many bacteria, including staph. The fruit rind (and juice, though weaker) is active against the malarial parasite *Plasmodium falciparum*, resistant and nonresistant varieties.

In India, the immature pomegranate fruit rind is a primary treatment for malaria. The rind is powdered and encapsulated in a product called OMARIA (Orissa Malaria Research Indigenous Attempt), which was developed by the Indian Red Cross, essentially to bypass the control over disease treatment by multinational pharmaceutical companies. It is part of the "Fight Malaria at Home" movement in India. All the work is done locally (i.e., in every village that needs it), including the harvesting of the pomegranate fruits, the powdering of the rind, and its encapsulation.

The powdered rind is encapsulated in gelatin capsules, each containing approximately 850 mg of powder. The dosing is one capsule every eight hours for three days, repeated in 14 days. Complete blood clearance of the parasite occurred in

several clinical studies. There are no side effects. Prophylactic use for from two weeks to six months has been found to significantly reduce the incidence of malarial infections (as well as measles, chicken pox, and conjunctivitis). Prophylactic dosing is one capsule for two days, five days off, repeat, then one capsule a month for four months. Children receive half the adult dose. No cerebral malaria cases were reported in any of those using OMARIA. The OMARIA preparation has been found to be potently active against both resistant and nonresistant strains of the malarial parasite in vitro and is now being developed for use in Africa.

Pomegranate has been found to have activity against a number of cancers. In vitro studies found that pomegranate extracts inhibited the growth of breast, prostate, colon, and lung cancer cells. In vivo studies found the same thing, including significant inhibition of prostate tumor growth in mice. And one human trial in the treatment of prostate cancer found that the use of the juice was accompanied by significant prolongation of prostate-specific antigen (PSA) doubling time.

Pomegranate juice has been found effective in the treatment of Behcet's disease, a form of systemic vasculitis, that is, inflammatory destruction of the blood vessels. The rind is antiangiogenic, reducing blood vessel formation in vivo. It is effective in the treatment of colitis.

It has shown strong chondroprotective effects against induced arthritis in knee joints and will help correct inflammatory damage at that location. It will reduce or prevent inflammation if taken prophylactically.

Pomegranate contains a number of potent antioxidant compounds, including the flavonoids myricetin and quercetin, anthocyanins, ellagitannins, and tannins such as gallic acid. Pomegranate (juice, rind, or fruit extract) has a broad range of anti-inflammatory effects and strongly suppresses inflammatory cell signaling induced by bacteria. Pomegranate inhibits NF-κB, TNF-α, IL-1β, IL-8, VEGF, TGF-β1, COX-2, PGE2, iNOS, MKK-3 (MAPK kinase kinase-3), p38 MAPK, ERK-1 and ERK-2, JNK-1 and -2, and transcription factor RUNX-2 in human osteoarthritis chondrocytes. Pomegranate

will reduce nitric oxide production 1.5-fold and IL-8 by 6.7-fold. PGE2 synthesis is reduced by 4.6-fold. It inhibits collagenase (MMP-1), gelatinase (MMP-2, MMP-9), stromelysin (MMP-3), matrilysin (MMP-7), elastase (MMP-12), and tropoelastin.

Pomegranate is systemic in that many of its constituents are circulated widely in the blood (peak in one hour, lasting about four hours). You need to repeat ingestion every three to four hours to keep levels of the active constituents in the blood high —though pomegranate metabolites can be found in the blood up to 48 hours after ingestion.

Studies on the amount of active constituents in the blood of volunteers showed virtually no difference between fruit extracts, rind extracts, and the juice. Within five minutes of pomegranate juice ingestion constituents can be found in the liver, spleen, heart, stomach, bowel, pancreas, lungs, and testes. After 20 minutes they can also be found in the bone marrow and kidneys. After 40 minutes they make it to the brain. All forms of pomegranate are potently antioxidative. The ingestion of 800 mg of pomegranate polyphenols raised oxygen radical absorption in human volunteers by 32 percent within one hour.

Pomegranate is synergistic with a number of herbs. Berberine plants will inhibit only 50 percent of cholera bacteria by themselves but will inhibit all of them if they are combined with pomegranate. Pomegranate inhibits ethidium bromide efflux mechanisms in a number of different types of bacteria. There is also some evidence, not conclusive, that it is effective against the MexAB-OprM efflux pump in Gram-negative bacteria. Thus the herb has been found to enhance the effects of a number of pharmaceuticals such as ampicillin, chloramphenicol, gentamicin, tetracycline, and oxacillin against 30 different MRSA and MSSA (methicillin-resistant and methicillin-sensitive *Staphylococcus aureus*) strains. It increases the postantibiotic effects of ampicillin from three to seven hours.

Dosage

I would recommend the use of 8 ounces of pomegranate juice every 3 hours during a mycoplasma infection. (***Note:*** 8 ounces of pomegranate juice will supply around 50 percent of the RDA of vitamins A, C, and E, 100 percent of folic acid, and 13 percent of potassium—it is a good nutrient to use for mycoplasma infections.) I would use the juice as the medium in which to take the herbal tinctures suggested in this book. And while, in India, the main form of the rind that is used is the powdered *immature* fruit rind, the powdered mature fruit rind is fairly easy to find. I would suggest adding 1 tablespoon of the powder to the morning, afternoon, and evening tincture/juice combinations.

The powdered peel is also high in vitamin C, potassium, pantothenic acid, potassium, and the B vitamins, which will help with the nutrient depletion in mycoplasma infection.

Side Effects and Contraindications

Pomegranate juice *may* lower blood pressure (but then again, it may not). It has been linked (weakly) to one case of rhabdomyolysis.

Herb/Drug and Herb/Herb Interactions

Pomegranate is a synergist with other substances. It will enhance the effects of a number of pharmaceuticals such as ampicillin, chloramphenicol, gentamicin, tetracycline, and oxacillin. It may be synergistic with warfarin. It may be additive with blood pressure medications. It will enhance the actions of berberine plants.

Caution should be exercised if you are on a lot of medications. Start slow and work up the amount you are taking just to make sure there are no synergisms with your medications.

Alternative

Noni juice, though I think it horribly overpriced for what it does, is an alternative. See the discussion in the next section.

SECONDARY ANTIBACTERIALS FOR MYCOPLASMA

There are a few other decent antibacterials for mycoplasma but for one reason or another, I don't think them a primary choice at this time. Among them are tea tree oil and *Anogeissus leiocarpus*. I don't think tea tree is all that systemic but it is a useful localized antibacterial. On the other hand, *Anogeissus leiocarpus,* an herb traditionally used in Africa to treat malaria, is a very good systemic antibacterial, you just can't get it in the U.S. And finally noni juice, which can be used instead of pomegranate if desired though I think it too expensive given the alternative.

Anogeissus (*Anogeissus leiocarpus*)

The anogeissuses are a genus of trees native to southern Asia and Africa. All of them are used extensively for crafts and medicines. *Anogeissus leiocarpus* is a tall evergreen tree native to tropical Africa. It's used in making traditional Malian mudcloth fabric, the leaves providing the yellow dye so common in that cloth. Medicinally, it is traditionally used in the treatment of malaria, babesia, trypanosomiasis, worm infestations, and gum diseases. Studies have found it active against *Aspergillus, Plasmodium, Staphylococcus, E. coli, Pseudomonas, Burkholdaria, Babesia, Bacteroides gingivalis,* and *B. melaninogenicus*, including resistant strains. In vivo studies with mice found it strongly active in the treatment of malaria infections, as effective as artesunate. It is potently antioxidative as well. It has been found effective in the treatment of asthma. The bark of the tree (or its stems) is normally what is used as medicine; water extracts tend to be the more effective antibacterials. The plant has very low toxicity.

Interestingly enough, it is traditional in Nigeria to use the leaves of this plant in the treatment of bovine mycoplasma, specifically *Mycoplasma mycoides*—infections are a common problem in cattle herds there. Nigerian researchers found that, indeed, the plant does have antibacterial actions against mycoplasma. Given that the plant is systemic, that it kills malarial and babesia parasites that are sequestered in red blood cells, that it has, apparently, a broad antibacterial range, it really is an incredibly good plant to use for mycoplasma infection.

Were this plant available in the U.S., I would suggest it as the primary antimycoplasmal antibacterial herb to use.

Side Effects and Contraindications

None noted in the literature (at least that I can find).

Herb/Drug and Herb/Herb Interactions

None that I can find.

Tea Tree oil (*Melaleuca alternifolia*)

Tea tree essential oil has been found, in vitro, to be effective against *M. hominis, M. fermentans,* and *M. pneumoniae*.

One study testing 25 clinically isolated strains of mycoplasma from the vagina, urethra, and cervix (*M. hominis, M. pneumoniae, M. fermentans*) found them all susceptible to tea tree oil—the minimum inhibiting concentration (MIC) for *hominis* (26 isolates) was 0.06 to 0.12, for *fermentans* (6 isolates) 0.01 to 0.06, and for pneumoniae (2 isolates) 0.01.

I would suggest the use of the essential oil as an inhalant in mycoplasma infections of the lungs and as an ingredient in a douche for genital mycoplasma infections.

Dosage

As an inhalant: 3–5 drops of tea tree oil in boiling water, inhale the steam, 2–3x daily.

As a douche: Add 5 drops of essential oil to a pint of water and douche once or twice daily.

Side Effects and Contraindications

Mild skin irritation when used topically. Overuse internally can cause light-headedness and dizziness. Normally this occurs from internal ingestion of the essential oil. The use of the steam or the essential oil in aromatherapy has no reported side effects along these lines.

Herb/Drug and Herb/Herb Interactions

None that I can find.

Noni (*Morinda citrifolia*)

Morinda citrifolia is a tree common in India, the Polynesian islands, and Hawaii where it has been in use for several thousand years for a variety of things. All parts of the plant are used in medicine—leaves, roots, bark, fruit. There is a lot of hype (currently) about *Morinda*—noni (the Hawaiian name for the plant) is the new herb-of-the-day. As well, *the* noni juice that everyone seems to be gaga about appears to be Tahitian noni juice, similar in its uniqueness (according to its marketers) to *the* rhodiola roots harvested near the Arctic Circle, apparently by fasting Russian virgins during the winter solstice. I dislike this kind of marketing hype; it does no one any good—well, except for the marketers and their bank accounts. The plant is not rare but is instead rather widespread around the world and very common where it grows; there is no reason for it to be so expensive.

Based on a number of things, I do think it a useful plant but the products available on the market are horribly overpriced and horribly overhyped. For what they do, mycoplasma-wise, pomegranate is a better option. Nevertheless …

Traditionally the green fruit, leaves, and roots were used by Polynesian cultures to treat menstrual cramps and irregularities, bowel problems, diabetes, liver disease, fevers, infected wounds, and urinary tract infections. The plant was considered to be a good tonic for regular use. The fruit is traditionally considered to be a decent food but some firsthand reports insist it smells like vomit. And yeah, one of its common names is indeed "vomit fruit." (Excited yet?)

The plant is, and has long been, used in traditional Indian, Japanese, Korean, and Chinese medicine. Asian cultures use the various parts of the plant as a tonic, to treat fevers, eye problems, skin wounds and abscesses, gum and throat problems, respiratory ailments, stomach pains, asthma, menstrual irregularities, arthritis, dysentery, urinary problems, diabetes, and venereal disease. In essence that list covers many of the mycoplasma-induced problems that can occur during infection.

Morinda fruit juice has been found active, in vitro, against three mycoplasmas: *M. pneumoniae, M. penetrans,* and *M.*

fermentans. The plant itself does have a wide range of antimicrobial effects though the root and leaves are the strongest. The root and leaf extracts are strongly antimicrobial against *Staphylococcus, Pseudomonas, Mycobacterium, Bacillus, E. coli, Salmonella, Shigella,* and *Aspergillus* organisms. *Morinda* juice's actions against *E. coli, Salmonella,* and *Shigella* bear out its traditional use for dysentery, its actions against staph, its use for infected wounds. It has some anthelmintic actions against intestinal worms and a fairly wide-ranging activity against some cancers. A number of in vivo studies found a strong analgesic action in the plant. One clinical trial found that it did help restore high-frequency hearing in older populations.

Noni juice is a pretty good antioxidant. It is a strong inhibitor of superoxide anion radicals and inhibits, as well, lipid peroxidation. It is an inhibitor of TNF-α, ERK-1 and ERK-2, JNK-1, nitric oxide, PGE2, COX-1 and COX-2. ***Note:*** It is apparently an immune modulator as other studies have found that in some circumstances it increases nitric oxide, interferon-gamma, IL-1β, and so on. No in-depth work on this has been done but speculation, based on traditional use and the simultaneous stimulatory and inhibitory actions on cytokines, is that it is a modulator rather than an inhibitor or a stimulant.

It does have some good protections on the CNS, in vivo. Noni juice is protective of neuronal damage, even preventative, during focal ischemia (mice). It does reduce stress-induced cognitive impairment (mice again). It prevents beta-amyloid-induced memory impairment (again in mice—who are getting smarter every second) and protects mouse brains from scopolamine-induced memory impairment (and remembering everything).

Dosage

I personally think the doses of noni need to be substantially higher than those suggested by manufacturers if you are going to use noni as a primary treatment for mycoplasma.

In general the tonic dose is considered to be 2 to 3 ounces per day, split between morning and evening. Some sources recommend that in chronic conditions 6 ounces a day should

be used and in acute conditions up to 32 ounces per day. And please note, the prices (U.S.) for noni juice are all over the place, from around $8 (16 ounces) to $25 (17 ounces). There are liter bottles for $20 and liter bottles for $30 and liter bottles for $40. There seems to be little quality control, though the prettier websites often have the more expensive products. Assuming that you are going to use 6 ounces a day for treating chronic mycoplasma, a 32-ounce bottle that costs you $20 will last you five days (with a bit left over). You are looking at about $120 per month for a minimum of six months. If you are going to use something this expensive I would recommend you use fermented wheat germ instead. However, as a supplemental addition to a complete mycoplasma protocol I think you may be able to get by with less of the juice than 6 ounces a day and still get some benefits from it.

An additional problem with most manufacturer suggested doses is that pharmacokinetic studies have found that noni juice reaches peak plasma concentration in two hours and is 50 percent depleted after four. For it to be effective for mycoplasma it needs to be taken every two to three hours. Because of that, if you are using it as a supplement to the full protocol, I would suggest taking 3 ounces per day, split into five lots (about half an ounce per dose). The first when you get up, before you eat anything. The others every three hours until bed.

Noni Extracts

There are, as well, noni extracts made from alcohol and water extractions of the roots, stems, leaves, bark, and fruit and various combinations thereof. The prices run from $10 per ounce to $50 per 3 ounces. Suggested dosage ranges run from 1 drop 3x daily to 15 drops per day in water on an empty stomach. If you really wanted a strong noni tincture extract to use for mycoplasma, it should contain root, leaves, and fruit. A useful dose would be ¼ teaspoon 3x daily.

Side Effects and Contraindications

Poverty.

Caution should be exercised if you have renal disease, specifically—the herb has a lot of potassium in it. If you are reducing potassium in your diet, well, this will add it back in.

Herb/Drug and Herb/Herb Interactions

Increases the effects of insulin.

A Few others

There are a number of other plants that have been found effective for mycoplasma but that are not available in the U.S. Among them are *Calotropis procera* (giant milkweed). Calotropis is native to Africa and Asia and is a common herb there but has never made it into the Western pharmacopoeia. Tests against mycoplasma, in vitro, found it stronger than tylosin, a macrolide antibiotic used in veterinary practice in Africa. Other studies, of which there are not that many, found it also strongly inhibitive of PGE2.

In vitro studies found *Artemisia herba-alba,* a plant commonly used in Iran—and of great interest to me in a variety of ways—and *Artemisia arborescens,* a plant common in the U.S., to both be active against mycoplasma. The trouble with the artemisias is that only some of their constituents are systemic. Artemisinin is, which is why the family, especially *Artemisia annua,* is useful for treating malaria. Unfortunately the antibacterial compounds, of which there are many, are not. So, these in vitro studies may not be of much use unless you are using the herbs for a douche or as an essential oil inhalant in lung infections.

Then there are …

Proteolytic enzymes: which can inhibit mycoplasmal fusion with host cells, especially T lymphocytes.

L-aspartic acid: which inhibits the growth of *M. bovis*.

Manganese chloride (MnCl2): which is concentrated in mitochondriarich tissues such as the brain, kidneys, pancreas, and liver and is often depleted by mycoplasmas. It is strongly inhibitive of the growth of *M. orale,* less so with *M. salivarium*.

Vitamin C: which, when give to chickens in their diet, was found to have increased their resistance to mycoplasma infection. Vitamin C also enhances apoptosis in carcinoma cells infected with *M. hyrohinis*. And finally …

Vitamin A: studies have shown that hosts with vitamin A deficiency are much more susceptible to mycoplasma infection. Levels of IFN-gamma are significantly reduced if vitamin A is added to the diet. Dosage: 600 mcg daily. ***Note:*** vitamin A is high in eggs, liver, fish liver oils, carrots, sweet potatoes, squash.

SUPPORT AND PROTECT ORGAN SYSTEMS

The mycoplasmas affect the mitochondria, lipoproteins in cell walls, glycoproteins (especially the mucins in mucus, proteoglycoproteins in the extracellular matrix, cartilage, glycocalyx, and collagen tissues), and components of the blood, especially red blood cells, platelets, and immune cells. These systems need to be supported in any treatment regimen. In other words, the protocol must contain substances that protect mitochondrial integrity and support proteoglycans, the blood, and mucous membrane systems. Endothelial cells, the lungs, the urogenital tract, the spleen and lymph system, the liver, and bone marrow are all important organs to support and protect as well.

Here are some of the most important herbs to use for helping the many organs of body affected by mycoplasmas.

RED BLOOD CELL PROTECTION

The primary herb for protecting red blood cells is *Sida acuta* or any of its close relatives. Other protectants are *Bidens pilosa* (or relations), ashwagandha, and N-acetylcysteine. (*Cryptolepis* and *Alchornea cordifolia* are also both very useful in treating hemoplasmas or mycoplasmas that are intracellularly sequestered in red blood cells.)

Sida

There are a lot of different sidas around the world. They live primarily in the tropics and subtropics but some species extend

into temperate regions. The main medicinal species studied has been *Sida acuta,* however as research has deepened on this species other sidas are coming to light as similarly potent, particularly *S. rhombifolia* and *S. cordifolia*. Two other species, *S. tiagii* and *S. spinosa,* have not been studied as extensively but their traditional uses, and some research, indicate they may possess the same medicinal actions. The sidas are invasives—in general, potent medicines that are making themselves known through insistence. I like them immensely. In the U.S. they tend to grow along the Gulf Coast and here and there in New Jersey and Pennsylvania.

The sidas are potent systemic antibacterial plants with a wide range of actions and contain one of the most potent systemic plant antibacterials, cryptolepine (as does *Cryptolepis*). They are antimalarial, antimicrobial, antibacterial, hematotonic, hematoregenerator, hematoprotectant, antioxidant (mild), anticancer (antineoplastic, antiproliferative), adaptogenic, analgesic, antipyretic, anthelmintic (fresh leaf juice), antiamoebic, antifertility activity (inhibit egg implantation in mice; however see the upcoming discussion of contraindications and side effects), antiprotozoal, insecticidal, anti-inflammatory, hepatoprotective, antivenin, antiulcerogenic, hypoglycemic. They are strongly protective of red blood cells, especially from microbial invasion. They are pretty good adaptogens.

They are active against a wide range of bacteria, including *Plasmodium* spp., *Staphylococcus aureus, E. coli, Bacillus subtilis, Mycobacterium phlei, Streptococcus pyogenes, Pasteurella multicocida, Salmonella typhimurium,* herpes simplex, *Campylobacter* spp., *Shigella boydii, S. flexneri, S. dysentariae, S. sonnei, Listeria innocua, Babesia* spp., *Pseudomonas aeruginosa, Candida* spp., *Aspergillus niger, A. fumigatus, Bacillus* spp., *Micrococcus luteus, Entamoeba histolytica, Salmonella enteritidis, S. paratyphi, S. typhimurium, Vibrio mimicus, V. parahaemolyticus, Klebsiella pneumoniae, Proteus vulgaris, Morganella morganii.* They haven't been tested for being active against mycoplasma but given their range of action, I think they probably are.

Sida acuta is widely used in traditional medicinal practice around the world to treat malaria, fevers, headache, skin diseases, infected wounds, diarrhea, dysentery, snakebite, asthma, GI tract problems, systemic infections, renal inflammation, toothache, sore gums, hysteria, bruises, eye infections (as eye drops), breast cancer, abscesses, neuralgia, and arthritis. James Duke's database lists 12 species of sida that have been used in traditional medicine, all for a similar range of complaints. The heaviest hits occur with *acuta, cordifolia, rhombifolia,* and *veronicaefolia*.

Various sida species have been used in India for over 5,000 years; it has a long history of use in Ayurvedic medicine. It has a wide range of use, including for nervous and urinary diseases and disorders of the blood and liver, strangury, hematuria, gonorrhea, cystitis, leukorrhea, chronic dysentery, epilepsy, facial paralysis, asthma, spermatorrhea, rheumatism, lingering debility from previous illnesses, intermittent diseases, rheumatic conditions, and cardiac complaints.

In traditional Chinese medicine the plants are used, just not as much. They are considered to be antibiotic, anti-inflammatory, analgesic, diuretic, and tonic. Sidas are commonly used for depression, bronchitis with cough and wheezing, and urinary tract inflammations. Less common uses are for dermatoses, itching, eczema of the scrotum, sores and boils, stomach pain, dysentery, gastritis, enteritis, tonsillitis, liver problems, jaundice, cervical tuberculous lymphadenitis, malaria, colds and flu, kidney stones.

Importantly, sida is an extremely potent protector of red blood cells, strongly active in protecting them from infestation from such organisms as *Plasmodium* and *Babesia*. It has been found in vivo to neutralize venom from the snake *Bothrops atrox,* a common and very poisonous pit viper in South America. The snake's venom is a hemotoxin that destroys red blood cells (rather than the neurotoxin more common to cobras and rattlesnakes). With snake venom, rather than its antimicrobial actions killing an infective organism, compounds in the plant neutralize a hemotoxic compound. In this sense sida represents a unique category of herbal medicines: hematotonic, hematoregenerator, hematoprotectant.

It is especially useful for anemia and I believe there are strong indications that the herb will be significantly useful for the treatment of certain forms of myeloma—cancer of the red blood cells. It is the only herb that I know of that is specific in this way for red blood cells.

Sida increases glutathione levels in the blood (important in coinfections), increases red blood cell numbers (making it good for anemia), and increases total white blood cell count, indicating an immune potentiation effect that may tie in with its reported adaptogenic actions in traditional practice. Numerous studies have found *Sida cordifolia* to possess very potent anti-inflammatory and analgesic activities, some of these coming from its ability to increase glutathione levels. The sidas are strong inhibitors of lipid peroxidation from bacterial membranes, inhibit quinolinic acid in the brain, and significantly reduce both LOX and COX. (A tincture of the plant has been found as active as the drug selegiline.) Unfortunately, in spite of consistent anti-inflammatory outcomes, few studies have been conducted on the sidas' effects on cytokine cascades. Use of the plant after myocardial injury showed significantly increased endogenous antioxidants in heart tissue.

In vivo studies have found *Sida acuta* to have a strong and reliable antiulcer effect, that is, it protects the stomach lining from the formation of induced ulcers. In vivo research has also found a strong analgesic action.

Several compounds from the plant have been found to inhibit induced preneoplastic lesions in mouse mammary tissue.

Sida tiagii during in vivo research has been found to have antidepressant and antiseizure effects (mice).

Tincture and the hot water extract are the strongest medicinal forms of the herb for internal use.

Dosages

As a tincture: 20–40 drops up to 4x daily. In the treatment of severe systemic staph infection the usual dose is from ½ teaspoon to 1 tablespoon, 3–6x daily. I prefer to not use this

high a dosage for longer than 60 days. That is usually sufficient.

As hot tea: As a preventative, 1–2 teaspoons of the powdered leaves in 6 ounces water, let steep 15 minutes, drink 1–2x daily. In acute conditions up to 10 cups a day.

Side Effects and Contraindications

The main side effect I have seen is that, for some people, sida can increase fatigue and symptoms of coinfection. If this occurs, reduce the dose. That will generally end the problem. This kind of side effect is not noted anyplace in the literature. My speculation is that sida breaks down biofilms and that in diseases such as bartonellosis once that happens, instead of the bacteria being limited to one location, they are then spread more widely throughout the body, increasing their negative impacts. (For more on biofilms, see the chapters on bartonella.) In the literature, there are no side effects noted, known, or reported, however …

- The herb is used traditionally to prevent pregnancy. It does interfere with egg implantation in mice. The herb should not be used if you are trying to get pregnant or if you are newly pregnant.
- Even though the herb is traditionally used in pregnancy, caution should be exercised if you are pregnant. I would be uncomfortable using it if I were pregnant but then, I would be uncomfortable anyway if I were pregnant.
- The herb contains ephedrine, although not in large quantities. There has been a lot of inaccurate, hysterical reporting on ephedra, even among researchers who should know better. Wikipedia is now among the worst offenders of overly conservative fearmongering—a departure from its original mission.

Although the main reason cited for banning ephedra in the U.S. is adverse effects, including death, what *is* accurate is that:

1. Weight loss and “natural energy” companies were the ones who marketed the supplements containing the herb

(usually along with caffeine and other stimulants). Herbalists did not support this use of the herb.

2. People wanting to lose weight or increase their energy took the supplements—often in huge doses, far beyond sanity.

Basically the herb was a way to make money off an aspect of the U.S.'s cultural insanity about how one should look to be beautiful or how much one should work to be useful, with, of course, predictable results.

In spite of this, the primary reason the herb was banned was that meth labs were using the herb to make meth. The adverse reactions from improper use of the herb were just the excuse. Ephedra is very safe when used properly; it really didn't need to be banned. The companies using it improperly just needed to be prohibited from doing so.

Nevertheless, just be aware that the herb contains *minute* (I repeat: *incredibly tiny*) amounts of ephedra and that a mild raciness or wakefulness may occur from using the herb—but it probably won't.

Herb/Drug and Herb/Herb Interactions

None known or reported, however:

- Since the herb is hypoglycemic, it *may* affect medications for diabetes. Just watch your blood sugar levels if you are diabetic.
- Since the herb contains ephedrine it probably should not be used with pharmaceuticals that possess similar effects.

ENDOTHELIAL PROTECTION

The endothelia are crucial to protect, especially in bartonella infections but also in mycoplasmal. There are a number of substances that will do so, including EGCG, but the most important is Japanese knotweed root.

Japanese Knotweed (*Polygonum cuspidatum*)

Japanese knotweed is a world-class invasive originally native to Japan, north China, Taiwan, and Korea. It is another

significant invasive that is specific for emerging bacterial infections. The root is the part of the plant used for medicine.

The herb has a wide range of actions: antibacterial, antiviral, anti-schistosomal, antispirochetal, antifungal, immunostimulant, immunomodulant, anti-inflammatory, angiogenesis modulator, CNS relaxant, CNS (brain and spinal cord) protectant and anti-inflammatory, antioxidant, antiatherosclerotic, antihyperlipidemic, antimutagenic, anti-carcinogenic, antineoplastic, vasodilator, inhibits platelet aggregation, inhibits eicosanoid synthesis, antithrombotic, tyrosine kinase inhibitor, oncogene inhibitor, antipyretic, cardioprotective, analgesic, antiulcer (slightly reduces stomach acid and protects against stress ulcers), hemostatic, and astringent.

A broadly systemic plant, Japanese knotweed modulates and enhances immune function, is anti-inflammatory for both arthritic and bacterial inflammations, protects the body against endotoxin damage, and is a potently strong angiogenesis modulator, highly protective of the endothelia of the body. It crosses the blood-brain barrier and is potently anti-inflammatory in the brain and CNS. It is highly specific for bartonella (and Lyme) infections, and good but of less importance in mycoplasma infections.

Knotweed is a very strong inhibitor of cytokine cascades initiated by bacteria. During Lyme infection, for instance, there is a spirochete-stimulated release of a number of matrix metalloproteinases (MMPs). The most common are MMP-1, MMP-3, and MMP-9. Production of MMP-1 and MMP-3 in Lyme arthritis occurs through a particular grouping of pathways—those of the mitogen-activated protein kinases (MAPKs), specifically JNK, p38, and ERK-1 and -2. MMP-9 production occurs through the JNK pathway and another, the protein kinase C-delta pathway.

While there are a number of herbs that can reduce autoinflammatory conditions stimulated by MMP-1 and MMP-3 (e.g., curcumin), the only herb that specifically blocks MMP-1 and MMP-3 induction through these three particular pathways is *Polygonum cuspidatum*. Resveratrol (one of the

plant's constituents) is also directly active in reducing MMP-9 levels through both the JNK and protein kinase C-delta pathways; it has been found to specifically inhibit MMP-9 gene transcription. Another component of the plant, rhein, inhibits the JNK pathway for MMP-1, MMP-3, and MMP-9 expression. Knotweed is also a formidable inhibitor of NF-κB, IL-8, PI3K, E-selectin, and VEGF.

Polygonum cuspidatum's constituents cross the blood-brain barrier, where they exert actions on the CNS: antimicrobial, anti-inflammatory, as protectants against oxidative and microbial damage, and as calming agents. The herb specifically protects the brain from inflammatory damage, microbial endotoxins, and bacterial infections.

Knotweed enhances blood flow especially to the eyes, heart, skin, and joints. This makes it especially useful in Lyme and its coinfections as it facilitates blood flow to the areas that are difficult to reach to kill the organisms. It is a drug and herb synergist, facilitating the movement of other herbs and drugs into these hard-to-reach places when taken with them.

It is also extremely effective for treating coinfection-initiated inflammatory arthritis. Its most potent constituents are the resveratrols, emodin, and polydatin. The plant root is so high in resveratrols that it is the main source of the supplement throughout the world.

While there is a long historical use of the plant in Asia, especially China and Japan, stretching back 2,000 years, there has been little knowledge of the plant in the West until recently. Research on and subsequent use of the plant as a phytomedicinal has been primarily because of its high content of resveratrol, a potent vasodilator and inhibitor of platelet aggregation (among other things).

The plant compounds in knotweed easily move across the gastrointestinal mucosa and circulate in the bloodstream. They cross, as well, the blood-brain barrier. Some 131 patents have been granted in the U.S. on the herb and its constituents for treating a variety of conditions, primarily cancer, inflammations, and neurodegenerative diseases.

In traditional Chinese medicine the herb is used for invigorating and clearing the blood, and for its antipyretic, detoxicant, antiinflammatory, antirheumatic, diuretic, expectorant, antitussive, and stasis-eliminating and channel-deobstructant actions. Primarily, it is used in the treatment of jaundice, rheumatic pain, strangury with turbid urine and leukorrhea, dysmenorrhea, retained lochia, bleeding hemorrhoids and anal fissure, wounds and injuries, scalds and burns.

Other uses include respiratory infections and repairing damaged skin: burns, carbuncles, skin infections, snakebite (usually as a poultice). It's also used for bacterial dysentery, acute infectious hepatitis with jaundice, hepatitis B (surface antigen positive), chronic active hepatitis, neonatal jaundice, cholelithiasis, cholecystitis (with damp heat or severe heat syndrome), trichomonas, bacterial vaginitis, hyperlipidemia, and psoriasis. (Basically, it is used to treat pathogenic heat in the blood, cough from lung heat, constipation from accumulated heat in the GI tract, jaundice and liver inflammation due to damp heat, and accumulated heat in the skin.)

There are literally hundreds of studies on the plant and its constituents. In the West these studies have primarily focused on the actions of resveratrol, followed (in descending order) by the whole plant and the constituents: trans-resveratrol, emodin, and polydatin. The scores of clinical and laboratory studies in China have been primarily on the whole plant and the single constituent polydatin.

The herb has been used for a long time in China for the treatment of burns. It has been found in clinical trials to promote scabbing (eschar formation) and inhibit bacterial infections in the damaged skin. The herb reduces exudation, prevents water and electrolyte loss, and hastens wound healing. In one study, 60 people with second- and third-degree burns were treated with the herb—10 to 71 percent of the body surface was burned, 15 were suffering skin infections. The second-degree burns healed in four to six days, the third degrees in 20 to 42 days. Other studies revealed similar outcomes. Reduced scarring and less tissue death is common

with the use of the herb for burns. This comes in large measure from its powerful angiogenesis-modulating (blood vessel generating and controlling) actions.

In burned skin, blood clots (thrombosis) within the capillaries lead to necrosis of the underlying tissues. Vasoconstriction, slow blood flow, and damage to underlying blood vessels are key conditions leading to thrombosis in burned skin. Clinical studies in China using special microscopes found that Japanese knotweed acted as a microcirculatory stimulant. It stimulated blood flow into burned skin, expanded the blood vessels, stimulated the healing of old blood vessels, and initiated the development of new ones.

Japanese knotweed is an angiogenesis *modulator*. That is, it stimulates the formation of new blood vessels and the healing of damaged ones in areas such as burned skin. But it also stops the development of new vessels and blood flow in areas where it should not occur, such as in malignant and benign tumor formation. It is a classic tonic herb in this respect and the only one I am aware of for maintaining the blood vessels themselves. It has, as part of this mode of action, specific modulating and protectant actions on the endothelial cells that line blood vessels.

Polygonum acts as an angiogenesis stimulant in a number of ailments: burns, chronic inflammations such as rheumatoid arthritis, debilitating ophthalmic disorders such as diabetic retinopathy and macular degeneration, brain disorders such as stroke, and various forms of heart disease such as coronary artery disease and angina. It acts powerfully as an angiogenesis inhibitor in both benign and malignant tumors. It may also come to soon play an important role in the treatment of a certain form of macular degeneration, so-called wet macular degeneration, in which the growth of abnormal blood vessels occurs in the eye.

In studies of heart disease, researchers found that resveratrol, one of the primary components of *Polygonum,* protected the cardiovascular system against ischemia-reperfusion injury, promoted vasorelaxation, protected and

maintained intact endothelium, was antiatherosclerotic, reduced LDL levels, was an antioxidant, and suppressed platelet aggregation. Chinese researchers found that the constituent polydatin was also broadly active in the cardiovascular system. They noted that it strongly stimulated vasorelaxation throughout the body, including the bronchial capillaries.

Polydatin is especially effective in treating burn shock, enhancing cardiac and microcirculatory functions. It restores decreased cardiac functions: output and stroke volume index. It restores pulse pressure to normal, decreases the number of adhesive white blood cells, and returns to near normal the amount of open capillaries. The degree of damage to scorched lung tissue is alleviated. It inhibits multiple-organ failure from burn shock.

Both polydatin and the whole herb enhance cardiac and microcirculatory functions and restore decreased cardiac functions. Resveratrol has also been found to possess similar actions. It inhibits tissue factor expression in vascular cells in response to pathophysiological stimuli, including bacterial, thus reducing inflammation in the heart and vascular tissue. It normalizes vascular endothelia.

The whole herb and its constituent resveratrol are both strong antioxidants. People who consume red wine (which contains resveratrol) or the herb have been found to have significantly increased antioxidant activity in their blood. This potent antioxidant action has been detected throughout the body. Interestingly, resveratrol seems to be an antioxidant modulator in that it will increase antioxidant action when needed (most of the time) but will lower it in instances where necessary, e.g., in leukemia cells.

Resveratrol is a potent inhibitor of the dioxygenase activity of lipoxygenase. Lipoxygenase is involved in the synthesis of mediators in inflammatory, atherosclerotic, and carcinogenic processes. By their potent inhibition of the dioxygenase activity of lipoxygenase, both the herb and resveratrol have pronounced effects on inflammatory processes such as arthritis, cholesterol levels in the blood, and cancer.

In part this is because resveratrol blocks eicosanoid production. Eicosanoids are powerful, very short-lived substances—quasi-hormones if you will—that are generated from three different fatty acids: dihomogamma-linolenic acid, arachidonic acid, and eicosapentaenoic acid (EPA, common in fish and fish oils). Arachidonic acid is the predominate generator in mammals, being stored in cell membranes. Through cyclooxygenase (COX) enzymes, arachidonic acid is transformed into potent proinflammatory and platelet-aggregating thromboxanes and inflammatory prostaglandins. Through lipoxygenase (LOX) enzymes it becomes the potent inflammatory, and white-blood-cell-stimulating, leukotrienes, hepoxilins, and lipoxins. The herb inhibits both LOX and COX pathway inflammations.

Resveratrol specifically inhibits the generation of arachidonic acid metabolites. These metabolites are involved in a number of autoimmune and allergic reactions, in tumor development, and in psoriasis-like conditions of the skin. Not surprisingly resveratrol causes a dose-dependent inhibition of the biosynthesis of prostaglandin E immunoreactive material.

Recent research has found that the plant and resveratrol interfere with the actions of nuclear factor-kappaB (NF-κB). This transcription factor is strongly linked to inflammatory and immune responses. It is active in the regulation of cell proliferation and apoptosis, cell transformation, and tumor development. It controls the gene expression of cytokines, chemokines, growth factors, cell adhesion molecules, and some acute-phase proteins, including the inflammatory mediators iNOS and COX-2. Bacteria such as *Borrelia* and its coinfections can activate NF-κB, causing a cascade of immune-mediated cellular reactions. The herb apparently modulates the actions of NF-κB rather than acting simply as its suppressor. Resveratrol also modulates interferon-gammainduced neopterin production and tryptophan degradation. Resveratrol also inhibits IL-6, IL-8, TNF-α, and ERK-1 and ERK-2.

Another component of knotweed, emodin, is highly protective of brain neurons and reduces pain by inhibiting the

activation of the P2X(7) receptors in the brain. In reduces impacts on the P2X(2/3) receptors as well.

The herb, in fact, is a potent immunomodulator. It normalizes immune response, especially in diseases where autoimmune reactions are stimulated (such as Lyme disease and lupus). It seems able to bring up immune function when necessary and reduce its local manifestations when overstimulated, e.g., in rheumatoid arthritis. This is a very strong aspect of the plant's actions.

The herb also stimulates the formation of fibroblasts. These undifferentiated cells migrate to injury sites, especially (in this case) in the skin and collagenous tissues, and undergo alterations to form new cells necessary for healing. In arthritis and psoriasis, the herb reduces inflammation and stimulates the production of new fibroblasts and their translocation to the areas of damage.

Good therapeutic outcomes were found in China in a clinical trial of the herb for 100 people with rheumatic arthritis, rheumatoid arthritis, lumbar hypertrophy, and osteoarthritis. The herb has been found to be especially effective in acute inflammatory diseases such as appendicitis, appendiceal abscess, tonsillitis, and pneumonia. In 45 people with pneumonia who were treated with the herb, body temperature dropped to normal in 24 to 36 hours. In 26 cases of acute appendicitis, 14 cases of appendiceal abscess, and 4 cases of perforated appendix complicated with peritonitis, all were cured by a decoction of the whole herb. Clinical studies have also found the herb to be effective in acute icteric viral hepatitis, inflammation of the bone and bone marrow, psoriasis, herpes, and cervix erosion.

In cancer studies, plant constituents from knotweed, primarily emodin and its derivatives—citreorosein, emodic acid, physcion, fallacinol, chrysophanic acid, and rhein—have been found to be potent oncogene signal transduction inhibitors through inhibiting protein tyrosine kinase and protein kinase C. Resveratrol acts to inhibit tumor growth, metastasis of tumors, and angiogenesis in cancer. Resveratrol inhibits DNA synthesis in cancer cells (specifically Lewis lung

carcinoma) and inhibits the binding of vascular endothelial growth factor to human umbilical vein endothelial cells. This constituent of the herb reduces the new blood vessels being created by cancerous clusters, eventually cutting off their supply of blood. Resveratrol has been found to be a significant inhibitor of cancer formation in vitro and in vivo for both mouse mammary gland and skin cancers. Dose-dependently, resveratrol inhibits up to 98 percent of skin tumors in mice; the percentage of mice with tumors, at the highest dose range, is lowered by 88 percent.

Resveratrol affects cancer at three stages of its life cycle: initiation, promotion, and progression. It inhibits metastases, cuts off tumor blood supply, and helps normalize cell differentiation. It is strongly antimutagenic.

The herb and its constituents have also been found to enhance and potentiate the action of other drugs and herbs when taken with them.

Japanese knotweed and its constituents also possess strong actions in the central nervous system and brain, and this range of activity is where a great deal of interest in the plant is being generated.

Knotweed and the constituents trans-resveratrol and resveratrol have been found to be strongly neuroprotective through a variety of actions in numerous studies. One of the herb's mechanisms of action in this regard is as an antioxidant. One study found that resveratrol and trans-resveratrol protected rat embryonic mesencephalic cells from a powerful pro-oxidant, tert-butyl hydroperoxide. Another study found that regular use of trans-resveratrol prevented streptozotocin-induced cognitive impairment and oxidative stress in rats (an Alzheimer's-like condition). And yet another found that trans-resveratrol protected and reversed many of the impacts of induced stroke in rats.

While the herb's antioxidant actions are important, trans-resveratrol, for example, has been found in a number of studies to strongly protect neuronal structures from damage through mechanisms other than antioxidant activity alone. Resveratrol has been found specific for protecting the brain from

neurotoxic substances such as the beta-amyloid peptides, which are associated with Alzheimer's disease.

Resveratrol and trans-resveratrol are specific for reducing inflammation in the brain and central nervous system. In spinal cord injuries resveratrol "remarkably" reduced secondary spinal cord edema, significantly suppressed the activity of lactate dehydrogenase, reduced malondialdehyde content in the injured spinal cord tissue, and markedly improved NA+/K+-ATPase activities. It immediately stimulated microcirculation to the injured tissues.

Low-level, chronic inflammation in the brain and central nervous system plays a major role in many neurodegenerative conditions. Both the herb and its constituents are specific for such inflammations. They have been found active for such things as amyotrophic lateral sclerosis and other motor neuron diseases, Parkinson's disease, Alzheimer's disease, bulbar atrophy, dementia, Huntington's disease, myasthenia gravis, stroke, multiple sclerosis, frontotemporal dementia, encephalomyelitis, traumatic brain injury, cerebral ischemia, and so on. The resveratrols specifically protect brain cells from assault, whether chemical or microbial in origin. The herb and its constituents, as well, stimulate microcirculation in the brain.

At least four patents have been accepted for this herb's constituents in the treatment of neurodegenerative disease. In vitro and in vivo studies have found the resveratrols effective for a number of these conditions. Some clinical reports support these findings and a number of clinical trials are under way.

Dosage

Capsules or tincture.

Capsules: Capsules of pure knotweed root can be had (try Green Dragon Botanicals at http://greendragonbotanicals.com) or you can buy "resveratrol," which is in fact only a standardized knotweed root formulation. That is, it is knotweed root standardized for the presence of a certain percentage of resveratrols. Most of the brands on the market are usable. Just make sure they are made from knotweed root

(it will say on the package someplace in tiny print) and not grapes. Dosage for either bartonella or mycoplasma is three capsules 3x daily.

Tincture: ¼–½ teaspoon 3x daily.

Contraindications and Side Effects

While a very safe herb, Japanese knotweed is contraindicated in pregnancy. Side effects of high dosages are primarily gastrointestinal in nature—dry mouth, bitter taste in mouth, nausea, vomiting, abdominal pain, diarrhea. In very rare cases loss of taste has occurred. It takes a while to return (months). If gastrointestinal side effects occur, reduce the dose.

Note: Some people have reported rather strong negative physical responses to the Source Naturals resveratrol. I am not sure why this is; however, those that do, having switched to another product by Paradise Herbs, report a better outcome. Just an FYI on that one.

Herb/Drug and Herb/Herb Interactions

Should not be used with blood-thinning agents. Discontinue use of the herb 10 days prior to any surgery. The plant is a synergist and may potentiate the effects of pharmaceuticals and other herbs.

LUNGS AND MUCOUS MEMBRANE PROTECTION

The primary herb for this is *Bidens pilosa* or its close relatives. Other herbs that are good are *Echinacea angustifolia* (*E. purpurea* is useless—really, not kidding), plantain, chickweed, violet, licorice, the mallows, elder, and fenugreek.

Bidens

There are a lot of different species of bidens. *Bidens pilosa* is the main species used medicinally (or at least on which most of the studies have been done) but there do seem to be a number of others in the genus that historical use and early research indicate can almost certainly be used similarly: *Bidens frondosa, B. tripartitus, B. ferulaefolia, B. alba* are all fairly potent, *frondosa* and *tripartitus* more so than *pilosa* in

their antimalarial effects; *B. maximowicziana, B. pinnata,* and *B. campylotheca* are all fairly strong as well.

The aerial parts of the plant are usually used but the roots will often work as well. ***Note:*** The plant is a great deal more active as an antibacterial and mucous membrane protectant if it is prepared fresh. The dried stuff is just not nearly as good. The plant was originally native to South America but has escaped and it is a potent invasive throughout much of the world. It probably grows around your house someplace.

The bidens are systemic herbal antibacterials with a fairly wide range of action. They are antimalarial, antibacterial, antimicrobial, anti-dysenteric, diuretic, hepatoprotective, hypotensive, anti-inflammatory, hypoglycemic, antidiabetic, styptic, vulnerary, immunomodulant, antiseptic, neuroprotectant, blood tonic, astringent, carminative, galactogogue, mucous membrane tonic, prostaglandin synthesis inhibitor. In fact, bidens is one of the most potent PGE2 plant inhibitors known. This wide range of actions makes it perfect for treating mycoplasmas.

Bidens is broadly antibacterial against *Plasmodium, Staphylococcus aureus, S. epidermidis, Mycobacterium tuberculosis, Entamoeba histolytica, Leishmania amazonensis, Serratia marcescens, E. coli, Pseudomonas aeruginosa, Enterococcus faecalis, Bacillus subtilis, B. cereus, Candida albicans, Klebsiella pneumoniae, Streptococcus faecalis, Shigella flexneri, Salmonella* spp., *Neisseria gonorrhea,* cytomegalovirus, herpes simplex virus 1 and 2. It is not very active against *Aspergillus*.

It has not been tested against mycoplasma but I suspect, based on what I know of it, that it will indeed be active against mycoplasma as well.

Bidens is exceptionally good for (in order of potency): 1) *any* systemic infections that are accompanied by problems in the mucous membrane anywhere in the body, especially chronic diarrhea, dysentery, UTI, vaginitis, and inflamed respiratory passages; 2) systemic staph; 3) malaria, babesia, leishmania.

The plant, in traditional use, has been used as a specific for a number of mycoplasma-type conditions: headaches, kidney problems, arthritis, ulcers, swollen spleen, cough, lung infections, rheumatism, infections, UTIs, rashes, and inflammation, and it's seen use as a neuroprotector. It has a long history of this kind of use in both Ayurveda and traditional Chinese medicine.

In China it is used for treating cardiac spasm, itching, gastroenteritis, appendicitis, colitis, irritable bowel syndrome, hemorrhoids, diarrhea, dysentery, difficulty swallowing, sore throat, tonsillitis, esophageal enlargement, jaundice, acute or chronic hepatitis, malaria, boils, abscesses, infections, fever, chills, joint pain, traumatic injury, sprains, swelling, contusions, rheumatoid arthritis, gastric and esophageal cancer, epilepsy in children, infantile fever with convulsions, malnutrition in infants, colds and flu, bronchitis, chest congestion, hemoptysis, allergies, lung irritation, pneumonia, insect bites, scorpion sting, and snakebite.

The Eclectic botanical physicians used it, primarily as an emmenagogue and expectorant, for amenorrhea, dysmenorrhea, uterine problems, severe cough, and asthma, as an infusion. An infusion of the seeds sweetened with honey was used for whooping cough. The plant was thought useful for heart conditions including palpitation, for colds, and for acute bronchial and laryngeal attacks.

The plant is a mucous membrane tonic and will not only stop the inflammation and act as a potent antibacterial in UTI infections but also heal the mucous membranes themselves. It has an affinity for mucous membranes and appears to act as a mucous membrane tonic. It is especially good for UTIs that are treated, return, are treated, return, *ad inuretherum,* especially if antibiotics have been used. The pain will usually go away in a day or two if you use bidens and within a couple of more days the problem should clear up.

It is specific for reducing elevated levels of uric acid in the blood, i.e., for treating gout or urate-based kidney stones. It is a decent diuretic and stimulates uric acid elimination from the body.

Because it is a mucous membrane tonic and is astringent, powerfully anti-inflammatory, and strongly antibacterial, bidens is specific for a number of troublesome diseases caused by resistant organisms: UTI, chronic diarrhea and dysentery, gastritis and ulcers (anywhere in the GI tract, from mouth to anus), inflamed mucous membranes in colds and flu and respiratory infections of any sort, sore throats from coughs or infection or even overuse of the throat, and vaginal infections. It's a good plant, too often overlooked.

Several of the plant's isolated polyacetylenes have been found to be more active than ampicillin, tetracycline, norfloxacin, and amphotericin B during in vitro studies. Ciprofloxacin and ofloxacin were more potent than the plant extracts. In one study, water extracts of the plant were found to be more effective against *E. coli* and *Bacillus cereus* than gentamicin. Bidens was found to potentiate the activity of tetracycline if taken along with that pharmaceutical.

Bidens pilosa was found to be as effective as atropine, promethazine, neostigmine, and hydrocortisone in protecting mice from the venom of *Dendroaspis jamesoni,* a snake in Cameroon whose venom contains a potent neurotoxin. The plant extract also potentiated the antivenom normally used to treat those snakebites (as did atropine and promethazine). It is a very potent neuroprotector against neurotoxins.

A number of in vivo studies revealed the herbal tincture to be highly antiulcerogenic, inhibiting gastric lesions induced by alcohol, and to be more effective than sucralfate. The herb significantly protected gastric mucosa and initiated mucosal healing through a number of mechanisms.

A number of studies have found the plant to possess antitumor activity. It inhibits angiogenesis (the formation of abnormal blood vessels, common in cancer and certain forms of macular degeneration), is antiproliferative, and directly reduces viable tumor cells (stimulates apoptosis). It possesses a strong antileukemic activity and numerous cell regulatory actions that normalize cellular function and growth.

Bidens has been found to be a strong antioxidant and anti-inflammatory. A double-blind, randomized crossover trial with

20 participants found the herb effective in the treatment of allergic rhinitis. In vitro and in vivo studies have found it highly effective in protecting erythrocytes from oxidative damage. The water-soluble fractions are more antioxidative than ethanol. The plant inhibits COX-2 expression (similarly to ibuprofen) and prostaglandin production. It is a prostaglandin synthesis inhibitor and a significant free-radical scavenger, comparable to alpha-tocopherol. It inhibits histamine release. Bidens also suppresses IL-1β, MAPK, and iNOS and inhibits lipid peroxidation by bacteria as well as NF-κB.

Bidens pilosa is a strong and reliable immune modulator. It has been found to modulate the differentiation of helper T cells and prevent Th-1-mediated autoimmune diabetes in nonobese diabetic mice. This has been attributed to a number of polyacetylenic compounds and a butanol fraction. The butanol fraction also reduces TH-2-mediated airway inflammation in mice. Hot water extracts of the plant stimulate interferon-gamma expression. The plant will increase immune action if it is low, and decrease it if high.

The plant should be prepared in specific ways to be most effective. The problem appears to be threefold: 1) some of the plant's most potent constituents begin to degrade as soon as the plant is dried—the plant constituents oxidize easily; 2) heat destroys them as well; and 3) the most potent constituents are considerably more soluble in alcohol than in water. Water infusions still do have a decent range of potency (as can be seen from the plant's traditional uses as a tea in Africa) but are not nearly what they could be if they are prepared as a cold alcohol/water maceration. Water extractions of the plant (teas, infusions, decoctions) even if it is dried will possess about half the antibacterial activity of an alcohol tincture (depending on how old they are) but they *will* possess most or all of the other actions described in this material (anti-inflammatory, antiallergenic, immune-modulating, and so on), especially the anti-inflammatory and antipyretic actions. The fresher the dried plant material the better.

Water infusions lose potency fairly rapidly; they should be made and used daily. They won't keep. Additionally, the older

the dried plant is, the less potent it will be—in either water or alcohol. The rapidity of degradation of the plant chemicals is, in part, why so many cultures that don't normally make alcohol tinctures resort to using the juice of the leaves of this plant, internally and externally, for disease.

Dosage

Fresh plant tincture: 45–90 drops in water up to 4x daily. In acute conditions (malaria, systemic staph), ¼–1 teaspoon and up to 1 tablespoon in water up to 6x daily for up to 28 days depending on severity.

Dry plant tincture (if you must): Double the dose of the fresh plant tincture.

As a tea: 1 teaspoon herb in 8 ounces hot water, let steep 15 minutes, drink 2–4x daily.

Side Effects and Contraindications

None noted in the literature.

Herb/Drug and Herb/Herb Interactions

None noted, however … one study does show bidens potentiating tetracycline. Caution should be exercised in using the plant if you are on diabetic medications as it will alter your blood glucose and insulin levels.

SUPPORTING MITOCHONDRIAL HEALTH AND FUNCTION

The mitochondria produce our energy. If they are specifically attacked, as they are during mycoplasma infections, energy levels drop considerably. This can, for some people, be incapacitating. There are a number of herbs and supplements that can help with this including coenzyme Q10 (not covered in this book), rhodiola and schisandra (both discussed in terms of immune support), luteolin (discussed as a secondary cytokine inhibitor), fermented wheat germ extract (weight loss), ginkgo (not covered herein), and motherwort.

Motherwort (*Leonurus cardiaca*)

Motherwort is an important supportive herb in that it provides protection for mitochondrial integrity and function and is very

good at reducing anxiety and sleeplessness.

Motherwort has been found to be strongly neuroprotective, especially in ischemia-reperfusion-induced mitochondrial dysfunctions in the brain, including the cerebral cortex. It significantly improves neurological outcomes and reduces ischemia-reperfusion impacts in the brain. It decreases reactive oxygen species (ROS) levels in the brain mitochondria and, importantly, reduces mitochondrial swelling and restores mitochondrial membrane potential. Motherwort decreases the expression of a protein, B-cell lymphoma 2 (Bcl-2), in the brain. Increased Bcl-2 levels in the body have been implicated in the generation of various cancers including prostate, as well as various psychiatric disorders of the CNS and autoimmunity problems, all part of the mycoplasma symptom range. Part of the function of the protein is interfering with apoptosis, that is, cell death. Motherwort decreases its expression and increases the levels of Bax. Bax is a protein, closely related to Bcl-2, that acts to increase apoptosis in cells. Bcl-2 and Bax normally exist in a modulated balance and their expression is controlled by a protein, p53. This protein is intimately involved in controlling the emergence of cancers in the body as well as protecting the genome from damage. It is sometimes referred to as “the guardian of the genome.”

All mycoplasmas suppress the expression of p53, thus decreasing Bax and increasing Bcl-2. This not only leads to cancer formation over long infection periods but also keeps cells that are infected by mycoplasmas from dying. This allows the bacteria to invade cells and scavenge their genome. Physiologically, in this instance, the mitochondria swell as they are infected, but cannot die, and are kept artificially alive while they are scavenged for nutrients. A major outcome of this is loss of energy due to mitochondrial malfunction. More crucially, it leads to damage in the brain that contributes to the psychiatric problems associated with mycoplasma infection.

Motherwort stops this process and protects the mitochondria in the brain, and presumably other cells in that location as well since it also decreases the production, and impact, of ROS in the brain. The herb exerts anti-inflammatory actions throughout the CNS and also exerts a moderate pain-relieving

action as well. Motherwort contains a number of chemical compounds among which is ursolic acid, which has been found to be a potent inhibitor of intracellular ROS induced by bacteria. Some studies have found that motherwort is higher in its antioxidative actions than both hawthorn and ginkgo.

Water extracts of motherwort completely inhibit tick-borne encephalitis (TBE) and induce resistance to the TBE virus in mice infected with it.

Motherwort slows and strengthens the heartbeat and has traditionally been used as a heart medicine. It is also a reliable and strong relaxant for anxiety. During anxiety episodes the heart rate increases; motherwort calms it down through a variety of mechanisms. In combination with this, it also significantly decreases anxiety by its actions in the CNS. Double-blind studies have found it to significantly help in the treatment of anxiety. It also has been found to significantly decrease sensitivity to light—a problem that often occurs during Lyme, bartonella, and mycoplasma infection.

Its actions are dose dependent.

Dosage

Tincture: ¼ teaspoon up to 6x a day.

Side Effects and Contraindications

The herb is contraindicated in pregnancy, stomach irritation has been so rarely reported as to make me question the source, and I don't know what to make of the one report of diarrhea. Tremendously high levels have been reported to cause uterine bleeding but I can only find one source for this and nothing in the journal papers that are so often hysterical about herbs. The herb has traditionally been used as an emmenagogue, that is, a substance to start a delayed menstrual cycle, so perhaps this why it is reported to cause uterine bleeding.

The plant does lower blood pressure, so if you already have low blood pressure, be careful with it. But just to make things more difficult the herb is also reported to raise blood pressure. I haven't seen this in practice in 25 years of use so am not sure what to make of that assertion.

Herb/Drug and Herb/Herb Interactions

Will produce additive effects if taken along with blood-pressure-lowering pharmaceuticals.

PROTECTING THE BRAIN

The brain is often very negatively affected by mycoplasma infection. To correct this, it is crucial to reduce the inflammatory cytokines that become active.

Inhibitors of ROS, TNF-α, IL-1β, ERK, and P2X(7) and substances that protect mitochondrial integrity will all help protect the brain and its neural structures. Many of the major ones are discussed elsewhere in this chapter: cordyceps, *Scutellaria,* Japanese knotweed, NAC, ashwagandha, and schisandra (in the discussion of immune support), motherwort, and kudzu root.

Also: herbs and supplements that stimulate the production of nerve growth factor (NGF) are very helpful. NGF is a small protein that is crucial for the growth, maintenance, and survival of neurons. When neuronal damage occurs, higher levels of NGF are essential in stimulating axonal regeneration. If you have severe damage in the brain, these can help with regeneration. Some of the better ones are *Polygala tenuifolia* (Chinese senega root, discussed earlier), *Hericium erinaceus* (lion's mane tincture, excellent but not covered herein), L-carnitine (not covered), *Centella asiatica* (not covered), deer antler (nope), huperzine A (and no, not covered), and the berberines.

However, if you are experiencing severe damage to the brain and CNS, especially with lesions, I would highly recommend you consider …

Greater Celandine (*Chelidonium majus*)

Greater celandine is native to Europe and western Asia; it's pretty widely established throughout the world now, including North America (some people even say it is native here). And, dear to my heart, it is an invasive, quite common in areas where mycoplama is endemic. Specifically, *Chelidonium* is invasive in most of the central and northeastern U.S., from

Georgia north throughout Canada and west to the Mississippi River. It is also invasive in Montana, Utah, Washington State, and Nebraska.

Greater celandine has a long history of use both in the West and in China. In Chinese medicine the herb has been used to treat blood stasis, as a pain reliever, to promote diuresis in edema, for ascites, for jaundice, and for cough. Its primary functional use in the West has been as a pain reliever, cough suppressant, antitoxin, and anti-inflammatory. It has been used for a very long time as a specific for jaundice, gout, toothache, ulcers, bronchitis, pulmonary infections, eye problems, infected wounds, wasting, GI tract problems, as a topical for abnormal growths, and as a blood tonic.

Its primary use now is as a mild sedative, antispasmodic, detoxifying herb, and for relaxing the muscles of the bronchial tubes, GI tract, and reproductive tract.

The plant has a nice cytokine-cascade suppressive effect. It inhibits NF-κB, TNF-α, IL-6, nitric oxide, Rho kinase, ERK, 5-LOX, 12-LOX, IFN-γ, B-cell proliferation, and gamma delta T cells in the spleen. Importantly, it is strongly inhibitive of the overactivation of the P2X(7) receptors in the brain, perhaps more than any other plant, making it specific for the kind of problems mycoplasma causes along those lines.

The plant is strongly anti-inflammatory due to its cytokine cascade inhibition, which is part of its pain-relieving actions. It is used in Korea as an anti-inflammatory (among other things) especially in the treatment of rheumatoid arthritis. Studies with mice (in Korea) found that the herb significantly reduced the levels of IL-6 and TNF-α in the spleen and lymph nodes, strongly suppressed the progression of arthritis in the knee joint of mice, as well as “dramatically” reducing the erosion of cartilage in the joint.

It has a decent range of antimicrobial activity. And was found strongly active against *Bacillus, Staphylococcus, Streptococcus, Enterococcus* (including resistant strains), and 98 percent of human dental plaque pathogens—and this presumably includes some of the mycoplasmas but the article is not clear on that point. It has some antiviral actions against

HIV, herpes virus, pox virus, and grippe virus. It is potently active against the tick-borne encephalitis virus in vitro and reduces the impacts of the disease in mice given aqueous extracts. And is antifungal against various candidas, resistant strains as well. It is strongly anthelmintic against *Dactylogyrus intermedius* parasites in fish. It is a biofilm inhibitor as well—a number of the compounds in the plant are active against the biofilm formation of various *Staphylococcus* species. It also is inhibitive of bacterial adhesion to human cells, probably from the herb's content of chelerythrine (see below). This range of actions bears out the plant's traditional uses for infected wounds and gums.

The plant has shown immunomodulatory activity in the spleen and bone marrow, has been found to strongly stimulate the production and release of bile, to be hepatoprotective and antiulcerogenic, to be antitumor, antispasmodic, radioprotective, and antiosteoporotic—primarily during in vivo and human trials.

One human trial found it to improve cellular and humoral immunity and nonspecific resistance to disease, significantly reducing the number of recurrences in children of chronic tonsillitis. Another clinical trial found that it was effective in reducing severe abdominal pain when compared with placebo. A number of clinical studies (in the Ukraine) looked at the effect of Ukrain, an extract of celandine, in the treatment of cancer. It has shown beneficial effects in the treatment of bladder, breast, pancreatic, rectal, and colorectal cancers.

The traditional uses of the plant and the range of actions that have been verified in scientific studies show it has a broad range of activity in many of the areas that mycoplasma infection has impacts. However, the most interesting are those that occur from one of its major constitutents: chelerythrine.

Greater celandine has over 30 different alkaloids, the main ones being coptisine (as in *Coptis chinensis*), sanguinarine (as in bloodroot and Mexican and opium poppy), chelidonine, and chelerythrine. The root has the most chelerythrine, running 2 to 3 percent by weight.

Chelerythrine is a very potent, and selective, protein kinase C inhibitor (at tiny doses of 0.66 micromolar), ATPase inhibitor, and alanine aminotransferase (ALT) inhibitor. It also very strongly blocks the P2X(7) receptors in the brain that ATP stimulates.

The mycoplasmas are intimately involved in the stimulation of protein kinase C (PKC). Their adherence to host cell membranes often depends on it. Inhibition of PKC significantly reduces, or even eliminates, cell adherence and the virulence of mycoplasmas such as *M. pneumoniae*. It stops vacuolization by *M. penetrans*. Many of the inflammatory cytokines initiated by the mycoplasmas (e.g., *M. hominis, M. arthritidis, M. arginini, M. fermentans, M. penetrans, M. pirum,* and *M. pneumoniae) depend on the stimulation of PKC. Inhibition of PKC downregulates the production of IL-6 and IL-8 as well as ERK-1, ERK2, and neutrophil respiratory bursts. Nitric oxide and PGE2 generation* have also been tied to PKC stimulation. Inhibition of PKC also stops the ability of mycoplasmas to induce HIV-1 movement into cells.

Chelerythrine is also a potent ATPase inhibitor. Most mycoplasmas generate and use ATPases. These are a class of enzymes that catalyze the decomposition of ATP, one of the ways they generate energy for themselves. The adhesion of mycoplasmas to host cell membranes is also dependent on ATPase activity. ATPase inhibitors can reduce mycoplasmas' ability to adhere to host cells by 50 percent. Inhibiting ATPase reduces the degree of impact that mycoplasmas have on host cells, keeps energy levels higher in the host, decreases the amount of energy the mycoplasmas have for themselves, and reduces their ability to attach to host cells and initiate breakdown.

High ATP levels in the brain lead to tremendous damage to the brain and CNS. ATP is also particularly stimulatory of the brain's P2X(7) receptors. Over time this produces neuronal excitotoxicity. In other words, excessive stimulation of P2X(7) receptors in oligodendrocytes is toxic to those cells. This causes oligodendrocyte death, myelin damage, and axon dysfunction.

Excess ATP production also leads to white-matter ischemia. Loss of motor and sensory function, neurobehavioral problems, and cognitive impairments can all result from these. There are an abundance of P2X(7) receptors on both myelin and oligodendrocytes. The oligodendrocytes and the myelin are both high in the glycolipids that the mycoplasmas need, especially galactosylceramides (galactocerebrosides). These are carried on the surface of mature oligodendrocytes and are released when those cells die. The mycoplasmas also scavenge and activate an enzyme, glutamine synthetase, from the oligodendrocytes. They use this to convert glutamate to one of the amino acids they need, glutamine, in the presence of ATP and ammonia. Cell damage causes significant ATP release from the damaged cell cytoplasm into the extracellular environment, where it quickly activates P2X(7) receptors on all cells in the brain, including astrocytes. This causes a dramatic increase in intracellular calcium levels, mediated by the P2X(7) receptors, which begins to cause significant damage in the CNS and brain. Levels of ATP (a neuroexcitant) continue to increase and levels of adenosine (a neuroprotectant) to decrease.

P2X(7) receptors are highly expressed in microglial cells in the white matter, on all myelin sheaths, and on oligodendrocytes. High levels of ATP immediately cause myelin destruction, oligodendrocyte cell death, and death of the microglia in the white matter, leading to small foci of necrosis throughout the white matter. Preventing P2X(7) receptor activation has been shown to reduce or even eliminate this. Activation of P2X(7) receptors is a root cause of neural pain as well. Deactivation will help alleviate peripheral nerve pain during mycoplasmal coinfection. Reducing P2X(7) activation will significantly reduce damage to the brain and CNS.

Mycoplasmas, especially *M. pneumoniae,* are also associated with increased levels of alanine aminotransferase (ALT) in the blood serum. This enzyme is released into serum when cells are damaged. The levels indicate how bad the damage is. Levels of this enzyme are high in the liver, which is why ALT levels are a measure of liver disease. ALT increases

in serum are not only indicative of liver problems but can also occur during Lyme coinfections. In fact, in the absence of liver disease, if ALT levels are rising in the blood, it is crucial to look for mycoplasma infection.

Chelidonium is an important herb in the treatment of mycoplasma, especially if there is severe brain and CNS inflammation. The only reason it is not listed as a primary herb for treating mycoplasma is the side effects issue.

Side Effects

Chelidonium is used by millions of people worldwide every day. In general, it is *very* safe. However, in recent years concern has been raised because it *occasionally* causes severe impacts on the liver. There are some 40 instances in the literature of chelidonium causing liver disease, specifically cholestatic hepatitis. This is jaundice with bile stasis due to severely inflamed intrahepatic bile ducts. More women than men are affected by it, usually older (56 years average), and the herb has to be taken for about a month before the first symptoms appear. All those so affected recovered upon discontinuance of the herb. Because of this the herb needs to be used with awareness. In general what the herb does, in those it affects this way, is to inflame the bile duct openings, causing them to swell and close. This creates the condition. This action of the herb is, in essence, an overstimulation. Many people use the herb to increase bile flow; for some people it just stimulates things too much. There has been a lot of overreaction to this, especially by herb-hostile physicians. So …

To put this in context, many antibiotic drugs will cause this condition; it is not uncommon—though with antibiotic drugs, the condition is not always reversible. Liver damage, often severe, is common as well with acetaminophen (i.e., Tylenol). Death and liver transplants are sometimes necessary. In contrast, this herb is extremely safe. Still …

The symptoms of cholestatic hepatitis are jaundice, itching, abnormal stools, and, sometimes, pain in the region of the gallbladder. In general, again, you have to take the herb for at least a month to develop symptoms. If you stop the herb, the

condition will improve almost immediately, with no long-term effects. So …

Pay attention to the impact the herb has on you and take action accordingly. In spite of this problem greater celandine is a very good herb for mycoplasma; its use is warranted.

Dosage

Tincture: Typical American dosage is 10–30 drops 3x daily for 30 days. English dosage is higher, generally 40–80 drops 3x daily. Chinese dosages are usually higher than that. I would begin with the American dosage and see how you respond. Then consider the English dosage if all goes well. In general, use for 30 days, wait a week, reinitiate use as necessary depending on physiological response to the herb.

Contraindications

Obstructed bile duct, pregnancy.

PROTECTING THE SPLEEN AND LYMPH SYSTEM

The spleen is deeply involved in the immune response of the body to bacterial infections; it is a major part of the lymph system. Protecting this system and its organs helps reduce symptoms, inhibits organ damage (which can sometimes be severe in coinfections, especially during bartonella infection), and enhances immune response to infection. ***Importantly,*** during mycoplasma infection, removal of the spleen has been found to immediately stimulate an acute mycoplasma infection that can lead, fairly quickly, to death. This has shown that the spleen plays a major role in controlling mycoplasma infections.

During mycoplasma infection the spleen may or may not be enlarged, the lymph nodes swollen or not, but during all mycoplasma infections the spleen absolutely has to be supported.

There are a number of herbs and supplements that can help. Among them are bidens, greater celandine, N-acetylcysteine, pomegranate, and cleavers. Poke root (not covered in this book) is also good but my favorite is red root. It really is deliciously good.

Red Root (*Ceanothus* spp.)

There are 50 or 60 or a million species of *Ceanothus* in the Americas, from Canada to Guatemala, no one seems to know exactly. The genus isn't native anyplace else but it has been planted as an ornamental throughout the world, especially in Europe. Most species can be used medicinally; the most common are *C. velutinus. C. cuneatus, C. integerrimus, C. greggii,* and *C. americanus*. All species are apparently identical in their medicinal actions. My personal favorite is *Ceanothus fendleri*, a.k.a. Fendler's ceanothus, which grows in my region and which I have been using for over 25 years.

Red root is an important herb in many disease conditions in that it helps facilitate clearing of dead cellular tissue from the lymph system. When the immune system is responding to acute conditions or the onset of disease, as white blood cells kill bacterial and viral pathogens they are taken to the lymph system for disposal. If the lymph system clears out dead cellular material rapidly the healing process is increased, sometimes dramatically. The herb shows especially strong action whenever any portion of the lymph system is swollen, infected, or inflamed. This includes lymph nodes, tonsils (entire back of throat), spleen, appendix, and liver. (Yes, it will help reduce an inflamed liver, though milk thistle is better.)

Essentially, if the spleen is swollen, that is, inflamed due to excess cytokine activity, the lymph system clogged, the nodes enlarged, the immune system depressed, and a chronic condition in place, red root is specifically indicated.

The herb helps tone and modulate function in the nodes and spleen and is highly protective of the spleen from microbial damage.

Red root has a very long history of use in the Americas. The indigenous cultures used the plant for a wide range of complaints from arthritis to influenza, though it was primarily used as an astringent. The early American herbalists loved it and the Eclectic botanical physicians developed the use of the plant considerably, using it as an astringent, expectorant, sedative, antispasmodic, and antisyphilitic. It was used specifically for gonorrhea, dysentery, asthma, chronic

bronchitis, whooping cough, general pulmonary problems, and oral ulcerations due to fever and infection. Its primary use however was for enlarged spleen and, to some extent, enlarged liver.

In recent years there has been a minor amount of exploration on the antimicrobial actions of red root. Several of the root compounds have been found active against various oral pathogens including *Streptococcus mutans, Actinomyces viscosus, Porphyromonas gingivalis,* and *Prevotella intermedia*. The flowers are active against *Staphylococcus aureus* and a couple of candida species; the roots probably are, too.

Betulin and betulinic acid, which are fairly prominent in the root, have a broad range of actions, both in vivo and in vitro: antiplasmodial, anti-HIV, anti-inflammatory, anthelmintic, antioxidant, antitumor, immunomodulatory. Ceanothane, another constituent, is fairly strongly antistaphylococcal, antiplasmodial, and antimycobacterial (and no, that is not a mycoplasma bacteria but one that causes TB).

There is some evidence that red root's activity in the lymph nodes also enhances the lymph nodes' production of lymphocytes, specifically the formation of T cells. Clinicians working with AIDS patients, who have historically low levels of T cells, have noted increases after the use of red root. It is especially effective in reducing inflammations in the spleen and liver from such things as excessive bacterial garbage, white blood cell detritus in the lymph, and red blood cell fragments in the blood in diseases like babesiosis. There is evidence, clinical, that it has broad action throughout the lymph system and helps reduce not only the spleen but also the appendix when inflamed and that it stimulates lymph drainage as well in the intestinal walls.

Dosage

Tincture: 30–90 drops up to 4x daily. In acute conditions, 1 teaspoon up to 6x daily.

Side Effects and Contraindications

No side effects have been noted; however it is contraindicated in pregnancy.

Herb/Drug and Herb/Herb Interactions

Red root should not be used with pharmaceutical coagulants or anticoagulants.

Alternatives

Poke root (*Phytolacca*) is an excellent alternative. Dosage however should be one-third that of red root. Cleavers will have some of the same effects but the dosage should be four times that of red root. The fresh juice of the plant is best. Cleavers, additionally, strongly inhibits elastase (by about 60 percent) and is useful for bacteria that use elastase as part of their infection strategy. If spleen problems are severe, the addition of bidens, greater celandine, and NAC will help immensely. NAC will strongly reduce the inflammatory cascade in the spleen.

CARTILAGE, COLLAGEN, AND JOINT SUPPORT AND PROTECTION

Mycoplasma can have tremendous impacts on cartilage and the joints. Herbs and supplements for reducing inflammation and protecting those tissues are very helpful in relieving symptoms. Some of the best herbs for protecting the joints, reducing inflammation, stopping chondrocyte breakdown, and repairing existing damage are greater celandine, olive leaf, teasel (not covered in this book), the berberine plants (e.g., phellodendron, coptis, goldenseal), ashwagandha, and green tea (EGCG). General anti-inflammatories such as NAC and so on will also help, as will some supplements that are specific for joints such as BioSil (tastes really horrible, like rotten fish … wait a minute!) and vitamin C (my preference is for effervescent salts, much better than tablets). However, a chondroitin and glucosamine sulfate combination can help as well, especially if your joints are experiencing severe impacts from a coinfection (please note restrictions on use).

Chondroitin/glucosamine Sulfate

Normally, I don't tend to recommend chondroitin since only about 20 percent of it is bioavailable—glucosamine is assimilated into the body much more readily. However, in this instance the combination is a good one as there is a lot of chondrocyte breakdown and the chondroitin will definitely help that problem. However …

Do not use chondroitin if you are experiencing nerve and brain damage from any coinfection. Chondroitin actually interferes with neuronal repair in the brain and nervous system and is upregulated in the CNS and peripheral nervous systems after injury. The main way that is counteracted is by the presence of NGF in the nervous system (see the discussion about protecting the brain, for NGF stimulants). If you do have CNS or peripheral nerve problems, take glucosamine sulfate by itself if you want to use a supplement for your joints besides the herbs/supplements already suggested.

Dosage

Use a chondroitin/glucosamine sulfate combination that gives you 1,500 mg glucosamine and 1,200 mg chondroitin daily.

IMMUNE SUPPORT

As with all coinfections, research has found that the degree of impact the disease makes is inversely proportional to the health of the immune system. That is, if the immune function is high, the disease impacts are small; if the immune function is low, the disease impacts can be tremendously deleterious.

There are many wonderful immune herbs in the world, my favorites are the adaptogens. These are plants that modulate immune function in response to environmental stressors, interior or exterior. If the immune function is too high, they lower it; if too low, they raise it. If you experience a stress event, the herb alters the immune function to respond to exactly that stressor.

I think the best of them are eleutherococcus (covered in the discussion of fatigue), astragalus (not covered in this book),

rhodiola, ashwagandha, and schisandra. These plants also have a nice range of action for protecting the joints and the neural networks of the body, including the brain, from inflammation-mediated damage. ***Note:*** There are some combination formulas that contain ashwaghanda, rhodiola, and schisandra in combination, usually in capsules, e.g., AdaptoStress3 Energy. If you decide to use that particular product, or something similar, rather than tinctures, take 3 capsules 3x daily.

Ashwagandha (*Withania somnifera*)

There are six species in this genus. *Withania somnifera* is the most commonly used though two other *Withania* species, *Withania obtusifolia* and *W. coagulans,* are used in much the same manner. The root is pretty much all that is used in Western practice but the whole plant is used in the rest of the world.

The root does have a nice range of actions, especially for mycoplasma-oriented problems. It is an immune tonic and modulator, stress-protective, alterative, anxiolytic, nerve sedative, neural protector, chondroprotector, collagenase inhibitor, reliable tonic sedative for insomniac conditions (especially if from stress or disease), antifatigue, amphoteric, antioxidant, anti-inflammatory, hematopoietic, antibacterial, diuretic, antipyretic, antitumor, and astringent. The leaves and stems are a nerve sedative, antipyretic, febrifuge, bitter, diuretic, antibacterial, antimicrobial, astringent, antitumor. Seeds: hypnotic, diuretic, coagulant. Fruit: immune tonic, antibacterial, alterative, astringent.

Ashwagandha has been a major medicinal plant in India for at least 3,000 years. They consider it tonic, alterative, astringent, aphrodisiac, and a nervine sedative. It has been used for TB, emaciation of children, senile debility, rheumatism, general debility, nervous exhaustion, brain fog, loss of memory, loss of muscular energy, and spermatorrhea. Its primary use is to restore vigor and energy in a body worn out by long-term constitutional disease or old age.

There have been an increasing number of studies on ashwagandha in the West since the turn of the millennium including a number of clinical trials. In one, 100 men and

women participated in a double-blind, placebo-controlled, randomized trial. The herb significantly reduced stress in all who took it. In another, a double-blind study with 60 healthy children ages 8 to 12 years found a marked increase in hemoglobin levels at the end of 30 days. Packed cell volume, mean corpuscular volume, serum iron, and hand grip were all increased at the end of 60 days. In another, a double-blind study with 101 healthy men ages 50 to 59 occurred, each taking 3 grams per day of ashwagandha for 1 year. All showed significantly increased hemoglobin and red blood cell counts, improvement in melanin levels, and decreased erythrocyte sedimentation rate, and three-quarters reported increased sexual performance.

There have been over 50 studies on the antineoplastic actions of the plant, primarily using the leaves. Tumor growth is retarded, tumor cell proliferation is reduced, side effects of radiation and chemotherapy are reduced, and life expectancy is increased.

The plant (or its extracts) has been found to be analgesic and antipyretic, the root extract highly chondroprotective of damaged human osteoarthritic cartilage matrix, and inhibitive of the gelatinase activity of collagenase type 2 enzyme.

The plant has also shown anxiolytic and antidepressant actions, strong antioxidant activities, to be neural protective (correcting scopolamine-induced memory loss in mice), to stimulate neuritic regeneration and synaptic reconstruction in damaged cortical neurons, and to completely inhibit dendritic atrophy. Treatment of rats for 14 days significantly improved nitropropionic-acid-induced cognitive dysfunction and oxidative damage; there have been at least 30 studies finding cognitive improvements in various animal species from the use of the root.

The plant has shown strong anti-inflammatory activity in various rheumatological conditions, it significantly reduces induced leukopenia in mice and significantly increases thyroid production of T3 and T4, and there have been at least 30 studies on the immune-potentiating and immune-modulation actions of the root in various animal species.

Dosage

Tincture: 30–40 drops up to 3x daily.

Side Effects and Contraindications

Avoid high doses in pregnancy; may be abortifacient in large doses. May cause drowsiness. Take the herb after dinner to find out just how sleepy it makes you before using it during the day. In rare instances: diarrhea, GI tract upset, vomiting at large doses.

Herb/Drug and Herb/Herb Interactions

May potentiate barbiturates (anecdotal); don't use with sedatives and anxiolytics.

Rhodiola (*Rhodiola rosea*)

No one knows just how many rhodiola species there are, but they do guess a lot: 36, or maybe 60, or probably 90. The primary medicinal that most people use is *Rhodiola rosea* but many of the related species are used medicinally in the regions in which they grow. Because of the interest in *R. rosea,* the genus is being intensively studied for activity: I have found medicinal studies of one sort or another on *R. crenulata, R. quadrifida, R. heterodonta, R. semenovii, R. sachalinensis, R. sacra, R. fastigiata, R. kirilowii, R. bupleuroides, R. dumusa, R. imbricata, R. rhodantha,* and *R. integrifolia*. The roots are what are used as medicine.

There have been some extravagant claims (easily found on the Internet) that *only* Russian *Rhodiola rosea,* harvested near the Arctic Circle (presumably by fasting virgins as the northern lights first emerge over the rim of the Earth during the winter solstice), contains the necessary active constituents for the herb to be useful. It's nonsense (what a shock). *All* the *Rhodiola rosea* plants, irrespective of where they grow or in what country, have nearly identical chemistry. They are all perfectly usable as medicine.

Rhodiola is an adaptogen, immune tonic, nervous system tonic, neural protectant, hippocampal protectant and tonic, mitochondrial tonic and protectant, endocrine tonic, adrenal protectant, ergogenic, antidepressant, antifatigue, antistressor,

strong antioxidant, potent cardiotonic, potent hypoxia antagonist, anticancer. Mental and muscular stimulant. Possibly a synergist; the plant is a strong inhibitor of CYP3A4 and P-glycoprotein.

It is specific for chronic, long-term fatigue, recurrent infections, recovery from long-term illness and infections, nervous exhaustion, chronic fatigue syndrome, chronic disease conditions with depression, low immune function, brain fog, acceleration of recovery from debilitating conditions.

Rhodiola, as far as I can tell, and in spite of assertions that it is a long-standing traditional Chinese medicinal, was a contribution to the medicinal plant world by the Russians due to their interest in adaptogens. This is pretty much a Russian-introduced category of medicinal herb—a plant that enhances general overall functioning, somewhat like a tonic but one that increases the ability of the organism to respond to outside stressors of whatever sort, diseases included. It enhances an organism's general resistance to multiple adverse influences or conditions. Rhodiola, like the stronger preparations of eleutherococcus, is considered to be not just adaptogenic but an adaptogenic stimulant—part of the reason it can cause jitteriness and wakefulness in some.

There is a lot of research on this plant right now, and more studies are occurring daily. There have been, unlike many other newish medicinal plants, a lot of human clinical trials with this herb. I am primarily going to look at the neuroprotective/neuroregenerative, immune, and antistress/antifatigue actions of the plant—they are strongly interrelated. The potent antioxidant actions of the plant are deeply interrelated with those as well.

Numerous rhodiola species have been found to be highly neuroprotective and neuroregenerative.

In vitro studies have found that compounds in both *Rhodiola sacra* and *R. sachalinensis* protect neurons against beta-amyloidinduced, staurosporine-induced, and hydrogen-peroxide-induced death. Salidroside, a common compound in many rhodiolas, protects cultured neurons from injury from hypoxia and hypoglycemia, protects neuronal PC12 cells and

SH-SY5Y neuroblastoma cells against cytotoxicity from beta-amyloid and against hypoglycemia and serum limitation, and protects neurons against hydrogen-peroxide-induced death. It does so by inducing antioxidant enzymes thioredoxin, heme oxygenase-1, and peroxiredoxin-1, downregulating the proapoptotic gene Bax, and upregulating the antiapoptotic genes Bcl-2 and Bcl-X(L). It also restores mitochondrial membrane potential and intracellular calcium levels following hydrogen-peroxide-induced loss.

In vivo studies have shown that *Rhodiola rosea* enhances the level of 5-hydroxytryptamine in the hippocampus, promotes the proliferation and differentiation of neural stem cells in the hippocampus, and protects hippocampal neurons from injury. *R. rosea* protects against cognitive deficits, neuronal injury, and oxidative stress induced by intracerebroventricular injection of streptozotocin. Salidroside protects rat hippocampal neurons against hydrogen-peroxide-induced apoptosis. A combination of rhodiola and astragalus protects rats against simulated plateau hypoxia (8,000 m/24,000 feet). It inhibits the accumulation of lactic acid in brain tissue and serum.

In human trials, a double-blind, placebo-controlled, randomized study with 40 women, ages 20 to 68, who were highly stressed, found that a *Rhodiola rosea* extract increased attention, speed, and accuracy during stressful cognitive tasks. *Rhodiola rosea* was used with 120 adults with both physical and cognitive deficiencies: exhaustion, decreased motivation, daytime sleepiness, decreased libido, sleep disturbances, concentration deficiencies, forgetfulness, decreased memory, susceptibility to stress, irritability; after 12 weeks, 80 percent of patients showed improvements. A double-blind, crossover, three-week study on stress-induced fatigue on the mental performance of healthy physicians during night duty found that *Rhodiola rosea* extract decreased mental fatigue and increased cognitive functions such as associative thinking, short-term memory, calculation and concentration, and speed of audiovisual perception.

The herb also has a number of antifatigue/antistress actions. In vitro studies found that salidroside stimulates glucose

uptake by rat muscle cells but more importantly, for mycoplasma, *Rhodiola rosea* extracts stimulate the synthesis or resynthesis of ATP and stimulate reparative processes in mitochondria.

In vivo trials found that *Rhodiola rosea* extracts increased the life span of *Drosophila melanogaster,* lowered mitochondrial superoxide levels, and increased protection against the superoxide generator paraquat; salidroside protects the hypothalamic/pituitary/gonad axis of male rats under intense stress—testosterone levels remained normal rather than dropping, secretory granules of the pituitary gland increased, and mitochondrial cells were strongly protected; *R. rosea* extract completely reversed the effects of chronic mild stress in female rats; rhodiola suppressed increased enzyme activity in rats subjected to noise stress—alanine aminotransferase (ALT), alkaline phosphatase, and creatine kinase levels all returned to normal, while glycogen, lactic acid, and cholesterol levels in the liver also returned to normal; *R. rosea* reduced stress and CRF-induced anorexia in rats; and so on.

In one clinical trial 24 men who had lived at high altitude for a year were tested to see the effects of rhodiola on blood oxygen saturation and sleep disorders, rhodiola increased blood oxygen saturation significantly and increased both sleeping time and quality; in a double-blind, placebo-controlled study of the effects of *R. rosea* on fatigue of students caused by stress, physical fitness, mental fatigue, and neuro-motoric indices all increased (other studies found similar outcomes); *R. rosea* intake in a group of healthy volunteers reduced inflammatory C-reactive protein and creatinine kinase in blood and protected muscle tissue during exercise; *Rhodiola rosea* in a placebo-controlled, double-blind, randomized study found increased physical capacity, muscle strength, speed of limb movement, reaction time, and attention —in other words it improved exercise endurance performance; a phase three clinical trial found that rhodiola exerts an antifatigue effect that increases mental performance and concentration and decreases cortisol response in burnout patients with fatigue syndrome; other studies have found

similar outcomes including the amelioration of depression and anxiety.

During clinical studies, *Rhodiola rosea* (in combination with schisandra, eleutherococcus, and leuzea) significantly increased both cell-mediated and humoral immune response in ovarian cancer patients; rhodiola significantly reduced problems and infection after the treatment of acute lung injury caused by massive trauma/infection and thoracic-cardio operations; a combination formula of rhodiola, eleuthero, and schisandra significantly enhanced positive outcomes in the treatment of acute nonspecific pneumonia.

Rhodiola, various species, has been found effective in the treatment of breast cancer. It inhibits the tumorigenic properties of invasive mammary epithelial cells, inhibits formation of superficial bladder cancer, suppresses T241 fibrosarcoma tumor cell proliferation, and reduces angiogenesis in various tumor lines. *Rhodiola imbricata* is highly protective in mice against whole-body lethal radiation.

The plant has also been found highly antioxidant in numerous studies, to be liver protective, and to be highly protective of the cardiovascular system.

The plant is adaptogenic, that is, it increases the function of the organism to meet whatever adverse influences are affecting it, whether stress or illness. Most of the attention has been paid to its ability to increase endurance and mental acuity but its effects on the immune system, though less studied than eleuthero, are similar.

Dosage

Tincture.

As a tonic: 30–40 drops 3–4x daily, usually in water.

In acute conditions: ½–1 teaspoon 3x daily for 20–30 days, then back to the tonic dose.

Side Effects and Contraindications

Some people experience jitteriness from the herb; you should not take it at night until you know if you are one of them.

Herb/Drug and Herb/Herb Interactions

None that I can find.

Schisandra (*Schisandra chinensis*)

There are some 19 or 47 or 82 species of schisandra (taxonomists actually have degrees). Many of them are used in Chinese medicine, usually as tonics and nervine relaxants. The plant is a sort of shrubby bushy viney sort of thing; the fruits are used as medicine. This is, like phellodendron, green tea, astragalus, cannabis, licorice, Chinese skullcap, and stephania (and so many others) one of the 50 fundamental herbs of Chinese medicine. The Russians, however, brought the plant to prominence when they discovered its adaptogenic actions, as they did rhodiola and eleutherococcus.

In Chinese medicine the fruit is used to cure leakage of energy from the lungs, to stop coughs, to tonify and enrich the kidneys, to restore the essence, and for diarrhea. It is used as a specific for urinary and sperm problems, for calming the heart, for irritability, insomnia, palpitations, dream disturbances, night sweats. It is essentially a tonic astringent.

Western research has found the plant specific for protecting the liver, as an antioxidant, adaptogenic, nervine tonic, mild antidepressant, for chronic coughs, asthma, and assisting childbirth.

The fruit increases antioxidant, especially glutathione, levels in mitochondria, protects them from ischemia-reperfusion injury, and stimulates their production of ATP, thus increasing energy levels. Schisandra enhances and lengthens the functional ability of mitochondria (in brain, heart, liver, kidneys) and reduces age-related mitochondrial breakdown. It reduces the breakdown of choline in the brain through the inhibition of increases in the enzyme acetylcholinesterase. It protects brain function by increasing antioxidant levels in the brain. Schisandra enhances and protects dendrites in the brain and stimulates synaptogenesis in hippocampal neurons. It protects and normalizes Ca+ processes in the cells of the brain, especially the hippocampus. It inhibits the formation of cellular peroxide.

Schisandra downregulates NF-κB and MAPK signaling pathways in cells stimulated by bacterial lipopolysaccharides. It downregulates PGE2, reduces nitric oxide production, and blocks the p38 MAPK, ERK-1 and ERK-2, and JNK phosphorylation. It inhibits iNOS and COX-2 expression, TNF-α, E-selectin, and VCAM-1. It suppresses TGF-β1 signaling by inhibiting Smad2 and Smad3 and MAPK pathways. It decreases the sensitivity of mitochondria to calcium-ion-induced permeability, thus protecting the mitochondria from damage by mycoplasmas.

The herb enhances and protects the function of the pituitary-adrenal-testes system, increasing energy levels. It decreases corticosterone levels and enhances testosterone levels and production.

Dosage

Tincture: ¼–½ teaspoon 3x daily

Side Effects and Contraindications

Rarely, abdominal upset, nausea, heatburn, skin rash. Very, very rarely.

Herb/Drug and Herb/Herb Interactions

The herb does have some potentiation effects on pharmaceuticals. Schisandra is an inhibitor of CYP3A and affects the disposition of drugs metabolized by that system in the liver. It will increase the oral bioavailability of midazolam; paclitaxel bioavailability is increased threefold. Caution should be exercised if you are using pharmaceuticals as the biopresence of the drugs may increase if you take schisandra as well.

SYMPTOM TREATMENT

There are a number of specific symptoms that can occur during mycoplasma infection. Here are a few of them, and some things that can help.

ANXIETY

Anxiety is common in both mycoplasma and bartonella infections. Some of the better herbs for this are Chinese skullcap, motherwort, ashwagandha (all discussed in this book), pasque flower, and coral root.

Pasque flower and coral root tinctures are very helpful, especially if taken over time. Their impacts build. Pasque flower dosages should be 10 drops every hour up to 6x daily. Coral root dosages are 30 drops up to 6x daily.

BRAIN FOG, CONFUSION

This should be alleviated by the protocol in the book. Of especial note are rhodiola, schisandra, NAC, knotweed, EGCG, and … I can't remember the last one.

EPILEPSY

The best approach to the treatment of epilepsy is a high-fat, that is, a ketogenic, diet. This has been successfully used in Britain for some time, especially in the treatment of childhood epileptic seizures. There is a lot of good research on it; it does work, basically by altering brain chemistry. Fasting can be used to treat epilepsy as well, but during a mycoplasma infection this can seriously lower nutrients in the body, increasing bacterial scavenging. A ketogenic diet is the best approach in this instance *if the seizures are severe*. The reduction of glucose in the brain and the increase of fats (ketones) stimulates the production of antioxidants, especially glutathione, and detoxifies the enzymes that are breaking down neuronal structures. Inflammation in the brain is sharply reduced, excitatory neurotransmitters are reduced.

If, however, the seizures are minor and occasional, the best overall herb is Chinese skullcap, discussed earlier. It will be most effective if combined with NAC. Bidens and sida can also be of some use.

FATIGUE

Many of the herbs in this book will help with fatigue including rhodiola and ashwagandha. During severe fatigue brought on by Lyme or coinfections, the best herb as a specific is eleutherococcus.

Eleutherococcus

There are 25 or maybe 38 species (taxonomists really are irritating) in the genus and while the primary one most people use is *Eleutherococcus senticosus* there is emerging evidence that a number of the species are also medicinally active in similar ways. *Eleutherococcus sessiliflorus* is used in Korea, identically to *senticosus*. *Eleutherococcus spinosus* (a.k.a. *E. pentaphyllus,* five-leaf aralia) is an invasive in the U.S. in Connecticut, Indiana, Kentucky, Massachusetts, Utah, and West Virginia, and, as well, Ontario, Canada. It is used similarly to eleuthero as a tonic adaptogen for general debility, rheumatic pains, and weakness. Its use should be explored as a now locally established, important immune plant and adaptogen.

The root is the most commonly used part of the plant, but the bark from the woody stems is actually higher in what is considered to be the most active constituent of the plant (eleutheroside B). The fruits are also usable and the leaves have some activity as well. The Chinese use every part of the plant in various ways for this and that.

The plant is an adaptogen, antistressor, immune tonic, antifatigue, immune potentiator, immunoadjuvant, andrenal tonic, MAO inhibitor, antidepressant, mental clarity stimulant, increases nonspecific resistance against a number of pathogens, and helps restore task endurance.

Though used in China for several thousand years eleutherococcus was brought to prominence by intensive Russian research in the latter half of the twentieth century. Then the emerging herbal renaissance in the U.S. caught wind of it, retitled the plant Siberian ginseng, and the boom was born. It became a major herb-of-the-day for a while, then was supplanted by rhodiola—the new kid on the block.

Acanthopanax gracilistylus and *A. senticosus* (a.k.a. *Eleutherococcus gracilistylus* and *senticosus*) are both used in Chinese medicine. The former plant goes by *wu jia pi* and is used for relieving rheumatic conditions and strengthening the tendons and bones, rheumatic arthralgia, weakness in the legs, retarded walking in children, general weakness and debility. It

does have some of the same eleutherosides in it. Eleutherococcus, in the Chinese system, is vital energy tonifying, spleen invigorating, kidney tonifying, and tranquilizing. It is used primarily for asthenia of the spleen and kidney, weakness and soreness of the lower back and knee, physical weakness, insomnia, frequent dreaming, and anorexia.

Eleutherococcus has a number of complex effects on the body; there are four important areas of impact: 1) the hypothalamus/pituitary/ adrenal system, 2) the immune system, 3) the liver and pancreas, and 4) the heart and circulatory system. All these actions combine together to produce the plant's unique adaptogenic actions.

In the hypothalamus/pituitary/adrenal system, eleutherococcus maintains the functioning of the system at optimum levels, altering its function in response to external factors. (As well, the herb appears to act as an adrenal tonic, helping restore function and health in both overworked and damaged adrenals.) If a person is under severe stress, the system ramps up; if the stress is less, the system activity lowers—in essence, the definition of an adaptogen. It helps the body adapt to external stressors, no matter what they are. The result of this is more energy, greater endurance, and enhanced response capacity to demands on the system.

In the immune system the herb has similar effects, in other words, it maintains its functioning at optimum levels in response to outside stressors. In this instance, the stressors are disease organisms entering the body. Studies have found that *how* the immune system responds depends on what kind of disease stressor is affecting it. The different parts of the immune system are activated to match the particular type of stressor that is affecting the organism. The herb has particularly strong effects on the spleen and spleen functioning. This is particularly important in treating both mycoplasma and bartonella infections.

Pharmacokinetic studies have found that the constituents from eleutherococcus are first concentrated in the liver, kidneys, spleen, and pancreas. Within two to four hours they

concentrate in the pituitary, heart, and adrenals. There are lesser concentrations in the thymus, testes, and brain. The concentration in the adrenals is three times that of the other organs. The constituents, once they reach the organs, begin exerting specific effects.

In the spleen, eleutherococcus stimulates the production of antibodies and facilitates the removal of antibody-coated bacteria. The production of monocytes is increased and their movement to injured tissues is facilitated as is their transformation into macrophages. This increases phagocytosis, macrophage activity, and both innate and adaptive immune responses. Dendritic cell numbers and function are also increased. Dendritic cells are highly present in tissues that contact the external environment: skin, nose, lungs, stomach, intestines, as well as in the blood. They interact with T and B cells to initiate and shape adaptive immune responses. They are a crucial and major part of the immune system and they are highly activated by eleutherococcus; in essence, they become more potently adaptable in their immune responses. Again, eleutherococcus's effects on the immune system are both stimulatory and modulatory; that is, the potency and sensitivity of the system is increased but how it behaves after that is dependent on the stressors the body is experiencing. Numerous studies, in vivo, have found that eleutherococcus significantly increases the survival time and number of survivors of mice injected with lethal microbes, irrespective of the disease organism used. It is highly stimulatory of the adaptive immune response to disease.

A number of clinical trials have shown significant immune-enhancing activity, including significant increases in immunocompetent cells, specifically T lymphocytes (helper/inducers, cytotoxics, and natural killer cells). Tests of the herb have repeatedly shown that it increases the ability of human beings to withstand adverse conditions, increases mental alertness, and improves performance. People taking the herb consistently report fewer illnesses than those who do not take the herb. Part of its power is its ability to act as a tonic stimulant on the adrenal glands. It normalizes adrenal activity and moves adrenal action away from a cortisol/catabolic

dynamic to a DHEA/anabolic orientation. Basically, this reduces stress and normalizes physiological functioning throughout the body.

Other studies have found that the herb heightens mental alertness and improves concentration and boosts the transmission of nerve impulses in the brain.

The Chinese have done a number of studies on the plant. In vivo studies have found the plant to have significant calming actions in the CNS, to be highly regulatory of the body's response to nonspecific stimuli, to increase tolerance to hypoxia, to be protective against radiation exposure, to be actively detoxicant, to be a potent antistressor, to rectify endocrine disorders, to modulate both red and white blood cell levels and blood pressure levels, to have a wide range of immune modulation actions, to be antineoplastic and anti-inflammatory, to optimize heart function, to be gonadotrophic, and to stimulate tissue regeneration.

Chinese clinical studies found the herb useful in treating physical symptoms due to anxiety (insomnia, palpitations, anxiety, dizziness, and so on), to reverse leukopenia due to radiation, to be highly effective in treating coronary diseases of various etiology, and to be effective in acute obstructive cerebral thrombosis, chronic bronchitis in elderly patients, altitude sickness, arthritis, and chronic fatigue.

Others studies have found the plant to have anticancer action, antioxidant activity, anti-inflammatory activity, to be of value in ischemic stroke, and to be fairly neuroprotective while at the same time increasing mental alertness and acuity.

Dosage

There are, in general, three primary forms of the herb that are used:

1. The Russian high-concentration tinctures, generally 2:1, 1:1, or 1:2;
2. Lower-strength 1:5 tincture formulations; and finally
3. Capsules, usually standardized in some way or other (though I prefer the powdered herb myself).

Most of the Russian studies were conducted using a 1:1 tincture in 30 to 33 percent alcohol. The dosage ranged from 2 to 20 milliliters per day (the smaller dose is a smidgeon under ½ teaspoon of tincture). This means people were taking from one-sixteenth to two-thirds of an ounce (and in some instances up to one and one-half ounces) of tincture per day. At an average cost of $7 to $12 per ounce of tincture (in the U.S.) this can be prohibitively expensive at the upper dosage ranges.

Dosage of the Russian formulation as an immune stimulant: The Russians generally dosed 2–16 ml, 1–3x daily for 60 days with a two- to three-week rest period in between. Russian researchers, at these kinds of dosages, saw responses within a few days or even hours of administration.

In this concentration, and at those doses, eleutherococcus is an immune *stimulant*, not a tonic. Using it at those doses in this concentrated a form is, in my opinion, specific for debilitating diseases accompanied by severe fatigue, brain fog, depression, muscle weakness, tendency to start getting better with inevitable relapse, and chronically depressed immune function.

You can, of course, take lower doses of the concentrated extracts, which would indeed make the tincture more tonic in nature.

Dosage of the Russian formulation in treating chronic, debilitating disease: *Please read carefully.* In chronic, highly debilitated conditions, the stronger Russian formulation is the only type of tincture that should be used—at least initially. I suggest the product sold by Herb Pharm, which is the only company I know of that actually exceeds the Russian specifications. Their formula is a 2:1 rather than a 1:1 (i.e., two parts herb to one part liquid rather than one and one).

For the first 30–60 days: 1 teaspoon 3x daily, the last dose occurring no later than 4 p.m. This dose can be increased if necessary.

After 60 days, discontinue the herb for two weeks.

Then repeat if necessary.

If symptoms decrease after using the Russian formulation for a while and immune function seems better, you can change to a 1:5 alcohol/water tincture, 30 drops 3x daily. This is weaker, but I like it much more as a long-term tonic adaptogen. In my experience this dosage and pattern of use is less stimulating to the system and the long-term effects are better. The body gradually uses the herb to build itself up over time, the herb acting more as a long-term tonic and rejuvenative than an active stimulant. With this type of tincture it is not necessary to stop every one to two months, nor have I seen any of the side effects that can occur with the stronger Russian formula. This weaker, American tincture, in my clinical experience, takes six months to become really effective and should be used at least that long; a year is better. It is great for long-term, mild chronic conditions that won't resolve that present, in Caucasians, with a pallid face, poor elasticity in the skin, mild skin eruptions, weak energy, monotonic voice, and general passivity.

Side Effects and Contraindications

Insomnia and hyperactivity can occur with use of the stronger Russian formulation, especially when taken in large doses. *Do not take after 4 p.m.*

Eleutherococcus is, in general, completely nontoxic and the Russians have reported the use of exceptionally large doses for up to 20 years with no adverse reactions. It is especially indicated for people with pale unhealthy skin, lassitude, and depression.

For almost all people no side effects have been noted. A very small number of people have experienced transient diarrhea. It may temporarily increase blood pressure in some people. This tends to drop to normal within a few weeks. Caution should be exercised for people with very high blood pressure (180/90) especially if combined with other hypertensives such as licorice.

With extreme overuse: tension and insomnia.

Herb/Drug and Herb/Herb Interactions

Increases the effects of hexobarbital, monomycin, kanamycin.

PAIN

The primary herbs for pain are greater celandine, kudzu, mother-wort, pasque flower, coral root, and Indian pipe. All will help. Indian pipe tincture dosages should be 30 drops up to 6x daily. Some people have reported a lot of help for pain during coinfections by the use of Theramine. Theramine is a dietary medication, a medical food—what a concept—that is only available through physician prescription. (What next, medical honey? Oh, wait …)

Theramine is a blend of L-arginine, choline, and L-glutamine. It is usually prescribed for fibromyalgia, headaches, back pain, joint pain, muscle pain. I am not sure how well it will work during mycoplasma infection but it has shown good effects during bartonella infections.

SLEEP DISORDERS

Lyme and its coinfections often cause sleep disturbances. I generally suggest three primary approaches to help that: motherwort, melatonin, and ashwagandha. Schisandra can also be of help. ***Note:*** Chinese skullcap can, sometimes, be a very good substitute for melatonin. By itself, it may normalize sleep patterns. Cannabis has also been of great help to a number of people, again, taken just before bed.

Melatonin

If liquid melatonin does work for you, it is a very good approach to use to help sleep. The secret is to take it just before bed, go to bed, read for half an hour or so, then turn off the light and go to sleep. If you read beyond the period of time in which it begins to take effect (just an FYI on this one) it won't work. Generally, melatonin takes just about an hour to really kick in. The liquid should be used, *not* capsules or pills. As all melatonin manufacturers are slightly different in what they are making, just follow the directions for how much to take (usually from three drops to three droppers full). Hold it in the mouth a minute or so, then swallow. This takes it directly into the bloodstream and bypasses the stomach, which you definitely want to do if you are working to alleviate sleep disorders. If you wake again at 3 a.m., as so many of us do,

take it again, same way, same dose. You should fall back to sleep in an hour at the most.

Note: Melatonin is present in some plants in fairly high quantities, Chinese skullcap is an excellent example. This is one of the reasons that regular use of that plant can help relax and calm the nervous system and promote sleep. Oats is another, which is, in part, why regular use of oatmeal as a food —every morning—will, over time, relax the entire nervous system and promote better sleep. It takes about a month. Melatonin is also a potent antioxidant and taking it in food will result in more melatonin binding to receptors in the brain, reducing inflammation. The use of a melatonin supplement *or* the regular consumption of melatonin-containing plants will definitely help reduce neurotoxicity in the brain.

Ashwagandha (*Withania somnifera*)

Ashwagandha (in the discussion of immune support for more) is a very good immune modulator, anti-inflammatory/antioxidant, neural protector, and antistressor but it is also very good for helping sleep. Many people can't take ashwagandha during the day because it makes them nod off at work. If you are one of the lucky ones that it makes sleepy, use it for sleep problems.

Dosage

Tincture: ½ teaspoon 1 hour before bed; powder or capsules: 1 gram an hour before bed.

Motherwort

Motherwort is excellent for helping sleep … if you take enough of it. It is an extremely safe herb; I have used up to one ounce of the tincture at a time for stress and sleep problems but usually keep it to anywhere from ¼ to ½ ounce of the tincture at a time. It is particularly good if blended with any of the *Pedicularis* species (elephant tree or lousewort—available from Elk Mountain Herbs at www.elkmountainherbs.com). I usually blend them in equal parts, ¼ ounce motherwort, ¼ ounce pedicularis. Whatever amount you take of the motherwort, take that much of the pedicularis.

Dosage

Begin with ¼ ounce of the motherwort tincture in a liquid of your choice (probably not coffee) and see how it works.

WEIGHT LOSS PROBLEMS

Mycoplasma infection, because the bacteria scavenge so many nutrients, can sometimes cause severe wasting, that is, no matter how much the person eats, they can't gain weight. There are two primary substances that have been shown to reverse this—fermented wheat germ and shiitake mushrooms. Fermented wheat germ is the most potent and could easily be added to any mycoplasmal treatment protocol due to the broad impacts it has on the disease. The only trouble is—it is *very* expensive.

Fermented Wheat germ

Mycoplasma infections cause a lot of problems in food animals, especially chickens housed in large chicken farms. The disease causes problems in egg production and quality as well as in the chickens themselves—wasting, severe weight loss, is common. In consequence, researchers regularly try various things in order to counteract the problem. One of them has been fermented wheat germ.

Fermented wheat germ is made by removing the wheat germ from the wheat during milling, fermenting it, separating out the fermented liquid, drying and granulating it, and then encapsulating it or leaving it as a granulated powder, depending on how it is to be taken.

A pretty nice trial was conducted on broiler chickens. Three groups of birds, 30 each, beginning at three weeks of age, were involved. All were exposed to aerosol infection with *M. gallisepticum,* which produces a disease similar to that caused by *M. pneumoniae* in people. While some remain asymptomatic, the usual symptoms for most birds are respiratory. A smaller percentage develop systemic problems and some die. All experience weight loss and poor development.

Of the three groups, one was treated with fermented wheat germ extract (FWGE), one with tiamulin—a potent antibiotic for mycoplasma infections in animals—and the third was left untreated. To be clear here: *none* of the three groups were completely cured of the disease but the differences in their health levels were significant and far fewer in the treated groups remained infected by the end of the study.

The health of the birds in the FWGE and antibiotic groups was virtually identical while those in the untreated group were much worse. Statistics are these: lesions (found upon dissection at the end of the study) in the FWGE group were 15, in the antibiotic group 11, in the untreated group 25. In the FWGE group, at death, *no* mycoplasma bacteria were isolated from the liver, spleen, brain, heart, or kidneys while mycoplasmal organisms were recovered from the respiratory tract samples 10 times (in the antibiotic group 3 times). In the untreated group mycoplasma was isolated 64 times from respiratory tract samples taken over the course of the study and, at dissection, was found in the brain, kidneys, heart, and spleen. The spleen was particularly hard-hit in the untreated birds. In the FWGE group, at the end of the study, 6 birds showed a serological response to mycoplasma, in the untreated group 25 did (as did 8 in the antibiotic group). Five of the untreated birds died, none in the treated groups died. The birds treated with FWGE did not develop clinical signs of infection, catarrhal pneumonia and pleurisy did not occur, and only a mild lymphohistiocytic bronchitis developed in a few of the birds.

This study is significant as it echoes clinical trials conducted with people with cancer. FWGE was first used as a medicinal nutrient for cancer patients in Hungary (where it was developed in the mid-1990s) and is now in common use in the Czech Republic, Bulgaria, Russia, and Romania. A long-term study with high-risk melanoma patients (with a seven-year follow-up) found that the progression-free time span in the FWGE group was 55.8 months versus 30 months in the non-FWGE group. Mean survival rate in the FWGE group was 66 months, in the untreated group 45 months. Quality of life was higher and the degree of pain and discomfort was lower in

the FWGE group. Similar outcomes have been found in trials in the treatment of oral cancer and colorectal cancer—in one colorectal study, metastasis rates were examined and were found to be significantly reduced. This was also found in the treatment of pediatric cancers but FWGE also significantly reduced the amount of febrile neutropenia that occurred in the children from medical treatment. FWGE has also been found to benefit the treatment of lung, breast, ovarian, gastric, thyroid, and prostate cancers, multiple myeloma, and non-Hodgkin's lymphoma. Quality of life increased, fatigue reduced, appetite increased.

One clinical trial has been conducted with FWGE in the treatment of rheumatoid arthritis. After one year all indices of the disease had improved, morning stiffness was significantly lessened, and steroid levels were reduced in half of the patients. In vivo studies (rats) found that it inhibits adjuvant arthritis and significantly inhibits both COX-1 and COX-2.

FWGE has also been studied in the treatment of lupus (mice) and found to be highly immunomodulatory, reducing overactive immune responses.

Numerous studies have found FWGE to possess antitumor, anti-metastatic, immune-modulating, and anti-inflammatory actions and to be highly nutritive. Improvements in appetite, energy, and mood generally occur within three weeks. After three months, significant shifts in clinical markers occur. It is exceptionally safe and no adverse reactions have been noted. Rarely, soft stools, unsettled stomach, mild dizziness, or mild nausea can occur.

Cost

The first product on the market was Avemar, which runs about $150 for a month's supply. Recently a decent competitor has emerged, OncoMAR, which runs about half that price. If you can get by the cost problems, I think its addition to the protocol for mycoplasma is highly warranted.

Dosage

The usual dosage is 8.5 grams per day as a single dose (150-pound person) in water or other liquid, taken before eating in

the morning.

Side Effects and Contraindications

Mostly GI tract problems: nausea, flatulence, soft stool, diarrhea. Contraindications? Gluten sensitivity?

Herb/Drug and Herb/Herb Interactions

None that I know of.

Shiitake Mushrooms (*Lentinus edodes*)

Shiitake was also used in treating chickens with mycoplasma infections. It restored the GI tract microbial community and increased nutrient uptake and body weight.

Shiitake is a potent nutrient. It contains all the essential amino acids, vitamins A, B group, C, and D, and a wide range of minerals. It is used in the treatment of cancer, fatigue, respiratory infections, and to modulate immune function among other things. It has a good track record in helping those conditions.

Dosage

Powder: 1–3 grams daily; tincture: ½ teaspoon 3x daily.

Side Effects and Contraindications

People with allergies sometimes have an allergic reaction. Or not. Dermatitis from contact or ingestion seems the main allergic reaction. I have seen a warning that pregnant and nursing women should not use the herb but I can't find a rationale for it. It is apparently contraindicated in eosinophilia.

Herb/Drug and Herb/Herb Interactions

None that I can find.

6

Bartonella

An Overview

It appears that chronic intravascular infection with a Bartonella *spp. may induce a degree of immunological anergy, resulting in undetectable levels of organism-specific antibodies in some chronically infected patients.*

EDWARD BREITSCHWERDT ET AL., "MOLECULAR EVIDENCE OF PERINATAL TRANSMISSION OF *BARTONELLA VINSONII* SUBSP. BERKHOFFII AND *BARTONELLA HENSELAE* TO A CHILD"

Depending on the immune status of the infected individual this bacterium can cause a wide spectrum of clinical manifestations.

A. T. PULLIAINEN AND C. DEHIO, "*BARTONELLA HENSELAE:* SUBVERSION OF ENDOTHELIAL CELL FUNCTION BY TRANSLOCATED BACTERIAL EFFECTOR PROTEINS"

Bartonellosis is a difficult and often very debilitating disease; its impacts on the central nervous system are often more severe than those of Lyme disease with which it is a common coinfection. Often misdiagnosed, the disease, and the various *Bartonella* species that cause it, has been little understood by the medical community though in recent years this has begun to change. (The best overview for clinicians—as this book was being written—in a peer-reviewed journal is Florin, Zaoutis, and Zaoutis 2008.)

Because few people have heard of bartonella, it is common to think it is either a fairly new disease or an extremely rare one. Neither perspective is accurate.

BARTONELLA, A FIRST LOOK

Bartonella infections have been around a long time; the diseases themselves have been described in the literature for at least a millennia. But the identification of the exact bacterial organisms involved is still fairly new. Only in the past 20 years have scientific researchers been able to even *see* the bacteria with any reliability in the laboratory. Once they were able to do so, they began to look more widely for them. They found that, indeed, the organisms have been infecting people for a very long time.

In 2005, researchers found *Bartonella quintana* DNA in the dental pulp of a 4,000-year-old human tooth; other researchers found it in the pulp of an 800-year-old cat. Analysis also found *B. quintana* as a common coinfection in the bodies of plague victims from the eleventh century and those of typhoid victims from the early nineteenth century. (Bartonella has always been an opportunistic coinfection.)

Carrion's disease (a.k.a. Oroya fever, verruga peruana), perhaps the most widely known of the bartonella diseases, has been known since pre-Incan periods; it's endemic to South America. The causal organism, *Bartonella bacilliformis,* was the first of the genus discovered, early in the twentieth century. But the identification of other bartonella bacteria as disease agents occurred very late in the twentieth century. In 1990 a patient with bacillary angiomatosis, that is, tumorous growths in the blood vessel walls, was identified as being infected with a bartonella species different from *bacilliformis*. This began a concerted effort in the scientific community for other bartonella bacteria that might be the unsuspected causes of human disease.

Bartonella henselae, the bacterium, was initially described in 1992. No one knew then what diseases it caused. But by 1997 it was found that it was the primary cause of cat scratch disease, which had first been named as such in France in 1950. And while *Bartonella quintana,* the cause of trench fever during World War I, was first cultivated in a laboratory in 1961, it wasn't firmly identified as to family and genus until the mid-1990s—once the research on bartonella had begun in earnest.

In the past 15 years some 30 different species of bartonella have been identified, at least 17 of which cause human infections. (*All* of this group of bacteria infect mammals and mammals only; it is their speciality.) New species are being found yearly—so many that some researchers simply say that the "genus *Bartonella* comprises an ever-expanding group" of bacteria. Many of these bacterial species cause human infection. In consequence, names such as cat scratch fever, trench fever, and Carrion's disease are being abandoned in favor of the more correct term: bartonellosis.

Bartonella organisms are what are called fastidious bacteria, that is, they are very particular about where they will live and what they will eat. Lyme spirochetes are similar in this respect and, as with Lyme, this has proved a difficulty for laboratory researchers. Reliable methods for growing bartonella in laboratories were only introduced in 2004 and research has lagged correspondingly. But once the bacteria could be grown, research also proliferated; there are now several thousand peer-reviewed articles available on PubMed, the free scientific research database on the Internet. This proliferation of research over the past 15 years has helped increase understanding of the nature of bartonella, where and how the bacteria live, and just what they do when they infect a host. But reliable diagnostic methods for bartonella have lagged behind and this is only now, very slowly, beginning to change.

There have been few tests, even for specific bartonella organisms, until recently and there are none in common use for bartonella bacteria *in general*. That is, if physicians have ruled out cat scratch fever as the cause of your problems, they will generally have no knowledge of or way to test for other *bartonella* organisms with which you might be infected. Newer and better tests *are* becoming available but the lack of awareness by physicians about how widespread the disease is as well as its wide-ranging symptom picture make diagnosis difficult. Physicians, in general, just don't know enough to even recommend a test for bartonella in most instances. And very few of them have any awareness of the newer tests that are available and where they are to be found.

Again, physicians just don't understand the bartonella family well and many of them are still using information decades out of date. Too many still believe, erroneously, that the disease is *only* transmitted by cats, or, if they are better informed, by body lice on the homeless. This misperception is common. If you speak to most physicians about your possibly having a bartonella infection they will almost always question you closely about your exposure to cats. But their insistent focus on cat transmission is highly inaccurate to the real world. In fact bartonella organisms can be, and often are, easily transmitted by a variety of arthropod vectors: fleas, sandflies, lice, ticks, mosquitos, midges, chiggers, biting flies, scabies, and a variety of other types of mites. In consequence, many people who have never been exposed to infected cats (or their fleas) or lice-infected homeless people are coming down with the disease.

It *is* true that *Bartonella henselae,* the bacteria responsible for cat scratch fever and perhaps the best known (to Americans) of this family of bacteria, can be transmitted by cat bites and scratches. But it is *not* true that cats and their fleas are the only reservoirs that can transmit the disease. One of the organism's tactics, ensuring its spread, is to invade the salivary glands of every organism it infects, including humans. Thus recent research has found it can also be transmitted by bites from a variety of animals and insects, including dogs. Ten percent of healthy dogs and 27 percent of sick dogs have been found to be positive for *Bartonella henselae* infection. Four different *Bartonella* species, in fact, all infectious to humans, have been found in dog saliva including *B. quintana,* the cause of trench fever. Nor are dogs, cats, and humans the only mammals that carry the disease: *B. henselae* has also been found in rats, as well as in whales, porpoises, and dolphins (undoubtedly spread to those ocean-living mammals by catfish). Research now indicates that this species of the genus may be much more widespread among mammals than the common belief about cats indicates.

Virtually every mammal harbors one or more Bartonella *species and their transmission typically involves a hematophagous arthropod vector.*

It has long been believed that *B. henselae,* if not transmitted through cat bite or scratch, could then only be transmitted by cat fleas (or cat-flea feces). Deeper research has shown that this bartonella species is widespread among many arthropod vectors: ticks, mosquitos, fleas from multiple animal species, and biting flies. Transmission through these routes has been well documented. Most of what physicians and researchers thought they knew about just this one bartonella organism has been found to be wrong—and there are 27 other bartonella species—at present count—out there.

Most bartonella species have been believed to be limited to one host species (i.e., human, or cat, or monkey, or cow) and one vector (i.e., louse, flea, or biting fly). As such it is still common to read in the literature that human infections with species thought to be limited to a particular host are "accidental" or "inadvertent." But the widespread presence of bartonella species among many different mammals and vectors makes this belief increasingly untenable. There is no way, for instance, that wild cetaceans are being infected by either cats or cat fleas (and certainly not catfish). Recent studies have found that the various strains of bartonella that are being discovered are widespread throughout the world. One strain found in a gopher flea in Boulder, Colorado, U.S.A., was found to be, most similar to one isolated from a squirrel in China. "This suggests," the researchers commented, "that specific strains of *Bartonella* have not coevolved with specific flea species. Our finding that the *Bartonella* strain in Boulder, CO is closely related to a strain detected in China suggests that *Bartonella* dispersed widely and frequently" (Jones et al. 2008, 1668).

Interestingly enough, most of the bartonella species identified so as far tend to be infectious to humans and mammals closely associated with them such dogs, cats, cattle, rats, mice, rabbits, and monkeys. Many of these animals exist in the wild but deer and cetaceans are two of the few groups that have little contact with humans that are also routinely infected.

INFECTION RATES

Reliable figures on the numbers of people infected by bartonella organisms are hard to come by. The U.S. Centers for Disease Control in Atlanta, Georgia, still have very little on the disease and their website (in 2012) still attributes most infections to cats. (Anywhere from 28 to 51 percent of cats in the U.S. are infected with bartonella, by the way, depending on the geographical location.) The CDC sets the numbers of the newly infected at about 22,000 per year in the United States (primarily by focusing on hospital admissions), but as Florin, Zaoutis, and Zaoutis (2008, e1414) comment, "This finding likely underestimates the true incidence, as most cases of *Bartonella* infection are not recognized or are treated on an outpatient basis."

As is true with the CDC estimate of yearly Lyme infections, the CDC figure for bartonella is tremendously misleading. *Even a cursory review of the literature shows it is off by a minimum of a factor of 100 and perhaps as much as 1,000.* Bartonella infection is rife and generally undiagnosed.

> *The true incidence of* Bartonella *infection is difficult to establish, because it is not a reportable disease in a majority of states in the United States.*
>
> T. FLORIN, T. ZAOUTIS, AND L. ZAOUTIS, "BEYOND CAT SCRATCH DISEASE: WIDENING THE SPECTRUM OF *BARTONELLA HENSELAE* INFECTION"

In a number of populations, for instance in medical patients with fever of unknown origin (FUO), newer research has found that bartonella is a common cause. One study in San Francisco, California, hospitals testing 382 patients with FUO found that in 18 percent (i.e., 69 people) the cause was a bartonella infection. Various studies have found that anywhere from 5 to 20 percent of FUO patients are positive for bartonella.

Exact figures for FUO, both outpatient and inpatient, are hard to come by. However, in 2007 in the United States, 20 percent of children had at least one visit to an emergency room. FUO was the presenting problem in 5.8 percent of those. In 2006 there were an estimated 73.7 million children

under 18 years of age in the U.S. Twenty percent of that figure is 14,740,000 children that had at least one emergency room visit. Of that number, 5.8 percent presented with FUO, or 854,920. A 5 percent infection rate would be 42,746. An 18 percent infection rate would give a figure of 153,885 bartonella infections. This is only indicative of course. Definitive work needs to be done on FUO rates in the U.S. *and* it needs to be correlated with bartonella as the infectious cause. But there are reasons to suspect these figures may not be that inaccurate. When homeless populations are examined, the infection picture is similar.

About 3.5 million Americans are homeless (one out of every hundred). Various studies have found that about 10 percent of homeless people who are tested are infected by *B. quintana,* an organism commonly spread by body lice. This would give a figure of 350,000 infections with that species of bartonella alone. Other studies have found that up to 33 percent of those with body lice are positive for bartonella as are 25 percent of those with head lice. Another three million people are *treated* for pubic lice each year in the U.S. (actual infection rates are much higher). Bartonella is carried by pubic lice but figures for infection rates through that medium are lacking in the literature. If the 10 percent figure for homeless infections transfers to pubic lice infections that would be another 300,000 bartonella infections per year—a 33 percent infection rate would put it nearer a million. And there are still other groups with large infection rates, few of them known to physicians.

Each year, somewhere between 40 and 100 people per million in the United States (studies vary as usual) develop a condition called infectious endocarditis. So, each year, somewhere between 12 and 32 million people develop the disease. It's usually caused by an infection, generally from bacteria such as staph or strep. People presenting with the condition are tested for the most common bacteria that cause the disease. But somewhere between 5 and 30 percent of cases are culture negative, that is, the usual, routine testing turns up no causative organism. Recent research has found that 12 percent of culture-negative endocarditis infections are caused

by bartonella. Running those simple numbers shows somewhere between 600,000 and 9 million infections per year that are caused by bartonella. While knowledge about bartonella and endocarditis is spreading among physicians, few of the journals are making this figure plain. The numbers are *very* high. And though this is starting to change, the majority of people suffering from bartonella endocarditis have never been properly diagnosed or treated. And, still, this is not the last of the groups commonly infected with bartonella.

An analysis of infection rates among various populations was carried out by Lamas et al. 2008. It is perhaps the best overview of infection trends in various population groups in different countries. The studies they reviewed examined anywhere from 53 to 630 people. The figures are sobering.

In the United States the studies showed that:

- Of 192 homeless, alcoholic, HIV-negative clinic patients, 20 percent were positive for bartonella.
- Of 199 age- and sex-matched *blood donors,* 2 percent were positive.
- Of 630 intravenous drug users, 37.5 percent were positive for unidentified bartonella species, another 22.9 percent positive for *B. elizabethae,* 1.4 percent for *B. henselae,* and 1.6 percent for *B. quintana*.
- Of 351 veterinarians, vet technicians, and others attending a veterinarian conference, 7.1 percent were infected with bartonella.
- Of 204 intravenous drug users in New York City, 46 percent were infected with *B. elizabethae,* 10 percent with *B. henselae,* 2 percent with *B. quintana.*
- Of 200 clinic patients, 12.5 percent were infected with *B. elizabethae,* 9.5 percent with *B. henselae,* 3.5 percent with *B. quintana*.
- Of 382 HIV patients with fever, 17 percent were infected with bartonella. (There are about 27 million HIV infections per year in the world.)

These figures are similar to those of studies from a number of countries. Highly interesting, and much more alarming,

figures emerge when some other unique groups are examined, especially the healthy and veterinarians.

> *A survey of hospitals in the United States discharging more than 750 pediatric patients annually indicates that cat-scratch disease is a problem in all sections of the country.*
>
> H. A. CARITHERS, "CAT-SCRATCH DISEASE: AN OVERVIEW BASED ON A STUDY OF 1,200 PATIENTS"

In Germany an examination of 270 *healthy* adults found 30 percent to be infected with *B. henselae*. In Greece a study of 500 *healthy* adults found nearly 20 percent to be infected with *B. henselae* and 15 percent with *B. quintana;* a study of 63 *healthy* children found nearly 16 percent to be infected with *B. henselae*. In Spain nearly 30 percent of 83 cat owners were found to be infected as were 5.9 percent of blood donors and 24.7 percent of 146 *healthy* individuals. In Italy, of 508 *healthy* children, 61.6 percent were infected with *B. henselae*. In Sweden 18 percent of 498 blood donors were infected with bartonella, most with *B. elizabethae*. In Japan 15 percent of 233 veterinarian professionals were infected with *B. henselae* as were 10 percent of 129 veterinarian students. In Brazil, of 437 *healthy* adults, 12.8 percent were infected with *B. quintana* and 13.7 percent with *B. henselae.* Some studies have found the infection rates in veterinarians to be as high as 45 percent and in people with occupational animal exposure longer than 10 years duration 57 percent—all without showing symptoms.

Intriguingly, the few studies conducted on blood donors in the U.S. and Australia have found that anywhere from 3 to 6 percent of donor blood is infected by bartonella. The National Blood Data Resource Center in Bethesda, Maryland, estimated that there were 14 million blood donations in the U.S. in 1999. This is equivalent to roughly 5 percent of the total U.S. population, a donation rate that has held somewhat steady since then. Three percent, to use the low-end infection figure, of 14 million is 420,000. Six percent is 840,000. Either way, bartonella-contaminated blood, in considerable quantities, is being given in transfusions each year in the United States. And no, blood is not routinely tested for the bacteria. (Bartonella

organisms are extremely hardy in blood supplies by the way. Studies on infected blood, stored for 35 days at 4 degrees Celsius, or 39 degrees F, found that the bartonella organisms were still strongly viable.)

But … if you extrapolate those numbers, assuming that 5 percent of the population donates blood and that 3 to 6 percent of the entire population is infected, as some studies show, you get a national carrier rate of between 8 and 17 million bartonella-infected people, people who show *no* symptoms. As researchers at the Centre for Infectious Diseases and Microbiology in Australia put it, "*B. henselae* is a slow-growing, fastidious Gram-negative bacillus that is difficult to isolate in culture media, and the high seroprevalence [in blood donors] suggests that human infections may be underrecognized" (Kyme, Dillon, and Iredell 2003, 621). The high prevalence of infection in blood donors is especially troubling since the people who normally receive transfusions are already ill, their immune systems already under stress. They represent a group who, rather than remaining asymptomatic as the donors are, will express acute disease once infected through the transfusions they receive in the hospital.

And then, of course, there are coinfection rates. Research exploring the rates of coinfectious organisms in ticks has found anywhere from 1 to 25 percent of ticks to be infected with both borrelia and bartonella. Bartonella has been found in 17 different species of ticks so far, all with worldwide distribution. With Lyme infections running around 200,000 per year in the United States (from Harvard studies) that would mean bartonella coinfections are occurring in from 2,000 to 50,000 of those with Lyme disease. (That first figure is almost certainly much too low; anecdotal reports from clinicians put the incidence much higher.)

No matter how you look at it, as increasing numbers of peer-reviewed journal papers make clear, the infection rates of bartonella, while not definitively known, are *very* high. Because the disease is so poorly understood by medical professionals, infections are quite often misdiagnosed or even undiagnosed. Few people are treated appropriately. The large

numbers of *B. elizabethae* infections, which appear nowhere in commonly available literature on the disease (e.g., CDC data), are worrying. And the high percentages of *healthy* adults and children that are infected represent a large pool of infected blood from which the disease can be spread through biting insects such as mosquitoes, ticks, and mites. They also represent a large pool of potential acute sufferers; bartonella infection tends to become acute if immune function becomes depressed.

Even low-end speculation indicates several million infections per year in the U.S. and if the various rates of infection in healthy adults (such as those in Brazil) are similar to those in the U.S. at least 80 million people are asymptomatic carriers. This estimate of 80 million is interesting in that it is about one-fourth of the population of the U.S. As one research group commented, "Most mammals that are reservoirs of *Bartonella* species have at any one time about one fourth to one third of their population that is bacteremic" (Chomel et al. 2009, 14).

The disease is endemic and it's is only going to get worse.

WHAT BARTONELLA IS

Bartonella is a Gram-negative bacteria. It belongs to a major phylum of bacteria called the Proteobacteria. The Proteobacteria are broken down into six groups: Alpha-, Beta-, Gamma-, Delta-, Epsilon-, and Zetaproteobacteria (essentially: A, B, C, D, E, and F—not very inventive, I know).

Interestingly, the Alphaproteobacteria also include *Ehrlichia* spp., *Anaplasma* spp., Rocky Mountain spotted fever, and the other rickettsias, which are all coinfections of Lyme. The Gammaproteobacteria include many human pathogens, most now antibiotic resistant: *Klebsiella* spp., *E. coli, Vibrio cholerae, Pseudomonas* spp., *Salmonella* spp. (including *Salmonella enterica,* the cause of typhoid fever), and *Shigella* spp. It also includes *Yersinia* spp., the organism responsible for the plague, another bacteria transmitted by fleas. The Betaproteobacteria include the bacteria responsible for gonorrhoea infections, also increasingly resistant. The

Epsilonproteobacteria include both *Helicobacter* and *Campylobacter* organisms.

There is strong evidence that both resistance and virulence factors are being shared among all members of this phylum. In other words, the various bacteria are teaching each other how to resist antibiotics and how to more easily infect people, thus making them sicker. They do this, usually, through sharing segments of DNA that have within them resistance and virulence information. Bartonella organisms are often coinfective with many of the bacteria in this phylum and, in many instances, such infection shows a remarkable synergy during the disease process. In other words, the bacteria work together to reduce the effectiveness of the immune response and thus enable long-term infection.

Bartonella, because they are Gram-negative, are harder to treat than Gram-positive bacteria such as staph. The labels *Gram-positive* and *Gram-negative* refer primarily to the bacteria in question taking a Gram (named after a person) stain, one way of identifying them. Of much more importance are the differences in their cellular structure.

Bacteria, similarly to us and our skin, have an external membrane surrounding their body that is known as the cell wall. Their interior is called the *cytoplasm,* then there is the *cytoplasmic membrane,* which covers the cytoplasm, then comes the *cell wall*. The cell wall consists primarily of a polymer called peptidoglycan. If the bacteria happen to be Gram-negative then they will have a second wall called the *outer membrane*. Between the two membranes in Gram-negative bacteria is a compartment, the *periplasmic space*. Gram-positive bacteria, because they lack that second membrane and the space between, have much thicker cell walls to protect them from outside events.

Because Gram-positive bacteria have only a single cell wall, even though it’s thicker, they are, in general, much easier to treat. With Gram-negative bacteria, two cell walls, rather than one, have to be penetrated. In essence, the bacteria have two chances to identify and deactivate antibacterials that are hostile to them. Even if an antibiotic passes through the outer

membrane and gets into the periplasmic space, it still has to go through the second wall to kill the bacteria.

Gram-negative bacteria also have a series of highly synergistic reactions to antibiotics, in essence using three primary mechanisms, all highly coordinated, to resist antibiotics. The first is the double cell wall. The second is the use of a special group of enzymes, *beta-lactamases,* that are especially effective in deactivating beta-lactam antibiotics (the antibiotics most often used to kill them), and finally they use a variety of multidrug efflux pumps. These efflux pumps essentially act like sump pumps; they pump out the antibiotic substances just as fast as they come in so that the bacteria are unaffected by them. (They can also alter the targets of the antibiotic, metabolize the antibiotic thus making it into a different, much safer, chemical, or even learn to use the antibiotic for food—they are very adaptable.)

Gram-positive bacteria rely on their thicker cell wall and very, very fast efflux pumps since they don't have a periplasmic space in which to hold the antibiotics while they deal with them. Some Gram-positive bacteria, such as the staphylococci, have incorporated the use of beta-lactamases to deactivate antibiotics—they learned about them from Gram-negative organisms.

Most bartonella species (there are a few exceptions) are fastidious, aerobic, slow-growing, pleomorphic, nonmotile, non-spore-forming, hemotropic, facultative intracellular coccobacillus bacteria. This means (respectively) that they are choosey in what they eat, like oxygen, take 24 hours to reproduce, have variations in their size and shape, don't have flagella and thus do not propel themselves (there are a couple that do), don't make spores, love blood, usually exist inside other cells (intracellular) but don't have to (facultative), and they are intermediate in their shape, roundish (cocco) but also elongated (bacillus). They are very tiny, 2 to 3 micrometers long and 0.2 to 0.5 micrometers wide—a micrometer (a.k.a. micron) is very tiny, only one millionth of a meter.

Bartonella can enter the body through a variety of mechanisms: bites, scratches, insects seeking a blood meal,

and ingestion. And they have a number of mechanisms for ensuring infection and spread in both vectors and host species.

TRANSMISSION DYNAMICS

To begin with, let's look at *Bartonella quintana* as an example of the genus. *Bartonella quintana* organisms can be found in a number of insect vectors such as fleas and ticks but, historically, their main route of transmission has been believed to be through body lice. Lice, like many arthropods that carry these kinds of diseases, live on blood meals. When uninfected lice consume blood from an infected person (similarly to the ticks that spread Lyme) they become infected with bartonella. Once ingested, the bartonella organisms travel to the gut of the louse and begin to replicate extracellularly on the surface of the endothelial cells of its GI tract, essentially forming biofilm colonies on and in the endothelial layer. As they do in other species, the bartonella bacteria stimulate the growth of the endothelial layer in order to produce a larger surface area for habitation. The bacteria grow slowly; this particular species doubles in numbers every 21.3 hours. It takes about four days for the bacteria to proliferate in an infected louse. Once they reach significant numbers they are released into the louse's feces for excretion.

Lice live about five weeks and infected lice excrete bacteria-laden feces continually. Each louse excretes 10 million bacteria per day (in their feces) onto the skin surface of whomever they are feeding on. And as the louse feeds it causes a skin irritation that stimulates the person to scratch. The act of scratching breaks the skin and also, at the same time, forces the bacteria-laden louse feces into the skin break, creating a form of self-inoculation. (Crushed lice bodies that enter the skin break will also cause self-inoculation.) Lice *can* infect during feeding simply through the saliva that enters the body through their bite but the primary route appears to be fecal. (This is very similar to how *B. henselae* infects cats though in that instance it is flea feces rather than louse, and again, the feces is heavily laden with bacteria.) The infection is spread from one person to another as lice move from the infected to the uninfected.

Bartonella is not transmitted to lice offspring but they, once hatched from eggs, ingest the same blood meals that their parents do and thus become infected. Lice lay an impressive number of eggs, sometimes daily—and the eggs are viable for up to two weeks.

Examination of louse feces shows that bartonella bacteria are attached to an exopolysaccharide-like matrix that is strongly interwoven into the fecal material—essentially the bacteria create a biofilm structure, a bacterial colony, within the feces. Bartonella bacteria in louse feces are still viable after one year. In essence lice feces, which can be spread also via dust, can be filled with bartonella that, if ingested or inhaled, will infect the person who does so.

While *B. quintana* has long been thought to be limited to lice as a vector and humans as the primary host species, the recent sophistication in identifying bartonella has led to the discovery of this species in monkey, cat, and gerbil fleas and cat teeth. Dogs, cats, and monkeys have all been found to be infected with the organism. In other words, they have been found to be natural hosts for this bartonella species. As with most types of bartonella, it appears as if this particular species is much more broadly infective and ecologically promiscuous than originally thought.

Rather than lice, fleas are one of the main vectors for *B. henselae*. The process is very similar to that which occurs in lice. In this instance the fleas reside on cats and become infected during a blood meal. The fleas spread to other cats, who ingest the feces while cleaning themselves, and thus become infected in their turn. Microscopic amounts of flea feces remain on the cat's claws and if they scratch a human, the feces enters the break and the person becomes infected, hence: cat scratch fever. However, bartonella organisms also enter the flea and cat salivary glands and they are also transmitted, occasionally, through flea or cat bites. Bartonella also invades flea reproductive organs and is apparently transmitted to offspring during reproduction. Fleas often contain numerous species of bartonella, some atypical of their normal hosts.

A broad variety of ticks carry numerous bartonella species, including *Ixodes, Dermacentor, Rhipicephalus,* and *Haemaphysalis* species. Anywhere from 1 to 60 percent of ticks in a particular geographical area have been found to carry bartonella organisms. The transmission process is very similar to that of Lyme disease. With Lyme bacteria, the organism spreads in the tick gut (much like it does with lice and fleas) and then infects the tick salivary glands. When the tick feeds some of its saliva enters the site of the bite and enters the bloodstream. It takes about 3.5 days for the bacteria to heavily colonize the newly infected tick (84 hours). At that point heavy concentrations of bacteria are disseminated to the salivary glands for injection into new hosts. Although there has been some controversy as to whether or not bartonella could be transmitted by ticks, recent research (Reis et al. 2011a and 2011b) has conclusively demonstrated tick transmission of the bacteria.

Biting flies also carry bartonella, specifically *Lipoptena, Hippobosca,* and *Melophagus* species. These various types of biting flies feed on ruminants (cows, sheep, horses, deer, and so on) that have been found to have high levels of bartonella infection in their populations. The same deer that are involved in the transmission cycle of Lyme have been found to be heavily infected with bartonella. The transmission route from fly to ruminant has not been intensively studied but appears to be both salivary and fecal.

GENETIC FLEXIBILITY AND EVOLUTION AMONG BARTONELLA

Bartonella organisms, like many related members of the Proteobacteria, are undergoing rapid genetic alterations in response to environmental factors such as climate change, habitat damage, and human damage. As Chomel et al. note:

> Massive natural or man-made changes to historically stable ecosystems that result in alterations in vector biology and reservoir host density, increased international movement of a wide range of reservoir hosts across continents, recent human behavioral and societal changes that bring animals into increasingly close human contact,

> as well as medical interventions, HIV infection and an aging immunosenescent human population contribute to ongoing and dynamic interactions among Bartonella species and their hosts and vectors. (Chomel et al. 2009, 16)

Studies have found that bartonella exists within infected hosts as a mosaic of different genetic variants (this is common with Lyme and *all* its coinfectious bacteria). This kind of variation is not found during in vitro studies, only in living hosts. In response to the immune system of the host bartonella, much like Lyme spirochetes, generates a number of genetic variants of itself in order to maximize survival in the host. The variants are able to live within different niches of the host more easily than others, e.g., the bone marrow or the lymph system. It is not uncommon that several variants can be found within those niches, the several strains exchanging genetic material in order to stay ahead of the immune response. The outer membrane proteins are often altered (as are many of the adhesion molecules such as BadA), which makes the variants harder to recognize by the immune system. Simple rearrangements of certain portions of the genome can create as many as 420,000 variants of the bacteria in a short period of time. As Chomel et al. (2009, 12) observe, "When the host produces antibodies targeted against the invading microorganisms, the infecting pathogen is usually killed. However, if the pathogen alters the protein expressed (antigenic variation), or no longer expresses the protein on its surface (phase variation), the microorganism can survive and multiply in the host." In those with persistent or chronic infection, both phase variation and antigenic variation appear to be the norm, with the immune system unable to keep up. Generally, the immune system is compromised in such cases, at least minimally.

All bartonella species contain a very similar, fairly small, core genome and multiple accessory genome structures that they can weave into the core genome if needed. Most of the accessory genomes exist as genomic islands and were obtained through horizontal gene transfer from other bacteria. Some of these genomic islands are host specific, much as they are in

Lyme spirochetes. Upon entry into a new host, the specific genomic island can be incorporated into the core genome to facilitate host infection. As Chomel et al. (2009, 11) comment, the horizontal gene transfer of so many genomic islands has "facilitated the remarkable evolutionary success of the modern lineage by conferring host adaptability" and has stimulated "the adaptation of the generally host-restricted bartonellae to novel hosts."

The impetus for genetic rearrangements comes from both the organism itself and the immune environment in which it finds itself. Examination of the bartonella genome has found a number of segments that are prone to rearrangement under environmental stress. In addition, bartonella bacteria, like most bacteria, are able to both give and receive plasmids, strands of genetic material that can be woven into the genome to alter phenotype. Essentially, they can alter their physical form to make themselves more resistant to antibiotics, more virulent, or more resistant to immune responses. Plasmids are exchanged with other bacteria, both inside and outside the genus. In general, bartonella can be found in about 25 percent of the population of any mammal species, including humans (though only a small portion will become symptomatic). And in any one mammal species, the bacteria's genetic variation is huge; one study found 22 genetic variants.

Many of the arthropod vectors of bartonella contain multiple species of the bacteria, all of whom exchange DNA segments in order to facilitate their adaptation to new hosts. Variants develop in hosts, vectors take a blood meal, ingesting new variants. The new variants from multiple species interact in the gut of the vector, alter their genome structures, and then are injected into new hosts. There is a continual and very elegant genetic recombination occurring.

> *Adaptation to different ecological niches can lead to rapid diversification of a single ancestor into an array of different species or ecotypes. This process, called adaptive radiation, typically occurs after the arrival of a founding population in a novel environment with unoccupied ecological niches ("ecological opportunity") and/ or by the acquisition of a novel trait ("evolutionary key innovation") allowing the exploitation of so far unapproachable niches… . This is of particular interest in case of host-adapted bacteria differentiating into*

divergent ecological niches and potentially resulting in the emergence of new pathogens.

P. ENGEL ET AL.,
"PARALLEL EVOLUTION OF A TYPE IV SECRETION SYSTEM IN RADIATING LINEAGES OF THE HOST-RESTRICTED BACTERIAL PATHOGEN *BARTONELLA*"

Research in 2007 found that, as the paper's authors commented, "isolates responsible for human disease are not drawn randomly from the feline reservoir" (Arvand et al. 2007, 1). In other words, there are unique human-infectious bartonella held in the cat that are specifically generated to infect the human hosts that own the cats. (In fact, *B. quintana,* which is considered to be human specific, is an evolved offshoot of *B. henselae* that adapted itself to live specifically in humans. Research has found that *B. henselae* is still easily able to shift its outer membrane proteins to allow it to infect human red blood cells.) Lindroos et al. (2006, 7426) note, "The variable gene pool in the *B. henselae* population plays an important role in the establishment of long-term persistent infection in the natural host by promoting antigenic variation and escape from immune response… . The results suggest multiple sources of human infection from feline *B. henselae* strains of diverse genotypes." In spite of numerous comments to the contrary, bartonella infection of human beings is not a random or accidental event; we are not inadvertent hosts. *All* mammals are potential hosts for *all* bartonella species and *B. henselae* (along with others that infect human companion animals) is not "accidentally" infecting humans. As Mietze et al. (2011, abstract) note, "The prevalence of barteonellosis among humans in Germany appears to be high and severe clinical cases have been described." This situation is not limited to Germany.

SYMPTOMS OF INFECTION

There are 19 bartonella species that have been found to cause human infection—and the numbers are increasing yearly. Three of these are limited to South America, one to Thailand. The symptom picture is broad. As Maurin and Raoult (1996, 278) comment, "The spectrum of clinical manifestations induced by Bartonella infections is startling."

B. henselae is the most commonly known of the disease-causing bartonellas. It is the source of the poorly named cat scratch disease, the symptoms of which are the best described of all bartonella infections in the medical literature. The most common primary symptom, often considered diagnostic in and of itself, is lymphadenopathy, an inflammation of the lymph nodes, especially near the site of the bite or skin break. The lymph swelling can be large, up to several centimeters, and last for several months. In some 48 percent of cases the node can suppurate. *However, lymphadenopathy is not present in all cases and its absence should not be relied upon for a negative diagnosis*. Other common symptoms are fever of unknown origin (FUO), hepatosplenic abscesses, bacteremia, neuroretinitis, photophobia, severe fatigue, muscle pain, reactive arthritis, Kikuchi's disease, osteomyelitis, bacillary angiomatosis, peliosis hepatis, erythema nodosum, skin lesions, endocarditis, encephalopathy, headache, ataxia, memory loss, paresthesia, aseptic meningitis, meningoradiculoneuritis, panniculitis, dementia, acute psychiatric symptoms including homicidal rage, anxiety, severe depression, brain fog, difficult thinking and articulating, and schizophrenic-like mental function. Bone pain may be severe and is common in the sole of the foot.

B. quintana causes endocarditis, trench fever, lymphadenopathy, bacillary angiomatosis, peliosis hepatis, central nervous system (CNS) infections, fatigue, and FUO. In some circumstances it can cause the same symptom picture as *B. henselae* and may also be transmitted by cats as well as dogs. It is not limited to louse transmission. Maurin and Raoult describe a typical nonasymptomatic infection:

> Headache, weakness, pain in the legs, malaise, dyspnea, giddiness, pain in the loins, shivering, abdominal pain, diarrhea, constipation, anorexia nausea, frequent micturition, restlessness, and insomnia… . Headache is most often severe, especially at the front of the head and behind the eyes. When occipital, it is often accompanied by a stiffness of the neck, and symptoms may therefore suggest meningitis. Pain may spread to the back and limbs, with leg pain being the most severe. This pain is

> often felt in the bones, specifically in the tibia. The patient will suffer regular cycles of profuse sweating and then shivering… . Areas of tenderness are associated with the pains involving muscles, tendons, bones, and joints. The spleen often becomes palpable… . The interval between attacks of pyrexia is usually between 4 and 8 days, with 5 days being the most commonly observed period. The term "quintan fever" [and the reason for the species name *quintana*] refers to the 5-day recurrences… . The chronically ill patient often complains of breathlessness on exertion, palpitations, pain over the precordium, giddiness, and disordered activity of the heart. Damp weather exacerbates all pain. In some cases, the infection is very persistent and acute febrile lapses occur months after quiescence. (Maurin and Raoult 1996, 280)

Here's a look at the other bartonella bacteria that are known to cause human infection and a brief look at the symptoms they cause. They are presented in order of prevalence of infection.

B. elizabethae: endocarditis, CNS infections, spleen and liver inflammation, fatigue, FUO.

B. clarridgeiae: lymphadenopathy, endocarditis, sepsis, CNS infection, spleen and liver inflammation, fatigue, FUO.

B. koehlerae: endocarditis, lymphadenopathy, CNS infection (mood swings, hallucinations, sensory neuropathy, severe headaches, anxiety, depression), muscle spasms, joint stiffness, decreased peripheral vision, spleen and liver inflammation, fatigue, FUO.

B. vinsonii subspecies berkhoffii (the primary species found in dogs): endocarditis, cardiac arrhythmia, arthralgia, uveitis, chorioditis, myalgia, headache, meningoradiculoneuritis, panniculitis, ataxia, paraparesis, fatigue, granulomatous rhinitis, intermittent epistaxis, FUO.

B. vinsonii subspecies *arupensis:* same as above.

B. washoensis: meningitis, fever, chills, vomiting, headache, nausea, myocarditis.

B. melophagi: skin lesions, fatigue, cough, muscle pain, severe chills, extreme pain in the feet, heart murmur, pericarditis, headaches, cognitive problems, muscle weakness, joint pain, facial tremors.

B. grahamii: neuroretinitis.

B. doshiae: same as *B. henselae* (see B. henselae).

B. alsatica: endocarditis, FUO, lymphadenitis.

B. mayotimonensis: endocarditis, heart murmur, aneurysm, shortness of breath, weight loss, fatigue, cognitive decline.

B. rochalimae: anemia, splenitis, fever, insomnia, fatigue.

B. volans: joint pain, CNS difficulties (memory problems, lack of coordination, difficulty walking, hallucinations, disorientation, anxiety, agitation, encephalopathy, involuntary motor movements, seizures), hyperglobulinemia, thrombocytosis, anemia, FUO, severe edema with fluid leakage through intact skin.

B. durdenii: same as *B. volans*.

B. bacilliformis: Carrion's disease (South America). Fever, joint pain, headache, blood-filled warts (which are unique to this species), anemia, congestive heart failure, pericardial effusion, neurological problems, and mononuclear pleocytosis.

B. clarridgeiae-like[*1]: fever, splenomegaly (Peru).

B. tamiae (Thailand): fever, headache, myalgia, anemia, mild liver function abnormalities. Multi-organ pathology is common. Mice injected with this species develop illness within six weeks and show ulcerative skin lesions, subcutaneous masses, lymphadenopathy, myocarditis, vascular necrosis, granulomatous hepatitis and nephritis, and hepatocellular and renal necrosis.

In general, the full symptom pictures of the newer bartonella organisms are unknown. It should be assumed that

most of them cause the full range of symptoms found in *B. henselae* infection except for *B. bacilliformis,* which is unique (described below).

SYMPTOM SPECIFICS

It is extremely common to see the words *rare, unusual, uncommon, infrequent,* and so on when many common bartonella symptoms are being discussed by physicians and researchers, especially in journal papers—the full range of symptoms, common to nonasymptomatic carriers, is unknown to most physicians. But a review of the literature (as well as anecdotal reports by those who treat bartonella) shows that these symptoms are anything but "unusual." As Florin, Zaoutis, and Zaoutis (2008, e1415) observe about the expanding symptom picture of merely one of the *Bartonella* organisms: "The clinical manifestations of infection with *B. henselae* are expanding with the improved ability to recognize the presence of the organism."

A review of journal articles on PubMed finds 67 articles relating to bone pain or problems in bartonella infection, 124 for heart complications, 68 for ocular manifestations, 40 for brain/neurological, 26 for renal, 121 for liver, and 102 for spleen. Most of these papers have been published since 2004.

Newer research shows that bartonella organisms tend to cluster in certain areas of the body such as the respiratory and oral mucosa, skin, lymph nodes, eyes, liver, spleen, kidneys, CNS system, and GI tract. In most instances where symptoms in these systems are present, the patients are either misdiagnosed or undiagnosed for bartonella. Very few are tested for the organism.

The following list comprises the main symptoms associated with bartonella infection that have been reported in the literature. They may occur as part of a complex constellation of symptoms or by themselves, as examples: blurred vision with headache, enlarged spleen with abdominal pain, back pain, or bone pain.

Lymphadenopathy

A 10-dollar word that merely means "disease of the lymph nodes." In this instance it usually means severe enlargement, often with tenderness, erythema, and warmth. Swallowing may be slightly impaired or painful. In up to 48 percent of cases the node may suppurate, that is, form and discharge pus. The infection may spread from that node leading to the inflammation of numerous nodes in that particular lymph line. Leukocytosis is common.

Fever is present in some 60 percent of cases. It can often be accompanied by granulomatous conjunctivitis (generally diagnosed as Parinaud's oculoglandular syndrome) on the same side of the body as the lymph enlargement. Conjunctivitis (a.k.a. pinkeye) is inflammation of the conjunctiva or outer layer of the eye and in many instances the eyelid's inner surface. A granuloma is a, usually, spherical mass of immune cells that surround and wall off infectious organisms.

Ocular Difficulties

The newer research that has emerged over the past decade has found that bartonella infections are often accompanied by eye involvement along a broad range. The most common symptoms are foreign body sensation, redness, serous discharge, increased tear production, blurred vision, photophobia, granulomatous conjunctivitis, neuroretinitis, sub-retinal lesions, retinitis, intermediate uveitis, inflammatory masses, angiomatous lesions, retinal serous detachment, choroiditis, retinal vasculitis, orbital abscess, vitritis, vitreous and diffuse retinal hemorrhages, sudden vision loss, and optic neuritis. Neuroretinitis, multifocal and focal retinitis, branch retinal artery and vein occlusions, and angiomatous lesions are the most common after conjunctivitis. Ulceration of the conjunctival epithelium is common. Two-thirds of people who present with neuroretinitis have been found to be positive for bartonella infection.

As Chappell et al. (2011, 112) comment, "Although neuroretinitis has been recognized as a distinct clinical entity for more than 120 years, it wasn't until the 1990s that the syndrome was definitively linked to *Bartonella* infection."

Neuroretinitis may occur in one or both eyes and is primarily characterized by blurred vision but may progress to loss of light perception, optic disk edema, serous retinal detachment, and macular star. Loss of vision is usually painless and abrupt and unilateral. In-depth study has regularly found the presence of small, whitish lesions in the retina or choroid of the eye from 50 to 3,000 micromillimeters in size. It may take months for vision to return to normal and even then there may be residual problems: abnormal color vision, subnormal contrast sensitivity, eye color alterations, and reduced visual acuity.

Bartonella may stimulate unrestrained blood vessel growth, and when this occurs in the eye the result is similar to certain forms of macular degeneration. Bartonella infection may also mimic Vogt-Koyanagi-Harada syndrome, which has similar symptoms.

Ear Involvement

Serous otitis media, rotational vertigo, labyrinthitis, acute or not. Auditory hallucinations.

Neurological Problems

The two most common problems are encephalopathy and mental status alterations, in other words, headaches of varying severity and mental clarity problems. The full spectrum of neurological problems can be severe, including seizures (grand mal or otherwise), status epilepticus, epilepsia partialis continua, cerebral arteritis, acute mastoiditis, meningoencephalitis, peripheral facial nerve paralysis and/or palsy, coma, aseptic meningitis, hydrocephalus, ptosis, demyelination, transverse myelitis, neuralgia, dysesthesia, radiculitis, Guillain-Barré syndrome, paraparesis, paresthesia, ataxia, tremors, aphasia, torticollis, epidural abscess, acute hemiplegia, distal axonal sensomotor polyneuropathy, dementia, acute-onset personality changes, agitation, panic attacks, subcortical fronto-parietal lesions, motor impairment, neurologic amyotrophy (muscle wasting), severe headache, depression, psychosis. Hallucinations, sensory neuropathy (diminished tactile sensation), and transient paresis. Peripheral visual defects accompanied by depression, anxiety, mood swings, severe headaches, muscle spasms, and interphalangeal

joint stiffness are a not uncommon constellation of symptoms. Examination of brain tissue commonly shows lesions in the white matter of the brain, basal ganglia, thalamus, and gray matter. Perivascular lymphocytic infiltrates and microglial nodules are common in such instances. It is not uncommon for the sensory and neurological systems to become exceptionally sensitive to any kind of external input. The cerebral spinal fluid, when tested, is usually normal.

The most common neurological problems are similar to a number of Lyme symptoms such as headache from meningitis, brain fog, depression, and difficulty with problem solving and remembering. However there is often a lack of emotional control and episodes of unexplained rage in up to 40 percent of those that experience neurological involvement during bartonella infection. Misdiagnosis as multiple sclerosis (or similar conditions), schizophrenia, bipolar disorder, or the flu is common as is improper prescribing in response.

Fever of unknown origin (FUO)

It is somewhat common with bartonella infection to have a chronic low-grade fever that comes and goes. It is usually longer than four weeks in duration, is accompanied by no diagnostic signs or symptoms of obvious disease, and normally falls within 100 to 102 degrees Fahrenheit. The fevers are usually accompanied by headache, malaise, listlessness, weight loss, and, sometimes, anorexia. Recent studies show that bartonella is the third leading cause of FUO. In about one-third of cases hepatosplenic involvement is present.

Hepatosplenic Complications

As Florin, Zaoutis, and Zaoutis (2008, e1420) comment, "*Bartonella* infection that involves the liver and/or spleen occurs more often than previously acknowledged." Both the liver and spleen are commonly enlarged during bartonella infection (hepatosplenomegaly). Angioproliferative lesions and abscesses typically occur in both organs. There may be intra-abdominal lymphadenopathy. Granulomatous hepatitis and necrotizing splenitis may occur as well. Epithelioid hemangioendothelioma, rarely. Occasionally the gallbladder

can be involved. More than 60 percent of those infected complain of abdominal pain. Low-grade fever is common. Other symptoms include weight loss, chills, headache, myalgias. Spontaneous rupture of the spleen can sometimes occur. Liver enzymes tend to be normal, white blood cells counts only slightly elevated. Upon examination both the liver and spleen may present a "Swiss cheese" appearance due to the large numbers of granulomas involved.

Only about half of those with hepatic or splenic manifestations of bartonella present with enlarged lymph nodes. There tends to be a consistent pattern of portal involvement, indicating a mode of transmission of ingestion rather than an insect taking a blood meal.

Renal Complications

Glomerulonephritis, renal microabscesses, urogenital pain, difficulty in voiding the bladder, UTI. Glomerulonephritis generally presents with hematuria (which may be gross or microscopic), low-grade proteinuria, and cola-colored urine.

Orthopedic Complications

Bartonella quintana infection was once commonly referred to as "shinbone" fever due to the common, and often painful, involvement of the shinbones during infection. It is now, rather belatedly, recognized that all bartonella infections can involve bone infection, not just *B. quintana*. Normally, it is the bone marrow rather than the bone itself that is infected.

The symptom picture is rather broad and includes bone pain, osteomyelitis, arthropathy, and arthritis. Knee, wrist, elbow, and ankle joints are the most commonly affected joints. The spine and pelvic girdle are the most commonly affected nonjoint areas but the skull, sternum, clavicles, humerus, femur, tibia, acetabulum, metacarpals, and metatarsals are also sometimes affected. Systemic bone marrow lesions may occur that can produce nonlocalized, skeletal, bone pain. Most commonly, when the bone is involved, there is pain and tenderness over the affected bone. Generally, bone involvement is limited to one bone. The bone marrow may contain numerous epitheloid, nonnecrotizing granulomas.

Myalgia and tendonitis are also common. In some instances the bone itself may be destroyed, such as the lumbar body of various vertebrae in the spine or portions of the clavicle, or it may present as acute mastoiditis with breakdown of the osseous septa. Women tend to have more bone involvement than men.

Pseudomalignancy

Granulomas and vasoproliferative neoplasias are common in bartonella infection. They may occur throughout the body and are sometimes misdiagnosed as tumorous growths. Lymphoma, breast tumors, rhabdomyosarcoma, and parotid malignancy are common misdiagnoses.

Skin Involvement

Rashes, scalp eschar, urticaria, skin lesions, skin ulceration that will not heal, petechiae, purpuras, leukocytoclastic vasculitis (Osler's nodes), interstitial granulomatous dermatitis, and angiomatous papillomatosis of the oral cavity.

Pulmonary Complications

Chest wall abscess, difficulty breathing, long-term unexplained cough, pneumonia, pleuritic chest pain, pleural effusion, bilateral infiltrates, widened mediastinum, apical pleural thickening, postmediastinal mass, diffuse bilateral reticulonodular pulmonary infiltrates, multiple bilateral pleural nodules. Cough of unexplained origin, pleural thickening, and pneumonia are the most common.

Cardiovascular Complications

These include myocarditis, endocarditis (with or without colitis), pericarditis (all inflammations in various parts of the heart), cardiac arrhythmia, cardiac murmur, anemia, mitral regurgitation, abdominal aortic aneurysm, anasarca, cardiac tamponade, thrombocytopenia, small vessel vasculitis, hemangiopericytoma, Raynaud's syndrome, lobular capillary hemangioma, monoclonal gammopathy, pseudoepitheliomatous hyperplasia, hypotension, and stroke.

In long-standing infections, echocardiography will usually reveal a mass on the mitral or aortic valve (or both). If not

caught soon enough there is often extensive damage of the heart valves that necessitates valve replacement. The use of antibiotics, unless very early in the infection, does not stop the valve damage and does nothing to heal it.

Angiomatosis, or overgrowth of new blood vessels, may occur, which may lead to lesions on the surface of the skin that refuse to heal. The endothelial lining of the blood vessels is always affected and often spreads and thickens. The blood cells are routinely infected, which may cause anemia.

Bartonella endocarditis symptoms include persistent FUO, heart murmur, weight loss, night sweats, chills, prostration, myalgia, fatigue, painful joints, shortness of breath, and cough. Petechiae, splinters, and purpuras may also occur. Vegetations occur in nearly 90 percent of those infected. Men tend to have more cardiac involvement than women.

Oddly enough, although millions of soldiers in WWI were infected with *Bartonella quintana* (a common cause of contemporary bartonella-caused endocarditis) there were few reported cases of endocarditis among them. Research indicates that bartonella species are undergoing rapid evolutionary adaptation resulting in greater infectious range and virulence.

Bacillary Angiomatosis

Proliferative vascular lesions that resemble Kaposi's sarcoma. Red or brown papules, angiomatous nodules, pedunculated lesions of deep subcutaneous masses may also occur. ***Note:*** This is most common in those who are immunocompromised, generally those with AIDS or on immunosuppressive drugs, but it is occurring more frequently in the immunocompetent. Various organs may be affected but the skin is the most common. Cutaneous lesions, which may be superficial, dermal, or subcutaneous, may sometimes bleed profusely when punctured. Surface lesions may be red, purple, or without color. The oral, anal, and GI mucosa can be involved.

Reproductive Complications

Urogenital infections, infertility or sterility, low birth weight, infection of fetus with resulting symptoms after birth, miscarriage, death of fetus or child soon after birth.

The first in-depth look at reproductive problems including perinatal transmission from bartonella occurred in February 2010 (Breitschwerdt et al. 2010.) That paper also contains an excellent description of the progress of the disease and the experience of people who were improperly diagnosed over a long period of time. Before finding a competent professional, over some 18 years, the family had seen primary-care physicians, an internist, gastroenterologist, urologist, infectious disease specialist, neurotoxin specialist, and several naturopaths. They were given a multitude of pharmaceuticals (which provided, at most, temporary relief) including numerous antibiotics, antifungals, cholestyramine for toxic mold, and so on; had all their mercury fillings removed; and had their house remediated for toxic mold. Nevertheless, the symptoms continued to increase in severity.

The initial symptoms were recurrent low-grade fever, fatigue, headaches, and urogenital pain that began to occur sometime in 1991. Progressively, the symptom picture began to include irritable bowel syndrome, interstitial cystitis, infertility, headaches of increasing severity, memory loss and confusion, irritability, insomnia, bladder dysfunction, balance problems, intermittent joint pain, muscle pain, restlessness, shortness of breath, episodic tachycardia, rashes, rectal puritis, hypersensitivity to various foods, fatigue, episodes of extreme anxiety, cognitive impairment, stabbing urethral pain, and chronic cough. The son, born in 1998, experienced increasing symptoms including night walking, night sweats, hyperactivity, irritability, dark circles under his eyes, frequent ear infections, and rapid eye blinking.

Eventually, focused diagnostic approaches (in 2009) found the same species of bartonella (*Bartonella vinsonii* subsp. *berkhoffii*) in mother, father, and child and in the autopsy tissue (liver) of the child's twin sister who had died nine days after birth—again in 1998. The mother was also infected with *B. henselae,* the same genotype of which was also found in the daughter's autopsy tissues (liver and brain) and in the son's blood serum. The death of the twin was originally attributed to hypoplastic left heart syndrome—essentially portions of the heart (mitral valve, left ventricle, aortic valve, and aorta) do

not form properly. The paper's authors concluded that the woman had been infected for at least 18 years, long before she became pregnant.

Bartonella has been found to severely affect the reproductive organs and tissues of rats, cows, sheep, mice, and cats. There are very high incidences of fetal death, miscarriage, impregnation failure, low birth weight. The presence of the bartonella organisms in the body increases substantially during pregnancy, especially in the last two-thirds of pregnancy.

In this particular instance, reproductive problems increased as time progressed. The original pregnancy was through in vitro fertilization, subsequent attempts all failed. An examination of the woman's cervical tissue found high levels of bartonella organisms, which were the underlying cause of her urogenital problems.

This particular case reveals that, as seen in numerous in vivo studies, reproductive damage from bartonella bacteria occurs as well in people. The damage to the daughter's heart occurred from bartonella infection of the developing organs in utero; the boy was infected then as well. Other instances of children with congenital heart defects who have subsequently been found to be infected with bartonella exist in the literature.

As well, there is strong indication that the infection was passed from the mother to the father sometime after they began dating, raising the possibility of horizontal transfer. Since bartonella routinely infects the salivary glands, it is possible that it was transferred through that route.

BARTONELLA DIAGNOSIS

People going to their physicians complaining of the most common bartonella symptoms are generally subjected to a number of routine tests, but rarely does that include a test for bartonella. And the routine tests used by most hospitals and physicians are nearly always negative; they show nothing wrong with the person. White blood counts are usually normal or only slightly elevated, platelet counts may be normal or slightly elevated or even diminished, cerebral spinal fluid

exams are usually normal, as are liver enzymes and erythrocyte sedimentation rates. At that point, most physicians don't really know what is wrong and simply begin to give a series of pharmaceuticals that may or may not work for the symptom picture. If they do, for some reason, test for bartonella, that is, in and of itself, not a guarantee of success in diagnosis. Most tests for bartonella currently on the market are not very effective.

Culturing bartonella organisms from fluids taken from an infected person is a lengthy process, taking two to six weeks. It is rarely successful due to the habitually low numbers of bacteria in the body; the bacteria, because there are so few of them, are extremely difficult to isolate, even in people known to be infected. Cultures from swollen lymph nodes, even in clear cases of cat scratch disease, rarely produce organisms since much of the swelling is due to organism-induced immune responses.

The IFA is another approach and it is much better. IFA or indirect fluorescence assay tests for antibodies to bartonella. Still, it is only 84 to 95 percent effective and often produces false negatives. An additional problem is its cross-reactivity with a number of other bacteria: Epstein-Barr virus, cytomegalovirus, *Coxiella burnetii, Toxoplasma gondii, Chlamydia* spp., and *Streptococcus pyogenes,* which can produce false positives. There is wide variation within and between bartonella species and thus a large range of antigenic variation. This creates problems for this kind of testing. IFA does not respond to all strains' and species' antibodies nor does it distinguish between prior or current infection. Generally, an antibody titer exceeding 1:64 is considered positive for recent bartonella infection. The accuracy of the test can be improved if both IgG and IgM are tested for as well. Nevertheless, ELISA testing in general is not very effective. IgG and IgM levels are extremely variable; there is no reliable pattern during bartonella infection. PCR (polymerase chain reaction) tends to be a better approach, especially if combined with IFA.

Molecular detection of bartonella DNA in blood, tissue, or cerebral spinal fluid using PCR is more effective for a broader

range of organisms than IFA but its sensitivity is lower, only 43 to 76 percent. The main drawback, and it is a big one, is that the most common PCR tests can only detect bartonella bacteria if they are present in the body above a certain level. Because bartonellas tend to remain at low levels in the body except during certain stages of the infection PCR testing often returns negative results even during active infection. Common PCR tests have been developed to identify the following species (if they are present in sufficient numbers): *henselae, bacilliformis, clarridgeiae, elizabethae, quintana,* and *vinsonii* subsp. *berkhoffii.* But they cannot recognize any of the other 11 species now known to infect people.

A new PCR test, recently introduced (2011) by Galaxy Diagnostics, is apparently a more sensitive form of the test, especially for immunocompetent individuals (i.e., non-HIV-infected, non-immunosuppressive-drug users). It is designed to stimulate growth of the bacteria to PCR-detectable levels. The test is purported to be 98 percent effective for 26 species of bartonella. (Unfortunately they did not respond to repeated inquiries from me about their test.)

It appears from current outcomes that a combination test using the Galaxy PCR and IFA is the most effective approach to a reliable diagnosis. But as with Lyme, the symptom picture that the person presents should be carefully analyzed in concert with any testing that has occurred. False negatives are extremely common with bartonella. As one group of researchers noted:

> The diagnosis of human bartonelloses should be considered for patients with classic manifestations of cat scratch disease, bacillary angiomatosis, or recurrent fever as occur in trench fever. But it should be also considered for those with severe or recurrent anemia, cholestatic liver, serositis of unknown cause, lymphadenopathy, chronic uveitis, and granulomatous or angioproligerative reactions of undefined etiologies. (Drummond, Gilioli, and Velho 2010, 1)

In my experience symptoms that should suggest bartonella infection include anemia, recurrent fever of unexplained

origin, recurrent headache (up to and including migraine levels), photophobia, unexplained cough, bone pain (especially in the foot), neurological problems (especially if there is homicidal rage or strong unexplainable incidences of anger), paresthesia, memory loss, ataxia, paraparesis, and any kind of heart problems.

The presence of bone pain, unexplained cough, photophobia, fatigue, and memory impairment is nearly always indicative of bartonella infection.

> *We propose that the initial arthritic signs, short-term memory loss, and incoordination were premonitory signs of* Bartonella *spp. infection, and that persistent infection contributed to localized edema, nonregenerative anemia, thrombocytosis, hyperglobulinemia, and a protracted debilitating illness accompanied by hallucinations, agitation, seizures, and death. Agitation, disorientation, and combative behavior have been reported in association with CSD [cat scratch disease] and physicians have implicated* Bartonella *spp. as contributors to agitation and treatment-resistant depression.*
>
> EDWARD BREITSCHWERDT ET AL., "A GROUNDHOG, A NOVEL BARTONELLA SEQUENCE, AND MY FATHER'S DEATH"

PHARMACEUTICAL TREATMENT

As with Lyme disease, pharmaceutical treatment of bartonella is mixed. All the species are developing resistance to antibiotics, however due to the disabling nature of the disease for many people antibiotics really should be used. If they work, recovery occurs within a few weeks though it may take months for all the symptoms to resolve. Unfortunately there is a lot of confusion among physicians about which antibiotics to use. Most are depending on in vitro studies that, as usual, don't translate well into clinical success. As Florin, Zaoutis, and Zaoutis (2008, e1420) comment, "There is a significant divide in the literature between in vitro efficacy of antibiotics and the ability to successfully treat in clinical practice. In vitro, *Bartonella* species have been found to be susceptible to a number of antimicrobial agents… . This broad spectrum of activity has failed to be borne out in clinical practice." Most antibiotics tested have been found to be only bacteriostatic, that is, they stop the bacteria from reproducing, but they don't kill them.

> *Elimination of* Bartonella *spp. by antimicrobial drugs in immunocompetent patients may be more difficult to achieve than is currently appreciated.*
>
> EDWARD BREITSCHWERDT ET AL., "A GROUNDHOG, A NOVEL BARTONELLA SEQUENCE, AND MY FATHER'S DEATH"

The most effective antibiotic for bartonella is telithromycin. (Trimethoprim was found to be very effective in another study.) This is followed, in order, by a number of other macrolides (clarithromycin, erythromycin, rifampin), then several fluoroquinolones (gatifloxacin, gemifloxacin, moxifloxacin), then a few tetracyclines (doxycycline, minocycline), then netilmicin and gentamicin among the aminoglycosides. A combination of two or more of these antibiotics was found to be the most effective approach. Bartonella bacteria are not very susceptible to vancomycin or ciprofloxacin. In general, antibiotics have only been found effective in from 58 to 87 percent of those treated. Often there is *no difference* in outcomes in those who receive antibiotics and those who do not. It is essential if successful antibiotic treatment is to occur that the right antibiotic combination be used and for the proper length of time. *Combinations of two or more antibiotics have consistently shown better outcomes.*

Although treatment for five days was effective in some cases, the most effective treatment regimen for antibiotics is two to three weeks for complete bacterial clearance. However, as Meghari et al. (2006, 384) have commented, "*Bartonella* infections are characterized by a high frequency of relapses after brief courses of antibiotic therapy." Pharmaceuticals have been found to be necessary in some cases for from eight months to two years before complete bacterial clearance was reported. And even then relapses can still occur.

In cases of brainstem encephalopathy or basal ganglia impairment high-dose methylprednisolone is very effective and helps prevent permanent damage. In general, however, corticosteroids are generally contraindicated in bartonella infections. (The corticosteroids are used to reduce the inflammation that the bacteria cause through their cytokine cascades. The proper plants will do the same thing.)

Some early clinical successes have used the following pharmaceuticals:

Doxycycline (erythromycin for children under eight) has shown the most effectiveness for neuroretinitis (100 mg twice daily for from 2 weeks to 4 months depending on immune status). If combined with rifampin (300 mg twice daily), especially in those with neurological involvement, the outcomes are much better, often producing full system clearance of the organisms. Increases of visual acuity and resolution of other eye problems are common with the combination.

Doxycycline (200 mg/day, as one oral dose, for 28 days) in combination with gentamicin (3 mg/kg/day for 14 days) has been found to work for chronic bacteremia in one randomized trial.

However, it is crucial to understand that in spite of the use of gentamicin in such cases, gentamicin will *not* kill intracellular bacteria, only the extracellular. For the intracellular bacteria, something like telithromycin must be used.

The treatment of endocarditis from bartonella is similar: doxycycline 100 mg 2x daily orally for 6 weeks in combination with gentamicin 3 mg/kg/day IV for 14 days.

Bacillary angiomatosis is most effectively treated with erythromycin (due to its antiangiogenic effect), 500 mg 4x daily orally for 12 weeks. ***Note:*** Because endothelial proliferation is present in **all** bartonella infections, irrespective of species, a combination pharmaceutical therapy that includes erythromycin is indicated. Combination therapies produce the best outcome in any event and the inclusion of erythromycin will do a lot to decrease the symptom picture associated with bartonella infection whether or not bacillary angiomatosis is present.

From both clinical observation and journal review it appears that the best combination overall for a first approach is either telithromycin or doxycycline combined with gentamicin and erythromycin.

Because the hyperprofusion of endothelial tissue can lead to a similar narrowing of the arteries as that produced by atherosclerosis (cholesterol buildup in the arteries) some physicians are resorting to angioplasty to open bartonella-blocked blood vessels. Erythromycin is a better first alternative as endothelial hyperplasia and angiogenesis generally resolve upon its use. During angioplasty a small balloon is inserted in the afflicted vein and the balloon is expanded, flattening the material obstructing the walls of the vessel. This provides symptomatic relief for some for a time but in many instances damages the vessel walls in the process and interferes with the ability of the body to heal the damage itself. The process itself is much more dangerous than erythromycin and much more expensive. The results are generally temporary; most people receiving angioplasty need heart-bypass surgery eventually. In one study 50 people received angioplasty; within one year 42 had to have it repeated, 11 still needed to be on hypertensive drugs. Since angioplasty does not cure the underlying cause of the problem, in this instance bacterial infection, the problem is likely to recur. Elimination of the bacteria, reduction of the cytokine cascade that is causing the inflammation, and protection of endothelial integrity is a much better route to go. Again, erythromycin should always be considered prior to angioplasty. The use of some of the herbal protocols mentioned later will also help the problem considerably.

As mentioned there is considerable resistance emerging among the bartonella species, and among the Proteobacteria as a group. *B. bacilliformis* is increasingly resistant to ciprofloxacin, rifampin, and erythromycin. In fact the organism is developing resistance to the entire quinolone group. *B. henselae* has emerged in resistant forms, showing resistance to azithromycin, pradofloxacin, gentamicin, and enrofloxacin. *B. quintana* is resistant to rifampin and tetracycline. Both *B. henselae* and *B. quintana* are showing increasing resistance to macrolides, the fluoroquinolones in particular. The organisms are developing resistance just as rapidly as other, better-known bacteria are—the so-called superbugs: staph, strep, klebsiella, and so on. The use of single

antibiotic regimens should be strongly avoided in order to prolong antibiotic effectiveness.

As with Lyme, many people who go through multiple antibiotic regimens find they are still infected with bartonella and still experience debilitating symptoms. Even if the antibiotics are successful, follow-up with numerous people has found that residual intraparenchymal lesions (i.e., lesions in the brain) and extrapyramidal abnormalities can persist for from months to several years. In other words, central nervous system debility of varying degrees of severity remains even after antibiotic treatment. It only slowly corrects itself.

BARTONELLA AND HERXHEIMER REACTIONS

Bartonella bacteria possess very low endotoxicity. This is crucial because endothelial cells have a very low tolerance for endotoxins. The lipopolysaccharide of the bacteria is at least 1,000 times less toxic than that of *Salmonella* bacteria. Herxheimer reactions during bartonella infection, if they exist, would seem to be occurring from something other than bartonella cellular death. For it is generally the lipopolysaccharide that is released during cell death that causes the toxic reactions known as herxing.

Some people do have periodic bouts of what they call herxing, usually in response to antibiotics. The nature of the bacteria doesn't lend credence to the herxing being from the bartonella. One thing to keep in mind however: Those antibiotics you are taking? They don't just kill bartonella. They kill a lot of other things as well.

ABOUT BIOFILMS

A biofilm is an aggregate that microorganisms can sometimes form. Various types of cells adhere to each other, usually on a surface of some kind. During the formation of a biofilm a few free-floating bacteria or other microorganisms attach to a surface. Once attached they begin increasing the power of the attachment, cementing themselves in place as it were. Other microorganisms then begin adhering to them, and then more. As this progresses the organisms begin building a matrix to hold them, very similar in some ways to the formation of coral

reefs in the ocean. An extracellular matrix begins to form around clumped microorganisms, providing protection to the microorganisms and allowing the development of a complex microcommunity. Channels are sometimes built into the matrix to allow the free flow of nutrients into and through the biofilm in order for the microorganisms to feed. Periodically, the colony releases free living bacteria into the exterior world surrounding the biofilm. It is not uncommon for some biofilms to essentially fossilize much like coral reefs.

Biofilm is a very ancient mechanism of protection for bacterial communities. It slows down the action of antibiotics, helps protect the community from immune action, allows a great deal of interspecies communication between microorganisms, and facilitates the exchange of DNA through lateral gene transfer.

Although there is a lot of concern about biofilms in the Lyme community, there should not be. Biofilms began forming billions of years ago and have always been present wherever microorganisms congregate. Nearly every living organism on Earth creates antibacterial substances; plants are especially active in doing so. A biofilm is just one response to that. Herbal medicines are exceptionally effective in treating resistant bacteria, whether they form biofilms or not.

One important point about biofilms: When biofilms form, the bacteria are protected with something like a shield that covers the community. They then feed in that one location. If, however, the biofilm is broken open, the bacteria spread into the system, often through the bloodstream. At that point, the symptom picture is often worse, that is, the symptoms return more strongly due to the presence of many bacteria infecting more locations. *If* there is a concerted antibacterial regimen, with an antibiotic that is effective, these newly released bacteria can then be killed more easily. But the antibiotics are not always effective.

I do discuss some biofilm-breaking agents (sida, NAC, greater celandine) in the section on mycoplasmas, if you wish to use them. I am not sure they are necessary.

There is a widespread belief that bartonella bacteria make biofilms during infection. There is one peer-reviewed journal that discusses this in some depth. However, those typical biofilms only formed in vitro. Bartonella do form aggregates but not a typical biofilm when they form them in vivo, that is, in living organisms, and the term really should not be applied in this instance (although most everyone does so). Instead bartonellas create vacuoles. Vacuoles can be imagined as being something like a balloon. The interior is filled with a mixture of bartonella organisms, macrophages, and lysed cell fragments. The balloon, or membrane of the vacuole, is a fairly resilient structure, intended to protect the organism. Vacuoles are created wherever bartonellas congregate. A liver filled with bartonella vacuoles looks something like Swiss cheese on cross section. Vacuoles are just another way that bartonellas protect themselves from the immune system. Herbs can treat them very effectively.

WHAT THE ORGANISM DOES IN THE BODY

Bartonella bacteria have "an unusually complex natural cycle," as researcher R. J. Birtles comments (2005, abstract). They are, much like Lyme spirochetes, essentially parasitic organisms. They live on and in a host (*always* mammals) from which they obtain the nutrients they need to survive. Lyme spirochetes break down collagen tissues to get the nutrients they need; *Bartonella* organisms scavenge nutrients from blood cells.

If you understand what bartonella (or any organism) does when it infects the body, it is much easier to design an effective protocol to treat it.

The transmission dynamics of bartonella have not been extensively studied although some routes of transmission are well understood. In those routes, bartonella infects an insect vector such as a flea or tick when the insects take a blood meal from an infected host. The bartonella organisms infect the GI tract of the vector and then spread to the salivary glands and feces of the insects. The bacteria then either are injected into the mammal host when the insects take a blood meal from them or enter the host when the animal ingests the feces or the

feces enter through a cut in the skin surface. Once inside the mammalian host other infection strategies come into play—not all of which are clearly understood.

Bartonella organisms, unless the host organism's immune function is low, do not generally exist in large numbers in either vectors or mammal hosts—the numbers of bacteria that flow into a new mammal host during a blood meal are small; symptoms only begin to occur once the organisms substantially increase in numbers.

As soon as the bacteria enter the bloodstream, they immediately colonize four sites: the red blood cells, the spleen, the liver, and the bone marrow. Both liver and spleen will, to various extents, become inflamed.

Bartonella bacteria only double in numbers (approximately) every 24 hours, so it takes anywhere from 12 to 62 days for there to be enough bacteria in the system for symptoms to appear. Generally, the symptoms are much like the flu: fatigue, fever, malaise, and a general poor feeling all around. The acute symptoms last several weeks, then the organism seems to find a balance with the new host, the numbers of bacteria drop considerably, and the symptoms cease. At this point, the person is either an asymptomatic carrier living in balance with the organism or else the body has eliminated the organism entirely. However, *many* people become asymptomatic carriers.

> *The low prevalence of clinical manifestations compared to the high prevalence of infection underlines the elegance of these parasites that carefully exploit their hosts in a manner that optimizes their transmission.*
>
> R. J. BIRTLES, "BARTONELLAE AS ELEGANT HEMOTROPIC PARASITES"

All of us have a number of disease organisms inside us that live in relative peace with us. Indeed, we couldn't survive without our bacterial partners. Bartonella problems begin to occur when the immune system is depressed, either slightly in those who are under stress because of life circumstances (or just poor self-caretaking) or significantly as in those with AIDS or people who are using immunosuppressive drugs. The more the immune system is depressed, the worse the

symptoms will be. People with mild immune suppression will experience a chronic relapsing type of fever that comes and goes. Again, the symptoms are much like a mild to moderate flu. With increasing immune suppression come increasing symptoms. In those with AIDS the symptoms are the most severe.

Once the initial infectious, acute phase passes and the bartonella bacteria are established in the body they begin to spread. The bacteria then colonize endothelial cells throughout the body, especially those that line the blood vessels. They also spread throughout the lymph system (generally preferring routes nearest the initial inoculation site) and continue to colonize the bone marrow. Approximately every five days they release new bacteria into the blood in order to keep the red blood cells infected so that mosquitos and other insect vectors can spread the infection to new hosts. Interestingly enough, *every* colonized site in the body will release new bartonella organisms *simultaneously*. Every colonized site is closely connected to the others through some as yet not understood means.

> *After primary infection of the natural mammalian host, a chronic, relapsing, nonclinical bacteremia occurs.*
>
> EMMANOULL ANGELAKIS ET AL., "POTENTIAL FOR TICK-BORNE BARTONELLOSES"

In treating Lyme disease, it is crucial to understand that the Lyme spirochetes have an affinity for collagen tissues. They break them down in order to obtain the nutrients they need to live. *Where* they break down collagen tissues is where the symptoms in the body occur. If they do so in the knee, you get Lyme arthritis, in the brain neurological Lyme, and so on.

Bartonella has a similar relationship with endothelial tissue. In essence it lives in and on endothelial tissue. Through a variety of mechanisms it stimulates the uncontrolled growth of endothelial tissue in the body, creating a condition called endothelial hyperplasia. The healthier the immune system, the less the hyperplasia; the weaker the immune system, the more hyperplasia that occurs until with AIDS patients you get

bacillary angiomatosis, the uncontrolled growth of blood vessels and endothelial tissue throughout the body.

Since bartonella lives in and on endothelial tissue, the more endothelial tissue there is, the more living space it has. It, in essence, creates more living space by making more endothelial tissue. It does this through the creation and release of a number of unique chemicals.

Where the endothelial growth occurs in the body is where symptoms occur. If it is in the eye, you get ocular bartonellosis. If in the kidneys, you get renal bartonellosis. If in the heart, you get cardiac bartonellosis, the primary symptom of which is usually endocarditis. Each location in which it causes endothelial overgrowth leads to bartonellosis in that location and each location has a very specific range of symptoms that occur as a result.

In many respects, bartonella is, like Lyme, one of the great stealth pathogens, one of the great impersonators, in that it can look like a large variety of disease conditions. This is one of the reasons that it is so often misdiagnosed. Another, as I have mentioned, is that few physicians know much about the disease—most are still using outdated CDC or medical school data on what bartonella is and is not and as a result don't know how to spot the condition when it arises.

FACTORS THAT AFFECT THE SYMPTOM PICTURE

In addition to the health of the immune system, there are some other factors that will lead to differences in the symptom picture and the course of the disease. These are: the specific bacterial species involved, its virulence, if there is any constitutional weakness in the body prior to infection, if there is any other type of chronic infection already in place, and the nature of the inoculation vector.

Most bartonella species engage in very similar behaviors when they infect a mammal host, the primary exception being *B. bacilliformis,* which (usually) only occurs in South America. *Bacilliformis* produces profound anemia (more so than the other species), which can lead to death. Those that survive usually experience the emergence of a number of

blood-filled warts on the body. In essence this is a limited and specific form of bacillary angiomatosis and is unique to this species. With the other bartonella species, there is a great deal of similarity in their actions in the body and thus in the symptoms they produce. But they will all be slightly different. There is a unique interaction between the bacterial species involved and the unique ecosystem that is an individual human body, so the symptom picture in each case will also be unique even if there are overlaps between other cases.

Constitutional weakness in the person infected is rarely considered but it plays a crucial part. Any part of the body that has experienced continual stress for long periods tends to be weaker than parts that have not experienced such stress. An example is joint wear in people who have worked in heavy construction. Over 30 years, the joints get a lot more stress and as a result are weaker than in someone who has not done that kind of work. Later in life, that wear tends to produce cartilage and joint problems. This kind of dynamic is present in all parts of the body, depending on your physical history. If you worked with paint and other such chemicals for 30 years, then the liver is going to be more highly stressed than it would be otherwise. If your heart has been stressed by a bad diet for decades or from emotional pain for a long period, then it is going to be weaker than otherwise.

In such instances, when bartonella enters the body, if it infects a part of the body that is already weakened, then the symptoms that occur are going to be a great deal more pronounced than otherwise. To make matters worse bartonella organisms do what they do in the body through stimulating inflammation in cellular tissues. If you already suffer from inflammation, say in your joints, the bacteria will tend to locate there since half their work is already done for them.

> *In a given patient,* Bartonella *organisms likely infect a substantial number of cellular targets.*
>
> EDWARD BREITSCHWERDT ET AL., "A GROUNDHOG, A NOVEL BARTONELLA SEQUENCE, AND MY FATHER'S DEATH"

If you are already suffering from another chronic infection, where the immune system is already stressed, then the

bartonella symptom picture is often going to be worse. If you are infected simultaneously with Lyme and bartonella, in other words, if bartonella is a coinfection of Lyme, then the impacts on the body are generally going to be more severe than otherwise. In-depth research has shown that the multiple infections are *synergistic* with each other, that is, they work together to produce unique forms of illness. They become harder to treat.

The *way* you are infected also plays a crucial part. This is especially true if you are infected by tick bite. Ticks generally remain in place for lengthy periods of time, several days at least. And during that time, the tick saliva is liberally injected into the bite site. Compounds in the saliva prevent clotting of the blood and affect the immune response, shutting parts of it down so that the body cannot reject the tick while it is attached. These compounds are used by the bacteria in the tick, along with the bacteria's own entry mechanisms, to facilitate entry into the body.

Overall, however, if you look deeply enough at the cytokine cascade of the organisms, you can begin to design an intervention that will slow or stop the disease progression and begin to correct the damage.

7

A Technical Look at Bartonella and Its Cytokine Cascade

> *Bartonellae are highly-adapted pathogens whose parasitic strategy has evolved to cause persistent infections of the host. To this end, virulence attributes of* Bartonella *include the subversion of host cells with effector molecules delivered via a type IV secretion system, induction of pathological angiogenesis through various means, including inhibition of apoptosis and activation of hypoxia-inducing factor, use of afimbrial adhesins that are orthologs of* Yersinia *adhesin A, incorporation of lipopolysaccharides with low endotoxic potency in the outer membrane, and several other virulence factors that help* Bartonella *infect and persist in erythrocytes and endothelial cells of the host circulatory system.*
>
> MICHAEL MINNICK AND JAMES BATTISTI, "PESTILENCE, PERSISTENCE, AND PATHOGENICITY: INFECTION STRATEGIES OF *BARTONELLA*"

Bartonella bacteria live inside two different kinds of organisms: insects and mammals. This gives them some unique abilities, some of which they share with Lyme spirochetes.

Inside the insect, the bartonellas live in an environment that is the same temperature as the air around them. Once they enter a mammal host they begin to live in an environment with a highly regulated temperature, higher than the air around it. As well, the immune system in the insect is much different than that in the mammal host so the bacteria must significantly adapt to multiple immune systems. With *Bartonella henselae* the bacteria must adapt to three organisms: fleas, cats, and

humans. (These bacteria are also found in a number of other mammals such as cetaceans, so their adaptive abilities are even broader.) One major difference between bartonella and Lyme is that bartonella organisms can be transmitted by a simple bite from insects such as mosquitos to mammals such as cats or even by a mere scratch from a cat to a human. It doesn't take long for transmission to occur. Lyme spirochetes are, in general, more commonly transmitted by tick bite and the tick needs to be attached for a fairly long time, as much as 24 hours, for transmission. (There are exceptions to this.) During Lyme transmission, the tick takes a blood meal from the host. The blood travels to the tick's stomach. There the Lyme spirochetes determine what kind of animal the tick is feeding on and immediately begin to alter their outer protein coats to enable them to live in that particular organism. Bartonella organisms, because they tend to be immediately injected into the new host, possess different mechanisms.

INITIAL INFECTION

The dynamics that occur after initial infection with bartonella have not been completely studied and what happens during the first three days is not yet fully understood. Only one route of infection, blood transmission, has been studied in any depth. The dynamics that occur when the bacteria are ingested by mammals have not been explored in any depth (but are probably similar to what happens when insects feed). Bartonella, when taken in by ticks and lice during a blood meal, immediately infect the epithelial cells of the GI tract and from there begin moving into the insects' salivary glands (and in mammals the bloodstream as well). From there they are injected into mammals when the insects feed.

The movement of bartonella from an arthropod vector into a mammal means that the bacteria are going from an ambient-temperature organism into a much hotter body-temperature animal. Additionally, there is a significant change in the nature of the blood they are exposed to. The hemoglobin in animals is filled with oxygen but insects don't have blood as we know it, but rather hemolymph, which doesn't carry oxygen (insects respirate directly from their body surfaces). As soon as the

bacteria enter the bloodstream of a mammal, they are exposed to large amounts of oxygen (a toxic substance). Mammal blood also has very different pH values than normally exist in the insect stomach. So, the bacteria have to begin living in an environment that is *very* different than that of an insect and they have to do so *immediately*. This gives you an idea of just how adaptable the bacteria are. In literally a few seconds they go from a low-oxygen, ambient-temperature, low-pH environment to a high-temperature, high-oxygen, high-pH environment. And in that few seconds they *immediately* adjust, comfortably so. Needless to say, the *immune* system they encounter is also very, very different than the one in the insect. Bartonella bacteria are exceptionally responsive to the environments they are in. They can analyze subtle shifts in the environment and then initiate alterations in their physiology that take place almost immediately in order to live in those altered circumstances.

The shifts that occur in things such as temperature, pH, oxygen content, and immune dynamics convey to the bacteria just what kind of mammal or insect they are in. These kinds of markers, in essence, tell them *how* they have to shift their physiology in order to survive in the new host.

One of the ways the bacteria give themselves time to analyze their environment and then make those alterations is that they form biofilms. To give an example: One of the main ways that bartonella is spread is through flea or lice feces. With lice, for example, as they feed they also excrete. And when they feed they cause an irritation that stimulates the person to scratch. Scratching breaks the surface of the skin and the feces is, in essence, injected through the break in the skin into the bloodstream.

Whenever bartonella bacteria are excreted into feces they form very strong and very stable biofilms, in which they can live quite happily for a year (at least). As soon as that biofilm formation enters the blood, the alteration in environment signals the bacteria to alter their form. They analyze the new environment and immediately begin altering their genomic structure. In essence they take plasmids, loops of DNA that are specific for allowing them to live inside that particular

mammal, and begin weaving them into their genetic structure. This immediately begins alterations in their outer membrane proteins. They then begin to release the cytokine interleukin-8 (IL-8), which stimulates the movement of CD34+ cells to their location. As soon as the CD34+ cells reach their location (a matter of seconds) the bacteria enter those cells, thus becoming protected from the immune system of their new host. And inside these cells they are spread throughout the body via the blood.

CD34+ CELLS

CD34+ cells are pluripotent stem cells that are generated in the bone marrow; they are sometimes called hematopoietic progenitor cells (HPCs). (Interestingly, both *Anaplasma* and *Ehrlichia* bacteria, closely related to bartonella, also infect HPCs.) These HPCs or CD34+ cells flow throughout the body via the bloodstream and as such reach nearly every cell and organ in the body. They are considered to be a primitive form of cell, undifferentiated and pluripotent, that is, they have the capacity to differentiate, to turn into, a variety of different kinds of cells whenever the body needs them to do so. Importantly for understanding bartonella, they are the progenitors of endothelial cells and red blood cells (as well as monocytes, macrophages, neutrophils, basophils, eosinophils, dendritic cells, platelets, T cells, B cells, NK cells). If the body needs a specific kind of cell, for instance an endothelial cell to help repair a damaged blood vessel, they can then transform themselves into that particular cell in order to facilitate healthy functioning in the body. Endothelial cells line all the blood vessels in the body and this constant repair keeps the blood vessel linings healthy. However, in this instance, the invading bacteria use that process for their own ends. Bartonella primarily live within endothelial cells. By entering CD34+ cells, they are immediately taken to locations throughout the body where endothelial inflammation is already occurring. This allows them to access the exact niche they need and to do so at the locations where endothelial integrity is already compromised.

In general, *any* part of the body that is experiencing inflammation will call CD34+ cells to it. Thus, once bartonella bacteria have infected the CD34+ cells, the parts of the body that then experience bartonella infection and associated symptoms are the ones that are already compromised.

IMPACTS OF BARTONELLA'S IL-8 PRODUCTION

One of the major mechanisms that the bacteria use to subvert the body's functioning for their own needs is the production of IL-8. Not only does IL-8 call CD34+ cells to the bacteria, it also causes an immediate decrease in the number of circulating neutrophils in the blood, a condition called neutropenia. The neutrophils (a.k.a. neutrophil granulocytes or polymorphonuclear neutrophils, a.k.a. PMNs) are white blood cells that form an essential part of the innate immune system and comprise up to 50 percent of all circulating white blood cells. They are among the first responders that the body produces to bacterial infections. IL-8 causes an immediate *reduction* of neurophil levels in the blood, *followed* fairly quickly by a major increase. This initial reduction allows the bartonella bacteria time to enter inside of some very specific cells in the body, thus hiding themselves from the innate immune system. (The adaptive immune system comes online much later.)

The increased IL-8 levels also immediately cause a rather dramatic and instantaneous increase in the amount of matrix metalloproteinase-9 (MMP-9) levels in the body. MMP-9 (also called gelatinase B) acts, among other things, to degrade extracellular matrix molecules. In this instance, this causes the HPCs (CD34+ cells) that are bonded to other cells in the bone marrow to break those bonds, stimulating an increase in free CD34+ cells. The IL-8 then causes the newly free CD34+ cells to flood the bloodstream (it *mobilizes* them) in huge numbers. Depending on the amount of IL-8 produced, within 20 minutes, blood levels of CD34+ cells can increase up to 100-fold. This immediately gives the bartonella bacteria more cells to invade and makes those cells more accessible.

When bartonella organisms infect CD34+ cells they are taken *inside* the cells, where they create a vacuole, an

intracellular compartment surrounded by a tough, protective membrane inside which the bacteria live. Although they can live extracellularly, bartonella bacteria are, in essence, intracellular organisms. Once inside a living organism, they, nearly always, tend to be surrounded by a vacuole rather than existing in a free bacterial state. Because they are inside the CD34+ cells, the body can't perceive them very well and the initial response of the innate immune system is ineffective.

Bartonellas also immediately begin to disable another aspect of innate immunity. Cells infected by bacteria tend to die fairly quickly, that is, they engage in apoptosis. Apoptosis, or cell death, thus eliminates the habitat of the invading bacteria. However, bartonella bacteria initiate processes that stop infected cells from dying, thus making sure that their habitat endures.

The infected CD34+ cells, as they are circulated throughout the body in the bloodstream, flow into the liver, spleen, and bone marrow, where they congregate on endothelial cells that need repair and begin forming colonies. The bacterial IL-8 production exacerbates this process, causing a clumping together of infected cells. The bacteria remain inside the CD34+ cells as they are transformed into endothelial cells to repair the local damage. They remain unaffected by the transformation occurring around them and then find themselves, happily, in exactly the location and cell they need for optimum growth.

During this period, which lasts for somewhere around three days (sometimes a bit longer), the bloodstream shows no bacterial presence at all. (Part of the reason that the infection process is so slow with bartonella bacteria is that they double in numbers slowly, about every 24 hours.) Throughout the process, the bacteria continue to alter their genomic structure (including altering the nature of their outer protein coat) to allow them to fit within their new ecological niche more effectively. Part of this process includes the generation of multiple genotypes of themselves, that is, slight variations in structure that will allow them to more effectively avoid the immune system and more efficiently invade different niches in the host. For example, during the initial three days or so of

infection they are unable to infect the mature red blood cells of the new host, something they must eventually do.

Once the bartonella bacteria are established in the endothelial cells, have finished altering their genome sufficiently, and have generated enough offspring in enough locations they begin to infect red blood cells. Approximately every five days, they *simultaneously,* from every colonized site, release new bartonella bacteria into the bloodstream. These new bartonella bacteria then colonize the red blood cells, making the organisms ready to be picked up by insects seeking a blood meal. This begins the transmission process all over again: new insects, new hosts.

BARTONELLA AND ENDOTHELIAL CELLS

Bartonella bacteria have the strongest affinity for two things in the body: endothelial cells and red blood cells. Both of them are essential to their survival.

The endothelium is a thin layer of cells that lines all the blood vessels in the body. Endothelial cells are a form of epithelial cells (to which bartonella can also adhere, as it can to monocytes, macrophages, and dendritic cells—any form of blood cell really). Epithelial cells line the cavities and surfaces of many of the glands and structures throughout the body such as the liver, spleen, and so on. Endothelial cells are in essence specialized epithelial cells—they line the cavities of blood vessels.

The endothelium works fairly actively to keep the blood vessels healthy through a number of mechanisms: it acts as a barrier to substances in the blood, essentially regulating the passage of substances into and out of the bloodstream; it prevents the passage of too much liquid into the body—if the endothelial layer is too porous, liquid flows into the body, causing edema; it also controls the movement of white blood cells into and out of the bloodstream; and it is intimately involved in vasoconstriction, vasodilation, and a large number of inflammatory processes.

Endothelial cells also line the interior surfaces of the heart and that particular endothelium is called the endocardium.

Endocarditis, which bartonella causes, is an inflammation of the endothelial cells of the heart. Endothelial cells also line all the lymphatic capillaries. They are also highly present in the liver, spleen, and bone marrow. All of these locations are ultimately invaded by the bacteria.

The endothelium also contains heparan sulfate, a special kind of polysaccharide found in animal tissues. Heparan sulfate is involved in a number of important processes including angiogenesis (the formation of new blood vessels) and blood coagulation. It is very similar to heparin (often used by physicians) in its molecular structure. The bacteria ultimately utilize heparan sulfate to help stimulate more blood vessel formation and thus more endothelial tissue in order to increase their habitat, which causes many of the symptoms they create in the body. They also continue to utilize CD34+ cells to increase habitat.

Even though they have already used the CD34+ cells to get to their endothelial location, the bartonella bacteria continue to stimulate the mobilization of CD34+ cells from the bone marrow. Because of the bartonella cytokine cascade, a continual inflammation at the endothelial colony site occurs. The bacteria-mobilized CD34+ cells continue to cluster at that location, again contributing to angiogenesis. CD34+ cells are intimately involved in maintaining vascular homeodynamics (that is, the healthy adaptation of the vascular system to moment-by-moment pressures). Too few CD34+ cells leads to inadequate repair of the endothelial lining of the blood vessels; too many is a factor in endothelial cell proliferation, i.e., angiogenesis. The bacteria also are highly stimulatory of vascular endothelial growth factor, a.k.a. VEGF, which, as its name implies, is involved in the growth of endothelial tissue. So, through three mechanisms (utilizing heparan sulfate, CD34+ cells, and VEGF), the bacteria increase the numbers of endothelial cells at their colony location.

As the endothelial tissue expands, the bacteria continue to create offspring, which they then release into the surrounding medium, where they then find, and invade, their own endothelial cells.

Bartonellas, like all bacteria, contain a number of different kinds of molecules on their outer surface. Some of these are what are called outer membrane proteins. (These are some of the things that our immune system uses to find and kill invading bacteria, which is why the bacteria are continually altering their structure.) Other structures are what are called adhesion molecules. These act as a kind of magnet or glue, causing a tight bond between the bacteria and the cells they have an attraction to, in this case endothelial cells (and, as well, many types of blood cells and extracellular matrix proteins, e.g., collagen, fibronectin, laminin).

The two primary adhesion molecules bartonella uses are called *Bartonella* adhesion A (BadA) and filamentous hemagglutinin (FhaB). These adhesion molecules cause the bacteria to tightly bond to the endothelial cellular surface (and cause aggregates of bacteria to clump together as well). Once the bacteria adhere to a cell they begin to stimulate processes that will cause the cell to take the bacteria, and any bacterial aggregates, inside it.

All bartonella bacteria contain two very specific forms of what are called type IV secretion systems (T4SSs). The first, denoted VirB, is used with endothelial cells (and several other types of cells) and the second, denoted Trw, is specific to the bacteria's invasion of red blood cells. T4SSs developed a very long time ago, ecologically speaking, and were originally used by Gram-negative bacteria to exchange DNA. In essence they are used by bacteria for communication and the subsequent alteration of both genotype and phenotype once DNA is exchanged. Many bacteria, throughout the bacterial world, as a result of antibiotic overuse, now use T4SSs to exchange the kind of DNA loops that confer antibiotic resistance. However, the T4SSs have also been modified in such a way as to allow bacteria to infect host cells.

The T4SS is, in essence, composed of a sort of tube, or translocation channel, that spans the inner and outer membranes that Gram-negative bacteria possess, *and* a filament, or pilius, that extends outward from the outer membrane of the bacteria. It can be imagined as similar to an umbilical tunnel that runs from one spaceship to another. It

allows, as Engel et al. (2011, 2) observe, the translocation of "a cocktail of evolutionarily related effector proteins into host cells of the primary infection niche where they modulate various cellular processes."

These effector proteins accomplish a number of things:

1. They mediate rearrangement of the actin cytoskeleton of the host cell. (All cells have a "skeletal" or "scaffolding" structure to them much as our bodies do, and actin is one of its main components.) The bacteria then stimulate the cell to create a vacuole or invasome at the cellular surface into which the bacteria insert themselves.

   The vacuole is actually something most cells can make. It is a common cellular process in which substances dangerous to cells can be sequestered in their own compartment. The bartonella bacteria subvert this process for their own ends, in essence creating a protected envelope in which they can survive.
2. The effector proteins also trigger a number of cytokines such as nuclear factor kappa-B (NF-κB), IL-8, intercellular adhesion molecule-1 (ICAM-1), and E-selectin. (E-selectin does a number of things but it also has the added benefit—for bartonella—of creating greater microvascular permeability, thus assisting the movement of the invasome into the interior of the endothelial cells.)
3. The proteins immediately inhibit endothelial cell apoptosis, that is, they stop the cells from dying.

Seven specific proteins in fact—called *Bartonella* effector proteins (Bep)—are injected into the host cells. Each one accomplishes a slightly different task. BepA stops apoptosis and stimulates angiogenesis or capillary sprouting. BepC, F, and G induce the internalization of the invasome by the host cells. Once internalized, the vacuole is stimulated to move close to the nucleus of the cell—the perinuclear region (this is not usually the case).

It generally takes about 12 hours postinfection for the bacteria to congregate on the surface of the endothelial cells; they are fully engulfed within 42.

THE BARTONELLA CYTOKINE CASCADE

As with most cytokine cascades, bartonella-stimulated cytokines control aspects of the innate immune response, various cell cycles, and vascular remodeling. The bacteria's cytokine cascade includes IL-8, NF-κB, TNF-α, IL-1β, SOD, MMP-2, MMP-9, VEGF, cathepsin B, PI3K, IFN-γ, MCP-1, ICAM-1, E-selectin, BepA, protein tyrosine phosphatase (PTP), ERK-1 and ERK-2, and hypoxia inducible factor 1 (HIF-1).

Bartonella bacteria are highly elegant in their co-option of the host immune system to enable them to infect endothelial cells. Once the bacteria begin clustering on the surface of the endothelial cells they induce an NF-κB and IL-8 upregulation of E-selectin and ICAM-1. In other words they intentionally induce an inflammatory response in the endothelial cells by releasing substances (in essence, outer membrane proteins) into the extracellular matrix surrounding the endothelial cells. These substances stimulate the cells to release both NF-κB and IL-8, which then cause both E-selectin and ICAM-1 production. E-selectin, which is also known as endothelial leukocyte adhesion molecule 1 (ELAM-1), stimulates the release of large numbers of polymorphonuclear neutrophils (PMNs) from the bone marrow and calls them to the endothelial cells. There the neutrophils "roll" along the top of the endothelial cells to which they eventually adhere. IL-8, whose production is generally dependent on NF-κB, is tremendously potent in stimulating many of the negative impacts that bartonellas have on endothelial cells. It is a highly angiogenic substance—that is, very stimulatory of new blood vessel formation. The bacteria also increase the number of IL-8 receptors (CXCR2) that exist *on* endothelial cells, in essence enhancing the angiogenic effects of IL-8 upon them. *Inhibitors of NF-κB and IL-8 have both been found to stop this process* and are perhaps the primary substances that can be used to interfere with bartonella infection in mammals.

IL-8, in contact with endothelial cells, causes the upregulation of matrix metalloproteinases, especially MMP-2 and MMP-9. These MMPs break down the extracellular matrix that surrounds endothelial cells and makes it more permeable.

This supports the development of new blood vessels and their penetration into the surrounding tissues.

IL-8 also stimulates endothelial cell proliferation, inhibits cellular death, and stimulates endothelial migration and new capillary formation. IL-8 increases the amount of epidermal growth factor (EGF) and its receptors on the surface of endothelial cells. This also plays a part in the spreading of endothelial tissue. *EGF receptor inhibitors have been found to block IL-8-induced migration and angiogenesis.*

Bartonella outer membrane proteins induce an NF-κB-dependent upregulation of IL-8, ICAM-1, and E-selectin in endothelial cells, which, in turn, causes, among other things, enhanced PMN rolling and adhesion.

Neutrophils are a very abundant form of white blood cell and are common in the blood. (About 50 percent of the white blood cells in circulation at any one time are neutrophils; they are the major components of pus.) Once signaled by something like E-selectin, they begin moving to sites of infection. At arrival they, normally, begin to engulf infectious bacteria to protect the body from disease. During bartonella infection however, the bacteria use the neutrophils as part of their infection strategy. As the neutrophils roll on the surface of the infected cells they are stimulated to secrete large amounts of vascular endothelial growth factor (VEGF). This, along with the CD34+ cells and heparan sulfate stimulation, causes uninfected endothelial cells to proliferate—and to migrate to new locations. This also causes significant alterations in the cytoskeleton of the endothelial cells, helping with further interiorization of bartonella-filled vacuoles.

Monocytes, a kind of pluripotent white blood cell, are also called to sites of bartonella infection through the upregulation of monocyte/ macrophage chemoattractant protein 1 (MCP-1) in infected endothelial cells. There, they begin differentiating into macrophages and dendritic cells, two potent members of the innate immune system. (Most monocytes are stored in the spleen where they are easily infected by the bacteria in that location.) Monocytes are slowish, taking 8 to 12 hours to reach the site of infection. Monocytes, macrophages, and dendritic

cells, when in close proximity to bartonella bacteria, will also begin to produce VEGF as well as interleukin-1β (IL-1β).

MCP-1 is itself angiogenic and will also promote vessel sprouting and formation. MCP-1 production is dependent on NF-κB production. *NF-κb inhibitors will reduce MCP-1 upregulation* and the subsequent movement of monocytes to a bartonella colony.

VEGF is a potent source of the endothelial sprouting that bartonella causes. *VEGF inhibitors have been found to stop about 50 percent of the endothelial growth caused by bartonella.* That only half of the growth is stopped indicates that there are other processes involved (as discussed herein). Nevertheless, the use of VEGF inhibitors along with other approaches is strongly indicated as this reduces the living space of the bacteria (thus reducing their numbers). Since many of the symptoms of bartonellosis come from bacterial stimulation of the endothelial layers, *reducing endothelial proliferation will reduce many of the symptoms people experience.*

Bartonella also stimulates the production of protein tyrosine phosphatases (PTPs). PTPs are a group of enzymes that are key regulatory proteins for controlling cell growth, proliferation, and transformation. PTPs stimulate the movement of bone-marrow-derived endothelial progenitor cells to infected sites and their transformation into endothelial cells. They also increase the amount and activity of VEGF, stimulating endothelial cell growth. Pervanadate, which is a pharmaceutical tyrosine phosphatase inhibitor, neutralizes this action of bartonella and decreases VEGF activity. *The use of any PTP inhibitor, herbal or otherwise, will decrease VEGF activity.*

Bartonella also increases the expression of extracellular-signalregulated kinase 1 and 2 (ERK-1 and ERK-2) and phosphoinositide 3-kinase (PI3K). Both of these enzymes are also involved in cellular functions such as cell growth and division, proliferation, differentiation, and survival. They also play strong roles in the endothelial cell proliferation (angiogenesis) that the bacteria stimulate. *Inhibitors of ERK-1,*

ERK-2, and PI3K have been found to stop endothelial tube sprouting and hyperplasia as well as IL-8 chemotaxis. Inhibition of PI3K has been found to stop endothelial cell migration, in consequence helping to prevent the formation of new capillaries.

What the bartonella bacteria do is subvert part of the human immune system through the use of their particular cytokine cascade. They use it to stimulate the growth and spreading of endothelial cells and new blood vessels. Angiogenesis is complex and involves a number of important steps: proliferation of new endothelial cells, their migration to new locations, and their reorganization into new forms through rearrangement of their actin cytoskeletons thus turning them into capillaries. The overproduction of E-selectin makes the surrounding tissues more porous so that the new capillaries can spread more easily through the surrounding tissues. In consequence, the endothelial cells enlarge and hyperproliferate and there is a pathological sprouting of capillaries throughout the adjacent tissues.

Colonies of bartonella bacteria are *always* immediately adjacent to the abnormally growing endothelial cells and tend to form an aggregate community there. The degree of endothelial alteration depends on a number of factors, specifically 1) the particular bartonella species involved, 2) how many of them are adjacent to the endothelial cells, and most importantly 3) the strength (or weakness) of the immune system.

Some species of bartonella are more potent in stimulating angiogenesis. The more bacteria there are, the more angiogenesis that occurs. The poorer the immune status, the more easily the bacteria can cause angiogenesis and the more of it there will be. *Antiangiogenic substances such as erythromycin have been found to be potently effective in stopping bartonella-caused angiogenesis.* In all cases of a bartonella infection, if you are using pharmaceuticals, erythromycin is indicated as a primary part of the protocol.

The bacteria also stop any tendency of the infected cells to die (antiapoptosis), thus increasing the cells' normal life spans

and interrupting the immune response of causing cell death to eliminate infected cells. This is part of how they keep a chronic infection going.

Bartonellas also stimulate the production of superoxide dismutase (SOD). During bacterial infection white blood cells generate superoxide and other reactive oxygen species (ROSs) to kill the bacteria. Superoxide is very toxic to living organisms, so most organisms make SOD in order to deactivate the superoxide if necessary. SOD is an incredibly efficient enzyme that can neutralize superoxide just as fast as it is produced by white blood cells. Bartonella bacteria stimulate the production of SOD in order to protect themselves from white blood cell superoxide and ROS production.

In essence, bartonellas use a complicated, highly synergistic process in order to increase the numbers of blood vessels and the endothelium that lines them so that they have more living space—and as well, more access to blood, which they need to survive. They use the natural responses of the human immune system to protect themselves from immune attack, hide in difficult-to-reach invasomes that are themselves inside endothelial cells, and produce a number of substances to deactivate various immune responses. Although they are commonly found inside both endothelial cells and red blood cells, bartonella bacteria can also be found on the surface of endothelial cells and within the extracellular matrix attached to fibronectin and collagen during the process of bacterial spread.

Unless stopped by either an ultimately effective immune response (which can take four to six months in the immunocompetent) or an effective intervention, bartonella infections can become chronic, resulting in long-term infection.

SKIN AND CNS INFECTIONS

Bartonella bacteria can sometimes cause nonhealing ulcers on the skin—essentially a surface endothelial cell inflammation. Examination of the ulcer will show tumor-like proliferation of blood vessels, swollen endothelial cells, inflammatory infiltrate with neutrophils and lymphocytes in the dermis and subcutis, and clusters of bacteria in the extracellular matrix

adjacent to the endothelial cells. In essence, the usual endothelial infection process but one that is occurring at the surface of the body rather than in the interior.

These kinds of lesions are sometimes internal—on various organs—but most often are on the surface of the skin. Close examination will show that the bacteria are attached to both fibronectin and collagen within the wound. Fibronectin infection has also been found, in some instances, to be involved in the development of bartonella endocarditis. The primary adhesion molecule (Pap31) that allows bartonella to adhere to fibronectin and collagen can be outcompeted by heparin, in other words, heparin can reduce bartonella binding to fibronectin and help reduce infection. *This is why heparin is sometimes useful in treating bartonella.*

Basically, wherever bartonella bacteria infect endothelial cells, you will see symptoms. Because the brain and central nervous system (CNS) need, like nearly every part of the body, a continual supply of blood, bartonella infection can sometimes occur in those locations as well. This leads to many of the cognitive problems that may occur during bartonellosis. The MMP breakdown of collagen can also cause problems with nerve sheaths in the brain, which will sometimes mimic diseases such as multiple sclerosis. However, the main problem during bartonella infection in the CNS occurs in the nerve sheaths that surround and supply blood to the nerves. Every nerve in the body is surrounded by a sheath of connective tissue called the epineurium, which is filled with blood vessels. When bartonella bacteria infect the endothelial cells in the epineurium's blood vessels, they cause an inflammatory spreading of the endothelial cells in that location. This causes a wide variety of impacts on the nerve itself and produces symptoms that range from tingling to severe pain to cognitive problems that can, again, mimic diseases such as multiple sclerosis.

Infection in the hippocampus can cause memory problems, unexplained rage, even to homicidal levels, and spatial disorientation. Infection in the cerebral cortex causes problems with memory, attention capacity, perceptual awareness, language use, and clarity of thought. Infection of the

hypothalamus can cause problems in body temperature (some people with bartonella feel very cold all the time), interfere with hunger impulses, increase fatigue, and interrupt sleep cycles.

Many of the CNS problems that come from bartonella infection can also be caused simply by the inflammation that the bacteria cause in the brain and CNS itself. Since infection with bartonella causes a specific type of inflammation in endothelial tissues, infection in the brain's blood vessels will cause a type of encephalitis or swelling of the brain. Infection in the meningeal capillaries will cause a type of meningitis, or swelling of the meninges, the protective membranes covering the brain and spinal cord.

Where the inflammation occurs in the brain determines just what kind of cognitive impacts and psychological stresses the disease causes. Headaches, often at migraine levels, are common.

RED BLOOD CELL INFECTION

In many respects, the ultimate target of the bacteria is the red blood cells. They need specific substances from mammal blood to survive and once they have established themselves in the endothelial layers of the blood vessels, they begin seeding new bacteria into the bloodstream. Bacterial seeding takes place every four to eight days, on average every five days, *simultaneously* from every infected site.

Studies have shown that the bartonella organisms that are released into the bloodstream during these intervals tend to be genetically different each time. In other words, the bacteria are developing unique strains every five days in order to avoid an effective immune response. Early on, large numbers of the bacteria are created and released into the blood. But this peaks between 10 and 14 days postinfection and thereafter begins to decrease until, some two to three months into the infection, normal PCR techniques can no longer detect bacteria in the blood. In essence, the initial acute phase is followed by a slowly developing chronic phase where the numbers of bacteria are generally too low for easy detection. The initial large-scale production of the bacteria enables them to infect

multiple sites in the body and thereafter to keep just enough bacterial presence in the blood to ensure bacterial spread via arthropods.

During their release into the bloodstream in a free state, the bacteria have uploaded specific adhesion molecules onto their outer surface that allow them to attract and stick to red blood cells. Once they do, they begin the process of engulfment once more, with, in this instance, a unique twist.

Because red blood cells aren't able to engulf other cells the way endothelial cells do, bartonella bacteria release a compound called deformin that causes a pore to open in the blood cell so that the bacteria can enter inside it. Normally only one or two bacteria attach to and enter each red blood cell. Once inside, they again form a vacuole within which they begin to replicate.

Each red blood cell can only hold a certain number of bacteria without exceeding the capacity of the cell, that is, without breaking open. Bartonella bacteria are very clever and generally limit their red blood cell numbers to eight. The bacteria do occasionally exceed this, causing a few red blood cells to burst open, thus spreading new bacteria through that route. Generally though, once eight bacteria have formed, they stop replicating.

Most bartonella bacteria (except *B. bacilliformis*) rarely kill the red blood cells they infect. They stay in the cells, circulating in the blood throughout the life of the cells. When red blood cells naturally die the bacteria harvest the cell components, or the red blood cells act as bacterial messengers, spreading the bacteria when a biting insect takes a blood meal, thus extracting them from the bloodstream of their current host.

Bartonellas are considered to be hemotropic, that is, specifically attracted to red blood cells. They are attracted to them because they need large amounts of *heme* in order to survive. Our red blood cells' cytoplasm is high in hemoglobin, a major component of which is heme (hence *hemo-globin*). Hemoglobin is an iron-containing molecule that binds oxygen. About two and a half million red blood cells or erythrocytes

are produced in the bone marrow every second. New ones, produced from progenitors, take about seven days or so to form, so production is constant. Excess red blood cells are stored in the spleen—another reason bartonellas like that organ. About 25 percent of our cells are red blood cells, 20 to 30 trillion in all. A complete circuit of our vessel system takes them about 20 seconds; they live for 100 to 120 days before they are scavenged by the body. As the red blood cells come into contact with cells that need oxygen, the oxygen in the blood diffuses through the cell membrane into the cells that need it.

Bartonella bacteria specialize in infecting mammals and interestingly, mammal red blood cells are unique among vertebrates in that they don't contain a nucleus. Neither do our red blood cells contain mitochondria or other cellular organelles. Bartonella bacteria thus have access to red blood cells that contain the most hemoglobin of any animal cells on the planet. In essence, you might say that they are blood-eating bacteria and they have specialized in the kinds of animals on the Earth that make the most potent blood.

Bartonellas have specific plasmids, groups of DNA strands, that allow them to infect specific mammals and each bacterial species tends to specialize in infecting one or a limited group of closely related mammals. When ecosystems are stable, they rarely jump species, unless their primary host is threatened by other mammal incursions. However, these DNA strands are promiscuously exchanged among different bartonella species, leading, especially during ecosystem disruption, to the bacteria successfully infecting different host species. As Vayssier-Taussat et al. (2010, 2) comment, "Such host-restricted pathogens may undergo a spontaneous host switch, which can lead to the evolution of pathogens with altered host specificity. Most human pathogens have evolved this way, and animal-specific pathogens have thus to be considered as an important reservoir for the emergence of novel human pathogens." Studies have found in fact that the *Bartonella* genus is undergoing rapid evolutionary shifts as the bacteria adapt to the increase in human population, human agriculture, and companion animals.

BARTONELLA USE OF HEME

Red blood cells live about four months. As they reach the end of their life span, they are circulated to the spleen, liver, and bone marrow for recycling. These are, as mentioned, the main locations of bartonella bacteria other than the endothelial lining of the blood vessels themselves.

When bartonella bacteria are released into the bloodstream and infect red blood cells they make no distinction between new and old red blood cells. Large numbers of bacteria exist inside old red blood cells as they are moved to the liver, spleen, and bone marrow for recycling. As the cells decompose, the bacteria scavenge heme, which, again, is essential to their survival.

Bartonellas are one of the few bacteria that cannot synthesize heme on their own and their requirement for heme is very high, approximately 100 times higher than *Porphyromonas gingivalis* and 1,000 times higher than *Haemophilus influenzae,* two other heme-hungry bacteria.

Heme is a source of iron for the bacteria and also acts as a potent antioxidant when bound to the outer cell membrane. Bartonella bacteria have specific parts of their cells that bind them to a red blood cell, open the blood cell itself, allow them to enter the cell, degrade hemoglobin molecules to break the heme off from the molecules, and factors that will break the heme apart into its constituent parts so that the bacteria can obtain the nutrients they need, iron among them. Each human erythrocyte contains about 270 million hemoglobin biomolecules. All of them are high in iron. There are about 2.5 grams of iron in the red blood cells, some 65 percent of the total in the body. The bacteria have picked the best source.

The bartonella bacteria in infected red blood cells use enough heme from the cells' hemoglobin molecules to prosper but just enough not to kill the cells or produce anemia (in most cases). The bartonella organisms in old red blood cells, when they are recycled, take the heme as the cells are broken apart in the liver, spleen, and bone marrow. And the bartonella organisms in endothelial cells accumulate heme by attracting

red blood cells to the PMNs that are rolling along the surface of infected endothelial cells.

Activated PMNs, as they roll on the surface of infected endothelial cells, oxidize hemoglobin in the red blood cells to methemoglobin. Methemoglobin is an altered form of hemoglobin in which the iron in the heme molecules is Fe3+ instead of Fe2+. Some of the symptoms of bartonellosis actually come from this process. The amount of methemoglobin produced in the body is directly proportional to the degree of inflammation that is occurring. The amount produced is also directly proportional to the degree and severity of symptoms that people with bartonellosis experience. Normally the percentage of methemoglobin in the blood is only 1 to 2 percent. Higher amounts, such as the amounts generated by bartonella infection, can cause anxiety, headache, dyspnea on exertion, fatigue, confusion, dizziness, tachypnea, palpitations, seizures, and arrhythmias—all symptoms associated with bartonellosis.

The point of this bacteria-initiated process, however, is for the endothelial-bound bartonellas to get as much heme as they need. The activated PMNs on the surface of the endothelial cells induce the endothelial cells to produce heme oxygenase and ferritin. As Balla et al. (1993, 9289) comment, “We believe that the rapid and marked induction by methemoglobin of endothelial heme oxygenase serves as a sensitive assay for the release of free heme from methemoglobin and its subsequent incorporation into the endothelium.” Endothelial cells exposed to methemoglobin actively take up both heme and iron, which, once inside the cell, are then acquired by the vacuole-encased bartonella organisms.

Additionally, those bartonella bacteria that are not existing intracellularly but living extracellularly in the bloodstream scavenge free heme and move heme from point to point, acting as delivery mechanisms for bacterial colonies that need more heme.

LYMPH NODE, SPLEEN, LIVER, AND BONE MARROW INVOLVEMENT

Bartonella bacteria typically invade four parts of the body (though they may infect *any* part of the body's endothelia): the lymph nodes, spleen, liver, and bone marrow. In all of those organs they typically form granulomas. In essence, these are large forms of the cellular vacuoles they create in the endothelia. You might think of them as organ invasomes. And they do the same things that vacuoles do: granulomas are small nodules that wall off bacteria or other foreign substances that the body is unable to eliminate.

The granulomas that bartonella causes are primarily found in the liver, spleen, lymph nodes, and bone marrow—though they can and have occurred in any part of the body. In the literature they might be called any of a variety of names: vacuoles, nodules, lesions, or granulomas. Those that occur in liver tissue tend to be microscopic but in some cases the liver can take on the appearance of Swiss cheese.

Generally, granulomas contain bartonella bacteria, CD4+ T cells (lymphocytes), monocyte-derived CD11b+ cells, epithelial cells, and endothelial cells. In the normal course of bartonellosis granulomas begin to form within six hours, continue to grow in size and number, reaching peak density around 12 weeks postinfection, and clear anywhere from three to eight months later.

The granulomas in the liver are predominantly in the perivascular region, that is, the spaces surrounding blood vessels, and in the intra-parenchymal region, essentially among and within the hepatocytes. One of the reasons that bartonella bacteria are so drawn to the liver is that liver cells (hepatocytes) are a form of epithelial cell. This makes the entire liver itself potential habitat and explains the formation of so many granulomas throughout that organ. In severe infections, often in the severely immunocompromised, the granulomas develop into multiple blood-filled cystic spaces, usually adjacent to the hepatic sinuses. This is usually accompanied by extremely high serum levels of VEGF.

The granulomas in the spleen are very similar to those in the liver, generally microabscesses that can be found throughout

the organ. In some instances the granulomas can be severe enough to cause spontaneous splenic rupture.

In general, the microabscesses in both organs are, early on, surrounded by monocytes. Intermediate lesions actually contain the monocytes. Late lesions contain few or none. Suppuration, a draining abscess, is common no matter their location.

Hepatosplenic involvement of this type is usually accompanied by prolonged fever and abdominal pain over the periumbilical and/or upper quadrant region, sometimes severe. Weight loss, chills, headache, and myalgia may also occur. The erythrocyte sedimentation rate is often elevated. Liver enzymes are generally normal. White blood cell and platelet counts are usually normal or nearly so.

In the lymph nodes, bartonella bacteria are primarily located in the endothelial tissues of the blood vessels, in the macrophages lining the sinuses of the lymph nodes, in nodal germinal centers, in nonnecrotic areas of inflammation, and in areas of expanding and suppurating necrosis. The usual vacuoles in the endothelial cells occur and are filled with bacteria. Some will exist extracellularly in the necrotic tissues.

Interestingly, CD34+ cells are necessary for T cells to enter the lymph nodes and are highly expressed on endothelial cells within the lymph nodes. Infected CD34+ cells are thus always entering the lymph—nodes and system—and allowing bacterial spread in those locations.

During some bartonella infections, especially with *B. henselae,* once the lymph nodes become infected there is a rather severe swelling of the nodes. A granulomatous lymphadenitis occurs, often by suppuration and necrosis. The infiltrate is composed of bacteria, a very high number of B cells, neutrophils, and macrophages. This severe lymph node enlargement occurs primarily from the immigration and proliferation of lymphocytes, primarily B cells. The lymph nodes tend to reach maximum swelling in three to four weeks and it can last for several months.

Granulomas, in general, tend to form in order to enclose bacteria that the body is having trouble eliminating. There the bacteria are sequestered while the immune system works on eliminating them. The granulomas that occur in the lymph during bartonella infection are surrounded by a ring wall composed of dendritic cells and macrophages. Dendritic cells are unique cells that act as messenger cells between the innate and adaptive immune systems. In other words, they focus on bacterial pathogens and, in essence, figure them out. They then begin making antigens that will inform the adaptive immune system how to respond to the infection.

These particular kinds of granulomas can also be found in the bone marrow. In essence the bone marrow will contain numerous small microabscesses or nodules identical to those in the liver and spleen. They can be widely spread throughout the bones. There is often pain associated in the bones at some of those locations. Bone pain is, in fact, one of the primary indicators of a bartonella infection.

Although not present in all cases, a maculopapular rash on the upper body and face is often associated with bartonella granulomas in the bone marrow. The granulomas in the bone marrow are typically epithelioid with a distinct doughnut-ring shape. There is a central lipid vacuole (fat droplet) with a fibrinous outer ring, giant cells, admixed neutrophils and eosinophils, and bartonella bacteria.

HEALING BARTONELLA

Treating bartonella infections, as you might be able to tell from this, is much more straightforward than treating mycoplasma. In essence, three primary things must occur: 1) the endothelium must be protected, 2) the red blood cells protected, and 3) the cytokine cascade interrupted. These three things alone will reverse the infection and most of the symptoms and eliminate the bacteria from the body. If the organs are protected, the immune system enhanced, and the symptom picture addressed everything necessary is then in place to heal bartonellosis.

8

Natural Healing of Bartonella

The Core Protocol and an Extended Repertory

> *Treatment of diseases associated with* B. henselae *remains a challenge, because CSD [cat scratch disease] is resistant to antibiotic therapy, treatment of endocarditis requires aminoglycosides, and treatment of bacillary angiomatosis requires macrolide antibiotics. In this respect, treatment of* B. henselae *infection is instructive, because it emphasizes the fact that the clinical effect of antibiotics on a disease relies not only on antibiotic susceptibility, but also on the bacterial location in the body and the immune status of the patient. Because of this empirical therapy, results have contradicted in vitro tests.*
>
> DIDIER RAOULT,
> "FROM CAT SCRATCH DISEASE TO
> *BARTONELLA HENSELAE* INFECTION"

Once you understand what bartonella does in the body, it is possible to create a treatment plan that will be much more effective than otherwise. It is crucially important, however, to keep in mind that each individual who has the disease will present with slightly, or very, different symptoms. So, the best approach is a core protocol that addresses the underlying dynamics of the disease with additional herbs and supplements to address the particular symptoms of the individual who is ill. This section addresses the core protocol for treating the disease.

Again: This protocol is not considered to be the *only* one effective for treating bartonella. It should be considered a good, solid starting point and then altered as your, or your individual patients', needs make it necessary. Dosages are also

guidelines. They are what we have found to be effective for bartonella for most people but for those who are very sensitive or for those who weigh much less or more than 150 pounds (70 kg), the doses should be altered.

Please understand as well that in general, most bartonella infections will resolve on their own without treatment if the immune system is relatively healthy. However the resolution takes time, anywhere from 4 to 12 months, and during that time the physical symptoms may be severe. In some instances, a long-term, chronic infection takes place. Both short-term and chronic infections can be effectively helped with natural protocols.

Too, the complexity of the disease symptoms in some people, which sometimes include extreme psychological disruption (which itself sometimes includes bouts of unexplained homicidal rage or deeply suicidal despair), demands a great deal of energy, time, and focus. The protocol might have to be subtly altered from month to month as the treatment progresses. For those severely affected by the disease, a focused and very personal treatment intervention is necessary and can take as long as 12 to 18 months before the process is completed. We have seen people who were being regularly hospitalized in psychiatric wards and those who were wheelchair-bound all be helped with a personally focused protocol. Usually it involved regular weekly or bimonthly contact for up to 18 months.

KEEP IN MIND

Bartonella is primarily present in the endothelial lining of the blood vessels, the red blood cells, and several specific organs: the liver, spleen, bone marrow, and lymph nodes. Primary impacts in the body occur in the blood vessels, heart, spleen, liver, bones, and central nervous system. The majority of the most common symptoms occur from damage in these areas. It is important to note that many people are asymptomatic carriers; in other words, they have the disease but do not become ill *unless their immune system becomes depressed*. Supporting immune health, then, is essential.

WHAT THE CORE PROTOCOL IS DESIGNED TO DO

The core protocol is oriented around reducing the cytokine cascade that bartonella causes, protection and normalization of the endothelial lining of the blood vessels, protection of blood cells, protection of the heart, protection of the spleen and liver, support of the lymph system, and immune support and protection. ***Please understand that if you do these things, the organisms cannot continue to survive in the body.*** The use of specific antibacterials is not essential. However, one of the herbs in the protocol, *Sida acuta,* is a very potent systemic, broadly active antibacterial. Several other antibacterials will be suggested if you truly desire to approach the disease through the use of antibacterial substances. All of them will have some degree of activity against bartonella organisms. Nevertheless, the most effective approach for recalcitrant bartonella is *not* antibacterial.

In general, any natural protocol will be most elegant if the herbs and supplements you choose do more than one thing—for instance, if the heart herb you choose also protects endothelial integrity or if the herb for reducing IL-8 production is also good at reducing MMP-9 levels while also increasing immune markers specific for bartonella. The most potent herbs will have impacts across a wide range, affecting various aspects of the cytokine cascade, providing protection to affected organs, *and* addressing a range of specific symptoms.

THE CYTOKINE CASCADE

The main elements of the cytokine cascade that bartonella initiates are increases in NF-κB, TNF-α, IL-8, IL-1β, MMP-2 and MMP-9, VEGF, cathepsin B, PI3K, IFN-γ, EGF, MCP-1, ICAM-1, E-selectin, BepA, Cu-Zn SOD, ERK-1 and ERK-2, HIF-1, and PTPs.

Reducing levels or inhibiting production of NF-κb, IL-8, VEGF, PTP, EGF, ERK-1 and ERK-2, and PI3K have all been found to short-circuit the cytokine cascade, stop endothelial proliferation, and significantly reduce symptoms if not stop them entirely. The most important are the inhibition or

reduction of NF-κb and IL-8 as these are the primary cytokine cascade initiators.

Bartonella bacteria are highly sensitive to CD4+ cell counts. Lower CD4+ levels allow the bacteria to invade the body more easily. Low CD4+ levels also produce significantly stronger symptoms. Bartonellas also specifically target the production of CD4+ cells and reduce their presence in the body. Increasing and protecting these cells is essential.

CYTOKINE-REDUCING HERBS AND SUPPLEMENTS

- **The herbs and supplements that reduce NF-κB are:** bidens, Chinese senega root, Chinese skullcap, cordyceps, EGCG, greater celandine, houttuynia, knotweed, kudzu, luteolin, olive oil, pomegranate, and schisandra.
- **The herbs and supplements that inhibit IL-8 are:** cordyceps, EGCG, isatis, knotweed, NAC, and pomegranate.
- **Those that inhibit EGF are:** berberine, EGCG, ginkgo, and quercetin.
- **Those that inhibit E-selectin are:** ginkgo, knotweed, kudzu, milk thistle, and schisandra.
- **Those that inhibit PTP are:** elder and hawthorn.
- **Those that inhibit ERK are:** Chinese skullcap, cordyceps, EGCG, greater celandine, knotweed, kudzu, and olive oil.
- **Those that inhibit VEGF are:** aralia, berberine, calotropis, Chinese skullcap, cordyceps, cranberry, EGCG, knotweed, licorice, pomegranate, and salvia.

If you then examine the effects of each of these herbs and supplements on the body, their traditional uses, the particular organ systems they protect, and the relevant scientific studies, you end up with a very nice protocol. As you can see, cordyceps, knotweed, EGCG, Chinese skullcap, and pomegranate are all hitting in multiple areas as specific inhibitors of the primary cytokines that have been found to be the primary upstream cytokines during a bartonella infection.

Inhibiting these will, in most instances, stop the majority of symptoms that the infection causes.

THE CORE PROTOCOL

The core protocol consists of three herbal/supplement regimens: 1) cytokine disruption, 2) organ protection, and 3) immune enhancement and support—a distant fourth is antibacterial assault.

The cytokine cascade intervention is provided by *Polygonum cuspidatum* (Japanese knotweed), epigallocatechin-3-gallate (EGCG) with quercetin, and cordyceps. Chinese skullcap, NAC, and vitamin E are also of benefit. Chinese skullcap should definitely be added if you are experiencing CNS problems.

Because of its many actions, I would highly suggest you use pomegranate juice in which to mix the herbal tinctures.

Organ protection is provided by *Sida acuta* for the red blood cells, hawthorn (*Crataegus*) for the heart, milk thistle (*Silybum marianum*) for the liver, red root (*Ceanothus*) for the lymph system and spleen, and EGCG (with quercetin), L-arginine, and Japanese knotweed for endothelial cell protection. NAC, bidens, alchornea, and cryptolepis are also protective of red blood cells. The three latter herbs are also potently antibacterial, broadly systemic, and specific for killing organisms that infect red blood cells as well as protecting red blood cells from infection.

The immune support regimen consists of rhodiola (*Rhodiola*) and ashwagandha (*Withania*). Besides their immune-modulating, adaptogenic, and cytokine-reducing effects, both these herbs specifically increase CD4+ cell counts.

The antibacterial regimen, should you desire to use it, consists of *Alchornea cordifolia,* isatis, and houttuynia. These herbs will help with inflammation and all have a broad range of antibacterial actions. *Sida acuta* is also a broad-spectrum and strongly systemic antibacterial and is broadly active against the Proteobacteria phylum.

Please note: L-arginine is important to consider using during bartonella infection. It has been found to reverse many of the effects of a bartonella infection because it is specifically protective of endothelial cells and function. A number of studies have found that it, by itself, can so interfere with bartonella colonization of endothelial cells that the disease progress is severely hampered.

Most of the herbs and supplements to use for bartonella infection have been covered in chapter 5. I will cover the remaining ones here.

Basic Protocol

Japanese knotweed (*Polygonum*): Tincture, ¼–½ teaspoon 3x daily.

EGCG with quercetin: 800 mg EGCG plus 1,200 mg quercetin daily.

L-arginine: 500–1,000 mg 3x daily.

Cordyceps: Tincture, ¼ teaspoon 3x daily; or powder, 1 tablespoon 3x daily; or capsules, 2,000 mg 3x daily.

Sida acuta: 30–60 drops 3–4x daily.

Red root: Tincture, ¼–½ teaspoon 3x daily.

Milk thistle seed: Standardized extract, capsules, 1,200 mg daily.

Hawthorn: Tincture, ¼–½ teaspoon 3x daily.

Rhodiola/ashwagandha combination, equal parts of each: Tincture, ½ teaspoon 3x daily.

Isatis/houttuynia/alchornea combination, equal parts of each: Tincture, ½ teaspoon 3x daily.

Pomegranate juice throughout the day.

Vitamin E (alpha-tocopherol): 200 IU or 150 mg daily (optional).

Add to the Basic Protocol, Based on Symptoms

With severe brain/CNS involvement:

1. Chinese skullcap tincture, ¼ teaspoon 3x daily, plus …
2. Greater celandine tincture, ¼ teaspoon 3x daily, plus …
3. Kudzu root tincture, ¼ teaspoon 3–4x daily.
4. N-acetylcysteine may also help, 2,000 mg 2x daily (once in the morning and once before bed), as will …
5. Motherwort tincture, ¼–½ teaspoon up to 6x daily.

With hypoperfusion of the brain:

1. Ginkgo tincture, ¼ teaspoon 3x daily.

With neural pain:

1. Greater celandine tincture, ¼ teaspoon 3x daily, plus …
2. Kudzu root tincture, ½ teaspoon 3–4x daily.

With anxiety/hysteria:

1. Pasque flower tincture, 10 drops each hour as long as necessary, and/or …
2. Motherwort tincture, ¼–½ teaspoon up to 6x daily, and/or …
3. Coral root tincture, 30 drops (one full dropper) up to 6x daily, and/or …
4. Chinese skullcap tincture, ¼ teaspoon 3x daily.

With extreme fear:

1. Chinese skullcap tincture, ¼ teaspoon 3x daily, and/or …
2. Vervain tincture, 30 drops up to 6x daily.

With sleep disturbance:

1. Melatonin liquid, taken according to the manufacturer's directions, 1 hour before bed, and/or …
2. Ashwagandha tincture, ½ teaspoon 1 hour before bed, or ashwagandha powder or capsules, 1 gram 1 hour before bed, and/or …
3. Chinese skullcap tincture, ¼ teaspoon 3x daily, and/or …
4. Motherwort tincture, ¼ *ounce* (yes, that is right) in liquid just before bed (if the melatonin does not help).

With severe fatigue, use the following for 6 months:

1. Eleutherococcus tincture (Herb Pharm formulation), ¼ teaspoon every morning, plus …
2. Rhodiola tincture, ¼ teaspoon 3x daily, plus …
3. Schisandra tincture, ¼ teaspoon 3x daily, plus …
4. Motherwort tincture, ¼ teaspoon 3x daily, and …
5. Fermented wheat germ extract, if you can afford it.

With unproductive cough:

1. Bidens tincture, ¼ teaspoon 3–6x daily.

With *severe* anemia or red blood cell lysis:

1. *Sida acuta* tincture, increase dosage to ½ teaspoon 3–6x daily until condition resolves, plus …
2. N-acetylcysteine, 4,000 mg 2x daily until condition resolves, plus …
3. Bidens tincture, ½ teaspoon 6x daily until condition resolves.

With wasting (i.e., severe weight loss):

1. Fermented wheat germ, 9 grams daily (best choice), and/or …
2. Shiitake mushroom, powdered or as food, 6–16 grams per day. A pure extract of lentinan can also be used, at 1–3 grams per day.

For detoxification and help with Herxheimer reactions:

1. Zeolite: liquid, 15 drops 3–4x daily; or powder, 2 heaping teaspoons daily; or three 00 capsules 3x daily.

For breaking up biofilms (if you must):

1. NAC, 4,000 mg 2x daily, and/or …
2. Greater celandine, ¼ teaspoon 3x daily, and/or …
3. Royal jelly (contains decanoic acid, which will help disperse biofilms), 1 teaspoon 3x daily.

A FINAL MATERIA MEDICA

Here is a bit about a few of the herbs and supplements that were not covered in the mycoplasma section.

Alchornea (*Alchornea cordifolia*)

There are about 60 species in the *Alchornea* genus, and six indigenous to Africa, of which *Alchornea cordifolia* is the main medicinal species (*A. laxiflora* is a reliable substitute).

Product warning: Unfortunately a number of websites and companies are listing scientific studies on the activities of *Alchornea cordifolia* under an entirely different plant—*Alchornea castaneifolia.* This is irritating. *A. castaneifolia* is somewhat popular among the entheogenic crowd and the Internet has scores of sites selling it under the identifier *iporuru* or some version of that name. Regrettably, most of the sites selling *A. castaneifolia* indicate that it has the same actions as *A. cordifolia* and point to studies on *A. cordifolia* to prove it. This just isn't accurate. The plants are **not**, *I repeat not,* interchangeable.

Alchornea is a very good systemic antibiotic herbal medicine. It is antimalarial, antibacterial, antimicrobial, antiprotozoal, antifungal, anti-amoebic, amoebicidal, trypanocidal, anthelmintic, anti-inflammatory, antianemic, and antidiarrheal. It relaxes bronchial tissues, relaxes smooth muscle tissue, is a good antioxidant, has antitumor activity, is antiseptic and somewhat antiviral, and has antidrepanocytary action, whatever that is. The herb should be considered in treating a number of Lyme coinfections: babesia, mycoplasma, bartonella.

The herb is active against a decent range of microbial organisms including *Plasmodium* spp., *Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Proteus vulgaris, Streptococcus pyogenes, Bacillus subtilis, Helicobacter pylori, Salmonella typhi, Shigella flexneri, Salmonella enteritidis,* enterohemorrhagic *E. coli, Proteus mirabilis, Klebsiella pneumoniae, Entamoeba histolytica, Babesia* spp., *Aspergillus* spp. It is particularly good against Gram-negative bacteria.

Alchornea cordifolia is widely used throughout every region of Africa in which it grows. It is used for urinary, respiratory, and gastrointestinal disorders, for asthma and cough, as a wash for eye infections, powdered for ringworm

and other skin infections, and as an anti-inflammatory. It is used for yaws, chancres, wounds, ulcers, dental caries, toothache, malaria, as a carminative, for its antitumor actions, and for conjunctivitis. It is used for urogenital infections, gonorrhea, hemorrhoids, constipation, TB, as an anodyne, diuretic, emmenagogue, blood purifier, tonic, for chills, fever, headache, myalgia, rheumatism, snakebite, thrush, sore throat, leprosy, jaundice, edema, worms, dysentery, diarrhea, epilepsy, anemia, tachycardia, respiratory problems, mouth ulcers, enlarged spleen, postpartum hemorrhage (topical), amoebic dysentery, trypanosomiasis, buccal ulceration, bronchitis.

There have been a number of good scientific studies on the plant and its activity against resistant and nonresistant bacteria, especially those in the same phylum as bartonella. It has shown activity as strong or stronger than many antibiotics. I think one of its real strengths is that it is highly protective of red blood cells. From deep examination of its uses and its impacts in controlled studies, alchornea appears to be a hemotonic, hemoregenerator, and hemoprotectant. The herb does have a long history of use in treatment for anemia, malaria, sickle cell anemia, and trypanosomiasis (a.k.a. African sleeping sickness), which is also a parasitic disease of the bloodstream.

Sickle cell anemia is a genetic disease resulting from a mutation in the hemoglobin structure. The cells undergo alterations, ending up as a sickle shape rather than round. This reduces the cells' ability to carry oxygen and starves the body of enough oxygen to function. About 25 percent of people in sub-Saharan Africa have the disease, which is passed from parent to child genetically; half of those in whom the disease becomes active die before the age of five, about 60,000 in Nigeria alone each year. Traditional healers have used *Alchornea cordifolia* for centuries in the treatment of the disease, and recent scientific study has found it highly effective. Essentially the plant prevents sickling of the cells (antidrepanocytary activity) and reverses cells that have already transformed. Of all the plants tested for sickle cell treatment, *A. cordifolia* has been found the most potent. In Lagos a relative, *A. laxiflora,* has shown the same activity. The

use of the herb reduced sickling by 85 percent and reversed 69 percent of sickled cells. The pharmaceutical treatment approaches normally used for sickle cell anemia are highly toxic but researchers commented that with this herbal preparation “toxicity … is not a problem.” The herb is sold as a standardized product, as a tea or capsules, in Lagos and called Cellod-S. Good outcomes have been reported in clinical practice.

The research on *Alchornea laxiflora* is limited but both its traditional use and the studies that exist seem to confirm that its actions are very similar to those of *A. cordifolia*. It grows in the same ecoranges and is considered interchangeable by the traditional practitioners. In vitro studies have found that the plant has anticonvulsant and sedative actions (in vivo studies have found this action in *cordifolia* as well) and is strongly antioxidant, anti-inflammatory, antimicrobial, and antibacterial against both Gram-positive and Gram-negative bacteria. The chemistry of the plant is very similar to *A. cordifolia*.

The herb is widely disseminated within the body and shows strong impacts in the brain and CNS. It has a number of potent effects in the spleen. It generates a lymphoproliferative effect on naive murine splenocytes and thymocytes and modulates the effects of the phagocytic and lysosomal enzyme activities of murine macrophages. It increases murine phagocytosis and intracellular killing capacity. Lysosomal acid phosphatase activity of peritoneal macrophages increased significantly.

Of 42 plants tested in one study, *Alchornea cordifolia* was found to have the most potent antioxidant effects. In vitro study found that the plant was highly protective of rat liver against hepatotoxins. In vivo study in mice found the same.

There have been a number of in vivo studies that have found the plant to have strong anti-inflammatory activity and to be very effective in the treatment of induced edema in rats. In vitro studies have found *Alchornea cordifolia* strongly anti-inflammatory by inhibiting human neutrophil elastase and superoxide anion.

Dosage

Studies have shown that a tea of the plant takes about three hours to really begin getting into the blood and it tends to hit peak presence one to two hours after that depending on the dose; dosage presence lasts about four hours. However, I suggest the use of a tincture.

Tincture: Take ¼ teaspoon of the tincture every 4 hours.

Side Effects and Contraindications

None noted, and no toxicity has been found for the plant, nor are there reports in the literature or by traditional practitioners of side effects, however large doses may have a sedative or depressant effect on the central nervous system.

Herb/Drug and Herb/Herb Interactions

None noted, however large doses should not be taken along with CNS depressants or sedatives.

L-arginine

L-arginine is an important amino acid normally present in the body. Its levels can drop during many bacterial infections, including those from bartonella and mycoplasma. L-arginine is a crucial amino acid, needed for the replication and division of cells, protection of endothelial integrity, healing of wounds, healthy immune function, and proper hormone activity. It is strongly protective of bones and helps repair bacterial damage to them. It significantly decreases the amount of time needed for wounds to heal.

L-arginine is important to use during bartonella infections in that it strongly protects the endothelial cells from the kinds of damage the bacteria cause. It reduces the cytokine cascade the bacteria initiate and stops them from creating more habitat. Researchers have found that the use of L-arginine can counteract the majority of detrimental effects that occur.

Dosage

One or two 500 mg capsules up to 3x daily.

Side Effects and Contraindications

L-arginine should be avoided in cases of shingles or herpes as it can exacerbate the outbreak. L-arginine will not usually

initiate an outbreak but existing viruses can use arginine to enhance their replication.

Supplement/Drug Interactions

L-arginine can affect blood sugar levels and should be used with caution if you are diabetic. It can also lower blood pressure and so should be used with caution if you are taking blood pressure medications.

Hawthorn (*Crataegus oxyacantha*)

Hawthorn is a member of the rose family. The berries of the hawthorn bush (and sometimes the leaves and flowers) have been used as a heart tonic for at least 2,000 years in Western medicine and for a bit less than 700 years in China. They are specific for nearly every manifestation of heart disease: atherosclerosis, cardiac arrhythmia, congestive heart failure, hypertension, and peripheral vascular disease. In vivo studies have found that the herb lowers blood pressure, increases blood vessel dilation throughout the body, lowers cholesterol levels in the blood, and is powerfully antiarrhythmic, slowing and normalizing heartbeat.

In vivo and in vitro studies have shown that hawthorn increases both the amplitude of heart contractions and its stroke volume. Studies also show that if blood pressure is too low, hawthorn raises it; if it is too high, hawthorn lowers it. It is in fact a normalizer of blood pressure and a regulator of blood flow within the body.

Dozens of clinical trials have been conducted with hawthorn extracts on thousands of people with heart disease. All have confirmed the herb's remarkable effectiveness.

In one study, 300 mg of the dried leaf was taken daily in a placebo-controlled, double-blind trial of 46 men with angina. After four weeks angina had been reduced in all patients by 86 percent. In another study 78 people with chronic heart failure were given 600 mg daily of hawthorn for eight weeks. Exercise tolerance significantly increased; heart rate and blood pressure both significantly decreased. And still another study showed that 87 percent of participants in a hawthorn trial experienced lower cholesterol levels and 80 percent had lower

triglycerides. All experienced lower blood pressure and more dilation in coronary vessels.

In another trial, 1,011 people were given a standardized extract, 900 mg, for 24 weeks. A significant improvement was seen in exercise tolerance, fatigue levels, palpitation, and dyspnea. Ankle edema and nocturia were reduced by 83 percent. A more stable heart rate and reductions in blood pressure were common. A significant reduction in the number of people with ST depression, arrhythmia, and ventricular extrasystole was seen.

Part of the reason that hawthorn reduces cholesterol is that it literally repairs the cellular structure of blood vessel walls. This makes it particularly useful during bartonella infections; it is synergistic with knotweed.

Hawthorn contains *procyanidins,* a flavonoid complex similar to those found in bilberry (anthocyanosides) and pine bark and grape seed (proanthocyanidins). Procyanidins protect collagen fibers from damage, increase their elasticity, and reinforce the cross-linking of collagen fibers to make them stronger and hence make the blood vessels less prone to cracking. Procyanidins increase intracellular vitamin C levels (which is necessary for collagen synthesis), stimulate circulation to peripheral blood vessels, are potent antioxidants, and are strongly anti-inflammatory. They also lower cell membrane permeability and help protect cellular integrity. Like proanthocyanidins, procyanidins promote insulin secretion by the pancreas and inhibit sorbitol accumulation within cells. Both sorbitol, a by-product of glucose metabolism, and glucose naturally damage blood vessel walls and cellular tissues if they are not properly processed by the body. It is, in fact, the increased sugar concentration of the blood that causes many of the circulatory problems suffered by diabetics. Hawthorn protects the vessels by increasing their strength and integrity while reducing substances in the blood that are caustic to vessel structure.

Hawthorn also has a direct effect on the diameter of blood vessels and arteries, causing them to dilate. This increases the oxygen being received by the heart. Hawthorn also changes

the rhythm and pattern of the heartbeat. The heart beats more slowly, the beats last longer, and the power is increased. The longer the herb is used, the more healing occurs in vessel walls and the more toned the muscle of the heart becomes.

Hawthorn does have some cytokine-inhibitory actions. It inhibits TNF-α, IL-6, nitric oxide, and protein tyrosine phosphatase.

Dosage

Capsules: 120–900 mg of the herb daily; tincture: ¼–½ teaspoon 3x daily.

The dosage range in most clinical studies has been from 120 to 900 mg daily. Most of these have used nonstandardized (i.e., raw herb) extracts, either in capsules or as an alcoholic tincture. Some practitioners are suggesting that the extracts be standardized for 1.8 percent vitexin-4′-rhamnoside or 10 percent procyanidin content. I think that a bit of overkill; the herb seems fine all on its own.

Side Effects and Contraindications

Hawthorn is a food-grade herb; it is tremendously safe. It is about as dangerous as its close relative apples. An incredibly tiny number of people have experienced headache, nausea, and palpitations from the herb.

Herb/Drug and Herb/Herb Interactions

The main problem is that hawthorn can lower blood pressure, so if you are taking blood pressure medications, caution is indicated. It may enhance the actions of digoxin. The herb is additive in its effects with knotweed and motherwort. Just take care if you are mixing the herb. Don’t stand up suddenly as you might experience light-headedness.

Stand s l o w l y.

Milk Thistle Seed (*Silybum marianum*)

Milk thistle has a wide range of actions, much of it on the liver. It is a hepatoregenerator, hepatoprotective, hepatotonic, antihepatotoxic, choleretic, anticholestatic, anti-inflammatory for both liver and spleen, and immunostimulant.

Milk thistle is strongly protective of the liver from the deleterious effects of microbial pathogens and chemical toxins. It stimulates the regeneration of damaged liver tissue and will tonify, restore, and normalize liver function. It will reduce liver and spleen inflammation and is particularly useful in combination with red root. It stimulates bile production and flow. It will enhance supportive immune functions, especially the stimulation of IL-4, IL-10, and interferon-gamma. All these will help counteract the effects of bartonella infection.

Milk thistle does reduce a number of cytokines as part of its actions. It inhibits TNF-α, NF-κB, E-selectin, hydrogen peroxide, and c-JNK.

It is specifically indicated in cirrhosis or severe liver impairment, acute or chronic hepatitis, elevated liver enzymes, bile insufficiency, liver or spleen inflammation, feelings of abdominal pressure, fatigue, poor appetite.

Milk thistle is one of the most potent herbs for protecting the liver against hepatotoxins and helping damaged liver tissue to regenerate. It is also the most extensively studied in clinical trial. The major active constituent is believed to be silymarin, which is found only in the seed and pericarp. Silymarin is actually a compound comprising three separate constituents of the herb. Milk thistle is also high in a number of other constituents including betaine, the primary constituent of beets.

Milk thistle is the primary contribution from Western herbal medicine in the treatment of acute liver disease. The herb was well recognized at least 2,000 years ago (then called *Cardus marianum*) for its efficacy in promoting bile flow, relieving hepatic stagnation, and, in folk use, as a treatment for mushroom poisoning. It enjoyed a resurgence in the eighteenth and nineteenth centuries when it was considered specific for spleen and liver inflammation and disease, faded, then resurged again through the research of German botanico-physicians in the 1960s. The research done since then firmly supports milk thistle as one of the most important herbs in the treatment of acute liver disease.

Milk thistle and its constituent silymarin have been extensively tested in human trials for many years. Human trials have followed from as few as six patients to as many as 2,000 for up to four years. All have found the herb useful.

The trials have found that in cases of chronic alcoholic liver disease, toxic liver damage, type II hyperlipidemia, and "fatty liver," use of the herb enhanced immune function (T-cell and CD8+ counts were raised); symptoms of tiredness, abdominal pressure, poor appetite, nausea, itching were relieved; superoxide dismutase activity of white and red blood cells increased; significant improvement in liver function occurred; total cholesterol levels decreased; there was normalization of serum transaminases and BSP (sulfobromophthalein) retention; ALT and AST levels decreased; serum total and conjugated bilirubin levels decreased; gamma-Gt and LAP values normalized; a marked decrease in triglycerides occurred; there was improvement in inflammation and toxic and metabolic-induced lesions verified through biopsy; and there was major improvement in liver enzyme activity.

There have been numerous clinical trials focusing on the use of milk thistle in treating hepatitis and cirrhosis. In hepatitis B trials there has been marked improvement of hepatic dysfunction and the disappearance of HBsAG (the surface antigen of hepatitis B virus) after treatment. Three trials focusing on acute hepatitis found shortened treatment time as determined by ALT levels; improvement of serum levels of bilirubin, ALT, AST; and much faster return of biochemical values to normal than with placebo. Nine studies focusing on chronic hepatitis found significant improvement in patient population, normalization of liver function as determined by biopsy, and relief of bloating, abdominal pressure, weakness, nervousness, insomnia. In general, the average time necessary for improvements to be seen in treating hepatitis was 30 to 40 days.

Eleven studies focusing on cirrhosis observed longer mortality rates; significant improvement in liver function tests (especially AST, ALT, and serum bilirubin); regression of inflammatory changes and regression of toxic and metabolic-induced lesions; significant improvement determined by liver

cell permeability, metabolic efficiency, and excretory function; and the reduction of symptoms such as bloating, insomnia, abdominal pressure, and increased body weight.

Perhaps the most impressive studies of the actions of milk thistle have been in cases of poisoning with *Amanita phalloides* mushrooms. These mushrooms contain one of the most potent liver toxins known—phalloidin. A number of interventions in poisoning cases in Germany found that milk thistle protected the liver from the action of the toxin and reversed the damage to the liver. Optimum results occurred if the poisoning cases were treated within 48 hours. Deaths were reduced from 50 percent to 10 percent.

Dosage

I strongly prefer the use of standardized milk thistle during any disease condition. I feel the seeds themselves are fine for general tonic use, not so much so if you already are ill.

Standardized tincture: standardized to somewhere around 80 mg silybum flavonoids, 40 drops 3x daily; standardized to 140 mg silybum flavonoids, 25 drops 3x daily.

Standardized capsules: 1,200 mg daily just before bed.

Side Effects and Contraindications

Milk thistle is a food-grade herb. It is about as dangerous as potatoes. An incredibly tiny number of people have experienced GI tract upsets of various sorts from it.

Herb/Drug and Herb/Herb Interactions

None that I know of.

9

A Very Brief Look at Treating Simultaneous Mycoplasma and Bartonella Coinfections

Some Final Considerations for Clinicians

An illness is like a journey to a far country; it sifts all one's experience and removes it to a point so remote that it appears like a vision.

SHOLEM ASCH

Concealing an illness is like keeping a beach ball under water.

KAREN DUFFY

You can see, from an examination of what these bacteria do in the body, that there is some degree of overlap in what they do during infections. They are definitely going to be synergistic with each other if someone is coinfected with both of them. Because of their similarities, they will hit heavily in several systems, most especially the spleen, red blood cells, and brain/CNS. The impact on the immune system will also be severe, especially if function is low to begin with.

During such a double infection it is very important to monitor spleen (and lymph system) health and function and to look for signs of red blood cell depletion (breathlessness, anemia) and CNS/brain difficulties. Energy levels will most likely be extremely low; this will have to be addressed.

Red root (or poke root) has to be used to help protect the spleen; this is crucial. The spleen will tend to be enlarged and congested. There is a strong chance that granulomas will occur in such a double infection and this will exacerbate the potential for splenic rupture. Red root is a potent anti-inflammatory for

the spleen. It will help reduce the inflammation, reduce the likelihood of rupture, and also help protect the lymph nodes and keep that system clear of congestion.

Red blood cell protection is fairly straightforward but you have to monitor dosages closely. The sida doses need to be worked with carefully as they can lead, if too high, to a resumption of symptoms that had seemed resolved. If so, just back off until they stop and keep it at that dose. I would definitely add NAC to any protocol at this point for its support of red blood cells, and I would seriously consider the use of alchornea and bidens tinctures.

The brain/CNS support is perhaps the most important as mental dysfunction can be extreme. It takes some effort and focus but a lot can be accomplished in this area by the use of CNS herbs, especially greater celandine, lion's mane, and Chinese skullcap. Kudzu won't hurt either.

Psychologically calming herbs are essential: pasque flower, coral root, motherwort, and Chinese skullcap (vervain has also shown a lot of very good effects). The regular use of pasque flower tincture over a few weeks can seem almost miraculous in its reduction of psychological hysteria. Motherwort will relax the musculature if it is a regular part of the daily intake, thus reducing the physiological holding patterns the fear has generated. Chinese skullcap is a unique blend of the actions of both of those herbs, strong as neither but with a deep penetrating blend of the two. And coral root … well, if someone is falling apart, there is nothing that will help more over time. And, of course, all these herbs have profound effects in the brain and CNS and will help reduce inflammation and protect neural structures themselves.

But most importantly, human contact is essential.

The fear that occurs from severe CNS/brain malfunction in people with these infections can be overwhelming. And it can be tremendously exacerbated if powerful rage is being stimulated—for there is almost no supportive place to work with such rage in the American culture, and most healers are terrified of it themselves. Nevertheless, it has to be addressed, and not merely by medicating the person or redefining their

behavior in some fashion ("You seem to have a lot of anger issues"). They actually need a safe place to express it, to someone who can go into that territory with them, while at the same time the hippocampal functioning (and damage) is being modulated through the herbs they are taking. Such modulation takes time and the person doing the modulating really does need to be the person helping with the rages—you can actually *see* the alterations occurring as you work with both the herbs and the person and adjust what you are doing accordingly. The American tendency to use psychotropic medications to submerge these kinds of rages (which will do nothing to heal hippocampal damage) is absolutely the worst thing to do and should *only* be considered *if* there is imminent threat of physical harm from the rage being acted out. And such use should be short term, only to stabilize the situation so that there is time for whatever protocol you are using to really begin to heal the damage. Remember: if *you* are terrified of the territory, you will only exacerbate *their* fear. (The lack of student training by nearly all schools of healing in dealing with the psychological dimensions of illness is, in my opinion, malpractice of the most egregious sort. Nevertheless, *you* don't have to settle for what you didn't get.)

And while you are working with those who are infected with these kinds of bacteria, keep in mind the terrible isolation that often accompanies these infections. If the illness has substantial CNS impacts, the people tend to lose most of their friends; their families, often in a short period of time, are at wit's end, having neither the emotional resources nor the understanding to cope with what is happening. The sense of isolation that develops can be soul destroying. It is crucial that, if you are working with such a population, you be able to be emotionally present with the person, spend as long as necessary to help them feel companioned, and continue to have regular contact, usually several times a week, throughout the process. (Limits, of course, will have to be set as well; the neediness levels are extreme.) If you have been taught to keep an emotional distance from your clients, then you should not work with this population. They *need* human contact—shouldering them off on a therapist is *absolutely not* a productive approach. It is useful *only* as an adjunct to your

own work with the person. *You* have to be the primary physician.

Massage is often very helpful and supportive in helping reduce the sense of isolation. ***Note:*** Swedish *only*—in no way should deep tissue work of any sort be attempted nor should the work be a hands-off energy style. *Touch* is essential: loving, caring, gently stroking touch.

It is time for our Western healing modalities to abandon the dated and not terribly effective approaches instilled in our schools of healing from the late nineteenth and twentieth centuries.

There is no reason so many people must remain in the dark or in so much pain.

10

What the Future Holds

Until man duplicates a blade of grass, Nature can laugh at his so-called scientific knowledge ... it is obvious that we don't understand one millionth of one percent about anything.

THOMAS EDISON

If you are not skeptical of your own skepticism you are not a skeptic but merely someone afraid to believe in anything other than your own sequestered, and very narrow, world view.

THE AUTHOR

We live in interesting times. If you look with any depth at the incidence of emerging and resistant infections over the past 30 years, especially the types of infections many people are calling stealth pathogens, it is clear that our relation to the microbial world is changing very quickly—and not in ways we are likely to enjoy.

We have taken the word of experts about our capacity to control bacteria and their movements into our lives. We have been told that bacteria are not very intelligent, that with the use of science we can defeat bacterial disease completely, we have been told that if we only wait, all diseases will be cured. And so we stopped thinking for ourselves, stopped using our own abilities to perceive, to see what is right in front of us.

One example: the many people who have contracted Lyme or one or more of the many coinfections of Lyme, as well as the many people contracting resistant infections, are much like the canaries in coal mines.

Canaries were taken down into the mines in earlier centuries because they would succumb to the effects of carbon monoxide and methane long before people did. They were in fact members of a group of what are called sentinel animals,

animals that respond more sensitively to environmental dangers and so serve as warnings to people that something dangerous is occurring.

Like the subtle damage caused by environmental disruption, carbon dioxide and methane are invisible, odorless, and tasteless. We don't notice them until it's too late. Emerging and resistant infections are invisible, odorless, and tasteless. But the many people falling ill with them are sentinels to us, informing us that we need to pay attention at a deeper level to what is happening around us.

Our future will increasingly be filled with these kinds of diseases. There is little we can do to stop them from spreading. But we can begin to take charge of our own health, learn about our bacterial neighbors, understand how to approach them and how to treat the diseases they cause. And most importantly, we can learn how to keep our immune health high so that we can find some sort of balance. We can begin to take charge of our own lives. It isn't the easiest thing to do but it sure beats the alternative.

I have to admit, as well, that the more I learn, the more fascinating it becomes to me that so many of the herbs that are useful for these diseases are invasives: Japanese knotweed, kudzu, isatis, houttuynina, greater celandine, *Eleutherococcus spinosus,* bidens, phellodendron, sida, ailanthus. Please understand, if you had to—*if you had to*—you could treat Lyme and all its coinfections, and most resistant bacteria, solely with these invasive plants. (And, perhaps not so surprisingly, many of them are very good edibles. I suspect we will all be getting a bit hungry by and by.)

Instead of trying to eradicate them we should be asking why they are here and what they are doing.

These plants do have many functions in healing ecosystem damage; they also have tremendous potential for healing ecosystem damage in us. But, much like our bacterial cousins, they are overlooked, thought to be merely dangerous un-American illegal aliens that should be eradicated to make our country safe.

That picture of the world isn't going to work much longer. It is time to begin to see what is right in front of us, to begin to rearrange our perceptions of the world around us. Time to respond to what the ecosystems of this planet are telling us. Time to take charge of our own lives and health.

It is a challenge when these kinds of illnesses come into our lives. But we can learn to heal, learn to use the plants that are around us, learn to enhance our own health. And we don't need experts to do it for us.

Perhaps in many ways that is the deep lesson of our time: that the solutions to our troubles are all around us, if only we will look around ourselves and begin to act on what we perceive, if only we stop waiting for Santa Claus, or an expert, to do it for us.

One thing is for sure: stepping outside that expert paradigm opens up a world that is much more vital than the one the experts live in. There really is nothing quite like not being afraid anymore.

I invite you to join us.

APPENDIX

Sources of Supply

Ooooh, look! A flower.

FOUR-YEAR-OLD ON A WALK

The tree which moves some to tears of joy is in the eyes of others only a green thing that stands in the way.

WILLIAM BLAKE

Many of the herbs I have talked about in this book—and, of course, a great many others—grow wild. Even if you live in a city you can find many of them cohabitating with you or only a short drive away. Since many of these herbs are invasives, most people will be glad for you to take them away.

If you need to buy your herbs, the Internet is a good way to seek them. I suggest running a web search for the herbs you are looking for to find the cheapest prices; if you are persistent you can often save half off normal retail.

If you are going to be buying a lot of herbs and you live in the U.S. it makes sense to buy a resale license from your state. The price is often minimal and it will allow you to buy wholesale; most wholesalers will want a resale certificate before they will sell to you.

And, of course, you can grow them yourself. Once established most of the herbs in this book will provide medicine for you and your family forever.

Here are some of the best sources I know of for the herbs in this book. All of them are in the U.S.

Woodland Essence

Kate and Don make wonderful tinctures and medicines and can sell you many of the herbal tinctures that I discuss in this book. If they don't have them, they can probably point you in the right direction.

392 Teacup Street
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www.woodlandessence.com

Horizon Herbs

Richo Cech has spent much of his life learning how to grow common and rare medicinals. He has seeds or young stock for most of the plants in this book as well as great information on how to grow them.

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Footnote

*1 Taxonomists haven’t yet named this species so this is what they call it.

Acronyms Used in This Book

ADP: adenosine diphosphate

AMP: adenosine monophosphate

AP: activator protein

ATP: adenosine triphosphate

ATPase: adenosine triphosphatase

BadA: *Bartonella* adhesion A

Bep: *Bartonella* effector proteins

BMP: bone morphogenetic protein

CCL: CC chemokine ligand

CNS: central nervous system

COX: cyclooxygenase

CRP: C-reactive protein

CSF: colony-stimulating factor

CXCL: CXC chemokine ligand

dNTP: deoxyribonucleotide triphosphate

EGCG: epigallocatechin gallate

EGF: epidermal growth factor

ELAM: endothelial leukocyte adhesion molecule

ERK: extracelluar-signal-regulated kinase

FUO: fever of unknown origin

FWGE: fermented wheat germ extract

GI tract: gastrointestinal tract

GM-CSF: granulocyte-monocyte colony-stimulating factor

HIF: hypoxia inducible factor

HPC: hematopoietic progenitor cell

ICAM: intercellular adhesion molecule

IFA: indirect fluorescence assay

IFN: interferon

IL: interleukin

iNOS: inducible nitric oxide synthase

JAK-2: Janus kinase-2

JNK: c-Jun N-terminal kinase

LOX: lipoxygenase

MAPK: mitogen-activated protein kinase

MCP: monocyte/macrophage chemoattractant protein

MDR: multidrug resistance

MIP: macrophage inflammatory protein

MMP: matrix metalloproteinase

MRSA: methicillin-resistant *Staphylococcus aureus*

NAC: N-acetylcysteine

NF-κB: nuclear factor kappa-B

NGF: nerve growth factor

NK cell: natural killer cell

NT5E: ecto-5′-nucleotidase

PCR: polymerase chain reaction

PGE2: prostaglandin E2

PI3K: phosphoinositide 3-kinase

PKC: protein kinase C

PMN: polymorphonuclear neutrophil

PTP: protein tyrosine phosphatase

RANTES: regulated on activation, normal T cell expressed and secreted

ROS: reactive oxygen species

SAPK: stress-activated protein kinase

SOD: superoxide dismutase

STAT: signal transducer and activator of transcription

Syk: spleen tyrosine kinase

T4SS: type IV secretion system

TGF: transforming growth factor

TIMP: tissue inhibitor of metalloproteinase

TNF: tumor necrosis factor

VCAM: vascular adhesion molecule

VEGF: vascular endothelial growth factor

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A book is the only place in which you can examine a fragile thought without breaking it, or explore an explosive idea without fear it will go off in your face.

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Stephen Harrod Buhner is an Earth poet and the award-winning author of ten books on nature, indigenous cultures, the environment, and herbal medicine. He comes from a long line of healers including Leroy Burney, Surgeon General of the United States under Eisenhower and Kennedy, and Elizabeth Lusterheide, a midwife and herbalist who worked in rural Indiana in the early nineteenth century. The greatest influence on his work, however, has been his great-grandfather C.G. Harrod who primarily used botanical medicines, also in rural Indiana, when he began his work as a physician in 1911.

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