[Note: This material was written as a chapter for the medical text: *Nutrition and Integrative Medicine: A Primer for Clinicians*, edited by Aruna Bakhru, Johns Hopkins University Press, 2018. I don't like John Hopkins very much and withdrew my participation as the restrictions on content and structure grew more onerous. Since I had already given them written permission the chapter still appeared but significantly revised and edited (not by me) to conform with those restrictions (which considerably cheapened the content). The edits demanded were not in accord with standard literary practice which is something I take very seriously. Among the other problems: none of the contributors were paid (which I didn't mind for various reasons but which the Authors Guild rightly frowns upon), more egregious was that each contributor was only given one copy of the book, which retails for $160 (giving the press a return of around $80 per book). This is something I did mind very much and consider insulting and rather piggish. As the Supreme Court once said, "We don't know the definition of piggish but we certainly know it when we see it."]

# ON THE SOPHISTICATION OF HERBAL MEDICINES

Stephen Harrod Buhner

> *In the late 1940s, the successes of Waksman and Schatz (streptomycin) and Duggar (tetracycline) led many to believe that bacterial infections were basically conquered. That conceit led to widespread misuse and outright abuse of antibacterial agents. Nonetheless, we still neither fully understand nor appreciate resistance to antibacterial agents . . . Many important advances in the practice of*

> *medicine are actually at serious risk. Multi-drug resistant bacteria are compromising our ability to perform what are considered routine surgical procedures . . . A ubiquitous phrase encountered in obituaries is "died from complications following surgery," but what is not well understood is that these "complications" are quite frequently multi-drug resistant infections.*
>
> Steven J. Projan, (2008, 417, 410) "Antibacterial Drug Discovery in the 21st Century"

> *The advantages of natural compounds are fewer side effects in comparison to orthodox medical drugs and the production of synergistic effects for a more positive treatment outcome.*
>
> Kitazato, et al. (2007) "Viral infectious disease and natural products with antiviral activity"

Since birth, I have been, as most western peoples have, immersed in a twentieth-century, reductionist, and overly mechanical form of rationality and science. That I was born in 1952, the scion of a powerful medical family which included a Surgeon General of the United States (Leroy Burney) and a President of the Kentucky Medical Association (David Cox), only exacerbated the condition. Indeed, physicians stretch back for more than two centuries in my family. Many of them were quite prominent; some contributed significantly to the development of modern medicine. It will then come as no surprise that from birth I was taught that plant medicines were simply a throwback to an earlier, more superstitious era of healing. I was told that they didn't work very well, that herbalism had, finally, been abandoned, overcome by the

emergence of scientific medicine and healing. I was also taught that, because of pharmaceutical innovations, we were on the verge of a disease free life for the first time in human history. As a later Surgeon General, William Stewart, put it when testifying to Congress, "It is time to close the book on infectious diseases" (Levy, 1992, 3)**.** Unfortunately, the real world, as it often does, has had other plans.

My encounter with those "other plans" awakened me from my certitude, from the map of the world that a reductive medical science had instilled in me. It began, as these things often do, when I became seriously ill. The physicians I consulted could not diagnose what was wrong; nothing they suggested helped. So, I made a rather unorthodox decision. I abandoned technological medicine and began using a plant that grew near my home in the Colorado mountains. Within a few weeks the condition resolved and the picture of the world that I had been given began to crumble.

For the past 35 years I have been working intensively with herbal medicines. In the process I have learned that herbal medicines are not nearly so foolish and unscientific as I was taught they were. In fact, in nearly every country on earth research is overturning nineteenth and twentieth-century biases about both plants and plant medicines. Plant medicines are, in actuality, not simply "raw drugs" but tremendously sophisticated interventives. They are especially good for treating resistant bacterial infections and what many researchers are now referring to as second generation bacteria, i.e., stealth infections. (They are also particularly good at modulating complex physiological processes in order to reduce or eliminate chronic disease conditions.) Stealth or second generation microorganisms include such things as the bacteria that cause Lyme disease (*Borrelia burgdorferi*) and others often associated with them such as babesial parasites.

As Baud and Greub (2011) comment: “These emerging pathogens may represent the tip of the iceberg of a large number of as yet unknown intracellular pathogenic agents.”

This material explores, to the limited extent possible in a single chapter, some of the sophistications of plant medicines as well as why they are so sophisticated. While I will share some of my personal experiences, the majority of the information I cite is taken from open-access, peer-reviewed journals and studies. To begin with, in order to grasp the sophistication of plant medicines, it is essential to understand just what bacteria and plants really are. They are not what the older, reductive, mechanicalistic paradigm has held them to be.

**Paradigm Conflicts**

We live in a time when two fundamental perspectives about the nature of the reality-matrix in which we are embedded are in conflict. One is the older, several-centuries-established and somewhat reductive paradigm of seeing the world as a conglomeration of unrelated parts that can, by dissection, be understood and manipulated. Within this paradigm it is assumed that a human being can stand outside of nature and objectively study it. Nature is, in many respects, considered to merely be a static, unchanging background to the human world. In consequence, there is a widespread belief that we can tinker with that background as we will and that there will be no unexpected side effects if we do so.

In many respects we have, as a species, reached the limits of this paradigm. News reports of ecological instability are published daily. The rise of antibiotic resistant bacteria as a major worldwide problem is only one of the signs of that older paradigm’s inaccuracy.

The second paradigm is quite different. Rather than being centered in the older

Euclidian/Newtonian/Cartesian (ENC) paradigm this emerging paradigm is concerned with nonlinearity/complexity/chaos theory and the related phenomenon of self-organization in biological systems. It is concerned with wholes rather than parts. Human beings are understood to be only one of a large number of ecologically expressed life forms. They are, as are all life forms, inextricably embedded within that whole. Dissection of nature, while known to produce useful understandings, is recognized to be of limited value. Taking apart the watch to understand how it works, as any eight-year-old soon learns, doesn't mean that it can be put back together again.

This second paradigm is slowly supplanting that older paradigm as increasing numbers of negative environmental outcomes occur from the older paradigm's use. Although much emphasis has been put on climate change perhaps nothing has more significance to human beings than the rise of antibiotic resistant bacteria. Within the older ENC paradigm, considered foundational to both medicine and science, it is believed possible to create a pharmaceutical, apply it in practice, and sincerely assert that there will be no environmental repercussions from doing so. It is possible, as well, to believe that we can eliminate all disease. But the more accurate view, grounded in complexity theory and self-organization, reveals a much different picture of the world. Within this more accurate model it is obvious that bacteria would, of necessity, develop resistance to antibiotics, that their learning curve would be exponential not additive, and that, as David Livermore, one of Britain's primary bacterial resistance researchers puts it, "It is naive to think we can win." (Bosley, 2010)

I believe that an understanding of both chaos theory and self-organization are crucial to accurately understand both microbial pathogens and the sophistication of plant medicines.

Regrettably a depth look is beyond the scope of this chapter. This touch on the subject is, of necessity, a light one.

**Self-organization**

Nothing has undermined the older, more mechanical view of the world than spontaneous self-organization and nonlinearity in living systems. As mathematician Steven Strogatz (2003) comments . . .

> *In every case, these feats of synchrony occur spontaneously, almost as if nature has an eerie yearning for order. And that raises a profound mystery: Scientists have long been baffled by the existence of spontaneous order in the universe. The laws of thermodynamics seem to dictate the opposite, that nature should inexorably degenerate toward a state of greater disorder, greater entropy. Yet all around us we see magnificent structures that have somehow managed to assemble themselves. This enigma bedevils all of science today. Only in a few situations do we have a clear understanding of how order arises on its own.*

Such synchrony always begins the same way. As researcher Scott Camazine (2001, 19) puts it, "At a critical density a pattern arises within the system." Thus, when a container is packed with increasing numbers of molecules, at a certain point, *which can never be predicted*, the random motions of the billions and billions of molecules will suddenly show an alteration in behavior. They will spontaneously synchronize, begin to act in concert, actively cooperate, become tightly

coupled together into one, interacting whole. The whole which comes into being at that moment of synchrony exhibits a collective, macroscopically ordered state of being. A unique more-than-the-sum-of-the-parts organism emerges of which the smaller subunits (the molecules) are now only a part. The molecules have *self-organized*. And . . . it just happens. Like water turning to ice – from a simple decrease of one degree of temperature a phase change occurs. Something new comes into being.

And that new thing? Neither its physical nor its behavioral nature can be predicted from a study of its parts – an analysis of the prior state. As Camazine, et al (2001, 11), comment

> *Complexity and complex systems generally refer to a system of interacting units that displays global properties not present at the lower level. These systems may show diverse responses that are often sensitively dependent on both the initial state of the system and nonlinear interactions among its components. Since these nonlinear interactions involve amplification or cooperativity, complex behaviors may emerge.*

There is no linear, additive process that can be reductively used to comprehensively understand how the total system that emerges at the moment of self-organization occurs. Nor is the emerging system predictable in its shape or subsequent behavior. As physicist Paul Davies (1989) comments, nonlinear systems "possess the remarkable ability to leap spontaneously from relatively featureless states to those involving complex cooperative behavior." Or as Michael Crichton (1997) once put it . . .

> *It did not take long before the scientists began to notice that complex systems showed certain common behaviors. They started to think of these behaviors as characteristic of all complex systems. They realized that these behaviors could not be explained by analyzing the components of the systems. The time-honored scientific approach of reductionism – taking the watch apart to see how it worked – didn't get you anywhere with complex systems, because the interesting behavior seemed to arise from the spontaneous interaction of the components.*

The emergent system, at the moment of self-organization, begins to *act* – to have behaviors. And just as a study of the parts of a self-organized whole cannot give a predictive idea of the larger whole's physical expression, so too the study of the smaller parts' behaviors cannot give an idea of the larger system's behavior. As Camazine, et al (2001, 8, 31), note, "an emergent property cannot be understood simply by examining in isolation the properties of the system's components . . . . Emergence refers to a process by which a system of interacting subunits acquires qualitatively new properties that cannot be understood as a simple addition of their individual contributions." Or as systems researcher Yaneer Bar-Yam (1997) puts it, "A complex system is formed out of many components whose behavior is emergent, that is, the behavior of the system cannot be simply inferred from the behavior of its components. . . . . Emergent properties cannot be studied by physically taking a system apart and looking at the parts (reductionism)."

At the moment of self-organization a *threshold* was crossed. On one side there was nothing but randomized molecular movements, on the other is sudden self-organization and emergent behavior. All self-organized systems remain very close to this threshold, just barely on

the self-organized side of the line. It is this dynamic balance point, near the edge of chaos, that makes the system so responsive to the interoceptive and exteroceptive inputs. It allows incredible innovations to occur in self-organized systems.

Michael Crichton (1997) described it impeccably . . .

> *Even more important is the way complex systems seem to strike a balance between the need for order and the imperative for change. Complex systems tend to locate themselves at a place we call "the edge of chaos." We imagine the edge of chaos as a place where there is enough innovation to keep a living system vibrant, and enough stability to keep it from collapsing into anarchy. It is a zone of conflict and upheaval, where the old and new are constantly at war. Finding the balance point must be a delicate matter – if a living system drifts too close, it risks falling over into incoherence and dissolution; but if the system moves too far away from the edge, it becomes rigid, frozen, totalitarian. Both conditions lead to extinction. . . . Only at the edge of chaos can complex systems flourish.*

At the moment of self-organization, the new living system enters a state of dynamic equilibrium. From that point on, the self-organized system retains an elegant sensitivity to that threshold point. It constantly monitors all inputs that touch it, for every input can potentially alter the self-organized state. The system then analyzes the nature of the input and crafts a response that will maintain self-organization. A very simple example of this is juggling.

First there are balls there, juggler here. But once juggling begins something more than the

sum of the parts comes into being. The juggler and the balls become one tightly coupled unit. In that moment the juggler becomes highly sensitized to every tiny perturbation of the balance point. Much more quickly than linear thinking can accomplish, some deeper part of the juggler analyzes minute alterations in ball arcs and crafts a response that keeps the balance point intact.

*Every* living (system, phenomenon, organism) is like this. *Every* one of them exists close to the balance point and every one works, at much greater degrees of complexity than juggling, to maintain that balance. This is done through a tight coupling to both the internal and external worlds.

In self-organized systems the information from the smaller subunit (in this example, the movement of the balls in space and time) travels to the larger whole. The larger system, what you might call the juggler/ball hybrid, remains highly sensitive to the balance point. It takes in information, analyzes it, and alters the juggler's behavior. In other words the system alters its nature to incorporate the balls' movement changes (interoceptive inputs) so that it can keep its self-organizational state intact.

Information from the external world (exteroceptive inputs) is taken in similarly. Floor perturbations which alter how the feet are balanced, the flow of air in the room, comments from the audience, and so on, all affect his stance, orientation, and balance which, in their turn, affect his capacity to keep the balls in the air. That exterior-to-the-system information is taken in and, again, below the level of conscious awareness, behavior is altered to keep self-organization – the homeodynamic balance – intact. This dynamic is ubiquitous in living systems. As James Lovelock (2003) comments, "No one doubts that humans are in thermostasis, yet our core temperatures range from 35 to 40 degrees Centigrade and our extremities from 5 to 45 degrees

Centigrade. This may appear imprecise, but it serves us well.

All living organisms remain extremely sensitive to the environment in which they are embedded. They all engage in highly sophisticated analysis of inputs. Every one of them, when sensing an input that can affect homeodynamic balance, generates a suite of responses and from those responses they *choose* a course of action.

By any useful definition of the term this *is* intelligent behavior. As the the Merriam-Webster dictionary defines it: Intelligence is "the ability to learn or understand or to deal with new or trying situations [or] the ability to apply knowledge to manipulate one's environment."

One of the major problems with the older ENC model of the world is that it routinely defines *real* intelligence as something that humans alone possess. All other organisms are considered to be, in a pyramidal descending order, less intelligent. In many respects most of the problems we are now facing as a species are being generated out of that inaccurate view of the world. Kevin Warwick (2001), a cyberneticist, observes succinctly that, "Comparisons (in intelligence) are usually made between characteristics that humans consider important; such a stance is of course biased and subjective in terms of the groups for whom it is being used."

I realize that to state that all self-organized systems are intelligent is problematical. To then assert that some are much more intelligent than human beings is to directly confront one of the most deeply held beliefs that we humans, and most scientists and physicians, possess. In and of itself, that will alienate many people from the content of this chapter. Nevertheless, it is root to the more holistic view of the world that is now emerging. It is also something that bacterial researchers have been saying for some time.

**Bacterial Intelligence**

Antibiotic resistant bacteria are now one of the (human) world's most serious emerging problems. Although most people have seen news reports about it one time or another, few realize that most if not all of the world's bacterial researchers now assert that within our lifetimes antibiotics will become increasingly useless. Within the next few decades, we face, as many microbiologists have pointed out, the emergence of untreatable epidemic diseases more deadly than any known in history. The problem is that too many antibiotics in too large quantities have been expressed into the world's ecosystems.

In an extremely short period of geologic time the Earth has been saturated with several *billion* pounds of non-biodegradable, often biologically unique pharmaceuticals designed to kill bacteria. Many antibiotics 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 such 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. As bacterial researcher Stuart Levy (1992, 75) comments, "It has stimulated evolutionary changes that are unparalleled in recorded biologic history."

What are these evolutionary changes? At the simplest level, it has stimulated the development of exceptionally sophisticated resistance mechanisms in *all* the planet's bacterial populations. Bacteria have literally begun rearranging their genomes in response. As those genomes shift, bacterial physiology and behavior alters, sometimes considerably. This kind of response is inevitable in any self-organized system. As Francisco Varela, et al (1989), observe, a self-organized biological network

> *will reconfigure itself to an unspecified environment in such a way that it both maintains its ongoing dynamics and displays a behaviour that reveals a degree of inductive learning about environmental regularities.*

As soon as bacteria encounter an antibiotic that can affect them, however minutely, they generate possible solutions. The variety and number of solutions they generate are immense, from inactivating the part of the bacterial cell that the antibiotic is designed to destroy, to pumping the antibiotic out of their cells just as fast as it comes in, to altering the nature of their cellular wall to make them more impervious. Some even go so far as learning to use the antibiotic for food.

The old-style, neoDarwinian, explanation for bacterial resistance, is that when a person takes an antibiotic all the *susceptible* bacteria are killed off but . . . there are always a few that are naturally resistant to the antibiotic. These survive to spread and thus resistance emerges. Occasionally you will also see statements that spontaneous mutations are arising that are naturally resistant to antibiotics; these mutated bacteria survive, have offspring, and thus spread. While there is some truth in that, a deeper look reveals a much different picture. Bacteria literally *remake* their genomes in order to alter their physical form. They then pass this innovation on to other bacteria as well as their own offspring which is, in essence, the inheritance of acquired characteristics, something neoDarwinianism has long held to be impossible.

Antibiotics entered general use in 1946. By 1953, after penicillin use was widespread, 64 to 80 percent of the bacteria had become resistant; resistance to tetracycline and erythromycin were also being reported. By 1960, resistant staph had become the most common source of hospital-acquired infections worldwide. (By 1995 an incredible 95% of staph was resistant to

penicillin.) In response to the 1960 outbreaks, physicians began using methicillin, a *B*-lactam antibiotic. Nevertheless, methicillin resistant staph (MRSA) emerged within a year. In 1968, the first severe MRSA outbreak in hospitals occurred in the U.S. Inevitably, MRSA strains resistant to all clinically available antibiotics (except the glycopeptides vancomycin and teicoplanin) emerged. In 1999, fifty-four years after the commercial production of antibiotics, the first staph strain resistant to all clinical antibiotics had infected its first three people.

Bacteria are the oldest forms of life on this planet and they have developed great sophistication in responding to threats to their well being. Among those threats are the thousands if not millions of antibacterial substances that have existed as long as life itself. The world is, in fact, filled with antibacterial substances, most produced by other bacteria, fungi, and plants. Bacteria learned how to respond to such substances a very long time ago. Or as Steven Projan (2008, 413) of Wyeth Research puts it, bacteria "are the oldest of living organisms and thus have been subject to three billion years of evolution in harsh environments and therefore have been selected to withstand chemical assault." Most of our antibiotics are actually just slight alterations of antibacterial substances already common in the world – substances that bacteria have long been aware of and are highly responsive to.

Bacteria share resistance information with other bacteria in a number of ways. They can do so directly, or simply extrude DNA containing the information from their cells, allowing it to be picked up later by roving bacteria. They often experiment, combining resistance information from multiple sources in unique ways that increase resistance, generate new resistance pathways, or even stimulate resistance forms that are not yet necessary. Even bacteria in hibernating or moribund states will share whatever information on resistance they have with any bacteria that

encounter them. As bacteria gain resistance, they pass that knowledge on to *all* forms of bacteria they meet. They are not competing with each other for resources, as standard evolutionary theory predicted, but rather, promiscuously cooperating in the sharing of survival information. “More surprising,” one research group commented (Salyers, 2008), “is the apparent movement of genes, such as *tetQ* and *ermB* between members of the normal microflora of humans and animals, populations of bacteria that differ in species composition.”

Irritatingly (for standard theory), bacteria appear to be generating resistance to antibiotics we haven’t even thought of yet. For example, after placing a single bacterial species in a nutrient solution containing sub-lethal doses of a newly developed and rare antibiotic, researchers found that within a short period of time the bacteria developed resistance to that antibiotic *and* to twelve other antibiotics they had never before encountered – some of which were structurally dissimilar to the first. Bacterial researcher Stuart Levy (1992, 101) observes that "it's almost as if bacteria strategically anticipate the confrontation of other drugs when they resist one."

In fact, bacteria are acting in concert so well in response to the human "war on disease" that it has led Levy (1992, 87) to remark that "One begins to see bacteria, not as individual species, but as a vast array of interacting constituents of an integrated microbial world." Former FDA commissioner Donald Kennedy (Frappaolo 1986) echoes this when he states that "The evidence indicates that enteric microorganisms in animals and man, their R plasmids, and human pathogens form a linked ecosystem of their own in which action at any one point can affect every other." Or as Lynn Margulis (and Dorian Sagan, 1997) once put it, “Bacteria are not really individuals so much as part of a single global superorganism.”

Bacteria are, in fact, responding socially, as a community. As science writer Valerie

Brown (2010) notes: “In a series of recent findings, researchers describe bacteria that communicate in sophisticated ways, take concerted action, influence human physiology, alter human thinking and work together to bioengineer the environment.”

Bacteria are considered, by those who have deeply studied them, not only to be intelligent but also to posses a sophisticated language and a highly developed social capacity. They are, in fact, not all that different than us. As bacterial researchers Eshel Ben-Jacob, et al (2004), put it

> *Bacteria use their intracellular flexibility, involving signal transduction networks and genomic plasticity, to collectively maintain linguistic communication; self and shared interpretations of chemical cues, exchange of chemical message (semantic) and dialogues (pragmatic). Meaning-based communication permits colonial identity, intentional behavior (e.g. pheromone-based courtship for mating), purposeful alteration of colony structure (e.g. formation of fruiting bodies), detection-making (e.g. to sporulate) and the recognition and identification of other colonies – features we might begin to associate with a bacterial social intelligence.*

Colonies of bacteria, as Ben-Jacob (2003) observes, “have developed intricate communication capabilities, including a broad repertoire of chemical signaling mechanisms, collective activation and deactivation of genes, and even exchange of genetic materials. With these tools they can communicate and self-organize their colonies into multicellular hierarchal aggregates, out of which new abilities emerge.”

Each bacterium, as he goes on to say, "has internal degrees of freedom, informatic capabilities, and freedom to respond by altering itself and others via emission of signals in a self-regulated manner." In a later paper (2006) he expands this considerably by noting that "each bacterium is, by itself, a biotic autonomous system with its own cellular informatics capabilities (storage, processing and assessment of information). These afford the cell plasticity to *select* its response to biochemical messages it receives, including self-alteration and the broadcasting of messages to initiate alterations in other bacteria."

Bacterial researcher James Shapiro (2006), at the University of Chicago, is particularly plain-spoken about how badly we have misunderstood bacteria.

> *Forty years experience as a bacterial geneticist have taught me that bacteria possess many cognitive, computational and evolutionary capabilities unimaginable in the first six decades of the twentieth century. Analysis of cellular processes such as metabolism, regulation of protein synthesis, and DNA repair established that bacteria continually monitor their external and internal environments and compute functional outputs based on information provided by their sensory apparatus. . . . My own work on transposable elements revealed multiple widespread bacterial systems for mobilizing and engineering DNA molecules. Examination of colony development and organization led me to appreciate how extensive multicellular collaboration is among the majority of bacterial species. [Studies] show that bacteria utilize sophisticated mechanisms for intercellular communication and even have the ability to commandeer the*

> *basic cell biology of "higher" plants and animals to meet their own basic needs. This remarkable series of observations requires us to revise basic ideas about biological information processing and recognize that even the smallest cells are sentient beings.*

Shapiro concludes his 23 page paper with this remarkable statement:

> *The take-home lesson of more than half a century of molecular microbiology is to recognize that bacterial information processing is far more powerful than human technology. . . . These small cells are incredibly sophisticated at coordinating processes involving millions of individual events and at making them precise and reliable. In addition, the astonishing versatility and mastery bacteria display in managing the biosphere's geochemical and thermodynamic transformations indicates that we have a great deal to learn about chemistry, physics, and evolution from our small, but very intelligent, prokaryotic relatives.*

Bacteria, in fact, show just the same sorts of complex and sophisticated behaviors that humans do, from language, to sentience, to intelligence, to the creation of cities (i.e., biofilms), to cooperation in groups, to complex adaptation to their environment, to protection of offspring, to species memory handed down through the generations. And, if the definition of tool is extended, as it should be, to the creation of chemicals that are designed to produce specific alterations in their environment – or even the sophisticated, insulated, electrical cables that some bacterial

communities use to heat their cities), their capacities include intelligent tool making.

That they don't have an organ, a brain, similar to the one in our heads, has misled us tremendously. As the molecular biologist Anthony Trewavas (2006, 6) comments . . .

> *Very early on, analogies were drawn between the connections that [bacterial] phosphorylation enables between bacterial proteins and the connections between neurone dendrites in higher animal brains. This led to their description as a phosphoneural network. The properties of these networks include signal amplification, associative responses (cross talk) and memory effects. Subsequent investigation indicated learning and the realization that these simple networks provide individual bacteria with informed decisions.*

And as neuroscientist Peggy La Cerra (2003) relates:

> *The hallmark of animalian intelligence systems is the capacity to predict likely costs and benefits of alternative paths of behavior. This logic is evident in our most ancient ancestors, bacteria. [As an example] E. Coli is a single-cell organism with a single molecule of DNA. This simplest of animals exhibits a prototypical centralized intelligence system that has the same essential design characteristics and problem solving logic as is evident in all animal intelligence systems including humans.*

Neural networks are generated any time a biological self-organization event occurs. And "the computational capabilities," that we recognize as integral to intelligence, as Chakrabarti and Dutta (2002) note, naturally "emerge out of the collective dynamics of the network, which is nonlinear." From that comes, as Trewavas (2006, 8) observes, "Information processing, learning, memory, decision making, choice, predictive modeling, associating memory, sensory integration and control of behavior." These are, as he notes, "all aspects of biological intelligence."

Though the rise of bacterial resistance has begun to stimulate a moderately wide recognition among scientists that microbial intelligence exists – a recognition very much lacking among most physicians and the general populace – it is for the concept of plant intelligence that the majority of scientists retain the greatest disdain.

**Plant Intelligence**

The old paradigm about plants, very common and (unfortunately) still believed by most people, is that plants are "passive entities subject to environmental forces and organisms that are designed solely for accumulation of phososynthetic products." But as Baluska, et al (2006, 31), comment:

> *The new view, by contrast, is that plants are dynamic and highly sensitive organisms, actively and competitively foraging for limited resources both above and below ground, and that they are also organisms which accurately compute their circumstances, use sophisticated cost-benefit analysis, and that take defined actions to mitigate and control diffuse environmental insults. Moreover, plants*

> *are also capable of a refined recognition of self and non-self and this leads to territorial behavior. This new view considers plants as information-processing organisms with complex communication throughout the individual plant. Plants are as sophisticated in behavior as animals but their potential has been masked because it operates on time scales many orders of magnitude longer than that operation in animals. . . . Owing to this lifestyle, the only long-term response to rapidly changing environments is an equally rapid adaptation; therefore, plants have developed a very robust signaling and information-processing apparatus. . . . Besides abundant interactions with the environment, plants interact with other communicative systems such as other plants, fungi, nematodes, bacteria, viruses, insects, and predatory animals*.

As with all self-organized systems, plants continually monitor their internal and external worlds for informational/functional shifts in the relevant fields. This includes such things as spatial orientation; presence, absence, and identity of neighbors; disturbance; competition; predation, whether microbial, insect, or animal; composition of atmosphere; composition of soil; water presence, location, and amount; degree of incoming light; propagation, protection, and support of offspring; communications from other plants in their ecorange; biological, including circadian, rhythms; and not only their own health but the health of the ecorange in which they live. As Anthony Trewavas (2006, 3) comments, this "continually and specifically changes the information spectrum" to which the plants are attending. Trewavas recognizes, as researchers in so many other fields are now doing, that the living organism, in this instance a plant, actually

*chooses* the optimum response from a plethora of alternatives. As he says, potential "responses can be rejected; the numbers of different environments that any wild plant experiences must be almost infinite in number. Only complex computation can fashion the optimal fitness response."

Some plants, such as sundew, are so sensitive to touch, for example, that they can detect a strand of hair weighing less than one microgram (one millionth of a gram) to which they then respond. But what is more revealing is that they can determine with great specificity *what* is touching them. Raindrops, a common experience in the wild, produce no touch response. This kind of mechanosensitivity, which is, in plants, similar to our own, is used much as we use our own: The plants analyze what is touching them, determine its meaning, and craft a response. And that response can involve rapid changes in their genetics and subsequent physical form or phenotype. As McCormack, et al (2006), comment, "Plants perceive much more of their environment than is often apparent to the casual observer. Touch can induce profound rapid responses . . . in *Arabidopsis*, changes in gene expression can be seen within minutes after touch, and over 700 genes have altered transcript levels within 30 min."

Plants, in fact, possess a highly sophisticated neural system – as Charles Darwin noted long ago in his book, *The Power of Movement in Plants*. The "brain" of plants *is* their root system. More accurately, what we are talking about here is their neural network, not the place it is housed – an important distinction. Our neural network is housed in an organ, the brain, but it is the neural network housed in our brain that is important, not the organ that contains it. Plants don't need that organ, their neural network is housed in the soil in which they are rooted. As such there is no limit on the size of a plant's neural network as there is on our own. Some aspen root systems cover hundreds of acres and are many thousands of years old – their neural network

dwarfs the human. Plants do have a "brain," and they always have. As Frantisek Baluska, et al (2004), comment. . .

> *Although plants are generally immobile and lack the most obvious brain activities of animals and humans, they are not only able to show all the attributes of intelligent behavior but they are also equipped with neuronal molecules, especially synaptotagmins and glutamate/glycine-gated glutamate receptors. Recent advances in plant cell biology allowed identification of plant synapses transporting the plant-specific neurotransmitter-like molecule auxin. This suggests that synaptic communication is not limited to animals and humans but seems widespread throughout plant tissues.*

A specific part of the plant root, the root apex, i.e., apices – the pointed ends of the root system – are a combination sensitive finger, perceiving sensory organ, and brain neuron. Each root hair, rootlet, and root section contains an apex; every root mass millions, even billions, of them. For example, a single rye plant has more than 13 million rootlets with a combined length of 680 miles. Each of the rootlets are covered with root hairs, over 14 *billion* of them, with a combined length of 6,600 miles. Every rootlet, every root hair, has at its end a root apex. Every root apex acts as a neuronal organ in the root system. In contrast, the human brain has approximately 86 billion neurons, about 16 billion of which are in the cerebral cortex. Plants with larger root systems, and more root hairs, can have considerably more brain neurons than the 14 billion contained in rye plants; they can even rival the human brain in the number of neurons.

The numerous root apices act as one whole, synchronized, self-organized system, much as the neurons in our brains do. As Baluska, et al (2006, 28-9), comment: The root apices

> *harbor brain-like units of the nervous system of plants. The number of root apices in the plant body is high, and all 'brain units' are interconnected via vascular strands (plant neurons) with their polarly-transported auxin (plant neurotransmitter), to form a serial (parallel) neuronal system of plants. From observation of the plant body of maize, it is obvious that the number of root apices is extremely high . . . This feature makes the 'serial plant brain' extremely robust and the amount of processed information must be immense.*

Plants remain extremely sensitive to environmental inputs. Plants analyze the inputs, then alter both form and behavior in response. As Trewavas (2003) observes . . .

> *Learning and memory are the two emergent (holistic) properties of neural networks that involve large numbers of neural cells acting in communication with one another. But, both properties originate from signal transduction processes in individual cells. Quite remarkably, the suite of molecules used in signal transduction are entirely similar between nerve cells and plant cells. . . . Learning results from the formation of new dendrites, and memory lasts as long as the newly formed dendrites themselves. The neural network is phenotypically plastic and intelligent behavior requires that plastic potential. Plant development is*

> *plastic too and is not reversible; many mature plants can be reduced to a single bud and root and regenerate to a new plant with a different structure determined by the environmental circumstances.*

In other words, if you take the cutting of a plant from one location and plant it in another, as the neural system of the new plant develops in the soil, analyzing its surroundings all the while, it alters, as it learns, the shape and formation of the plant body it develops. This, more effectively, fits it into the environment in which it is now growing. In short, plants possess a highly developed root brain which works much as ours does to analyze incoming data and generate sophisticated responses.

**Chemical Innovation in Plants**

To really understand why plant medicines are so effective in healing practice, it is crucial to understand that plants have been infected by pathogenic organisms for far longer than our species has been emergent on this planet. They can't run, they can't hide, they can't call the doctor. In consequence they have become tremendously sophisticated at identifying the pathogenic organisms that attack them as well as the most effective responses to those attacks. They are the world's best chemists.

As an example, studies have continually found that when plants are being eaten by insect predators they release volatile compounds that will call the *exact* predator of that insect. As Ian Baldwin (2001) at the Max Planck Institute observes, "It's known that tobacco, corn, lima beans, tomatoes, cucumbers, oil seed rape – a whole bunch of different species – give off these signals

when they're attacked by larvae [caterpillars]." As he continues, "Our study demonstrates that the volatile (airborne chemical) bouquet that is released after attack is very complex. Predators are attracted, and laying moths are repelled."

These volatiles are very specific in their chemical structure. They have to be in order to work, even a slight molecular re-arrangement will make them ineffective. Plants, over hundreds of million of years, have learned to create chemicals that perform very specific functions. Among these are the creation of a suite of complex compounds that are very specific for countering microbial infections. But they don't just create antibacterial substances to kill pathogenic microbes. They also create potent anti-resistance compounds as well as synergists that make their compounds more effective. Plants have never used the "silver bullet" approach in the treatment of their infections, presumably because, over time, it doesn't work.

Reductive approaches have, however, applied that "silver bullet" paradigm to the natural world. In consequence, a major thrust of twentieth-century research into plant medicines has been to identify what plant compounds produced the "active" effects. Pharmaceutical companies sponsored much of this research – they wanted to identify useful compounds from which to generate new drugs, including antimicrobials. One of the more famous findings, generated out of a desire to counter resistance in malarial organisms, is the compound artemisinin, found in *Artemisia annua*. Relatively recently, artemisinin was isolated then semi-synthetic analogs were created and widely used to treat both resistant and non-resistant malarial infections. Unsurprisingly, within a short period of time the malarial parasite began to develop resistance to these compounds, just as they have done with pharmaceuticals. The semi-synthetic analogs were patentable, which artemisinin was not, but the molecular alterations also increased the

bioavailability of the isolated compound. Artemisinin, by itself, is not all that bioavailable. But something quite different occurs when the whole plant is ingested, when the artemisinin is taken along with the other compounds in the plant.

Plants utilize a multi-component approach to disease treatment rather than monotherapy and there are good reasons for this. When their antimicrobial compounds are examined *in situ* more subtle elements of their response to infections begins to emerge. A crucial aspect of this is the importance of *context* – none of these constituents were developed by the plants in isolation. They were generated while the plant was immersed in an ecological scenario to which it was interactively responding. The "active" constituent is, *in reality,* the expression of a complicated chemical communication in which *none* of the other plant compounds are irrelevant. Unsurprisingly, artemisinin is more active (and more bioavailable) against malarial parasites if administered with the *Artemisia* flavonoids artemetin and casticin which are normally present in the plant.

Artemetin is a fairly strong anti-inflammatory, is hypotensive, modulates mitochondrial function, is antineoplastic, and is protective of endothelial function – primarily through antioxidant and antiapoptic actions. It, like casticin, appears to modulate apoptosis, protecting healthy cells from apoptosis and while stimulating apoptosis in damaged cells (such as cancer cells). Casticin is an immunomodulator (reducing a variety of overactive white blood cell responses), suppresses a number of cytokines (e.g., IL-1beta, IL-6, MCP-1), inhibits prolactin release (making it useful for treating hyperprolactinemia), is strongly antiinflammatory, and is antineoplastic.

Neither of these compounds possess direct anti-plasmodial actions. Comparatively little

research, compared to artemisinin, has been conducted on the medicinal activity of flavonoids such as artemetin and casticin. As Ferreira, et al, comment (2010), "Based on what is currently known, or strictly based on the chemical structure of flavonoids, it is quite hard to predict the full spectrum of their biological activity." Speculation is that these flavonoids might, among other things, facilitate artemisinin interaction with heme, leading to the release of the artemisinin peroxide that generates its antimalarial effects. Still, no one knows for sure. As well, flavonoids chelate metals such as iron and copper as part of their antioxidant actions. Thus these flavonoids might be producing their synergistic effects by reacting with iron and converting Fe (+3) to Fe (+2). Fe (+2) is crucial to the bioactivity of artemisinin as it stimulates the release of (short-lived) toxic free radicals that produce some of the antimalarial actions of artemisinin. Further, these kinds of flavonoids strongly inhibit serine-threonine kinases. There is evidence that they might also inhibit *Plasmodium* kinases, in consequence hindering protozoal development and proliferation. But again, no one really knows why they are so synergistic with artemisinin.

There are other metabolically active flavonoids in *Artemisia annua* such as quercetin, chrysoplenetin, and chrysosplenol-D. These also have synergistic effects against plasmodial parasites. Quercetin has weak anti-plasmodial activity but its stronger effects seem to occur from other actions. For example, it inhibits mammalian thioredoxin reductase release, an enzyme that is essential for the survival of the erythrocytic stage of *P. falciparum*. Chrysosplenol-D and chrysoplenetin are also weakly active against the malarial parasite but are highly synergistic with artemisinin *in situ*, significantly potentiating its effects. In mammals, these two compounds act as P-glycoprotein inhibitors. This facilitates the movement of artemisinin through the intestinal membrane and into the blood making it more bioavailable. The compounds act similarly within

the plant body, facilitating the dispersal of artemisinin throughout the plant. They are also, like other flavonoids, anti-inflammatories. Additionally, these compounds exert a suppressive effect on the multi-drug resistance pump common in *P. falciparum*.

And there are still more flavonoids such as apigenin, lutiolin, and kaempferol that themselves exert synergistic effects. In other words, there is a suite of "active" compounds in the plant which all work together to produce antimalarial effects. There is no one "active" constituent.

Interestingly, malarial infection itself potentiates the pharmacokinetics of artemisinin in the body. Plasma concentrations are *higher* when someone is infected and lower when they are not. Further, ingesting the properly prepared tea (made from the whole, flowering plant) results in a much faster absorption of artemisinin than taking the pure compound orally. As well, mice infected with a lethal dose of *P. falciparum* were found to survive only five days when treated with pure artemisinin but for eleven days when given the properly prepared tea.

The Chinese have used *Artemisia annua* for several thousand years and are very clear about proper preparation of the plant. While simple teas are sometimes used the strongest preparations are made through two similar approaches. Both use the upper two-thirds of the plant in flower. (The flowering plant is much higher in both artemisinin and the flavonoids.) In essence, the fresh flowering plant is harvested, *soaked* in hot water for 4-12 hours (in a covered container), then the herb is wrung out (like a dishcloth), then pounded to express the plant juices. Alternatively, instead of hot water hot milk is used. Milk (with its fats), if available, will extract 80 percent of the artemisinin from the plant, water extractions run from 25 percent with the dried herb to 60 percent in the fresh plant. (The plant is never boiled in the water as that significantly

reduces the amount of artemisinin that is extracted.) Pounding will bring out approximately 20 times more artemisinin than soaking the dried plant and four times more than soaking the fresh plant. Pounded infusions produce between 18 and 27 mg/kg of artemisinin and suppress parasitemia 2.6 times better than pure artemisinin dosed at 30 mg/kg.

Examination of the "active" constituents in other plants also show this kind of sophisticated complex of synergistically acting compounds. For example, berberine, a strong plant antibacterial, is very active against a large number of resistant and non-resistant bacterial organisms. It is considerably more active, however, if administered with another constituent, 5'-methoxyhydnocarpin (5'-MHC), that is common in goldenseal and other berberine-containing plants, This constituent, 5'-MHC, is a potent efflux pump inhibitor. It reduces or eliminates the ability of resistant *Staphylococcus* bacteria to eject, from inside their cellular membranes, antibiotic substances that might harm them.

In response to the bacterial generation of resistance to berberine (millennia ago), the plants created a new chemical, 5'-MHC, which has no known function other than to act as an efflux inhibitor, enabling the berberine to remain effective. If goldenseal were standardized for berberine content (which some people insist is important) and if, for some reason, the plant being standardized contained no 5'-MHC, its effectiveness as an antimicrobial would be significantly diminished. Yet 5'-MHC is not considered important enough as a standardization marker since it is not an "active" constituent.

Such complexities are hardly limited to the berberine plants. The anticonvulsant actions of the kava lactones in *Piper methysticum* (i.e., yangonin and desmethoxyyangonin) are much stronger when used in combination with other kava constituents that are generally considered

irrelevant in any standardization missives. As well, concentrations of yangonin and another lactone, kavain, are much higher in the brain when the *whole plant* extract is used instead of the purified lactones themselves. In other words, some of the other constituents in kava help move the bioactive lactones across the blood/brain barrier and into the brain where they will do the most good. Blood plasma concentrations of kavain is reduced by 50 percent if the purified compound is used rather than an extract of the plant itself.

Plant compounds in *Isatis tinctoria*, a potent antiviral and antiinflammatory herb, are also highly synergistic. Tryptanthrin, a strong antiinflammatory in the plant, possesses very poor skin penetration capacity. However, when the whole plant extract is applied to the skin, penetration of tryptanthrin is significantly enhanced. In other words, applying a salve of pure tryptanthrin to the skin, despite its anti-inflammatory nature, won't do you much good. But if you make the plant itself into a salve, the tryptanthrin moves rapidly into the skin and helps reduce skin inflammation. Tryptanthrin is, unfortunately, the only compound that is considered important to standardize in the plant.

Some additional sophistications can occur for those who wish to go even deeper. Among them are the *synergy* that occurs among the healing agents that are used. The use of healing agents (pharmaceuticals *or* herbs) always involves synergy between the agents used – though this is rarely addressed in a positive light. It's usually the side effects of drug combination or drug/herb combination that are highlighted. However, herbs *are* synergistic with each other and can be positively synergistic with pharmaceuticals as well. For example, Chinese skullcap root (*Scutellaria baicalensis*) and licorice (*Glycyrrhiza spp*) are synergists; they enhance the action of other herbs with which they are combined. Many herbs can, as well, enhance the action of

pharmaceuticals. For example, Japanese knotweed (*Polygonum cuspidatum*) root, when used along with formerly ineffective antibiotics, can enhance the drugs' actions enough to make them effective.

Plants are complex, nonlinear, self-organized living systems. Neither they, nor their constituent elements, can be viewed, or understood, in isolation. This is because at the moment of self-organization complexities that can't be found by the reductive mind come into play. In other words, a complex synergy of interactions comes into being and it has nothing to do with "active" constituents. Every part is "active," every part is essential.

**Resistance to Plants?**

A common question is whether or not bacteria will develop resistance to antibacterial plants. The answer is that they already have . . . multiple times over millennia. The important thing to keep in mind is that plants are living beings. The plant we harvest this year is not the same as that from last year. Their constituent makeup is constantly in flux. If a pathogen develops a new resistance mechanism the plant will, quite rapidly, develop a response. This is another reason why standardization of plant medicines is a fool's errand. It places a static frame of reference on something that is never static. Evolution is an ongoing process. Plants move nearly in unison with resistance dynamics in bacteria – they continually develop new chemicals with which to counter them. As the comparative zoologist Richard Lewontin (2000) puts it, "The characteristic of a living object is that it reacts to external stimuli rather than being passively propelled by them. An organism's life consists of constant mid-course corrections." And plants are extremely sensitive to even the slightest alteration in the information spectrum they take in. Generation of

new chemical responses occur extremely rapidly.

Chemical innovations flow into and out of the plant over time in response to environmental inputs. There is no such thing as a "standard" chemical profile of a plant medicine, a truth that is difficult for reductive medicalists. Every plant's chemical profile is different from season to season and from location to location. It's supposed to be that way. Evolution has not ended. The diseases we encounter are altering themselves all the time. They possess tremendous genetic flexibility. But, fortunately for us, so do the plants. They alter their genome and their chemical relationships right along with the bacteria. The alterations in plant chemical profiles are essential for them to remain functional medicines. As bacterial dynamics shift, the plants, *worldwide*, shift their chemical production and constituent spectrum in response.

**Stealth Pathogens**

Plant medicines are exceptionally good for healing resistant infections. They are also very good at dealing with what is coming to be known as stealth infections such as the spirochete that causes Lyme disease. Stealth pathogens are very different than the bacteria (first-generation pathogens) for which antibiotics were created in the latter half of the twentieth-century (such as *Staphylococcus*). At present the major members of the Lyme group of infectious microorganisms are *Anaplasma, Babesia, Bartonella, Borrelia, Chlamydia, Ehrlichia,* and *Mycoplasma*. Rocky Mountain Spotted Fever and the other *Rickettsia* are a growing presence as are a number of *Wolbachia* organisms. At least 20 others, which are much less well known and generally, at this point, significantly less common, are beginning to be recognized as growing threats. Coinfection can occur with any of them.

The past several decades have seen a shift in the way many researchers are approaching disease treatment, nowhere more so than with these kinds of stealth pathogens that, due to their nature, often cause a wide range of symptoms. Researchers Ian Clark, et al (2004) for example, have done some marvelous work on the dynamics of cytokines specific to various disease conditions, especially malaria and its close relative babesia. They note that . . .

> *It is our view that focusing on malaria in isolation will never provide the insights required to understand the pathogenesis of this disease. How can the illnesses caused by a spirochete and a virus be so clinically identical: typhoid readily diagnosed as malaria and malaria in returning travelers so commonly dismissed as influenza? . . . Understanding why these clinical confusions occur entails appreciating the sequence of events that led up to the cytokine revolution that has transformed the field over the last 15 years.*

Cytokines are small cell-signaling molecules released by cells that are damaged, cells of the immune system, and the glial cells of the nervous system. They are important in intercellular communications in the body. As it turns out, many disease organisms have learned to use cytokines for their own purposes.

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. This stimulates the innate immune system to respond; it sends specific immune cells to that location to deal with the problem. Those cells then initiate their own cytokine response to deal with the infection. Stealth

pathogens subvert this process, enabling their successful infection of the body. As well, many stealth pathogens release, on their own, many different types of cytokines, simply to jump start the process.

These kinds of microorganisms, once they enter the body, release an initial, and very powerful, cytokine – for example tumor necrosis factor, aka TNF. That cytokine stimulates the infected cell to produce and release others, and those generate still others – all of which have potent impacts on the body. Thus a *cascade* of cytokines occurs. This cascade (and any subsequent immune response) is carefully modulated by the pathogen to produce the exact effects it needs to facilitate its spread in the body. It modulates the cytokine dynamic in the body as expertly as an accomplished violinist plays a composition by Mozart. The microorganism uses the cytokines for a variety of purposes: to allow its entry into protected niches in the body (such as the brain), to facilitate its sequestration inside our body's cells (thus hiding it from the immune system), to break apart particular cells in order to get nutrients, and to shut down the parts of our immune response that can effectively deal with the infection. It is this cascade of carefully modulated cytokines that, in fact, create most of the symptoms that people experience when they become ill from a stealth infection. Even tiny alterations in the existing cytokine profiles inside our bodies can cause significant shifts in disease symptoms. Clark, et al (2004) comment that, "In one IL-2 [interleukin-2] study, 15 of 44 patients developed behavioral changes sufficiently severe to warrant acute intervention and 22 had severe cognitive defects."

Many researchers are now insisting that the most important thing is not the microbial source of infection but rather the cytokine cascade that is generated. This is especially true during coinfections with multiple stealth pathogens. One of the better articles on this is Andrea Graham,

et al. “Transmission consequences of coinfection: cytokines writ large” that appeared in *Trends in Parasitology*, volume 23, number 6, in 2007. They comment that “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 microparasite replication” as well as symptom picture, treatment approaches, and treatment outcomes. As they also 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 Lyme, the *Chlamydiae,* and Rocky Mountain Spotted Fever. Crucially, they 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 can utilize inflammatory processes that are already occurring in the body (e.g., pre-existing arthritis) to facilitate successful infection.

**Borrelial Infections**

In order to give you an idea of how sophisticated this can be, here is a very brief look at a portion of the cytokine process that Lyme bacteria utilize during infection.

*Borrelia* bacteria are particularly fond of collagenous structures in the body. They, in fact, need to break these structures down into constituent elements in order to gain the nutrients they need to survive and reproduce. Thus they are very sophisticated at modulating the body’s cytokine responses to do so. Wherever the breakdown occurs is where symptoms emerge. If in the joints, arthritis. If in the heart, cardiac problems. If in the brain, neurological symptoms.

*Borrelia* utilize specific cytokine sequences in order to accomplish the breakdown.

Commonly, they stimulate ERK, JNK, p38, and NF-*k*B in sort-of that order. Once the bacteria attach themselves to the body's cells, the bacterial flagellin upregulates NF-*k*B. This is generally followed by the upregulation of interferon-alpha (IFN-*a*), Interleukin-10 (IL-10), IL-8, IL-1*B*, IL-6, tumor necrosis factor alpha (TNF-*a*), and metalloproteinases (MMPs). Again, sort-of in that order. (Levels of these cytokines increase a minimum of ten times as soon as the body's cells are exposed to *Borrelia*.)

However, the bacteria always utilize multiple, redundant processes to generate this cytokine cascade. The listed, linear, order-of-emergence outlined above does occur. So, too, does simultaneous emergence; so, too, does emergence in a different order (MMPs right after IL-8, for example). They utilize multiple, redundant processes in order to facilitate infection and circumvent the immune response. They are very good at what they do.

Other, more specialized cytokines emerge as the cascade continues. Still, these are the primary upstream cytokines that a Lyme infection stimulates. Interrupting their emergence, inhibiting them, is one of the most effective strategies for treating an infection, especially in people for whom antibiotics have not worked. This can turn the condition around, generally within a few months, sometimes within weeks. Herbal medicines are specific for modulating cytokine cascades – plants, when infected, experience these cascades, just as we do.

I have done depth work on each of these cytokines and the plant medicines that can interrupt their emergence in a number of my books – again, much too long for this chapter. Here is a brief look at only one of them, the matrixmetalloproteinases.

Matrixmetalloproteinases (MMPs) are, more accurately, metal dependent proteases (hence the "-metallo-"). They are a group of enzymes that are specific for degrading extracellular

matrix (ECM) components and collagen. (Because of their action on the ECM, elevated MMPs facilitate the penetration of the spirochetes through extracellular matrix component barriers more deeply into the body.) MMPs are sometimes referred to as collagenases, in other words, enzymes that degrade collagen. They are also involved in a number of other functions, including cell proliferation, migration, adhesion, and differentiation. They help angiogenesis (new blood vessel formation) by breaking apart the ECM which allows passage through it for new vessels. Bone development, wound healing, learning, and memory are also dependent on healthy MMP function. During Lyme disease the major impacts occur on collagen and ECM degradation *in every location where symptoms occur, from skin, to joint, to heart, to brain.* Malfunctions in MMP expression and behavior are linked to a wide range of pathologies, from arthritis, to neurological problems, to cerebral hemorrhage, to cancer and its metastasis, to vertebral disc problems, to atrial fibrillation and aortic aneurisms, to septic shock. They are especially damaging to the brain and CNS. (Most of these problems are commonly associated with borrelial infections.)

The type of MMPs that the spirochetes stimulate differs depending on a number of factors, including host immune strength, genospecies and strain type, and whether or not there are prexisting inflammatory conditions already present. (If, for example, you already have arthritic inflammation in any of your joints, the spirochetes take advantage of it, stimulating it even further for their own purposes.) The most common Lyme-stimulated MMPs are MMP-1, -3, and -9. (MMP-2, -8, -13, and -19 are sometimes present as well). The spirochetes stimulate the monocytes and primary human chondrocytes (mature cartilage cells) in the synovial fluid to release MMP-1 and -3. The neutrophils that are called to locations of spirochete invasion release

large quantities of MMP-9. Production of MMP-9 and 130 kDa gelatinase (aka MMP130) in the nervous system occur through borrelial impacts on astrocytes and microglia. During neuroborreliosis, MMP-3 is common in the spinal fluid. The MMPs in the CNS break down the myelin sheaths that surround the nerves which is why the disease so closely resembles multiple sclerosis and other, similar, nervous system diseases.

MMPs are highly synergistic with, and need, plasminogen. The combination of these two compounds causes the most damage in infected sites. Lyme spirochetes possess a plasminogen-binding factor on their outer membrane. Plasminogen, in consequence, binds to their outer protein coats which raises plasminogen concentrations wherever spirochetes are located. Once MMPs are stimulated, they synergistically interact with the plasminogen causing significant glycosaminoglycan (GAG) and hydroxyproline release from affected structures. If the collagen being scavenged is in the joints, cartilage damage occurs. If in the heart, heart disease. If in the brain, neurological pathology. Once the GAGs are released, the spirochetes release *Borrelia* glycosaminoglycan binding protein (Bgbp). This binds GAGs to the spirochetes protein surfaces allowing them to more easily ingest them as a nutrient source.

MMP production, especially MMP-1 and -3, is stimulated through unique Lyme-initiated pathways, all involving mitogen-activated protein kinases (MAPKs). Specifically, the c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein (p38), and extracellular signal-regulated kinase 1/2 (ERK ½) pathway. MMP-9 production occurs both through the JNK pathway and another, the protein kinase C-delta pathway.

While there are a number of herbs that can reduce the autoinflammatory conditions stimulated by MMP-1 and -3 (e.g. curcumin-containing herbs) the only herb that specifically

blocks MMP-1, and -3 induction through this particular pathway is the root of *Polygonum cuspidatum,* also known as Japanese knotweed. 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 specifically inhibits MMP-9 gene transcription. Rhein, another constituent in the herb, inhibits the JNK pathway for all three MMPs: -1, -3, and -9. *Polygonum cuspidatum's* constituents also, rather easily, cross the blood/brain barrier where they exert specific actions on the central nervous system. They are antimicrobial, antiinflammatory, and act 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.

After more than a decade of use, we have found this one herb to be foundational for stopping the damage that *Borrelia* cause, especially in the nervous system. Once the inflammation is stopped, rebuilding the damaged neural structures can occur, restoring function and quality of life. Often times, the body’s natural repair mechanisms can accomplish this on their own, other times herbs that facilitate the rebuilding of nerve sheaths and other damaged neural structures are necessary. (Some additional MMP-9 inhibitors are *Cordyceps*, EGCG, NAC, *Olea europaea, Punica granatum, Salvia miltiorrhiza, Scutellaria baicalensis*. *Cordyceps* is also a MMP-3 inhibitor; *Punica granatum* inhibits MMP-1 and -3.)

Inhibiting MMP production stops most of the breakdown of collagenous structures in the body, inhibits GAG releases, and will often halt the development of the disease. If the bacteria cannot breakdown collagen, they cannot feed. If they cannot feed, they cannot reproduce and spread.

**A Few Comments on Dosages and Treatment Approaches**

Plant medicines are quite different than pharmaceutical drugs. While safety and reliability are commonly said to be the major drive for standardization of plant medicines, there is also a desire to make them more amenable to standardized dosing regimens. Unfortunately, there is just too little understanding of the complexity of plant medicines and their interaction with the human body to accurately do so.

As an example: For the past 20 years, we have been suggesting the use of *Cryptolepis sanguinolenta* tincture for the treatment of MRSA infections that refuse to respond to antibiotics. Cryptolepis is a potent broad spectrum, highly systemic, antibacterial herb. We have found it to be specific for all Gram-positive bacteria, malarial and babesial parasites, and a few Gram-negative organisms. We have never seen it fail in treating MRSA. However, dosing can range considerably, from one teaspoon three times daily to one tablespoon six times daily depending on the severity of the infection and the individual's response to the herb. We generally start with one teaspoon three times daily, increase to six times daily, and so on, increasing as the situation demands. Other herbs, in other situations, may necessitate a much wider range of dosing.

Specifically, and counterintuitively, plant tinctures may produce sufficient healing effects when given in tablespoon doses *or in drop doses*. That is, for some people one tablespoon of the herbal tincture may be necessary to produce effects, for others three to four drops will do so. This is often hard to accept for people trained in a pharmaceutical mindset. Nevertheless, while rarely recognized, pharmaceuticals also possess that kind of range of action. Nothing has revealed this more than studies of pharmaceutical pollution in the world's waters.

Louis Guillette, a reproductive endocrinologist and professor or zoology at the University

of Florida, is an expert in the study of endocrine-disrupting chemicals in the environment. He has often focused on pharmaceutical estrogens and estrogen mimics in water supplies and streams. Resultant male reproductive problems have been documented in panthers, birds, fish, alligators, frogs, bats, turtles, dogs, and humans. This includes, in some instances, complete feminization of males. His research has consistently found that androgen levels, ratios, and free testosterone levels are all significantly altered by these environmental pollutants.

Guillette (2000) has commented that the levels of chemical pollutants necessary to produce these effects are incredibly tiny. As he says: "We did not [test] one part per trillion for the contaminant, as we assumed that was too low. Well, we were wrong. It ends up that everything from a hundred parts per trillion to ten parts per million are ecologically relevant. . . . at these levels there is sex reversal . . . [The research] shows that the highest dose does not always give the greatest response. That has been a very disturbing issue for many people trying to do risk assessment in toxicology."

Because all life forms are nonlinear, self-organized systems they are exceptionally susceptible to even tiny inputs, which explains, to some extent, why homeopathic preparations work as they do. The grossest homeopathic preparations begin at six parts per trillion. Despite regular attacks on homeopathic medicines by mainstream medicalists, we have seen some homeopathic preparations produce significant alterations in disease conditions. Such *tiny* inputs, whether of homeopathics or herbal medicines, can cause physiology to shift, sometimes significantly.

Unfortunately for a reductive orientation, the inescapable truth is that medicinal plant dosages run along a rather broad spectrum. While suggested dosages for most plant medicines

exist, I have found in practice that each person who is ill presents with unique disturbance of their body ecology. The cytokine cascade, even in people with the same disease (e.g., Lyme), can be subtly, or sometimes significantly different. The presence of existing conditions, the health of the immune system, the degree of fragility or robustness, life circumstances . . . all will have an impact on the effective dose. This is why healing, no matter whether one is pharmaceutically or herbally based, remains more an art than a science. I suspect this will always be true.

Ultimately, every herbal protocol can be more accurately be compared to a bouquet of flowers than anything else. The individual flowers will posses a range of colors but when they are combined they become a unique entity possessing specific visual effects. I have found this a useful metaphor when creating a complex blend of plants for treating stealth pathogens. Even slight modulation of the herbs or dosages will produce an entirely different entity, with, sometimes, substantially different effects.

I may begin with an analytical understanding of what is happening and what I am attempting to create, but once a protocol is created for a particular person, there is the necessity to constantly adjust the blend to get the optimum outcome. Every time the patient enters my office, they are different. I have to look closely enough to perceive that difference and compare it to how they were before to understand how the protocol must be altered in response. Further, I have to constantly remind myself that each person has a slightly different form of infection, comprised, quite often, of multiple coinfectious agents.

Once I have a sense of the reality of that person's disease complex, I can begin to subtly modulate the process of its resolution. It is a *conversation* not a monologue that is occurring. I use the herbs to respond to what is being communicated. The body and the organisms respond to

the intervention. I then take in and interpret what they are saying and generate a new response. In this it is crucial to see the person that is in front of me every time they enter the office. They are *not* the same person they were the last time I saw them. Nor is the disease complex.

While initial training, whether medical or herbal, may be analytical – a simple "if A then B" orientation – over time a much different approach to healing begins to emerge. Long exposure to a variety of people and disease conditions and sustained experience in treating them generates a *feeling* sense of the unique person/disease complex that enters the treatment room. This is often referred to as intuition but I think it too inexact a term. A sense, much like that which occurs in a juggler emerges. Some deeper part of the self senses the exact disturbance of the balance point that is in play and one begins, without reference to analytics, to *know* how to respond. It is not a *thinking* thing that occurs but a feeling thing. Analytical analysis remains tremendously useful, of course, but enters the process only when confusion arises about what is going on in the person or how to respond to it. Although this is rarely talked about, I have never met a competent physician who does not, eventually, approach healing in this way.

This is why true healing will always be more of an art than a science and why a combination of mind (thinking) and feeling are essential. Both are crucial in the process. Stealth infections need focus of mind, the ability to think deeply, in order to understand and treat them. But they also necessitate a well-trained and focused feeling sense as well. One without the other simply is not enough.

We are entering a time when the older models of healing are beginning to fail with increasing regularity. The world that exists outside our limited picture is intruding with greater frequency into our awareness. As frightening as this can be, we are being forced to confront the

limitations of our thinking and actually do something new. Successful habitation of our planet means that we must adapt, just as the microbial populations of the world are doing. What better teachers could we ask for than the resistant and stealth pathogens that now plague us or the plants whose complexity can successfully treat them?

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