CHAPTER 27

Ecological Pharmacy: Molecular Biology to Systems Theory

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First, the world of life, taken as a whole, forms a single system bound to the surface of the earth; a system whose elements, in whatever order of association they may be considered, are not simply thrown together and molded upon one another like grains of sand, but are organically interdependent like . . . molecules caught in a capillary surface.

—TEILHARD DE CHARDIN, 1943

In the middle of the last century, some years before the discovery of DNA, Erwin Schrödinger, in his classic 1944 book *What is Life?,* inspired a generation of scientists with his timeless philosophical question: "How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?" (Schrödinger, 1944). To start at the microscopic, individual level, life (in the words of Schrödinger) depletes free energy and produces high entropy waste that maintains internal order.

Until recently, the approach in physics and chemistry has been that of reductionism, to study only the components of any given system. Biology has also given excessive authority to reductionism that collapses higher level accounts, such as social or behavioral events, into molecular ones (Rose, 1999). Influenced by such an approach, life may appear to be merely the sum of its chemical and physical parts. This view has come to dominate all sciences, including the medical sciences.

Contemporary science has overemphasized the reductionist model in its exploration of our world. Reductionism tends to attribute reality to component properties rather than the outcome that emerges from the interaction of the components (Kirchoff, 2002). And although reductionism is a powerful approach, the structure and functional aspect of a system's components gives us little indication of the behavior of the corresponding networks (Buehler, 2003a,b). The properties of a system cannot be understood by accounting only for the properties of its components.

The medical sciences, and especially pharmacology, have fully embraced the reductionist construct, implying that human health can be reduced to the modulation of specific genes and proteins. The laboratory modeling has, until recently, limited observations to the interaction between one gene or protein with a single chemical. Such simplistic modeling has led to some life-saving drugs, but has also lead to pharmaceutical drugs (even when properly prescribed) being an embarrassing and unfortunate leading cause of death in the United States. A broader model accounting for evolution and biology's extraordinarily ability to adapt to the environment is suggested below.

GAIA THEORY: INTERDEPENDENCE OF ORGANISM AND ENVIRONMENT

Teilhard de Chardin, a visionary French Jesuit, paleontologist, biologist, and philosopher who was fascinated with evolution and its connection with spirituality, recognized the limitations of reductionism. De Chardin was involved with early archaeological investigations of Peking Man (and the first evidence of the use of fire from nearly one million years ago; but all the evidence mysteriously disappeared from a railroad car during the Japanese occupation of China in World War II). He insisted that life must be studied in its totality on a large scale as a single, unitary system. As he contemplated the Earth and its life forms in the 1940s, he suggested the term *geobiology* to embrace all

life systems and their environment as a self-organizing whole (Galleni, 1995).

Within two decades of de Chardin's writing, a significant paradigm shift from the quantitative "clockworks" view to an exploration of the qualitative emergent view of self-organizing systems and even life itself, took place. A system's approach was starting to be supported in other sciences (Capra, 1996). For example, in Germany, Hermann Haken developed his nonlinear laser theory, and Manfred Eigen experimented on catalytic cycles; in the United States, Heinz von Foerster focused his interdisciplinary team on self-organization; in Belgium, Ilya Prigogine grasped the now-understood connections among nonequilibrium systems and nonlinearity; and in Chile, Humberto Maturana was postulating autopoiesis and life. In Denmark, Per Bak developed self-organizing principles relative to complexity or "chaos" theory (see Chapters 1 and 2).

These paradigms all converged on systems as a whole, coupled with Teilhard de Chardin's insistence that the Earth must be studied as a unity—together with both geological and biological points of view (Galleni, 1995)—perhaps led the British atmospheric chemist James Lovelock to one of the biggest revolutions in viewing our planet that perhaps we will ever know (Lovelock & Margulis, 1974).

Lovelock worked as a consultant to the U.S. National Aeronautics and Space Administration (NASA) in the early 1960s. NASA contracted Lovelock to aid in the quest to detect life on Mars. Lovelock, contemplating the chemistry of the atmosphere, found that an atmosphere that is out of chemical equilibrium was the signature of life on a planet. An atmosphere rich in oxygen and methane, for instance, demonstrates that organisms are responsible for the uneven mix. Earth has just that atmosphere (Lovelock, 1979). Through this investigation, Lovelock had a flash of insight one day: the planet Earth as a whole is a self-organizing system. He saw the unity of the biosphere—a global organism (Turney, 2005).

Just a few years later, the further study of these features of the Earth resulted in the idea that life vigorously regulated terrestrial conditions, a sort of "planetary homeostasis" (Turney, 2005). By observing the geological evidence and paleoclimatic evidence, Lovelock, influenced by ecology, physiology, cybernetics, and system analysis, hypothesized that the ocean's salinity, the gaseous atmospheric concentration, and the surface temperatures were maintained in narrow ranges by feedback loops of organisms responding to variations in their environments (Lovelock, 1979).

Lovelock postulated that the climate and chemical composition of the Earth's surface are kept in homeostasis at optimum levels by and for the biosphere (Lovelock & Watson, 1982). The notion was that the biosphere adaptively regulated the Earth (Lovelock & Margulis, 1974). In time, Lovelock (1995) saw self-organization as emerging from the ensemble of biota and environment. He saw the flow of sunlight upon the planet and feedback systems from living organisms to automatically generate comfortable life conditions that synchronistically evolved with the needs of the organisms on the planet. He called this idea a living planet, the Gaia hypothesis. It is now called Gaia theory.

Collaboration with the Nobel Prize winner Lynn Margulis introduced autopoietic theory into Gaia science, presenting Earth as an autopoietic planet where the biosphere as a whole is autopoietic. Margulis suggests that planetary autopoiesis is the aggregate, emergent property of the many gas-trading, gene-exchanging, growing and evolving organisms in it (Margulis & Sagan, 2000).

A model as whole and beautiful as Gaia was predictable. Chemists and physicists probing matter were finding that nature did not consist of isolated components, but rather appeared as a complex web of relations among the various parts of a unified whole. As Heisenberg expressed decades before the Gaia hypothesis was formulated, "the world thus appears as a complicated tissue of events, in which connections of different kinds alternate or overlap or combine and thereby determine the texture of the whole" (Capra, 1982).

Life has existed on the Earth for over 3.8 billion years (Lenton, 2002). During this time, the Earth's surface has been subject to increasing solar luminosity declining volcanic and tectonic activity, and to such perturbations as massive asteroid impacts (Lovelock & Margulis, 1974; Watson & Lovelock, 1978; Lenton, 2002). For example, despite the fact that the heat of the sun has increased by 25% over the last 4 billion years, the Earth's surface temperature has remained relatively constant, creating an agreeable environment for life (Lovelock, 1987).

Gaia theory suggests that practically all metabolisms are intimately connected to the flow of chemical compounds (Lovelock, 1989). For instance the greenhouse gases of carbon dioxide, methane, and sulfur compounds can produce highly reflective clouds, thus affecting the temperature of the Earth's surface and, in turn, influencing the metabolism of life (due to temperature change) on the planet that again changes the flow of chemical compounds to the surface and atmosphere (Kleidon, 2004).

It seems that life affects the Earth's surface environment at a planetary level, significantly increasing the cycling of free energy, essential elements, and water, inducing extreme thermodynamic disequilibrium of the atmosphere and altering the chemistry of the atmosphere, oceans, land surface, and crust (Lovelock, 1987). In turn, the state of the environment influences life, creating feedback loops between life and its environment (Lenton, 2002). These circular processes are organized through feedback loops that are found in every living system. The unusual aspects of the Earth's hypothesized feedback loops is that they link together living and nonliving systems. For instance, Gaia theory weaves together plants, microorganisms, and animals with rocks, oceans, and the atmosphere (Capra, 1996).

In this construct, life and the environment evolve together as one system so that not only does the species that leaves the most progeny inherit the environment, but the environment that favors the most progeny is itself sustained (Kirchner, 2003). This life-enhancing interplay of environment and organism can be understood as an emergent property of evolution because life-enhancing effects would be favored by natural selection (Lenton, 1998). This concept—also radical—requires a rethinking of the neo-Darwinist view of evolution.

Lovelock deduced the following principles from his observations of the planet (Lovelock, 1989):

1. Life is a global phenomenon. There cannot be sparse life on a planet. It would be as unstable as half of a buffalo. Living organisms must regulate their planet; otherwise the inevitable forces of physical and chemical evolution would render it uninhabitable.
2. Gaia theory supplements Darwin's great vision. The evolution of the species needs to be considered hand in hand with the evolution of their environment. The two processes are closely linked as a single indivisible process. To say that the organism that leaves the most progeny succeeds is not enough. Success also depends upon coherent coupling between the evolution of the organism and the evolution of its material environment.
3. Finally, Gaia theory requires a mathematical model that accepts the nonlinearity of nature without being overwhelmed by the limitations imposed by the chaos of complex dynamics. The theory makes the seemingly irrelevant observations of ecological oscillations relevant (Lotka, 1925).

With these principles, Lovelock provides an analogy between the ability of a living organism and communication systems to maintain life and low entropy levels, mainly through a continuous energy leakage into the surroundings (Onori & Visconti, 2012).

At its simplest, the idea that the entire ensemble of living organisms in its interaction with the environment—the biosphere—can be considered a single system has become the basis for a whole series of unfolding programs of research (Turney, 2005).

Some 40 years after Lovelock's realization, a statement issued from a joint meeting in 2001 of the International Geosphere-Biosphere Programme, the International Human Dimensions Programme on Global Environmental Change, the World Climate Research Programme, and the International Biodiversity Programme in a meeting in Amsterdam to study our planet begins with: "The Earth System behaves as a single, self-regulating system comprised of physical, chemical, biological and human components." It seems the science of Gaia has become conventional wisdom (Turney, 2005).

Even some scientists who do not agree with Gaia theory acknowledge what Lovelock's vision has added to the study of Earth Sciences (Volk, 2002; Turney, 2005). The very term "Earth Science" exists because of Lovelock's work. Volk (2002), who does not embrace Gaia's implications, says, "I was inspired by Lovelock's early writings to move into issues about the effects of life on a global scale that led to technical work I would not otherwise have accomplished ... Gaia became a way of thinking, a mantra to be mindful of the biggest scale." Many critics accept that it is essential to understand the Earth system as a unity, rather than as a set of disconnected components (Kirchner, 2003).

One of the issues is the defining feature of complex systems like Gaia, making it extremely difficult to analyze. The planet is not a well-designed machine, but a complex ensemble of life that constantly rebuilds itself within a range of variable parameters, like all living organisms. This creates a model impossible to analyze from a reductionist perspective (Kirchner, 2003).

Free and Barton (2007) point out that the overall prediction (i.e., that most real global biotic systems tend towards long-term stability) obviously cannot be tested. There are, however, some useful secondary predictions:

1. A coupled life–environment system shows better resistance and resilience than would the abiotic equivalent, and recovers faster from perturbation (has greater elasticity).
2. Small-scale biotic systems and those lacking efficient nutrient recycling and photosynthesis are less resistant and resilient than those of large scale and possessing these attributes.
3. Life–environment feedbacks should tend to stabilize the system on geological time scales.
4. As life and environment coevolve, the biosphere will tend towards greater stability and remain within tighter environmental bounds.
5. The stability of the biosphere should not depend on the presence of particular species or ecosystems, which can only have arisen by chance, and should be possible in a biosphere composed solely of microorganisms.

According to the more complex models of systems theory, Lovelock's proposal of very different and complex realities (like the biosphere and the inert environment) operating—in a unified and harmonious way—in the creation of a super-system may be both unexpected and provocative (Onori & Visconti, 2012). Another supportive model for Gaia theory comes from quantum mechanics from Byrne (2011). He recently identified entanglement as the most important discovery of quantum physics, in that it allows for the knowledge of everything there is to know about a composite system, without knowing everything about the individual constituents (see Chapter 14).

Yet a deeper reservation is that a living planet has all the hallmarks of scientific communities coming to grips with a major paradigm shift, a revolution in science (Kuhn, 1962). Whether or not one agrees with the enchanted vision of a biotic Earth, the issue is more than academic. Gaia theory stimulates us to draw together diverse lines of theory and experiment, investigate their connections, and query into whether they can be extended to the spatiotemporal scale of a closed system, the biosphere (Free & Barton, 2007). Given current concerns about anthropogenic

perturbation of the biosphere, all relevant scientific disciplines should contribute to predicting its response. It is vital to comprehend how our planet functions and how it is likely to respond to immature fostering and guardianship (Lenton, 2002).

Capra (1996) points out that the conception of the universe as an interconnected web of relations is one of the major themes that recur throughout modern physics. The elucidation of the patterns and relationships between a system's components may provide models which provide a more accurate depiction of reality. He goes on to suggest that Gaia is a mere realization of this line of reasoning. Moreover, such a systems approach may provide a wider perspective to understanding the process of evolution, inviting us to recognize that humans belong to a process that is much more grand than the human species.

COHERENT COUPLING, EXPANDING THE COEVOLUTION CONSTRUCT, ADAPTATION TO THE ENVIRONMENT

Isolating the organism from its environment has been a fundamental tenet of studying biological processes. In almost all medical research laboratories around the world this practice is still followed in hopes of further insight into life processes. However, this may lead to incomplete conclusions. Maturana and Varela (1987) propose that due to organisms being inexorably interwoven with their environments, it is impossible to speak of environment and organism as separate entities. They presented this interrelationship as *structural coupling* (and later called coherent coupling) in the landmark book *The Tree of Knowledge*. They define coherent coupling as a history of recurrent interactions leading to the structural congruence between two (or more) systems (Maturana & Varela, 1987). In other words, autopoietic (self-organizing) unities, such as organisms and the environment, can undergo coupled histories of structural change due to their consistent and constant interactions. Coherent coupling recognizes the congruence between autopoietic systems (Maturana, 1975). This can include the system and its environment or systems affecting systems. In this paradigm, the environment is seen as a medium, which illustrates the interwoven nature between organism and environment. Development of the autopoietic systems involved thereby arises from transformations that each invokes in the other. This concept very much challenges the neo-Darwinist evolutionary theory, which in some authors' opinions drastically underestimates the effects and inseparability of the environment and organism (Thaler, 1994; Cairns, 1996; Scapini, 2001). Such interdependent relationship is considered unique and diachronic and is a defining principle of an organism and the environment (Scapini, 2001).

The construct of coherent coupling dictates that organism and environment are mutually enfolded in multiple ways, and what constitutes the world of a given organism is enacted by that organism's history of coupling with its environment (Varela et al, 1991). Indeed, on a human level it is well accepted at this juncture that our interwoven nature with our environment provides constant perturbation requiring a systemic reorganization of physiologic functions (Schulkin, 2003) (see Chapter 2).

Whereas some researchers are realizing the profound relations the environment has with physiological function, especially in regard to health and disease, other researchers have taken it a step further. Cairns et al (1988) published a controversial paper some years ago, stating that mutations can be environmentally directed, supporting the historical "Lamarckian" view of biology. Following Cairns's work a few years later, Thaler (1994) came to the same conclusion, stating that the environment can invoke genotypic change and postulated that both the environment as well as the organism's *perception* of the environment can induce genetic engineering genes to rewrite themselves and thus, rewrite sections of DNA code. Cairns and Thaler are suggesting a complex engagement of organism and environment. What they perhaps did not yet know was that they provided Maturana and Varela with molecular evidence for their coherent coupling construct. This greatly challenged the prevalent Neo-Darwinist perspective that sees mutations as random events, not potentially adaptive, as suggested by Cairns and Thaler. Such an adaptive response, well beyond haphazard natural selection, infers a primary form of intelligence that had developed billions of years ago (Pechere, 2004).

The construct of coherent coupling provides the understanding of an autopoietic systems' ability to be extensively "shaped" by interactions with its environment over time, and vice versa. Many may see this construct as the fitting of a system to its environment, but that is not what is meant by coherent coupling. Rather, this construct denotes congruence between autopoietic systems and environment due to reciprocal changes. It is also important not to confuse this construct with coevolution, a subset of evolution that includes population genetics and theoretical ecology. Although coevolution accounts for species–species or species–environment interactions, it differs from the coherent coupling paradigm in that the species are still seen separately from their environment and surrounding species. Coevolution theory still follows the central dogma of biology: information flows from DNA to RNA, to protein and, by extension, to the cell and on to multicellular systems. Crick originally, purely arbitrarily, formulated this "dogma" as a negative hypothesis that states that information cannot flow from protein to DNA (Crick, 1970). What the doctrine of the central dogma of biology implies is that a cell's/organism's experience has no effect on the DNA sequence (Figure 27-1).

Maturana and Varela (1987) challenge the central dogma by implying that experience can have an effect on DNA. They point out that the confusion is seeing DNA as "uniquely responsible" instead of having an "essential

Figure 27-1 The central dogma of biology.

participation". Although the organisms and environment are recognized as autonomous in the coherent coupling model, they are also recognized as inseparably engaged in mutually affecting relationships. The result is ontogenic adaptation of the organism to its medium: "the changes of state of the organism correspond to the change of state of the medium" (Maturana, 1975). Thus organisms are seen as "shaped" due to historical recurrent interactions with their environment, just as the environment has been shaped by its interactions with the organism (see Chapter 2).

On a microcosmic scale, for instance, cellular membranes have coherently coupled with the abundance of sodium and calcium ions. This observation is made through the specialization of proteins in the membrane to allow for active transport and the inclusion of metabolic processes in which sodium and calcium participate. This fact implies that the genome adapted to the reoccurring experience of the membrane with sodium and/or calcium. On a macrocosmic scale, the paradigm of coherent coupling leads to an easy realization of the Gaia hypothesis wherein the planetary environment (e.g., temperature, ocean salinity and atmospheric gases) is modified by various species, and in turn, these species phenotypically and genotypically morph to the environment. It has been stated that all "evolution is coevolution" (Kauffman, 1995) and that all "development is co-development" (Gilbert, 2002). Thus, could it be that all evolution and all development is environmental coupling?

Ultimately interpreting Maturana and Varela's work results in the idea that the coupling of organisms with a high capacity for adaptation goes beyond response to the physicochemical dimension. The fluidity of morphological, physiological and psychological plasticity of an organism firmly embeds that organism with its surroundings, creating a dynamic response to recursive perturbations. Put simply, the phenotype depends to a significant degree on the environment, and this is a necessary condition for integrating the developing organism into its particular habitat (Gilbert, 2002).

COUPLING OF HUMANS WITH PHYTOCHEMISTRY: PLANT–HUMAN COALITIONS

The constant interwoven nature of organism and environment requires some sort of exchange of information to account for species plasticity. Markos (1995) defines this exchange that allows species to read their environment, thus integrating into Gaia, as "informational flow." The informational flow relevant to the discussion between plants and humans is, in its most basic form, chemistry—molecular messaging—although there are likely many other cues that are important to plant-human coalitions (for example, botany of desire).

The secondary metabolites of plants are well known to modulate the relations—both positive (i.e., attractant) and negative (i.e., repellent)—among plants and their consumers. The presence of secondary compounds in plants provides information to other species, and due to a reiterative history of interactions, generates a mutually enfolding between plants and humans. Plants have always provided shelter, clothing, food and medicine for humans. In turn, humans (and animals) transport, seed, cultivate, and with metabolic waste, fertilize plants.

Higher primates have been evolving and have been exposed to plant chemistry for about 88 million years. The higher primates, considered to be omnivores, are nevertheless, herbivores as well. Over such an evolutionary time scale, all higher primates relied on the predictability of vegetative parts of plants as food sources (Johns, 1996). This circumstance includes *Homo sapiens*, with 5 million to 7 million years of exposure to phytochemistry. Of course, this exposure to various plant parts exposed the consumer to thousands of secondary metabolites. Estimates of the number of plants in the early human diet range from 80 to 220. Clearly, if *Homo sapiens* consumed such a regular number and volume of plant foods, they were exposed to a very high number of phytochemicals. A very conservative estimate would be in the range of 80,000 to 220,000, and quite likely much higher. Ames et al (1990) makes an estimate of the number of secondary metabolites in the current human diet taking into account only those secondary metabolites that are also known to function as natural pesticides. He observes that even with the great reduction in diversity and variety in the human diet compared to hunter-gatherer ancestors, the modern number of established natural pesticides in the diet is about 10,000 compounds. Thus, even now humans are constantly exposed to a great amount of "information" from plants.

If humans have coherently coupled with plants, then by default this means that plants have shaped humans through informational molecular exchange, and vice versa; humans have shaped plants by this means, as well as by conscious horticulture. This shaping, if the hypothesis is solid, should range from DNA to protein and include epigenetic activity. Epigenetic influences (through DNA methylation, chromatin remodeling, and microRNA-regulated transcriptional silencing) allow environmental inputs to shape human phenotype through alteration in gene expression. For instance, methyl-CpG-binding proteins and amino acids (such as methionine, cysteine, serine, and glycine) play a role in single-carbon metabolism (Niculescu & Zeisel, 2002; Valinluck et al, 2004), and key phytonutrients and phytochemicals (such as vitamins B6, folate, betaine, choline, selenium epigallocatechin-3-gallate, resveratrol, genistein, and curcumin) have also been shown to modulate epigenetic activity (Tammen et al, 2013). This author suggests that as further research

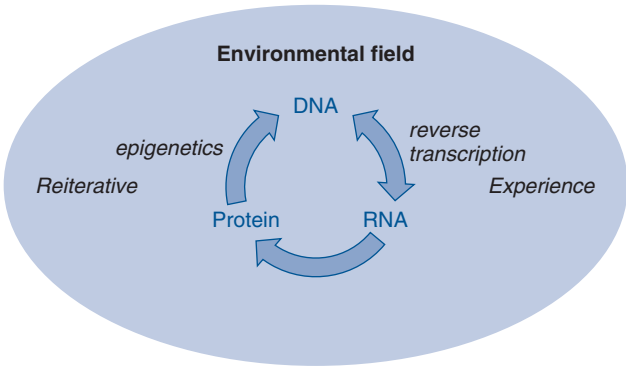

Figure 27-2 The central dogma of biology revised.

unfolds, epigenetic modulation through numerous phytochemicals will be recognized in the coming years as a key piece of an adaptive response, important in long-term human health.

It is easy to see that humans have shaped plants by looking at the cultivation of crops; the original species of any of the crop plants have changed drastically due to human intervention. It should also be obvious, although not quite as easy to recognize, that plants have shaped humans. One obvious, well-known example is the "shaping" of the cytochrome P450 (CYP 450) genes. This ancient superfamily of enzymes consists primarily of microsomal and mitochondrial proteins and in humans represents about 75 different CYP 450 genes (Danielson, 2002) (Figure 27-2).

Danielson (2002) points out that CYP 450 genes allow animals to generate a metabolic resistance to plant compounds designed to dissuade plant grazing, and conversely, to allow plants to generate new compounds to deter herbivory. He goes on to point out that these CYP 450 genes in plants and animals have been engaged in a cyclical process, generating novel compounds in plants and generating resistance in animals. Jackson (1991) discusses the observation that particular plant compounds (such as alkaloids, glycosides, phenolics, uncommon proteins, unusual free amino acids, steroids, essential oils, terpenes, and resins) are capable of altering the metabolism and potentially changing the biological fitness of humans as well as their domesticated animals, and even the obligate parasites of each species. She points out that detoxification of plant compounds represents an avenue of potentiating individual and group shifts in gastrointestinal function, structure, and endocrine metabolism. But this influence on physiology does not just stop with transient functional effects.

CYP 450 genes have an unusual ability to evolve rapidly, following a quick-paced, nonlinear time course (Nelson et al, 1993; Danielson, 2002). A large-scale expansion of the CYP 450 gene family is thought to have provided a cache of proteins from which novel isoforms provided adaptive strategies for metabolizing plant compounds. The resulting diversity in these genes is thought to be due to the recurring exchange of molecular information among the secondary metabolites of plants and mammals needing new enzymes to detoxify these plant compounds (Gonzalez & Nebert, 1990). Therefore, the rich exposure of humans to phytochemistry ultimately promoted human biological variability affecting our genes (Gonzalez & Nebert, 1990; Jackson, 1991; Nelson et al, 1993). Was it haphazard mutations that lead to such abilities? Or were genotypic changes, as Cairns and Thaler's work suggest, environmentally directed?

Another example of coherent coupling between plants and humans are the steroid receptors. Specifically, the estrogen receptor is the original member of the steroid receptor family (Hawkins et al, 2000; Wu et al, 2003). The gene structure and ligand-binding properties of the classical estrogen receptor (ER-α) are known to have been highly conserved over 300 million years of vertebrate evolution. Thus, the binding of an estrogenic chemical to ER-α in fish, amphibians, reptiles, birds, and mammals (including humans) shows relatively little difference (Katzenellenbogen et al, 1979; Pakdel et al, 1989; White et al, 1994; Welshons et al, 2003). Orthodox thought of this protein as occurring only in vertebrates requires revision. The microbial organisms known as mycorrhiza, living on the roots of plants, have a receptor called NodD, which has a high amount of genetic homology with the human estrogen receptor. Plants also express an identical protein to the human 5α-reductase enzyme (Li et al, 1997; Fox, 2004). Steroids and flavonoids, produced by plants, bind these proteins (Gyorgypal & Kondorosi, 1991; Baker, 1992). Thus, molecules that have similar shape and electronegativity as the estrogens, such as select isoflavones, are utilized as a communication strategy between plants and fungi, for example (Gyorgypal & Kondorosi, 1991).

A perspective from an evolutionary context suggests that the communication strategy of plants pertains to us as well. Phytochemical messenger molecules used by symbiotic soil fungi can be sequestered by humans, bind to estrogen receptors, and thereby influence gene expression. In discussing that the NodD and the estrogen receptor share no common evolutionary ancestry, Fox (2004) attempts to explain this observation by invoking the construct of convergent evolution—that these different species have responded to similar environmental signals, via natural selection, with the same adaptive traits. However, this result leaves the homology between these proteins to mere chance. If we view this through the lens of the coherent coupling paradigm, it offers an example of interspecies plasticity in response to environmental context.

Through this lens, humans and plants would be seen to shape themselves to mutual signals. Wynne-Edwards (2001) postulates that plants chosen for domestication may have a higher occurrence of phytoestrogens. This could potentially enhance the ovulatory cycle in women, which might mean there are more humans to cultivate more crops—an arguable benefit for the particular plant species. Wynne-Edwards goes on to point out that humans

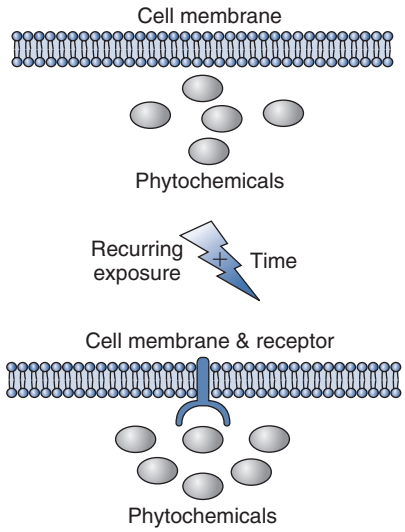

Figure 27-3 Coherent coupling between phytochemistry and eukaryotic cells.

have receptors in the nose and cheeks that bind native steroids and plant compounds, which in turn signal the brain. Studies have demonstrated that mammals will consume steroids in foods at some times and reject them at other times, depending on physiological and reproductive conditions (e.g., in pregnancy, rats will reject foods with steroids in them). Thus, true to the coherent coupling paradigm, there is a plasticity of response between animals and plants (Figure 27-3).

The effects of flavonoids, nonsteroidal secondary metabolites of plants, share key similarities in mycorrhiza and mammals. Flavonoids can regulate gene transcription in both groups. Moreover, some of these flavonoids can modulate the endocrine system and regulate mammalian physiology through activity on steroid receptors and prostaglandin synthesizing enzymes (Baker, 1995). In addition, humans express a protein, the 5α-reductase enzyme, that is homologous in sequence and identical in function (the reduction of steroid substrates) to a plant protein (Li et al, 1997; Fox, 2004). Hence, it should be of no surprise that plants have a long history of utilization in treating endocrine ailments; currently, phytochemistry is being explored for the regulation of human fertility. This leads Baker (1992) to suggest that flavonoids may have an evolutionary role in steroid hormone activity. It also provides an obvious example of informational exchange between plants and humans.

More recent work with a class of flavonoids known as isoflavones demonstrates intriguing epigenetic activity. Agouti mice, with their yellow coats and adult-onset obesity, diabetes, and tumor production, were protected from obesity by giving their mothers genistein at levels equivalent to a high soy diet. This phenotypic change correlated with methylation of the Avy locus (Dolinoy et al, 2006). In addition, supplementation of obese yellow agouti mice during pregnancy with methyl group donors (such as betaine, choline, folic acid, and vitamin B_{12}) showed a reduction in the occurrence of obesity, diabetes and cancer, as well as altered coat color, in the offspring (Waterland & Jirtle, 2003).

That flavonoids are considered, conditionally, essential nutrients (Challem, 1999) adds to the intrigue. In other words, humans have "coupled" with these particular flavonoid "signals" to such a degree that they enhance our long-term health (Manthey & Buslig, 1998; Martinez-Valverde et al, 2000). One wonders how many other plant compounds, with regular consumption, enhance human health. As research on plant metabolites continues, it is increasingly apparent that many phytochemicals are at least favorable, if not necessary, to human health. Just considering the vitamins and minerals from plant origin makes it obvious that human physiological processes are dependent on the phytochemistry of plants. Moreover, the evolutionary history of humans ingesting plants with myriad phytochemicals suggests that the interface of multiple phytochemicals with mammalian physiology may be informative about pharmacology and induce an adaptive (hormetic) response to the environment (Vaiserman, 2011).

HORMESIS AND XENOHORMESIS—ADAPTATION TO THE PHYTOCHEMICAL ENVIRONMENT

There are a number of reasons that the complex chemistry inherent in ingestion of a plant acts differently than that of an isolated chemical. Of these reasons, pharmacokinetic potentiation, pharmacodynamic convergence, and hormesis/xenohormesis are the best known and the easiest to discuss in the existing framework of pharmacology. Although pharmacokinetic potentiation involves processes related to absorption, distribution, metabolism, and excretion (ADME), pharmacodynamic convergence involves modulation of multiple biochemical pathways, membrane dynamics, receptor-binding cooperativity, and shifts of the degrees of freedom of proteins (enzymes and receptors). Although both of these modes of activity are unique to the ingestion of chemical mixtures, they are commonly put under the rubric of synergy, even though they would ideally be discussed separately. The last mode, hormesis, is well established in the field of toxicology and is slowly encroaching into physiology and pharmacology. Regardless of the scientific discipline of origin, it is a useful construct for understanding how plant chemistry interfaces with living systems. Xenohormesis provides an overarching construct to embrace much of what has been previously discussed.

Hormesis Defined

The term *hormesis* is derived from the Greek word *hormon,* meaning "to excite." In other words, on ingestion of a hormetin, physiological processes are stimulated. Simply put, hormesis is the paradoxical effect of a toxic chemical or radiation at low dose (Trewavas & Stewart, 2003).

TABLE 27-1 *Previous Terms Applied to the Hormesis Dose Response*

Compensatory response	Bell-shaped
Facilitation-inhibition	β-curve
Intermediate disturbance hypothesis	Bidirectional
Paradoxical dose responses	Biphasic
Reverse	J-shaped
Stimulatory-inhibitory	U-shaped
Subsidy-stress gradient	
Previous Laws Referring to Hormesis	
Hebb Law	
Yerkes-Dobson Law	
Arndt-Schulz Law	

From Calabrese EJ, Baldwin LA. Defining hormesis. *Hum Exp Toxicol* 2002;21:91–7, copyright ©2002 by Edward Arnold. Reprinted by permission of SAGE.

Stebbing (1982) defined hormesis as low-dose stimulation followed by higher-dose inhibition. A more complete definition by Calabrese and Baldwin (2002), who have spent the last few decades bringing hormesis back to the attention of physiologists and pharmacologists, is "an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis." The idea behind hormesis is based on dose response; a beneficial physiological upregulation induced from small doses of a "toxin." Many terms have been used to describe this effect (Table 27-1), including the common biphasic dose response.

Calabrese and Baldwin point out that the hormesis dose-response phenomena has been labeled with diverse terminology and that there are also several biological "laws" referring to hormesis (see Table 27-1). Although this circumstance suggests that the phenomenon has repeatedly been "discovered" by different research groups, it is also an unfortunate comment on the lack of learning and conceptual integration across scientific disciplines.

The hormesis dose-response data suggest that there is a common regulatory strategy for biological resource allocation and a plasticity of regulatory processes dependent on environmental perturbations due to a long history of coherent coupling or coevolution with phytochemistry (Spelman, 2006).

History of Hormesis: Politically Suspect but Scientifically Solid

As mentioned previously, the hormetic response is oriented toward dose-response effects of substance. Although Calabrese and coworkers have brought this construct back into acceptance in the sciences, it had long been recognized in ancient systems of pharmacology.

For example, in the 5000-year-old Ayurvedic and Siddha systems of India, there is a tenet that *everything*, even poisons, can be used as medicine if properly utilized (see Chapter 31). As such, very small amounts of heavy metals were used to rejuvenate the system in the weak, convalescing, and aging. In the sixteenth century, Paracelsus, a Swiss chemist, was known to use toxic substances with particular attention to dose (Wood, 1992; Gurib-Fakim, 2006). Although there is much skepticism about this therapy, it is written that his results were particularly positive (Wood, 1992). Nonetheless, Paracelsus' therapies included the use of heavy metals, such as mercury. Centuries later this usage led to the well-known term of "quack," derived from an old term for mercury, which was known as quicksilver (or *quacksalver*)—although ironically (or perhaps mercurially) mercury was actually a key "antibacterial" treatment of regular medicine in the preantibiotic era. Published research by the late 1800s had demonstrated that chemicals toxic to yeast could stimulate growth and respiration if used in lower doses (Calabrese et al, 1999).

By the 1920s a researcher committed a foible in the politics of science by associating the phenomena of hormesis with homeopathy (Calabrese, 2006). Considering that this association was only a few years after the Flexner Report (see Chapter 22), any association with homeopathy was like a death sentence to any scientific hypothesis, regardless of reproducible evidence. Although the Flexner Report had resulted in the needed elimination of many of the ineffective schools of medicine of the early twentieth century, it also, apparently by design, put on its "hit list" any school teaching a system of medicine besides allopathy. Not helping matters, there was also a paucity of explanations based on the biochemical understanding of hormesis at that time (Stebbing, 1982). However, laboratory observations of the hormesis phenomena continued unbiased in other parts of the world, such that a German journal, *Zell-Stimulations Forschungen,* was established to report hormetic effects (Calabrese et al, 1999). By 1943, the scientific method cut through the politics in the United States; researchers at the University of Idaho reproducibly observed the phenomena, calling it hormesis, unaware of its previous labels (Calabrese et al, 1999).

About 50 years later, a newsletter of original research, *Stimulation Newsletter*, lasted just over a decade, reporting the enhancement of plant growth and yield by exposure to low-dose radiation (Calabrese et al, 1999). By the 1980s in the United States, despite still lingering skepticism of the hormesis phenomena, a book providing a lengthy review of the research on radiation hormesis was published (Luckey, 1980). By the end of the twentieth century, through the work of the Calabrese group, a substantial database of dose-response studies demonstrating hormesis as common and reproducible, had caught the attention of physiologists and pharmacologists (Calabrese, 2006). Hormesis as a scientific principle is solid; but is it here to stay?

BOX 27-1 *Well-Researched Plant Compounds Beneficial at Low Dose but Detrimental at High Dose*

Allyl isothiocyanate	Limonene
Caffeic acid	Perillyl alcohol
Catechins	Quercetin
Curcuminoids	Resveratrol
Hypericin	Sulforaphane

From Trewavas & Stewart (2003); Mattson & Cheng (2006).

Utility of Hormesis: Understanding Humans and Relations to the Environment

Hormesis is not just relevant to poisons such as heavy metals, synthetic pesticides, radiation and pollutants. Needed substances such as vitamins, minerals and oxygen are also toxic at excessive doses (Calabrese et al, 1999). Nor is this principle only observed with natural compounds such as listed in Box 27-1. This principle applies to endogenous compounds as well. Biosynthetic compounds moving through the human system, such as the adrenalines, adenosine, androgens, estrogens, nitric oxide, opioids, many peptides, and prostaglandins, all may have beneficial effects at low concentrations but detrimental effects at high concentrations (Calabrese, 2006). Some pharmaceuticals are also known to adhere to this principle. For example, low doses of antibiotics may actually enhance reproduction of pathogenic bacteria, whereas higher doses are toxic to these microbes (Calabrese et al, 1999). Probably the best known and most commonly consumed hormetin is alcohol. Ethanol, a chemical solvent, can clearly be toxic. However, at low doses ethanol as a biochemical metabolite is known to be beneficial to health and protective against cardiovascular diseases and some cancers.

Calabrese and Baldwin (2002) suggest the hormesis response provides a biological buffering response to protect against environmental and endogenous insults. The observation of this response in so many different organisms and cell types against such diverse chemical groups (and radiation) suggests a system-wide feedback response resulting in upregulation of many regulatory processes (Calabrese et al, 1999) and an evolutionary-wide biological strategy (Calabrese & Baldwin, 2002). By overcompensation to an initial disruption via an environmental stressor, an organism is protected against the possibility of further exposures (Calabrese et al, 1999).

The hormetic dose response seen in so many phytochemicals also suggests that the mode of activity for health enhancement by fruits, vegetables, and spices may be, at least partially, due to the evolutionary protective responses previously mentioned. Furthermore, it argues against a strictly "antioxidant" mode for the health benefits of plant-based foods, which has become a common assumption among many clinicians and researchers. Like exercise and caloric restriction, many phytochemicals may act as mild stressors to induce an adaptive response via upregulation of multiple genes inducing a protective effect (Calabrese, 2005; Mattson & Cheng, 2006).

At this juncture, some researchers thinking outside the box are applying the hormesis construct to grasp the relationship between the natural pesticides occurring in plants and human health. Many of the secondary compounds plants produce are antifeedants, antimicrobials, and insecticides for the plants' protection (Poitrineau et al, 2003). The well-respected researcher Bruce Ames points out that, of all the pesticides in the diet, those that are naturally produced by the plant itself or synthetic pesticides applied to the plant by farmers, 99.9% are naturally occurring (Ames et al, 1990). This becomes particularly relevant to human health in that many of these natural "pesticides" such as flavonoids (Baker, 1998) and coumarins (Zangerl & Berenbaum, 2004) are known to be beneficial to human health in multiple ways, including having anticancer activity and beneficial cardiovascular effects (Hoult et al, 1994; Knekt et al, 1996; Hollman & Katan, 1997; Lin et al, 2001; Nijveldt et al, 2001; Baba et al, 2002; Hamer & Steptoe, 2006). At low doses these compounds appear to activate adaptive cellular stress-response pathways (Mattson & Cheng, 2006). However, at high doses, many of these compounds can become carcinogens (Trewavas & Stewart, 2003).

Diets high in animal based-foods (to the exclusion of plant-based foods), and processed foods may lack the protective effect of diets high in phytochemicals (Johns, 1996). Ames and Gold (2000) point out that about 80% of U.S. and 75% of U.K. citizens eat insufficient fruit and vegetables to provide even minimal protection against cancer. After summarizing 200 epidemiological studies, Block et al (1992) reported that a phytochemical-rich diet from fruits and vegetables reduced cancer risks by about 50%. Knoops et al (2004) found that among individuals ages 70 to 90 years, adherence to a phytochemical-rich diet was associated with a more than 50% lower rate of all-cause and cause-specific mortality. Norris et al (2003) show that good health habits, one of which includes a phytochemical-rich diet, are associated with a 10- to 20-year delayed progression of morbidity. What might seem paradoxical to the casual observer, is that many phytochemicals, evolutionarily derived to protect plants from predators, are detrimental to health at higher doses. The exposure to secondary plant metabolites, many of which were naturally selected to protect plants against bacteria, insects, and herbivores, can be protective to human health. However, in excess doses, many of these natural microbicides and insecticides are toxic. In insufficient doses, human health may be compromised. At ideal doses, human health may be enhanced due to the hormesis principle and therefore be more resistant to disease processes and better able to respond to changing environmental circumstances (Johns, 1996).

Xenohormesis

Another well-known example of a hormetic process is exposure to low concentrations of certain phytochemicals. Unsurprisingly, organisms have evolved the ability to detect stress markers produced by other species in their habitats. Because the majority of life forms on the planet either feed on, or live in, close proximity to photosynthesizing organisms (photoautotrophs), there is a long-term evolutionary relationship between photoautotrophs (plants and photosynthetic bacteria) and heterotrophs (fungi and animals). Much of this relationship is based on the secondary metabolites from plants. Plants are known to synthesize compounds, such as stress markers, in response to environmental conditions. These phytochemicals, in turn, may be utilized by their surrounding heterotrophic neighbors as cues to impending environmental changes. Thus, when ingested or absorbed by coexisting life forms (such as bacteria, fungi, animals or humans), certain phytochemicals may provide a chemical signature of the state of the environment. In this way, organisms might prepare themselves in anticipation of potential adverse environmental conditions (Howitz & Sinclair, 2008; Menendez et al, 2013).

This interspecies hormesis is known as xenohormesis, the phenomenon in which an organism detects the chemical signals of another species regarding the state of the immediate environment or the availability of food (Menendez et al, 2013). The polyphenols are one example of phytochemical compounds carrying information about the immediate environment. This class of compounds includes the anthocyanidins, catchins, chalcones, flavanones, flavones, isoflavones, and tannins. Spelman and Duke (2006) suggest that the metabolic expense of generating such molecules would create a "chemical economy," an efficient and multiple use of one molecule. Indeed, these molecules are known to be multifunctional in that they are, all at once, antioxidants, antibiotics, fungicides, herbivory deterrents, and UV protection. However, they are also known to play a role as signaling molecules—carrying environmental information to heterotrophs. Stafford (1991) proposes that the original role of the polyphenols was as signaling molecules and that their other properties evolved later. Flavonoids do provide cues to plant development (Taylor & Grotewold, 2005) and it has also been proposed that flavonoids were the original steroid signaling molecules (Baker, 1992).

Accumulating evidence does suggest that mammals sense plant stress–signaling molecules. The mammal that could respond to molecules such as the polyphenols, would have an advantage over those competitors that could not interpret these environmental cues. A possible explanation for this phenomenon is based in evolutionary biology. Kushiro et al (2003) propose that the biosynthetic pathways for signaling compounds originated in a common ancestor of plants and animals. As the phyla diverged, the heterotrophs eventually lost their ability to *synthesize* polyphenols, but retained the ability to *respond* to these messenger molecules. The retention of the ability to respond to these molecular cues likely allowed for an anticipatory adaptation to environmental changes (Howitz & Sinclair, 2008).

At the least, recurring interactions between phytochemicals and heterotrophic proteins over an evolutionary time scale may have generated conditional requirements for some phytochemicals (Spelman et al, 2006). The consumers of these molecules have been shown to respond by inducing cellular defenses and resource conservation (Howitz et al, 2003). For example, it is well known that that the polyphenols butein, fisetin, and the very well-publicized resveratrol, extend the life span in fungi, nematodes, flies, fish, and mice (Westphal et al, 2007). In addition, the same concentrations of polyphenols that are required to extend life span in the laboratory (approximately 10 μM) are also detectable in the leaves and fruits of stressed plants (Howitz & Sinclair, 2008).

The xenohormesis hypothesis varies from the hormesis model. In xenohormesis, the stress occurs in one organism (inducing an upregulation of particular signaling molecules), whereas the coexisting species (which have evolved to sense the surrounding chemical ecology) are the beneficiaries (Howitz & Sinclair, 2008). In regard to the age-old process of adaptation to the environment, it is sensible to propose that absorbed phytochemicals carry information about the status of the environment and imminent changes in an animal's food supply. The evidence that stress-induced plant compounds upregulate pathways that provide stress resistance in animals/humans provides an evolutionary imperative for anticipatory adaptation. Plant consumers would sensibly have modes to perceive these chemical cues and react to them in ways that are beneficial.

The hormesis and the xenohormesis hypothesis are not mutually exclusive. Responses to absorbed toxins (hormesis) and the ability to respond to molecules of environmental origin as molecular signals (xenohormesis) were likely concurrent developments in evolution. Howitz and Sinclair (2008) point out that both responses are likely at play in animals' response to complex mixtures of phytochemicals.

Although xenohormetic compounds are often detrimental to smaller insects and microorganisms, the subtoxic levels at which humans consume them may result in moderate cellular stress responses. This could induce stress-response adaptation pathways, leading to increased expression of genes that encode cytoprotective proteins such as antioxidant enzymes, chaperones, growth factors, phase 2 detoxification enzymes, and mitochondrial proteins (Menendez et al, 2013).

This environmental coupling may have resulted in a conditional dependence on phytochemicals for the modulation of particular proteins as well. For example, the nucleotide-binding sites of protein kinases appear to bind the polyphenolic flavonoids and stilbenes with reasonable affinity. The evidence indicates that these polyphenols do

not compete with the enzyme's nucleotide substrates, rather they bind elsewhere (Howitz et al, 2003; Gledhill et al, 2007). Molecules such as resveratrol and quercetin have been found to bind not to conserved domains, but to hydrophobic pockets (Gledhill et al, 2007). This observation may partially explain their ability to modulate multiple proteins. Howitz and Sinclair (2008) suggest that this property is consistent with these polyphenol-protein interactions being driven by selective pressures rather than coincidental binding—and also suggests that these interactions are likely potentiating with one another and with endogenous regulators.

There are also data that demonstrate that many of these compounds bind to the same binding pockets as endogenous regulators (Baker, 1992). Both types of interactions help substantiate the claimed observations of *synergy* so often cited for multi-component extracts from medicinal plants (Spelman et al, 2006). At the least, ingestion of the phytochemical mixtures in fruits, vegetables and herbs likely involve multiple interactions that go well beyond ligand binding and involve subtler molecular dynamics (see Molecular Models of Activity later in this chapter) (Spelman, 2005).

The xenohormesis hypothesis makes a number of predictions that rest squarely on organisms' relationship to coupling with their environments (Lamming et al, 2004; Howitz & Sinclair, 2008):

1. There is likely a substantial cache of medicinal molecules that are upregulated in stressed plants that can benefit the user.
2. Xenohormetic phytochemicals serve as messenger molecules by interacting with a variety of enzymes involved in regulating stress responses and survival.
3. These molecules should be relatively safe for human consumption.
4. There may be conserved domains in enzymes and receptors that do not interact with endogenous molecules.
5. Many phytochemicals, due to a history of recurrent interactions with heterotrophic proteins may have resulted in a structural congruence that potentiates the effects of endogenous regulatory molecules.

If the above predictions hold true, then xenohormesis may provide the philosophical underpinnings as to why many phytochemicals have been documented to enhance health parameters.

The xenohormesis hypothesis, when fully recognized, has implications for the foundations of pharmacology. Whereas classical pharmacology is based on high affinity and high selectivity, many physiologically active phytochemicals are known to function with broad specificity and low affinity (Ágoston et al, 2005). This reality creates a quandary for the pharmacological paradigm as many phytochemicals are known to affect multiple proteins. "Polyvalent" binding, whereby a small molecule binds to multiple proteins, is considered an inferior pharmacological strategy by pharmaceutical standards. However, it may well have been the original mode of upregulating defensive physiological responses, and it may well provide distinct pharmacological advantages based on evolutionary biology.

Danger of a Second Rejection by the Politics of Science

This argument is science based and a logical extension is that the use of food and medicinal plants for enhancement of health is biologically preferred to the use of isolated, synthetic drugs. Many critics of the beneficial health effects of plant-based foods and medicines claim there is not enough (a high enough "dose") of any one chemical present in plants to make them therapeutically useful (Spinella, 2002). Although this argument is consistent with medicinal plants sometimes being called "crude drugs," it also demonstrates a gross misunderstanding of the pharmacology of complex mixtures. Furthermore, it completely misses the hormesis phenomenon.

The argument that foods and medicinal plants are not effective for inducing physiological change because they are too dilute to have activity contradicts the entire hormesis database of studies demonstrating that minute doses of substances do have general and reproducible biological responses. At the same time, the hormesis principle should call into question the practice of concentrating an active constituent from a plant by standardization. Although we must be assured of the quality and identity of medicinal plant preparations, concentration of any one constituent in a medicinal plant preparation may, in some cases, breach the dose for beneficial activity and move toward a detrimental dose, particularly if the compound operates through a hormetic mode of activity. Nonetheless, understanding hormesis can help the allopathic community understand one of the possible modes of activity for medicinal plants. The hormesis principle was once dropped like a "hot potato" in the early part of the twentieth century because of the association with homeopathy. Will hormesis be shunned because of its ability to help explain observations on the health benefits of medicinal plants?

Viewing hormesis in an ecosystem context, hormetic responses measured by growth effects can turn out to be a result of altered competition between species. If a competitor, parasite, or disease of a species is more susceptible to a certain chemical than is the species itself, then the species will experience relief from a resource-demanding stress factor and hence increase growth at low concentrations of that chemical. This effect (also a basic principle behind the beneficial effect of pharmaceuticals such as penicillin on vertebrates) leads to the xenohormesis hypothesis.

ECOLOGICAL PHARMACY AND THE BASIS OF PHARMACOLOGY

The aforementioned evidence logically leads to a discussion on pharmacology; that is, how has adaptation to phytochemical exchange influenced the physiological processes of organisms consuming plants. A key point is that ingestion of plants, a process that has been going on for 300

million years for vertebrates, 88 million years for higher primates, and 7 million to 10 million years for humans, leads to exposure to an array of plant compounds in every swallowed mouthful. Never has the consumption of edible foodstuffs involved a single, isolated compound. This reality is of pharmacological significance. The current model in pharmacology attempts to induce physiological changes through the ingestion of one chemical at a time.

In an unspoken oversight of the medical sciences, the rationale for the approach of isolation and purification of active constituents from "crude drugs" has never actually been made explicit (Vickers, 2002). The general conclusion drawn from a century of research on active constituents from medicinal plants is that medicinal plants typically contain numerous active compounds (Singer & Underwood, 1962; Williamson, 2001; Gilbert & Alves, 2003; Spelman, 2005; Spelman et al, 2006). There is a key point regarding the economics around the use of food and medicinal plants for human health. Multiconstituent plant medicines were not forsaken because of research that demonstrated harmful or ineffective activity, but because they were too complex to study in their multiconstituent form (Vickers, 2002). Nevertheless, pharmacological modeling has used isolation as a fundamental tenet of inducing physiological shifts in humans. Unfortunately, this methodology is deficient in revealing the mode of activity of the bulk of food and medicinal plants as it neglects the concerted, synergic, additive and/or antagonist activities of multiconstituent remedies (Cech, 2003). Moreover, it grossly simplifies physiological processes to only those parameters possible to observe in reductionist models. Thus, fitting the biology to the method; rather than the method to the biology (see Chapters 1 and 3).

A pharmacological paradigm should be supported by a foundation of human adaptation to the informational input from plants. Physiological processes, down to the level of genes, have undergone a history of recurring biochemical interactions with complex phytochemistry that has led to the structural congruence of humans and plants. The previously discussed shifts in DNA, epigenetics, the homology of proteins, and the ligand–receptor relations among humans and plants are examples of "structural congruence." Human biology has integrated with that of plants so that multiple concurrent biochemical perturbations are ordinary. Reiterative exposure to minute doses of numerous plant metabolites provides constant stimuli for biological adaptation (Jackson, 1991). In turn, this adaptation has profound effects on human health.

Jackson (1991) aptly calls attention to system stability, writing that system diversity is proportional to system stability. Another way of expressing this relation in regard to human health is that the stability of health may be seen as a function of exposure to phytochemical diversity. Keith and Zimmerman (2004) suggest that many genes may require complementary action to modify disease processes. In other words, therapy could be more effective if pharmacological agents engaged with more than one biochemical site. Quite likely, the majority of the multitude of plant constituents that ancient humans regularly consumed throughout evolutionary process had a positive effect on many of the health-modifying genes due to the millions of years of history of recurring exposure to multi-component phytochemical mixtures. Observations consistently indicate that people with a phytochemical-rich diet have a significantly improved health status over those with a diet low in phytochemicals (McCarty, 2004). To this author, it seems highly likely that many of the chronic health conditions observed in humans may actually be due to a dietary deficiency in phytochemistry. Minimally processed plant-based foods appear to be important in modulating physiological processes.

Keith and Zimmerman (2004) point out that there are an estimated 10,000 health-modifying genes. It is quite likely that phytochemicals interface with a large percentage of these genes. Unfortunately, the current number of pharmacological targets, approximately 300 to 400, is anemic as compared to the broad phytochemical-gene interfaces that occur in diets rich in plant-based foods.

A pharmacological model that accounts for millions of years of exposure to arrays of phytochemicals not only would recognize plants as inherent sources of medicines, but of a multi-target approach that single-chemical, stand-alone interventions cannot offer (Keith & Zimmermann, 2004). And it returns to the origins of pharmacology, where what humans regularly ingested, somewhere between 80 and 220 plants with an estimated 80,000 to 220,000 secondary metabolites, modified multiple physiological processes in a concerted manner. The understanding of the translational response of numerous proteins to multiple perturbations, such as provided through phytochemistry, holds promise for the fields of medicine and biology—not because it is new insight, but because it is an ancient process that shaped human physiology. Such a paradigm shift would also advance the understanding of biological molecular networks and open up further, more useful therapeutic strategies.

MOLECULAR MODELS OF ACTIVITY

Cellular Membrane and Signal Transduction

Cellular morphology is the result of nonlinear and dynamic molecular flux, especially related to the cell membrane. Although the membrane has been described as a system driven by thermodynamic equilibrium (Aon et al, 1996), it can also accurately seen as an emergent structure consisting of highly asymmetrical structures and phase transitions (Perillo, 2002).

Typically, mammalian cellular plasma membranes consist of about eight major classes of lipids (Simons & Vaz, 2004) that include embedded proteins in its bilipid structure. Signal transduction and the complex behavior of chemical reactions are coupled to the dynamics of

membranes. Thus, the membrane has been closely scrutinized in hopes of further understanding cellular ability to receive, process, and respond to information. Unfortunately, there has been (and still is) an epistemological divide between the analysis of the complex behavior involved in biochemical events and the structural aspects of the membrane involved in signaling phenomena, especially in relation to signal transduction involving exogenous molecules (Perillo, 2002).

Until very recently, explanations of signal transduction were based on a linear model involving successive steps in the decoding process focused on compounds with high affinity and selectivity. However, the membrane is key in its interactions with the ensemble of phytochemicals to which early humans were consistently and constantly exposed. The membrane may also respond to compounds that do not exhibit high affinity and high selectivity to a particular receptor species. Ignoring these interactions may lead to erroneous conclusions in the basic cell sciences.

Significantly, systems properties of heterogeneous molecular ensembles could induce minute differences in the strength of attractive forces among molecules and increased degrees of freedom within a pharmacological system (Buehler, 2003a,b). Just as phase separations and self-assembly processes are systems properties of molecular ensembles, a phytochemical matrix interacting with another biological system requires a pharmacological systems approach (Spelman, 2005). The author proposes three modes of pharmacological activity for phytochemical matrices based on recently elucidated behaviors of the cell membrane; two involve the bilipid membrane and one is based on concerted activity. There are likely many more modes of activity not accounted in the below models.

Cooperative Binding by Receptors: Receptor Mosaics

Proteins form multimeric complexes capable of emergent functions (Agnati et al, 2005a). Thus the discovery of direct receptor–receptor interactions has profoundly shifted the understanding of receptor signal transduction. First, such interactions rigorously challenge the historical belief that the receptor is the minimal unit for drug recognition/activity. Second, the model that high-affinity, high-specificity compounds are superior ligands is also under review (Kenakin, 2004). The existence of various types of receptor mosaics (clusters of receptors functioning as a unit that demonstrate cooperative binding) suggests a plasticity of the steric conformation of receptors (Agnati et al, 2005b). In the receptor mosaic model, each receptor is seen as a subunit of a multimeric protein.

Recall the cooperative binding of oxygen to hemoglobin. After one oxygen molecule binds to hemoglobin, the affinity by the other binding pockets for oxygen increases. Thus, the likelihood of subsequent binding of oxygen molecules is increased.

Cooperativity is considered a mode of self-regulation by multimeric proteins (Koshland & Hamadani, 2002) and is hypothesized to be so for receptor systems as well (Agnati et al, 2005b). In receptor mosaics, the conformational change caused by the binding of the first ligand is transmitted to adjacent receptors with reciprocal contact to change the affinity for subsequent ligand binding. The change in affinity is due to the conformational change induced by the first bound ligand, which induces sequential changes of the multimeric protein's neighboring subunits. This change in protein conformation may make subsequent binding easier (positive cooperativity) or more difficult (negative cooperativity).

Because a phytochemical matrix consists of hundreds of compounds, including groups of constituents that vary slightly in their structure but are based on a common backbone (Yong & Loh, 2004), there may be both high-affinity ligands and lower affinity ligands for a given receptor. Once the high-affinity ligand binds to a species of receptor, other receptors, due to intramolecular transfer of the conformational change to the adjacent peptides, may be able to bind the lower affinity ligands and play a role in cellular messaging. Accordingly, the search for only high-affinity compounds in plants (and microbes) may miss lower affinity compounds that could bind within receptor mosaics due to cooperative binding. This is one possible molecular explanation of the synergy explanation so often invoked by phytotherapists to suggest that plant medicines and foods cannot be reduced to an "active" constituent. The receptor mosaic model also suggests that an expansion is needed of the traditional pharmacological methodology of searching for only high-affinity ligands within plant chemistry (Figure 27-4).

Shifts in Membrane Electronics and/or Shape: Nonspecific Membrane Interactions by Exogenous Molecules

Many components of signal transduction, such as receptors, are anchored in the plasma membrane and therefore are subject to the biochemical milieu of the plasma membrane. Of the four basic receptor signaling modes—gated ion channels, metabotropic receptors, receptor enzymes, and the steroid receptor—three are directly linked to plasma membrane processes. This lipid-rich, two-dimensional environment allows for hydrophobic interactions leading to alterations in component access, orientation and effective concentration (Weng et al, 1999). Hence, modulation of the molecular organization of the membrane may have an effect on signal transduction.

Many drugs are amphiphilic (hydrophobic) molecules and a common site of action for these compounds is the plasma membrane (Perillo, 2002). Among the amphiphilic compounds, many of the central nervous system depressants (Goodman et al, 2001) will, due to their molecular properties, self-aggregate into micelles (Hata et al, 2000; Kitagawa et al, 2004). Despite significant molecular investigation into modes of activity for some of the hydrophobic drugs (e.g. the local anesthetics) no specific receptors have been elucidated (Franks & Lieb, 1984; Schreier et al,

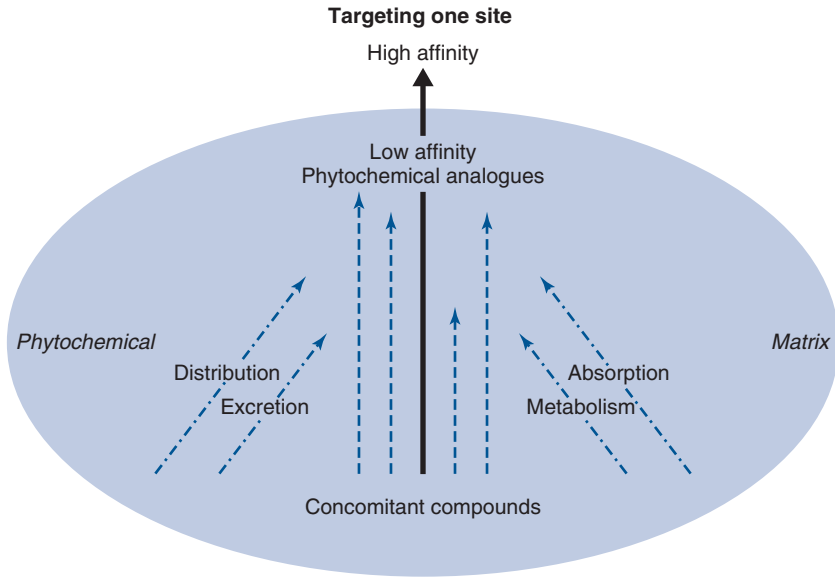

Figure 27-4 The current pharmacological model searches for only high-affinity and selectivity compounds, overlooking lower affinity compounds for receptor (and enzyme) binding. However, given the receptor mosaic model, the low-affinity compounds typically accompanying high-affinity compounds in plant extracts may cooperatively bind affecting signal transduction. Additionally, the concomitant compounds commonly improve pharmacokinetics (absorption, distribution, metabolism and excretion) of the low- to high-affinity compounds.

2000). Rather, these compounds demonstrate activity along the plasma membrane surface itself (Fernandez, 1980; Perillo, 2002; Kitagawa, et al, 2004).

Hydrophobic and amphiphilic compounds and the resulting micelles, may induce shape changes, membrane disruption, vesiculation, and solubilization (Schreier et al, 2000; Kitagawa et al, 2004). Consequently, exogenous molecules may generate membrane asymmetries resulting in membrane tensions (Garcia et al, 2000; Perillo & Garcia, 2001). As expected, given the thermodynamics of open systems far from equilibrium, the membrane perturbations due to curvature tensions and the flux of molecular movements from one monolayer to the other shift the resting state of the membrane and reorganize cellular shape (Perillo, 2002; McMahon & Gallop, 2005). Changes in the curvature of the membrane, as well as composition have demonstrated changes in function of the membrane when it interfaces with an exogenous molecule (Farge & Devaux, 1993; Mui et al, 1993; Garcia & Perillo, 2002; McMahon & Gallop, 2005). Given that protein conformation is dependent on molecular interactions, structural changes may also induce alterations in protein conformation (Simons & Vaz, 2004; Zimmerberg & Kozlov, 2006). This phenomenon could result in signal transduction (Groves & Kuriyan, 2010).

Notably, many of the secondary compounds of plants are amphiphilic or hydrophobic (e.g., hyperforin from St. John's wort and the curcuminoids in *Curucma longa*, alkylamides from *Echinacea* spp.) and would accordingly likely display similar behavior. Given the evolutionary history of plant ingestion by humans, membrane interactions by "non-active" compounds in plants were likely routine. Consumption of a plant led to ingestion of "active" constituents *and* other phytochemicals that influence membrane dynamics. Consequently, with recognition of evolutionary precedent, the combination of compounds affecting the membrane and active compounds binding to receptors was part of routine physiology. This may be a partial explanation why many isolated plant constituents do not appear to function in the same way as when given in a whole plant extract.

Polyvalent Activity: Biochemical Convergence

The last two modes of activity were discussed in the realm of an isolated cell. However, signal transduction involves networks of cells, tissues and organs. Following the science of physics, molecular biology is slowly moving from the study of the components of signaling, to the context in which the signal participates. Study at the molecular level of components alone will not advance the understanding of when and why cells interact in their typically nonlinear, non-local, multiple-feedback loops (Maini, 2002).

Physiology does not run in linear, sequential processes one chemical at a time. Robust systems, like living organisms, are likely quite responsive to numerous but subtle chemical perturbations (Ágoston et al, 2005). Thus multisystem analysis will probably be found to be essential to understanding signaling networks (Plavec et al, 2004). Allowing for models that include multi-target and multipathway assaying could clearly elucidate the informational connectivity of networks. Aon et al (1996) refer to the network of interactions established between the dynamic

subsystems through common intermediates or effectors (hormones and second messengers) as *dynamic coupling*.

It is well established that the overall combination of non-nutritive phytochemicals appears to be key in plants' positive effects on health, that the health-giving effects of plants are *not* always related to the nutrient content (McCarty, 2004), and that significant consumption of secondary compounds from plants play important roles in the prevention of chronic diseases (Liu, 2003). Whereas some constituents are interfacing with receptors and membranes, others are influencing pharmacokinetics. For example, concomitant compounds, frequently considered nonactive constituents, can affect absorption, distribution, metabolism, or excretion of other constituents, enhancing (or antagonizing) their bioavailability (Eder & Mehnert, 2000). Moreover, as the xenohormesis hypothesis suggests, many of the phytochemicals that have been removed from our foodstuffs and medicinal preparations may upregulate beneficial physiological processes.

Recognition of such subtle perturbation would eventually create the understanding of a disease-modifying molecular network and further pharmacological target potential. Monitoring of targets affected by polyvalent groups of compounds will almost certainly lead to the recognition of yet further biochemical webs. Moreover, as our knowledge of the range of perturbable sites improves, proteins expressed from mere "housekeeping" genes will likely be recognized as disease modifying. The outcome could be an expansion of the understanding of the disease-modifying gene network and further therapeutic targets (Keith & Zimmermann, 2004). Such perspective will likely lead to the acknowledgment that a multi-target perturbation, as happens with the consumption of minimally processed plant products, holds the potential for significantly more therapeutic activity than single-chemical, stand-alone interventions.

The ingestion of plants leads not only to the potential of multiple compounds interfacing with multiple targets, but also for single compounds, due to their broad specificity, to engage multiple targets. Generally, the pharmacological sciences consider these molecules "dirty" because of their lack of selectivity. Such molecules are thought to have more potential for generating adverse events because of "off-target" effects than does a highly selective chemical. However, dozens, if not hundreds, of multifunctional compounds are known natural products chemistry to be quite safe (Corson & Crews, 2007). For example, the well-known phytochemical group of the salicylates is known to interact with multiple proteins. The ubiquitous catechins, such as epigallocatechin-3-gallate, have demonstrated considerable chemopreventative activity via induction of apoptosis, inhibiting multidrug resistance pumps, promotion of cell cycle arrest, and inhibiting cyclooxygenase-2 (Khan et al, 2006). The curcuminoids are documented to engage over 60 molecular targets to protect against cancer and regulate the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins (Goel et al, 2008). The not uncommon resveratrol modulates the function of over two dozen enzymes and receptors, leading to protection against cancer, atherosclerosis, and diabetes while promoting endurance (Howitz & Sinclair, 2008).

Csermely et al (2005) have found, using network models of pharmacology, that the partial inhibition of multiple targets offered by a mixture of chemicals is often more efficient than the complete inhibition of a single target. For example, Wald and Law (2003) suggested that a combination of six drugs at subclinical doses—a baby aspirin, three blood pressure drugs (at half the standard dose), a statin, and 800 mcg of folic acid—could extend life by 11 years (Figure 27-5).

In addition, in a meta-analysis encompassing 56,000 patients with hypertension, Law et al (2003) concluded

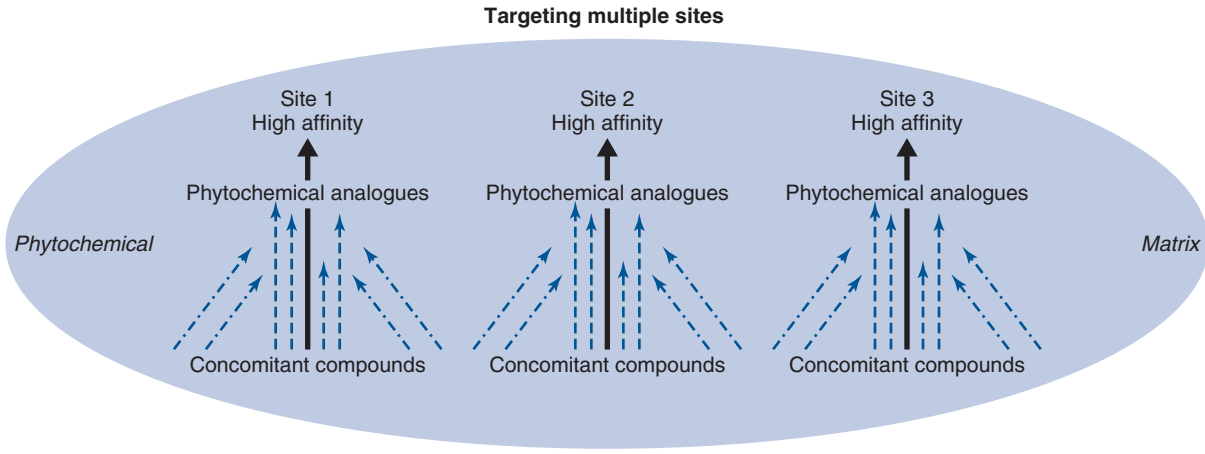

Figure 27-5 Physiology is a complex process that operates in a symphonic manner with multiple receptors, enzymes and genes being affected in any given second. When ingesting a plant extract or food, the phytochemistry triggers many sites concurrently that can then converge on a positive outcome.

that combinations of two or three drugs at half the standard doses delivered comparable therapeutic effects comparable to those of one or two full-dose antihypertension medications. Not surprisingly, the multiple low-dose drug combination was preferable due to the reduction in side effects. Clinicians have historically overcome single target insufficiency by using combination drug therapy such as seen in today's clinical protocols for HIV, tuberculosis, and cancer. Csermely et al (2005) propose that partial drug inhibition by multiple drugs could prove to be a superior pharmacological strategy to strong inhibition by one drug action at a single target. This is likely due to the need for complementary action on multiple targets to modify disease processes (Keith & Zimmermann, 2004).

When combinations of various pharmacological compounds are screened, the natural outcome will almost certainly necessitate further exploration of the connectivity of physiological pathways. Borisy et al (2003) discuss the unexpected but beneficial interactions that a systemic screening of combinations of small molecules reveals. They report, for example, that an antipsychotic agent coupled with an antiprotozoal drug demonstrates antineoplastic activity, and that a fungistatic compound coupled with an analgesic drug produces antifungal activity against resistant strains of *Candida albicans*. In these instances, however, these ensemble properties, if broken apart and studied in isolation, would have never been realized.

It appears that the ensemble properties of a chemical matrix are necessary for physiological and pharmacological effects, and that the purification process from whole plant to isolated compound is inadequate for the elucidation of pharmacological activity (Wagner, 1999; Wang et al, 2004). Moreover, the phytochemical matrix, rather than the phytochemical isolate, offers an opportunity for an enhanced perspective: the study of phytochemical matrices interfacing with mammalian systems, with the addition of improved technology, will almost certainly elucidate molecular networks that have been unseen with previous methodology. The medical sciences would do well to heed Exteberria (2004), who suggests that the properties of a unity cannot be accounted for by accounting for the properties of its components.

SUMMARY AND CONCLUSION

If Gaia theory is accurate, then it stresses the need for seeing humans not as the end-point of evolution, but as cells existing within a larger, grander life form. Medical scientists would do well to realize that we are part of something larger than ourselves. And as such, humans are interdependent on each other, the environment, and other life forms. We are a system within a system within a system, interdependently woven with an inseparable reliance on our planet.

Gaia theory also provides a global context in which to understand life and its adaptive brilliance and highlights the coupling of organism with its environment. This pertains to humans and their coupling with plants. While plants have provided shelter, clothing, food, and medicine, they have also shaped us, influencing our genome, epigenome, and proteome. Moreover, plants have xenohormetically provided environmental molecular messaging that has proven to be physiologically beneficial for humans.

Given that a large number of phytochemicals can directly or indirectly modulate gene expression, and that common phytochemicals appear to play a key role in signal transduction, it follows that the human genome is selected for multiple, concerted biochemical perturbations due to millions of years of recurrent interaction of mammalian genes with heterogeneous phytochemical matrices. The phytochemical intake for Paleolithic humans has been estimated to be at least eight times greater than that of modern humans (and is likely an order of magnitude higher). Many studies have consistently detected that an important association of chronic diseases with lower consumption of plant-based foods, which may be due to decreased intake of phytochemicals. Thus intake of fruits, vegetables, herbs and spices remain critically important in human health.

Our current models of physiology and pharmacology unfortunately still do not fully account for the importance of plants in the human diet. Nutrition and pharmacology are still focused on single constituents and do not recognize the complexity of human physiology interfacing with phytochemical matrices. The multiconstituent nature and ensemble of plant properties likely participate in emergent physiological behavior when ingested by humans. If the ensemble properties of a phytochemical chemical matrix are important for physiological and pharmacological effects, then the purification process from whole plant to isolated compound is inadequate for the elucidation of pharmacological activity of plant-based foods and medicines. Although isolation is methodologically convenient, and economically rewarding, it is not representative of real-time physiology or reflective of human evolution with millions of years of exposure to complex chemical matrices from plants. Pharmacology based on the affinity, selectivity, and acceptable toxicity of an isolated active constituent requires a serious update to match the current understanding of molecular biology. Although the reductionist model has provided some life-saving drugs, basing pharmacology on structure and function provides little indication of the behavior of the interacting biological networks. Even "non-active" compounds in a phytochemical matrix likely play a role in biological networks.

Because biological systems are known to both adapt to environmental context and to reorganize in order to adapt, logical conclusions can be reached:

1. Pharmacological input that presents both high- and low-affinity compounds binding to receptor mosaics is important in signal transduction.
2. There are a multitude of plant compounds that can influence membrane dynamics, which is also likely important in signal transduction.

3. Phytochemical matrices act in a polyvalent manner by perturbing multiple sites.

Thus many phytochemicals act on multiple targets, functionally converging on therapeutic outcomes. Phytochemical matrices may provide an enhanced pharmacological efficiency as compared to isolated compounds. Moreover, the use of phytomedicines, as compared to isolated chemicals, appears to offer a reduced risk of adverse events in the treatment of many diseases.

It seems that the recognition of human evolutionary experience could not only guide the development of a framework for the anemic preventive medicine field, but lead to enhanced understanding of signal transduction for improved pharmacological therapeutics.

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