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The chemistry of defense: Theory and practice

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ABSTRACT **Defensive chemicals used by organisms for protection against potential consumers are generally products of secondary metabolism. Such chemicals are characteristic of free-living organisms with a limited range of movement or limited control over their movements. Despite the fact that chemical defense is widespread among animals as well as plants, the vast majority of theories advanced to account for patterns of allocation of energy and materials to defensive chemistry derive exclusively from studies of plant–herbivore interactions. Many such theories place an undue emphasis on primary physiological processes that are unique to plants (e.g., photosynthesis), rendering such theories limited in their utility or predictive power. The general failure of any single all-encompassing theory to gain acceptance to date may indicate that such a theory might not be a biologically realistic expectation. In lieu of refining theory, focusing attention on the genetic and biochemical mechanisms that underlie chemical defense allocation is likely to provide greater insights into understanding patterns across taxa. In particular, generalizations derived from understanding such mechanisms in natural systems have immediate applications in altering patterns of human use of natural and synthetic chemicals for pest control.**

Irrespective of taxon, the chemicals that play a prominent role in interspecific interactions are rarely the same substances used by an organism to meet the daily challenges of living, such as respiration, digestion, excretion, or, in the case of plants, photosynthesis. They are, in both plants and animals, of "a more secondary character" [to borrow a phrase from Czapek (1)]. These secondary compounds are generally derived from metabolites that do participate in primary physiological processes. In plants, for example, secondary compounds such as alkaloids, coumarins, cyanogenic glycosides, and glucosinolates derive from amino acid; tricarboxylic acid cycle constituents are involved in the formation of polyacetylenes and polyphenols; glucose, aliphatic acids and other "primordial molecules" (2) play a role not only in primary metabolism but in secondary metabolism as well. In insects, many defensive secretions are derived from the same amino acids used to construct proteins [among them, quinones in many beetles and cockroaches derive from tyrosine, formic acid in ants from serine, isobutyric acid in swallowtail caterpillars from isoleucine and valine, and alkyl sulfides in ants from methionine (3, 4)]. Presumably, secondary compounds are physiologically active in nonconspecific organisms precisely because of their secondary nature; it is to be expected that most organisms possess effective means for metabolizing, shunting around, or otherwise processing primary metabolites and it is the unusual chemical that circumvents these mechanisms to cause toxicity.

Unlike primary metabolites, which are practically universal constituents of cells, tissues, and organs, secondary compounds are generally idiosyncratic in distribution, both taxonomically and ontogenetically. Chlorophyll, for example, the principal photosynthetic pigment, is found in virtually all species of angiosperms, in virtually all life stages of virtually all individuals. In contrast, the furanocoumarins are secondary compounds known from only a handful of angiosperm families (5). Within a species (e.g., *Pastinaca sativa*), there is variability in furanocoumarin content and composition among populations (6, 7); within an individual, there is variation among body parts during any particular life stage (8) and temporal variation in the appearance of these compounds over the course of development (9); there are even differences in the content of individual seeds, depending upon their location in an umbel (10), fertilization history (11), and their position within the schizocarp (12).

Secondary chemicals are by definition taxonomically restricted in distribution, yet despite this fact there are patterns in production and allocation that transcend taxa (13). Their presence in an organism is generally characterized by specialized synthesis, transport, or storage. Levels of abundance are subject to environmental or developmental regulation and, unlike primary constituents, which may be present in virtually all cells of an organism, chemical defenses are typically compartmentalized, even in those cases in which the chemicals are acquired exogenously, as when sequestered from a food source. There often exists a system for external discharge, delivery, or activation, not only as a means of ensuring contact with a potential consumer but also as a means of avoiding autotoxicity until a confrontation arises; and of course these compounds are almost invariably, by virtue of structure, chemically reactive (e.g., able to be taken up by a living system, to interact with a receptor or molecular target, and to effect a change in the structure of the molecular target). The remarkable convergence of structural types in plant and insect secondary metabolites is at least suggestive that the processes leading to biological activity in both groups share certain fundamental similarities (14).

Secondary chemicals can be said to be defensive in function only if they protect their producers from the life-threatening activities of another organism. Distinguishing between offensive and defensive use of chemicals is difficult, and present terminology does little to assist in making that distinction. The term "allomone" is frequently used synonymously with "chemical defense," yet allomones are not necessarily defensive in function. An allomone has been defined as a chemical substance beneficial to its producer and detrimental to its recipient (15), so chemicals used by a predator to lure prey (16) are rightly regarded as allomonal but are not obviously defensive. By the same token, chemicals that reduce competition for limited resources, clearly beneficial to the producer, may be defensive of those resources but are not necessarily defensive in the life of the organism producing them. Allelopathic

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compounds produced by a plant species may increase fitness of a plant by preempting a resource, such as water or soil nitrogen, that might otherwise be exploited by other plants (17), but in the sense that such compounds can kill potential competitors (such as nonconspecific seedlings) they are used in an offensive fashion, as for range expansion at the expense of another organism.

A defensive chemical, then, is a substance produced in order to reduce the risk of bodily harm. As such, most are poisons—defined as "any agent which, introduced (especially in small amount) into an organism, may chemically produce an injurious or deadly effect" (18). This rather restrictive definition may not be universally embraced by chemical ecologists. On one hand, the definition implies an interaction with another organism and, particularly with respect to plants, secondary compounds may fulfill many functions in the life of the producer organism other than producing injurious or deadly effects on other organisms (19, 20). Many plant secondary compounds, for example, are inducible by UV light and presumably serve to protect (or "defend") plants from damaging effects of UV exposure (21); by no stretch of the imagination can such compounds be considered poisons, since they exert no injurious effects on the damaging agent, the sun. In this context, they can no more be considered "defenses" than cell wall constituents can be considered "defenses" against gravity. On the other hand, some investigators, while acknowledging the fact that secondary chemicals have deleterious effects on other organisms, are reluctant to ascribe their presence, particularly in plants, to selection pressure exerted by those organisms (22–24). Calling certain secondary chemicals "defenses" would be giving credence to the assertion that they exist only by virtue of the selection pressures exerted by consumers. Nonetheless, an examination of the distribution, pattern of allocation, chemical structure, and modes of action of secondary compounds in a broad cross section of organisms reveals so many striking convergences and similarities that the notion that variation in the distribution and abundance of chemicals that act as poisons results at least in part from selection by consumer organisms certainly seems tenable, if not inescapable.

Distribution of Defenses

One line of evidence, admittedly circumstantial, that consumers have influenced the evolution of chemical defenses is their taxonomic distribution. There are entire phyla in which chemical defenses have never been identified (Table 1). Undoubtedly, in many cases this absence of chemical defenses may result simply from an absence of studies explicitly designed to discover them—for many small, obscure organisms, life histories, let alone chemistries, are poorly known. This problem may not be as severe a problem as it might appear, because chemically defended organisms often call attention to themselves by way of aposematic coloration (Table 1) (in fact, it may well be that effective defenses, particularly chemical ones, may be a prerequisite for a conspicuous life-style among smaller organisms). Nonetheless, any reported absence of chemical defense may be artifactual due to incomplete information. With that caveat in mind, it is interesting to note that conspicuously abundant on the list of the chemically defenseless are phyla comprised exclusively of parasitic animals. As well, chemical defenses are absent in entirely parasitic orders within classes (Phthiraptera and Siphonaptera in the class Insecta, for example). These organisms are subject to mortality almost exclusively by their hosts, and poisoning or otherwise severely impairing a host is unlikely to enhance lifetime fitness of a parasite (particularly those parasites that cannot survive more than a few hours without one).

Chemical defenses are also rare in organisms at the top of the food chain—organisms that are themselves at low risk of being consumed. Large vertebrates, by virtue of size, speed, and strength, often occupy that position in both terrestrial and aquatic ecosystems (carnivores and odontocetes, for example). Chemically defended mammals include skunks and the duck-billed platypus, both opportunistic scavengers (32). Among birds, chemical defense has been demonstrated to date only in the pitohui (25), which feeds on leaf litter invertebrates (J. Daly; ref. 79), but likely exists in the conspicuously colored female hoopoe, which "has a strongly repulsive musty smell that emanates from her preen gland, and is believed to have a protective function like attar of skunk" (33). Hoopoes are also opportunistic feeders that consume debris along with insects and other invertebrates. It is somewhat surprising that chemical defenses are not more frequently encountered among small birds, but the absence of reports may be due to the tendency of investigators to assume conspicuous plumage results from sexual selection, rather than aposematism and distastefulness (25).

In contrast with fast, strong predators, organisms with a limited range of movement, or limited control over their movements—those that cannot run away from potential predators—are well represented among the chemically defended (Table 1). Sessile marine invertebrates are particularly accomplished chemists; these include in their ranks sponges, anthozoan corals, crinoid echinoderms, polychaetes, bryozoans, brachiopods, and tunicates (26, 34). Completely consistent with the pattern is the virtually universal presence of toxins in plants, ranging from mosses to angiosperms (4), most of which remain firmly rooted to the ground for most of their lives and occupy the bottom rung of most food chains. It is interesting to note that chemically defended taxa tend to be more speciose than those lacking chemical defenses, but whether this relationship reflects sampling vagaries or causation is anybody's guess.

Patterns of Allocation

Secondary chemistry differs from primary chemistry principally in its distributional variability and it is this variability that has intrigued ecologists for the past 30 years. Theories [or provisional hypotheses (35)] to account for the structural differentiation and function of secondary metabolites, as well as the differential allocation of energy and materials to defensive chemistry, abound, but they are almost exclusively derived from studies of plant–herbivore interactions (Table 2). This emphasis may be because the function of secondary chemicals in plants is less immediately apparent to humans, who have historically consumed a broad array of plants without ill effects, so alternative explanations of their presence readily come to mind. The fact that animals upon disturbance often squirt, dribble, spray, or otherwise release noxious substances at humans and cause pain leads to readier acceptance of a defensive function [although there are skeptics who are unconvinced of a defensive function of certain animal secondary compounds—Portier (48), for example, reports that "Certains auteurs voient dans les glandes nucales (of swallowtail caterpillars) un appareil d'élimination de substances toxiques ou tout au moins inutilisables contenus dans la nourriture"]. Why plants, by virtue of their ability to photosynthesize, should occupy a unique place in theories of chemical defense allocation is unclear. Plants produce secondary compounds as derivatives of primary metabolism; animals do the same. In fact, plants may be rather unrepresentative of chemical defense strategies as a whole in that they rarely coopt defense compounds from other organisms via sequestration, although there are exceptions to the general rule [e.g., parasitic plants (49–51)].

The relative importance of consumer selection pressure in determining patterns of production of secondary compounds varies with the theory. Coley *et al.* (44) suggest that resource availability and the concomitant growth rate of a plant, more

Table 1. General survey of the distribution of chemical defenses (3, 25–30) and certain life history characteristics (31) in animals

Animal phyla in which chemical defenses are rare or unreported

- Platyhelminthes,[*,†] 15,000 spp.
- Rhynchocoela,[†] 650 spp.
- Gnathostomulida, 80 spp.
- Gastrotricha, 400 spp.
- Rotifera, 2000 spp.
- Kinorhyncha, 100 spp.
- Acanthocephala,[*] 500 spp.
- Nematoda,[*] 1500 spp.
- Nematomorpha,[*] 100 spp.
- Phoronida,[‡] 10 spp.
- Pogonophora,[‡] 80 spp.
- Onychophora, 70 spp.
- Echiurida, 100 spp.
- Tardigrada, 400 spp.
- Pentastomida,[*] 60 spp.
- Priapulida, 9 spp.
- Chaetognatha, 65 spp.
- Chordata: Cephalochordata, 28 spp.
- Chordata: Vertebrata
    - Chondrichthyes, 800 spp.
    - Aves,[†] 8600 spp.
    - Mammalia, 4500 spp.

Animal phyla in which autogenous chemical defenses are documented

- Porifera,[†,‡] 5000 spp.
    - Sesquiterpenes, sesterterpenes, dibromotyrosine derivatives, isonitriles, isothiocyanates, polyalkylated indoles, macrolides, quinones, ancepsenolides, sterols
- Coelenterata:[†,‡] Anthozoa
    - Alcyonaria, 9000 spp.
        - Sesquiterpenes, diterpenes, alkaloids, prostaglandins, pyridines
    - Zoantharia
        - Peptides, proteins
- Ectoprocta,[‡]
    - Tambjamine pyrroles, 4000 spp.
- Brachiopoda,[‡] 300 spp.
- Mollusca:[†] Gastropoda, 50,000 spp.
    - Opistobranchia
        - Sesquiterpene dialdehydes, dimenoic acid glycosides, haloethers
    - Prosobranchia
        - Triterpenes
    - Pulmonata
        - Polyproprionates
- Annelida (Polychaeta[†,‡]), 5300 spp.
    - Phenolics
- Arthropoda:[†] 800,000 spp.
    - Insecta
        - Hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids, quinones, esters, lactones, phenolics, steroids, alkaloids, cyanogenic glycosides, sulfides, peptides, proteins
    - Arachnida
        - Quinones, alkaloids, cyanogenic glycosides
- Echinodermata,[†] 6000 spp.
    - Holothuroidea
        - Steroidal glycosides, saponins
    - Crinozoa[‡]
        - Polyketide sulfates
    - Asterozoa
        - Phenolics, saponins, steroidal glycosides
- Chordata, 1250 spp.
    - Tunicata[†,‡]
        - Bipyrrole alkaloids, cyclic peptides, quinones, macrolides, polyethers
    - Vertebrata: Osteichthyes[†], 22,000 spp.
        - Alkaloids, peptides
    - Amphibia,[†] 3150 spp.
        - Alkaloids
    - Reptilia,[†] 7000 spp.
        - Alkaloids, hydrocarbons, aldehydes, acids

[*] Many species parasitic.
[†] Many species conspicuously colored.
[‡] Many species sessile.

than its potential risk of herbivory or its historical association with herbivores, determine the type and quantity of chemical defenses in plants; while "the predictability of a plant in time and space may influence the degree of herbivore pressure . . . it should be included as a complementary factor," rather than as the sole driving force in the evolution of chemical defenses and their allocation patterns. Bryant *et al.* (43) suggest that carbon and nutrient availability alone can determine patterns of chemical defense allocation; according to this hypothesis, "environmental variations that cause changes in plant carbohydrate status will lead to parallel changes in levels of carbon-based secondary metabolites" (52). Such theories, along with the contention that "the evolution of plant defense may . . . have proceeded independent of consumer adaptation" (23), are in many ways reincarnations of "overflow metabolism" or "biosynthetic prodigality" hypotheses that reappear intermittently (53, 54). Yet how overflow metabolism can generate and maintain biochemical *diversity*—hundreds of biosynthetically distinct and unique classes of secondary metabolites—is an enigma.

Table 2. Chemical defense theories

	Ref.
Theories to account for allocation of chemical defenses in plants	
Plant stress hypothesis	36
Latitudinal pest pressure gradients	37
Plant defense guilds	38
Apparency theory	39
Toxin/digestibility reduction continuum	40
Optimal defense theory	41
Optimal defense theory	42
Carbon/nutrient balance hypothesis	43
Resource availability hypothesis	44
Environmental constraint hypothesis	45
Plant vigor hypothesis	46
Growth-differentiation balance hypothesis	47
"Probability" hypothesis	23
Theories to account for allocation of chemical defenses in animals	
?????	

Essentially (and rightly) undisputed is the fact that novel secondary compounds arise by genetic accident—by mutation or recombination—so it is not altogether surprising that, given the idiosyncratic nature of mutations, the distribution of biosynthetic classes of compounds is idiosyncratic as well. At issue, however, is how certain mutations become established within a population or species. Mutant individuals can increase in representation in populations either as a result of positive selection or as a result of random genetic events, such as drift; fixation by drift occurs only when there is no negative selection against the trait. It is a virtual certainty that at least some portion of the chemical variability of plants (and probably of all organisms) is nonadaptive—vestiges of past selection pressures no longer experienced due to extinctions, transient occurrences of secondary metabolites generated by indiscriminant enzymatic transformations, and the like (23). But predictable and highly specific accumulation of particular types of chemicals in taxonomically related species in particular organs in particular portions of the life cycle regulated by promoters that respond to chemical cues from consumer organisms (55, 56) seems inconsistent with such nonspecific processes.

Very little discussion to date in plant–insect interactions has centered on why certain secondary metabolites are built the way they are and why they act the way they do on consumer organisms. In vertebrates, "overflow metabolism" ends up almost exclusively converted to adipose tissue, despite the demonstrable ability of at least a few vertebrates to manufacture secondary metabolites; such tissue, in times of nutrient deprivation, is in fact readily mobilized by its producer. Why plants, which have the capacity to make glucose and, from glucose, the storage material starch, should make secondary compounds as "overflow" metabolites is unclear. Since glucose is a starting material for much of secondary metabolism, it is difficult to conceive of how such elaborate pathways could evolve in the absence of any selection pressure other than whatever problems may be associated with fixing too many carbon atoms. The suggestion that "high tissue carbohydrate carbon concentrations cause more carbon to flow through pathways leading to the synthesis of carbon-based secondary metabolites [and that] this effect of mass action on reaction rates is . . . stronger than any enzymatic effects such as feedback inhibition due to end-product accumulation" (52) runs counter to the many observations that secondary metabolite production is otherwise finely regulated by enzymes physically, temporally, and developmentally within a plant (57). In fact, such physiological responses to sunlight sound positively pathological.

Recent allocation theories generally classify chemicals based on criteria other than specific structure or biosynthetic origin. "Carbon-based" compounds (43, 52) are considered as a more-or-less homogeneous group, despite the fact that they include biosynthetically unrelated groups with wildly different activities as well as transport and storage requirements. The same is true for "N-based" compounds; the dichotomy between N-based and C-based compounds does not appear to take into consideration the fact that N-based compounds may actually contain more carbon atoms than smaller C-based compounds, and C-based compounds may require more investment in N-based enzymes for synthesis and storage than do many N-based compounds. Rather, there is a focus on whether or not secondary compounds are easily metabolized, or turned over, by the plants producing them [as in Coley *et al.* (44), "mobile" and "immobile" defenses] or whether they are accumulated in large or small quantities (39). Yet more defense does not necessarily lead to better defense—adding small amounts of biosynthetically different chemicals may by synergism enhance existing defenses more effectively than greatly increasing the concentration of those existing chemicals (58); such interactions cannot be evaluated if only a single type of chemical is quantified. Secondary chemicals are not like muscles—pumping them up is not always the most effective strategy for overcoming an opponent.

Despite the growing number of studies failing to confirm at least one of the predictions of the carbon/nutrient balance hypothesis [24 such studies are cited in Herms and Mattson (59)], it remains popular as a testable hypothesis, as do several of its predecessors as well as its successors. In fact, none of these theories has really ever been resoundingly rejected; they all more-or-less coexist, by virtue of supportive evidence in some system or other. Studies of plant–herbivore interactions are in a sense unique in the field of chemical ecology; no other area is quite so rife with theory. One problem with attempting to develop an all-encompassing theory to account for patterns of defense allocations [as called for by Price (35) and Stamp (60)] is that such a theory may not be a biologically realistic expectation even for just the plant kingdom. Most theories certainly suit the specific systems from which they were drawn, which of necessity constitute only a tiny fraction of all possible types of interactions; it is when they are generalized that the fit breaks down. That many theories coexist is at least in part due to the fact that they are not mutually exclusive—they all share certain elements. If there is a recurrent theme in the past century of discussion, it is that chemical defenses confer a benefit and exact a cost. Much current controversy centers not on the existence of costs and benefits but on the magnitude of those values. Resource availability hypotheses (43, 44) focus on material costs of production; herbivory-based hypotheses (39–42) focus on benefits accrued. So if a ratio is to be tested, better that it simply be the benefit/cost ratio—that is, the benefits of a chemical, in terms of fitness enhancement in the presence of consumers, relative to the costs of a chemical, in terms of fitness decrements resulting from its production, transport, storage, or deployment.

This approach is not without its shortcomings, the greatest of which is that costs and benefits have proved to be exceedingly difficult to measure. There is far from a consensus on what constitutes an appropriate demonstration of costs of chemical defense (57, 61, 62). In many theoretical discussions of costs of defense, particularly in plants, costs are measured in terms of growth rates (44, 59, 63), rather than in terms of reproductive success. In many empirical estimates of costs, the chemical nature of the defense is not defined (64) or secondary metabolites are measured in bulk (65), without any regard to their individual activities. On the other side of the coin, measuring the benefits of synthesizing a particular chemical compound requires an intimate knowledge of the interactions of the producer organism with its biotic environment. Bioassays of both plant and animal defenses tend to be done with isolated compounds against laboratory species that are easily reared (66); in the future, bioassays may need to be done with more ecologically appropriate species (and possibly with a whole suite of agents acting simultaneously) (67). None of these requirements is likely to make this enterprise any more tractable than it is at the moment.

There are advantages, however, in taking such a basic approach to understanding chemical defense allocation. First of all, expressing costs and benefits in terms of fitness couches the discussion in an evolutionary framework, a framework that is missing from many current discussions of plant–herbivore interactions. No discussion of adaptation can be purely ecological, since the process of adaptation is an evolutionary one; in all of the discussions of life history syndromes associated with defensive strategies (39–42, 59), virtually no evidence exists that any of the traits characterizing these syndromes are genetically based or, equally important, genetically correlated and likely to evolve in concert. Current patterns of allocation observed today are the result of an evolutionary process and are likely to change in the future as a result of evolutionary processes; it is difficult to appreciate ecological patterns without at least a rudimentary understanding of their evolutionary underpinnings and understanding the evolutionary process necessitates identifying selective agents and quantifying the selective forces they exert.

Restoring evolution to a place of prominence in future discussions of chemical defense means greatly increasing attention to the genetics of chemical defense production and allocation. Research pursuits in the study of chemical defense that should receive a renewed interest in this context include (*i*) investigation of multiple classes of secondary metabolites within a species, (*ii*) establishment of the genetic basis for chemical variability within a species, (*iii*) testing for toxicological interactions and genetic correlations, (*iv*) determination of genetic correlations between chemistry and life history traits, (*v*) precise estimation of consumer effects on fitness and influence of chemical variation on those effects, and (*vi*) elucidation of modes of action and mechanisms of genetically based counteradaptation in consumers. All of these pursuits require a sophisticated understanding of the biochemistry of a particular system, such that individual metabolites, not functional categories of secondary compounds, are identified, quantified, and monitored. The fact that secondary compounds may be involved in functions other than defense against consumers cannot be overlooked, particularly if expected genetic correlations fail to materialize.

An additional advantage of examining chemical defense allocation in the simplified context of benefit/cost analysis in particular systems is that such an approach is essentially unbiased relative to taxon. Theories derived from plant–herbivore interactions place an undue emphasis on the ability of plants to synthesize their primary metabolites from inorganic elements, but that ability may not necessarily be reflective, or predictive, of abilities to synthesize secondary metabolites. There is undeniably some degree of linkage between primary and secondary metabolism—at the very least, dead plants do not manufacture secondary metabolites—but there is little evidence to support the linear relationship that is assumed to prevail between them. If secondary metabolism cannot be totally divorced from primary metabolism in studying the ecology and evolution of chemical defense, irrespective of whether it takes place in plants, animals, or any other organisms, it may be productive for a while at least to arrange for a trial separation and see whether paradigms change.

Special Case: Human Chemical Defenses

One compelling reason for examining patterns of chemical defense across taxa, and across trophic tiers, in order to distill out basic elements is that such an approach is essential in understanding chemical defense allocation in a seriously understudied species—*Homo sapiens.* By all rights and purposes, human beings should not utilize chemical defenses; as top carnivores in many food webs, they are rarely if ever consumed by other organisms [but see "Little Red Riding Hood," in Lang (68)]. Notwithstanding, humans have used every variant on chemical defense manifested by other organisms (Table 3). Like insects (69), parasitic plants (49–51), some birds (70), and marine invertebrates (26, 67) and vertebrates (71), humans have coopted plant toxins to protect themselves against their consumers; the use of botanical preparations to kill insects, parasitic and otherwise, antedates written history (72). Many of the chemicals in use today as biocides, including antibiotics, are derived from other organisms. Natural products provide ≈25% of all drugs in use today (73) and botanical insecticides (or their chemically optimized derivatives) are still widely used as pest control agents (74). More recently, like many species of plants (4), insects (3), marine invertebrates (26), and vertebrates (27), humans have taken to synthesizing their own defensive compounds from inorganic materials, primary metabolites or from small precursor molecules, although this synthesis takes place in a laboratory or factory rather than in a cell or gland. In doing so, humans face many of the same challenges faced by other organisms that synthesize chemicals (Table 3)—in addition to the actual synthesis, the storage, transport, and avoidance of autotoxicity all exact an economic cost, and the product is "selected" by consumers based on its efficacy and its range of uses relative to other products.

Although there are similarities between humans and other organisms in the acquisition of chemical defenses, there are striking differences in the deployment of these defenses (Table

Table 3. Human chemical defense characteristics

Parallels between humans and other organisms	
Humans face	*Other organisms face*
Material and energy construction costs	Material and energy construction costs
Shipping, storage, and handling costs	Solubility, transportability, autotoxicity costs
Delivery costs, environmental impact, and autotoxicity considerations	Problems associated with delivery—toxicity to mutalists, increased visibility to specialists
"Opportunity costs"—alternative practices	"Opportunity costs"—alternative functions
Customer satisfaction associated with efficacy and versatility	Selection for mode of action, degree of efficacy, and range of organisms affected
Loss of sales due to resistance acquisition	Loss of efficacy due to consumer adaptation
Differences between humans and other organisms	
In humans, chemicals are used	*In other organisms, chemicals are used*
Prophylactically	Inducibly (elicited by damaging agent)
To kill	To minimize impact of consumer
In a broadcast fashion	In a tissue- or otherwise site-specific fashion
As single purified toxins	As variable mixtures

3). Whereas most organisms use chemical defenses to minimize their own risk of being consumed, humans use chemicals in an offensive fashion, with the express purpose of killing off not only potential consumer organisms but also potential competitors for food or shelter. Throughout history, humans have even used chemicals to kill off conspecific competitors, a use of chemicals that is certainly unusual in the natural world (75). But humans have for the most part adopted the chemicals used by other organisms as defenses without at the same time investigating the manner in which these chemicals are deployed.

In general, chemical defenses in other organisms reflect the probability of attack and relative risk of damage (42); humans have in recent years developed a tendency to use chemical defenses prophylactically, even when potential enemies are absent. Humans tend to select those chemical agents that kill, rather than repel or misdirect, a large proportion of the target population; from a plant's perspective, the ultimate goal of chemical defense is to avoid being eaten, a goal that is as achievable if the plant is never consumed in the first place as it is if the consumer dies after ingesting a mouthful of toxin-laced tissue. Most organisms manufacture complex mixtures of chemicals for defense, some of which may actually be inactive as pure compounds (58); humans tend to prefer highly active individual components. It is perhaps the ecologically inappropriate deployment of these natural products (and their synthetic derivatives) by humans that has led to the widespread acquisition of resistance in all manner of target species and the concomitant loss of efficacy of these chemicals (76).

Efforts in recent years to identify natural sources of insecticidal and other pesticidal materials have increased, at least in part due to continuing problems with nontarget effects of synthetics and the widespread appearance of resistance to these compounds. Natural products are thought to offer greater biodegradability and possibly greater specificity than synthetic organic alternatives (77). However, the search for new biocidal agents is being conducted essentially as it has been done for the past century, with mass screening, isolation of active components, and development of syntheses for mass production of the active components (77, 78). Little or no effort is being expended by those interested in developing new chemical control agents in elucidating the manner in which plants or other source organisms manufacture, store, activate, transport, or allocate these chemicals. By understanding the rules according to which organisms defend themselves chemically, there is perhaps as much to be gained, in terms of developing novel and environmentally stable approaches to chemical control of insects and other pests, as there is by isolating and identifying the chemical defenses themselves.

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