



## THE FUNCTION OF ALLERGY: IMMUNOLOGICAL DEFENSE AGAINST TOXINS

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### ABSTRACT

*This paper proposes that the mammalian immune response known as "allergy" evolved as a last line of defense against the extensive array of toxic substances that exist in the environment in the form of secondary plant compounds and venoms. Whereas nonimmunological defenses typically can target only classes of toxins, the immune system is uniquely capable of the fine-tuning required to target selectively the specific molecular configurations of individual toxins. Toxic substances are commonly allergenic. The pharmacological chemicals released by the body's mast cells during an IgE antibody-mediated allergic response typically cause vomiting, diarrhea, coughing, tearing, sneezing or scratching, which help to expel from the body the toxic substance that triggered the response; individuals frequently develop aversions to substances that have triggered such responses. A strong allergic response often includes a decrease in blood pressure, which slows the rate at which toxins circulate to target organs. The immune system identifies as toxic the following kinds of substances: (1) those low-molecular-weight substances that bind covalently to serum proteins (e.g., many plant toxins); (2) nontoxic proteins that act as carriers of toxins with low molecular weights (e.g., plant proteins associated with plant toxins); (3) specific substances of high molecular weight that harmed individuals in ancestral mammalian populations for a span of time that was significant from the standpoint of natural selection (e.g., the toxic proteins of bee venom).*

*Substances that bind covalently to serum proteins generally are acutely toxic, and because many of these substances also bind covalently to the DNA of target cells, they are potentially mutagenic and carcinogenic as well. Thus, by protecting against acute toxicity, allergy may also defend against mutagens and carcinogens. The toxin hypothesis explains the main phenomena of allergy: why IgE-mediated allergies usually occur within minutes of exposure to an allergen and why they are often so severe; why the manifestations of allergy include vomiting, diarrhea, coughing, sneezing, scratching, tearing, and a drop in blood pressure; why covalent binding of low-molecular-weight substances to serum proteins frequently causes allergy; why allergies occur to many foods, pollens, venoms, metals, and drugs; why allergic cross-reactivity occurs to foods and pollen from unrelated botanical families; why allergy appears to be so capricious and variable; and why allergy is more prevalent in industrial societies than it is in foraging societies. This hypothesis also has implications for the diagnosis, prevention, and treatment of allergy.*

### INTRODUCTION

**A**LLERGY IS COMMONLY perceived to be an immunological anomaly. In the

nonallergic immune response, the activation and proliferation of immune defenses against a foreign antigen usually ensure swift containment of that antigen upon subsequent expo-

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sures, with decreasingly severe pathological consequences. In the allergic response, by contrast, the activation and proliferation of immune defenses against an antigen can cause increasingly severe pathological consequences upon subsequent exposures to that antigen. Most antigens that cause significant nonallergic immune responses are pathogens, such as bacteria and viruses, whereas most allergenic antigens (allergens) are seemingly innocuous substances, such as foods and pollens, which are often tolerated by the immune systems of many individuals.

#### *Allergies Are Usually Viewed as Immunological Mistakes*

Although many of the physiological mechanisms of the allergic response have been revealed since the discovery by Ishizaka and Ishizaka (1967) of the allergy-inducing IgE class of antibody, a functional explanation of allergy has remained elusive. Currently there are two main views of allergy. One view is that allergy is an aberrant or malfunctioning form of immunological response: "Allergy appears to be a genetically determined disorder characterized by a tendency to form IgE antibodies in response to challenge with protein antigens. The basic defect may be a dysregulation of immune responsiveness, affecting also the antibody pattern normally induced" (Hammarstrom and Smith, 1987:529); such statements are not uncommon in the allergy literature. It is this view that is generally presented to the allergic public, in statements such as "Researchers have found that, ironically, allergy results from malfunctioning of the immune system" and "It is not yet known where in this system the 'mistake' that leads to allergy occurs" (National Jewish Center for Immunology and Respiratory Medicine, 1986:1,2). This view, however, cannot account for the evolution of a specific class of mammalian antibody (IgE) whose sole known purpose is to trigger the symptoms of allergy.

The other main view of allergy is that it functions to defend against helminths (parasitic worms)—a view that places allergy in the traditional immunological role of defending against pathogens and their harmful products. High levels of IgE antibodies often accompany chronic helminth infections, leading some researchers to conclude that the allergic response

evolved to protect mammals against helminths (e.g., Godfrey, 1975; Dessaint and Capron, 1989). Other researchers, however, have noted that the IgE antibodies produced during helminth infections appear to be ineffective in combatting such infections and, in fact, may cause more harm than good to the host through injurious tissue inflammation (Ogilvie and Jones, 1973; Mitchell, 1979; Jassim et al., 1987). Furthermore, the overwhelming majority of allergens are not helminths, helminth products, or substances containing helminths; rather, they are pollens, foods, drugs, venoms, and metals. The hypothesis that allergy functions to combat helminths cannot account for the IgE-mediated responses (IgE responses) to the thousands of naturally occurring substances that have turned out to be allergenic, and it implies that the vast majority of allergic responses are immunological mistakes (i.e., it implies that allergic responses are to substances that IgE antibodies were not designed by selection to target). Dessaint and Capron (1989:118), for example, suggest that "a number of clinically significant allergic responses to environmental antigens may reflect the inappropriate activation of immunologic circuits or effector pathways ordinarily initiated by helminths." Were the function of allergy to protect against helminths, however, the mechanisms of allergy would be so ill-designed for their intended purpose that they almost always malfunction. (The helminth hypothesis is discussed in detail below.) Platts-Mills (1987) refines the helminth hypothesis, suggesting that immunological hypersensitivity (as allergy is often described) may be the unfortunate but necessary cost of maintaining sufficient immune surveillance against helminths. It is not clear, however, why IgE-mediated responses should be the only kind of immune response to pathogens that frequently entails severe hypersensitivity to seemingly innocuous substances. In summary, each of the aforementioned explanations for allergy regards most incidences of allergy as immunological errors in which the immune system responds to primarily innocuous substances as if they were dangerous.

#### *The Mechanisms of Allergy Manifest Evidence of Adaptive Design*

The evolutionary persistence of the allergic capability, despite its physiological costs, im-

plies the existence of an adaptive benefit for this capability that outweighs the costs; this undermines the view that allergy is an immunological error. The specialized mechanisms that collectively constitute the allergic response appear to manifest adaptive design in the precision, economy, efficiency, and complexity with which they achieve the goal of producing allergy [see Williams's (1966) criteria for detecting adaptive design]. IgE antibody molecules are functionally distinguished from other classes of antibodies by their allergy-inducing properties, and they are structurally distinguished from other classes by a particular chain (type epsilon) in one of their molecular subunits. The IgE class of antibodies is thought to have evolved in vertebrates within the last 300 million years, before the evolution of modern mammals (Hadge and Ambrosius, 1984). Although most mammalian species have not been tested for IgE antibodies or allergic capability, IgE-mediated allergic responses are known to occur in many placental species, including monkeys, dogs, rats, mice, cows, rabbits, and guinea pigs (Neoh et al., 1973; Klein, 1982: 549; Stokes et al., 1987; Kepron et al., 1987). Allergy-like symptoms occur in nonplacental mammals and in many nonmammals as well. The marsupial quokka (*Setonix brachyurus*), for example, has an IgE-like antibody that induces immediate hypersensitivity (Manning and Turner, 1976:157); this antibody may be homologous to the IgE. Various species of reptiles and birds suffer immediate symptoms that resemble mammalian allergies when re-exposed to a particular antigen in immunization experiments (Gershwin, 1978). Fletcher and Baldo (1974) have shown that flatfish have immediate hypersensitivity responses to fungal extracts (but these responses apparently occurred upon initial rather than subsequent exposure to the extract, and so may neither functionally resemble mammalian allergies nor represent homologous genes). These findings indicate that the evolutionary age of IgE-mediated allergy is likely to match or surpass that of placental mammals, which Prager and Wilson (1988) report to be 60 to 80 million years.

The immunological mechanisms of allergy constitute a network of specialized cells and molecules that recognize a specific antigen as foreign and initiate its containment. The sur-

faces of the immune system's B lymphocytes (B cells) and T lymphocytes (T cells) exhibit specific molecular configurations that enable them to bind to antigens that complement those configurations. The set of all B cells and T cells displays a vast array of molecular configurations, enabling the immune system to defend against a vast array of antigens. In order to elicit a primary immune response, an antigen generally must have a minimum molecular weight of about 2,000; antigens of lower molecular weight usually can trigger an immune response only if they are bound as haptens to a high-molecular-weight carrier, such as a serum protein. B cells in the bloodstream and lymphatic system bind to antigens that complement their molecular binding sites (surface immunoglobulin molecules) and, when activated by T cells, secrete numerous antibodies (immunoglobulin molecules) that neutralize the antigens and mark them for elimination. Mammalian antibodies are produced as five classes—IgM, IgA, IgD, IgG, IgE—which differ in their concentrations in the bloodstream, their distribution sites throughout the body, their tendencies to bind to certain types of antigen, and the physiological responses they elicit.

The only known immune response mediated by IgE antibodies is immediate-type allergy, in which symptoms are usually manifested within a few minutes to an hour after exposure to the allergen. (The IgE response to helminths can be regarded as a type of allergy, and will be discussed below.) The serum levels of IgE antibodies are normally orders of magnitude lower than the levels of IgM, IgG, and IgA antibodies, but they often increase manyfold at the onset of allergy. There is substantial individual variation in IgE and other antibody levels (Geller-Bernstein et al., 1988). In general, IgE levels are higher in allergic than in nonallergic individuals (Berciano et al., 1987; Abdullah et al., 1987; Bennett et al., 1987; Husz et al., 1988; Burrows et al., 1989), but the respective ranges overlap. What may be important in the relationship of IgE levels to allergy is not the absolute serum level of IgE, but rather, for any given individual, the ratio of the IgE antibody levels before and after the development of allergy and the ratio of IgE levels to those of other classes of antibodies.

Certain types of allergy have delayed symptoms (typically beginning about 24 hours af-

ter exposure to the allergen) which are mediated primarily by T cells rather than by IgE antibodies. Although most of the following discussion refers to classical, IgE-mediated allergy, T-cell-mediated allergy—in particular, contact allergy, which can occur after contact with substances such as poison ivy—is discussed below in relation to the type of allergens that typically elicit it. Although T-cell-mediated responses in general are regarded as adaptive, T-cell-mediated allergies are usually regarded as maladaptive. A similar functional hypothesis for IgE-mediated allergy and T-cell-mediated contact allergy is presented here.

Allergy occurs upon reexposure to an antigen that has previously triggered the formation of IgE antibodies. IgE antibodies are produced when helper T cells induce antigen-bound B cells to proliferate and differentiate into IgE-secreting plasma cells. Many of these IgE antibodies then bind to specialized IgE receptors on the surfaces of mast cells, which contain various potent allergy-inducing chemicals, such as histamine (Wasserman, 1980; Morley et al., 1984), and which are present in the connective tissues and on many epithelial surfaces, including those of the respiratory tract, gastrointestinal tract, urinary tract, nasal passages, and skin (Meggs and Metcalfe, 1984; Schick and Austen, 1987). [IgE antibodies also bind to receptors on basophils, which in essence are circulating mast cells, and on eosinophils; these cells are present in the bloodstream and connective tissue (Gleich and Adolphson, 1986).] IgE antibodies that are synthesized locally in response to allergens can circulate in the bloodstream and become distributed on mast cells throughout the body (Platts-Mills, 1984). The allergic response begins when an allergen binds to IgE antibodies that are bound to mast cells, immediately activating the mast cells to degranulate and release their chemicals. The degranulation of mast cells in the upper gastrointestinal region causes immediate vomiting; in the lower intestinal region, diarrhea; in the respiratory tract, constriction of the bronchial tubes and coughing; in the nasal passages, sneezing; and in the skin, itching that leads to scratching (Meggs and Metcalfe, 1984; Hood et al., 1984:461; Sheffer, 1988). Thus, as soon as the immune system detects an allergen it initiates a sequence of physiological events to rapidly expel the allergen. (Tearing, which occurs

during some allergic responses, may serve to expel the allergen from the eyes, as pointed out to me by Paul Ewald.) The chemicals released by mast cells also cause dilation of the peripheral blood vessels, leading to peripheral pooling of the blood that results in a drop in blood pressure and, in severe cases, anaphylactic shock (Hood et al., 1984:461).

If allergy is an adaptation, then the above-mentioned effects must serve some function. As Platts-Mills (1984) emphasizes, a biological role for IgE antibodies must be associated with the release of chemicals from mast cells, because the quantity of IgE antibodies produced in an allergic response is insufficient to neutralize or agglutinate the antigen. The allergic response thus differs markedly from other immune responses in that IgE antibodies perform their main functional role by co-opting nonimmunological mechanisms (e.g., vomiting, diarrhea). The allergic response appears to be well designed to hinder the allergen from entering the bloodstream and circulating to the various organs. Vomiting, diarrhea, sneezing, coughing, shedding tears, and scratching mediate the expulsion of the allergen from the stomach, intestines, nasal passages, lungs, eyes, and skin, respectively. The drop in blood pressure is likely to retard the rate at which the allergen circulates through the bloodstream. The inflammation of tissues helps to wall off the allergen in localized areas and thereby prevent its rapid dissemination throughout the body.

These design features of allergy indicate that the allergic response evolved to defend against some sort of immediate danger. Allergy does not generally occur to viruses, bacteria, or protozoa (Platts-Mills, 1984), nor would many of the symptoms of allergy—particularly the drop in blood pressure—be very effective against these pathogens. (Vomiting and diarrhea, however, are rapidly acting defenses against the toxins of ingested bacteria.) A subsequent encounter with a pathogen usually does not pose an immediate danger, because pathogens are quickly killed (and thus not allowed to replicate) by the immunological defenses that have been generated against them during the previous exposure. The symptoms of allergy would, on the other hand, be highly effective against toxins. Toxins can be present in significant amounts with each exposure—for example,

with each wasp sting or each bite of mushroom. Penetration of the body by toxins that have proved to be harmful in the individual's past necessitates urgent, critical action because many toxins can harm an organism within minutes of entering the bloodstream. By binding to target cells, some toxins can cause irreparable harm to the neurological, cardiovascular, endocrine, reproductive, metabolic, renal or other physiological systems (Freeland and Janzen, 1974). Furthermore, unlike pathogens, specific plant and venom toxins are generally avoidable, in that the plants and venomous animals themselves are generally avoidable; the severity and rapidity of an allergic attack may facilitate the identification of the offending allergen so that it can be avoided in the future. Protection against toxins thus seems to be a likely candidate for the function of allergy.

Toxins have played a significant but under-recognized role in allergy research. They were crucial to the 1902 discovery of allergic anaphylaxis—when toxins from the tentacles of a poisonous jellyfish, injected into dogs already sensitized to the toxins, caused vomiting, diarrhea and fatal shock (Portier and Richet, 1902). Nevertheless, the possibility that allergy evolved to defend against toxins has been overlooked, and the toxicity of most allergens has not been appreciated. For example, Platts-Mills (1984:1-2) states that “the substance that elicits the [allergic] reaction does not appear to be harmful in the absence of the immune or allergic responses [to it]. For example, pollen grains, hay dust and nickel are not toxic materials in themselves.” These materials, however, *are* toxic: pollen grains contain an array of toxins—e.g., phenolic acids, sesquiterpene lactones, and alkaloids (Stanley and Linssens, 1974; Ohmoto et al., 1978; Mabry and Gill, 1979; Herminghaus et al., 1988; Meurer et al., 1988); hay dust is often infested by toxic fungal spores (Davies et al., 1984); and nickel is one of the most carcinogenic of the many toxic metals in the natural environment (Kasprzak, 1987).

This paper argues that allergy is designed to be a last line of defense against toxins; that is, the allergic response is triggered when the individual's primary antitoxin defense mechanisms have proven on a previous occasion to be insufficient in preventing a specific toxin from persisting in the bloodstream and damag-

ing cells. Because toxins are so prevalent in the environment, mammals have developed a multitude of ways to combat them (discussed below). Most of these defenses, however, are general defenses that are effective against toxins of diverse molecular configurations, rather than specialized defenses that target specific toxins (Ames et al., 1990b). For example, the continual shedding of the epithelial surfaces of organs that are regularly exposed to toxins, such as the gut, lungs, and skin, helps to protect against all types of toxin. Other defenses, such as DNA repair enzymes and antioxidants, protect against damage caused by many different types of toxin. Even the most specialized nonimmunological defenses against toxins—detoxification enzymes produced by the liver and other organs—generally target classes of toxicity rather than only the specific molecular configuration of a particular toxin (see Jacoby, 1980).

It is highly adaptive for a part of the immune system to be specialized for targeting specific toxins because, of all the types of defense mechanisms against microscopic entities, only the immune system is capable of fine-tuning itself so as to selectively target the specific molecular configurations of the foreign antigens it encounters. (By analogy, even though animals have various general defense mechanisms against pathogens, it is highly adaptive for them also to have immune systems capable of targeting specific pathogens.) The part of the immune system that is specialized to defend against toxins would be expected to differ in some of its design features from the parts that are specialized to defend against pathogens because eliminating toxins and eliminating pathogens require different tactics. IgE antibodies defend against plant and venom toxins indirectly—by initiating a sequence of chemical events to expel the toxins or to slow their circulation throughout the body; by contrast, the immune system for the most part defends against pathogens directly—by killing either the pathogens themselves or the cells that they have infected. The immune system provides the major mode of defense against pathogens, but only the “back-up” mode of defense (allergy) against toxins.

Evidence for the hypothesis that the allergic capability evolved as a defense against toxins (hereafter, the “toxin hypothesis”) includes the

following: (1) Toxins are ubiquitous. In addition to causing acute damage, many toxins are mutagenic or carcinogenic and cause irreparable, cumulative damage. (2) Chemical correlates of toxicity, such as the covalent binding of exogenous substances to serum proteins, frequently trigger allergy. Covalent binding is correlated with allergenicity, acute toxicity, mutagenicity and carcinogenicity. (3) Most known allergens appear to be either themselves toxic substances or carrier proteins that bind well to low-molecular-weight toxins. (4) The symptoms of allergy have the attributes of an evolved mechanism: the chemicals released by mast cells cause vomiting, diarrhea, coughing, sneezing, scratching, and tearing—which may rapidly expel toxins—and a decrease in blood pressure—which may slow the rate of circulation of toxins to target organs. (Although a life-threatening allergy-induced drop in blood pressure, like a life-threatening fear-induced increase in adrenalin, would rarely be advantageous, a mild to moderate decrease in blood pressure would be advantageous if it retarded the flow of blood that contained dangerous levels of toxin, just as a moderate increase in adrenalin is advantageous to an animal threatened by a predator.)

#### TOXINS ARE UBIQUITOUS IN THE NATURAL ENVIRONMENT

A toxin, broadly defined, is a nonnutritional substance that exerts a biodynamic effect on the body (Schultes and Hofmann, 1987:10). All plants produce toxins—commonly referred to as “secondary plant compounds”—to deter predation by animals and infection by pathogens. Since the production of secondary compounds entails large energetic costs to a plant, natural selection would rapidly eliminate the production of any such compound that was not toxic to some of the plant’s herbivorous predators or pathogens. Plant toxins harm animals in a variety of ways, such as by blocking receptor sites for neurotransmitters, interfering with specific cellular functions, or inhibiting enzymes that degrade other types of toxin. Different toxins are designed to harm different physiological systems. Most plant species synthesize at least a few dozen toxins in order to defend against a wide array of herbivores that differ in their susceptibilities to different toxins. Under the stress of herbivore attack, many plants

significantly elevate their levels of toxin (Beier, 1990; Harvell, 1990). Toxins exist even in the most seemingly innocuous parts of plants, such as the edible parts of bananas, potatoes, oranges, cherries, cabbage, spinach, celery, cocoa, and nutmeg (Ames et al., 1990a). [For reviews of natural plant toxins see Rosenthal and Janzen (1979), Keeler and Tu (1983), Concon (1988a), and Beier (1990).]

Many non-plant organisms also use toxic defenses. Diverse species of insects, reptiles, and marine animals produce venom to deter predators or to capture prey. Various pathogens are also toxic: many gram-positive bacteria secrete potent exotoxins, and gram-negative bacteria shed endotoxins when they die (Alcock, 1983). Toxic substances are also present in the inorganic environment. Certain metals in the natural environment, such as nickel and lead, are highly toxic in doses exceeding trace amounts (Kasprzak, 1987). Herbivorous animals absorb metals primarily by eating plants that have taken up metals from the soil (see Veien and Andersen, 1986). Some nuts, for example, contain metals at concentrations that would be toxic to humans if humans relied on them as a main food source (Furr et al., 1979).

#### *Many Toxins Are Also Mutagenic or Carcinogenic*

Although the function of plant toxins is to cause acute toxicity, a secondary effect of many of these chemicals is to cause mutation or cancer. For example, exogenous substances that exert acute toxic effects by binding covalently and nonselectively to cellular macromolecules often can also bind covalently to DNA and cause mutations. Exogenous substances that cause cancer appear to do so either by mutating DNA directly or by being sufficiently toxic to cause substantial cell death and subsequent cell proliferation (Ames, 1989). Natural mutagens and carcinogens are widespread among plants (Ames et al., 1990a). For example, the naturally occurring carcinogen allyl isothiocyanate is in cabbage, cauliflower (Buttery et al., 1976), brussels sprouts (MacLeod and Pikk, 1978), and radish (Cole, 1975); the carcinogen and mutagen 8-methoxysoralen is in celery (Beier et al., 1983) and parsnip (Ivie et al., 1981); and the carcinogen safrole is in cinnamon (Lemberkovics and Petri, 1988), black pepper (Richard and Jennings, 1971), nutmeg

(Archer, 1988), and cocoa (van der Wal et al., 1971). In summary, many toxins also are mutagens and carcinogens; hence, by defending against environmental toxins, particularly those that bind covalently, allergy simultaneously confers some protection against mutation and cancer.

### *Mammals Have Numerous Defenses against Toxins*

Because toxins are so dangerous and ubiquitous, and are so often coupled to nutritious sources of food, many animals have evolved elaborate physiological and psychological mechanisms to detect, avoid, destroy, and eliminate toxins. Allergy seems to be designed to be a last line of defense against toxins when these other mechanisms prove insufficient, either because of a defect in one of the mechanisms or because of the ability of a particular toxin to evade these defensive mechanisms. Plant toxins are not equally effective against all potential herbivores, and herbivore defenses are not equally effective against all potential toxins (which is the major reason why humans find only a small subset of plant species edible). Mammalian defenses against toxins are diverse and multi-level; they include the following adaptations: (1) Mechanisms for detecting and avoiding dangerous levels of toxin, such as the olfactory and gustatory perception of bitter and pungent compounds, which are commonly correlated with toxicity (Garcia and Hankins, 1975; Chapman and Blaney, 1979). (2) Mechanisms for remembering which foods have caused deleterious effects and for developing aversions to such foods (Rozin and Kalat, 1971; Freeland and Janzen, 1974). (3) Mechanisms for avoiding overloading the body with any one toxin, such as seeking a diversity of plant foods; even specialized herbivores seek dietary diversity—koalas, for example, eat sixteen different species of eucalyptus and, in captivity, will refuse to eat if offered only one species (Freeland and Janzen, 1974). (4) Mechanisms for circumventing the most toxic parts of foods, such as the peeling of fruits [humans, in addition, cook many of their foods, which deactivates some of the toxins (Kingsbury, 1983; Stahl, 1984)]. (5) Mechanisms for trapping or neutralizing toxins before they are absorbed into the circulatory system, such as the secretion of IgA antibodies at the epithelial surfaces

of the nasal passages, lungs, gastrointestinal tract, and genitourinary tract. (6) Mechanisms for detoxifying toxins—for example, the extensive array of enzymes in the liver, the major organ of detoxification, and in the gastrointestinal tract, skin, lungs, and various other organs (Freeland and Janzen, 1974; Gram, 1980; Bickers and Kappas, 1980). (7) Mechanisms for preventing mutation and cancer, such as the machinery for DNA repair. In humans, for example, specialized enzymes must repair the damage from approximately 10,000 endogenous oxidative hits per cell per day (Ames, 1989). The reason that most cancers occur in old age may be, at least in part, the result of the senescence of these protective mechanisms (see Fraga et al., 1990). The existence and effectiveness of such mechanisms testifies to the potency of mutation and cancer as selective forces throughout mammalian evolutionary history. (8) Mechanisms for preventing mutated cells from proliferating, such as the continual shedding of the surface layers of the gastrointestinal tract, lungs, skin, genitourinary tract, and eyes (Wright and Alison, 1984).

The lipid-solubility of many toxins that are ingested, inhaled, or touched enables them to permeate blood vessels and lymphatic vessels readily and thus enter the circulatory system. To prevent the body from being harmed by circulating toxins, the detoxification enzymes in the liver must degrade them rapidly to non-toxic excretable compounds that can be eliminated by the kidneys. For example, an average medicinal dose of the drug pentobarbital is degraded by human detoxification enzymes within a few hours, whereas without these enzymes the drug would not be completely inactivated for over 100 years (Freeland and Janzen, 1974). Detoxification generally comprises two phases: in the first phase, enzymes catalyze the conjugation of the molecule to a reactive group, creating an intermediate compound; in the second phase, enzymes catalyze the conjugation of this intermediate compound to an endogenous substrate (Monks and Lau, 1988). The resultant molecule is water-soluble and is therefore easily excreted by the kidneys, unlike most toxic parent compounds, which are lipophilic and therefore difficult to excrete because of the permeability of blood vessels to lipophilic substances and the consequent reabsorption into the bloodstream of such sub-

stances from the kidneys (Welling, 1986). Without detoxification enzymes, herbivores would succumb to the toxic effects of almost all of the secondary plant compounds they ingest (Kingsbury, 1983). The coevolutionary struggle between plants and their herbivorous predators, between toxins and detoxification systems, has resulted in wide interspecies and intraspecies variation in the composition of enzymes, so that a toxin that is lethal for one mammal may be detoxified readily by another (Freeland and Janzen, 1974; Rhoades, 1979). The relationship of variability in enzyme composition to variability in allergy susceptibility is discussed below in the section on the seeming capriciousness of allergy.

Although a mammal may maintain only small stores of most types of detoxification enzymes, because of the energetic costs of synthesizing and maintaining enzymes, the presence of a toxin frequently induces the liver and certain other organs to increase the production of enzymes capable of degrading that particular toxin (Breckenridge, 1975). Enzyme induction is therefore an important mammalian defense against the continually evolving array of toxic compounds in the environment. The repeated administration of a particular toxin can induce the synthesis of enough enzymes to cause a measurable increase in liver weight (Breckenridge, 1975; Parke, 1975). Detoxification enzymes generally target classes of toxicity, so that each type of enzyme is effective against a range of toxins with similar chemical properties. Enzymes induced by one toxin can therefore increase the detoxification rates of certain other toxins.

The process of enzymatic metabolism, however, converts some exogenous compounds to their toxic states. Many plants, for example, exploit the detoxification mechanisms of herbivores in order to avoid intoxicating themselves with their own defensive chemicals: the plants manufacture compounds that are biologically inert when first ingested by a herbivore but that become activated to their toxic forms during the first phase of the herbivore's enzymatic detoxification process (Fowden and Lea, 1979). These toxic intermediate compounds can persist in the herbivore's circulation if sufficient second-phase substrates are not immediately available for conjugation (Monks and Lau, 1988). Toxic intermediates

can sometimes reach carcinogenic levels when they are created faster than they can be deactivated by means of conjugation to second-phase substrates; studies in both mice and humans, for example, have found that high levels of the enzyme aryl-hydrocarbon-hydroxylase are correlated with increased risk for certain types of cancer (Amsbaugh et al., 1986). Furthermore, compounds that induce the synthesis of certain detoxification enzymes, particularly of the cytochrome P-450 family of enzymes, can potentiate carcinogenesis by increasing the rate of production of the reactive intermediates that are formed during the detoxification of other compounds (Parke, 1975).

Anything that undermines a general defense against toxins—resulting, for example, in increased mucosal permeability, deficient numbers of IgA antibodies guarding the epithelial surfaces, or insufficient production of detoxification enzymes—can increase the rate of penetration of toxins into the bloodstream or the duration of toxin circulation. Toxins that reach the bloodstream can interact with serum proteins to form immunogenic structures that trigger the production of IgE antibodies and the induction of allergy. IgE antibodies can target the specific molecular configurations of toxins that have evaded the general defense mechanisms against toxins.

#### CUES OF TOXICITY SHOULD ELICIT ALLERGY

Because the array of toxic compounds in the environment is immense and ever evolving, the immune system usually cannot "anticipate" the specific toxic compounds that it will encounter. Furthermore, the diversity of antibodies, although immense, is nonetheless limited by a set number of genetic components available for constructing antibodies. The immune system therefore seems to have evolved ways to recognize cues of toxicity (i.e., molecular configurations that have been correlated with toxicity for a span of time that is significant from the standpoint of natural selection), enabling it to discriminate between typically harmful and harmless exogenous compounds. Once the immune system has identified an antigen as a toxin, antibodies can be fine-tuned (through a mechanism discussed below) to have greater affinity for that antigen.

The cues that the immune system uses to determine whether a compound is likely to be

toxic appear to involve the interaction of the compound with other molecules in the body, whether of endogenous or exogenous origin. Most plant toxins are of low molecular weight (<1,000 daltons). In order to elicit an initial immune response, a low-molecular-weight compound (hapten) must bind to a larger carrier molecule, such as a protein (Mullin et al., 1983; Layton et al., 1986, 1987). Most low-molecular-weight drugs, for example, are allergenic only when bound covalently to a carrier protein (Kasper and Schneider, 1987). An unbound low-molecular-weight compound usually can trigger an immune response only if antibodies were previously formed to the compound when it was conjugated to a carrier protein. (This may represent a physiological constraint; or, the immune system may be designed so as not to respond to unbound low-molecular-weight compounds, because a low-molecular-weight compound that rarely binds to proteins is not likely to interact with and harm bodily tissues.) Two immunogenic targets that may represent cues of toxicity are: (1) exogenous haptens covalently bound to endogenous or exogenous carrier proteins; and (2) exogenous carrier proteins of potentially reactive exogenous haptens.

#### *Covalent Binding*

Covalent binding of a low-molecular-weight compound to a protein—particularly serum albumin—is strongly correlated with toxicity, mutagenicity, carcinogenicity, and allergenicity. Almost every type of compound that reaches the bloodstream binds in some degree to serum proteins—particularly serum albumin, one of whose main functions is to bind to circulating compounds (Young and Tilghman, 1986). If the bond between a hapten and a serum protein carrier is covalent—that is, so strong as to be generally irreversible—then the hapten cannot be filtered by the kidneys and persists in the circulation for prolonged periods, enabling the immune system to form antibodies to it (Schneider, 1983; Amos and Park, 1985). Indeed, covalent binding between a hapten and a carrier protein is usually a requirement for the induction of an IgE response to the hapten (Layton et al., 1986, 1987). Some low-molecular-weight compounds that bind strongly but not covalently to proteins can be allergenic, but such compounds are rare

(Schneider, 1983). Chemically inert low-molecular-weight compounds can become allergenic if they are enzymatically converted to reactive metabolites that then bind covalently to host proteins (Chesham and Davies, 1985). Host serum proteins are very effective carriers in the induction of allergies to a wide variety of haptens (Kramps et al., 1981; Baur, 1983; Wass et al., 1989).

Compounds that bind covalently to serum proteins are frequently toxic, mutagenic or carcinogenic because they also bind covalently and nonselectively to other macromolecules, including DNA and RNA (Albert, 1985; Oesch, 1987). "Any chemical capable of forming covalent bonds with DNA of somatic and reproductive mammalian cells *in vivo* is a potential mutagen, carcinogen, and teratogen" (Randerath et al., 1985:57). Furthermore, ". . . the covalent binding index (CBI), defined as micromole of chemical bound per mole of DNA nucleotide/millimole of chemical administered per kilogram body weight of animal, exhibits a good quantitative correlation with the hepatocarcinogenic potency of chemicals of diverse structure" (Randerath et al., 1985:57, paraphrasing Lutz, 1979, 1982). Examples of naturally occurring compounds that bind covalently to DNA are methyleugenol (in apples and cloves), safrole (in black pepper, cinnamon, and cocoa), myristicin (in carrots and nutmeg), estragole (in tarragon and sweet basil), and aflatoxin B (produced by a mold that parasitizes many species of nuts and grains) (Randerath et al., 1985). Three of these compounds—methyleugenol, safrole, and estragole—were found by Miller et al. (1983) to be carcinogenic in high doses in mice or rats. Among the most potent allergens and carcinogens are the reactive metabolites produced during the first phase of detoxification, which bind covalently to proteins, DNA, and RNA (Hodgson and Levi, 1987; Monks and Lau, 1988).

The connection between covalent binding, toxicity, and allergenicity is especially strong in contact allergy (a delayed, T-cell-mediated skin allergy, which is described in more detail below). The potential of a low-molecular-weight compound to be a contact allergen is highly correlated with its ability to bind covalently to carrier proteins (Roberts and Williams, 1982; Roberts et al., 1988). Of the hundreds of sesquiterpene lactones (mostly produced by

plants of the family Compositae) that have been investigated, an alpha-methylene-gamma-lactone grouping—which permits covalent binding to carrier proteins—appears to be both a necessary condition for allergenicity and a primary condition for cytotoxicity (Mitchell and Dupuis, 1971; Lee et al., 1971; Rodriguez et al., 1977; Woerdenbag, 1986). The induction of photoallergy (light-activated allergy) requires the covalent binding of the photoallergen to a carrier protein; photoallergens exhibiting very different chemical structures have in common the ability to bind covalently to human serum proteins (Barratt et al., 1987). Covalent binding to carrier proteins is so important that it can be used to screen potential photoallergens (Barratt and Brown, 1985). Because covalent binding can cause both allergenicity and carcinogenicity, it may even be possible to use allergenicity to screen potential carcinogens.

The persistence in the bloodstream of an exogenous compound bound covalently to a serum protein indicates that the compound is potentially highly toxic (since its chemical structure enables it to bind covalently to tissue macromolecules), has evaded detoxification mechanisms, and probably poses the threat of future infiltration (since it is currently in the environment). This signifies to the immune system that defenses should be built up to rapidly recognize and eliminate that compound upon subsequent encounters. A covalently binding toxin binds irreversibly to tissue proteins and other macromolecules and thus is more likely than a non-covalently binding (reversibly binding) toxin to cause irreparable harm, perhaps cumulatively, upon each exposure. Therefore, if the toxin hypothesis is correct, IgE antibodies should be designed to target antigenic features that signify an exogenous compound bound covalently to a serum protein.

#### *Exogenous Carrier Proteins*

Although thousands of different exogenous proteins may invade a mammalian body during its lifetime, only a small subset can elicit IgE responses: viral and bacterial proteins, for example, almost never elicit IgE responses, whereas toxic proteins, which are commonly found in venom, often elicit IgE responses. However, many nontoxic proteins, such as var-

ious pollen and food proteins, can also elicit IgE responses. The toxin hypothesis predicts that nontoxic exogenous proteins that become allergens do so because they are either carriers of toxins or reliable correlates of toxins.

An exogenous carrier protein provides a large immunogenic target, and antibodies can typically form stable complexes with a variety of sites on a protein (Getzoff et al., 1987). When circulating exogenous proteins are bound to haptens, they sometimes stimulate the proliferation of anti-carrier IgE antibodies (Cirstea et al., 1984; Layton et al., 1986, 1987). Proteins that are especially efficient carriers of a wide spectrum of toxins—for example, proteins with hydrophobic pockets that readily bind lipophilic substances—may be the most common targets of IgE antibodies.

Natural selection might have favored IgE responses to carrier proteins if, in a natural environment, a protein that was coupled to a toxin on one occasion was likely to be coupled to that toxin in the future (for example, both toxin and protein were constituents of the same plant). The carrier protein, though not itself toxic, would signify potential toxicity. The production of IgE antibodies to an exogenous protein would be especially adaptive if the protein was "delivering" a reversibly bound low-molecular-weight compound capable of being converted into a potent toxin. Many secondary plant compounds are not very reactive until activated to their toxic forms by the herbivore's enzymes; only then are they capable of binding covalently to tissue macromolecules. Such a toxin in its less reactive state, if bound to a carrier protein, would be bound non-covalently, and thus would be likely to disassociate from the protein and be converted to an active toxic state. By targeting a carrier protein that is bound to a potentially reactive compound, the immune system might cause the expulsion of the compound and thereby prevent it from being released and activated. In experiments by Layton et al. (1986, 1987), covalently bound conjugates of haptens and carrier proteins frequently gave rise to IgE antibodies to the hapten, whereas electrostatically bound (more weakly bound) conjugates frequently gave rise to IgE antibodies to the carrier protein. An IgE response mounted to an exogenous carrier protein may function to rapidly identify and eliminate the protein's toxic or potentially toxic hapten. Further experi-

ments are needed to elucidate the relationship between haptens and their carriers in the triggering of IgE antibody production.

#### HOW IgE SPECIFICITIES FOR TOXINS AND CARRIER PROTEINS ARE SELECTED

The toxin hypothesis, like any functional hypothesis of allergy, implies that natural selection has functionally differentiated the IgE class from other classes of antibodies. IgE antibodies respond to different kinds of antigens than other classes of antibodies do; viruses and bacteria, for example, almost never trigger IgE-mediated allergy, and individuals with allergies typically produce normal antibody spectrums in response to nonallergenic antigens, indicating that the greatly elevated levels of IgE antibodies that occur during allergy are responses to a select group of antigens (Hammarstrom and Smith, 1987).

The question of how a given class of antibody acquires its specificity for a particular kind of antigen or antigenic structure is significant because the binding sites of antibodies of every class are determined by the same genes (called variable-region, or V-region, genes). Millions of different antibodies are produced by a very limited amount of genetic material; the extreme diversity of antibodies results from the somatic rearrangement and mutation of the V-region genes (French et al., 1989). In the production of a new B cell, the V-region genes are rearranged to form a unique genetic pattern; this rearrangement is completed before the B cell interacts with any antigen or becomes differentiated (i.e., becomes specialized to secrete antibodies of a particular class). Before antigenic stimulation, a B cell expresses only IgM and IgD antibodies on its surface. After antigenic stimulation, a B cell can terminally differentiate into an IgM-secretor or it can switch to express and secrete a different class of antibody, such as IgE (a process called class switching) (French et al., 1989). Class switching is thought to be regulated primarily by helper T cells, which recognize antigens bound to B-cell surface molecules and secrete factors that activate B-cell proliferation and differentiation. An antigen-stimulated B cell can also undergo mutation of the rearranged V-region genes (a process called somatic hypermutation) at a rate 10,000 times greater than the spontaneous mutation rate of eukaryotic

DNA (Golding et al., 1987). Somatic hypermutation accounts for much of the immunoglobulin diversity (Gojobori and Nei, 1986). Class switching and somatic hypermutation are independent processes that occur during B-cell differentiation (French et al., 1989), and hypermutation can occur both before and after class switching (Allen et al., 1987; Manser, 1989). When an antigen stimulates the proliferation of hypermutated B cells, the cells that proliferate most rapidly are those expressing antibodies with the greatest affinity for the stimulating antigen; by this process are produced antibodies progressively finely tuned to the stimulating antigen (Tonegawa, 1988).

There are at least three developmental stages at which antibodies (such as those of the IgE class) could be shaped to respond specifically to particular types of antigen (such as those bearing immunogenic determinants indicating toxins or toxin-carrier conjugates):

(1) The initial rearrangement of the V-region genes may be developmentally programmed in ways that ensure the production of certain antibody specificities (Schroeder et al., 1987). During human and mouse fetal life, preferential rearrangement of certain V-region genes occurs, regulating the production of particular antibody specificities (Schroeder et al., 1987). Such antibody specificities may include those that target particular types of toxin or toxin-carrier conjugates.

(2) Certain antigenic stimuli appear to selectively induce class switching. Stavnezer et al. (1988:7704) have found that "The process of class switching, whereby B cells switch from production of one class of immunoglobulin (Ig) to another, is highly regulated as different classes are expressed in response to different antigens and at different sites in the body." They found, for example, that bacterial lipopolysaccharide induces a cell line of IgM-secreting B cells to switch to IgA. It is possible that antigenic stimuli indicating toxins or toxin-protein conjugates selectively induce IgE class switching. [When helper T cells interact with antigens on B-cell surfaces, they can secrete a variety of factors that lead to B-cell proliferation and differentiation; one of these factors, interleukin-4 (IL-4), has been found in mice to preferentially direct class switching of IgM- to IgE-secreting B cells (Finkelman et al., 1988; Lebman and Coffman, 1988) and to increase the

clone size of proliferating IgE-secreting B cells (Savelkoul et al., 1988).]

(3) The mechanism that directs somatic hypermutation of the V-region genes may selectively fine-tune B cells to exhibit high affinity for particular antigenic structures (e.g., for structures indicating certain types of toxicity). Some of the same hypermutations have been found to occur repeatedly, indicating, according to French et al. (1989), that "hot spots" for particular types of hypermutation have been selected for.

The ability of the immune system to recognize that an antigen is a covalently binding toxin or an exogenous carrier protein of a potentially covalently binding toxin would depend on the mechanism by which B cells process and present antigens to T cells. A B cell whose surface immunoglobulin has recognized (bound) an antigen requires T-cell recognition of its antigen in order to be activated to an IgE-secreting cell. B-cell recognition of antigens, however, differs from T-cell recognition of antigens (Pierce et al., 1988). The surface of a B cell bears many identical immunoglobulin molecules that can trap antigens whose native configurations complement the specific configurations of those molecules. An antigen that binds to a B cell's surface immunoglobulin molecule is usually internalized for processing—that is, it is taken up inside the B cell to intracellular compartments where enzymes cleave it into fragments. In the case of a protein antigen, for example, processing entails unfolding the protein to expose its internal antigenic determinants and cleaving it with proteases into constituent peptides (Werdelin et al., 1988; Chain et al., 1988). The processed peptides are then bound to a set of the cell's own molecules, known as major histocompatibility (MHC) class II molecules, transported to the surface of the B cell, and presented to helper T cells (Yewdell and Bennink, 1990). If a helper T cell recognizes a peptide as nonself, by binding to the peptide/MHC complex, it secretes various factors that activate the B cell to proliferate, to differentiate into a particular class, and to secrete antibodies of the same specificity as the B cell's surface immunoglobulin (or hypermutated versions of that immunoglobulin) (Abbas et al., 1990). Depending on the antigenic stimulus, the T cell may be able to preferentially direct the B cell to differentiate into

an IgE-secreting cell (by, for example, secreting IL-4). In general, the B cell can bind to and process self antigens as well as nonself antigens (Lorenz and Allen, 1988), whereas the T cell discriminates between self and nonself antigens and regulates B-cell activation accordingly. (By processing self antigens, such as serum albumin, the B cell can expose foreign antigens that superficially mimic self antigens.)

What is important with respect to understanding the development of allergic responses is that the specificities of the B-cell surface immunoglobulin molecules differ markedly from the specificities of the T-cell antigen receptors that bind the B cell's processed antigen fragments coupled to MHC class II molecules. The binding of the T cell to the peptide/MHC complex induces the proliferation of B cells with affinity for a determinant on the native antigen (rather than for the peptide that bound the T cell). Thus, if the T cell binds to an antigen fragment whose source was a hapten-carrier protein conjugate, it could induce a B-cell response either to the hapten or to the carrier, depending on whether the B-cell surface immunoglobulin was specific for the hapten or the carrier.

If T cells do indeed direct class switching of B cells depending on the type of antigenic fragment coupled to MHC molecules that they detect on the B-cell surface, then T cells may preferentially induce switching to the IgE class upon recognizing a peptide covalently bound to a hapten. In order to restrict induction of anti-carrier IgE antibodies to (exogenous) carriers of toxic or potentially toxic haptens, a non-covalently bound carrier-hapten complex that is internalized by a B cell must, once processed, be recognized by a helper T cell as toxic. What follows is a speculative account of how this might occur. A non-covalently bound hapten that is capable of being enzymatically activated to a reactive, covalently binding toxin might, when internalized by the B cell for enzymatic processing, be converted by the B cell's enzymes—particularly by the cytochrome P-450 enzymes—to its toxic state. This activated toxin could then bind covalently to one of the peptides from the carrier protein and be transported to and displayed on the B cell's surface. B cells contain substantial amounts of the cytochrome P-450 enzymes (Selkirk et al., 1975; Freedman et al., 1979;

Crespi et al., 1985), which catalyze the conversion of a wide array of nontoxic molecules to highly toxic, covalently binding intermediate compounds in the first phase of the detoxification reaction. A helper T cell that recognizes the covalently bound hapten-peptide complex coupled to MHC molecules might secrete factors such as IL-4 to induce differentiation of the B cell to the IgE class. In summary, IgE antibodies might be generated to proteins that are exogenous carriers of potentially reactive (potentially toxic) haptens in the following way: a B cell with specificity for the carrier protein could bind a non-covalently bound hapten-carrier conjugate, enzymatically convert the carrier's nonreactive hapten to a reactive, covalently binding hapten, and expose the covalently bound hapten-peptide complex to helper T cells, which would then induce the B cell to differentiate and secrete antibodies with specificity for the carrier protein.

Mechanisms designed to induce allergic responses preferentially to proteins bound to toxic and potentially toxic haptens may, in certain circumstances, potentiate dysfunctional allergic responses to bystander proteins. IgE responses to such proteins as ovalbumin, an egg-white protein, can be potentiated by administering the protein with potent inducers of IgE antibodies, such as ricin, a toxic plant protein (Thorpe, et al., 1989). Potentiation of allergy to bystander proteins might arise in the following ways: (1) A B cell whose surface immunoglobulin binds to a protein might be in the vicinity of a second B cell that happens to be interacting with a T cell, and might "intercept" a signal to differentiate to an IgE-secreting cell that was intended for the second B cell (previously activated B cells that are bystanders at the site of T-cell activity, for example, can be stimulated to proliferate by the T-cell-derived factors — Abbas et al., 1990). (2) A protein from one food source that binds to a toxic or potentially toxic hapten from another food source in the gastrointestinal tract or the bloodstream could induce an IgE response, just as if it were the original carrier of that toxin; this process could be exacerbated by the "carrier effect," in which a hapten conjugated to one carrier protein (e.g., serum albumin) induces antibodies that bind to that hapten when it is conjugated to a second carrier protein (Mitchison, 1971a; Neveu, 1987). Antibodies can then

form to the second carrier alone (Mitchison, 1971b) (although whether these anti-carrier antibodies are of the IgE class has not been reported). (3) A B cell whose surface immunoglobulin has specificity for a certain protein might, through pinocytosis (the engulfment of substances by the cell membrane) internalize, process, and present to T cells a different protein bound to a toxic hapten, resulting in T-cell activation of that B cell which is specific for the first protein. (Pinocytosis is one way that B cells trap antigens, though it is much less efficient than immunoglobulin binding.)

#### COMMON ALLERGENS EXHIBIT THE PROPERTIES PREDICTED BY THE TOXIN HYPOTHESIS

If the toxin hypothesis is correct, common allergens should exhibit molecular configurations that correlate strongly with toxicity. The compounds most likely to be allergenic are: (1) low-molecular-weight toxins that bind covalently to serum proteins; (2) nontoxic protein carriers of low-molecular-weight toxins; and (3) specific high-molecular-weight toxins, such as snake venom, that harmed individuals in ancestral mammalian populations for a span of time significant from the standpoint of natural selection. Most likely there are additional cues of toxicity yet to be discovered. (For example, the immune system may have developed ways to recognize molecular configurations indicative of toxins that are lethal to nonregenerating nerve cells.) By targeting only those compounds most likely to be toxic, the immune system avoids hypersensitive responses to every exogenous compound it encounters. Thus, the risky allergic response is normally mounted only to a compound that constitutes a toxic threat.

In a natural environment allergies should fall into one of three categories: (1) a typically adaptive, defensive response to a toxic allergen; (2) a maladaptive, side-effect response, such as to a bystander protein; and (3) a maladaptive response to a manipulation of the mammalian machinery of allergy by another organism. [See Ewald's (1980) evolution-minded categorization of physiological responses to infectious diseases; also see Williams and Nesse (1991, Table 2).] For the allergic capacity to have been maintained by natural selection, the benefits conferred by adaptive allergies throughout mammalian evolutionary history must typically have

outweighed the costs imposed by maladaptive allergies. The following subsections review the common allergens—classified by their usual route of entry into the body—and discuss the reasons for their allergenicity.

#### *Injected Allergens (Drugs, Venom)*

Various drugs cause serious allergic responses in sensitized individuals, especially when administered by injection, a process that bypasses the detoxification enzymes of the primary epithelial tissues. Drugs exert biodynamic effects on the body, and so are by definition toxic substances (Brody et al., 1965). Most drugs are derivatives of, synthetic mimics of, or based on prototypes of plant toxins; but they are available in concentrations far more potent than plants can afford to manufacture. Allergies occur in response to a wide spectrum of drugs, but primarily to those, such as penicillin, that bind covalently (or whose metabolites bind covalently) to serum proteins (Schneider, 1983; Bundgaard, 1983). Although covalent binding is not an absolute requirement for allergenicity, drug allergens that do not bind covalently are very rare (Schneider, 1983; Bundgaard, 1983). If allergy is designed to defend against toxins that evade enzymatic detoxification, allergic susceptibility to drugs and ability to detoxify drugs are expected to be inversely related. Allergy is not expected to develop, however, in response to most drugs that do not bind covalently.

The toxic venom of various insects, snakes, and marine animals is frequently very harmful when injected directly into a victim's bloodstream by stingers or fangs, and some venom neurotoxins bind irreversibly to their target receptors (see Tu, 1977). Not surprisingly, many venoms, such as honey-bee venom, tend to be highly allergenic (Evans and Summers, 1986). Susceptibility to insect venom allergy, unlike susceptibility to pollen or food allergy, is not correlated with susceptibility to allergy in general (Evans and Summers, 1986), which may indicate that selection has designed mammalian immune systems to recognize specific insect venom toxins. The toxic proteins in the venom of such marine animals as jellyfish can also induce toxin-specific IgE antibodies and cause severe allergic responses (Fisher, 1986:702). As mentioned above, toxins extracted from jellyfish tentacles led to the dis-

covery of allergic anaphylaxis: dogs who recovered within a few days from an initial sublethal dose of toxin suffered fatal anaphylactic shock within an hour of a subsequent equal or slightly greater dose of toxin two to three weeks later (Portier and Richet, 1902). Though sometimes fatal, allergy-induced anaphylaxis often could be lifesaving by slowing the circulation of venom [the first-aid procedures for treating venomous snake bite—implementing a constrictive band near the bite to retard lymphatic flow (Gifford, 1984) and immobilizing the victim to slow the heart rate (Chapman, 1968)—are similarly designed to slow the circulation of venom].

#### *Ingested Allergens (Foods)*

Almost any food can be allergenic because almost any food can contain toxins or proteins that bind as carriers to that food's toxins. Toxins are rarely investigated as the possible allergenic culprits of foods. Although toxins may provide the stimulus for the development of allergies to plant-derived foods, the specific immunogenic targets may include the plant's proteins that bind to the toxin or that are otherwise reliably correlated with the toxin. The specific allergenic constituent of an allergy-producing food may be difficult to identify, since food constituents usually are degraded in the stomach and intestines, where they undergo conformational changes or conjugations to other substances, resulting in antigenic structures different from those of the undigested constituents. Nevertheless, there is strong evidence that many food allergies stem from toxins in the foods or from food proteins that bind as carriers to toxins.

Virtually all plant foods contain toxins, although cooking deactivates some of them. Allergy to toxins may explain the puzzle of allergic cross-reactivity to plant foods from unrelated botanical families: such foods may be cross-reactive because they contain the same toxin. A number of studies, for example, show that a high percentage of persons allergic to birch pollen (family Betulaceae) are also allergic to some or all of the following foods: apples, pears, peaches, cherries, apricots, plums, almonds (all from the family Rosaceae), hazelnuts (family Betulaceae), carrots (family Umbelliferae), potato skins (family Solanaceae), walnuts (family Juglandaceae), Brazil nuts

(family Lecythidaceae), and, to a lesser extent, celery, oranges, peanuts, tomatoes, onions, parsley, and coconuts (Hannuksela and Lahti, 1977; Eriksson, 1978; Lahti and Hannuksela, 1978; Eriksson et al., 1982; Dreborg and Foucard, 1983; Lowenstein and Eriksson, 1983; Eriksson, 1984; Halmepuro et al., 1984). The most common allergic symptoms caused by eating these foods are swelling and itching of the lips, mouth, and tongue, laryngeal disturbances, rhinitis, and hives (Hannuksela and Lahti, 1977). Chemical analyses reveal that birch pollen and the edible parts of every plant food listed above contain high amounts of the phenolic acids known as cinnamic acids (although the data on Brazil nuts and coconuts measured total quantities of phenols rather than quantities of individual phenolic compounds). In particular, birch pollen and every fruit and vegetable in the primary list contain very high quantities (up to 700 parts per million fresh weight) of caffeic acid or its quinic acid esters, chlorogenic acid and neochlorogenic acid (birch and hazel pollen: Meurer et al., 1986; Meurer et al., 1988; apple and pear: Mosel and Herrmann, 1974a,b; peach, apricot, plum, and cherry: Moeller and Herrmann, 1983; potato: Schmidlein and Herrmann, 1975; carrot: Sarkar and Phan, 1974; Stoehr and Herrmann, 1975).

Caffeic and chlorogenic acids are phenolic toxins that oxidize easily, forming reactive quinones, which can covalently bind to proteins (Stich et al., 1981; Hurrell et al., 1982). Caffeic acid, furthermore, has been reported to be mutagenic, carcinogenic (Ito and Hirose, 1987; Fung et al., 1988; Ito et al., 1990), and clastogenic (breaks chromosomes) (Hannam et al., 1983). The nuts in the primary list, although found in one study to have very high concentrations of phenolic compounds (Macfarlane et al., 1988), were found in another study to have relatively low concentrations of cinnamic acids (Senter et al., 1983). This latter study, however, measured the acids in the meat of the nuts, and did not include the edible seed coats, which would be likely to contain the highest concentration of these acids; furthermore, the high allergenic potential of nuts may result in part from their high concentrations of certain metals, including some of the transition metals (Furr et al., 1979), which considerably enhance the genotoxicity of the cinnamic acids

(Stich et al., 1981; Hannam et al., 1983). The foods listed secondarily in the cross-reactivity literature as allergenic have lower, but still significant, amounts of caffeic acid and its derivatives (orange: Reschke and Herrmann, 1981; tomato: Schuster et al., 1986; celery: Herrmann, 1978; peanut: Dabrowski and Sosulski, 1984; coconut: Macfarlane et al., 1988; onion: Schmidlein and Herrmann, 1975; parsley: Stoehr and Herrmann, 1975). In the cinnamic acid studies cited above, only two common foods [radish and red cabbage (Shafers and Herrmann, 1982a; Winter et al., 1987)] that are sometimes eaten raw (cooking degrades these toxins) are reported to contain modest concentrations of caffeic or chlorogenic acids yet are not mentioned in the literature as part of this cross-reactive group. Since many herbs and spices have extremely high levels of these toxins (up to 19,000 parts per million for dried basil) (Schulz and Herrmann, 1980), they would be expected to elicit an allergic response in persons with allergies to the above cluster of foods if eaten uncooked in substantial quantites.

The hypothesis that caffeic and chlorogenic acids are the allergenic constituents of the above-mentioned cross-reactive foods is also supported by evidence that these toxins are the allergenic constituents of certain other plants. Chlorogenic acid has been reported to be highly allergenic to many people exposed occupationally to the dust of green coffee beans (Freedman et al., 1962; Bariana et al., 1965), which contain this acid in very high concentrations (up to 5% of the dry weight of the green coffee bean is chlorogenic acid — Baltes, 1977). [The allergenicity of chlorogenic acid has been challenged by Layton et al. (1966, 1968), who maintain that proteins are the allergenic constituents of coffee beans. Freedman (pers. commun.), points out, however, that many of his original experiments demonstrating the allergenicity of chlorogenic acid in people with coffee-bean allergy used synthetically prepared chlorogenic acid, which could not have been contaminated with coffee proteins.] Various phenolic compounds have been reported to produce immediate symptoms of allergy (e.g., wheal-and-flare responses in skin prick tests of sensitized individuals) (Brostoff, 1987), and caffeic acid esters of propolis (the bee-glue from poplar buds) have been found to cause strong contact allergy (Hausen and Wollenweber, 1988; Hashimoto

et al., 1988). Brostoff (1987) has even suggested that plant phenolics may be the allergenic constituents of various foods, pollens, and dusts.

Another indication that toxins—particularly the cinnamic acids, such as caffeic and chlorogenic acids—are likely to be the common allergens in the above-listed cross-reactive foods is that the allergenicity of these foods is quickly attenuated with storage time (especially if the food has been finely chopped) or by heat, which is why people with apple allergies can tolerate apple sauce or apple cake (Eriksson, 1978; Dreborg and Foucard, 1983). According to Lahti and Hannuksela (1978:146), "the most confusing factor" about the cross-reactivity of botanically unrelated foods is the extreme lability of the allergens, which "would seem to speak in favour of enzymes and other easily destroyable compounds" as the allergenic culprits. Chlorogenic acid is so easily destroyed by cooking or roasting that people who are allergic to the chlorogenic acid in green coffee beans are able to drink ordinary roasted coffee (Freedman et al., 1962). Chlorogenic acid is degraded so rapidly because it oxidizes easily, which is what causes the fruits and vegetables that contain it to turn brown when cut and exposed to air (Schafers and Herrmann, 1982b).

According to Calkhoven et al. (1987:382), "The nature of the components responsible for the cross-reactivity has not yet been established." Plant toxins, however, have not been investigated as the possible culprits. Rather, the allergens in these cross-reactive foods have generally been assumed to be proteins, and the loss of allergenicity with storage time of apples, for example, has been thought to result from the binding of oxidized phenols to plant proteins, resulting in changed conformation of the proteins (Bjorksten et al., 1980). (Bjorksten et al. were able to prepare apple extracts that maintained their allergenicity by adding to the apple extract various compounds, including one to inhibit the oxidation of phenols. Since the resulting centrifuged extract was not tested for the presence of phenols, however, it is not known whether its allergenic constituents were unoxidized phenols, such as the neochlorogenic acid that is present in apples in high concentrations, or apple proteins, as the authors suggested.) Proteins from foods containing these phenolic toxins may very well become allergenic as a result of their association with the toxins.

Two smaller clusters of cross-reactive plant foods and pollens include: (1) ragweed pollen, watermelon, banana, cantaloupe, and honeydew; and (2) mugwort pollen, celery, and various spices (Dreborg, 1988). Whether the allergic cross-reactivity of the plants in each of these clusters is due to a common toxin remains to be investigated.

Examples of high-molecular-weight allergenic toxins from plant foods are various lectins, which probably are evolutionarily ancient. Dietary lectins are not always degraded by cooking or digestion; if they are absorbed into the bloodstream, they can cause blood cells to agglutinate and proliferate. According to Freed (1987), some lectins can bind to virtually all types of mammalian cells and induce allergy, and the most cytotoxic lectins are the ones most likely to cause food allergy (Freed, 1987). Wheat, a common allergen in modern societies, contains the lectin, wheat germ agglutinin, which binds particularly strongly to human tissues (Freed, 1987).

Some toxins in allergenic plant foods are produced by parasitic fungi. Aflatoxins from *Aspergillus* spores, for example, are potent carcinogens (Randerath et al., 1985) that commonly contaminate peanuts and grain and that can cause food poisoning (Rockwell, 1988). Many mold species cause IgE-mediated allergy (Karlssoon-Borga et al., 1989), although whether this allergy is specifically triggered by the toxins in the mold needs to be investigated. Allergy to peanuts, for example, may represent an IgE response to the aflatoxin or to the peanut proteins that have been associated with the aflatoxin on previous exposures.

Allergenic foods of animal origin also can contain potent toxins. Many species of allergenic fish are frequently contaminated by toxins produced by algae or plankton (Wright and Robertson, 1987; Concon, 1988a). Shellfish, particularly mussels, clams, oysters and scallops, are common transvectors of paralytic toxins from the planktonic dinoflagellate *Gonyaulax*, particularly during red tide (Savvedra-Delgado and Metcalfe, 1984). Clupeotoxin, possibly produced by dinoflagellates, appears sporadically in herring, anchovy and sprat. Ciguatoxin, which causes ciguatera poisoning, is thought to be produced by toxic microalgae and contaminates over 300 species of marine fish, including swordfish and various snappers, basses, flounders, eels, and mack-

erels (Saavedra-Delgado and Metcalfe, 1984; Concon, 1988a). Fish also can be contaminated by toxic metals; cod, for example, one of the most allergenic fish in Scandinavian waters, is frequently contaminated by a form of mercury that is highly toxic to mammalian nerve and brain tissue (Concon, 1988b).

The toxin hypothesis predicts that the allergies to seafoods arise from contamination of seafoods by toxins. Both the toxins and the seafood proteins to which the toxins are conjugated could induce the production of IgE antibodies. Many planktonic toxins are of fairly low molecular weight (see Ragelis, 1984) and would have to bind to proteins in order to become immunogenic. The allergenic cod protein (allergen M), whose main known function is to bind calcium ions (King, 1976; Aas, 1987), might be expected also to bind planktonic or metallic toxins with high affinity. Individuals who are allergic to a particular species of aquatic animal could be tested for sensitivity to the toxins that commonly contaminate that species.

Among the most commonly allergenic foods for humans, however, are cows' milk and chickens' eggs, which are not themselves toxic (although they are sometimes contaminated by toxin-producing bacteria, by antibiotics or, in the case of milk, by plant toxins ingested by the cow). The major allergens that have been isolated from eggs are the nontoxic egg-white proteins ovalbumin, ovomucoid, and ovomucin; the major milk allergens are the nontoxic proteins bovine serum albumin, alpha-lactalbumin, beta-lactoglobulin, and casein (King, 1976). These proteins may become allergenic by binding as carriers to plant toxins in the digestive tract or bloodstream. There is evidence that these proteins can be effective carriers of low-molecular-weight toxins. Ovalbumin, for example, has been shown to bind to various food odorants (Maier, 1969) (many food odorants, such as allyl-isothiocyanate, the pungent carcinogen synthesized by cabbage, are low-molecular-weight toxins) and to many metals (Arora et al., 1984; Goux and Venkatasubramanian, 1986). In fact, ovalbumin is commonly used in experiments in which an effective carrier for haptens is required. Of the milk proteins, beta-lactoglobulin, alpha-lactalbumin, and casein bind readily to various volatile flavor compounds (Maier, 1969; Franzen and Kinsella, 1974; Yabumoto et al., 1975;

O'Neill and Kinsella, 1987). Soy protein, another common allergen, also binds well to a variety of compounds (Damodaran and Kinsella, 1981). In short, egg, milk, and soy proteins are effective carriers of a variety of haptens.

Since milk and eggs are not toxic, allergic responses to them are probably maladaptive. For most of human evolutionary history, adults did not drink milk and probably did not consume eggs (or egg products) nearly as often as many modern humans do. Many adult humans lack sufficient enzymes, such as lactase, to degrade milk proteins (Sategna-Guidetti et al., 1989). Although the proteins of a given plant would tend to be reliably associated with the plant's toxins, animal proteins that become allergenic by binding to low-molecular-weight plant toxins from the diet would not be reliably associated with any particular toxins, hence allergies to such proteins would be maladaptive.

#### *Inhaled Allergens (Pollen, Animal Dander)*

Respiratory allergies can be caused by inhaling any of a variety of substances, such as a wide range of occupational toxins, fungal spores, pollen, and animal dander and hair. Repeated exposure to toxic occupational substances is a common cause of respiratory allergy: for example, farmers can acquire respiratory allergy to insecticides, metal refiners to metals, dyers to reactive dyes, and pharmaceutical workers to various antibiotics and other drugs (Davies et al., 1984). One notorious occupational respiratory allergy is extrinsic allergic alveolitis (EAA), also known as farmer's lung disease, which occurs as a delayed response to the fungal spores on moldy hay dust. IgE antibodies to the mold can often be detected in patients with EAA (Gari et al., 1986), although the onset of symptoms is usually delayed until 6 to 8 hours after exposure. Mold allergies are not uncommon: Karlsson-Borga et al. (1989) detected IgE antibodies to 16 different mold genera among patients with suspected mold allergy. The fungal antigens of moldy hay are so allergenic that, according to Platts-Mills (1984), in some regions 50 percent of the exposed population suffers from EAA (but see Malmberg et al., 1988). The fungi frequently isolated from moldy hay are of the genus *Penicillium*, which is thought to produce at least 97 different toxic metabolites, and of the genus *Aspergillus*, which is thought to produce 64 different toxic metabolites (Emanuel et al.,

1975). Intoxication by these fungal toxins causes pulmonary mycotoxicosis, a sudden, acute infection that is clinically very different from the allergy caused by the fungi (Emanuel et al., 1975). EAA and pulmonary mycotoxicosis appear to be mutually exclusive afflictions: patients with EAA do not have active fungal infections of the lungs (Platts-Mills, 1984), and patients with pulmonary mycotoxicosis do not have EAA (Emanuel et al., 1975). Since intoxication seems to occur only in the absence of allergy to the toxins, allergy may protect a large percentage of the population exposed to fungi against the toxic effects of fungal metabolites.

Inhalation of pollen grains can cause hayfever, when the nasal passages are affected, and asthma, when the lungs are affected. (Respiratory allergies to pollen usually involve wind-pollinated rather than insect-pollinated plants, presumably because the air contains vastly larger quantities of the former.) Pollen grains contain a wide spectrum of toxins—for example, phenolic acids, sesquiterpene lactones, and alkaloids (Stanley and Linskens, 1974; Ohmoto et al., 1977; Mabry and Gill, 1979; Fisher and Mitchell, 1986; Herminghaus et al., 1988; Meurer et al., 1988). Ewald (pers. commun.) suggests that plants may produce pollen toxins as either antibrowsing or antitrampling defenses. A connection between respiratory allergy and pollen toxicity was postulated early in the century by Noon (1911), who believed that hayfever is intoxication by pollen toxins, and who used pollen extracts to try to stimulate the production of pollen antitoxin, analogous to inoculation against bacterial toxins. Nevertheless, the main pollen allergens that so far have been isolated and identified are nontoxic water-soluble proteins. (Proteins, however, are probably the only pollen constituents that have been tested for allergenicity.) These pollen proteins are reliably associated with low-molecular-weight pollen toxins and probably bind the toxins to some extent, which could account for their allergenicity. Platts-Mills (1984:4), adding to the work of Berrens (1974), has hypothesized that "irritant materials" in pollen could have adjuvant (stimulating) effects on the IgE antibody responses to the nonirritant proteins. Indeed the "irritant" toxins in pollen may induce IgE antibody responses to nontoxic proteins that bind these toxins.

Whether pollen allergies are typically adap-

tive in modern industrial environments is unclear. Pollen allergies appear to be more prevalent and severe among people in industrial societies than they are among people in nonindustrial societies, although it seems unlikely that the former suffer greater exposure to pollen. Possible reasons for heightened sensitivity to respiratory allergens in industrial societies are discussed in a later section.

Individuals with allergies to the dander or hair of dogs, cats, mice, rats, or horses are usually sensitized to the animal's serum albumin, although other constituents of dander have also been implicated as allergens (King, 1976; McKey, 1979). Allergies to animal dander and hair could result from contact of the animal's fur with plant oils whose toxins then bind to dander and hair proteins. (More speculatively, it is also possible that the allergenicity of non-human mammalian serum proteins results from their structural resemblance to homologous human serum proteins conjugated to toxic haptens.) Allergy to animals is probably a maladaptive result of the evolutionarily novel situation of living with them in closed quarters.

#### Skin Allergens

Many plant toxins and their synthetic analogs cause allergic skin reactions such as hives (urticaria) and eczema. Allergic contact dermatitis to a plant is so commonly caused by the plant's low-molecular-weight toxins that writings on plant contact allergens read like handbooks of natural toxins (e.g., Fisher and Mitchell, 1986). The allergic response to skin allergens, which includes inflammation and itching, may be immediate (primarily mediated by IgE antibodies) or delayed (primarily mediated by T cells).

Delayed hypersensitivity to contact allergens occurs primarily to low-molecular-weight antigens that can bind covalently to endogenous proteins (and are therefore toxic) (Roberts and Williams, 1982). According to Belsito (1989), the delayed hypersensitivity response is as follows: The antigens are trapped near the surface of the skin by Langerhans cells, bone-marrow-derived epidermal cells which, like B cells, process antigens and present antigenic fragments (coupled to MHC Class II molecules) to helper T cells. The antigens are usually bound covalently to proteins from the Langerhans cell surface, the skin, or the serum be-

fore processing and presentation. On first exposure to the covalently binding antigens, Langerhans cells migrate to local lymph nodes, where they come into contact with many T cells. Helper T cells with specificity for the processed antigens release a variety of factors, initiating the inflammation of skin tissues and the destruction of skin cells that may have been contaminated by the antigens. Mast cells are thought to be activated as well, releasing their inflammatory chemicals. The T cells then proliferate and circulate, so that if the individual is reexposed to the antigens the Langerhans cells will not need to migrate far to find a T cell capable of recognizing the antigen and inducing the appropriate inflammatory response.

The protection conferred by delayed T-cell-mediated allergy is similar to that conferred by immediate IgE-mediated allergy: inflammation of the infected area, which contains the toxin, and itching, which leads to the removal of toxin-contaminated skin cells via scratching. But because delayed responses are localized and occur on a slower time scale, the risk of anaphylactic shock associated with IgE-mediated allergy is avoided. When toxins are bound to proteins near the site of entry—and, hence, are not free to circulate in the bloodstream and bind to vulnerable internal tissues—the damage can be contained locally, and so the risky IgE response presumably would not be warranted.

Examples of toxic contact allergens include the urushiol from poison oak and poison ivy, many of the mutagenic or otherwise toxic oleoresins from vegetables and spices, such as capsicum pepper and nutmeg (Damhoer et al., 1985; Fisher, 1986), and toxins from such common vegetables as garlic, onion, and celery (Fenwick and Hanley, 1985; Berkeley et al., 1986). Among the most allergenic of the plant toxins are certain sesquiterpene lactones in the pollen of ragweed and parthenium weed, plants whose pollen causes widespread contact allergy as well as respiratory allergy, although not necessarily in the same person (Fisher and Mitchell, 1986:439). As previously discussed, many sesquiterpene lactones are allergenic, mutagenic, and cytotoxic to mammals, and those that are allergenic are those that bind covalently to proteins and that are, therefore, potential mutagens and carcinogens (Rodri-

guez et al., 1977; Woerdenbag, 1986; Gaspar et al., 1986; Thastrup et al., 1987).

Prolonged exposure to occupational materials derived from plants (all of which contain toxins) also can cause allergy. For example, bookbinders sometimes become sensitized to the resins of their binding materials, carpenters to wood, and surgeons to the rubber of surgical gloves (Fregeert, 1981). Many synthetic chemicals that are found in many household and industrial products are also allergenic (Foussereau et al., 1982; Fisher and Mitchell, 1986), particularly if they are lipophilic, of low molecular weight and, thus, analogs of plant toxins.

Metals, which can be very toxic, often provoke skin (and respiratory) allergies, and can be mediated either by T cells (Belsito, 1989) or by IgE antibodies (Novey et al., 1983). Metallic salts can cause contact allergy even though they form non-covalent complexes with proteins (Belsito, 1989). Trace amounts of many metals are present naturally in soil, plants, and animal tissues, and are required for proper nutrition; human serum even contains a special protein to bind nickel (Kasprzak, 1987). Excessive amounts of metals, however, are harmful and sometimes lethal. Many metals are genotoxic or carcinogenic to mammalian cells by inducing DNA strand breaks (Furst, 1987). Nickel, perhaps the most allergenic metal (Fisher, 1986), is also one of the most carcinogenic (Kasprzak, 1987). Epidemiological studies have shown that individuals exposed occupationally to large amounts of certain nickel compounds have a significantly increased risk of cancer (Kasprzak, 1987). Eisenbud (1987) notes that of the 15 metals on which studies of carcinogenicity and allergenicity have been performed, the four metals that are unambiguously carcinogenic in humans or animals (arsenic, beryllium, chromium, and nickel) are also strongly allergenic in humans. Thus, the link between allergenicity and carcinogenicity is especially striking in metals.

### *Helminths*

Parasitic worms (helminths) frequently induce substantial IgE proliferation and sometimes even fatal anaphylaxis (Ogilvie and Jones, 1973). Various researchers have viewed

the presence of IgE antibodies during helminth infections as indicating that the function of allergy is to protect against such infections (Godfrey, 1975); some researchers give examples of possible IgE involvement in the expulsion of and resistance to helminths (Dessaint and Capron, 1989). Other researchers, however, note that IgE antibodies do not seem to be necessary to expel worms (Mitchell, 1979; Jassim et al., 1987). According to Jassim et al. (1987), high levels of IgE antibodies to adult worm antigens in helminth-infested individuals do not decrease susceptibility to subsequent helminth infection, and helminth-infested individuals with low IgE levels to adult worm antigens do not appear to be immunologically compromised in their defenses against the worms. According to Ikeda and Tani (1988), the IgE response to the helminth *Paragonimus ohirai* confers little protection against reinfection. Protection against helminths has been shown to involve many parts of the immune system, including T cells, which in mice can confer immunity to some helminths when the cells are passively transmitted to offspring through lactation (Kumar et al., 1989); neutrophils and eosinophils, which bombard helminths with oxygen radicals (Kazura et al., 1985) and toxic proteins (Gleich and Adolphson, 1986); macrophages, which secrete factors that are cytotoxic to some helminth larvae (James et al., 1990); and, possibly, various classes of antibodies, which are produced during helminth infections (Lopes et al., 1990). The risk of fatal anaphylaxis in a potentially chronic and generally unavoidable disease seems to be a high price to pay for the tenuous benefits obtained by mounting IgE responses to helminths. Thus, the high costs and dubious benefits of allergic responses to helminths, coupled with the fact that the vast majority of allergies have nothing to do with helminth infections, imply that the function of allergy is not to protect against helminths.

An alternative hypothesis to explain the high levels of IgE antibodies surrounding helminth infections is that helminths release toxins into the host's tissues and bloodstream, and it is these toxins, rather than the helminths themselves, that IgE antibodies target. The IgE responses to helminth infections are usually to substances excreted or secreted by the worms. IgE antibodies target the excretory/secretory

antigens of many helminths, such as *Schistosoma mansoni* (Maddison, 1986)—notorious for eliciting IgE responses—*Onchocerca volvulus* (MacKenzie et al., 1986), and *Wuchereria bancrofti* (Ambroise-Thomas and Peyron, 1986). These antigens may be toxins that either are synthesized by the worms or are absorbed by the worms from the host's diet and then excreted or secreted into the host's circulation. Various studies indicate that some of the antigens excreted or secreted by helminths are toxic to host cells: extracts of many metazoal parasites have cytotoxic or inhibitory effects on host lymphoid cells (Mitchell, 1979); the helminth *Angiostrongylus cantonensis* secretes soluble antigens that can depress certain host immunological activities (Dobson and Yong, 1987); pork tapeworm (*Taenia solium*) cysts release substances at death that are toxic to the host's central nervous system (Alcock, 1983:128); and cestodes, in their early stages, secrete enzymes that help them to penetrate host tissues (Ogilvie and Jones, 1973).

Helminths may sequester toxic secondary plant compounds from the host's diet and release them into the bloodstream as weapons against the host, just as certain insects sequester plant toxins as an antipredator defense. On the other hand, helminths may simply absorb toxins along with nutrients from the host's diet and then excrete or secrete the toxins into the bloodstream as waste products. Host hypersensitivity to these dietary toxins might be exacerbated by helminth absorption of host serum proteins and subsequent excretion of these proteins conjugated to dietary toxins. The excretory/secretory products of the helminth *Brugia pahangi*, for example, include host serum albumin (Maizels et al., 1985); in one study, a third of helminth excretory/secretory products consisted of host serum albumin (MacKenzie et al., 1986). Dietary toxins that become conjugated to excreted/secreted worm proteins could also trigger IgE responses to the worm proteins. If sequestered dietary toxins are the allergens in helminth infections, then perhaps IgE-mediated inflammation could be partially alleviated by eliminating from the diet those foods that contain the toxins most often sequestered by the helminths. (The relationship between allergies to helminth excretions/secretions and allergies to foods among helminth-infested individuals is unknown.)

Helminths may even manipulate the host's machinery of allergy for their own ends by releasing toxins that elicit allergic responses. For example, Mitchell (1979) has hypothesized that helminths may deliberately trigger allergy in order to feed on the nutritious serum proteins that accumulate in the resulting inflamed tissues. More speculatively, helminths may secrete toxins as decoys that divert the immune system's eosinophils and basophils from attacking helminths to attacking allergens. Eosinophils and basophils are granule-containing white blood cells (leukocytes) in vertebrate blood and connective tissue that possess specific receptors for IgE and IgG antibodies and that are active in immune responses to various antigens, including common allergens, helminths, and possibly certain tumors (Gleich and Adolphson, 1986). During an allergic response, chemicals released from mast cells summon eosinophils to the site of the allergen, where IgE antibodies cause them to degranulate and release various enzymes, toxic proteins, and other substances (Gleich and Adolphson, 1986).

As mobile chemical arsenals, eosinophils and basophils probably evolved multiple defensive functions, perhaps including the chemical destruction of both allergens and helminths (although the type of eosinophil that combats allergens may differ from the type that combats helminths). Eosinophils and basophils may help to destroy or neutralize toxic allergens by releasing enzymes that detoxify them (just as neutrophils, related leukocytes, release enzymes during bacterial infections that detoxify toxic bacterial lipopolysaccharides—Munford and Hall, 1986). During helminth infections, however, the eosinophils and basophils that travel to the site of infection appear to help combat helminths by secreting various proteins, some of which are toxic to certain species of helminth (Gleich and Adolphson, 1986). It is possible that helminths are able to divert the focus of eosinophilic attack from themselves to allergens by releasing allergenic toxins derived from the host's diet.

Comparing allergies and helminth-induced IgE responses leads one to speculate that IgE antibodies may have two separate defensive functions: one against toxins, the other against helminths. After the basic mechanisms of allergy evolved, natural selection may have co-

opted certain of these mechanisms to expel helminths. If so, one might expect to find separate subpopulations of mast cells, basophils, and, possibly, IgE antibodies, involved in defending against the two classes of antigens, so that the dangerous chemicals that are important only for defense against toxins would not be released during helminth infections. In particular, whereas mast cells specialized to defend against toxins should be selected to contain high concentrations of chemicals, such as histamine, that can lower blood pressure, mast cells specialized to defend against helminths should not. Mast cells and basophils do display heterogeneity (Cohan et al., 1989): rodents, for example, have two types of mast cells, which appear to differ in morphology, biochemistry, and function (Irani and Schwartz, 1989). All mast cells so far studied contain substantial amounts of histamine, although the amount can vary dramatically among different types of mast cells in different locations in the body (Barrett and Metcalfe, 1987). In rats and monkeys, for example, the histamine content is significantly lower (by 30-fold in rats) in mast cells of the intestines than in those of the lungs or peritoneum (Barrett and Metcalfe, 1987). Since helminths are far more likely to parasitize the intestines than any other part of the body, the substantially reduced histamine content of the intestinal mast cell may be evidence of specialization for helminth infections; on the other hand, the intestinal mast cell may contain reduced levels of histamine in order to prevent anaphylactic reactions to dietary toxins released by helminths into the bloodstream. Intestinal mast cells of rats and monkeys contain little or no heparin, in contrast to lung mast cells (Barrett and Metcalfe, 1987). Heparin is an anticoagulant which is effective in inhibiting the procoagulant activities of some of the many toxic enzymes in snake and insect venoms (Higginbotham and Karnella, 1971; Joshua and Ishay, 1973; Teng and Ko, 1988; Melo and Suarez-Kurtz, 1988; Williams and White, 1989). Heparin's presence in most mast cells may therefore have evolved partly as a defense against venoms. Its absence in intestinal mast cells may promote defense against helminths (since heparin inhibits the killing of helminths by toxic eosinophil proteins, such as major basic protein and eosinophil cationic protein—Hamann et al., 1990) or minimize the

damage caused by allergic responses to dietary toxins released by helminths.

As yet, there is no evidence for differences in the types of mast cells that are triggered in helminth infections and allergic responses that occur in the same part of the body, nor for the existence of distinct subpopulations of IgE antibodies. In general, however, immune responses to helminths do differ from immune responses to allergens; for example, neutrophils are important components in the defense against helminths (Horii et al., 1988), whereas neutrophils are not significant in allergy (and even lack receptors for IgE antibodies—Walsh and Kay, 1986). Although it is extremely unlikely that allergy originally evolved to protect against helminths, it is possible that some of the mechanisms of the allergic response may have been co-opted or altered for defense against helminths.

### *Allergy Mimics*

True allergies—which are immunologically mediated—should be distinguished from physiological intolerances whose symptoms mimic allergies. Various symptoms of food intolerance, for example, may result, not from allergy, but from a toxic effect of a substance, or from a protective but nonimmunological response to a toxic substance, or from an inability to efficiently digest a substance (e.g., lactose in milk). Some plants and insects even provoke symptoms that mimic allergies by releasing histamine into their predators and victims (Richman and Baer, 1986; Moneret-Vautrin, 1987). Moreover, since the machinery of allergy is ancient, it would be surprising if some organisms had not evolved counterstrategies to exploit the dangers inherent in this machinery. Indeed, cobra venom contains a chemical that triggers mast-cell degranulation independently of IgE antibodies (Morrison et al., 1975).

#### ALLERGENS ARE USUALLY AVOIDABLE

Because IgE-mediated (immediate-type) allergic responses entail potentially serious risks, reexposure to allergens can be dangerous. Selection therefore would be expected to favor the mounting of IgE responses primarily to avoidable toxins, hence the avoidability of allergens should be an essential aspect of any adaptationist account of allergy. Plant and insect toxins—common allergens—tend to be relia-

bly associated with their sources, which are conspicuous entities that mammals can usually avoid. Contact allergens (which elicit T-cell-mediated allergy) are often unidentifiable (and thus often unavoidable) because the delay in developing the allergic response weakens the association between the response and its source; however, contact allergy is very rarely life-threatening. Similarly, inhaled allergens, although to some extent avoidable (by relocation), are less avoidable than ingested or injected allergens, but are also much less likely than ingested or injected allergens to be life-threatening (perhaps because relatively small amounts of inhaled allergen reach the bloodstream). Allergens in a natural environment that elicit potentially life-threatening IgE-mediated responses are almost always identifiable and avoidable.

By contrast, mammals usually cannot perceive and avoid specific viruses, bacteria, and other pathogens: since a pathogen is not produced by the sources in which it is found, it is less likely to be reliably associated with any particular source. Furthermore, pathogens, unlike toxins, generally replicate inside their hosts, and consequently parasitize their hosts for indefinite periods of time. A host that is exposed on one occasion to a particular pathogen may become exposed to that pathogen chronically. Thus, IgE responses to pathogens could be exceedingly dangerous and, therefore, would be selectively disadvantageous. With the exception of helminths, which may manipulate the host's machinery of allergy, pathogens generally do not trigger immediate-type allergies.

Bacteria, however, do produce toxins. Because bacteria colonize mammalian intestines, mammals are chronically exposed to at least low levels of bacterial toxins. Over the course of mammalian evolution toxin-producing bacteria probably parasitized every individual that lived long enough to reproduce. Mammalian immune systems therefore evolved mechanisms other than IgE antibodies to cope with bacterial toxins, mechanisms that take into account the unavoidability and chronicity of these toxins. Helminths, unlike other pathogens, frequently induce the formation of IgE antibodies; but if the sources of helminth allergens are plant toxins ingested by the host, then helminth toxins are indistinguishable from dietary toxins, and the immune system is "tricked" into

responding to an unavoidable and chronic pathogen as if it were an avoidable plant toxin.

The immune system appears to have evolved mechanisms to determine whether a particular toxin is avoidable, by using chronicity of exposure as a sign of unavoidability, and to reduce the proliferation of IgE antibodies to unavoidable toxins. In chronic human allergies, the levels of the subclass IgG4 antibody often rise; IgG4 antibodies compete with IgE antibodies in binding to allergens (Urbanek, 1988). (In certain nonhuman mammals other subclasses of IgG antibodies function similarly to the IgG4 subclass in humans—Mota, 1986). After prolonged exposures to an allergen, levels of IgG4 antibodies often surpass those of IgE (Shakib, 1986). In chronic helminth infections, for example, IgG4 levels rise markedly, whereas in early or acute infestations IgG4 levels are low (Catty et al., 1986). One of the functions of IgG4 antibodies may be to block the production of dangerous IgE antibodies to chronically encountered toxins.

IgG4 “blocking” antibodies are generally thought to account for the success of desensitizing inoculations against pollen and venom allergies: low levels of allergenic extracts injected at regular intervals over a prolonged period cause IgG4 levels to rise dramatically and block the access of IgE antibodies to the allergens (Nakagawa, 1986; Stanworth, 1986). The protective effects of IgG4 antibodies have been demonstrated in the cases of pollen, dust-mite, and bee-venom allergies (Aalberse et al., 1983; Nakagawa, 1986; Stanworth, 1986). This prolonged artificial immunization with allergens mimics chronic natural exposure to allergens. Through periodic desensitizing injections of allergenic extracts, the immune system may be “tricked” into recognizing the allergens as chronic and, therefore, as unavoidable. (If the purpose of IgG4 blocking antibodies is to prevent severe allergic responses to chronic allergens, then IgG4 antibodies should rise only in response to risky levels of allergen. Individuals with chronic allergies to pollen and other inhaled allergens may not develop IgG4 blocking antibodies spontaneously if the level of allergen that reaches the bloodstream as a result of inhalation is much lower than the level that would reach the bloodstream as a result of desensitizing inoculations.)

#### ALLERGIES ARE MORE PREVALENT IN INDUSTRIAL SOCIETIES

Many people in industrial societies suffer from allergies; epidemiologists' estimates of the prevalence of respiratory allergy alone range from 5 to 27 percent (Weeke, 1987). Although the literature on allergy among preliterate peoples is sparse, allergy is generally thought to occur substantially more frequently in industrial than in preliterate societies (Black, 1980; Weeke, 1987). The incidence and prevalence of allergy in industrial societies is therefore most likely a highly skewed representation of the incidence and prevalence of allergy throughout most of human evolutionary history.

One cause of the increased incidence and prevalence of allergy in industrial societies may be the dramatic reduction of breast-feeding (women in hunter-gatherer societies typically breast-feed their children for at least three years). Various studies have found that the breast-feeding of infants correlates negatively with the incidence of allergy in infants and children (Saarinen et al., 1979; Chandra, 1979), but other studies have found no such correlation (Fergusson et al., 1981; Van Asperen et al., 1984). [Van Asperen et al. (1984) review many studies on the relationship between breast-feeding and allergy.] Frick (1987) emphasizes that preventing the development of allergy in infants may require exclusive breast-feeding for at least six months. Breast-feeding could suppress the development of allergies if the maternal IgA antibodies (which bind to and neutralize antigens in the gastrointestinal tract without inflaming the surrounding tissues) in colostrum and breast milk compete with the infant's IgE antibodies, thereby preventing ingested antigens from stimulating excessive production of IgE antibodies (Frick, 1987). If allergy and breast-feeding are negatively correlated, then many allergic people in industrial societies can be expected to produce an unnaturally high and non-optimal level of IgE antibodies.

Respiratory allergies, such as those to pollen, are very common in industrial societies (comparative data on hunter-gatherer societies are not available). In addition to infant feeding practices, various factors, such as viral respiratory infections, may increase the risk of developing respiratory allergies. Various re-

searchers have noted that the onset of respiratory allergies in children correlates with the onset of respiratory infections (Frick, 1987; Busse, 1989). In an experiment designed to investigate this relationship, Frick and Brooks (1983) found that puppies injected at regular intervals with both pollen extracts and live viral vaccines mounted significantly greater IgE responses to the pollen than did puppies injected only with pollen extracts. Most children in industrial societies come into contact with large numbers of people from whom they catch numerous respiratory infections; by contrast, children in hunter-gatherer societies come into contact with many fewer people and thus are probably less likely to suffer from a continuous series of viral respiratory infections. Viral infections might conceivably increase susceptibility to allergy simply by augmenting the numbers of circulating T cells and B cells that are available to respond to allergens. Air pollution might also exacerbate allergy to airborne allergens, such as pollen (Miyamoto et al., 1988). For example, in experiments designed to investigate possible causes for the dramatic increase in pollen allergy in Japan since the 1950s, Miyamoto et al. (1988) found that mice injected with a combination of diesel exhaust particles and either ovalbumin or cedar pollen produced significant levels of anti-ovalbumin IgE or anti-cedar IgE, whereas mice injected with ovalbumin or cedar pollen alone produced very low levels of IgE.

Respiratory allergies to other airborne antigens, such as dust mites, are probably much more common among people in industrial societies, who establish fairly permanent homes, than they are among hunter-gatherers, who lack the household materials, such as blankets and carpets, that collect dust and provide breeding grounds for dust mites. Furthermore, by resettling frequently, hunter-gatherers avoid continual exposure to at least some of the airborne allergens of any particular locality.

The difficulty of identifying and avoiding the allergenic culprits in foods and skin-care products has undoubtedly exacerbated the incidence and prevalence of allergy in industrial societies. A hunter-gatherer who experiences an immediate allergic reaction to a fruit, vegetable, or fish, for example, can fairly reliably identify the offending food and avoid it in the future. People in industrial societies, on the

other hand, are exposed to many hidden ingredients in their foods (e.g., fish oil in ice cream), which are introduced during manufacturing or preserving processes (Radcliffe, 1987) and which are not easily identifiable by sight, scent, or taste. Furthermore, an allergen may be a common constituent of many processed foods and not easily avoidable; wheat, for example, which is a fairly common allergen, is an ingredient in many breads, cereals, pastas, crackers, and other foods. Skin allergies often result from prolonged daily contact with substances—such as detergents, soaps, shampoos, and occupational chemicals—that are widely used in industrial societies but not in hunter-gatherer societies. Most skin-care products contain an assortment of potential allergens, and it is often very difficult to pinpoint the specific allergenic constituents of allergenic products.

The environments in which the human machinery of allergy was shaped by natural selection differ considerably from modern industrial environments. Ancestral humans probably developed allergies from time to time to substances that were generally identifiable and avoidable, whereas humans in industrial societies often suffer chronically from allergies to substances that cannot be easily identified or, for reasons related to occupation or hygiene, cannot be avoided. (Similarly, wild mammals probably suffer fewer allergies than their domestic counterparts do.) Although they are in many respects evolutionarily novel, industrial environments often constitute excellent testing grounds for adaptationist hypotheses because the patterns predicted by such hypotheses may be manifested in an exaggerated fashion in these environments; for example, the mechanisms that underpin the human cravings for sugar, fat, and salt are manifested more dramatically in modern fast-food cuisine than they are in hunter-gatherer cuisine (Symons, in press). An appropriate test of the toxin hypothesis is not whether a particular allergy is adaptive in an evolutionarily novel industrial environment but, rather, whether the allergy conforms to the pattern predicted by this hypothesis (which is based on specific assumptions about the selection pressures that operated in the environment of evolutionary adaptedness) (Symons, pers. commun.).

**ALLERGY IS EXPECTED TO BE  
HIGHLY VARIABLE AMONG INDIVIDUALS**

One of allergy's most salient characteristics is its apparent capriciousness. Allergy should be expected to be highly variable among individuals, however, since, according to the toxin hypothesis, it was designed by natural selection to function as a last line of defense against toxins, and therefore to respond to the variability in individual phenotypes and environments. Individual differences in the occurrence of allergies arise from individual differences in genetic predisposition to allergy; exposure to particular toxins; effectiveness of primary defenses against toxins, including such factors as quantity and type of detoxification enzymes and permeability of epithelial surfaces to toxic antigens; and life history (e.g., whether or not an individual was breast-fed).

Genetic differences account for some of the individual variation in allergy, and individuals who are especially susceptible to allergies often have family histories of allergy. Inheritance of particular alleles of the major histocompatibility region of the genome predisposes individuals to certain allergies (de Weck et al., 1977).

The degree of susceptibility to a particular toxin depends largely on the availability of enzymes capable of detoxifying that toxin. "All these enzymes differ in quantity, subcellular localization and sometimes also in substrate specificity between organs, development stages, sexes and species. They therefore represent an important contributing factor to differences in susceptibilities [to toxins and carcinogens]" (Oesch, 1987:174). The set of genes coding for detoxification enzymes exhibits an unusually high degree of polymorphism (Meyer et al., 1988; Johnson et al., 1988), and susceptibility to certain allergies is in part a function of enzyme phenotype (Brostoff, 1987). Furthermore, because each individual has a unique dietary and environmental history, each has induced different levels of enzymes. Since enzyme induction significantly influences susceptibility to toxins, it probably also influences susceptibility to allergy.

The immune system must be able to mount IgE responses to an immense array of toxins and carrier proteins. Which toxins will succeed in permeating epithelial tissues, evading detoxification enzymes, and stimulating IgE anti-

bodies depends on a multitude of factors, accounting for much of the variability of allergies. Because allergies stem from so many factors that are not readily apparent to the allergic individual or to investigators of allergy, allergies may appear capricious even though they usually represent responses to definite toxic threats.

**ALLERGY-CANCER CORRELATIONS**

Although allergy is not specifically designed to prevent cancer, it may help to do so by expelling or destroying mutagenic and carcinogenic toxins. At least 22 epidemiological studies have measured the correlation between developing allergy and developing cancer. [Most of these studies are reviewed by Vena et al. (1985); studies not in Vena et al. include Allegra et al. (1976), Hallgren et al. (1981), Moussa et al. (1985), McDuffie et al. (1988), and McWhorter (1988).] Of the 22 studies, 16 found a negative correlation between allergy and cancer (i.e., individuals with a history of allergy were less likely to develop cancer), 3 found no correlation, and 3 found a positive correlation. Clear relationships between types of allergy and types of cancer, however, cannot be abstracted from these heterogeneous studies: some of the studies analysed only a small subset of cancer types; many did not control for smoking, age, and sex; and most did not differentiate allergy from non-IgE-mediated allergy-like symptoms (asthma and hives, for example, are usually regarded in the medical literature as having both allergic and nonallergic etiologies). Although the preponderance of studies reporting an inverse relationship between allergy and cancer may appear to support the toxin hypothesis, such correlational studies should be interpreted cautiously.

Among the studies that found a negative correlation are the following: Vena et al. (1985), in a retrospective study of 13,665 cancer patients and 4079 controls matched for age and sex, found that men with a history of allergy had a lower risk of cancers of the mouth, lung, larynx, digestive system, urinary system, and of all sites combined, and that women had a lower risk of cancers of the digestive and reproductive systems—particularly cancers of the cervix—and of all sites combined. Hallgren et al. (1981), in a study of 217 bronchial carcinoma patients and 389 noncancer controls, reported an incidence of allergy 5 times higher

among the controls. Cockcroft et al. (1979), in a study of 392 cancer patients and 303 controls, found that allergies occurred more than twice as often in controls as in patients with cancers of endodermal origin, such as cancers of the lungs and digestive tract, tissues that are heavily exposed to carcinogens. Ure (1969), in a study of 140 patients of a gynecological ward, found that the women who suffered from hay-fever-type allergies (20%) and the women who suffered from malignancies (28%) constituted mutually exclusive groups. By contrast, McWhorter (1988), in a follow-up study of 6108 people surveyed before 1976, found that people who had been diagnosed as having allergies had a higher risk of cancer; a history of hives was a particular risk factor for lymphatic-hematopoietic cancers.

The authors of most of the studies that found negative correlations cautiously suggest that allergy may protect against cancer. Rosenbaum and Dwyer (1977) even propose that IgE antibodies and the pharmacological substances released during allergic responses may directly promote tumor resistance. A key question in interpreting allergy-cancer correlations, however, is whether a particular allergy occurs because the individual has heightened allergic capability, heightened exposure to a particular toxin, or heightened susceptibility to a particular toxin. The toxin hypothesis would predict a negative correlation between allergy and cancer only if the variability in allergy represented variability in the immunological capacity to target and eliminate toxins. As Ewald (pers. commun.) has pointed out, positive correlations between allergy and cancer would be expected if people with allergies simply had less effective primary detoxification mechanisms or were exposed to higher doses of toxins than people without allergies.

Furthermore, the fact that allergy-cancer correlations have been determined only in evolutionarily novel industrial environments creates additional problems of interpretation. As a hypothetical example, if not being breast-fed turned out to be a risk factor for cancer, then a positive correlation between allergy and cancer would not necessarily indicate a causal connection, since not being breast-fed is apparently a risk factor for allergy (Symons, pers. commun.). Moreover, the effect of allergy on cancer risk may depend on whether the symp-

toms of allergy are acute or chronic. Allergy inflames tissues, and chronic allergies do so chronically. Chronic inflammation from any cause is a risk factor for cancer because it leads to chronic cell proliferation and the production of oxygen radicals, both of which promote carcinogenesis (Ames, 1989). Chronic allergies may increase the risk of cancer even if sporadic allergies lower the risk.

Further epidemiological and experimental studies to determine the relationships between toxins, particular types of allergy, and particular types of cancer might shed light on the etiology of certain cancers. For example, it is possible that the (apparently) higher incidences of gynecological cancers in women without allergies result from higher concentrations of toxin that have been circulated to the highly vascularized uterine lining or deposited in the cervix during menstrual shedding of the uterine lining. Most human cancers arise from epithelial tissues, such as the gut lining, skin or lungs (Wright and Alison, 1984), which are heavily exposed to environmental carcinogens and which are lined by mast cells and IgE antibodies. By targeting covalently binding toxins, IgE antibodies may help to protect these tissues from carcinogenic transformation.

#### THE TOXIN HYPOTHESIS, BUT NOT THE HELMINTH HYPOTHESIS, ACCOUNTS FOR THE MAIN PHENOMENA OF ALLERGY

If allergy had evolved primarily to protect against helminths, it would represent astonishingly poor design by natural selection. (As discussed above, however, it is possible that some of the mechanisms of allergy have been co-opted or altered for defense against helminths.) To support this assertion, 12 phenomena that a successful theory of allergy should account for will be discussed. These phenomena constitute the most distinctive or puzzling features of allergy. Some of the phenomena are of more concern in one part of the allergy literature than in other parts; for example, covalent binding is discussed widely in the literature on drug allergy but not in the literature on pollen allergy. The first 4 phenomena can be accounted for both by the toxin hypothesis (TH) and by the helminth hypothesis (HH); the remaining 8, however, can be accounted for only by the toxin hypothesis.

*Phenomena Explained Both by the Toxin Hypothesis and by the Helminth Hypothesis*

(1) The manifestations of allergy include vomiting, diarrhea, coughing, sneezing, scratching, and tearing.

TH: These manifestations are means of rapidly expelling dangerous toxins before they reach target organs.

HH: A similar argument could be made: some of these manifestations could be means of expelling helminths. Platts-Mills (1987) notes that coughing might dislodge helminth larvae from the respiratory tract and diarrhea might hinder helminths from penetrating the gastrointestinal tract.

(2) Chronic allergies are frequently accompanied by high levels of IgG4 "blocking" antibodies.

TH: Chronicity of exposure to a particular allergen signifies to the immune system that the allergen is unavoidable. IgG4 antibodies accompany chronic allergies in order to block IgE antibodies and protect against anaphylactic shock caused by unavoidable allergens.

HH: A similar argument could be made: IgG4 antibodies appear to partially block IgE responses to helminths in chronic infections (Hussain and Ottesen, 1985; 1986). Jassim et al. (1987) and Hussain and Ottesen (1988) have pointed out that high levels of IgG4 antibodies may inhibit potentially dangerous IgE responses to helminths. One might reasonably ask, however, why natural selection would have designed IgE antibodies to defend against a pathogen that is so often chronic.

(3) Eosinophils have receptors for IgE antibodies and degranulate during an allergic response.

TH: Eosinophils are mobile chemical weaponries that probably have multiple defense functions, perhaps including both the enzymatic detoxification of toxins and the destruction of helminths.

HH: The function of eosinophil degranulation in IgE responses is the destruction of helminths (even though most allergens are not helminths).

(4) Helminth infections often induce IgE antibodies.

TH: Helminth excretions and secretions, which are the primary targets of IgE antibodies during helminth infections, are likely to contain toxins absorbed from the host's diet; it is these toxins that are probably the allergens. As Mitchell (1979) has pointed out, helminths may even manipulate the host's machinery of allergy in order to feed on inflamed host tissues.

HH: IgE antibodies are induced to helminth excretions and secretions in order to combat the helminths.

*Phenomena Explained Only by the Toxin Hypothesis*

(5) Blood pressure drops in a strong allergic response.

According to the toxin hypothesis, the drop in blood pressure, which is caused by the histamine released from mast cells and basophils, functions to slow the rate at which toxins are circulated to target organs.

The helminth hypothesis literature does not confront this issue.

(6) Anticoagulants are released during an allergic response.

Heparin is an anticoagulant. Many snake and insect venoms contain enzymes that are toxic because of their coagulant properties (Yarleque et al., 1989; Williams and White, 1989). Heparin inhibits many of the procoagulants and certain other toxins of snake and insect venom (Higginbotham and Karnella, 1971; Sun and Walker, 1986; Teng and Ko, 1988). Higginbotham and Karnella (1971) even suggest that mast cells of the skin, which contain significant amounts of heparin, may be uniquely adapted for defense against bee venom. Heparin therapy for the treatment of bites by the Russell's viper, a snake whose venom kills more than 1000 people in Burma every year, is currently undergoing experimental trials (Than-Than et al., 1988).

Since heparin also inhibits certain eosinophil proteins that are toxic to helminths, including major basic protein and eosinophil cationic protein (Hamann et al., 1990) and, to some extent, eosinophil-derived neurotoxin (Molina et al., 1988), the helminth hypothesis cannot account for the release of

heparin during allergic responses. Intestinal mast cells, unlike mast cells of the lungs, for example, have little or no heparin (Barrett and Metcalfe, 1987); since helminths primarily parasitize the intestines, selection may have reduced the heparin content of intestinal mast cells so that helminth infections would not cause the release of this potentially dangerous chemical and so that eosinophil defenses against helminths would not be thwarted.

(7) Covalent binding of low-molecular-weight substances (haptens) to carrier proteins frequently triggers allergy.

Covalent binding of haptens to proteins signifies toxicity and potential DNA damage and, thus, is expected to trigger allergy.

The helminth hypothesis literature does not confront this issue.

(8) IgE-mediated allergy is risky (potentially lethal).

The danger of IgE-mediated responses implies that allergy was designed to counter threats, such as toxins, that can cause serious harm within minutes of entering the circulation.

Immune responses to nonhelminth pathogens, such as viruses and bacteria, are rarely as risky as IgE-mediated responses. Since helminths, like other pathogens, do not seriously harm their hosts within minutes of parasitizing them, the risk entailed by IgE responses to them seems dysfunctional. Of the myriad dangerous pathogens, why would helminths alone require such urgency and risk? This question has not been addressed by proponents of the helminth hypothesis.

(9) Symptoms of allergic responses often become more severe with repeated exposures to an allergen.

This phenomenon is compatible with the toxin hypothesis: the risk from multiple exposures to a toxin is sometimes cumulative and, thus, the severity of the response to the toxin might reasonably be expected to increase with subsequent exposures; in addition, the initial allergic response may be suboptimal, as is often the case with other immune responses; and it is also possible that the deterrent effect of the allergic response

may need to be augmented (particularly if the risk from the toxin is cumulative). That the severity of an allergic response tends to increase with repeated exposures implies that allergens are avoidable; and most toxin-containing substances are, indeed, avoidable (e.g., mammals can modify their behavior to avoid disturbing venomous bees or ingesting particular allergenic plants).

This phenomenon is incompatible with the helminth hypothesis. A mechanism designed to produce an increasingly dangerous response to each successive contact with a pathogen that is usually unavoidable and chronic, as helminths are, makes no adaptive sense. [African children with helminth infections sometimes die suddenly—apparently due to anaphylactic shock caused by IgE responses to the worms (Ogilvie and Jones, 1973).]

(10) Allergies occur to many foods, pollens, venoms, metals, and drugs.

The toxin hypothesis easily accounts for the allergenicity of plant foods, pollens, venoms, metals, and drugs: these substances either contain toxins or are toxic.

Some proponents of the helminth hypothesis have accounted for IgE responsiveness to the thousands of nonhelminth allergenic substances by the following line of reasoning. (1) Allergies to these substances are merely by-products of modernization. (2) In preindustrial environments, widespread allergies to nonhelminth antigens would not have occurred because antihelminth IgE antibodies would have saturated all available mast cells, leaving no mast cells free to bind IgE antibodies specific for nonhelminth antigens. (3) In industrial environments, however, where helminth infections are comparatively rare, IgE antibodies lack helminths to bind and so instead bind innocuous targets, such as pollen and food proteins (Godfrey, 1975). (Of course, this line of reasoning tends to undermine the helminth hypothesis: IgE antibodies and mast cells are permanently at war with helminths precisely because they are not effective in expelling helminths.)

Substantial evidence, however, is inconsis-

tent with the above account. Many helminth-infested individuals mount strong IgE responses to nonhelminth antigens (Teo et al., 1985), although not necessarily to the same antigens that are commonly encountered by individuals at higher socioeconomical levels (Lynch, DiPrisco-Fuenmayor, and Soto, 1983; Lynch, Lopez, Isteriz, and Tenias-Salazar, 1983). Among natives of the southern maldives, for example, high IgE levels caused by helminth infections do not prevent asthma, which is common (Wolstenholme, 1979). Among South Africans, individuals with high levels of IgE antibodies to helminths have higher levels of IgE to common inhaled allergens than do individuals without IgE antibodies to helminths (Joubert et al., 1980). Among children of Caracas, Venezuela, there is a very high incidence of allergy, even though many of the allergic children have helminth infections (Lynch and DiPrisco-Fuenmayor, 1984). The Waorani Indians of eastern Ecuador, who have very high IgE levels and high incidences of helminth infection, can be readily sensitized to pollen allergens (Lerrick et al., 1983). In rats, high IgE levels resulting from helminths do not appreciably protect against other allergies (Jarret and MacKenzie, 1980), except in the case of rats bred to be low IgE-responders (Turner et al., 1985). Furthermore, whether human populations manifest low or high prevalence of allergy depends, in general, on whether they are rural or urban, not on whether helminth infections are present or absent (Lynch et al., 1984).

Proponents of the helminth hypothesis have noted that a large percentage of the IgE antibodies produced in helminth infections appear to be "irrelevant"—i.e., not specific for helminth antigens (Turner et al., 1982). The IgE antibodies synthesized during helminth infections, however, may not be designed to counter worm antigens at all but, rather, to counter toxins that helminths sequester from the host's diet and then release into the bloodstream, often conjugated to the host's serum albumin. The supposedly "irrelevant" IgE antibodies may, therefore, have been appropriately induced to toxins.

(11) Allergy appears to be capricious.

The apparent capriciousness of allergy is perhaps the biggest stumbling block to the acceptance of any adaptationist account of allergy. The toxin hypothesis, however, leads to the expectation of wide variability in allergy among individuals and populations because, as discussed above (p. 47) allergy is a last line of defense, rather than a primary defense, against toxins.

The helminth hypothesis cannot account for the variability of the IgE response to any allergen, including helminths.

(12) Allergic cross-reactivity occurs among certain foods and pollen from unrelated botanical families.

According to the toxin hypothesis, cross-reactivity occurs because certain unrelated plants contain the same toxins.

The helminth hypothesis cannot account for allergic cross-reactivity to plants (or, indeed, for any allergic reactivity to plants).

In summary, the helminth hypothesis suffers from severe limitations: it cannot account for most of the salient phenomena of allergy, and the evidence that allergies help to combat helminth infections is tenuous. The toxin hypothesis, by contrast, accounts for or is compatible with all of the salient phenomena of allergy.

#### UNDERSTANDING THE FUNCTION OF ALLERGY MAY FACILITATE THE PREVENTION, DIAGNOSIS, AND TREATMENT OF ALLERGIES

Understanding the relationship between allergies and toxins may lead to novel approaches to the prevention, diagnosis, and treatment of allergy. The development of food allergies might be prevented or mitigated, for example, by cooking foods sufficiently to degrade their toxic constituents, or by diversifying the diet to prevent excessive exposure to any particular toxin and to induce detoxification enzymes to a wide variety of toxins.

The diagnosis of allergy, which includes isolating and identifying allergens, might be aided by focusing on toxins and their carrier proteins in allergenic substances; the treatment of allergy, in turn, would benefit from more accurate diagnoses. Conventional desensitization immunotherapy, for example, might be improved if the identification of specific allergens

facilitated the development of purer allergenic extracts. Treatments to prevent or mitigate allergic attacks might include the use of specific detoxification and digestive enzymes to degrade particular allergens. Individuals with respiratory allergies, for example, might use inhalants containing enzymes that degrade particular pollen toxins or pollen proteins, while individuals with food allergies might ingest tablets containing enzymes that degrade particular food toxins or food proteins. Various researchers have noted that the presence of digestive enzymes can mitigate allergy by degrading specific allergens, such as cows' milk proteins (Stanworth, 1985; Kniker and Rodriguez, 1987; Sprague and Milam, 1987).

Ewald's (1980) evolution-minded guidelines for the treatment of infectious diseases may also be of use in deciding whether or not to suppress an allergic response; see also Williams and Nesse (1991, Table 2). This decision will depend upon whether the allergic response represents (1) an adaptation to defend against a toxin; (2) an adaptation of an organism, such as a helminth, to manipulate the victim's ma-

chinery of allergy; or (3) a maladaptive, side-effect response to an innocuous substance that benefits neither the allergy sufferer nor a toxin-producing organism. Allergic responses that represent manipulations and maladaptive side effects may be safely suppressed, but non-life-threatening and non-debilitating allergic responses to toxins may be better left untreated. As Rosenbaum and Dwyer (1977:17) have written, "the somewhat disreputable IgE may yet make the list of immunobiological heroes."

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