American College of Physicians American Society of Internal Medicine

CME Patient Care Advocacy Annual Session PRACTICE MANAGEMENT SHOP NEWS ABOUT US

Annals of Internal Medicine

Current Issue

Past Issues

Library for Internists

Subscriptions

Info for Authors

Reprints & Permissions

Submit Letters Online

Customer Service

Advertising

Recruitment Advertising

Search Classifieds

Printer-friendly format
Email this page



Annals of Internal Medicine REVIEWS

Mosquitoes and Mosquito Repellents: A Clinician's Guide

Annals of Internal Medicine, 1 June 1998. 128:931-940. Mark S. Fradin, MD

This paper is intended to provide the clinician with the detailed and scientific information needed to advise patients who seek safe and effective ways of preventing mosquito bites. For this review, clinical and analytical data were selected from peer-reviewed research studies and review articles, case reports, entomology texts and journals, and government and industry publications. Relevant information was identified through a search of the MEDLINE database, the World Wide Web, the Mosquito-L electronic mailing list, and the Extension Toxicology Network database; selected U.S. Army, U.S. Environmental Protection Agency, and U.S. Department of Agriculture publications were also reviewed.

N,N-diethyl-3-methylbenzamide (DEET) is the most effective, and best studied, insect repellent currently on the market. This substance has a remarkable safety profile after 40 years of worldwide use, but toxic reactions can occur (usually when the product is misused). When DEET-based repellents are applied in combination with permethrin-treated clothing, protection against bites of nearly 100% can be achieved. Plant-based repellents are generally less effective than DEET-based products. Ultrasonic devices, outdoor bug "zappers," and bat houses are not effective against mosquitoes. Highly sensitive persons may want to take oral antihistamines to minimize cutaneous reactions to

mosquito bites.

Ann Intern Med. 1998;128:931-940. Annals of Internal Medicine is published twice monthly and copyrighted © 1998 by the American College of Physicians.

The quest to make humans less attractive to mosquitoes has fueled decades of scientific research on mosquito behavior and control. In the United States, mosquito bites are mostly a nuisance. Worldwide, however, mosquitoes transmit disease to more than 700 000 000 people annually and will be responsible for the deaths of 1 of every 17 people currently alive (1). Malaria results from infection with a protozoan carried by mosquitoes and, according to reports from the World Health Organization, causes as many as 3 000 000 deaths annually (2). Mosquitoes transmit the arboviruses responsible for yellow fever, dengue hemorrhagic fever, epidemic polyarthritis, and several forms of encephalitis (some of which are found in the United States). Bancroftian filariasis is caused by a nematode transmitted by mosquito bite.

Historically, the strategies for reducing the incidence of mosquito-borne disease have been two-pronged, centering around habitat control (through chemical and biological means) and the use of personal protection in the form of insect repellents. This paper reviews the scientific data on chemical (synthetic) and natural (plant-derived) insect repellents currently available, debunks some of the popular myths about alternative repellents, reviews effective techniques for reducing mosquito populations in the local environment, and provides the clinician with the practical information needed to advise patients on how to safely and effectively reduce their likelihood of being bitten by mosquitoes.

Methods

By doing a MEDLINE search with the keywords *DEET*, insect repellents, mosquito, citronella, and permethrin,

pertinent articles published in English-language journals between 1966 and 1997 were identified and reviewed. The World Wide Web and the Extension Toxicity Network database were also searched for toxicology data and other pertinent information. Selection from the bibliographies of relevant articles augmented the database search. Major distributors of natural insect repellents were contacted and asked to provide scientific data, if available, supporting the efficacy of their products.

The Mosquito Life Cycle

Mosquitoes are found all over the world, except in Antarctica. These two-winged insects belong to the order Diptera. Members of the genera *Anopheles*, *Culex*, and *Aedes* are most commonly responsible for bites in humans. There are approximately 170 species of mosquitoes in North America alone.

To develop, mosquitoes require an environment of standing water. As a group, they have adapted to complete their life cycle in diverse aquatic habitats, including fresh water; salt water marshes; brackish water; or water found in containers, old tires, or tree holes. The life cycle of the mosquito has four stages. The female mosquito lays her eggs, up to several hundred at a time, on the surface of the water or in an area subject to flooding. Unhatched eggs of some species can withstand weeks to months of desiccation, remaining viable until the right conditions for hatching occur. The eggs of most species hatch in 2 to 3 days, and the larvae feed on organic matter in the water for about a week until they change into pupae. The pupae live at the surface of the water for 2 to 3 days before metamorphosing into adult mosquitoes.

Only female mosquitoes bite. Male mosquitoes feed primarily on flower nectar, whereas female mosquitoes require a blood meal to produce eggs. They usually feed every 3 to 4 days; in a single feeding, a female mosquito

typically consumes more than its own weight in blood (3). Certain species of mosquitoes prefer to feed at twilight or nighttime; others bite mostly during the day.

Some mosquito species are zoophilic (preferring to feed on animals) and others are anthropophilic (showing a preference for human blood). In some mosquito species, seasonal switching of hosts provides a mechanism for transmitting diseases from animal to human. (It is worth noting, however, that mosquitoes cannot transmit HIV because the virus neither survives nor replicates in mosquitoes and the blood from the last bitten person is not flushed into the next person during subsequent feeds. In addition, the circulating viral load of most HIV-infected persons is so low that the theoretical risk that a mosquito bite would transmit HIV is estimated to be less than 1 in 10 000 000 [4, 5].)

Stimuli That Attract Mosquitoes

The factors involved in attracting mosquitoes to a host are complex and are not fully understood (6-11). Mosquitoes use visual, thermal, and olfactory stimuli to locate a host. Of these, olfactory cues are probably most important. For mosquitoes that feed during the daytime, movement of the host and the wearing of dark-colored clothing may initiate orientation toward a person (3, 12). Visual stimuli seem to be important for in-flight orientation, particularly over long ranges, whereas olfactory stimuli become more important as a mosquito nears its host.

It has been estimated that 300 to 400 compounds are released from the body as by-products of metabolism and that more than 100 volatile compounds can be detected in human breath (9). Of these odors, only a fraction have been isolated and fully characterized. Carbon dioxide and lactic acid are the two best-studied mosquito attractants. Carbon dioxide, released mainly from breath but also from skin, serves as a long-range airborne attractant and can be detected by mosquitoes

at distances of up to 36 meters (3, 13-15). Lactic acid, in combination with carbon dioxide, is also an attractant. Mosquitoes have chemoreceptors on their antennae that are stimulated by lactic acid. These same receptors may be inhibited by N,N-diethyl-3-methylbenzamide (DEET)-based insect repellents (16).

At close range, skin temperature and moisture serve as attractants (3, 9, 17). Different species of mosquitoes may show strong biting preferences for different parts of the human body (such as the head or feet), which may be related to local skin temperature and eccrine sweat gland output (18, 19). Anhidrotic persons show markedly decreased attractiveness to mosquitoes (6). Other volatile compounds, derived from sebum, eccrine and apocrine sweat, or the cutaneous microflora bacterial action on these secretions, may also act as chemoattractants (6, 20, 21). Whole-host odors are more attractive than carbon dioxide and lactic acid alone (22). Floral fragrances from perfumes, soaps, lotions, and hair-care products may also attract mosquitoes (23).

The attractiveness of different persons to the same or different species of mosquitoes varies substantially (17, 24). In general, adults are more likely to be bitten than children (17, 25), although adults may become less attractive to mosquitoes as they age (6). Men are bitten more readily than women (3, 26). Larger persons tend to attract more mosquitoes, perhaps because of their greater relative heat or carbon dioxide output (27).

Insect Repellents

Despite the obvious desirability of finding an effective oral mosquito repellent, no such agent has been identified (28, 29). Thus, the search for the perfect topical insect repellent continues. This ideal agent would repel multiple species of biting arthropods, remain effective for at least 8 hours, cause no irritation to the skin or mucous membranes, cause no systemic toxicity,

be resistant to abrasion and rub-off, and be greaseless and odorless. No available insect repellent meets all of these criteria.

Efforts to find such a compound have been hampered by the numerous variables that affect the inherent repellency of any chemical. Repellents do not all share a single mode of action, and surprisingly little is known about how repellents act on their target insects (30, 31). Moreover, different species of mosquitoes may react differently to the same repellent (32).

To be effective, a repellent must show an optimal degree of volatility, making it possible for an effective repellent vapor concentration to be maintained at the skin surface without evaporating so quickly that it loses its effectiveness. Many factors play a role in how effective any repellent is, including the frequency and uniformity of application, the number and species of the organisms attempting to bite, the user's inherent attractiveness to blood-sucking arthropods, and the overall activity level of the potential host (33). Abrasion from clothing, evaporation and absorption from the skin surface, washoff from sweat or rain, higher temperatures, or a windy environment all decrease repellent effectiveness (17, 34-37). Each 10 ° C increase in temperature can lead to as much as a 50% reduction in protection time (37). The repellents currently available must be applied to all exposed areas of skin; unprotected skin a few centimeters away from a treated area can be attacked by hungry mosquitoes (33, 35).

Chemical Insect Repellents

N,N-Diethyl-3-Methylbenzamide (DEET)

Previously called N,N-diethyl-m-toluamide, N,N-diethyl-3-methylbenzamide (DEET) remains the gold standard of currently available insect repellents. This substance was discovered and developed by scientists at the U.S. Department of Agriculture and was patented by the U.S.

Army in 1946. It was subsequently registered for use by the general public in 1957. It is a broad-spectrum repellent that is effective against mosquitoes, biting flies, chiggers, fleas, and ticks. Twenty years of empirical testing of more than 20 000 other compounds has not resulted in another marketed chemical product with the duration of protection and broad-spectrum effectiveness of DEET (30, 33, 38-41). The U.S. Environmental Protection Agency (EPA) estimates that more than 38% of the U.S. population uses a DEET-based insect repellent every year and that worldwide use exceeds 200 000 000 people annually (42).

Formulation of Available Products with DEET

In the United States, DEET is available in 5% to 100% concentrations in multiple formulations, including solutions, lotions, creams, gels, aerosol and pump sprays, and impregnated towelettes (Table 1).

Until 1989, the standard-issue insect repellent of the U.S. military consisted of 75% DEET in an alcohol base. Complaints about the aesthetic feel of this product and concerns about potential toxicity under long-term daily use led to U.S. Army-sponsored studies to produce new formulations. The 3M Company (St. Paul, Minnesota) developed a slow-release, polymer-based product containing 35% DEET; this has become the repellent provided to all U.S. military personnel. This product is available to the general public exclusively through the Amway Corporation (New York, New York) under the brand name HourGuard (Table 1). If lower-strength formulations of extended-release DEET are desired, Minnetonka Brands (Eden Prairie, Minnesota) offers products containing 6.5% and 10% DEET (Table 1).

Efficacy

As a general rule, higher concentrations of DEET provide longer-lasting protection. Unfortunately, no guidelines are available to help consumers decide what

concentration of DEET is appropriate for their specific needs. The number of variables that affect a repellent's effectiveness precludes assigning an "insect repellent factor" to individual products.

Mathematical models of the effectiveness and persistence of mosquito repellents show that the protection offered by a repellent is proportional to the logarithm of the dose (concentration of the product). This curve tends to form a plateau at higher repellent concentrations, providing relatively less additional protection for each incremental dose of DEET that exceeds a 50% concentration (43, 44). In one laboratory study, 50% DEET provided about 4 hours of protection against *Aedes aegypti* mosquitoes, but increasing the DEET concentration to 100% provided only 1 additional hour of protection (45). In another study, 12.5% DEET provided over 6 hours of protection against *Aedes albopictus*; doubling the DEET concentration to 25% increased the protection time only to about 8 hours (46).

Extended-release formulations of DEET have made it possible to reduce the repellent concentration without sacrificing duration of action. When tested under laboratory and several different environmental and climatic field conditions, the 35% DEET polymer formulation by the 3M Corporation was as effective as 75% DEET in repelling mosquitoes (19, 47-50). The polymer formulation provided up to 12 hours of more than 95% protection, depending on the environmental conditions and species of mosquito tested (46, 48, 49, 51). One study showed that Minnetonka Brands' 6.5% liposphere microdispersion of DEET was effective for up to 2.5 hours and that their 10% product was effective for about 1 hour longer (52).

How To Choose and Apply DEET Repellents

For casual use, a high concentration of DEET is not needed. Products with 10% to 35% DEET will provide adequate protection under most conditions. The

American Academy of Pediatrics recommends that repellents used on children contain no more than 10% DEET (53, 54). Products with a DEET concentration of more than 50% are probably best reserved for circumstances in which insect biting pressures are intense and in which other factors, such as high temperature and humidity, may promote rapid loss of repellent from the skin surface. The EPA issued guidelines to consumers about proper application of insect repellents (Table 2) (55).

Repellents may be applied directly to the skin or to clothing, window screens, mesh insect nets, tents, or sleeping bags. Persons who are particularly concerned about potential toxicity from DEET may limit application of the repellent to their clothes. If DEET-treated garments are stored in a plastic bag between wearings, the repellent effect can last for many weeks (24).

Repellents containing DEET must be carefully applied because they can damage plastics (such as watch crystals and eyeglasses frames), rayon, spandex, other synthetic fabrics, leather, and painted or varnished surfaces. DEET does not damage natural fibers, such as cotton or wool, and has no effect on nylon. The lay literature contains many accounts of the unpleasant odor or greasy feel of DEET, but careful testing has shown a full spectrum of aesthetic responses to these products (56).

Consumers who apply both a DEET-based insect repellent and a sunscreen should be aware that the repellent may reduce the sunscreen's effectiveness. A limited study in 14 volunteers using the 3M polymer-based 33% DEET repellent and a sunscreen with sun protection factor 15 revealed a mean decrease in sun protection factor of 33.5% when the two agents were applied sequentially (57). Combination products in which the insect repellent and sunscreen have been formulated together, however, would be expected to provide the sun protection factor stated on the label.

Pharmacology

Numerous studies have evaluated the percutaneous absorption, metabolism, and rate of excretion of DEET (58-61). Initial data suggested that 9% to 56% of the applied dose was absorbed through the skin (59). A carefully conducted study from 1995 that used human volunteers showed that the average dermal absorption of 100% DEET was 5.6%; for 15% DEET in ethanol, an average of 8.4% of the dose was absorbed (58). Because of its lipophilic nature, DEET was rapidly absorbed within 2 hours after application; was eliminated from the plasma within 4 hours after being rinsed off the skin; and was primarily excreted in the urine, mostly within 12 hours. Tape stripping revealed that the chemical does not accumulate in the stratum corneum.

Bioavailability experiments conducted with Minnetonka Brands' 10% DEET liposphere formulation showed that percutaneous absorption was one third of that of a 10% alcohol-based DEET solution (52). In contrast, U.S. Army studies that used an in vitro pigskin model did not show any reduced percutaneous absorption (expressed as a percentage of the applied dose) of the 3M polymer formulation compared with 75% DEET in alcohol (62).

Toxicity

Used by millions of people worldwide for 40 years, DEET has a remarkable safety profile. As part of the 1980 EPA Reregistration Standard for DEET, more than 30 studies were conducted to assess acute, chronic, and subchronic toxicity; mutagenicity; oncogenicity; and developmental, reproductive, and neurologic toxicity (Table 3) (42, 63, 64). The results of these studies did not require any change to the product to comply with EPA safety standards, nor did they indicate any new toxicities with normal use. Studies of high doses of DEET orally administered to mice and rats did not reveal any potential in humans for teratogenicity or

oncogenicity.

Case reports of potential DEET toxicity exist in the medical literature and are summarized in <u>Table 4</u>. The reports of greatest concern involve 14 cases of encephalopathy, 13 of which were in children younger than 8 years of age (63, 66-71, 75). Three of these children died, 1 of whom had an ornithine carbamoyl transferase deficiency (67) that might have predisposed her to DEET-induced toxicity (66). The other children recovered without sequelae. Many of these persons had a history of long-term, excessive, or inappropriate use of DEET repellents, and the details of exposure are frequently poorly documented. Animal studies in rats and mice have shown that DEET is not a selective neurotoxin (42, 61, 63).

Toxicology studies in rats and dogs in which sublethal intraperitoneal injections were used revealed that DEET could induce dose-dependent hypotension and bradycardia; however, these conditions occurred at dosages that would be almost impossible to attain with cutaneous applications of DEET (78). Only one case of bradycardia and hypotension has been documented in the medical literature (79).

Initial repeat-insult patch tests of 100% technical-grade DEET or 50% DEET in ethanol conducted over 21 consecutive days showed no sign of skin irritation (42). Subsequently, 14 cases of contact urticaria and irritant contact dermatitis (mostly in soldiers) have been reported (81-85). The antecubital fossa seems to be particularly sensitive to developing bullous irritant contact dermatitis if DEET products are allowed to remain on this area overnight (86).

A 1994 study reviewed 9086 cases of DEET exposure reported to 71 poison control centers from 1985 to 1989 (76). More than half (54%) of the persons involved had no symptoms at the time of the call to the poison control

center. The most commonly reported symptoms were related to spraying repellent in the eyes (DEET is a known eye irritant [42]) or inhaling it. Symptoms were least likely to occur after accidental ingestion of small amounts of the repellent. Although most exposures were in children, there was no evidence that children younger than 6 years of age were more likely than older children or adults to develop adverse effects after use of a DEET repellent. No correlation was found between the severity of symptoms and age, sex, or concentration of applied DEET. Eighty-eight percent of exposed persons did not require treatment at a health care facility. Of the patients who were seen, 81% were sent home, and only 5% required hospitalization. Of the patients in whom follow-up was available, 99% had no long-term sequelae.

In summary, DEET has had a remarkable safety profile during more than 40 years of use by millions of people worldwide. Careful product choice and application of the repellent according to EPA guidelines will greatly reduce the possibility of toxicity. Conservative use of low-concentration DEET products is most appropriate for children.

Questions about the safety of DEET may be addressed to the EPA-sponsored National Pesticide Telecommunications Network, available by telephone every day from 6:30 a.m. to 4:30 p.m. Pacific Standard Time at 800-858-7378 or on the World Wide Web at http://www.ace.orst.edu/info/nptn/.

Skin-So-Soft

Avon (New York, New York) Skin-So-Soft bath oil received considerable media attention several years ago when some consumers reported it to be effective as a mosquito repellent. When tested under laboratory conditions against *Aedes aegypti* mosquitoes, this product's effective half-life was 30 minutes. Against *Aedes albopictus*, Skin-So-Soft oil provided 40 minutes of protection from bites, a duration 10 times less than that of 12.5% DEET (46). It has been proposed that the

limited mosquito repellent effect of Skin-So-Soft oil could be caused by its fragrance or the presence of diisopropyl adipate and benzophenone in the formulation, both of which have some repellent activity (40). Avon now markets products under the Skin-So-Soft label that contain an EPA-recognized repellent (Table 5).

Plant-Derived Repellents

Thousands of plants have been tested as potential sources of insect repellents (39, 40, 87). None of the plant-derived chemicals tested to date demonstrate the broad effectiveness and duration of DEET, but a few show repellent activity. Plants whose essential oils have been reported to have repellent activity include citronella, cedar, verbena, pennyroyal, geranium, lavender, pine, cajeput, cinnamon, rosemary, basil, thyme, allspice, garlic, and peppermint (40, 88-91). Unlike synthetic insect repellents, plant-derived repellents have been relatively poorly studied. When tested, most of these essential oils tended to give short-lasting protection, usually less than 2 hours. Readily available plant-derived insect repellents are listed in Table 5.

Citronella

Citronella is the active ingredient most commonly found in "natural" or "herbal" insect repellents marketed in the United States. It is registered with the EPA as an insect repellent. Citronella oil has a lemony scent and was originally extracted from the grass plant *Cymbopogon nardus*. Limited data are available from studies that directly compared the efficacy of citronella-based products with that of DEET-based products. In one study, 0.01 µmol of DEET per L of air was sufficient to prevent 90% of mosquitoes from landing on their targets; a 1000-fold higher concentration of citronellol (one of the active chemicals in citronella oil) was required to achieve a similar effect (31).

Studies show that citronella can be an effective repellent,

but it provides shorter complete protection time than most DEET-based products. Frequent reapplication of the repellent can partially compensate for this. The manufacturer of Natrapel (Tender Corp., Littleton, New Hampshire) has laboratory data showing that their 10% lotion reduced mosquito bites by 84% during a 4-minute test period. In contrast, 14% DEET reduced biting by 96% in the same test period. Buzz Away (Quantum, Inc., Eugene, Oregon) with 5% citronella oil provided an average protection time of 1.9 hours against *Aedes aegypti* (92). In field testing, Buzz Away Oil provided an average of 88% repellency during a 2-hour exposure. In general, the repellency of Buzz Away was greatest within the first 40 minutes after application and decreased over the remainder of the test period (93).

Citronella candles have been promoted as an effective way to repel mosquitoes in the backyard. One study compared the ability of commercially available 3% citronella candles, 5% citronella incense, and plain candles to prevent bites by *Aedes* mosquitoes under field conditions (94). Persons near the citronella candles had 42% fewer bites than controls, who had no protection (a statistically significant difference). However, burning ordinary candles reduced the number of bites by 23%. The efficacy of citronella incense and plain candles did not differ. The ability of plain candles to decrease biting may result from their action as a decoy source of warmth, moisture, and carbon dioxide.

The citrosa plant (*Pelargonium citrosum* 'van Leenii') has been marketed as being able to repel mosquitoes through the continuous release of citronella oils. Unfortunately, when tested, these plants offer no protection against bites (95, 96).

Bite Blocker

Bite Blocker (Consep, Inc., Bend, Oregon) is a plantbased repellent that was released in the United States in 1997. Bite Blocker combines soybean oil, geranium oil, and coconut oil in a formulation that has been available in Europe for several years (97). Studies conducted at the University of Guelph, Ontario, Canada, showed that this product gave more than 97% protection against *Aedes* mosquitoes under field conditions, even 3.5 hours after application. During the same period, a 6.65% DEET-based spray afforded 86% protection, and Avon Skin-So-Soft citronella-based repellent gave only 40% protection (98). A second study showed that Bite Blocker provided a mean ± SD of 200 ± 30 minutes of complete protection from mosquito bites (99).

Permethrin

Pyrethrum is a powerful, rapidly acting insecticide, originally derived from the crushed and dried flowers of the daisy *Chrysanthemum cinerariifolium* (100).

Permethrin is a human-made synthetic pyrethroid. It does not repel insects but works as a contact insecticide, causing nervous system toxicity that leads to the death or "knockdown" (out of the air) of the insect. The chemical is effective against mosquitoes, flies, ticks, and chiggers. Permethrin has low toxicity in mammals, is poorly absorbed by the skin, and is rapidly inactivated by ester hydrolysis (101).

Permethrin should be applied directly to clothing or other fabrics (such as tent walls [102] or mosquito nets [103]), not to skin. The spray form is nonstaining, nearly odorless, and resistant to degradation by heat or sun and maintains its potency for at least 2 weeks, even through several launderings (104, 105). The combination of permethrin-treated clothing and skin application of a DEET-based repellent creates a formidable barrier against mosquito bites (19, 106, 107). In a field trial conducted in Alaska, persons wearing permethrin-treated uniforms and a polymer-based 35% DEET product had more than 99.9% protection (1 bite/h) over 8 hours, even under conditions of intense biting pressures; unprotected persons received an average of 1188 bites/h (108).

Permethrin-based insecticide sprays available in the United States are listed in <u>Table 5</u>. To apply to clothing, spray each side of the fabric (outdoors) for 30 to 45 seconds, just enough to moisten it. Allow the garment to dry for 2 to 4 hours before wearing it.

Reducing Local Mosquito Populations

Consumers may still find advertisements for small ultrasonic electronic devices that are meant to be carried on the body and purportedly emit sounds that repel mosquitoes. Many studies conducted in the field and laboratory show that these devices do not work against mosquitoes (109-111). Encouraging natural predation of insects by setting up bird or bat houses in the backyard has also been unsuccessful in reducing local mosquito populations (112). Likewise, backyard bug "zappers," which lure and electrocute insects, are ineffective (113). Mosquitoes continue to be more attracted to humans than to the devices. One study conducted in homeowners' backyards showed that of the insects killed by these devices, only 0.13% were female mosquitoes (114). An estimated 71 billion to 350 billion beneficial insects may be killed annually in the United States by these electrocuting devices (114). The most effective way to reduce a local population of mosquitoes is to eliminate sources of standing water, such as old discarded tires, clogged gutters, planters, bird baths, or tree stump holes.

Relief from Mosquito Bites

Cutaneous responses to mosquito bites range from common localized wheal-and-flare reactions to delayed bite papules, rare systemic Arthus-type reactions, and anaphylaxis (115-117). Bite reactions are the result of sensitization to mosquito salivary antigens, which lead to the formation of specific IgE and IgG antibodies (118-121). Immediate-type reactions are mediated by IgE and histamine, whereas cell-mediated immunity is

responsible for the delayed reactions.

Several strategies exist for relieving the itch of mosquito bites. Topical corticosteroids can reduce the erythema, itching, and induration. Topical diphenhydramine and caine-containing derivatives should be avoided because of concerns about inducing allergic contact sensitivity. Oral antihistamines can be effective in reducing the symptoms of mosquito bites. Cetirizine was given prophylactically in a double-blind, placebo-controlled, 2week, crossover trial to 18 persons who had previously had dramatic cutaneous reactions to mosquito bites (122). Persons who received the active drug had a statistically significant 40% decrease in the size of the wheal response at 15 minutes and the size of the bite papule at 24 hours. The mean pruritus score, measured 0.25, 1, 12, and 24 hours after the mosquito had bitten, was 67% less than that of the untreated controls. These studies have not been done with astemizole, terfenadine, loratadine, or fexofenadine. In highly sensitized persons, prophylactic treatment with nonsedating antihistamines may safely reduce the cutaneous reactions to mosquito bites.

Acknowledgments: The author thanks Donald Baumgartner (U.S. Environmental Protection Agency); Donald Barnard, PhD (U.S. Department of Agriculture); Nigel Hill (London School of Hygiene and Tropical Medicine); and Robbin Lindsay, PhD (Department of Environmental Biology, University of Guelph) for providing data that were not readily available in the medical literature. The author has received no monetary support from any of the manufacturers whose products are mentioned in this paper.

Requests for Reprints: Mark S. Fradin, MD, Chapel Hill Dermatology, 891 Willow Drive, Suite 2, Chapel Hill, NC 27514.

References

- **1. Taubes G.** A mosquito bites back. The New York Times Magazine. 1977;24 Aug:40-6.
- **2. Shell ER.** Resurgence of a deadly disease. The Atlantic Monthly. 1997; Aug: 45-60.
- **3. Clements AN.** The Physiology of Mosquitoes. Oxford: Pergamon Pr; 1963.
- **4. Miike L.** Do insects transmit AIDS? Washington, DC: Office of Technology Assessment Health Program, U.S. Congress; 1987.
- **5. McHugh CP.** Arthropods: vectors of disease agents. Laboratory Medicine. 1994;25:429-37.
- **6. Maibach HI, Skinner WA, Strauss WG, Khan AA.** Factors that attract and repel mosquitoes in human skin. JAMA. 1966;196:263-6.
- **7. Curtis CF.** Fact and fiction in mosquito attraction and repulsion. Parasitology Today. 1986;2:316-8.
- **8. Keystone JS.** Of bites and body odour. Lancet. 1996;347:1423.
- **9. Bock GR, Cardew G, eds.** Olfaction in Mosquito-Host Interactions. New York: J Wiley; 1996.
- **10. Bowen MF.** The sensory physiology of host-seeking behavior in mosquitoes. Annu Rev Entomol. 1991;36:139-58.
- **11. Davis EE, Bowen MF.** Sensory physiological basis for attraction in mosquitoes. J Am Mosq Control Assoc. 1994;10(2 Pt 2):316-25.
- **12. Gjullin CM.** Effect of clothing color on the rate of attack of *Aedes* mosquitoes. J Econ Entomol. 1947;40:326-7.
- **13. Gillies MT.** The role of carbon dioxide in host-finding by mosquitoes (Diptera: Culicidae): a review. Bulletin of Entomological Research. 1980;70:525-32.
- **14. Gillies MT, Wilkes TJ.** The range of attraction of animal baits and carbon dioxide for mosquitoes. Studies in a freshwater area of West Africa. Bulletin of Entomological Research. 1972;61:389-404.
- **15. Snow WF.** The effect of a reduction in expired carbon dioxide on the attractiveness of human subjects to mosquitoes. Bulletin of Entomological Research. 1970:60:43-8.

- **16. Davis EE, Sokolove PG.** Lactic acid-sensitive receptors on the antennae of the mosquito, *Aedes aegypti*. J Comp Physiol. 1976;105:43-54.
- **17. Khan AA.** Mosquito attractants and repellents. In: Shorey HH, McKelvey JJ, eds. Chemical Control of Insect Behavior. New York: J Wiley; 1977:305-25.
- **18. de Jong R, Knols BG.** Selection of biting sites by mosquitoes. In: Bock GR, Cardew G, eds. Olfaction in Mosquito-Host Interactions. New York: J Wiley; 1996:89-108.
- **19. Kline DL, Schreck CE.** Personal protection afforded by controlled-release topical repellents and permethrintreated clothing against natural populations of *Aedes taeniorhynchus*. J Am Mosq Control Assoc. 1989;5:77-80.
- **20. Schreck CE, Kline DL, Carlson DA.** Mosquito attraction to substances from the skin of different humans. J Am Mosq Control Assoc. 1990;6:406-10.
- **21. Knols BG, de Jong R, Takken W.** Trapping system for testing olfactory responses of the malarial mosquito *Anopheles gambiae* in a wind tunnel. Med Vet Entomol. 1994;8:386-8.
- **22. Geier M, Sass H, Boeckh J.** A search for components in human body odour that attract females of *Aedes aegypti*. In: Bock GR, Cardew G, eds. Olfaction in Mosquito-Host Interactions. New York: J Wiley; 1996:132-48.
- **23. Foster WA, Hancock RG.** Nectar-related olfactory and visual attractants for mosquitoes. J Am Mosq Control Assoc. 1994;10 (2 Pt 2):288-96.
- 24. Curtis CF, Lines JD, Ijumba J, Callaghan A, Hill N, Karimzad MA. The relative efficacy of repellents against mosquito vectors of disease. Med Vet Entomol. 1987;1:109-19.
- **25. Muirhead-Thomson RC.** The distribution of anopheline mosquito bites among different age groups. Br Med J. 1951;1:1114-7.
- **26. Gilbert IH, Gouck HK, Smith N.** Attractiveness of men and women to *Aedes aegypti* and relative protection time obtained with DEET. Florida Entomologist. 1966;49:53-66.
- 27. Port GR, Boreham PFL. The relationship of host

- size to feeding by mosquitoes of the *Anopheles gambiae* Giles complex (Diptera: Culicidae). Bulletin of Entomological Research. 1980;70:133-44.
- **28.** Khan AA, Maibach HI, Strauss WG, Fenley WR. Vitamin B₁ is not a systemic mosquito repellent in man.
- Trans St Johns Hosp Dermatol Soc. 1969;55:99-102.
- **29. Strauss WG, Maibach HI, Khan AA.** Drugs and disease as mosquito repellents in man. Am J Trop Med Hyg. 1968;17:461-4.
- **30. Davis EE.** Insect repellents: concepts of their mode of action relative to potential sensory mechanisms in mosquitoes (Diptera: Culicidae). J Med Entomol. 1985;22:237-43.
- **31. Wright RH.** Why mosquito repellents repel. Sci Am. 1975;233:104-11.
- **32.** Rutledge LC, Collister DM, Meixsell VE, Eisenberg GH. Comparative sensitivity of representative mosquitoes (Diptera: Culicidae) to repellents. J Med Entomol. 1983;20:506-10.
- **33. Schreck CE.** Protection from blood-feeding arthropods. In: Auerbach PS, ed. Wilderness Medicine: Management of Wilderness and Environmental Emergencies. 3d ed. St. Louis: Mosby; 1995:813-30.
- **34. Maibach HI, Akers WA, Johnson HL, Khan AA, Skinner WA.** Insects. Topical insect repellents. Clin Pharmacol Ther. 1974;16(5 Part 2):970-3.
- **35. Maibach HI, Khan AA, Akers WA.** Use of insect repellents for maximum efficacy. Arch Dermatol. 1974;109:32-5.
- **36. Gabel ML, Spencer TS, Akers WA.** Evaporation rates and protection times of mosquito repellents. Mosquito News. 1976;36:141-6.
- **37.** Khan AA, Maibach HI, Skidmore DL. A study of insect repellents: effect of temperature on protection time. J Econ Entomol. 1972;66:437-8.
- **38. Quarles W.** Lighted and baited mosquito traps. Common Sense Pest Control. 1996;12:5-11.
- **39. Jacobson M, ed.** Glossary of plant-derived insect deterrents. Boca Raton, FL: CRC Pr; 1990.
- **40. King WV.** Chemicals evaluated as insecticides and repellents at Orlando, Fla. USDA Agricultural Handbook.

- 1954;69:1-397.
- **41.** Materials evaluated as insecticides, repellents, and chemosterilants at Orlando and Gainesville, Fla., 1952-1964. USDA Agricultural Handbook. 1967;340:1-424.
- **42. U.S. Environmental Protection Agency.** Office of Pesticides and Toxic Substances. Special Pesticide Review Division. N,N-diethyl-m-toluamide (DEET) Pesticide Registration Standard (EPA-540/RS-81-004). Washington, DC: U.S. Environmental Protection Agency; 1980. (PB81-207722)
- **43.** Rutledge LC, Wirtz RA, Buescher MD, Mehr ZA. Mathematical models of the effectiveness and persistence of mosquito repellents. J Am Mosq Control Assoc. 1985;1:56-61.
- **44. Buescher MD, Rutledge LC, Wirtz RA.** Tests of commercial repellents on human skin against *Aedes aegypti*. Mosquito News. 1982;42:428-33.
- **45.** Buescher MD, Rutledge LC, Wirtz RA, Nelson JH. The dose-persistence relationship of deet against *Aedes aegypti*. Mosquito News. 1983;43:364-6.
- **46. Schreck CE, McGovern TP.** Repellents and other personal protection strategies against *Aedes albopictus*. J Am Mosq Control Assoc. 1989;5:247-50.
- **47.** Mehr ZA, Rutledge LC, Morales EL, Meixsell VE, Korte DW. Laboratory evaluation of controlled-release insect repellent formulations. J Am Mosq Control Assoc. 1985;1:143-7.
- **48. Gupta RK, Rutledge LC.** Laboratory evaluation of controlled-release repellent formulations on human volunteers under three climatic regimens. J Am Mosq Control Assoc. 1989;5:52-5.
- **49. Schreck CE, Kline DL.** Repellency of two controlled-release formulations of deet against *Anopheles quadrimaculatus* and *Aedes taeniorhynchus* mosquitoes. J Am Mosq Control Assoc. 1989;5:91-4.
- **50. Annis B.** Comparison of the effectiveness of two formulations of deet against *Anopheles flavirostris*. J Am Mosq Control Assoc. 1990;6:430-2.
- **51. Gupta RK, Rutledge LC.** Controlled release repellent formulations on human volunteers under three climatic regimens. J Am Mosq Control Assoc. 1991;7:490-3.

- **52. Domb AJ, Marlinsky A, Maniar M, Teomim L.** Insect repellent formulations of N,N-diethyl-m-toluamide (deet) in a liposphere system: efficacy and skin uptake. J Am Mosq Control Assoc. 1995;11:29-34.
- **53. Garrettson LK.** Commentary-DEET: caution for children still needed. J Toxicol Clin Toxicol. 1997;35:443-5.
- **54. Shelov SP, ed.** Caring for Your Baby and Young Child: Birth to Age 5. New York: Bantam Books; 1991:639.
- **55.** U.S. Environmental Protection Agency, Office of Pesticide Programs. Using Insect Repellents Safely (EPA-735/F-93-052R). Washington, DC: U.S. Environmental Protection Agency; 1996.
- **56.** Rutledge LC. Some corrections to the record on insect repellents and attractants. J Am Mosq Control Assoc. 1988;4:414-25.
- **57. Montemarano AD, Gupta RK, Burge JR, Klein K.** Insect repellents and the efficacy of sunscreens. Lancet. 1997;349:1670-1.
- **58.** Selim S, Hartnagel RE Jr, Osimitz TG, Gabriel KL, Schoenig GP. Absorption, metabolism, and excretion of N,N-diethyl-m-toluamide following dermal application to human volunteers. Fundam Appl Toxicol. 1995;25:95-100.
- **59. Robbins PJ, Cherniack MG.** Review of the biodistribution and toxicity of the insect repellent N,N-diethyl-m-toluamide (DEET). J Toxicol Environ Health. 1986;18:503-25.
- **60. Qiu H, Jun HW, Tao J.** Pharmacokinetics of insect repellent *N,N*-diethyl-*m*-toluamide in beagle dogs following intravenous and topical routes of administration. J Pharm Sci. 1997;86:514-6.
- **61. Schoenig GP, Hartnagel RE Jr, Osimitz TG, Llanso S.** Absorption, distribution, metabolism, and excretion of *N,N*-diethyl-*m*-toluamide in the rat. Drug Metab Dispos. 1996;24:156-63.
- **62.** Reifenrath W, Hawkins G, Kurtz M, Bernardo E, Dahlberg E, Jesse R. Controlled Release Personal Use Arthropod Repellent Formulation: In Vitro Evaluation of Evaporation/Penetration Characteristics, Water Wash

- Resistance, and Interaction with CW Agent Analogs. San Francisco: Presidio of San Francisco; Division of Cutaneous Hazards, Letterman Institute of Research; 1986.
- **63. Osimitz TG, Grothaus RH.** The present safety assessment of DEET. J Am Mosq Control Assoc. 1995;11(2 Pt 2):274-8.
- **64.** Completed Studies for the DEET Toxicology Data Development Program. Washington, DC: The DEET Joint Venture Group, Chemical Specialties Manufacturers Association; 1996.
- **65.** Snyder JW, Poe RO, Stubbins JF, Garrettson LK. Acute manic psychosis following the dermal application of N,N-diethyl-m-toluamide (DEET) in an adult. Clin Toxicol. 1986;24:429-39.
- **66.** Heick HM, Peterson RG, Dalpe-Scott M, Qureshi IA. Insect repellent, N,N-diethyl-m-toluamide, effect on ammonia metabolism. Pediatrics. 1988;82:373-6.
- **67. Heick HM, Shipman RT, Norman MG, James W.**Reye-like syndrome associated with use of insect repellent in a presumed heterozygote for ornithine carbamoyl transferase deficiency. J Pediatr. 1980;97:471-3.
- **68. de Garbino JP, Laborde A.** Toxicity of an insect repellent: N-N-diethyltoluamide. Vet Hum Toxicol. 1983;25:422-3.
- **69. Zadikoff CM.** Toxic encephalopathy associated with use of insect repellant. J Pediatr. 1979;95:140-2.
- **70. Osimitz TG, Murphy JV.** Neurological effects associated with use of the insect repellent *N,N*-diethyl-*m*-toluamide (DEET). J Toxicol Clin Toxicol. 1997;35:435-41.
- **71.** Lipscomb JW, Kramer JE, Leikin JB. Seizure following brief exposure to the insect repellent N,N-diethyl-m-toluamide. Ann Emerg Med. 1992;21:315-7.
- **72. Gryboski J, Weinstein D, Ordway NK.** Toxic encephalopathy apparently related to the use of an insect repellent. N Engl J Med. 1961;264:289-91.
- **73.** Roland EH, Jan JE, Rigg JM. Toxic encephalopathy in a child after brief exposure to insect repellents. Can Med Assoc J. 1985;132:155-6.
- **74.** Seizures temporally associated with the use of DEET

- insect repellent-New York and Connecticut. MMWR Morb Mortal Wkly Rep. 1989;38:678-80.
- **75. Edwards DL, Johnson CE.** Insect-repellent-induced toxic encephalopathy in a child. Clin Pharm. 1987;6:496-8.
- **76. Veltri JC, Osimitz TG, Bradford DC, Page BC.** Retrospective analysis of calls to poison control centers resulting from exposure to the insect repellent N,N-diethyl-m-toluamide (DEET) from 1985-1989. J Toxicol Clin Toxicol. 1994;32:1-16.
- **77. Tenenbein M.** Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents. JAMA. 1987;258:1509-11.
- **78. Leach GJ, Russell RD, Houpt JT.** Some cardiovascular effects of the insect repellent N,N-diethyl-m-toluamide (DEET). J Toxicol Environ Health. 1988;25:217-25.
- **79. Clem JR, Havemann DF, Raebel MA.** Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult. Ann Pharmacother. 1993;27:289-93.
- **80. Miller JD.** Anaphylaxis associated with insect repellent. N Engl J Med. 1982;307:1341-2.
- **81. von Mayenburg J, Rakoski J.** Contact urticaria to diethyltoluamide. Contact Dermatitis. 1994;9:171.
- **82. Maibach HI, Johnson HL.** Contact urticaria syndrome. Contact urticaria to diethyltoluamide (immediate-type sensitivity). Arch Dermatol. 1975;111:726-30.
- 83. Wantke F, Focke M, Hemmer W, Gäz M, Jarisch
- **R.** Generalized urticaria induced by a diethyltoluamide-containing insect repellent in a child. Contact Dermatitis. 1996;35:186-7.
- **84. Amichai B, Lazarov A, Halevy S.** Contact dermatitis from diethyltoluamide. Contact Dermatitis. 1994;30:188.
- **85. Reuveni H, Yagupsky P.** Diethyltoluamidecontaining insect repellent: adverse effects in worldwide use. Arch Dermatol. 1982;118:582-3.
- **86. Lamberg SI, Mulrennan JA Jr.** Bullous reaction to diethyl toluamide (DEET). Resembling a blistering insect eruption. Arch Dermatol. 1969;100:582-6.
- 87. Sukumar K, Perich MJ, Boobar LR. Botanical

- derivatives in mosquito control: a review. J Am Mosq Control Assoc. 1991;7:210-37.
- **88.** Quarles W. Botanical mosquito repellents. Common Sense Pest Control. 1996;12:12-9.
- **89. Grainger J, Moore C.** Natural Insect Repellents for Pets, People and Plants. Austin: The Herb Bar; 1991.
- **90. Brown M, Hebert AA.** Insect repellents: an overview. J Am Acad Dermatol. 1997;36(2 Pt 1):243-9.
- **91. Duke J.** USDA Agricultural Research Service Phytochemical and Ethnobotanical Databases. (http://www.ars-grin.gov/|mfngrlsb/)
- **92. Spero NC.** Repellent Testing against Adult Mosquitoes in the Laboratory. Baltimore: Insect Control and Research; 1993. Sponsored by Quantum, Inc.
- **93. Surgeoner GA.** Efficacy of Buzz Away Oil against spring *Aedes* spp. mosquitoes. Guelph, Ontario: Department of Environmental Biology, University of Guelph; 1995. Sponsored by Quantum, Inc.
- **94. Lindsay RL, Surgeoner GA, Heal JD, Gallivan GJ.** Evaluation of the efficacy of 3% citronella candles and 5% citronella incense for protection against field populations of *Aedes* mosquitoes. J Am Mosq Control Assoc. 1996;12(2 Pt 1):293-4.
- **95.** Matsuda BM, Surgeoner GA, Heal JD, Tucker AO, Maciarello MJ. Essential oil analysis and field evaluation of the citrosa plant "*Pelargonium citrosum*" as a repellent against populations of *Aedes* mosquitoes. J Am Mosq Control Assoc. 1996;12:69-74.
- **96. Cilek JE, Schreiber ET.** Failure of the "mosquito plant", *Pelargonium x citrosum* 'van Leenii', to repel adult *Aedes albopictus* and *Culex quinquefasciatus* in Florida. J Am Mosq Control Assoc. 1994;10:473-6.
- **97.** Finally, a safer insect repellent. University of California at Berkeley Wellness Letter. 1997;13:2.
- **98. Lindsay RL, Heal JD, Surgeoner GA.** Comparative evaluation of the efficacy of Bite Blocker, Off! Skintastic, and Avon Skin-So-Soft to protect against *Aedes* species mosquitoes in Ontario. Guelph, Ontario: Department of Environmental Biology, University of Guelph; 1996. Sponsored by Chemfree Environment, Inc.
- **99. Lindsay RL, Heal JD, Surgeoner GA.** Evaluation of Bite Blocker as a repellent against spring *Aedes* spp.

- mosquitoes. Guelph, Ontario: Department of Environmental Biology, University of Guelph; 1996. Sponsored by Chemfree Environment, Inc.
- **100.** Casida JE, Quistad GB. Pyrethrum flowers: production, chemistry, toxicology and uses. Oxford: Oxford Univ Pr; 1995.
- **101.** Insect repellents. Med Lett Drugs Ther. 1989;31:45-7.
- **102. Schreck CE.** Permethrin and dimethyl phthalate as tent fabric treatments against *Aedes aegypti*. J Am Mosq Control Assoc. 1991;7:533-5.
- **103.** Lines JD, Myamba J, Curtis CF. Experimental hut trials of permethrin-impregnated mosquito nets and eave curtains against malaria vectors in Tanzania. Med Vet Entomol. 1987;1:37-51.
- **104.** Schreck CE, Posey K, Smith D. Durability of permethrin as a potential clothing treatment to protect against blood-feeding arthropods. J Econ Entomol. 1978;71:397-400.
- **105.** Schreck CE, Carlson DA, Weidhass DE, Posey K, Smith D. Wear and aging tests with permethrintreated cotton-polyester fabric. J Econ Entomol. 1980;73:451-3.
- **106.** Gupta RK, Sweeney AW, Rutledge LC, Cooper RD, Frances SP, Westrom DR. Effectiveness of controlled-release personal-use arthropod repellents and permethrin-impregnated clothing in the field. J Am Mosq Control Assoc. 1987;3:556-60.
- **107. Sholdt LL, Schreck CE, Qureshi A, Mammino S, Aziz A, Iqbal M.** Field bioassays of permethrin-treated uniforms and a new extended duration repellent against mosquitoes in Pakistan. J Am Mosq Control Assoc. 1988;4:233-6.
- **108.** Lillie TH, Schreck CE, Rahe AJ. Effectiveness of personal protection against mosquitoes in Alaska. J Med Entomol. 1988;25:475-8.
- **109. Belton P.** An acoustic evaluation of electronic mosquito repellers. Mosquito News. 1981;41:751-5.
- **110.** Lewis DJ, Fairchild WL, Leprince DJ. Evaluation of an electronic mosquito repeller. Canadian Entomologist. 1982;114:699-702.

- **111. Foster WA, Lutes KI.** Tests of ultrasonic emissions on mosquito attraction to hosts in a flight chamber. J Am Mosq Control Assoc. 1985;1:199-202.
- **112. Mitchell M.** Mythical mosquito control. Wing Beats. 1992;3:18-20.
- **113.** Nasci RS, Harris CW, Porter CK. Failure of an insect electrocuting device to reduce mosquito biting. Mosquito News. 1983;43:180-3.
- **114. Frick TB, Tallamy DW.** Density and diversity of non-target insects killed by suburban electric insect traps. Entomological News. 1996;2:77-82.
- 115. McCormack DR, Salata KF, Hershey JN, Carpenter GB, Engler RJ. Mosquito bite anaphylaxis: immunotherapy with whole body extracts. Ann Allergy Asthma Immunol. 1995;74:39-44.
- **116. Reunala T, Brummer-Korvenkontio H, Palosuo T.** Are we really allergic to mosquito bites? Ann Med. 1994;26:301-6.
- **117. Reunala T, Brummer-Korvenkontio H, Lappalainen P, Rasanen L, Palo**suo T. Immunology and treatment of mosquito bites. Clin Exp Allergy. 1990;20 Suppl 4:19-24.
- 118. Reunala T, Lappalainen P, Brummer-Korvenkontio H, Coulie P, Palosuo T. Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies. Clin Exp Allergy. 1991;21:617-22.
- 119. Brummer-Korvenkontio H, Lappalainen P, Reunala T, Palosuo T. Immunization of rabbits with mosquito bites: immunoblot analysis of IgG antimosquito antibodies in rabbit and man. Int Arch Allergy Appl Immunol. 1990;93:14-8.
- **120. Peng Z, Yang M, Simons FE.** Immunologic mechanisms in mosquito allergy: correlation of skin reactions with specific IgE and IgG antibodies and lymphocyte proliferation response to mosquito antigens. Ann Allergy Asthma Immunol. 1996;77:238-44.
- **121.** Brummer-Korvenkontio H, Palosuo T, Francois G, Reunala T. Characterization of *Aedes communis*, *Aedes aegypti* and *Anopheles stephensi* mosquito saliva antigens by immunoblotting. Int Arch Allergy Appl Immunol. 1997;112:169-74.

122. Reunala T, Brummer-Korvenkontio H, Karppinen A, Coulie P, Palosuo T. Treatment of mosquito bites with cetirizine. Clin Exp Allergy. 1993;23:72-5.

Home | Site Directory | Search | Journals | CME | Patient Care | Register | Jobs at ACP-ASIM |

Privacy Policy

© 1996-2002, American College of Physicians-American Society of Internal Medicine. All rights reserved.

Contact us: On the web | By mail or phone