

secretory cells. Initial onset of chromhidrosis is usually noted at puberty, when apocrine glands become active, and persists indefinitely throughout life.¹ A prickling sensation in the facial skin or an aura of warmth may be noted to precede colored sweat formation.^{1,3} Patients also may experience a 48- to 72-hour symptom-free period after manual or pharmacologic emptying of the glands.^{1,3} It is thought that the glands may be depleted of pigment that is later replenished.

The causative factors of apocrine gland secretion are not well understood. In general, apocrine glands are more sensitive to stimulation by adrenergic than by cholinergic substances.⁹ Adrenergic-blocking agents appear to inhibit sweating, as does the catecholamine-depleting drug reserpine. The glands may be stimulated humorally because denervation does not abolish response to an emotional stimuli. Thus secretion of the apocrine gland is controlled by both neural and humoral components.⁹ However, anatomic identification of nerve fibers in proximity to apocrine sweat glands has not been demonstrated. Because unmyelinated fibers are found closer to capillaries than to secretory cells it has been hypothesized that local circulation conveys neurotransmitters to the effector cells of the sweat gland.^{9,10} Nerves surrounding eccrine sweat glands are nonmyelinated C fibers of sympathetic postganglionic fibers.¹¹ Substance P is a potent vasodilator,¹² and substance P-positive nerve fibers have been found around eccrine sweat glands.¹¹ This finding suggests that substance P may play a role in sweat production and that substance P depletion with capsaicin could be clinically useful. The relationship between such substance P-rich sensory fibers and the apocrine glands is still unknown.

This report documents the successful suppression of apocrine chromhidrosis after topically

applied capsaicin. The return of apocrine chromhidrosis within a few days after discontinuing capsaicin eliminates the possibility of spontaneous resolution. The suppression of chromhidrosis by capsaicin compared with no treatment and treatment with its vehicle confirms that capsaicin was the inhibitor of this process. The results observed in this patient suggest a possible relationship between substance P and apocrine sweat production and warrant more basic and clinical investigations.

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Chronic pruritic eruption in patients with acquired immunodeficiency syndrome associated with increased antibody titers to mosquito salivary gland antigens

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Five of seven patients with acquired immunodeficiency syndrome (AIDS) who had pruritus and a chronic, nonspecific-appearing skin eruption had increased antibody titers to antigens in the salivary glands of *Aedes taeniorhynchus*, a salt marsh mosquito common to South Florida. We hypothesize that the pruritus and skin lesions in patients with AIDS represent a form of chronic "recall" reaction. Increased antibody titers to mosquito salivary gland antigens may be a consequence of nonspecific B cell activation, a feature of AIDS. (*J Am Acad Dermatol* 1989;21:421-5.)

Patients with acquired immunodeficiency syndrome (AIDS) often have persistent pruritus and excoriated papules, particularly on the legs (see Fig. 1). No explanation for the distribution and chronicity of the eruption, nor a history of recent exposure to pets, biting insects, chemicals, or other agents that might produce pruritus, have been found. Also, persons in close contact do not have similar symptoms, suggesting a nontransmittable problem. Other causes of pruritic skin eruptions, such as drug reactions, infestations, and cutaneous infections, are not found and would not explain their persistence and distribution.

Because of the clinical pattern, we hypothesize that in some cases this eruption may be a form of chronic insect bite reaction. If this were so, increased circulating titers of antibody to mosquito salivary gland antigens might be present in serum. The increased titers could be a consequence of the increased nonspecific B cell activity known to occur in patients with AIDS.¹ These antibodies could bind in vivo to structural protein in the dermis

previously altered by haptenylated mosquito salivary gland antigens, precipitating a reaction.

CASE REPORT

A 35-year-old man with AIDS was seen because of pruritus, most severe on the legs and forearms, that had been present for more than 6 months and was worsening. Topical treatments had little effect. This man was not taking medications at the time of the initial visit.

There were no primary skin lesions. The patient had many excoriations, most numerous on the legs (Fig. 1). Potassium hydroxide preparations did not demonstrate mites or hyphae. Examination of several skin biopsy specimens showed papillary and mid dermal perivascular lymphohistiocytic inflammatory infiltrate of varying density with scattered eosinophils. The pattern was not diagnostic but suggestive of a hypersensitivity reaction. Clinically the rash resembled an accentuated chronic insect bite reaction.

The patient failed to respond to a variety of topical medications and was eventually managed on intermittent courses of orally administered corticosteroids.

Methods. Colonized female *Aedes taeniorhynchus*, a salt marsh mosquito common to South Florida, were used in this study. Larvae were reared at 27° C under 12-hour light-dark cycles.² Before use, newly emerged adults were maintained on a 10% sucrose solution and allowed to mate for 4 to 6 days in 45 cm square cages.

Serum was obtained from the following groups of

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Fig. 1. Excoriated papular eruption of legs.

persons: control subjects, those who were human immunodeficiency virus (HIV)-positive but were not symptomatic, those who had AIDS-related complex (ARC), those who had AIDS without a skin rash, and those who had AIDS and a chronic pruritic eruption that could not be explained by a definable cause and that appeared clinically to be suggestive of an insect bite reaction. Control subjects had had 2+ to 4+ binding reactions of antibody to salivary glands from *A. taeniorhynchus*, determined with the use of undiluted serum as the source of primary antibody in an immunohistochemical assay identical to that described later and a grading system described in a previous report.³

Mosquitoes were fixed in formalin solution, embedded, and sectioned at 4 μ m at the level of the salivary glands. An avidin-biotin-peroxidase method was used to visualize binding of primary antibody to mosquito salivary glands.³ Appropriate positive and negative controls were included in each experiment. The final titer was determined as one dilution before the unequivocal absence of antibody binding.

Serum was obtained from BALB/c mice that had been exposed repeatedly to *A. taeniorhynchus* and had developed circulating antibodies against mosquito sali-

vary gland antigens. Four-micrometer sections were taken from biopsy specimens of skin lesions that resembled insect bite reactions. These specimens were taken from patients with AIDS who had increased titers of antibody against mosquito salivary gland antigens (discussed later). Sections were exposed to mouse anti-*A. taeniorhynchus* mosquito salivary gland antigens primary antibody. A standard avidin-biotin-peroxidase assay was used to visualize the binding reaction as described earlier.

RESULTS

Binding of circulating antibodies to mosquito salivary gland antigens was detectable at low titers, generally 1:2 to 1:32 (Table I), in serum from control subjects. Titers in serum from persons infected by HIV but who were asymptomatic, from persons with ARC, and from patients with AIDS with no rash were similar to those of control subjects. Five of the seven patients with a chronic pruritic eruption had high titers of antibody to mosquito salivary gland antigens, ranging from 1:64 to 1:512. The other two patients had titers similar to those of control subjects. Mosquito salivary gland antigens could not be detected in the skin lesions of patients with increased antibody titers to mosquito salivary gland antigens, determined with the use of a mouse anti-*A. taeniorhynchus* mosquito salivary gland antigens antibody.

DISCUSSION

Saliva from mosquitoes and other hematophagous arthropods contains a large variety of macromolecules that function to lubricate the mouth parts of the mosquito,⁴ to facilitate blood vessel location in the host in the vicinity of the mouth part,⁵ to inhibit platelet clotting in the vicinity of the mouth parts,⁶ and to induce erythema at the bite site.⁷ A survey of serum from normal subjects for IgG antibodies to mosquito salivary gland antigens from several species of mosquitoes revealed a complicated array of species-unique and species-shared antigens.⁸ The pattern of antigens recognized varied from person to person and from species to species and must reflect the unique exposure history of each person to the large number of mosquito species. In addition, the specific antigens in mosquito saliva that elicit and perpetuate cutaneous reactions after the mosquito bite are not known.

Patients infected by HIV have a variety of skin changes, some well characterized such as Kaposi's

Table I. Antibody titers to mosquito salivary gland antigens of *A. taeniorhynchus* in HIV-positive patients with varying symptoms

No. tested	Control subjects	HIV-positive patients			
		Without symptoms	ARC	AIDS (no pruritic rash)	AIDS (pruritic rash)
1	1:2	1:4	1:4	1:8	1:4
2	1:4	1:8	1:8	1:8	1:8
3	1:4	1:8	1:8	1:16	1:64
4	1:8	1:16	1:32	1:16	1:128
5	1:8				1:256
6	1:16				1:256
7	1:32				1:512

sarcoma and herpes simplex, others of obscure cause such as seborrheic dermatitis-like changes,⁹ yellow nail syndrome,¹⁰ interface dermatitis of unknown cause,¹¹ and intractable pruritus.¹²

The separation of the patients in this report from others with HIV infection and pruritus and/or nonspecific skin lesions rests solely on the distribution of the eruption, which suggested to us an exogenous source such as arthropod bite. These patients uniformly denied recent exposures to biting insects. Furthermore, the lack of resolution of these reactions was an unusual feature, which suggested a chronic reaction and not a self-limited one. Patients in this report had AIDS; were being treated with a number of medications, including zidovudine, sulfamethoxazole-trimethoprim, diamidophenylsulfone, and others; and had a variety of HIV-associated cutaneous findings including oral candidiasis and Kaposi's sarcoma. Each patient differed in the sequence and combination of medications used and the invariable presence of HIV-related illnesses. Clinically there were no recognizable primary skin lesions. All patients had excoriated papules that seemed to be located most often on the legs. Histologic findings were not specific but showed an inflammatory process of variable intensity and were composed primarily of lymphocytes, histiocytes, and scattered eosinophils. Epidermal changes varied and reflected excoriation. The histologic patterns did not permit precise classification of the eruption or the placement of this "entity" in any of the other poorly defined pruritic eruptions associated with HIV infection. Serum samples of five of the seven patients had elevated titers of antibody to mosquito salivary gland antigens when compared to the other groups studied (Table I). The avidin-biotin-peroxidase

assay was used because of the inability to identify specific antigens in mosquito saliva that might be haptenylated to dermal structural protein and the difficulty in preparing sufficient antigenic material as a reagent for an enzyme-linked immunoassay.

Without the specific identification of mosquito salivary gland antigens at the sites of "reactivation," it is not possible to state that the chronic eruption in these patients is directly related to increased titers of antibodies to mosquito salivary gland antigens. The failure to find mosquito salivary gland antigens within the skin lesions may be due to the small quantities of antigen retained as bound hapten, a level below the sensitivity of the immunohistochemical assay. However, work in other species supports this hypothesis. Benjamini et al.^{13,14} noted that oral secretions of the cat flea became immunogenic after irreversible association with fibrous proteins, suggesting that haptenylation of a host protein is important in the development of hypersensitivity to flea salivary gland material. Furthermore, extracts of bite sites could be used to induce hypersensitivity in naive animals. Michaeli et al.¹⁵ demonstrated that the flea hapten was associated with extracted collagen from bite sites. The injection of this acid-soluble collagen derived from bite sites induced sensitivity without the aid of adjuvant. Michaeli et al.¹⁶ also demonstrated an in vitro reaction of flea oral secretions and extracted collagen, resulting in a complex that seemed to be associated with hypersensitivity to flea bites. The work of Hudson et al.¹⁷ suggests that a sufficient level of immunologic sensitivity is necessary to induce a localized immune response. Animals exposed to multiple flea bites did not react until the fifth day, at which time all unreactive bite sites

developed inflammation. We hypothesize that small quantities of haptenylated protein, the residue of prior insect bite reactions, reside locally for an indefinite period. In patients with AIDS and increased antibody titers to mosquito salivary gland antigens, binding to haptenylated flea or mosquito antigens elicits a local reaction. In two of seven patients with similar signs and symptoms, antibody titers to mosquito salivary gland antigens were similar to those of normal control subjects. Possible explanations for this include the following: (1) The hypothesis is generally incorrect; (2) The two patients with normal titers in our assay have increased antibody titers to a mosquito salivary gland antigens that is unstable to formalin fixation and paraffin embedding; (3) These two patients have increased antibody titers to mosquito salivary gland antigen but not to mosquito salivary gland antigens from mosquito species not tested, which do not cross react to antigens from *A. taeniorhynchus*; (4) These patients have increased antibody titers to salivary gland antigens from a species other than *A. taeniorhynchus*, such as the flea; and (5) The pruritus in these patients is not related to "recall" reactions at previous bite sites.

HIV infection induces both immune deficiency and immune stimulation. Central to the pathologic finding of infection by this virus is a reduction in the numbers and function of helper T lymphocytes. However, HIV infection also stimulates B cells and suppressor T lymphocytes. Many changes occur in infected persons that are indicative of B cell activation, including an increase in serum IgG and IgA, an increase in circulating immune complexes, and an increase in the numbers of immunoglobulin-secreting B cells.¹ There is evidence to suggest that HIV may directly stimulate B cells and that infection is not necessary for this phenomenon to occur.¹⁸ HIV infection may also stimulate B cells indirectly by removing helper T lymphocytes, which normally act as a constraint on B cell activation/maturation. The serum antibodies against HIV antigens are only a tiny fraction of the increased serum IgG seen in AIDS. Recently Bix et al.¹⁹ suggested defective T cell-mediated suppression of Epstein-Barr virus-activated, autologous B cells in AIDS as a likely contributing factor in the spontaneous activation of B cells in HIV-infected persons. If our hypothesis is correct, the chronic pruritic, papular, excoriated eruption seen in these five patients is a consequence of nonspe-

cific B cell activity of clones of cells that elaborate the antibody specific for bound mosquito salivary gland antigens or salivary gland antigens of other hematophagous insects.

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Chronic pruritic eruption in AIDS

Epidermolysis bullosa simplex with mottled pigmentation

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A patient with epidermolysis bullosa simplex with mottled pigmentation is described. Clinical features include blistering of the skin, especially of the extremities; healing without scars; slight atrophy of the skin; and striking mottled pigmentation of the trunk. Histologic examination of a biopsy specimen from freshly frictioned, clinically uninvolved skin indicated a split inside the basal keratinocytes, focal hyperpigmentation of the basal cells, and pigment incontinence without an inflammatory infiltrate. Indirect immunofluorescence demonstrated focal discontinuity of the basement membrane zone. Electron microscopic examination revealed basal keratinocytes with few intact intracellular organelles, aggregated tonofilaments, and subnuclear splitting with the basal parts of the cells adhering to the basement membrane. Both normal basement membrane and zones of irregular and interrupted structures were seen. Hemidesmosomes and anchoring fibrils appeared to be normal. (J AM ACAD DERMATOL 1989;21:425-32.)

Epidermolysis bullosa hereditaria is a heterogeneous group of genetic disorders¹⁻³ that has been divided into three major varieties according to level of blistering: epidermolytic, junctional, and dermolytic. The epidermolytic types are collectively called epidermolysis bullosa simplex. They usually heal without scarring and are inherited in an autosomal dominant manner. The simplex group is divided further into eight subtypes, of which epidermolysis bullosa simplex generalisata Köbner⁴ and epidermolysis bullosa simplex localisata Weber-Cockayne⁵ are the most common. The other forms are rare (Table I).⁶⁻¹¹

In 1979 Fischer and Gedde-Dahl⁶ described a Swedish family with epidermolysis bullosa simplex and a striking irregular pigmentation, which the authors designated as mottled pigmentation. Both anomalies were inherited in an autosomal dominant fashion. The important clinical features were blistering, mainly in the extremities; healing without scars; slight atrophy; and a bizarre dyspigmentation. With the use of electron microscopy, Gedde-Dahl et al.¹² found primary lipolytic changes in the basal cells but no pigment anomaly. The mottled pigmentation seemed different from previously known pigmentary disorders, and the authors hypothesized clonal autosomal inactivation to explain this disorder.⁶

Many epidermolysis bullosa variants, mainly junctional and dystrophic, have been characterized by immunohistologic techniques. Several antigens of the dermoepidermal junction zone have been identified biochemically,^{13,14} and antibodies to

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