Brief reports of new clinical or laboratory observations, cases of unusual importance, and new developments in medical care will be considered for publication in this section. Manuscripts must be typed double-spaced. Text length must not exceed 750 words; no more than 10 references and one figure or table can be used. See "Information for Authors" on page I-6 for form of references. Manuscripts should include an abstract of not over 100 words. Reports will be reviewed by consultants when, in the opinion of the editors, such review is needed. The Editor reserves the right to shorten reports and to make changes in style.

Aspartame-Induced Granulomatous Panniculitis

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THE LOW-CALORIE ARTIFICIAL SWEETENER, aspartame (NutraSweet; G.D. Searle & Co., Skokie, Illinois), a synthetic combination of aspartic acid and the methyl ester of phenylalanine, is currently used in many diet sodas, cereals, and chewing gums and as a substitute for granulated sugar. Although the Food and Drug Administration has approved aspartame for routine use (except in patients with phenylkentonuria), its potential for toxicity remains controversial (1-4). This report describes the first confirmed case of aspartame-induced granulomatous panniculitis.

A 22-year-old, otherwise healthy woman had numerous, bilateral, nontender, nodular lesions on both legs for 2 months. The patient denied having used any oral, systemic, or topical medications during the preceding 6 months. She also denied any history of recent infections or trauma, and she had no accompanying constitutional symptoms. For the previous 6 years, the patient had habitually consumed between 1080 to 1320 mL (36 to 44 fl oz) daily of a popular saccharin-containing diet soft drink. Approximately 10 weeks before presenting for evaluation, she had switched to the same manufacturer's new aspartame-sweetened diet soda. She made no other changes in her diet. Two weeks later, the patient first noted the onset of several nontender, deep nodules on her left thigh. New lesions subsequently appeared elsewhere on her legs while the previous lesions slowly enlarged; none disappeared.

On examination, numerous deep nodules ranging from approximately 0.5 to 5 cm in diameter were palpated bilaterally on the thighs and calves. The overlying skin appeared normal. The nodules were firm and in some areas coalesced to form large deep plaques that were freely movable over the underlying fascial tissues. No adenopathy or other cutaneous or mucous membrane lesions were present; the rest of the general physical findings were normal.

Complete blood and differential count, erythrocyte sedimentation rate, serum electrolyte and amylase levels, and urinalysis findings were normal; liver function tests, serum protein electrophoresis, direct and indirect immunofluorescence studies, tuberculin tine test, and tests for antinuclear antibody and anti-streptolysin-O were negative. The patient refused a chest roentgenogram. Histologically, a septal panniculities with lymphocytes and histiocytes predominated within the thickened fibrotic septae. Many multinucleated histiocytic giant cells and a lymphohistiocytic infiltrate extended into the adjacent fatty lobules, consistent with erythema nodosum (Figure 1).

The patient was advised to stop using the recently introduced aspartame-sweetened beverage. During the next 4 weeks, no new lesions appeared and all previous lesions spontaneously resolved without residua. She was then advised to resume daily consumption of the suspected aspartame-sweetened diet drink; 10 days later, she again developed the nodular lesions on both legs, this time in greater number than before. Withdrawal of the beverage once again resulted in gradual and complete resolution of all lesions.

The patient was next challenged with pure aspartame, 50 mg four times daily, in capsule form (supplied by G.D. Searle & Co.). Ten days later, nodules reappeared on her legs. Withdrawal of aspartame resulted in spontaneous clearing of all lesions.

Widely used, aspartame is 180 times sweeter than sucrose and is metabolized primarily to aspartic acid, phenylalanine, and methanol (5). No previous reports could be found in the literature conclusively linking aspartame

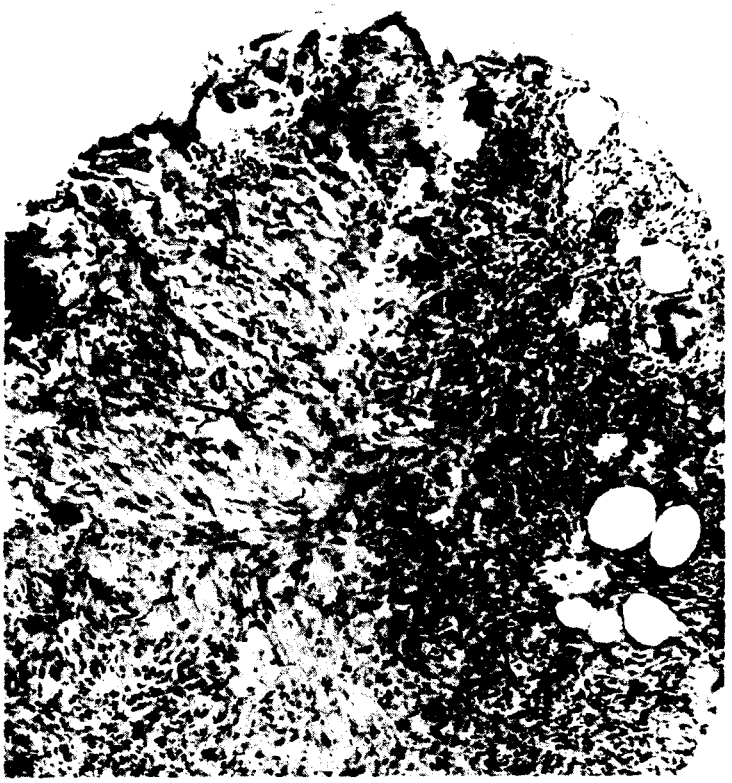

Figure 1. Septal panniculitis composed of histiocytes, multinucleated histiocytic giant cells, and lymphocytes within a thickened fibrous septum. A lymphohistiocytic infiltrate extends into the adjacent lobule. (Hematoxylin and eosin; × 100.)

to any cutaneous eruptions (6). Several unconfirmed reports of "dermal eruptions" and urticaria have been received by the manufacturer according to Robert L. Alberti, M.D., Director of Medical Communications, G.D. Searle & Co. In addition, the Adverse Drug Reaction Report System of the American Academy of Dermatology has received one unconfirmed report of a macular, erythematous, confluent pruritic eruption in a man who had consumed large amounts of an aspartame-sweetened diet cola (Report no. 1170031284, reported 12 March 1984 and transferred to the FDA 10 April 1984).

The precise classification and pathogenetic mechanism of the panniculitis in my patient are unclear. Absence of tenderness in lesions, overlying skin changes, constitutional symptoms, and residual pigmentary changes upon resolution is inconsistent with erythema nodosum (7), whereas the histopathologic finding of septal panniculitis strongly favors that diagnosis (8).

The formation of toxic metabolites of aspartame, either during the drug's shelflife or as metabolic byproducts, offers one possible explanation for the reaction seen in this patient. Boehm and Bada (9) have recently reported that the heating of aspartame results in conversion of some of its amino acids to their racemates. Although they note that the possible toxicity of consuming large amounts of these racemates remains to be determined, they speculate that some food or beverage components may catalyze the racemization of aspartic acid and phenylalanine in aspartame at room temperature. Furthermore, despite extensive prior testing, no such reaction has yet been reported, suggesting that this phenomenon may be idiosyncratic rather than dose-related. Fortunately, in the present patient, mere discontinuation of the aspartame-containing beverage resulted in complete and relatively rapid resolution of the condition without residua.

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