The patient described in this report had autoimmune CIU exacerbated by progesterone therapy. The role of progesterone in initiating and exacerbating this disorder is unknown. In the clinical disorder progesterone-induced urticaria, a high prevalence of prior use of progesterone supplementation for use as an oral contraceptive has been linked to disease manifestations.[6] A hypothesis was that antibodies directed to synthetic progesterone might cross-react to endogenous progesterone, eliciting a reaction.[6] However, the patient described above had reported onset of cyclical symptoms during early puberty before exposure to supplemental progesterone.

Immune mechanisms might also play a role in the pathogenesis of progesterone-induced urticaria. Interestingly, in 1921, Geber[7] performed an autologous serum-like skin test, whereby a wheal-and-flare reaction was noted in the skin to a patient's own premenstrual serum. Others have demonstrated a positive Prausnitz-Küstner test result or passive transfer test result using serum from patients with progesterone-induced urticaria transferred to healthy control subjects.[8] In the patient described in this report, her symptoms of urticaria and angioedema were found to be associated with the antibodies to the high-affinity IgE receptor. An autologous serum skin test was not performed. It is interesting that her symptoms followed a cyclical menstrual pattern in early puberty, whereas more recently, her symptoms were severely exacerbated by supplemental progesterone therapy. This could be a case of both CIU and progesterone-induced urticaria-angioedema. A consideration that progesterone might be involved in the clinical manifestations of CIU is speculative, but assessing the role of progesterone in other patients with CIU might be important.

The described patient successfully underwent progesterone desensitization, with a remarkable decrease in her symptoms evident by means of amelioration of her angioedema and discontinuation of prednisone use. Because the exact role of progesterone therapy in provoking the patient's symptoms is unclear, the mechanism by which an increased tolerance to supplemental progesterone was associated with a decrease in her symptoms is unknown. The observed effect could be a result of IgE-dependent mechanisms or nonimmunologic pharmacologic tolerance, such as that seen with aspirin or drug desensitization.[9] However, this novel approach to the treatment of CIU exacerbated by progesterone is similar in concept to desensitization with corpus luteum extract injections, which was performed in the 1950s.[1] This protocol could be used for other patients with a history of disease refractory to treatment who wish to avoid bilateral oopherectomy.

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TABLE I. Progesterone desensitization protocol

Time (h)	Dose
00:00 (first day)	0.1 mg
00:45	1 mg
01:30	5 mg
02:15	10 mg
03:00	25 mg
00:00 (next day)	50 mg
00:45	100 mg
01:30	100 mg

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Body burden of mercury is associated with acute atopic eczema and total IgE in children from southern Germany

To the Editor:

Atopic eczema (AE; atopic dermatitis) is the most common inflammatory skin disease among children. Interactions among susceptibility genes, the host's environment, and immunologic factors are involved in its pathogenesis.[1] Most patients show sensitizations against environmental allergens with high serum levels of total and allergen-specific IgE.[1] Increasing prevalence rates of AE during the last decades have been attributed to changes in environmental factors.[1]

With industrialization, heavy metals have been increasingly released into the environment, which may be incorporated through food, water, air, tobacco smoke, and medical prostheses.[2] A variety of these metals, such as arsenic, cadmium, and mercury, are of relevance to human health. They may interact with body stores of iron, vitamin C, and other essential nutrients, induce genomic instability, exert immunomodulatory effects, and cause contact dermatitis in sensitized persons.[3] Low doses of mercury salts have been shown to induce an immune response with polyclonal B cell activation, high levels of

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TABLE I. Results of logistic regression analyses evaluating associations between AE and urinary concentration of heavy metals

	OR* (95% CI)	
	History of AE	Acute AE
Urinary cadmium concentration	1.34 (0.79-2.30)	1.06 (0.57-1.97)
Urinary arsenic concentration	1.21 (0.57-2.57)	1.37 (0.58-3.23)
Urinary mercury concentration	0.66 (0.29-1.47)	1.68 (1.06-2.68)

*ORs when changing exposure from the 5th to the 95th percentile (0.45 μg/L mercury, 0.44 μg/L cadmium, and 11.8 μg/L arsenic). Adjusted for sex, social status, number of persons in home, parental history of AE, exposure to environmental tobacco smoke, and urinary creatinine.

TABLE II. Linear regression analyses for total serum IgE levels (log-transformed) as dependent variable and metal concentrations in urine

	n	Adjusted change* in geometric means (95% CI)
Urinary cadmium concentration	264	1.35 (0.93-1.95)
Urinary arsenic concentration	262	1.18 (0.68-2.04)
Urinary mercury concentration	260	−1.54 (1.12-2.11)

*Change in geometric mean value (95% CI) when changing exposure from the 5th to the 95th percentile (0.45 μg/L mercury, 0.44 μg/L cadmium, and 11.8 μg/L arsenic). Adjusted for sex, social status, persons in home, parental history of AE, exposure to environmental tobacco smoke, urinary creatinine, and case/control status.

IgE, and autoantibody production.[4] Recently, it could be demonstrated that mercury also enhances IgE-dependent mediator release from human basophils.[5] In contrast, cadmium seems to inhibit IgE synthesis but enhance mast cell degranulation.[6]

On the basis of the assumption that body burdens of (heavy) metals may serve as triggering factors, we investigated their associations with AE and total and specific IgE in a nested case-control study. The study base consisted of a cross-sectional study with all school beginners in Augsburg, Bavaria, in 1996 (n = 1673). Of these individuals, we recruited 164 children with AE and 213 controls (196 boys, 181 girls).

Parents completed a standardized questionnaire with basic allergy questions of the International Study of Childhood Asthma and Allergy in Childhood survey and were interviewed about parental history and the child's symptoms of atopic diseases and environmental risk factors, including exposure to metals.

All children received a skin examination according to the criteria of Hanifin and Rajka. AE severity was assessed with the Scoring Index of Atopic Dermatitis (SCORAD) system. Total and specific serum IgE was measured by enzyme immunoassay (allergens: mite, cat, egg white, milk, ascaris, soya bean, birch pollen, mug wort pollen, timothy grass pollen, *Alternaria*, *Blatella germanica*; CAP-FEIA, Pharmacia, Sweden). Childrens' dental restorations, including the number of amalgam fillings, were evaluated. At the day of examination, arsenic, cadmium, and mercury were measured in morning urine by atomic absorption spectrometry.[7] Urinary creatinine was determined by using a commercial test kit (Merck AG, Darmstadt, Germany) to adjust for differences in urine concentration. The concentrations of mercury, cadmium, and arsenic did not exceed actual reference values.[7] Mean concentrations were 0.12 μg/L mercury, 0.18 μg/L cadmium, and 7.02 μg/L arsenic.

Seventy-three of the children with AE were classified as having acute AE because of actual skin lesions, and 98 as having a history of AE because of a physician's diagnosis of AE in the past.

Logistic regression analysis was performed to assess the independent influence of the exposure variables (heavy metal content of urine) on the risk of acute AE or AE in history while controlling for known or assumed risk factors (sex, social status, family size, parental history of AE, exposure to environmental tobacco smoke, urinary creatinine). The parameter estimates were transformed to odds ratios (ORs) with 95% CIs (profile-likelihood method), giving an estimate of the maximal effect in the population after exclusion of extremes. The range units of the exposure concentrations of arsenic, cadmium, and mercury were different. To ensure comparability, ORs were calculated to describe the change in AE prevalence when changing the exposure from the 5th to the 95th percentile (inner 90% range). Results were considered statistically significant if the CI did not include the 1. Logistic regression was also applied to assess the influence of urinary metal concentrations on specific IgE (any positive: >0.35 kU/L). To test the association with total IgE, log-linear regression models were performed.

Children with amalgam fillings (n = 47) showed significantly higher urinary mercury concentrations than children with no fillings or other fillings (0.12 μg/L vs 0.27 μg/L; $P = .01$, t test).

Urinary mercury excretion was significantly correlated with the number of amalgam fillings ($r = 0.31$; $P < .001$).

Regression analysis revealed significantly higher urinary mercury concentrations in children with acute AE compared with children with history of AE or controls (OR, 1.68; 95% CI, 1.06-2.68; Table I). This association did not remain significant when restricting the analysis to children without amalgam fillings (OR, 1.10; 95% CI, 0.42-2.89). It was independent from total IgE. Children with acute AE showed no significant association between urinary mercury concentration and AE severity. There was no relationship between arsenic or cadmium levels and AE.

Linear regression revealed a significant relationship between mercury concentration but not with the other metal concentrations and total IgE (Table II).

There was no significant association between metal concentrations and presence of specific IgE.

The results of this population-based case-control study in children with AE show a strong association between the

body burden of mercury and disease state, indicating a possible role for mercury as triggering factor.

Exposure to mercury in the general population mainly results from dental amalgams, with mercury concentrations in urine and blood associated with amalgam exposure.[2,3]

Health problems caused by mercury released from dental amalgam have been subjects of controversial debates. However, extensive scientific risk evaluations could not demonstrate a clear-cut relationship. In contrast, toxic and immunomodulatory effects of mercury compounds are well-known.[3,4] $HgCl_2$ directly activates murine mast cells and enhances mediator release, including IL-4, thereby facilitating T_H2-lymphocyte development and polyclonal IgE production.[4,8] In addition, $HgCl_2$ enhances anti-IgE–induced secretion of histamine, leukotriene C4, IL-4, and IL-13 from human basophils in a dose-dependent fashion. These effects were observed at mercury concentrations comparable with those measured in the children of this study.[5]

Nonlethal exposure to various forms of mercury is known to induce autoimmunity (HgIA) in susceptible rats, which is characterized by significant increases of IL-4 and IL-10 and hypergammaglobulinemia predominantly of the T_H2-related IgG1 and IgE isotypes.[8,9] Recent findings provided evidence that HgIA is also dependent on IFN-γ, and that the immunomodulatory effects of mercury strongly depend on the host's genetic background.[10]

In conclusion, we observed a clear-cut relation between body burdens of mercury and acute but not chronic AE. Children with amalgam fillings exhibited significantly higher urinary mercury concentrations than children without, and there was a significantly higher risk for acute eczematous lesions with higher urinary mercury concentrations.

In addition, there was a positive and linear association between exposure to mercury and serum levels of total but not specific IgE. It might be speculated that mercury exacerbates allergic disorders by promoting a T_H2-cytokine profile and facilitating production of IgE against yet unknown antigens, such as autoantigens.

Further investigations are necessary to elucidate the interrelation among amalgam fillings, body burdens of mercury, and the formation of acute eczematous lesions in AE, its underlying mechanisms, and its clinical significance.

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Is glucosamine safe in patients with seafood allergy?

To the Editor:

Glucosamine, an aminomonosaccharide that plays a role in cartilage formation and repair, has been shown to restrict the progression of knee osteoarthritis.[1-5] This product, which is sold as a dietary or nutritional supplement, has been withheld from patients with arthritis who are allergic to shellfish because it is derived from crab, lobster, or shrimp shells.[6,7] The warning on the label instructs patients allergic to shellfish to consult a physician. Of course, without any clinical trials, most physicians would advise patients with shellfish allergy to avoid this therapy. Glucosamine is often sold in combination with chondroitin sulfate, which is derived from either cattle or shark cartilage.[7]

Shellfish allergy is caused by IgE antibodies to antigens in the flesh of the shellfish and not the shell; therefore it should be safe for patients with shellfish allergy to take glucosamine supplements. With approval from the Saint Louis University Institutional Review Board, patients with shellfish allergy were identified on the basis of history and positive skin test responses on chart review.

After informed consent was obtained, subjects underwent skin prick testing to appropriate shellfish, a positive histamine control (10 mg/mL), a negative saline control, and glucosamine. Standard commercially available extracts for shellfish scratch testing are provided as