# Haptens May Explain Huge Rise in Atopic Disease

BY BRUCE JANCIN

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GOTHENBURG, SWEDEN – While the hygiene hypothesis is hands down the most popular explanation offered for the dramatic increase in atopic disease in developed countries in recent decades, it's not the only plausible explanation.

The hapten-atopy hypothesis holds that the 400% rise in atopic dermatitis, asthma, and hay fever during the past 50 years is caused at least in part by the revolutionary increase in exposure to chemical haptens in the personal environment during the same time frame, Dr. John P. McFadden said at the congress.

**Exposure to haptens has exploded and may account in part for the 400% rise in atopic disease in the past 50 years.**

DR. McFADDEN

Haptens are low-molecular-weight organic chemicals that aren't allergenic on their own but can bind to a peptide or protein, thereby altering its configuration and rendering it foreign and allergenic. Examples of haptens include antibiotics and some other drugs, as well as chemicals present in toiletries, processed foods, powdered milk, preservatives used in vaccines, and metal jewelry, explained Dr. McFadden of St. John's Institute of Dermatology, St. Thomas' Hospital, London.

He noted that Scottish investigators have documented a relentless rise in cases of childhood asthma and eczema in that country from 1945 to 1997 occurring in parallel with an increasing prevalence of adult nickel allergy.

"Obviously, association doesn't prove causation. But there does seem to be a change, not just in nickel exposure, but in exposure to other haptens," the dermatologist observed.

Indeed, exposure to haptens has exploded in modern life. For example, global sales of toiletries quadrupled during 1959-1976. Today more than 80% of baby skin care products contain chemical fragrances. Various brands of powdered milk contain a mean of 12 haptens each. In 1992, just 6% of young women living in Tokyo dyed their hair; by 2001, this figure had jumped to 89% – and meanwhile the incidence of atopic disease in the Tokyo area doubled. Antibiotics weren't in general use until the second half of the 20th century. And that's when pierced earrings took off in popularity as well, Dr. McFadden noted.

Also, epidemiologic studies show that certain maternal occupations predispose to the birth of atopic children. Among these occupations are hairdresser, beautician, cleaner, electroplater, bar staff, dental assistant, confectionary maker, and book binder. What these diverse occupations have in common is increased environmental exposure to haptens.

The cornerstone of the hygiene hypothesis is that major improvements in public health have led to a cleaner home environment, resulting in less microbial stimulation of immune function and a consequent predisposition to atopic disease. Under audience questioning, Dr. McFadden conceded the hygiene hypothesis "may have some validity," but he added he finds it troubling that many adherents of the hypothesis have "a tendency to be slightly lazy in explaining away discrepancies.

"When you go back home," Dr. McFadden continued, "I want you to ask your allergist colleagues three questions: One, the biggest reduction in infections came at the end of the 19th century, with improvements in sanitation and nutrition – not in the second half of the 20th century, when the greatest increase in atopic disease occurred – so why was there no reported increase in allergy back then? Two, they say our immune systems haven't met infections, but actually the vaccination programs mean our immune systems think we've met polio, tetanus, diphtheria, and measles, all by the age of 1 year – how does that fit with the hygiene hypothesis? And three, studies have

repeatedly shown that respiratory infections are associated with the development of atopic disease, and we've all seen cases of eczema that are triggered by cutaneous infections – how does that fit in?"

The hapten hypothesis holds that persistent low-grade exposure to environmental haptens via the skin and oral routes at key times of Th2 cytokine immune dominance – namely, pregnancy and the first year of life – can lead to atopy.

Dietary hapten intake may interfere with oral immune tolerance mechanisms, while repeated cutaneous exposure to haptens could skew the innate immune system into promoting Th2 responses.

"We're postulating that all of this hapten exposure probably doesn't matter the rest of the time, but during these vulnerable periods it may be important," Dr. McFadden said.

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Last year he and his coworkers laid out in detail the proposed immunologic mechanisms driving the hapten-atopy hypothesis (Trends Immunol. 2009;30:67-74).

Consistent with their hypothesis, mouse studies have shown that repeated low-grade exposure to haptens can result in two types of non-tolerogenic response: the classic one, namely, allergic contact dermatitis, but also atopic dermatitis.

In humans, it's well established that repeated exposure to haptens can cause allergic contact dermatitis, but it is as yet unknown if hapten exposure contributes in any way to atopic dermatitis. But it's an issue well worth pursuing, in Dr. McFadden's view.

"The question as to whether increases in environmental hapten exposure are contributing to atopy is a legitimate one," he said.

Dr. McFadden disclosed that he has no relevant financial interests. ■