

Haptens May Explain Huge Rise in Atopic Disease

BY BRUCE JANCIN

EXPERT ANALYSIS FROM THE ANNUAL CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREAL DISEASE

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 chem-



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

DR. MCFADDEN

ical haptens in the personal environment during the same time frame, Dr. John P. McFadden said at the congress.

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 hy-

pothesis "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

**For patients with type 2 diabetes
whose blood glucose is not controlled
with OADs alone**

**IT MAY BE TIME
TO CONSIDER
A LANE
CHANGE**

Indications and Usage for Lantus® (insulin glargine [rDNA origin] injection)

Lantus® is a long-acting insulin analog indicated to improve glycemic control in adults and children (6 years and older) with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Lantus® should be administered once a day at the same time every day.

Important Limitations of Use: Lantus® is not recommended for the treatment of diabetic ketoacidosis. Use intravenous short-acting insulin instead.

Lantus® SoloSTAR® is a disposable prefilled insulin pen.

Please see additional Important Safety Information for Lantus® continued on the next page.

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 mecha-

nisms, 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.

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. ■

Persistent low-grade exposure to environmental haptens via the skin and oral routes at key times of Th2 cytokine immune dominance may lead to atopy.

ADVERTISEMENT

AS DIABETES PROGRESSES, OADs ALONE MAY NOT BE ENOUGH

According to the UKPDS, up to 50% of β -cell function may be lost by the time patients are diagnosed with type 2 diabetes, and it may continue to decline, on average, by about 5% annually.¹ A recent article by DeFronzo showed that, in patients with highly impaired glucose tolerance, as much as 80% of β -cell function may be lost by the time of diagnosis.² It is this progressive β -cell function loss that is primarily responsible for the development of diabetes and the incremental rise in A1C.²

Patients may not know that their pancreas is no longer making enough insulin and that their disease has progressed.^{3,4} National data from 2003 to 2004 showed that about 40% of patients with diabetes did not have adequate glycemic control.^{5a} And because blood glucose control is important, all available therapeutic options—including insulin—should be considered in the treatment of diabetes.

Many patients with type 2 diabetes may eventually need insulin to achieve or maintain glycemic control.^{3,6} Unfortunately, patients may blame themselves for what they perceive as 'failure' to control their glucose levels.³ And because patients' attitudes toward their disease play an important role in diabetes self-care behaviors, it's likely that this negative mindset may adversely impact diabetes self-management.⁷

^aGlycemic control defined as A1C <7%.

OADs=oral antidiabetic drugs;

UKPDS=United Kingdom Prospective Diabetes Study.

Patients may not know that their pancreas is no longer making enough insulin and that their disease has progressed.^{3,4}



Learn more at www.RethinkInsulin.com

From the maker of
LANTUS® SoloSTAR®



A POSITIVE "INSULIN TALK" MAY HELP REASSURE PATIENTS

The results of having a positive insulin talk can be impactful: in a survey, about 80% of patients with type 2 diabetes who were taking OADs said they'd consider taking insulin if their doctor recommended it.⁸

By starting the dialogue now, you can help your patients have a better understanding of insulin and the glucose-lowering role it plays as part of an overall diabetes treatment plan, which may include diet, exercise, and other diabetes medications.^{3,9}

For appropriate patients, starting insulin earlier in the disease continuum can help improve glycemic control.^{6,9-11} Insulin is an effective medication for lowering blood glucose levels.

So, engage patients in talks early and as needed to help turn their negative mindset of failure into a positive opportunity to manage their blood glucose.

Important Safety Information for Lantus® (insulin glargine [rDNA origin] injection)

Contraindications

Lantus® is contraindicated in patients hypersensitive to insulin glargine or one of its excipients.

Warnings and Precautions

Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral antidiabetic treatment.

Please see additional Important Safety Information for Lantus® continued on the next page.

INSULIN

IMPROVING BLOOD GLUCOSE CONTROL SHOULDN'T WAIT