Emerging and Novel Topics: Alpha Gal and the Role of Carbohydrate Antigens in Delayed Anaphylaxis

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• Consultant for: None
• Speaker’s Bureau for: None
• Major Stock Shareholder for: None
• Other Financial or Material Support from: Phadia Immunology Reference Laboratory, Thermo Fisher Scientific

I will not be discussing products that are investigational or not labeled for use under discussion.
In 2006, we knew about four things including two forms of anaphylaxis that didn’t make sense.

- A patient with carcinoma of the colon died of anaphylaxis within 20 minutes of starting his first infusion of cetuximab*.

- A 43-year-old hunter reported three episodes of anaphylaxis, each starting four hours after eating beef.

- A village in Kenya where 70% of the children had IgE antibodies to cat without exposure or symptoms.

and: You cant grow Azaleas in Central Virginia.

*.

Bert O’Neil, UNC
Measurement of IgE ab to Purified Allergens Using Streptavidin Solid Phase

Fel d 1, mouse IgG, Der p 1, Lol p 1, Asian lady bug, retuximab, infliximab etc.

Cetuximab + Biotin

Streptavidin CAP plus ~5ug Biotinylated Cetuximab

Cetuximab Solid Phase*

* Assay in parallel with standard curve gives results for anti-Cetuximab IgE in IU/ml.  
  *Erwin, Custis, et al JACI ’05,  Erwin et al JACI ’09.*
| Type of Reaction and Subject No. | Type of Cetuximab | Galactose-α-1,3-Galactose | Mammalian Allergens |
|--------------------------------|
|                               | SP2/0\| | CHO\| | Mouse IgG\| | Cat | Dog | Fel d 1\| | Beef |
| Hypersensitivity reaction      |                   |                     | international units per milliliter |
| Anaphylaxis related to cetuximab | 41.6 | 0.35 | 13.8 | 0.35 | 3.16 | 2.60 | 0.35 | 3.02 |
| 2                              | 38.8 | 0.35 | 35.2 | 0.35 | 13.20 | 12.30 | 0.35 | 12.46 |
| 3                              | 20.2 | 0.35 | 12.6 | 0.35 | 9.34 | 9.77 | 0.35 | 6.92 |
| 4                              | 11.1 | 0.35 | 2.9 | 0.35 | 1.94 | 1.86 | 0.35 | 1.82 |
| 5                              | 4.9  | 0.35 | 2.0 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 |
| 6                              | 4.2  | 0.35 | 2.7 | 0.35 | 1.54 | 1.50 | 0.35 | 1.66 |
| Recurrent anaphylaxis unrelated to cetuximab | 131.0 | 1.89 | 38.9 | 1.75 | 41.50 | 34.50 | 3.64 | 32.90 |
| 7                              | 69.2 | 0.35 | 42.1 | 1.19 | 27.70 | 32.00 | 0.35 | 26.20 |
| 8                              | 55.1 | 0.35 | 32.2 | 0.43 | 22.20 | 25.10 | 0.35 | 13.80 |
| 9                              | 43.5 | 0.35 | 32.3 | 0.35 | 37.30 | 29.40 | 0.35 | 3.48 |
| 10                             | 81.1 | 0.35 | 100.0 | 0.35 | 14.30 | 14.70 | 0.35 | 8.75 |
| 11                             | 13.0 | 0.35 | 9.0 | 0.78 | 8.86 | 8.84 | 0.35 | 8.90 |
| Mean                           | 27.7 | NA  | 25.5 | ND  | 10.30 | 9.93 | NA  | 7.16 |
| No hypersensitivity reaction   | 0    | 0   | 0   | 0   | 0    | 0    | 0    | 0    |
August 29th, 2014 (Charlottesville, VA)

- 43 year old man with metastatic colon cancer developed anaphylaxis within 2 minutes of starting his first infusion of Cetuximab*
- Prolonged circulatory collapse-resuscitation
- Transferred to ICU at local hospital
- Generalized organ failure including ARDS and hepato-renal syndrome

September 3rd, 2014

- Life support withdrawn

<table>
<thead>
<tr>
<th>Serum IgE to alpha-gal</th>
<th>Total IgE</th>
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<tbody>
<tr>
<td>3.1 IU/mL</td>
<td>149 IU/mL</td>
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</table>

*Information from Kevin Lawrence, MD
Glycosylation of cetuximab as shown in Chung et al ’08 and the true structure of the Fc fragment of IgG *


Karl Landsteiner
Defined the ABO system and recognized the presence of other closely related “B like” oligosaccharides on mammalian cells which also gave rise to antibody responses in humans. But also established the concept of a hapten.


Commins and Platts-Mills; Current perspectives, JACI ‘09

Mammalian blood group oligosaccharides

Plant derived cross reactive carbohydrate determinants : CCD’s
In 1989 Sandra Latimer identified a group of friends in Georgia who had developed a novel form of allergy to meat: these reactions: i) started weeks or months after tick bites ii) were caused by mammalian meats, and iii) took three or more hours to start.

She told Dr Deutsch in Athens, and he told the Georgia allergy Soc.
Features Associated with Delayed Urticaria and Anaphylaxis in Patients with IgE to Galactose-alpha-1,3-galactose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Urticaria Only (n=87)</th>
<th>Anaphylaxis# (n=249)</th>
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<tbody>
<tr>
<td><strong>I. Age of Onset</strong></td>
<td></td>
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<tr>
<td>0 – 20 years</td>
<td>20%</td>
<td>16%</td>
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<tr>
<td>21 – 40 years</td>
<td>20%</td>
<td>25%</td>
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<tr>
<td>41 – 50 years</td>
<td>22%</td>
<td>24%</td>
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<tr>
<td>&gt;50 years</td>
<td>39%</td>
<td>35%</td>
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<td><strong>II. Atopy</strong></td>
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<tr>
<td></td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>III. Severity of Reaction</strong></td>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>Moderate</td>
<td>45%</td>
<td>75%</td>
</tr>
<tr>
<td>Severe</td>
<td>12%</td>
<td>25%</td>
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</tbody>
</table>

#Anaphylaxis was based primarily on patient reports, many cases were improved by the time they reached the emergency facility
Analysis of IgE to alpha-gal and mammalian allergens, inhalant allergens, foods and venoms.

Anaphylaxis, Non-Atopic (n=115)

Anaphylaxis, Atopic (n=130)
Anaphylaxis, Non-Atopic (n=109)

- Total IgE (kU/l)
- Alpha-gal sIgE (kUA/l)

- 30%
- 10%
- 3%
**Mammalian Meat Challenge**

**Results in Subjects with IgE to alpha-gal**

<table>
<thead>
<tr>
<th>Allergics (n=12)</th>
<th>Urticaria</th>
<th>Time to symptoms (hrs:min)</th>
<th>Treatment required</th>
<th>Tryptase elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9*/12</td>
<td>2:30 – 6:00</td>
<td>9/12</td>
<td>3**/12</td>
</tr>
</tbody>
</table>

*Two subjects received epinephrine (i.e., these reactions are probably better defined as delayed anaphylaxis to mammalian meat)*

**Tryptase:**
- Subject FC-03: 3.8 ng/ml (baseline) → 13.4ng/ml (2 hrs) → 18.3 ng/ml
- Subject FC-08: 4.2ng/mL (baseline) → 18.2ng/mL (4 hrs) → 20.1 ng/mL
- Subject FC-10: 4.9 (baseline) → 6.2 (4 hrs) → 9.9 (5 hrs) → 10.7 (6 hrs)

*Commins et al JACI . June 2014*
Delayed clinical and ex-vivo response to mammalian meat in patients with IgE to galactose alpha-1, 3-galactose.

Commins SP, James HR, Pochan S, and Platts-Mills. JACI July 2014
Mammalian meat challenge
Subject #FC-10: sIgE to alpha-gal = 29.1 IU/mL; total IgE = 201

4hrs 25min after eating mammalian meat: pruritus followed by urticaria on right flank
Hypothesis: Alpha-gal may enter the circulation as a glycoprophospholipid

\[ \alpha1,3 \beta1,4 P \beta1,4 \alpha1,3 P = \text{Galactose} \]

\[ = \text{N-acetylglucosamine} \]

Alpha-gal moieties

Chylomicron

Hypothesis:

\[ \alpha1,3 \beta1,4 \]

\[ \alpha1,3 \beta1,4 \]

\[ \text{Galactose} \]

\[ \text{N-acetylglucosamine} \]

HDL  LDL  IDL  VLDL

Chylomicron
Jefferson was concerned that she had not been inoculated with smallpox. Paris was not safe indeed King Louis XV had died of smallpox in 1774.

At Dr Suttons house outside Paris, Sally was scarified with a ‘mild’ strain of smallpox. In 1798 Jenner reported successful use of cowpox to inoculate.

This form of inoculation was not novel. Jenner simply recommended that Vaccinia should replace Variola.

Inoculation with one virus lead to complete protection from a related virus.
John Snow: London water supplies: 1854

Merrell Wyman’s map of the White Mountains pollen free zones 1872

Blackley’s Pollen sampling equipment: 1873
Asthma admissions in England 1955-2005

Asthma Admissions MUSC ‘55–97

Total MUSC asthma discharges in each five-year period from 1958 to 1997 for children age 0-18.

Asthma in Finnish Army Recruits 1920-1990
Sequential rises in three different allergic diseases

1870: Blackley (UK) and Wyman (USA) define hay fever

1911: Noon starts SCIT for hay fever

1946: New York initiates ragweed eradication

1995-2000: Peak of asthma prevalence & severity

2003: First recognition of rise in peanut allergy

Reactions to Cetuximab

Delayed anaphylaxis to beef

Rocky mountain spotted fever

Spread of the lone star tick

Incidence rates (per 1,000,000 persons)

- 0
- 0.1-0.9
- 1.0-9.9
- 10.0-14.9
- 15.0+
Pruritic reactions to tick bites and the prevalence of IgE ab to alpha-gal

\[ \chi^2 = 26.8 \]
\[ p < 0.001 \]

Red bars are patients who reported more than two weeks itching after tick bites.

Commins et al JACI 2011
Lyme Disease in Virginia: July 2013

Bites from *Ixodes scapularis*

Erythema chronicum migrans rash

- **Non-pruritic**
- Is not associated with increased total IgE or positive IgE to alpha-gal
- Treated successfully with Doxycycline
Hypersensitivity to Ticks and Lyme Disease Risk

Georgine S. Burke,*† Stephen K. Wikel,† Andrew Spielman,‡ Sam R. Telford,¶§ Kathleen McKay,*† Peter J. Krause,*† and the Tick-borne Infection Study Group

*The likelihood of Lyme disease infection decreased with >3 reports of tick-associated itch (odds ratio 0.14, 95% CI 0.94–0.03, p = 0.01).

Emerg Infect Dis. 2005. 11:36-41
Changes in IgE ab to Alpha-gal (IU/ml) and in Total IgE (IU/ml) after multiple bites from larval ticks.

<table>
<thead>
<tr>
<th>Date</th>
<th>IgE to Alpha-gal</th>
<th>Total IgE#</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/26/06</td>
<td>0.49</td>
<td>127</td>
</tr>
<tr>
<td>5/21/07</td>
<td>16.9</td>
<td>199</td>
</tr>
<tr>
<td>10/9/07</td>
<td>48.3</td>
<td>350</td>
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<tr>
<td>11/6/07</td>
<td>130</td>
<td>532</td>
</tr>
<tr>
<td>2/9/09</td>
<td>33</td>
<td>360</td>
</tr>
</tbody>
</table>

Several bites from adult ticks May '07
Multiple bites (~200) from seed ticks August '07

Serum IgE ab assays 5/14/08: Cat 38, Dog 44, Beef 39, Pork 37.5; Chicken, Turkey, Cod, Dust Mite, Roach and Ragweed all <0.35 IU/ml

#Total IgE of this subject had been consistently less than 200 IU/ml since 1980.

Odocoileus virginianus  A.americanum  TAE P-M Aug 7th 2007
Investigation of the response to tick bites
i) Cellular responses in the skin.
ii) Phenotype of circulating CD-19+ve B cells.
iii) Deep Sequencing of IgE CDR (complementarity determining regions) in patients following bites.
iv) IgE responses to seed ticks in mice.
Sensitized, 2 days post Seed Ticks: Eosinophils (H&E)
Sensitized, 2 days post Seed Ticks: Eosinophils (H&E)
Sensitized, 2 d post *A. americanum*: T & B Lymphocytes (IHC)
Antibody responses to oligosaccharides show little evidence of memory & are thought to be at least relatively T independent, both for IgM and IgG2.

In mice and man there are clear examples of genetic defects that disrupt germinal center formation but do not prevent IgE production.

We are studying an IgE response to an oligosaccharide that is induced by a parasite in a relatively civilized population.

Questions:
1) Can we define what happens in the skin?
2) Does the IgE response to alpha-gal involve somatic hyper-mutation (SMH) ?.
Deep sequencing data from Scott Boyd, Stanford, on B cells from Virginia, showing Mutation frequency of IgE compared to IgG.
## Convergent IgE CDR3 Amino Acid Sequences

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Isotype Diversity in the Response to Low (A) or High (B) Allergen Exposure: Aalberse and Platts-Mills JACI 2004

A. \( \mu \)  
   \( \text{TH2} \)  
   \( \text{CD25}^+ T\text{Reg} \)  
   IL-4  
   \( \varepsilon \)  
   Lymph Node or Bone Marrow  
   \( \varepsilon \)  
   \( \text{IgE} \)

B. \( \mu \)  
   Germinal Center  
   \( \gamma_1 \)  
   IL-4  
   \( \gamma_4 \)  
   IL-4  
   \( \varepsilon \)  
   T\text{cell}  
   Tr1  
   IL-10  
   \( \gamma_1 \)  
   \( \gamma_4 \)  
   \( \text{IgG}_1 \)  
   \( \text{IgG}_4 \)  
   \( \text{IgE} \)

\( \neq \) Apoptosis of IgE-Switched B Cells  
* Circulating Memory Cells

The enigma of IgE B-cell memory in human subjects: J.Davies, T.Platts-Mills and R.Aalberse, JACI 2013
Cat extract (and IgE assays) can be made from dander and/or epithelium, which contain many different proteins.

**Gronlund H, et al.** The carbohydrate galactose-α-1,3-galactose is a major IgE-binding epitope on cat IgA. *JACI*. 2009; 123:1189.

**Commins et al** *JACI* 2011

Cat IgA is Fel d 5. See [www.allergen.org](http://www.allergen.org).

**Case III** | **Dander** | **Epithelium** | **Tick Bites**
--- | --- | --- | ---
Fel d 1 | 18 kDa | 18 kDa | Alpha-gal on a protein (e.g., cat IgA*)
(uteroglobin) | 69 kDa | 69 kDa | 200 kDa
Fel d 2 | 69 kDa | Cross reacts Pork-albumin | Cross reacts with all Non-primate mammals
(cat albumin)

*Gronlund H, et al. The carbohydrate galactose-α-1,3-galactose is a major IgE-binding epitope on cat IgA. *JACI*. 2009; 123:1189.

**Commins et al** *JACI* 2011

Cat IgA is Fel d 5. See [www.allergen.org](http://www.allergen.org).
External antigen uptake by Langerhans cells with reorganization of epidermal tight junction barriers

Akiharu Kubo,¹,² Keisuke Nagao,¹,² Mariko Yokouchi,¹ Hiroyuki Sasaki,³,⁴ and Masayuki Amagai¹

Keio University and Osaka University, Japan

Common items containing triclosan:
• Dial liquid handsoap and antibacterial body wash
• Colgate Total toothpaste
• Ultra concentrated Dawn antibacterial dish soap
• Neutrogena Body Clear body wash, etc.

Products no longer containing triclosan following protests:
• Old Spice High Endurance deodorant
• Clearasil daily face wash
• Clean & Clear foaming facial cleanser
In 2006, we knew about four things including two forms of anaphylaxis that we now know are all explained by the increased exposure to lone star ticks and the resulting sensitization to galactose alpha-1,3-galactose.

- A patient with carcinoma of the colon died of anaphylaxis within 20 minutes of starting his first infusion of cetuximab.*
- A 43-year-old hunter who reported three episodes of anaphylaxis, each starting four hours after eating beef.
- A village in Kenya where 70% of the children had IgE antibodies to cat without exposure or symptoms.

and: You can't grow Azaleas in Central Virginia.

* Bert O’Neil, UNC
Colleagues: 2006-2015

University of Virginia
Scott Commins
Libby Kelly
Peter Heymann
Anubha Tripathi
Jake Hosen
Sharma Satinover
Hayley James
Lisa Workman
Josh Kennedy

Elizabeth Erwin/Ohio
Matt Perzanowski/Columbia
Gus Litonjua, Harvard
Diane Gold, Harvard

Africa and Europe
Eva Ronmark, Sweden
Bo Lundback, Sweden
Lucy N’Ganga, Kenya
Joseph Odiambo, Kenya
Adnan Custovic, Manchester

Alpha-Gal Research
Christine Chung, Nashville
Beloo Mirakhur, BMS
Qinwei Zhou; ImClone
Tina Hatley, Bentonville.
Louis Matos.
Tilo Biederman

And the many other colleagues who have enrolled or referred adult and pediatric cases with the alpha-gal syndrome.
Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children.

Convergent IgE Sequences Vary in Mutations
Alpha-gal specific IgE titers in patients presenting to clinic with anaphylaxis or asthma

AJRCCM 2012, 185:723

Red dots indicate subjects with a history of anaphylactic reactions.

Anaphylaxis, urticaria, or angioedema subjects

Cat in home

No cat in home

Asthma

Controls
<table>
<thead>
<tr>
<th>Subject #</th>
<th>Date Serum Obtained</th>
<th>Details of Recent Tick Bite(s)</th>
<th>Time Post Tick Bite(s)</th>
<th>Total IgE kU/L</th>
<th>Alpha-gal IgE kUA/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>02/07/13</td>
<td>History: alpha-gal positive</td>
<td>--</td>
<td>300</td>
<td>36.2</td>
</tr>
<tr>
<td>1</td>
<td>05/03/13</td>
<td>1 <em>A. americanum</em> Tick</td>
<td>1 day</td>
<td>341</td>
<td>23.4</td>
</tr>
<tr>
<td>1</td>
<td>05/14/13</td>
<td>(see above)</td>
<td>12 days</td>
<td>335</td>
<td>23.9</td>
</tr>
<tr>
<td>1</td>
<td>08/29/13</td>
<td>Multiple (~30) Seed Ticks</td>
<td>4 days</td>
<td>334</td>
<td>40.5</td>
</tr>
<tr>
<td>1</td>
<td>09/04/13</td>
<td>(see above)</td>
<td>10 days</td>
<td>373</td>
<td>73.4</td>
</tr>
<tr>
<td>1</td>
<td>09/20/13</td>
<td>(see above)</td>
<td>26 days</td>
<td>633</td>
<td>290</td>
</tr>
<tr>
<td>1</td>
<td>09/27/13</td>
<td>(see above)</td>
<td>33 days</td>
<td>562</td>
<td>266</td>
</tr>
<tr>
<td>1</td>
<td>10/10/13</td>
<td>(see above)</td>
<td>46 days</td>
<td>584</td>
<td>214</td>
</tr>
<tr>
<td>1</td>
<td>02/19/14</td>
<td>(see above)</td>
<td>178 days</td>
<td>419</td>
<td>56.3</td>
</tr>
<tr>
<td>2</td>
<td>01/25/11</td>
<td>History: alpha-gal positive</td>
<td>--</td>
<td>11.3</td>
<td>6.49</td>
</tr>
<tr>
<td>2</td>
<td>05/15/13</td>
<td>1 <em>Wild Type</em> Tick</td>
<td>2 days</td>
<td>10.1</td>
<td>0.72</td>
</tr>
<tr>
<td>2</td>
<td>05/23/13</td>
<td>(see above)</td>
<td>9 days</td>
<td>11.0</td>
<td>2.17</td>
</tr>
<tr>
<td>3</td>
<td>07/25/12</td>
<td>History: alpha-gal naïve</td>
<td>--</td>
<td>18.5</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>3</td>
<td>09/25/13</td>
<td>1 <em>A. americanum</em> Tick</td>
<td>108 days</td>
<td>19.6</td>
<td>&lt;0.35</td>
</tr>
</tbody>
</table>
John Snow monitored and reported on the effects of taking water from Thames Ditton rather than Battersea and provided the best evidence that controlling water supplies was the best approach to preventing the spread of enteric infections.

Map of London water supplies 1856
Norrbotten, Sweden

199/219
$r = 0.92; p < 0.001$

Association with asthma
$p < 0.001$

Kabati, Kenya

9/127

$97/127$

$r = 0.77; p < 0.001$

No relationship to asthma
Bites of *Amblyomma americanum* can be Extremely Pruritic.
Bites of adult or larval ticks have been associated with rapid rises in IgE ab and total IgE.
As was the case in most of North America, these deer were “nearly extirpated“ by 1900 as a Result of over-exploitation and loss of habitat to agriculture.

In the Piedmont deer restoration Started in 1951 and the first open season for deer in the Piedmont was 1958.

Since then numbers in Eastern North America have risen from 500,000 to greater than 2 million.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Shoes universal; water clean.</td>
</tr>
<tr>
<td>1920</td>
<td>Helminths and malaria eradicated on Staten Island.</td>
</tr>
<tr>
<td>1924</td>
<td>Last abattoir closed; horses becoming rare.</td>
</tr>
<tr>
<td>1932-50</td>
<td>Ratner &amp; Silverman: Allergic Disease 10-13%.</td>
</tr>
<tr>
<td>1946</td>
<td>City initiated ragweed eradication campaign because of the severity of hay fever.*</td>
</tr>
<tr>
<td>1982</td>
<td>Mayor Koch: Asthma rated #1 medical problem of the city.#</td>
</tr>
<tr>
<td>1996</td>
<td>Emerging epidemic of asthma in NYC schools.</td>
</tr>
<tr>
<td></td>
<td>“200 of 1,100 students in E. Harlem on treatment.”¹</td>
</tr>
<tr>
<td>1997</td>
<td>Mayor Giuliani declares war on rats.²</td>
</tr>
</tbody>
</table>

Dr John Snow
(1813-1858)

Challenged the prevailing theory of miasmas (smells and bad air from putrefying matter) as the cause of diseases such as cholera, typhoid and bubonic plague.
Traced the 1854 Broad street cholera outbreak in Soho to a water pump.
Monitored the great experiment which demonstrated that water provided by a company which took their water from above London sewage was much safer.
Administered chloroform analgesia to Queen Victoria for the birth of her eighth child.
Bretton Woods was recognized in the early 1900s as a hay fever resort by the United States Hay Fever Association (founded in 1873), and also in the 1930s through the 1950s, along with other areas in the White Mountains, as a retreat for ragweed hay fever sufferers.
By the 1880s hay fever (also called June Cold, Rose Cold, hay asthma, hay cold, or autumnal catarrh) had become the pride of America’s leisure class.
Investigating the bites of Amblyomma americanum

- Local rash
- Extremely Pruritic
- Associated with increased total IgE and increased IgE to alpha-gal.

A. Americanum bite at 48 hours
Alpha-gal cases have now been reported from:
- Australia
- Sweden
- France
- Germany
- Spain
- Japan
- China
- Zimbabwe
- South Africa
- England

IgE ab to alpha-gal have been reported from Kenya & Ecuador.
Delayed Anaphylaxis to Red Meat (Late Night Anaphylaxis).

i) Onset of allergic reactions to beef, pork or lamb in adult patients who have previously tolerated meat.
ii) Skin tests to beef weak or negative.
iii) History of tick bites that itch for two weeks or more.
iv) Positive serum assays for IgE to beef, pork or lamb, explained by IgE ab to Alpha-gal

Chung et al NEJM 2008
Commins et al JACI 2009
Commins et al JACI 2011
Kennedy et al Pediatrics 2013
Commins et al JACI 2014

Tick Bite Causes Potentially-Deadly Allergic Reaction To Meat For Man from Texas

June 26, 2013.: CBS, Dallas/Fort Worth, Texas
Three diseases related to Tick Bites that are not decreasing in “developed” countries.

**Tick borne encephalitis (TBE):**

Jaaskelainen et al, Emerg Infect Dis: 2006

**Lyme disease:**

Burke et al, Emerg Infect Dis: 2005

**Delayed anaphylaxis to red meat:**

Commins et al, JACI: 2009 and 2014

Van Hage et al, JACI: 2014

Biederman et al, JACI : 2014
Galactose-α-1,3-Galactose-Specific IgE Is Associated with Anaphylaxis but Not Asthma

**TABLE 4. IgE ANTIBODIES TO α-GAL, FEL D 1, AND INDOOR ALLERGENS AMONG SUBJECTS (AGE 18–50) PRESENTING TO AN EMERGENCY DEPARTMENT IN VIRGINIA**

<table>
<thead>
<tr>
<th></th>
<th>All ED Subjects</th>
<th>Asthma ED Subjects</th>
<th>Control ED Subjects</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>130</td>
<td>60</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>IgE to α-gal (IU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.35</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>1.04 (0.43–2.5); P = 0.93</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0.76 (0.16–3.6); P = 0.73</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0.33 (0.03–3.3); P = 0.35</td>
</tr>
<tr>
<td>IgE to Fel d 1 (IU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.35</td>
<td>22</td>
<td>17</td>
<td>5</td>
<td>4.7 (1.6–13.8); P = 0.005</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>8.4 (0.99–70); P = 0.05</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IgE to indoor allergens: dust mite, cockroach, or Fel d 1 (IU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.35</td>
<td>60</td>
<td>41</td>
<td>29</td>
<td>1.6 (0.81–3.2); P = 0.18</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>46</td>
<td>32</td>
<td>14</td>
<td>2.9 (1.4–6.2); P = 0.006</td>
</tr>
<tr>
<td>&gt;10</td>
<td>35</td>
<td>26</td>
<td>9</td>
<td>3.5 (1.5–8.2); P = 0.004</td>
</tr>
</tbody>
</table>

Commins et al. AJRCCM. 2012;185:723.
Commins and Platts-Mills; Current perspectives, JACI '09

GLYCObIOLOGY AND EXTRACELLULAR MATRICES: β(1,2)-Xylose and α(1,3)-Fucose Residues Have a Strong Contribution in IgE Binding to Plant Glycoallergens

Ronald van Ree, Marion Cabanes-Macheteau, Jaap Akkerdaas, Jean-Pierre Milazzo, Corinne Loutelier-Bourhis, Catherine Rayon, Mayte Villalba, Stef Koppelman, Rob Aalberse, Rosalia Rodriguez, Loïc Faye and Patrice Lerouge

J. Biol. Chem. 2000, 275:11451-11458. doi: 10.1074/jbc.275.15.11451
The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose

Scott P. Commins, MD, PhD,a* Hayley R. James, BS,a* Elizabeth A. Kelly, MD,a Shawna L. Pochan, CNM, MPH,a Lisa J. Workman, BA,a Matthew S. Perzanowski, PhD, MPH,b Katherine M. Kocan, PhD,c John V. Fahy, MD,d Lucy W. Nganga, MD,e Eva Ronmark, PhD,f Philip J. Cooper, MB BS, PhD,g,h and Thomas A. E. Platts-Mills, MD, PhD, FRSA

Charlottesville, Va, New York, NY, Stillwater, Okla, San Francisco, Calif, Nairobi, Kenya, Umea, Sweden, Quito, Ecuador, and Liverpool, United Kingdom     JACI  e-pub March 2011

- IgE antibodies to the oligosaccharide α-gal are related to 2 forms of anaphylaxis that are most common in the south-eastern United States (eg, anaphylaxis during cetuximab infusion and anaphylaxis after eating mammalian meat).

- Tick bites are directly related to the presence of these IgE antibodies as assessed prospectively, by history of tick bites, and by analyses of the areas where these IgE antibodies are found.

- This IgE antibody response provides a model of an ectoparasite-specific response that has significant clinical consequences.
Glycans produced by human (A), hamster (CHO) (B), and mouse (NS0 or SP2O) (C) cell lines. The production of the alpha 1-3 linkage is dependent upon the activity of alpha-1,3-galactosyltransferase, which is silenced in humans.
Spontaneous deep inspiration is the first line of defense against bronchospasm (more potent than isoprenaline).

Fredberg JJ et al AJRCCM 159:959 '99

Sigh rates fall among students watching a screen compared to reading.

Hark et al, Annals of Allergy : '05, 94:247

Shim et al Physical deconditioning as the cause of breathlessness among Obese teenagers with a diagnosis of asthma. PLOS ONE 2013