Food allergens: Challenges for risk assessment

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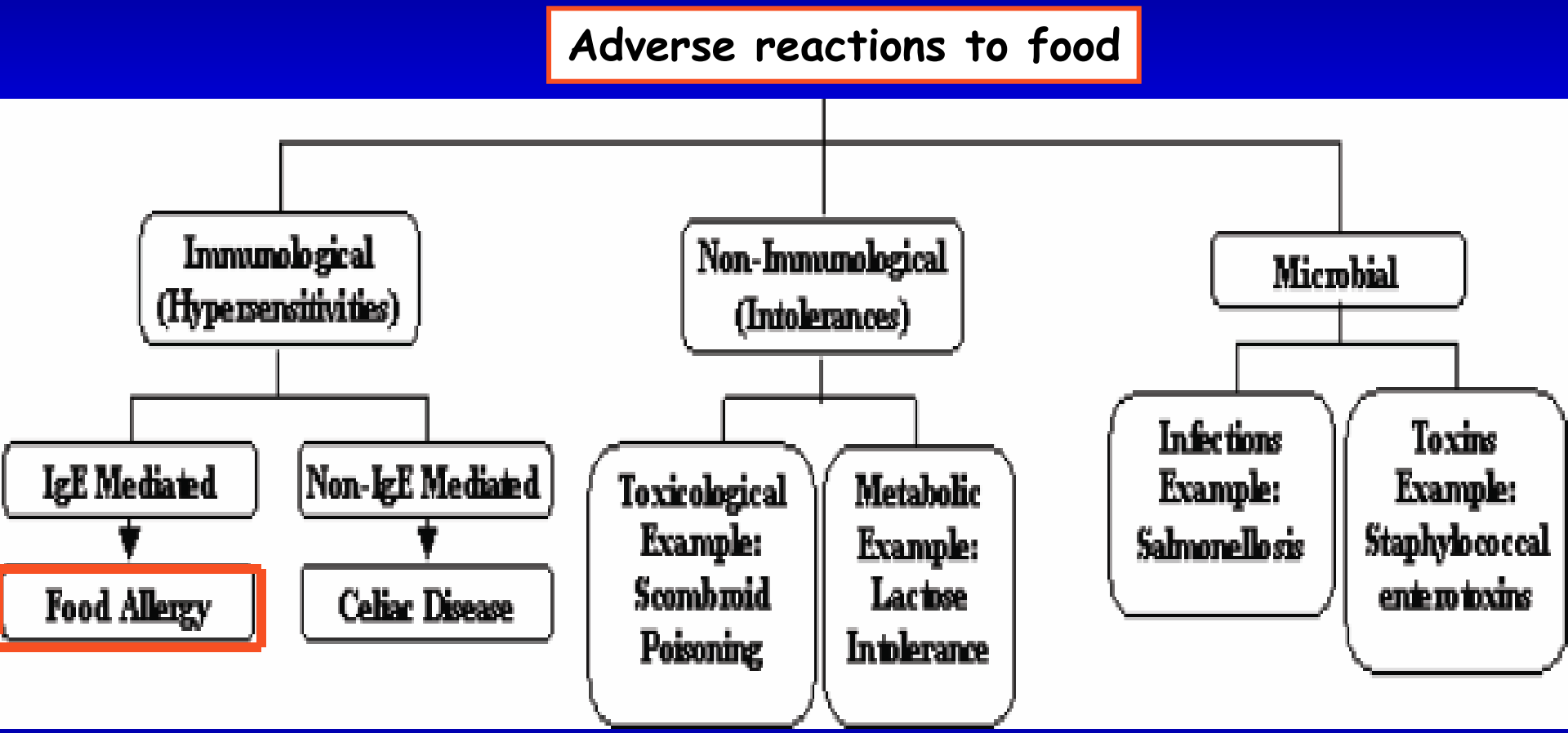
Goals

- Introduce "food allergy"
- Describe challenges for risk assessment
  - Food allergen
  - Food allergic reaction - mechanisms and key scientific issues
  - Threshold/ Biological end point
    - Food challenge/ Eliciting doses
    - Severity
- Conclusions

"Food allergy"

- Serious public health problem:
  - 30000 ER visits/ 2500 hospitalizations/ 150 deaths/yr
- Increased prevalence over past 20 years
  - 4% of total US population: Infants > adults
- Over 150 foods implicated; wide distribution of major allergenic foods:
  - US: peanut, tree nut, soy, egg, milk, wheat, fish, shellfish
  - Europe: ... sesame, mustard, celery
  - Japan:… buckwheat
- No effective treatment – Avoidance / product labeling is key!
- Lifetime risk + consumer fears ⇒ psychosocial impact

"Food allergy"



http://www.cfsan.fda.gov/~dms/alrgn2.html#ii

Food allergen

- Food – peanut, soy, milk, etc.
- Protein in food – Ara h1, Ara h2, Ara h3, etc. (peanut)
  - One food ⇒ multiple allergens
  - Not all foods/ allergens the same

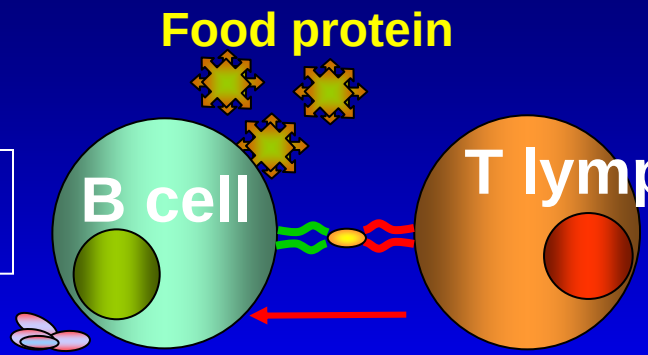
- Widely distributed in food supply

Food allergic reaction

- Unique toxicological response:
  - Immunological
  - Two phase (sensitization and elicitation)
  - Amplifier mechanism
- One exposure
- Minute amounts can trigger (*thresholds)
- Potentially fatal

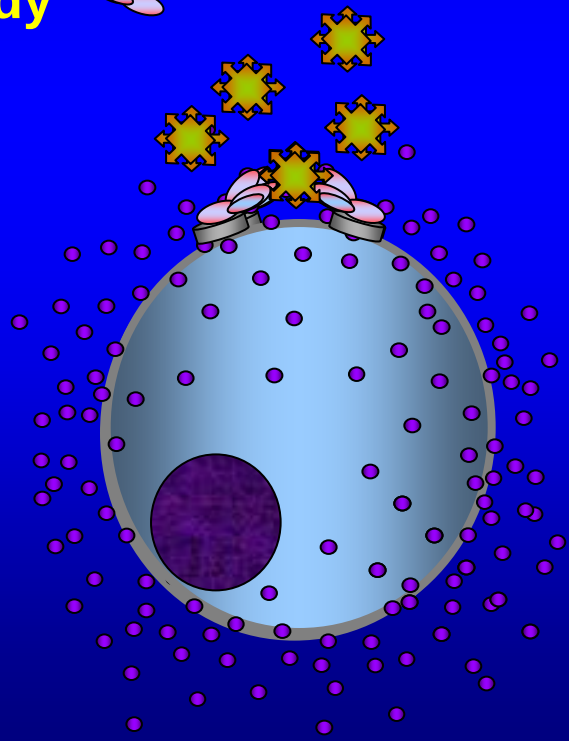
ALLERGY

Sensitization



IgE
Antibody

Elicitation/ Reactivity



Anaphylaxis

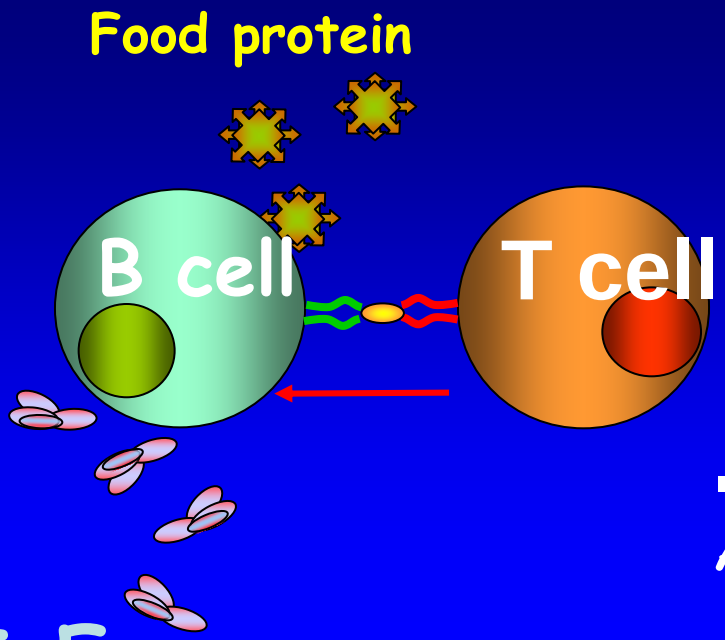
Skin- itchiness, flushing, hives, swelling, eczema

GI- nausea, vomiting, abdominal pain, diarrhea

Respiratory- tightness, runny nose, wheezing, throat closing/swelling

Vascular- dizziness, low blood pressure, heart irregularities, shock

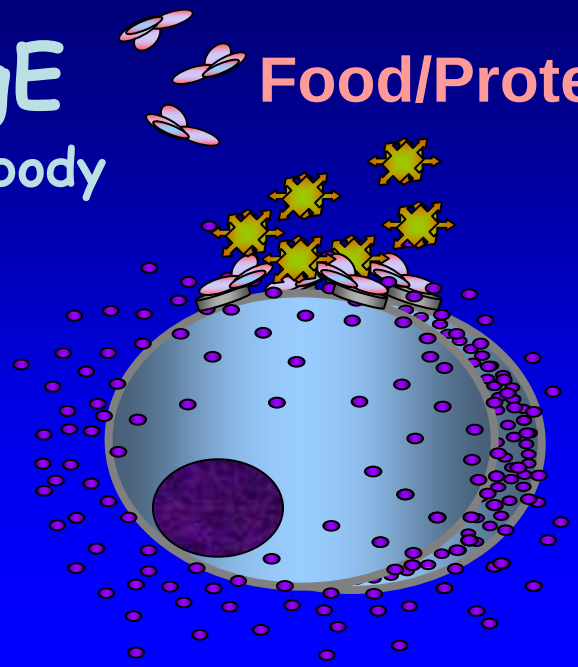
- Subjective



Sensitization

- Few individuals affected - genetic AND environmental factors
  - Exposure, cultural, ??processing
- Diagnose by * food-specific IgE levels
- Risk assessment: Novel food proteins

"Allergenicity safety assessment of foods derived from recombinant DNA plants- Codex Alimentarius, 2003"



Food protein

•IgE independent ~20%

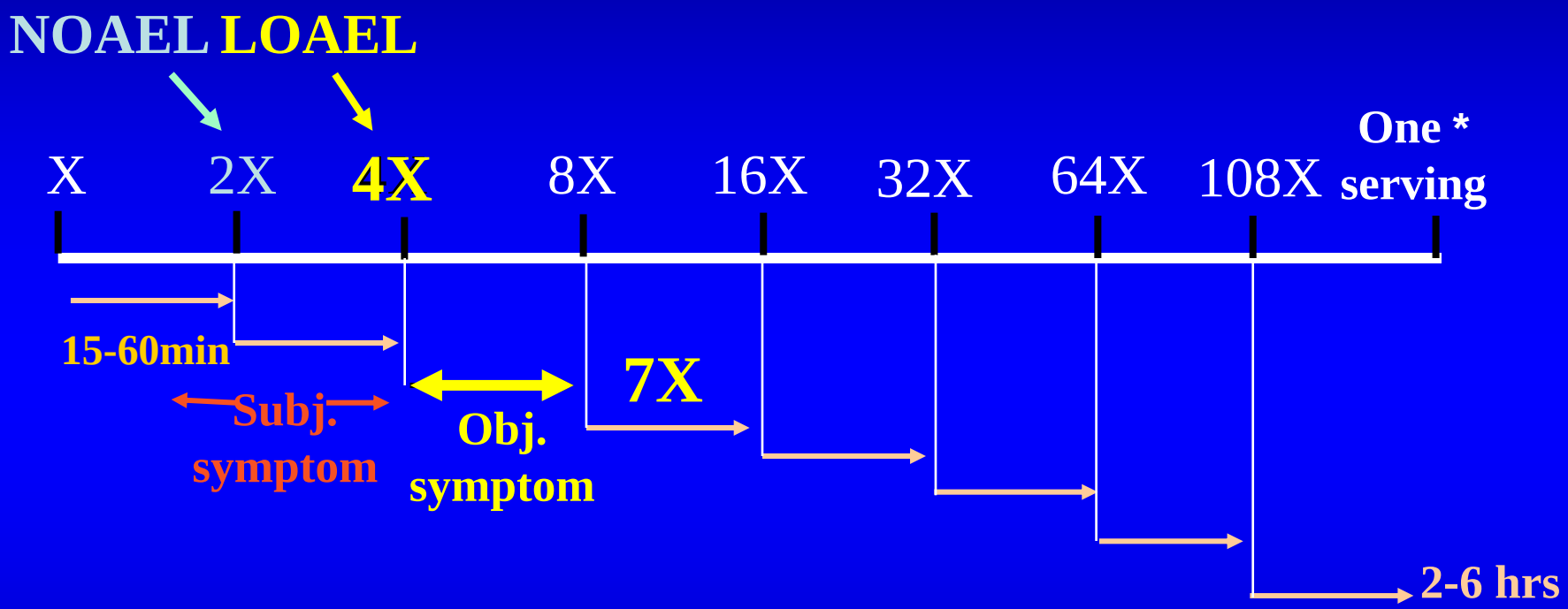
Elicitation/ Reactivity

- Dose-dependent release of mediators, cytokines (Amplification mechanism)
  - Rapidly progresses in severity
- Varies according to allergen type/ bioavailability / meal
  - GI absorption, alcohol use
  - Food matrix, exercise
- Specific IgE levels – poor predictors
- Genetics/ host sensitivity to mediators
- Risk assessment: Allergen "Thresholds"
  - Safe exposure dose
  - Biological end points?

Biological end point

- No validated animal models
- No good serum marker for predicting reactivity and/or severity
- Food challenge ⇒ eliciting dose
  - Double-blinded placebo-controlled (DBPC) food challenge in humans
  - Real-life exposure
- Reaction severity considerations

Food Challenge – typical protocol



- Dose escalation of divided doses in food vehicle (w/ placebos) to final target dose*
  - Starting dose (X) varies (usually mg doses)
  - Time interval varies (15-60 min)
  - Usually 2 to 10-fold (X) dose increments over 2-6 hrs
- Stop after objective sign; some also record subjective symptoms
- Report eliciting dose - discrete (4X) and/or cumulative (7X) – interpreted as Lowest Observed Adverse Effect Level (LOAEL); prior dose is No Observed….(NOAEL)

Food Challenge – data gaps

- Purpose mainly for diagnosis not for minimal eliciting dose determinations
  - Many first dose responders – NOAEL rare; ? true LOAEL
- Lack of standardization of allergen doses/ use of different food matrices for challenge
- Selection bias – patients with most severe reactions (anaphylaxis) often excluded.
  - Is the most sensitive population tested?
  - Children vs adults
  - Adolescents and individuals w/ asthma – fatal reactors

Reaction severity end point

- Allergic dose-response severity is on a continuum

Subjective Objective Anaphylaxis Death

- Anaphylaxis poorly defined – many end points possible
  - Early subjective/ objective complaints may be mild/ short-lived or signal something worse
- Symptoms may not be reproducible on subsequent rechallenge
- Potentiating/ mitigating factors for severity
  - Anxiety/stress; medications; asthma
- Do challenges mimic real-life severity exposures?

Conclusion: Food allergen = unique risk

- Allergens are normal constituents in food
- Potentially fatal
- No hazard to a large majority of population ⇒ ? label
- One food ⇒ Multiple allergens
- Complex and unique immune response – two phases (sensitization and elicitation/reactivity)
- Lack of good biological marker(s) for predicting reactivity and/or severity – many end points possible
- Dose-response relationship not well defined
  - Human food challenge data limited
  - Varies among different allergens and meals
  - Wide individual variability in response

Comparison to traditional food safety assessment approaches

Animal feeding models

- Genetic Homogeneity
- One ingredient in food
- Defined endpoints for severity
- NOAEL defined
- Reproducible
- Dose response

Allergen food challenges

- Genetic Heterogeneity
- Multiple allergens in food
- Multiple endpoints; severity not well defined
- LOAEL mainly;rare NOAEL
- May not be reproducible
- Dose distribution