In 1865, chemist Justus von Liebig patented an infant formula made of cow's milk, wheat and malt flour, and potassium bicarbonate.
By 1946, the proportion of newborns exclusively breastfed at hospital discharge was only 38%.

Ads from the 1940s from Nestle and Carnation

By the mid-1960s the typical age at introduction of solids had decreased from 6-7 months to 4-6 weeks.
**Prophylaxis of Allergic Disease in the Newborn**

**Intervention:**
- No cow’s milk during first 6 months
- Mother refrains from eating eggs and cheese

**Studies of Hydrolyzed Formula, 1988 - 1997**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Diet</th>
<th>Effect of diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Eeckhaut et al. 1988 [23]</td>
<td>45</td>
<td>4</td>
<td>p&lt;0.05</td>
<td>CMPA, anaphylaxis</td>
</tr>
<tr>
<td>Chandra and Hazlewood 1985 [34]</td>
<td>269</td>
<td>12</td>
<td>CMPA, anaphylaxis, ACD, eosin, ALT, CMPA-16 H.R. Anaphylaxis ACD, CMPA-16 H.R. Anaphylaxis, H.R. Anaphylaxis, CMPA-16 H.R. Anaphylaxis, CMPA-16 H.R. Anaphylaxis</td>
<td></td>
</tr>
</tbody>
</table>

**Fraudulent data on hydrolyzed formula**


- 1995: An inquiry conducted by Chandra’s former employer, the Memorial University of Newfoundland, concluded that “scientific misconduct has been committed by Dr. Chandra.”
Clinical trial
- 59 intervention and 106 control
- Mothers avoided cow’s milk, egg, and peanut during the last trimester of pregnancy and lactation
- Infants avoided cow’s milk until age 1 (casein hydrolysate supplementation before age 1)
- Egg until 2
- Peanut and fish until 3

Infants at high risk for developing allergy, identified by a strong (biparental; parent, and sibling) family history of allergy may benefit from exclusive breastfeeding or a hypoallergenic formula or possibly a partial hydrolysate formula. Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:

- Breastfeeding mothers should continue breastfeeding for the first year of life or longer. ... Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.

AAP Committee on Nutrition 2000

Despite these recommendations, food allergy rates kept rising:
2008 AAP Guidelines

- At the present time, there is lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Similarly, antigen avoidance during lactation does not prevent atopic disease.

- For infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy. Exclusive breastfeeding for at least 3 months protects against wheezing in early life.

- In studies of infants at high risk of developing atopic disease who are not breastfed exclusively, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in early childhood.

- Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk.

LEAP study

- 640 infants with severe eczema, egg allergy, or both and peanut SPT < 5mm
- Enrolled between 4 and 11 months of age
- Randomized to 2 groups – peanut avoidance or regular peanut consumption
- Final outcome determined by a peanut food challenge at 5 years
- Stratified based on baseline peanut skin test
LEAP Study Design

LEAP Study: Prevalence of Peanut Allergy at Age 5

Preventing Food Allergy Through Early introduction: Remaining Questions

- Duration of Intervention
- Duration of Protection
- Who to treat
- When to intervene
- Which foods
- How much
The LEAP-On Study

- 1303 unselected 3 month olds
- Randomized to exclusive breast feeding to 6 months or introduction of:
  - Peanut
  - Cooked egg
  - Cow’s milk
  - Sesame
  - Whitefish
  - Wheat

No differences were seen for milk, wheat, sesame, or fish
Who to treat (and what went wrong with prior guidelines?)

- We gave broad-sweeping recommendations based on low quality evidence
- Caveats were ignored
- We reasoned from faulty mechanistic theories
- We gave into the pressure to “do something”
- We underestimated the possibility of harm

Summary of Guidelines for the Prevention of Peanut Allergy in the United States

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Infant Criteria</th>
<th>Recommendation</th>
<th>Earliest Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe eczema, egg allergy or both</td>
<td>Strongly consider evaluation by sIgE and/or SPT, and if necessary an oral food challenge; Based on test results, introduce peanut containing foods</td>
<td>4 – 6 months</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate with family preferences and cultural practices</td>
</tr>
</tbody>
</table>
Concerns related to screening:

- 11% of those screened in LEAP study were excluded because of large peanut SPT (>4mm)
  - By 5 years of age 78% were peanut allergic but how many were allergic as infants?
  - Of those randomized, 2.2% failed the baseline challenge
  - All had predominately mild cutaneous symptoms
- 60% of peanut allergic children have no history of egg allergy or severe eczema
  - ~10% of siblings of peanut allergic children have peanut allergy
  - We don’t have good data on those with milder eczema
- Our screening tests are not very good

Koplin JACI 2016, Du Toit JACI 2016

Far more babies (people) are sensitized than allergic to peanut (food) allergens:

- 22% of LEAP participants had positive peanut IgE
  - Remember that only 2.2% failed baseline challenges
  - There was no statistically significant relationship between peanut IgE and failing the baseline challenge
  - Of those with positive peanut IgE, 96% passed the oral food challenge
  - If peanut IgE > 2, 95% passed
  - If peanut IgE > 5, 95% passed
  - If peanut IgE > 15, 92% passed
  - Among the 11 with peanut IgE > 20, 100% passed

SPT may be better, but still not great

- Of those with detectable peanut SPT, 87% passed challenge
  - If SPT > 1mm, 87% passed
  - If SPT > 2mm, 76% passed
  - If SPT > 3mm, 70% passed
  - Remember that study excluded those with SPT more than 4 mm

Other issues with the Guidelines

- How to best define the “at-risk” population
  - Milk allergy never mentioned as a risk factor
- Feasibility and implementation of the guidelines
- At what age should peanut be started?
  - May contradict WHO Guidelines for exclusive breast feeding through 6 months
- The potential for unintended consequences
- What about other foods?

Wood and Burks: JACI Editorial 2017
### Potential for Unintended Consequences

- In a birth cohort study (in Ireland) ~5% of babies had severe eczema or egg allergy (19% had eczema overall).
- From the Editorial:
  - In the United States, even if only babies with severe eczema are screened, this would translate to about 200,000 infants per year for whom screening would be recommended and at least 40,000 who would have a positive peanut IgE based on the LEAP data.
  - The feasibility of guideline implementation may therefore actually be complicated, rather than facilitated, by this approach. Even more importantly, unless these infants with positive IgE testing can access specialty care in a timely manner, they have a true risk of being diagnosed with peanut allergy, unnecessarily avoid peanut, and be placed at higher risk of developing peanut allergy such as those in the avoidance group in the LEAP study.

### Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease

A Systematic Review and Meta-analysis

- There was moderate-certainty evidence from 2 trials (1550 participants) that early peanut introduction at 4 to 11 months was associated with reduced peanut allergy (RR, 0.29; 95%CI, 0.11-0.74; I² = 66%; P = .009). Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases per 1000 population.
- Nine trials studied the effect of egg introduction at 4 to 6 months of age. Of those, five studies with 1915 participants showed moderate-certainty evidence of a lower risk for egg allergy compared with later egg introduction (risk ratio [RR], 0.56; 95% confidence interval [CI], 0.36 - 0.87; P = .009). For a population with a 5.4% incidence of egg allergy, the absolute risk reduction was 24 cases.

### Negative studies of early egg introduction

- Palmer JACI 2013: 86 infants with moderate-to-severe eczema
  - No difference in egg allergy (33% vs. 51%, p=0.11)
  - 31% of those randomized to egg had an allergic reaction on introduction
- Palmer JACI 2016: 420 infants without eczema
  - No difference in egg allergy (7% vs 10%, p=0.2)
  - 6.1% stopped taking powder due to an allergic reaction
- Bellach JACI 2016: 406 infants without egg sensitization
  - No difference in egg allergy (5.6% vs. 2.6%, p=0.24) or sensitization (2.1% vs. 0.6%, p=0.35)
  - Prior to randomization 16 were egg allergic, including 11 with anaphylactic reactions

Other Foods: We do not have good data
Preventing Food Allergy Through Early Introduction: Remaining Questions

- Duration of Intervention
- Duration of Protection
- Who to treat
- When to intervene
- Which foods
- How much

Are there approaches other than early feeding that might prevent food allergy?

- Given the difficulties – and even lack of apparent effect – of early feeding of multiple foods, other approaches would be desirable
- Aggressive control of eczema early in life, based on the dual-exposure hypothesis
- Manipulation of microbial populations (with pre- or probiotics)
- Fish oil
- Vitamin D supplementation (HealthNuts data that infants with vitamin D level ≤50 nmol/L at 12 months had an increased risk of peanut and egg allergies)
- No published studies in these areas showed an effect and none can be considered useful yet clinically
- There is no evidence that maternal dietary restrictions or hypoallergenic milk formulas affect the onset of food allergy

Suitability for Practice

<table>
<thead>
<tr>
<th></th>
<th>Recommended</th>
<th>Not Yet Recommended</th>
<th>No data</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Clear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td></td>
<td>Overall RR: 0.56 (95%CI 0.36-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/5 trials negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety concerns?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk, Wheat, Fish, Sesame</td>
<td>No specific benefit seen in EAT study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy, Tree Nuts</td>
<td>No data from intervention trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin barrier therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>