HYGIENE HYPOTHESIS:
CONCEPT, EVIDENCE & IMPLICATIONS

KHALID COOVADIA
Outline

- The Hygiene Hypothesis
  - Blackley 1900’s
  - Strachan 1990’s
  - ISAAC Studies 2000’s

- Hill Criteria

- Concepts emerging from the HH
  - Older siblings
  - Animal Exposure / farming environment
  - Infections
  - Exposure to Microbes / endotoxin
  - Antibiotics
  - Gut Flora
  - Immunizations & Vaccines
  - Lifestyle Factors
    - Childhood nutrition / maternal breastfeeding
    - Obesity / physical activity
    - Vitamin D
    - Pollution
    - Medication

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Charles Blackley 1900’s

- Anecdotally – association of affluence with allergy dates back to the 19th century
- CB 1st described that Hay Fever was caused by allergy to grass pollen
  - Described allergy as the disease of urban educated classes
  - Rare among farmers, despite high exposure to pollen

Interestingly,
Several recent studies have shown a reduced prevalence of AR &/or objectively measured atopy in children living on farms vs other children living the same rural areas, but not on farms

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Family size is inversely related to prevalence of childhood atopic diseases

Supported by numerous studies which showed that atopy, AR, and AD were inversely related to increasing numbers of siblings.

“These observations ... could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally ... Over the past century declining family size, improved household amenities and higher standards of personal cleanliness have reduced opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic disease.”

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1989 Strachan described a lower prevalence of allergic rhinitis in adolescents who had increasing numbers of either older or younger siblings.

He proposed that with improved living conditions and smaller families led to a decrease in infections within the family.

Infections then led to risk of allergy.

Supported by the POSTNATAL IMMUNE DEVIATION theory.
POSTNATAL IMMUNE DEVIATION Theory

- **At birth** – the human immune system is favoured towards a Th$_2$ response and that exposure to infections would allow a gradual shift towards a Th$_1$ mediated response
- The “normal immune response balance”
Counter-Regulatory or Gate Keeper Mechanism

- Over the same time interval of the previous 2-3 decades, the prevalence of both Th\textsubscript{1} & Th\textsubscript{2} diseases increased at the same rate, despite a drop in prevalence of infectious diseases.

- Increase in immune mediated disease was caused by lack of infections – which resulted in a less well developed immune regulatory response – characterized by low levels of IL-10 – which an immunosuppressive cytokine.

- Accounted for the low prevalence of allergy in tropical areas with high rates of parasitic infections
  - High levels of parasites were associated with strong Th\textsubscript{2} immune responses to parasites but with low levels of allergic diseases.
If an environmental change was related to the increase of both allergic and autoimmune diseases, it should satisfy 2 criteria:

1) It must be something that is present throughout the evolution of the mammalian immune system.

2) It must be something that has been progressively depleted from the environment of developed countries during the last 2-3 decades.
Based on the evidence that microbes making up the normal intestinal flora are different in children with and without atopy and also between children growing up in developed countries vs those growing up in developing countries.

This theory was supported by those who explained the increase in allergic conditions among children treated with antibiotics.
Recently there has been a major shift in disease profiles – both in developing and developed countries. Developed countries are dealing with an epidemic of allergic diseases. Developing countries – with increased levels of urbanization, better access to healthcare, and the effects of “westernization” are now reporting increasing prevalence of allergic diseases.

**WHY ALLERGY?**

**WHY NOW?**

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HH: Mechanism of Action

- $\text{Th}_1$ mediated immune responses are driven by bacterial / viral infections
- $\text{Th}_2$ mediated immune responses are antibody mediated responses – which leads to allergic/autoimmune diseases

- HH: inappropriate stimulation of $\text{Th}_1$ causes upregulation of $\text{Th}_2$ – which then leads to allergic mediated disease
# AB Hill’s Criteria (1965)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Meaning of Criteria</th>
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</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>The cause or exposure to the cause must precede the effect of the outcome. This is the one absolute criterion</td>
</tr>
<tr>
<td>Strength</td>
<td>The should be a strong association typically as measured by a relative risk or odds ratio</td>
</tr>
<tr>
<td>Dose-Response</td>
<td>An increase or decrease in exposure results in an increase or decrease in the disease</td>
</tr>
<tr>
<td>Consistency</td>
<td>The relationship is repeatedly observed by different persons, in different places, under different circumstances</td>
</tr>
<tr>
<td>Biologic plausibility</td>
<td>The relationship makes sense in light of current biological knowledge</td>
</tr>
<tr>
<td>Specificity</td>
<td>Exposure to the factor on interest only leads to one effect. This is the weakest of the criteria</td>
</tr>
<tr>
<td>Analogy</td>
<td>Cause and effect relationships have already been established for similar exposures and diseases or for experimental or animal models of the disease</td>
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Older Siblings

- Strachan – inverse relationship between the number of siblings in a family and the incidence of AR
- Older siblings seemed to have a greater effect than younger siblings
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>Older children expose younger children to infections / unhygienic household</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Increasing no. of older siblings decreased incidence of AR</td>
</tr>
<tr>
<td>Consistency</td>
<td>Reproduced in many studies</td>
</tr>
<tr>
<td>Biologically plausible</td>
<td>If more siblings = more infections <em>therefore</em> more infections cause a shift in immune system</td>
</tr>
<tr>
<td>Analogy</td>
<td>Conflicting literature Relationship between older siblings and a decrease in other immune related diseases (Type 1 DM) – showed Type1DM is less common in families with multiple children</td>
</tr>
</tbody>
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Animal Exposure

- **Theory**: animal exposure increases exposure to various bacterial products such as endotoxin & glucans – thereby affecting the development of the immune system.

- Braun-Fahrlander et al. demonstrated that children living on farms and exposed to livestock were at lower risk of developing allergic conditions than other children living in the same rural towns, but not exposed to livestock.
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<tr>
<td>Strength</td>
<td>Odds ratio 0.1-0.3 (risk of allergy reduced by 70-90%)</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Studies show a relationship between level of endotoxin exposure and reduction of risk of allergy</td>
</tr>
<tr>
<td>Consistency</td>
<td>Various studies have replicated B-F’s findings</td>
</tr>
<tr>
<td>Biologic Plausibility</td>
<td>Potent effects of endotoxin on the immune system well documented in laboratory &amp; epidemiological studies</td>
</tr>
<tr>
<td>Specificity</td>
<td>Endotoxin exposure is related to atopic conditions (AR/Allergic asthma) but not to non-allergic wheeze.</td>
</tr>
</tbody>
</table>
What about Pets?

- Early allergy exposure leads to IgE mediated sensitization – the earlier and more intense the exposure, the greater the risk of allergic disease.
  - Various birth cohorts examining the relationship between pets exposure and the development of allergies have been studied.

- **Dogs were protective against allergy**
- **Cat exposure increases risk of allergy**
  - (Modified Th2 response to cat allergen)

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<table>
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| Temporality         | Studies uniformly examine early pet exposure in the home and the development of allergic disease later on in life  
Show a 50% reduction in risk of allergic disease! |
| Dose – response     | These results have not been re-producable  
• 1 study showed a much stronger effect of exposure of 2 or more pets vs 1 pet only (not repeated in other studies)  
• Few studies have shown a direct link between pet allergen concentrations in the home and a reduced risk of allergy. |
| Biological plausibility | Pet exposure in the home exposes children to endotoxin – thereby exerting a protective effect on these children |
| Specificity         | Some studies show that dog exposure is protective whilst cat exposure isn’t……  
One theory is that high levels of cat exposure leads to a modified Th2 response to cat allergy |
Urbanization → “Westernization”

- 1990’s International Study of Asthma & Allergy in Childhood (ISAAC)
  - 463,801 children studied
  - 155 centers
  - 56 countries

- Reported increased prevalence of asthma, AR and AD in developed countries vs. developing countries

- 20 – 60 fold differences between centers
Urumqui < Beijing < Hong Kong

- Comparable ethnic backgrounds
- Different environmental exposures
- Hong Kong children = highest prevalence of asthma
- Beijing > Urumqui
- Represent the global trend towards “westernization” and increase prevalence of allergy

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East vs West (Post Cold War Studies)

- East European ISAAC studies
  - Significantly lower rates of AR / Nasal allergies / atopy measured by SPT’s or sIgE
  - Wheeze (13-14 yrs)
    - Sweden/Finland = 11.2% - 19.7%
    - Estonia / Latvia / Poland = 2.6% - 5.9%

- 2003-06  East vs West Germany
  - 17 641 children aged 1-17 studied for asthma, allergic illnesses and atopy
  - NO differences in prevalence
  - ? Dramatic decrease in family size in former Eastern Germany
  - ? Changes in dietary habits
  - ? Changes in indoor exposures (double glazed windows, heaters etc)

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Bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children


- 1457 children aged 10-14 years
- Rural Transkei, Peri-Urban CT, Suburban CT
- Study Method: Questionnaire
- 418 – Histamine Challenges
- 492 – SPT’s conducted

Harris A. Steinman¹, Hilton Donson¹, Michelle Kawalski¹, Ann Toerien² and Paul C. Potter¹
¹Allergology Unit, Groote Schuur Hospital and ²Red Cross Children’s Hospital, Rondebosch, South Africa

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Schools = comprises results from the other "white" schools in various suburbs of Cape Town

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Challenge to HH & Urbanization???

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Infections / Microbes

- Viral Respiratory Infections
- Alteration of GIT flora
- Parasitic infections

- Others:
  - TB infection / BCG vaccination have Th1 promoting properties
  - Role of Chlamydia / Mycoplasma exposure – causing asthma
  - Does RSV infection early in life pre-dispose us to developing asthma later on in life?
  - Matricardi et al. (USA) described that detectable antibodies to Hep A, Toxoplasma Gondii & HSV 1 were assoc. with lower risks of developing asthma & AR (all are acquired via the O-F Route)

"Indeed, we found that infections transmitted by contaminated food and the orofecal route were inversely related -in a dose-dependent manner--to atopy and respiratory allergies,"

- Paolo M. Matricardi, MD, (lead study author)

- Children drinking non-pasteurized milk were shown to have reduced risk of developing allergic disease (large European Study)

- Gale – based on experimental data performed on mice (showed a decrease in development of Type 1 DM) if exposed to pinworm. He postulated that this may have an effect on allergic disease – as the incidence of pinworm infestation only declined in the past few decades.

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Large Meta-analysis (Marra F. et al in Chest 2006) reviewed 4 prospective & 4 retrospective studies comparing the incidence of asthma to exposure to antibiotics.

- Of the 12,082 children reviewed – 1,817 had asthma.
- They also described a dose-response relationship – more exposure to antibiotics was assoc. with greater chance of developing asthma.

- Results may be biased by the low statistical power of the prospective studies.
- Weakness: Perhaps antibiotics were given for symptoms which preceded asthma?
Gut Flora

- Intestinal micro-flora differ from infants in developed and developing countries

- Alterations in GIT Flora due to antibiotic use may be the explanation b/w early antibiotic exposure & the development of atopy.

- More research is required to validate these theories.
Immunization

- Immunization programs = decreased infections
- \( \text{Th}_1 \rightarrow \text{Th}_2 \) Immunity?

Currently – little evidence to support that immunization to common illness contributes to development of asthma

**But**

Prior infections with common illnesses (previously prevented by vaccines) increased the risk of allergic disease.

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Lifestyle Factors

- **Maternal diet & Childhood nutrition**
  - Intake of fish (omega 3 fatty acids) – protective for eczema
  - Margarine – increases risk of allergy
  - Salt Hypothesis (1987) – stated that a possible cause of the asthma epidemic was due to increased salt intake.
    - Further studies showed no clinical association between increased salt intake and asthma (metacholine challenge).

- **Obesity & lack of exercise**
  - Adipose tissue produces pro-inflammatory Th2 cytokines – which may contribute to increased prevalence of asthma
  - Is there a link between lack of exercise and asthma?
    - Large European Cohort: Physical activity has been shown to be protective in the development of asthma

- **Vitamin D**
  - Prevalence of asthma & allergic diseases appear to be highest, the further away from the equator

- **Stress**

- **Pollution**
  - Indoor pollution (East vs West Germany)

- **Medication – Aspirin**
  - 1970’s reduction in use of Aspirin in children due to Reye’s syndrome
  - Aspirin inhibits cyclooxygenase 2 – promotes Th2 in PGE2 – may increase risk of allergy

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The epidemiology of allergic diseases is complex and ever evolving. Its causes are multi-factorial – mainly between genetic and environmental factors. There are large geographical differences in the prevalence of allergic diseases. Lifestyle plays an important role in determining the prevalence of allergic diseases.
Dear World
Please don’t FORGET about us
From: Children of Somalia

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