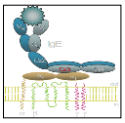

The IgE 50 years' celebration in Stockholm
6th of October 2017.

Part I: History and epidemiology

Epidemiology; past and present

Stephen T Holgate
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Henry Hyde Salter
(1823-71)
On asthma: Its Pathology and Treatment, 1860

Charles Harrison Blackley
(1820-1900)
Experimental Researches on the Causes and Nature of Catarrhus aestiuus, 1873

Otto Carl Prausnitz
(1876-1963)

Heinz Küstner
(1897-1963)

Prausnitz C, Küstner H. Studien iibu die Heberernpfindlickeit. Zbl Bakt Abt I Orig 1921; 86: 160-9

Lausanne 1968

S Gunnar O Johansson

Alfred William Frankland

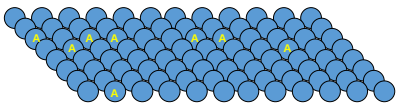
Harry Morrow-Brown

Treatment of chronic asthma with prednisolone: significance of eosinophils in the sputum
Morrow Brown H: Lancet. 1958: 2; 1245-7

Overwhelming evidence that atopy is among the strongest driver of asthma in childhood

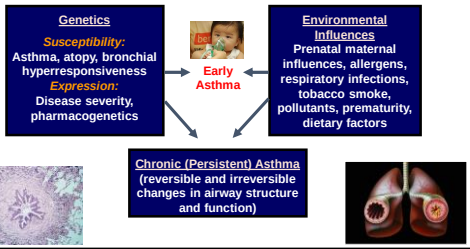
1. Clifford RD, Pugsley A, Radford M, **Holgate ST**. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. Arch Dis Child. 1987; 62: 66-73.
2. Clifford RD, Howell JB, Radford M, **Holgate ST**. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. Arch Dis Child. 1989; 64: 1133-9.
3. Clifford RD, Radford M, Howell JB, **Holgate ST**. Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren. Arch Dis Child. 1989; 64: 1126-32.
4. Sporik R, **Holgate ST**, Cogswell JJ. Natural history of asthma in childhood--a birth cohort study. Arch Dis Child. 1991; 66: 1050-3.
5. Clough JB, Williams JD, **Holgate ST**. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough and wheeze. A 12-month longitudinal study Am Rev Respir Dis. 1991; 143: 755-60.
6. Corne J, Smith S, Schreiber J, **Holgate ST**. Prevalence of atopy in asthma. Lancet. 1994; 344: 344-5.
7. Rhodes HL, Sporik R, Thomas P, **Holgate ST**, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. J Allergy Clin Immunol. 2001;108: 720-5.
8. Rhodes HL, Thomas P, Sporik R, **Holgate ST**, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. Am J Respir Crit Care Med. 2002; 165: 176-80.

What determines the organ expression of the atopic trait in diseases such as asthma?



Is there something about the type of atopy that involves the airways to lead to asthma?

Gene-environment interactions in the development of asthma



Genome-wide prediction of childhood asthma and related phenotypes in a longitudinal birth cohort
Spycher BD et al. J Allergy Clin Immunol. 2012; 130: 503-9

ORMDL3 is an inducible lung epithelial gene regulating metalloproteases, chemokines, OAS, and ATF6.
Miller M et al. Proc Natl Acad Sci U S A. 2012; 109:16648-53.

Transfection of ORMDL3 in human bronchial epithelial cells mobilises activating transcription factor 6 (ATF6), an unfolded protein response (UPR) pathway, implicated in tissue stress and remodelling.

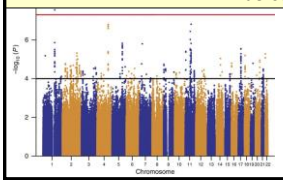
However, environmental exposures are critical for the development of atopy characterised by allergen-specific IgE especially to aero- and food-allergens

Chromosome

Meta-analysis identifies seven susceptibility loci involved in the atopic march.
Marenholz I et al. Nat Commun. 2015 Nov 6;6: 8804

Eczema often precedes the development of asthma in the 'atopic march'. Genetcs - multi-stage GWAS on infantile eczema followed by childhood asthma in 12 populations of 2,428 cases and 17,034 controls.

However, environmental exposures are critical for the development of atopy characterised by allergen-specific IgE especially to aeroallergens



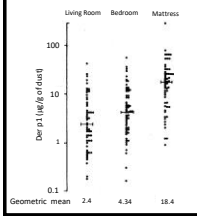
chromosome 12q21.3 (OR 1.58; P=5.3 × 10^{-9}).

- Additional susceptibility loci identified at genome-wide significance are FLG (1q21.3), IL4/KIF3A (5q31.1), AP5B1/OVOL1 (11q13.1), C11orf30/LRRC32 (11q13.5) and IKZF3 (17q21).

Predominantly eczema loci increase the risk for the atopic march. Eczema may play an important role in the development of asthma after eczema - ?allergen sensitisation through the skin.

Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study in genetically at risk children; 1979-89.
Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. N Engl J Med. 1990; 323: 502-7.

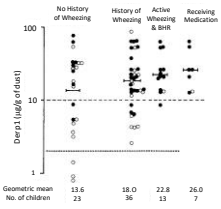
Levels of the House-Dust Mite Antigen, *Der p* I, in Dust Collected from Various Sites in the Homes of 59 Children in 1978.




Tom Platts-Mills


Richard Sporik

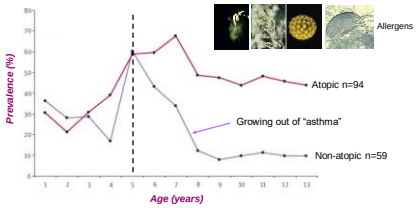
Relation between the Highest Concentration of *Der p* I Measured in House Dust in 1978 and the Four Clinical Groups in 1989.




Erika von Mutius

Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study

The presence of atopy predicted the development of childhood asthma, while non-atopics grow out of their wheeze



Illi S et al. Lancet 2006

House dust mites proliferate in damp "sealed" homes: are they responsible for the rising asthma trends in asthma?


Anne Woolcock

- But what are those environmental factors?
- Contrary to expectations draconian allergen reduction strategies failed to impact on either the origins of asthma in high risk children or established asthma!
- By reducing dust mite exposure, are we reducing other critical elements of exposure in the environment?

Bronchial mucosal manifestations of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic non-asthmatics and healthy controls
Djukanović R, et al. Eur Respir J. 1992; 5: 538-44

- Endobronchial biopsies in 13 symptomatic atopic asthmatics, 10 atopic nonasthmatics and 7 normals.
- Numbers of mast cells in submucosa no different between groups, but e.m. showed mast cell degranulation, although less marked in atopic non-asthmatics, was a feature of atopy in general.
- Numbers of eosinophils greatest in asthmatics, low or absent in normals and intermediate in atopic non-asthmatics.
- Subepithelial basement membrane thickness on e.m. thickest in asthmatics, intermediate in atopic non-asthmatics and thinnest in normals.


Ratko Djukanovic

Airways eosinophilia, degranulation of eosinophils and mast cells and increased subepithelial collagen are a feature of atopy in general and that the degree of change may determine the clinical expression of this immune disorder.

What happens to airway inflammation and remodelling as adolescents "grow out" of asthma?

The Isle of Wight Birth Cohort (1989/90 Study)

Children born on the Isle of Wight between 1st January 1989 and 28th February 1990 were recruited at birth to allow the monitoring of the natural history of asthma and allergies.

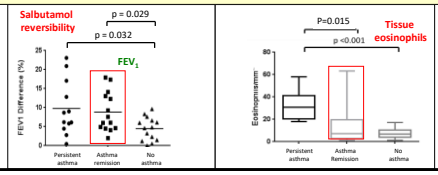
The children were followed up at one, two, four, 10 and 18 years of age.

Asthma transition from age 10-18 years

Asthma changes between age 10 and 18 years

	Number	Total	Percent
Persistent	125	181 (asthma at age 10 yrs.)	69.06%
Remission	56	181 (asthma at age 10 yrs.)	30.94%
New onset	56	198 (asthma ta age 18 yrs.)	28.28%

While early allergen sensitisation is important in predisposing to asthma, what are the features of this?



Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study

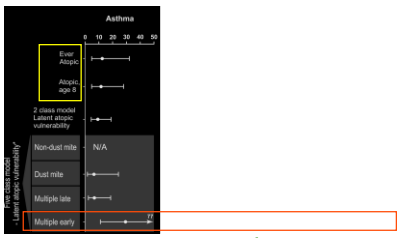
Simpson A et al. Am J Respir Crit Care Med. 2010; 181: 1200-6

Adnan Custovic

- To redefine the atopic phenotype by identifying latent structure within a complex dataset, taking into account the timing and type of sensitization to specific allergens, and relating these novel phenotypes to asthma.
- In a population-based birth cohort in which multiple skin and IgE tests have been taken throughout childhood, machine learning approach used to cluster children into multiple atopic classes in an unsupervised way.
- Reviews at age 1, 3, 5 and 8 years; 1030 children reviewed at age 8 years (87%)
- SPTs and IgE (8 common inhalant & food allergens) measured at each follow-up visit
- Then investigated the relationship between these classes and asthma (symptoms, hospitalisations, lung function and airway reactivity).

Latent Atopic Vulnerability Classes and Asthma

Likelihood of developing asthma age 8 years (odds ratio)

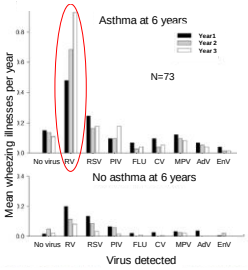


Simpson et al. Am J Respir Crit Care Med. 2010

Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children

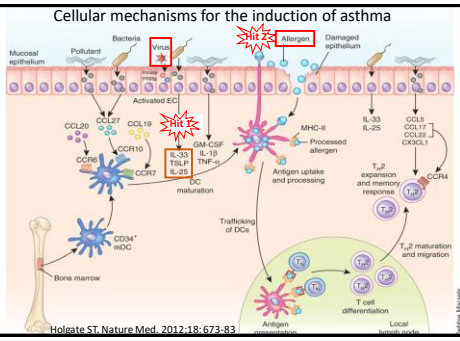
Robert Lemanske

- Define the relationship between specific viral illnesses and early childhood asthma development.
- 259 children were followed prospectively from birth to 6 yrs of age.
- Viral aetiologies were identified in 90% of wheezing illnesses.
- By age 3 yrs, wheezing with rhinovirus "RV" (OR, 25.6) was much more strongly associated with asthma at age 6 years than allergen sensitization (OR, 3.4).
- Nearly 90% (26 of 30) of children who wheezed with "RV" in yr 3 had asthma at 6 yrs.



Jackson DJ. et al. Am J Respir Crit Care Med. 2008

Cellular mechanisms for the induction of asthma



Holgate ST. Nature Med. 2012;18:673-83

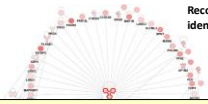
Persistent activation of interlinked Th2-airway epithelial gene networks in sputum-derived 3 cells from aeroallergen-sensitized symptomatic atopic asthmatics

Jones AC et al. bioRxiv preprint first posted online Jul. 13, 2016; doi: http://dx.doi.org/10.1101/063602.

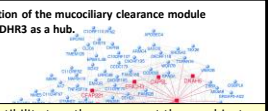
Vast majority of atopics do not develop asthma-related wheeze, despite ongoing exposure to aeroallergens to which they are strongly sensitised, indicating that additional pathogenic mechanism(s) operate in conjunction with Th2 immunity to drive asthma pathogenesis.

- Systems analyses to identify gene networks operative at baseline in sputum-derived RNA from HDM-sensitised subjects with/without wheezing history; identify networks characteristic of the ongoing asthmatic state.
- HDM sensitised-nonwheezers displayed baseline gene expression in sputum including IL-5, IL-13 and CCL17.
- HDM sensitized wheezers showed equivalent expression of these classical Th2-effector genes, but their overall **baseline sputum signatures were more complex, comprising hundreds of Th2-associated and epithelial-associated genes**, networked into two separate co-expression modules:

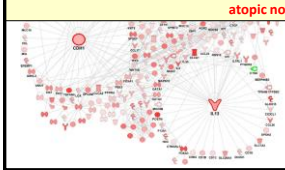
- **The first module was connected by the hubs EGFR, ERBB2, CDH1 and IL-13.**
- **The second module was associated with CDHR3, and contained genes that control mucociliary clearance**.



Reconstruction of the mucociliary clearance module identifies CDHR3 as a hub.



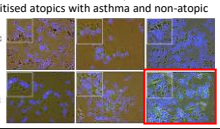
The molecular mechanism(s) that determine susceptibility to asthma amongst these subjects involve **interactions between Th2- and epithelial function-associated genes within a complex co-expression network, which is not operative in equivalently sensitised/exposed atopic non-asthmatics.**



Expression of CDHR3 in bronchial epithelial cells from HDM sensitised atopics with asthma and non-atopic controls

Nonatopic control

Atopic asthmatic



Mechanisms for the induction and consolidation of asthma

Impaired innate immunity — Epithelial "set point" altered

↓

Epithelial cell "injury" — Barrier function breached

↓

Engagement of adaptive immunity — Allergen sensitisation

↓

Inflammation with release of mediators — IgE, mast cell, eosinophil

↓

Ineffective resolution of inflammation — Persistence
(tolerance ↓, apoptosis↓, cytotoxicity↑) — Exacerbation

↓

Initiation of fibrosis/smooth muscle↑ — Modelling

↓

Consolidation of fibrosis/smooth muscle — Remodelling

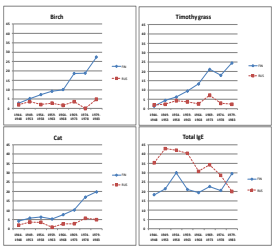
Changing worldwide trends in asthma

- Asthma and related allergic diseases have increased markedly in Western countries over the past 50 years, and this has been attributed to urbanization and associated changes to diet and lifestyle[1].
- The urban-rural gradient in prevalence demonstrated most strongly in children who grow up in environments with a wide range of microbial exposures (e.g. traditional livestock farms or in families who have adopted a more 'naturalistic' diet and lifestyle), who are protected from childhood asthma and atopy in proportion to their level of exposure to bacterial and fungal microbes[2].
- This protective effect against the onset of asthma in children is even more apparent if the microbial exposure (for example, working with animals or drinking unpasteurized milk)[3] occurred throughout the mother's pregnancy[4].

1. Alfvén T. et al. Allergy. 2006 Apr;61(4):414-21. 2. Ege MJ, et al. N Engl J Med. 2011 Feb 24;364(8):701-9.
3. Ege MJ, et al. J Allergy Clin Immunol. 2007 May;119(5):1140-7. 4. Ege MJ, et al. J Allergy Clin Immunol. 2008 Aug;122(2):407-12, 412.e1-4.

The Karelia Allergy Study: younger generations are more allergic in Finland but not in Russia

Tari Haahtela



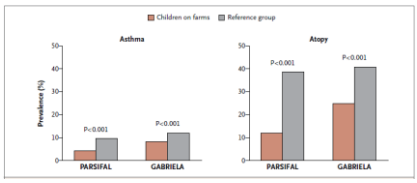
Laatikainen T, et al. Allergy 2011; 66: 886-92.

Bavarian women milking cows and their offspring exposed to a unique inhaled and food environment

Erika von Mutius

Prevalence of asthma and atopy among children living on farms as compared with reference groups

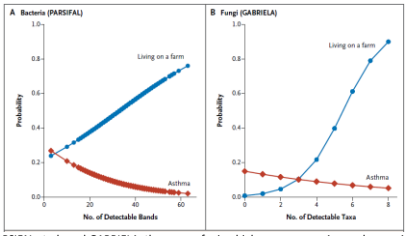
Ege MJ, et al. N Engl J Med. 2011; 364: 701-9



The PARSIFAL study population included 6843 school-age children 6 to 13 years of age, and the GABRIELA study population included 9668 children between 6 and 12 years of age. Calculations of prevalence in GABRIELA were weighted on the basis of the total number of children who were eligible for inclusion in the study (34,491 children).

Relationship between microbial exposure and the probability of asthma

Ege MJ, et al. N Engl J Med. 2011; 364: 701-9.



In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

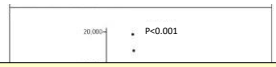
Innate immunity and asthma risk in Amish and Hutterite farm children

Stein MM, et al. N Engl J Med. 2016; 375: 411-21

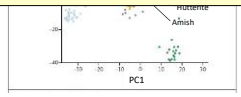
Communal branch of Anabaptists from Austrian province of Tyrol trace their roots to the Radical Reformation of the 16th century

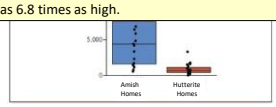
Analysis of genetic association

Endotoxin levels in airborne dust from 10 Amish and 10 Hutterite homes

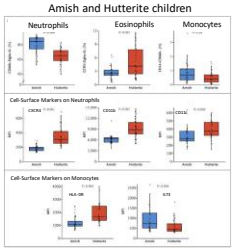


Despite the similar genetic ancestries of Amish and Hutterite children, prevalence of asthma and allergic sensitization was 4 and 6 times as low in the Amish, whereas median endotoxin levels in Amish house dust was 6.8 times as high.





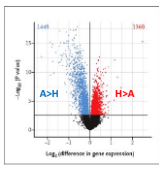
Proportions of peripheral-blood leukocytes and cell-surface-marker phenotypes in Amish and Hutterite children



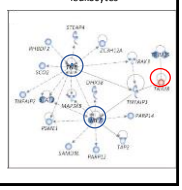
Innate immunity and asthma risk in Amish and Hutterite farm children
Stein MM, et al. N Engl J Med. 2016; 375: 411-21

Gene-Expression profiles in peripheral-blood leukocytes from Amish and Hutterite children

Volcano plot; differences in baseline Gene expression in blood leukocytes from Amish and Hutterite children

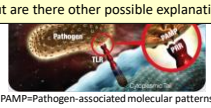


Network of differentially expressed genes in untreated blood leukocytes

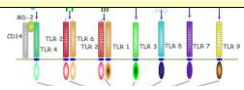


Microbial sensing receptors of the innate immune response

- Scalable triggering of innate immunity, as a principal determinant of allergy, is attractive.
- In different environments, ambient air concentration of the TLR4 agonist, lipopolysaccharide, can vary by as many as 5 logs, with the highest levels being encountered in association with livestock farming and pet ownership.
- But are there other possible explanations?



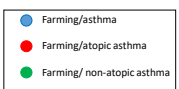
PAMP=Pathogen-associated molecular patterns
PRR= Pathogen recognition receptors

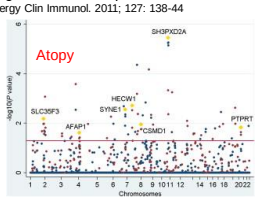


Inflammation in adults, tolerance in babies and infants

Gene-environment interaction for childhood asthma and exposure to farming in Central Europe

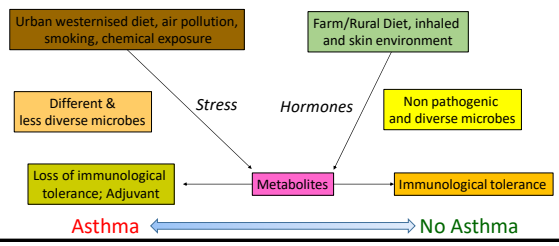
Ege MJ et al. J Allergy Clin Immunol. 2011; 127: 138-44





- The genome-wide interaction study did not reveal any significant interactions with SNPs within genes in the range of interacting allele frequencies from 30% to 70%, for which our study was well powered.
- Among rarer SNPs, 15 genes identified (e.g. glutamate receptor encoded by the "metabotropic 1" gene) with strong interactions for asthma or atopy in relation to farming, contact with cows and straw, or consumption of raw farm milk.

Microbiome and exposome programming of metabolome



Childhood allergies and asthma: New insights on environmental exposures and local immunity at the lung barrier.
Smits HH, et al. Curr Opin Immunol. 2016; 42: 41-7.