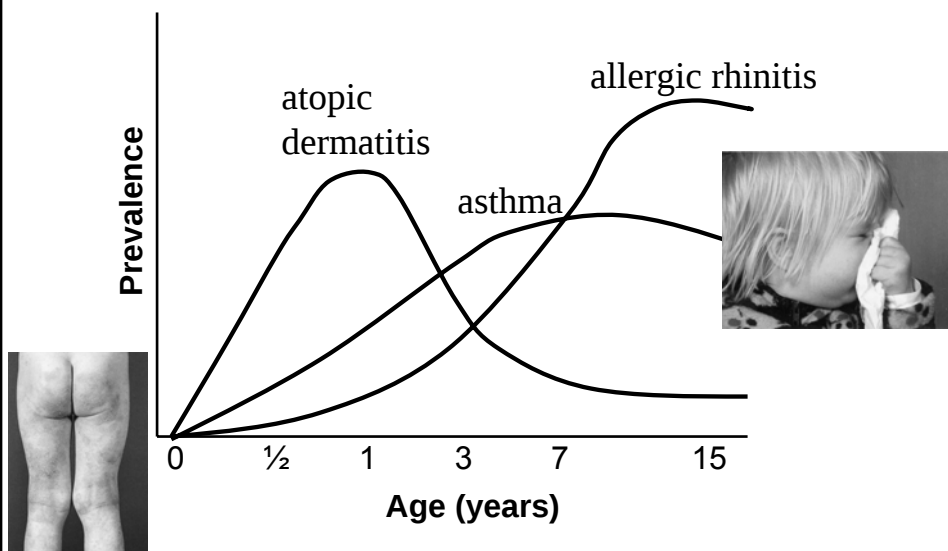


Allergiske og Autoimmune Sygdomme: - epidemiologiske aspekter af hygiejneteorien

Allan Linneberg
Forskningscenter for Forebyggelse og Sundhed
Region Hovedstaden



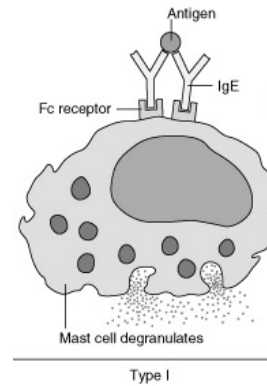
"The allergic march in childhood"



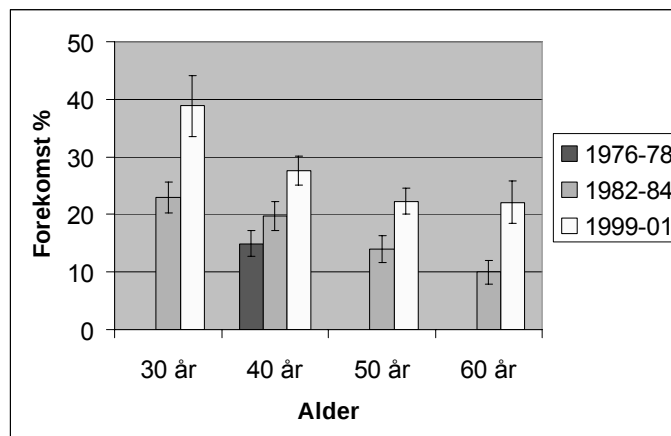
The discovery of IgE

As early as 1919, from a case of transient asthma caused by blood transfusion, the presence in serum of a factor causing allergy was proposed.

Despite intense search, this factor was not identified until 1968, when immunoglobulin E (IgE) was officially recognized by the World Health Organization.

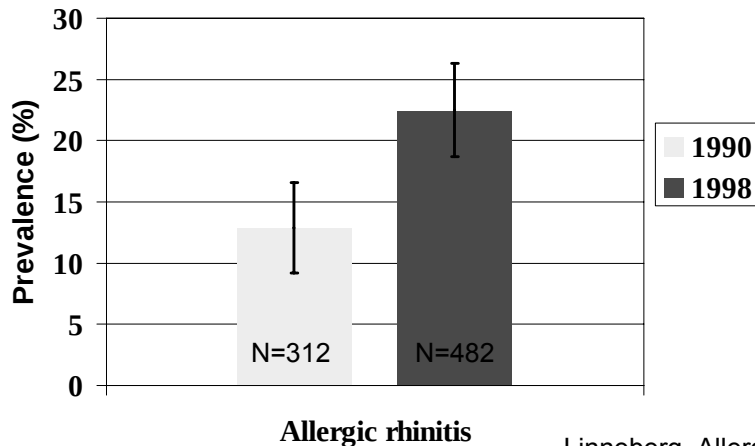


Forekomst af luftvejsallergi (sIgE i blod) i København 1976 til 2001 (n=7.820)



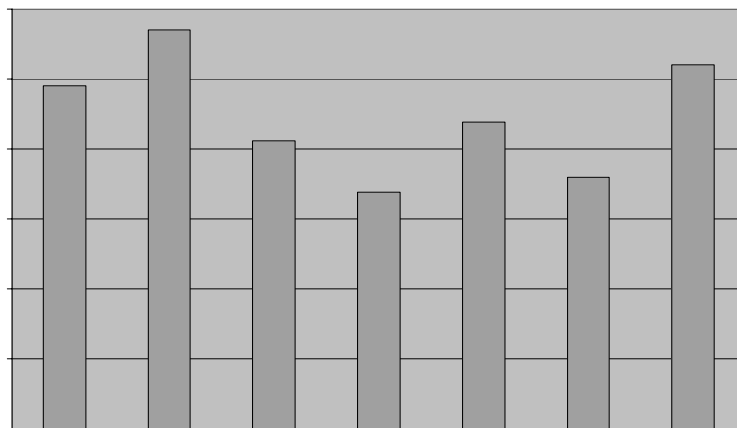
12-month prevalence of allergic rhinitis among 15-41-year-olds in Copenhagen

Allergic rhinitis = combination of relevant symptoms and positive allergy tests (IgE sensitisation against relevant allergens)



Prevalence of allergic rhinitis confirmed by clinical examination in Europe

Median prevalence 22.7%
(52% of these were grass pollen allergic)



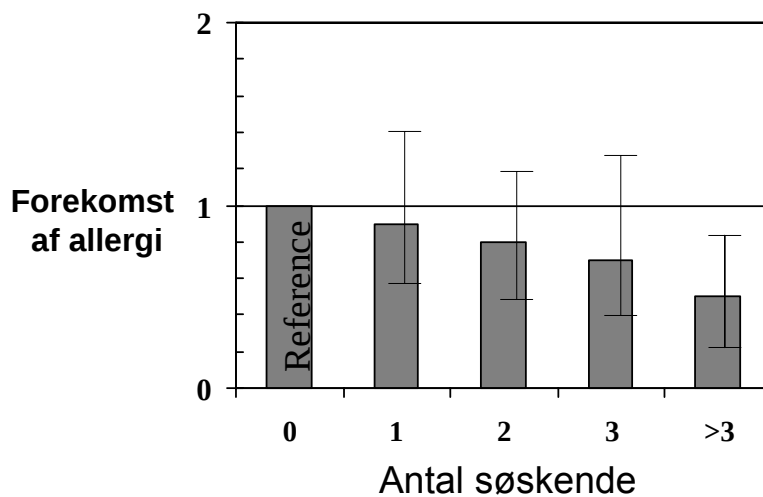
Bauchau, Durham, Eur Respir J 2004

Table 1— Incidence rates of diabetes in Denmark per 100,000 person-years

Age (years)	1970– 1976	1980– 1984	1996– 2000	Annual Increase %	
10–14	22.07	21.27	26.21	0.27	0.11
0–14*	14.03	14.58	19.4	1.23	0.0000
Boys*	14.6	15.9	20.2	1.20	0.0008
Girls*	13.5	13.0	18.7	1.28	0.0009

Svensson, Diabetes Care 2004

Søskende effekten!

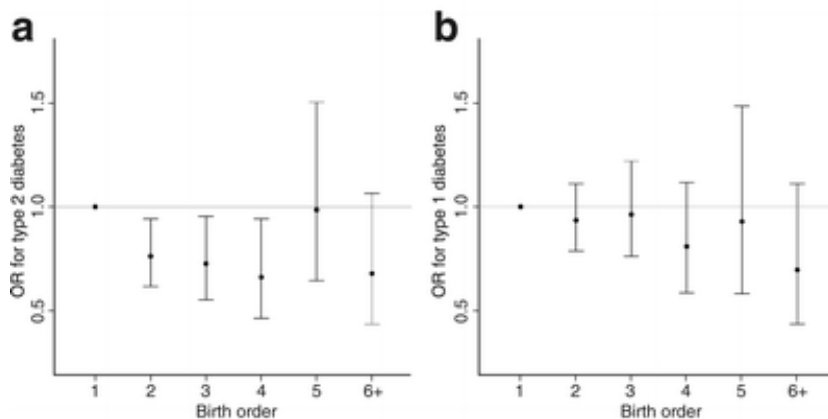


Linneberg, Clin Exp Allergy 2001

The sibling or birth order effect

- Allergy, atopic eczema, and asthma
- Diabetes (type 1 and 2)?
- Preclampsia
- Multiple sclerosis?
- Brystkræft (paritet)

Antal søskende (birth order) og diabetes



Lammi, Diabetologica 2007

The hygiene Hypothesis (as of 1989)

The decrease in allergic disease with increasing number of older siblings could be explained if infections early in life transmitted by unhygienic contact with older siblings were protecting them from allergic disease

David Strachan, BMJ 1989

Mæslinge sagen!

- Shaheen, Lancet 1996: Et lille (ca. 260) studie i Afrika viste lavere forekomst af allergi (priktest) hos personer, der havde haft mæslinger i barndom sammenlignet med personer der var vaccineret og ikke havde haft mæslinger!
- Senere studier viser nok samlet set ingen sammenhæng imellem mæslinge infektion eller vaccination og allergi (fx Paunio, JAMA 2000)

Infektioner og atopisk dermatitis

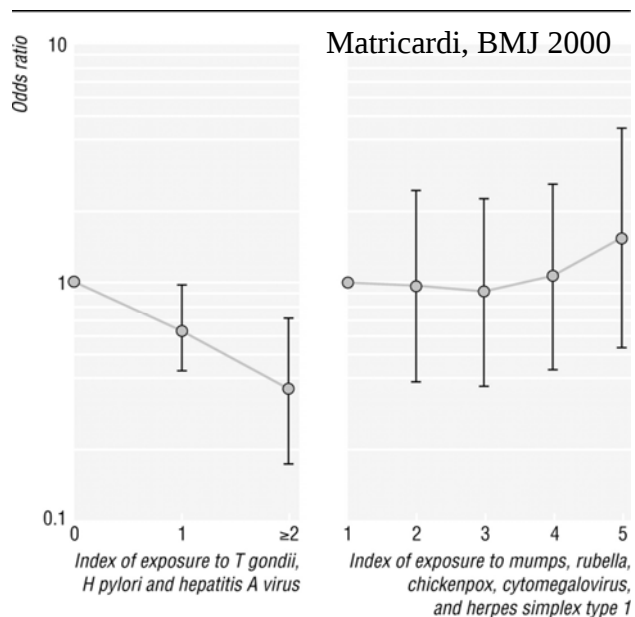
In the Danish National Birth Cohort the risk of atopic dermatitis

- increased with increasing number of infections in early life
- Decreased with increasing number of markers of microbial exposure (farm residence, pet keeping, early daycare)
- Decreased with increasing number of siblings independent of markers of microbial exposure

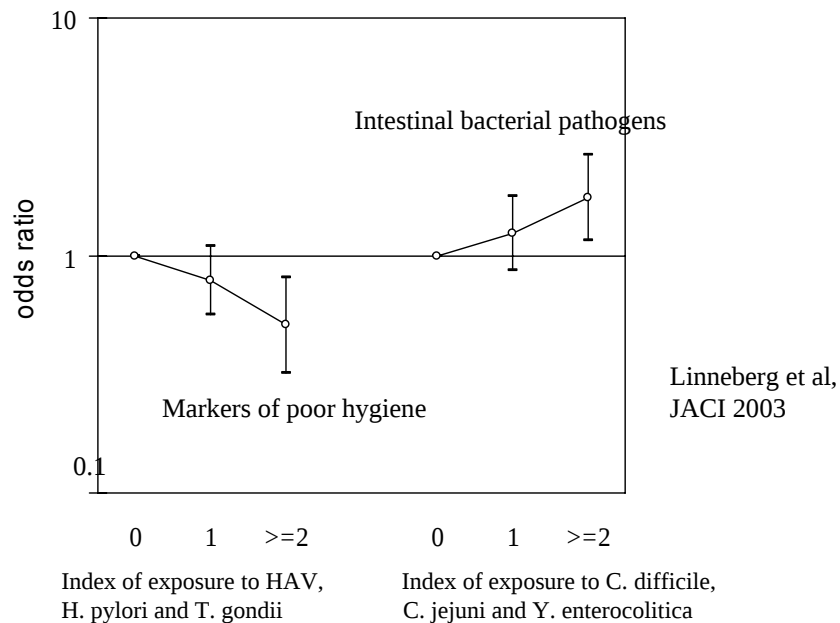
Benn, BMJ 2004

The hygiene hypothesis

Risk of atopy



Allergy and IgG to foodborne microorganisms



Hygiejnehypotesens første revision

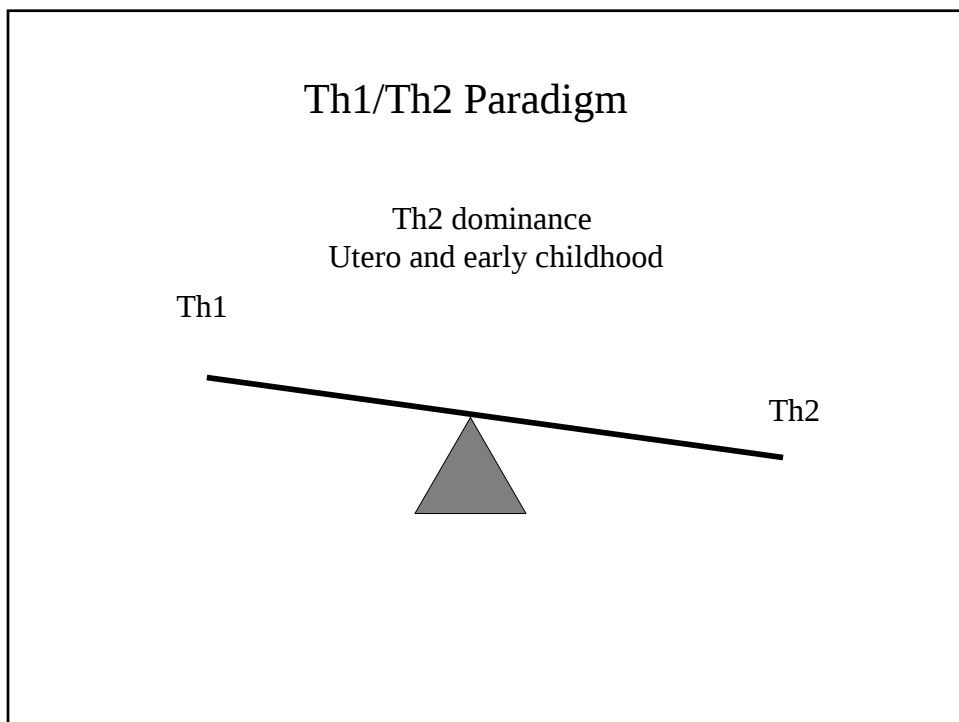
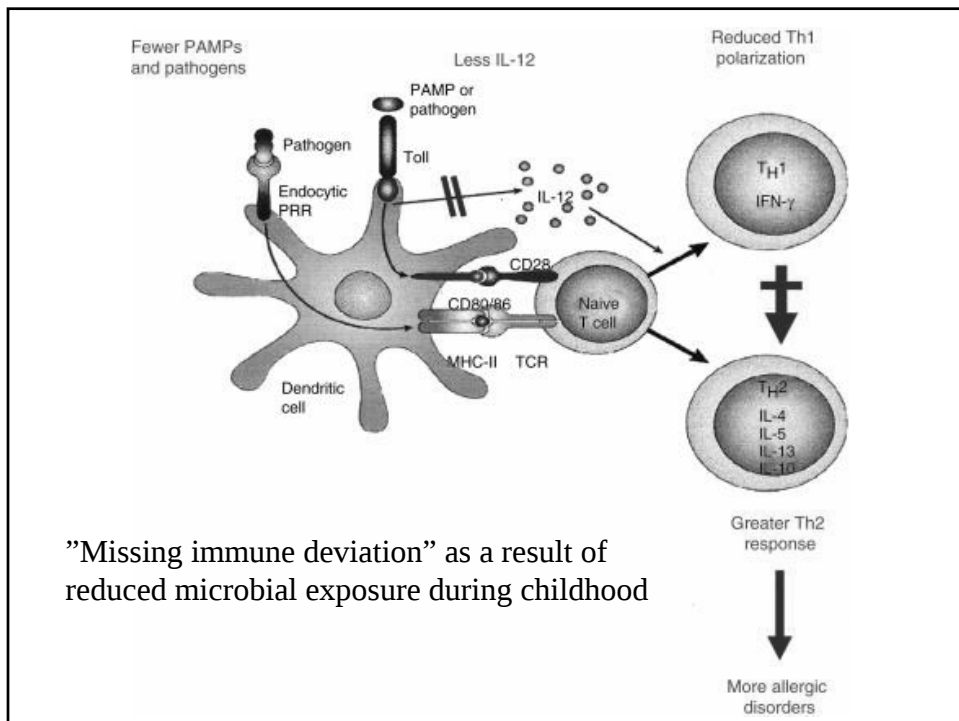
betydningen af tarmfloraen for tolerans og normal immun-udvikling tidligt i livet

- Sammenligninger af Svenske og Estoniske børn har peget på forskelle i mælkesyrebakterier med mulig allergirelation
- Men ikke alle studier kunne senere bekræfte dette.
- Mus med steril tarm kan ikke udvikle tolerans
- Initiale små studier publicerede lovende resultater probiotika som forebyggelse (Kalliomäki, Lancet 2000)
- Efterhånden en del randomiserede studier af intervention/forebyggelse med probiotika. Samlet set er data ikke konklusive (review: Prescott, J Allergy Clin Immunol 2007)

Th1/Th2 Paradigm

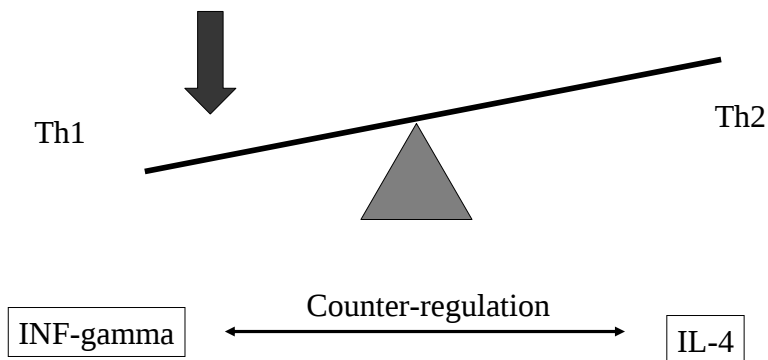
Oversimplified view on possible activities of CD4⁺ T-cell subsets

T-cell subset	Related cytokines	Protective activity	Immunopathology
Th1	INF-gamma	Intracellular bacteria and some viruses	Granulomatous disorders, (some autoimmune disorders, e.g. Crohn's disease)
Th2	IL4, IL5, IL13	Helminths, parasites	Allergic diseases

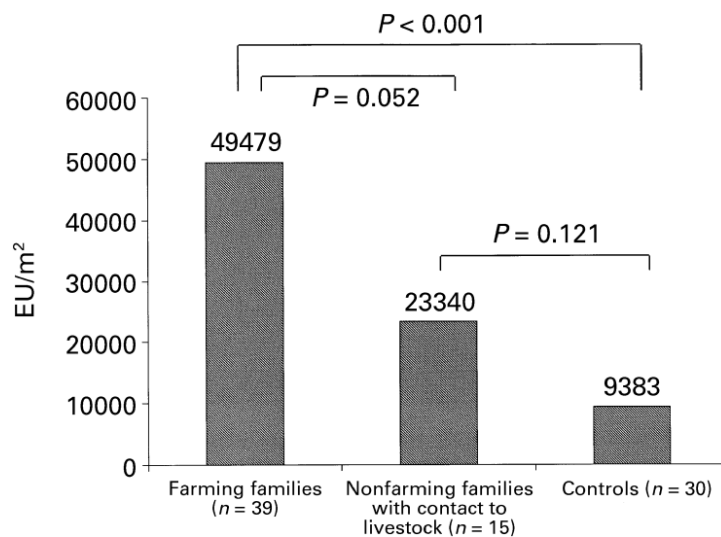


Th1/Th2 Paradigm

Normal Th1 deviation by
pathogen/microbial
Stimulation in early life

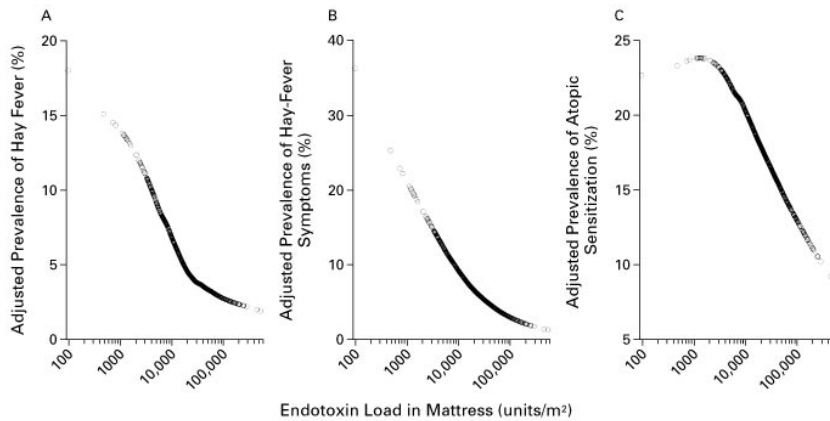


Farm environment and endotoxin



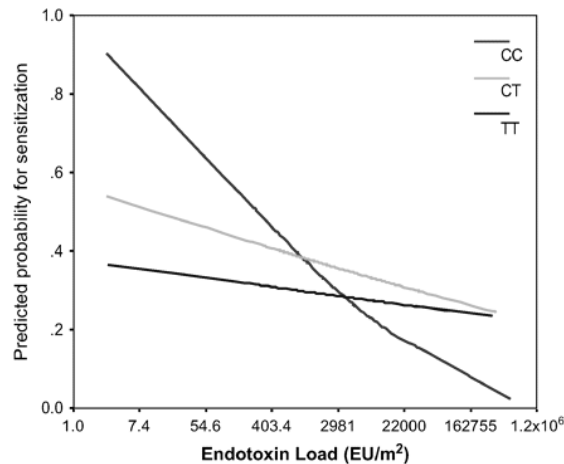
Von Mutius, Clin Exp Allergy 2000

Endotoxin and risk of allergy



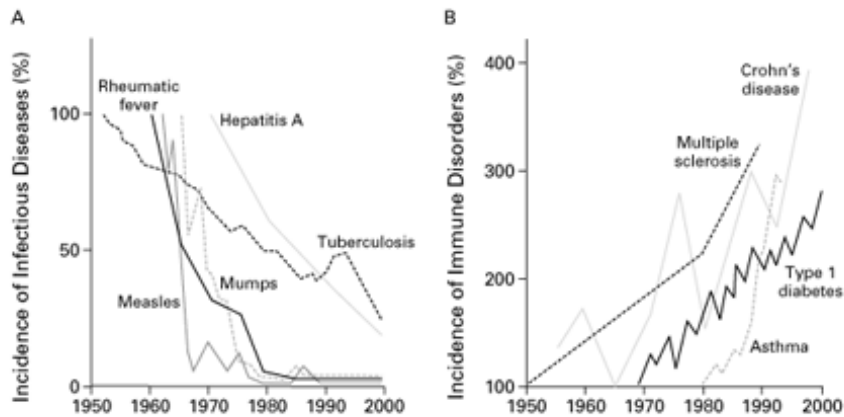
Braun-Fahrlander, N Engl J Med 2002

Fitted predicted probability curves for allergic sensitization at 5 yr of age in relation to environmental endotoxin load in children with CC, CT, and TT genotypes in the promoter region of the CD14 gene (CD14/-159 C to T) derived from the logistic regression analysis



Simpson, AJRCCM 2006

Th1/Th2 deviation or Co-existence of Allergic and Autoimmune diseases

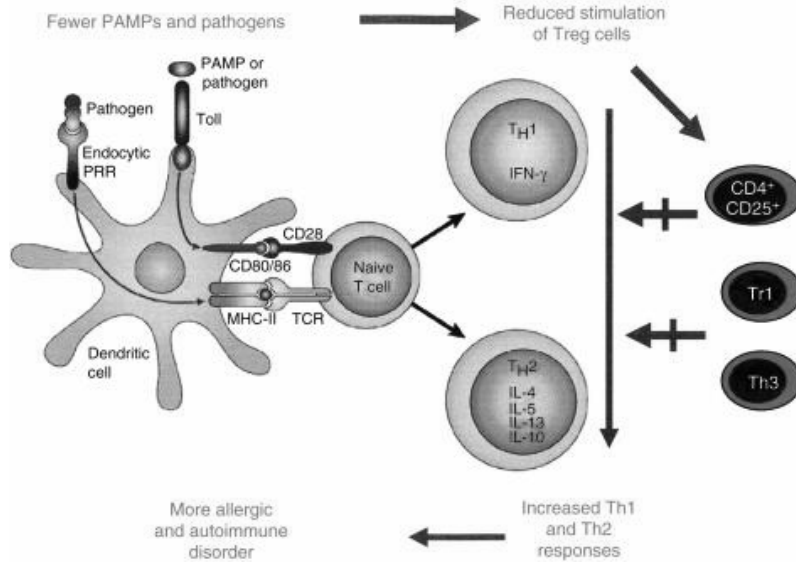


Bach, N Engl J Med 2002

Oversimplified view on possible activities of CD4⁺ T-cell subsets

T-cell subset	Related cytokines	Protective activity	Immunopathology
Th1	INF-gamma	Intracellular bacteria and some viruses	Granulomatous disorders, (some autoimmune disorders, e.g. Crohn's disease)
Th2	IL4, IL5, IL13	Helminths, parasites	Allergic diseases
Th17	IL17	Extracellular bacteria and some fungi	Chronic inflammatory and autoimmune disorders (e.g. rheumatoid arthritis)
Treg	TGF-beta1	Tolerance against self	Autoimmunity

Romagnani, Clin Exp Allergy 2006



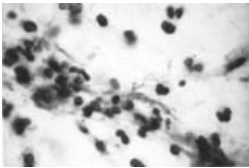
"Reduced immune regulation" as a result of reduced microbial stimulation of Tregs

Historien om BCG vaccination og allergi

- Tuberkulose og BCG vaccination inducerer et stærkt Th1 respons
- Flere studier pegede på, at BCG vaccination og Tuberkulose beskytter imod allergi
- Mange observationelle studier fandt dog ikke sammenhæng
 - Alm, Lancet 1997
- Randomiserede studier med BCG vaccination få og ikke overbevisende
 - Heat-killed BCG in asthmatics showed no effect (Shirtcliffe, Clin Exp Allergy 2004)

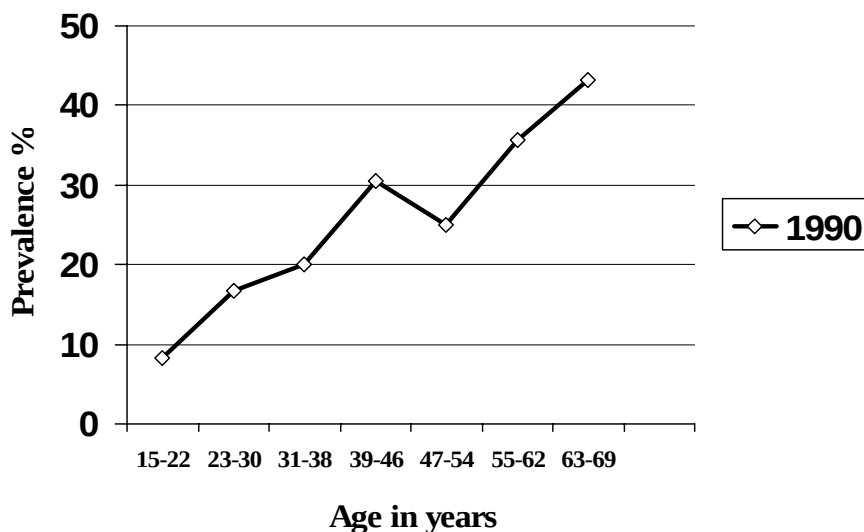
Mykobakterier: "old friends" hypothesis

- Der er mange typer af mykobakterier og med enkelte undtagelser (tuberkulose) er disse ikke pathogene (saprophytære)
- Udsættelsen voldsomt mindsket pga. rent vand og øget hygiejne
- Dyreforsøg har vist at *M. Vaccae* kan inducere tolerans via regulatoriske T celler og ikke Th1 deviation, snarere suppression af både Th1 og 2.
- Randomiserede studier inkonklusive
- Andre "Old friends": Orme, *Helicobacter*, HAV m.m.

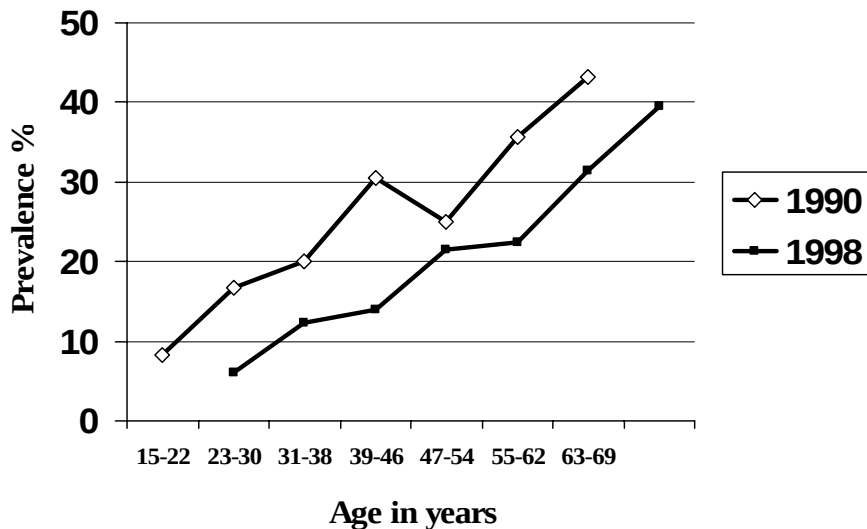


Review: Rook, Immunobiology 2007

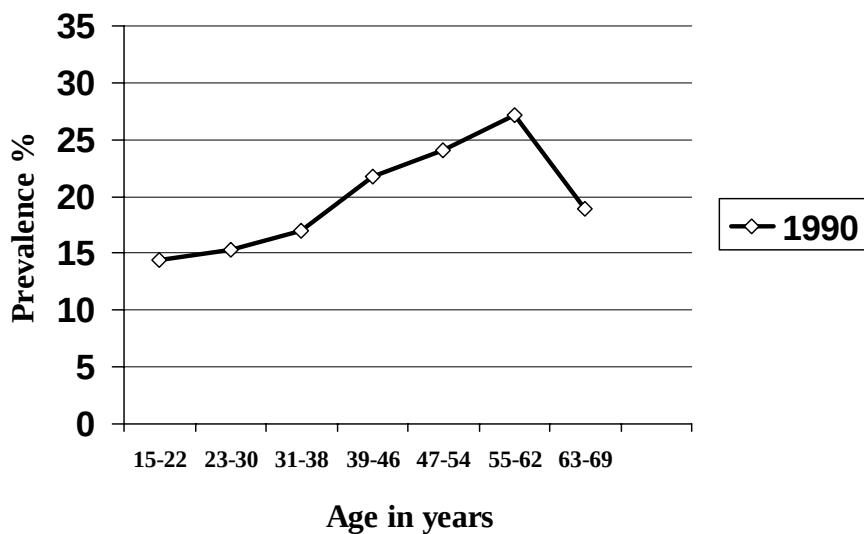
Age-specific changes in the prevalence of IgG Seropositivity against *Helicobacter pylori* in a cohort of Danish adults



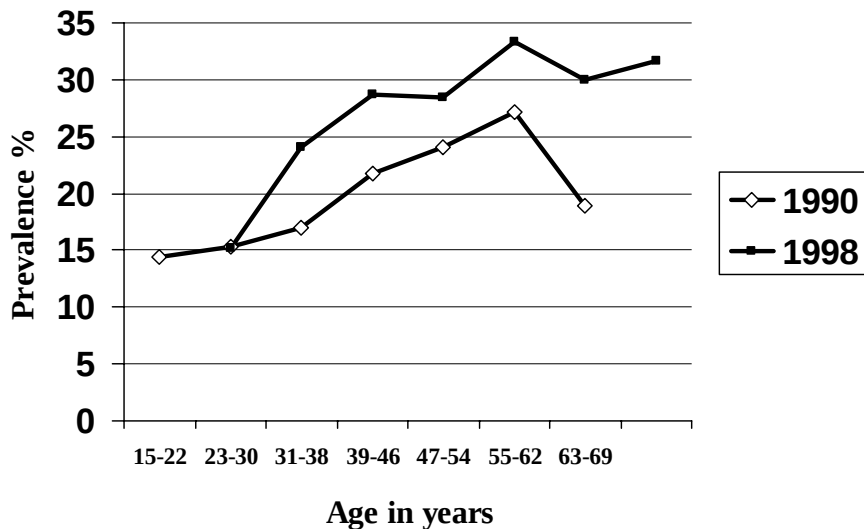
Age-specific changes in the prevalence of IgG Seropositivity
against Helicobacter pylori in a cohort of Danish adults



Age-specific changes in the prevalence of Seropositivity
against Clostridium difficile in a cohort of Danish adults



Age-specific changes in the prevalence of Seropositivity against Clostridium difficile in a cohort of Danish adults



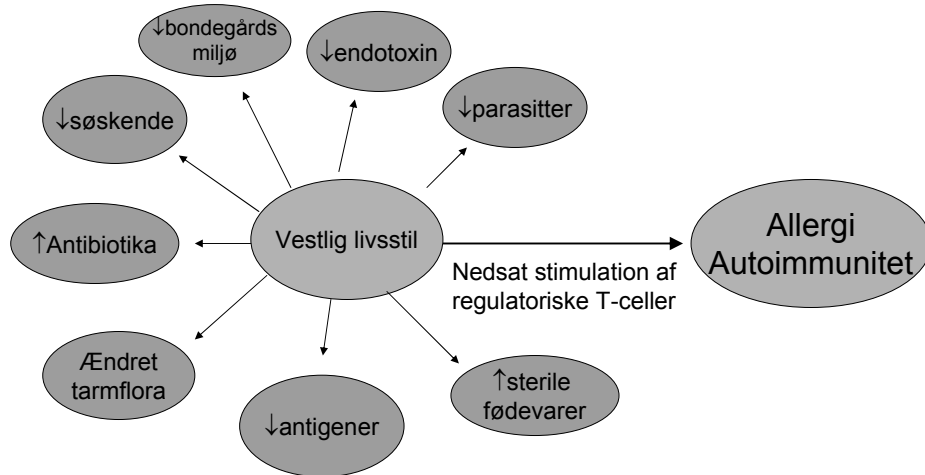
Paradox!

Opståen (eller i hvert fald udløsning) af autoimmune sygdomme synes relateret til infektioner, f.eks.

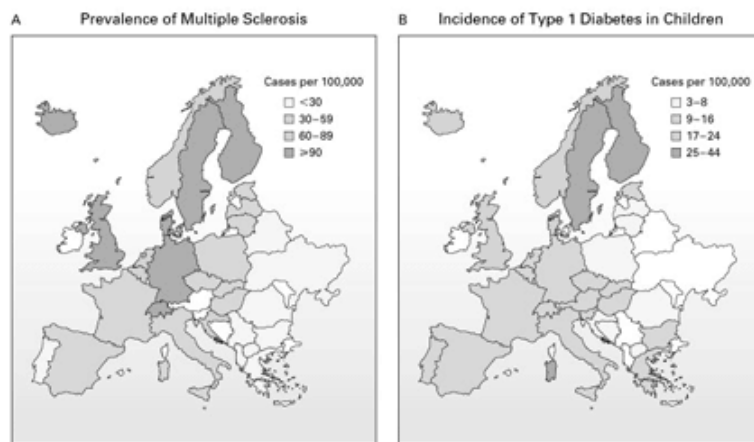
- Guillain-Barré syndrom og Campylobacter
- Sclerose og EBV

Hygiejne hypotesen

Ændringer i det mikrobielle miljø !



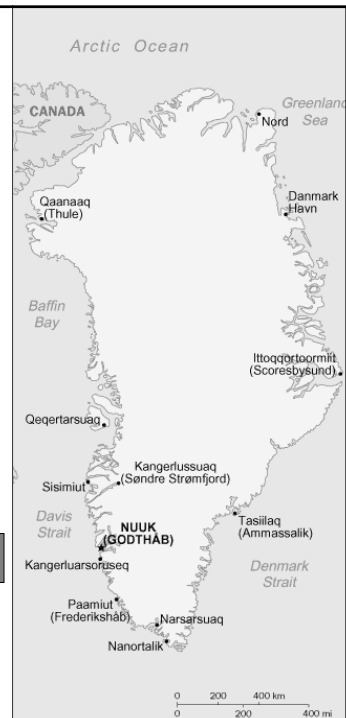
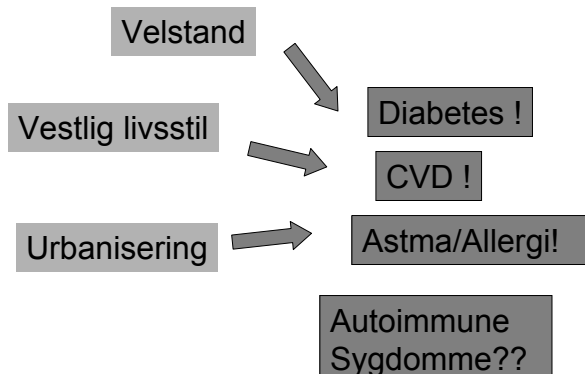
North-South gradient in MS and T1DM



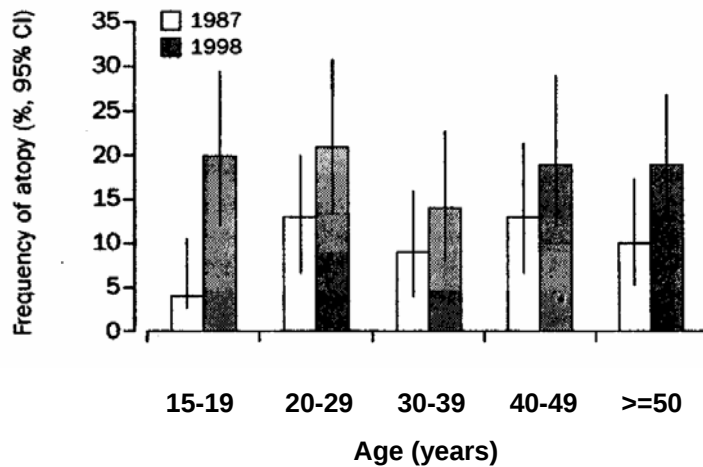
DISCLAIMER:

Det følgende er Allans forslag til revision
af hygiejnehypotesen

Hvad sker når en befolkning
oplever stigende velstand,
urbanisering og vestlig livsstil?



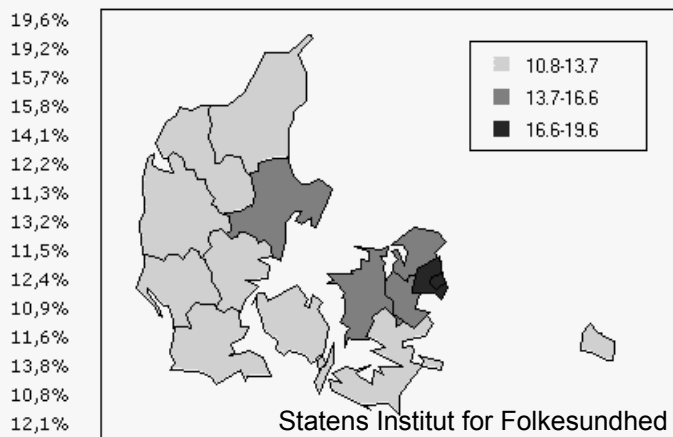
Prevalence of allergy (specific IgE in serum) in Greenland between 1987 and 1998



Krause, Lancet 2003

Urbanisering

Forekomst af selv-rapporteret allergi i Danmark



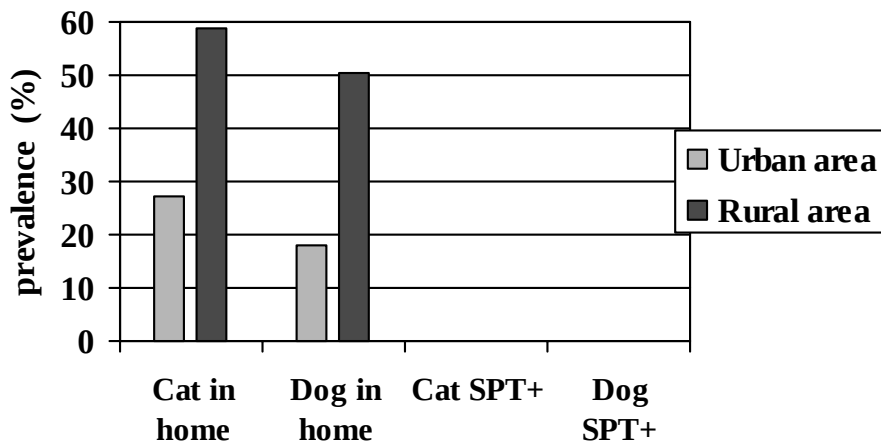
Hvad sker der, når voksne personer flytter fra land- til by-område (fra lav- til høj-risiko-område?)

Risiko for udvikling af allergi over 8 års periode:

	<u>Risiko</u>	<u>Odds ratio</u>
Personer, som var flyttet til København fra provinsen	14,2%	3.4 (1.6-7.2)
Personer, som altid havde boet i København (uden at få allergi)	7,0%	1 (reference)

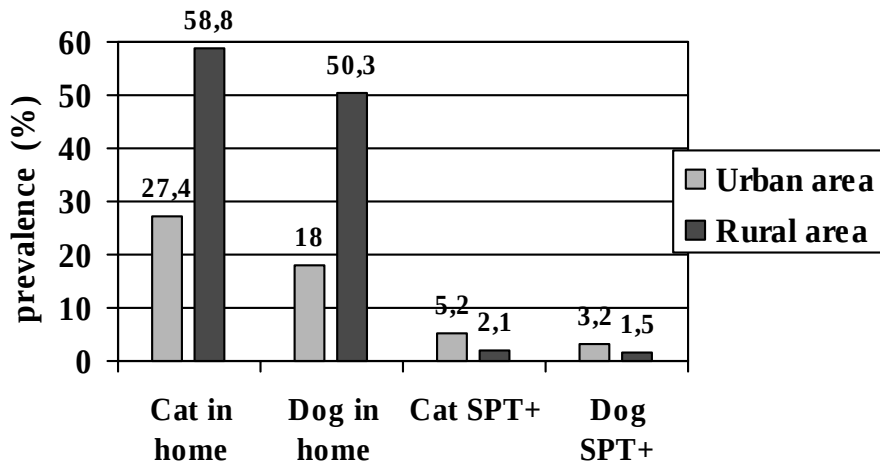
Linneberg, Allergy 2005

Prevalence of pets in the home and pet allergy in relation to urbanization in Greece



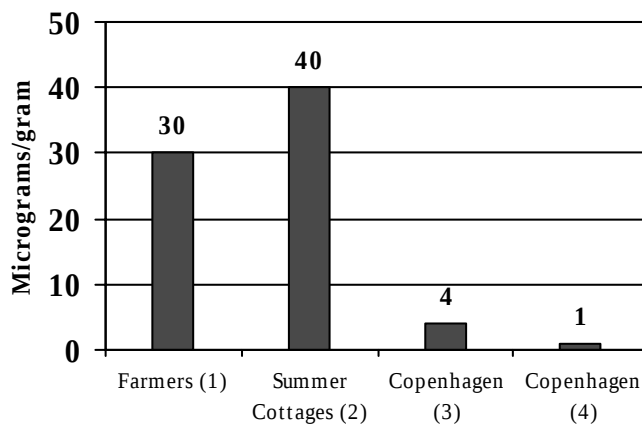
Priftis, Allergy 2007

Prevalence of pets in the home and pet allergy in relation to urbanization in Greece



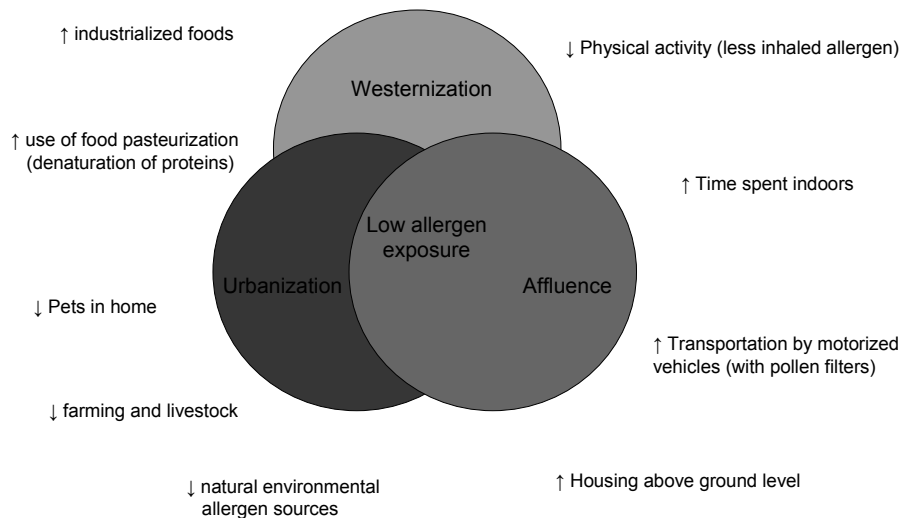
Priftis, Allergy 2007

Studies on levels of House Dust Mites in mattress dust in Danish homes



- 1) Iversen, Clin Exp Allergy 1990
- 2) Korsgaard, Allergy 2005
- 3) Sidenius, Ann Agric Environ Med 2002
- 4) Mosbech, Clin Exp Allergy 1991

Lifestyle changes related to low allergen/antigen exposure



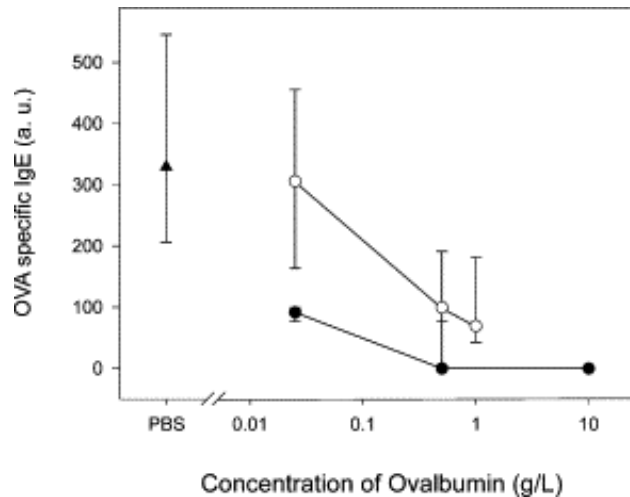
The concept of immune tolerance

- In 1911, HG Wells showed that anaphylactic reactions to ovalbumin in guinea pigs could be prevented by prior oral administration of ovalbumin

Wells & Osborne, J Infect Dis 1911

- This immune unresponsiveness (tolerance) is crucial to avoid hypersensitivity reactions against common allergens (from plants, animals, mites etc).

Animal studies clearly show that high allergen exposure (by oral, respiratory, or injection route) induces tolerance, while low dose increases risk of sensitization



Clausen et al, Toxicology 2003

Induction of tolerance by Allergen-Specific Immunotherapy in humans – a scientific fact !

- Metaanalyses concludes that SIT improves symptoms in
 - Allergic rhinitis
 - Injection route: Calderon, Cochrane Database 2007
 - Sublingual route: Wilson, Cochrane Database 2003
 - Allergic asthma (Abramson, Cochrane Database 2000)
- A longterm effect after discontinuation of s.c. SIT has been reported (Durham, New Eng J Med 1999)

Allergen Avoidance?



Does House Dust Mite (HDM) avoidance work?

- Randomized studies of the primary preventive effect of HDM avoidance

3 studies comparing HDM avoidance only to placebo

→ no effect

Koopman, Am J Respir Crit Care Med 2002

Marks, J Allergy Clin Immunol 2006

Woodcock, Am J Respir Crit Care Med 2004

- 1 metaanalysis of the effect of HDM avoidance for treatment of asthma → no effect

Gotzsche, Cochrane Database 2004

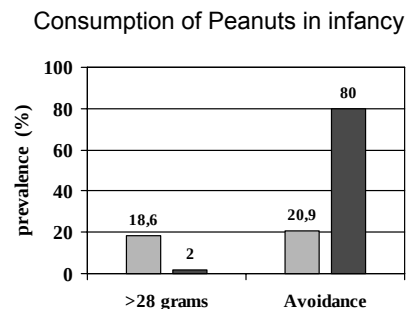
Woodcock, N Eng J Med 2003

Elimination diet (ED) in food allergy ?

- Only one randomized study comparing effects of ED to Specific Oral Tolerance Induction (SOTI) in children allergic to cow's milk and Hen's egg
- Tolerance in terms of negative double-blind food challenge was 36% and 35% for ED and SOTI, respectively
- Importantly, additionally 30% in the SOTI group was able to integrate the allergenic food in the diet reducing risk of severe reactions

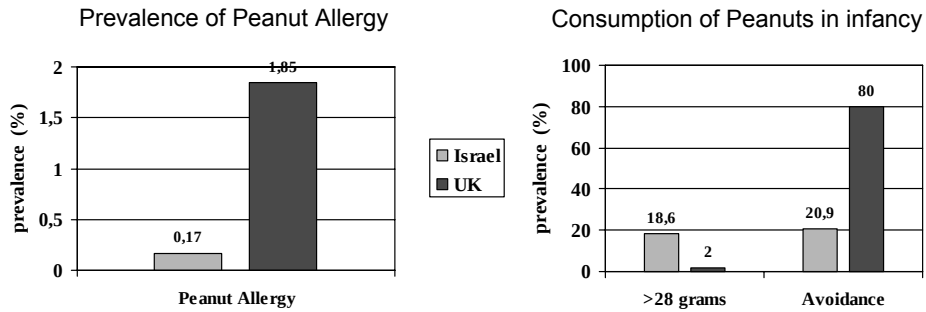
Staden, Allergy 2007

Peanut allergy in Israeli infants living in Israel and the UK



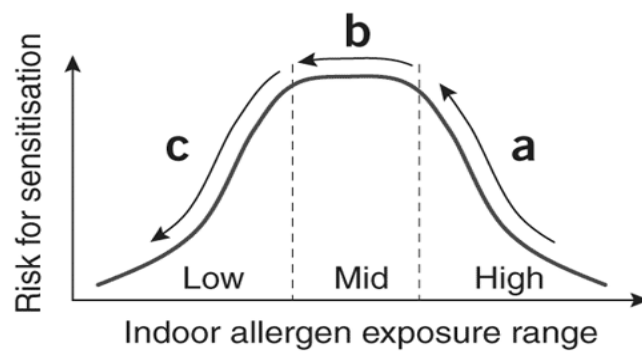
Du Toit, JACI 2008

Peanut allergy in Israeli infants living in Israel and the UK



Du Toit, JACI 2008

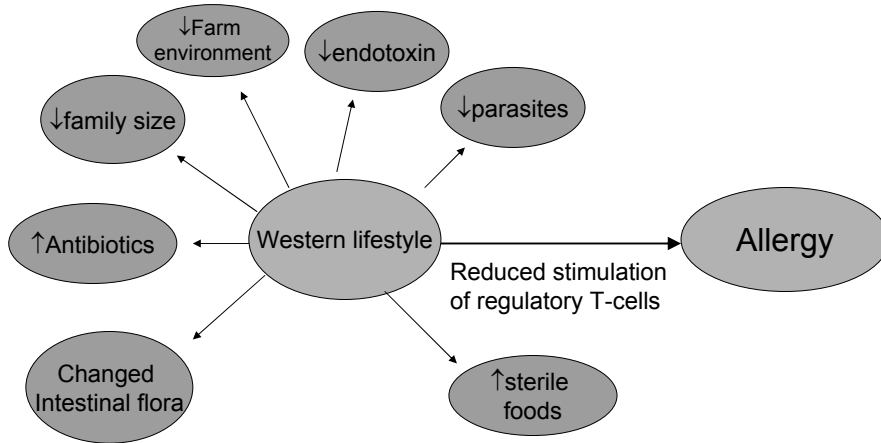
Is the exposure-sensitization curve
"bell" shaped?



Holt, Nat Immunol 2005

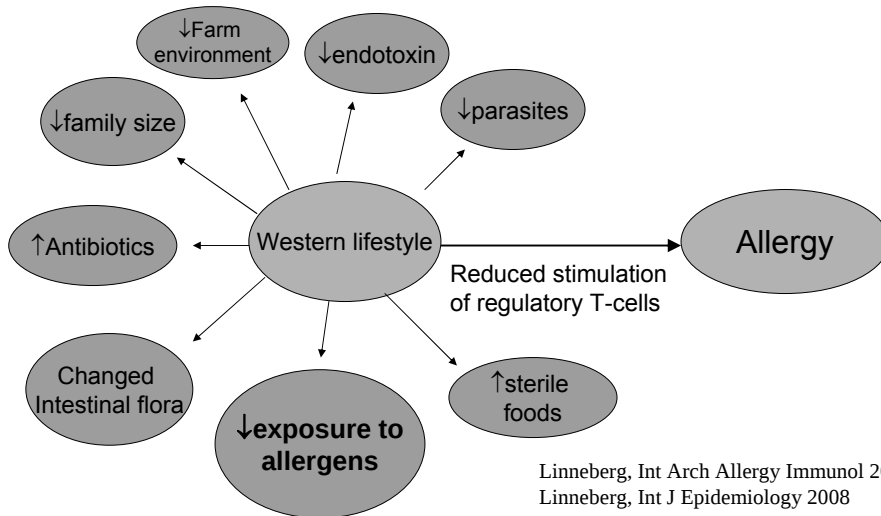
Hygiene Hypothesis

Changes in microenvironment



Hygiene Hypothesis

Changes in microenvironment



Linneberg, Int Arch Allergy Immunol 2008
Linneberg, Int J Epidemiology 2008

Antigen specifik Immunterapi ved autoimmune sygdomme

- oral eller nasal administration har færre bivirkninger
- By-stander suppression!
- Eksempel: oral insulin hos nydebuterede T1DM patienter
- Forsøg på mennesker har indtil nu været skuffende

Reviews:

- Faria, Clinical Developmental Immunology 2006
- Yamamoto, Expert Opinion, 2007

Konklusion

- Hygiejne hypotesen lever stadig, men fortolkningen af den observationelle epidemiologi lider under inkonsistente resultater
- Interventionsstudier med terapeutiske principper med udspring i hypotesen vil gøre os klogere (bør underkastes samme strenge krav til evidens som lægemidler)
- Det er meget vigtigt at erkende, at hygiejnehypotesen kan vise sig at være helt eller delvis forkert. Vi bør være åbne overfor nye ideer. Livsstil? D-vitamin? Fedme?

