A little bit of dirt won't hurt

The Achilles' heel of allergy?

Harry Wichers

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Contents

- Allergy
- Causes - Hygiene
  - Microbiota
- Achilles' heels
- Solutions - Microorganisms
  - Bioactive compounds
- …And then home…

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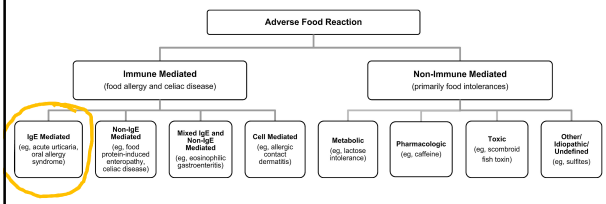
What is allergy



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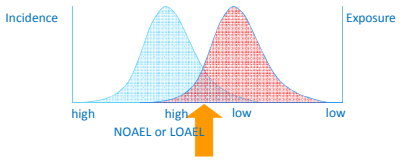
Objective

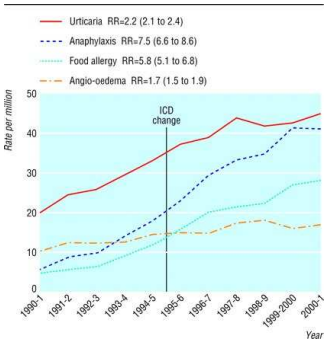
Thresholds and exposure

De-sensitisation therapy Immune modulation	Avoidance (technology/HACCP)



The objective is to reduce the risks that are associated to allergen exposure

The problem



Circumstantials?

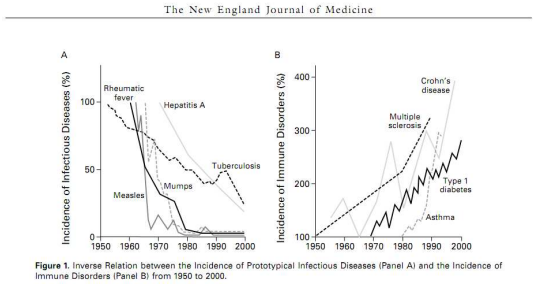
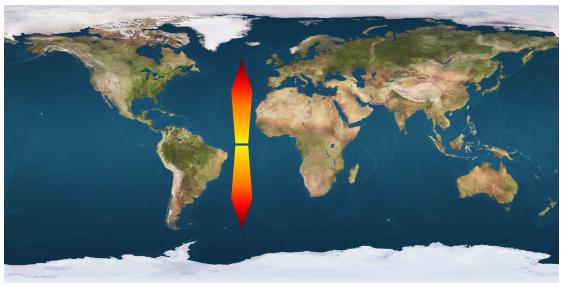


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.
In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[13] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

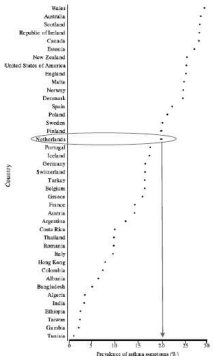
Bach, 2002

Circumstantials?



Bach, 2002

Circumstantials? Asthma prevalence



Drawbacks of hygiene?

GI-tract and microbiota

Mechanisms of Environmental Effects I

Digestive Diseases

Dig Dis 2011;29:144–153
DOI: 10.1159/000323877

Hygiene and Other Early Influences on the Subseq of the Immune System

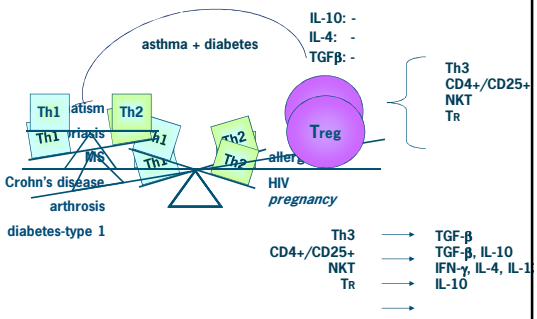
Graham A.W. Rook

University College London (UCL), London, UK

Abstract

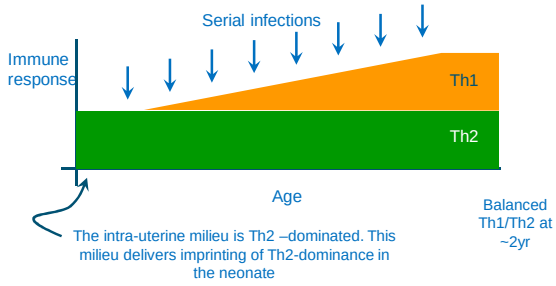
The current 'Darwinian' synthesis of the hygiene (or 'Old Friends') hypothesis suggests that the increase in chronic inflammatory disorders that started in Europe in the mid-19th century and progressed until the late 20th century is at least partly attributable to immunodysregulation resulting from lack of exposure to microorganisms that were tasked by co-evolutionary processes with establishing the 'normal' background levels of immunoregulation, a role that they perform in concert with the normal microbiota. This is an example of 'evolved dependence'. The relevant organisms co-evolved with mammals, already accompanied early hominids in the Paleolithic era and are associated with animals, mud and faeces. These organisms often establish stable carrier states, or

Immunology of allergy: homeostasis

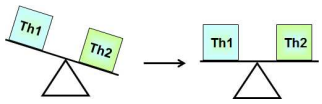


Causes

Neonatal and infantile immune system



Solution?



Via (controlled dietary) application of PAMPs/MAMPs/microbes?

Innate activation → Th1-activation?

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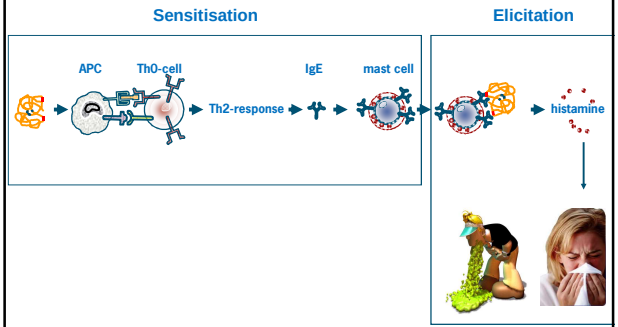
The theoretical framework



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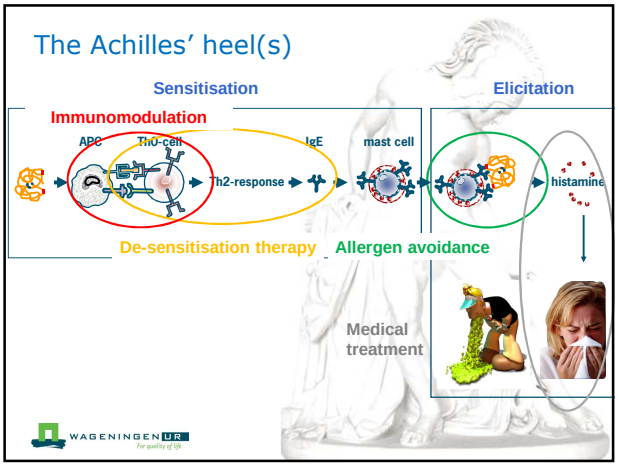
The Achilles' heel(s)



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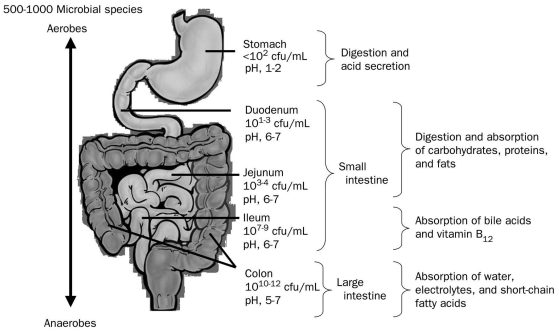
GI-tract and microbiota



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GI-tract and microbiota

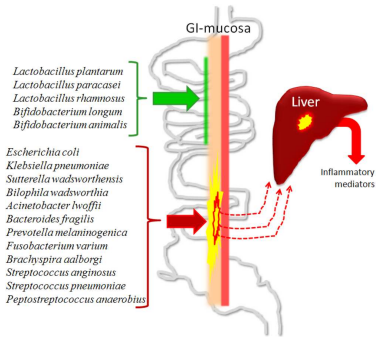

Figure 2: Eubiosis vs. Dysbiosis

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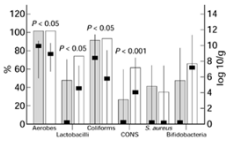
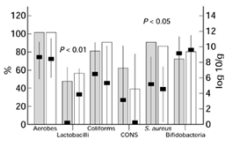
Hakansson + Molin *Nutrients* **2011**, *3*, 637-682

Causes



2-y olds in Estonia



2-y olds in Sweden

Grey: allergic children; white: non-allergic children

Probiotics

Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial

Lancet 2001; **357:** 1076–79

Marko Kalliomäki, Seppo Salminen, Heikki Arvilommi, Pentti Kero, Pertti Koskinen, Erika Isolauri

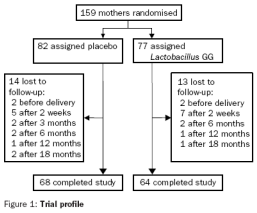


Figure 1: **Trial profile**

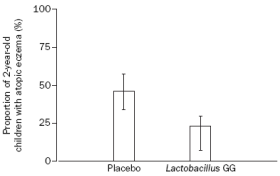
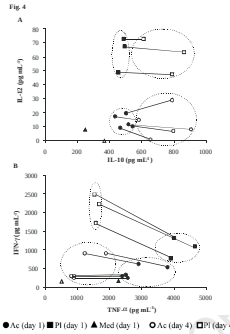


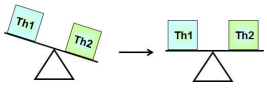
Figure 2: **Treatment effect of *Lactobacillus* GG on atopic disease**

Bars are 95% CI.

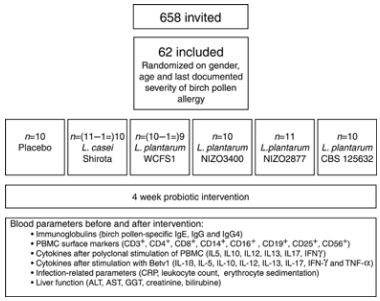
Probiotics



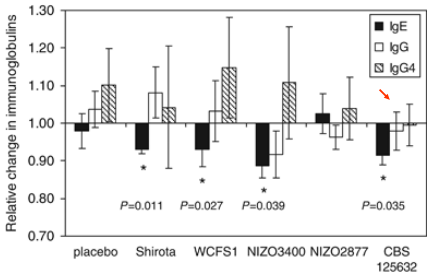
Specific probiotic strains promote specific polarisation in hPMBC-cultures



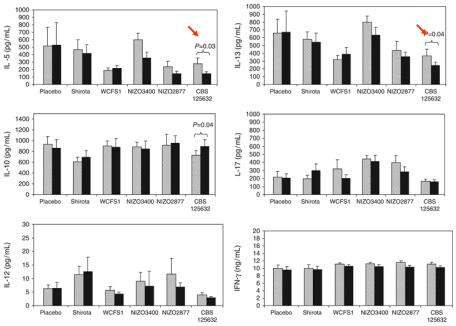
Study design



Probiotics reduce birch-pollen-specific IgE, but not IgG and IgG4



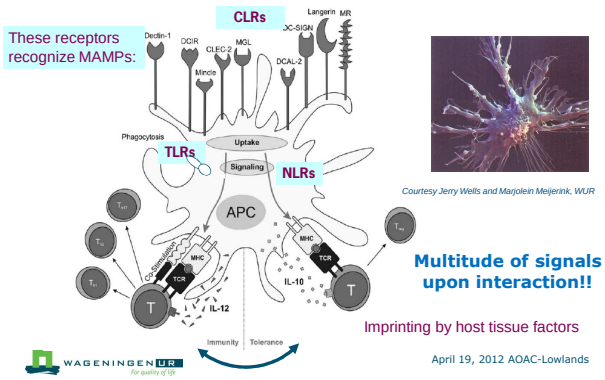
L. plantarum CBS125632 affects cytokine production of αCD3/αCD28-stimulated PBMC



Immune modulation and allergic disease

- LGG given to 159 pregnant women (at risk for allergy) for 2 weeks and to the babies for 6 months; 50% less infants in LGG group than placebo had atopic eczema at 2 y (Kalliomäki 2003)
- LGG and *Bifidobacterium lactis* Bb12 shown to decrease severity of atopic eczema (Isolauri 2000) and in a similar study serum IL-10 elevated significantly in LGG group (Pessi 2000)
- PandA-study: Ecologic PandA® (mix of 3 strains) prevents eczema in high risk-children in first 2y of life (Niers *et al*., 2009)
- *L. plantarum* decreases allergy markers in adult birch pollinosis sufferers (Snel *et al*., 2011)
- LGG not effective in preventing pollen allergy in teenagers (Helin 2002); more studies required in adults
- Second study with LGG unsuccessful in primary prevention (Kopp 2008). See also negative study of Taylor *et al*., 2007

Allergic disease: probiotics



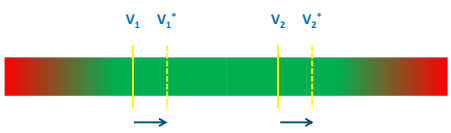
Courtesy Jerry Wells and Marjolein Meijerink, WUR

Multitude of signals upon interaction!!

Imprinting by host tissue factors

Responses patient- and strain dependent

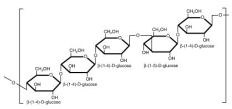
- Responses strain-dependent: phenotype is important
  - Is it MAMPs? Which MAMPs? PGN? S-layer proteins?
  - Induction of mucosal transcription strain-dependent
- Responses patient-dependent: phenotype again
  - Is a 'disease' phenotypically the same for everyone?
  - Enterotypes – consequences?



Bron *et al*, NRI 2011

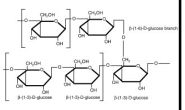
ß-Glucans

- Yeast
- Fungi
- Cereals
- Lychen
- Bacteria



cereal β-glucan

Polymer of β-(1-4)-D-glycopyranosyl units separated by single β-(1-3)-D-glycopyranosyl units.



yeast β-glucan

Polymer of β-(1-3)-D-glycopyranosyl units with branching at β-(1-6)-D-glycopyranosyl units

β-Glucan type	Structure	Description
Bacterial		Linear β1,3 glucan (i.e. Curdlan)
Fungal		Short β1,6 branched, β1,3 glucan (i.e. Schizophyllan)
Yeast		Long β1,6 branched, β1,3-glucan (i.e. WGP β-glucan, Betafectin™)
Cereal		Linear β1,3/β1,4-glucan (i.e oat, barley, rye)

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Volman *et al* Physiol Behav 94: 276 (2008)

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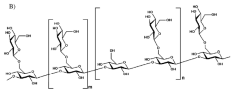
ß-Glucans

Murine ova-allergy model (BALB/c, oral challenge)



International Immunopharmacology

Rhinitis, sinusitis, and ocular diseases

Alleviation of seasonal allergic symptoms with superfine β-1,3-glucan: A randomized study

Jun Yamada, MD, PhD,[a,b] Junji Hamuro, PhD,[b] Hiroki Hatanaka, MD,[a,b] Kuniko Hamabata, MD,[a,b] and Shigeru Kinoshita, MD, PhD[b] *Kyoto, Japan*

Toshio Suzuki [c], Masahiro Sakanaka [D]

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JACI 119 1119 2007

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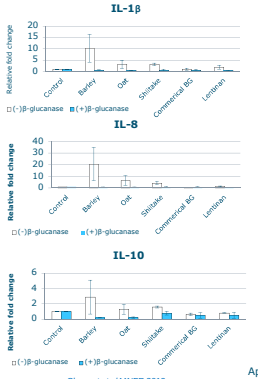
ß-Glucans activate THP-1 macrophages



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Chanput *et al* MNFR 2012

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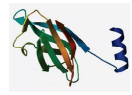
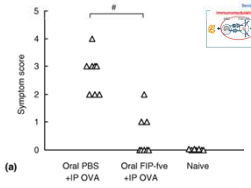
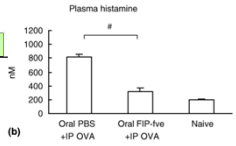
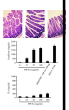
Fungal Immunomodulatory Proteins

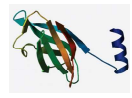


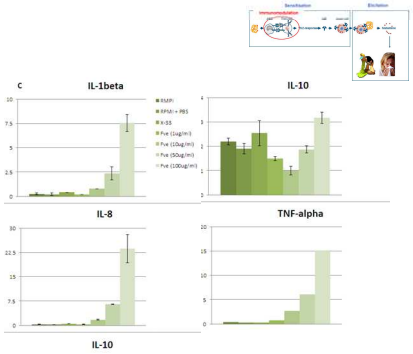




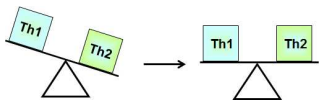


Fungal Immunomodulatory Proteins





And then home…



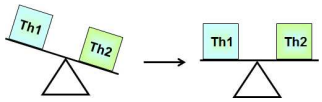
- *In vitro*/*ex vivo*-screening meaningful in this setting
- Better definition of probiotics may structure the debate

A little dirt won't hurt?

Is there a common mechanism?

3 'Food components' appear to have an impact on allergies:

- Probiotics
- β-Glucans
- FIPs



Possible common mechanism:

- All are microbial components;
  - Is this activation of innate immunity, and subsequent Th1-activation?

A little dirt won't hurt?

Thank you for your attention

harry.wichers@wur.nl