

TUBERKULÓZA A ASTMA – SETKÁNÍ NA KŘIŽOVATCE GENETIKY A CIVILIZACE

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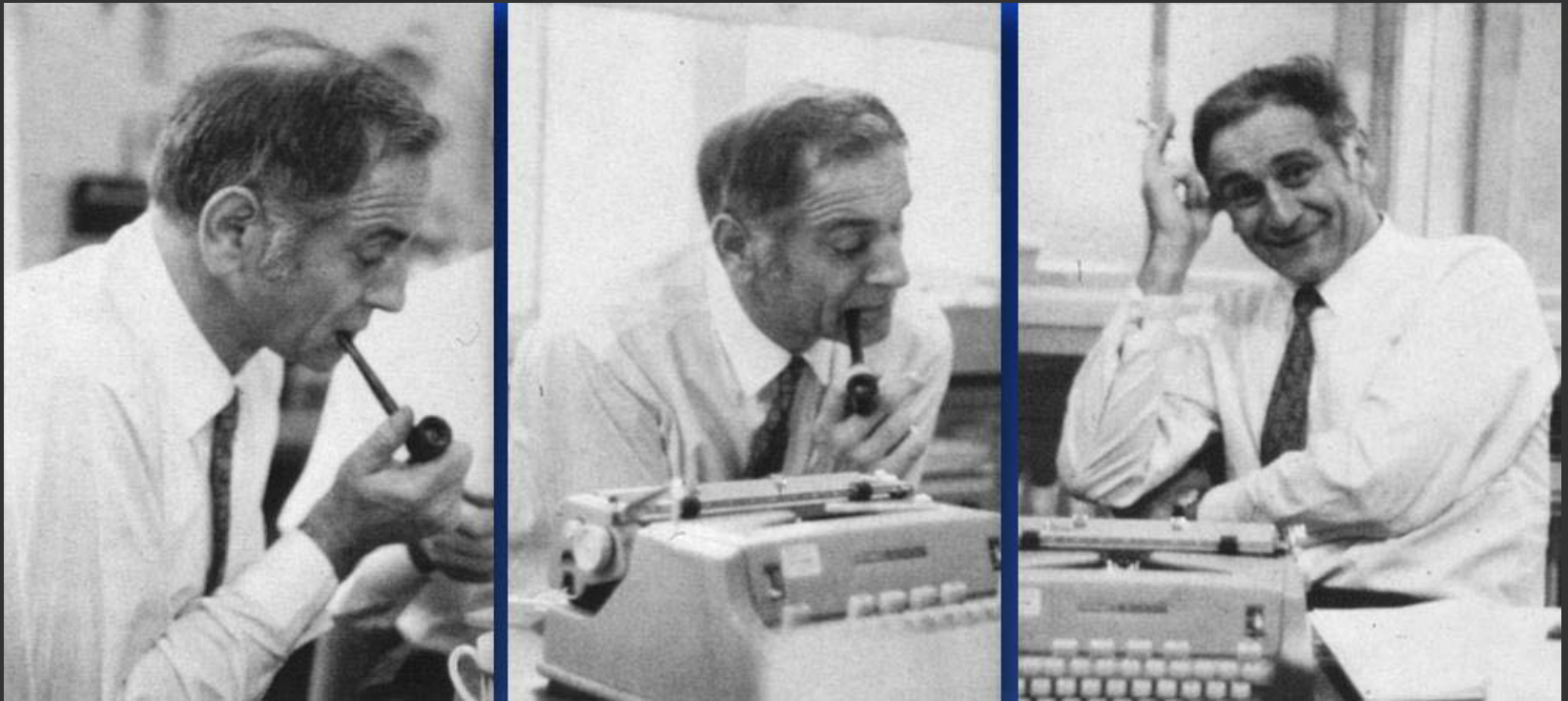
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GENETIKA : možnosti, variace a limity
stabilně zakódované ve
strukturu DNK

versus

EXPRESSE GÉNŮ : co se vyvine z jedince
na základě jeho
genetického kódu

Milan Hašek – In Memoriam



The TB Problem



exposure

75%

25%

no infection

infection

90%

10%

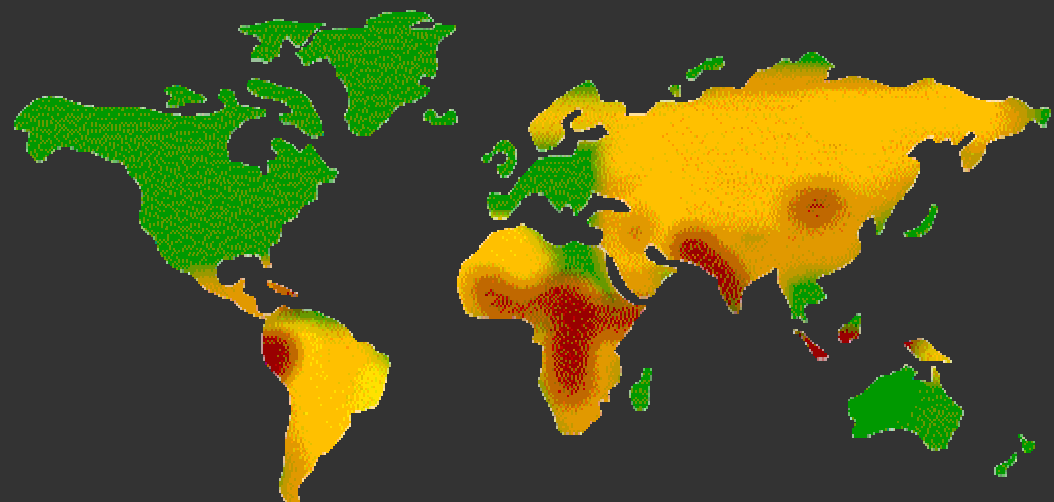
latent TB

active TB

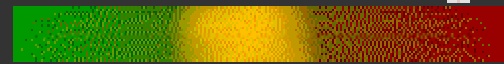
Healthy
5-10%/lifetime

HIV/AIDS
5-10%/year

(10 x ↑ Risk)



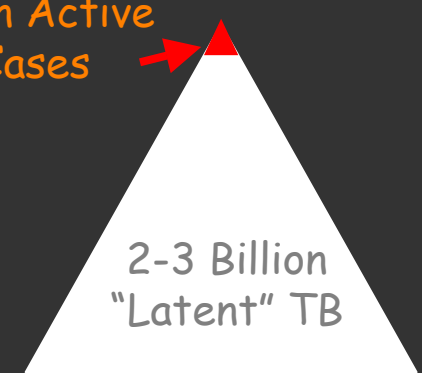
TB mortality

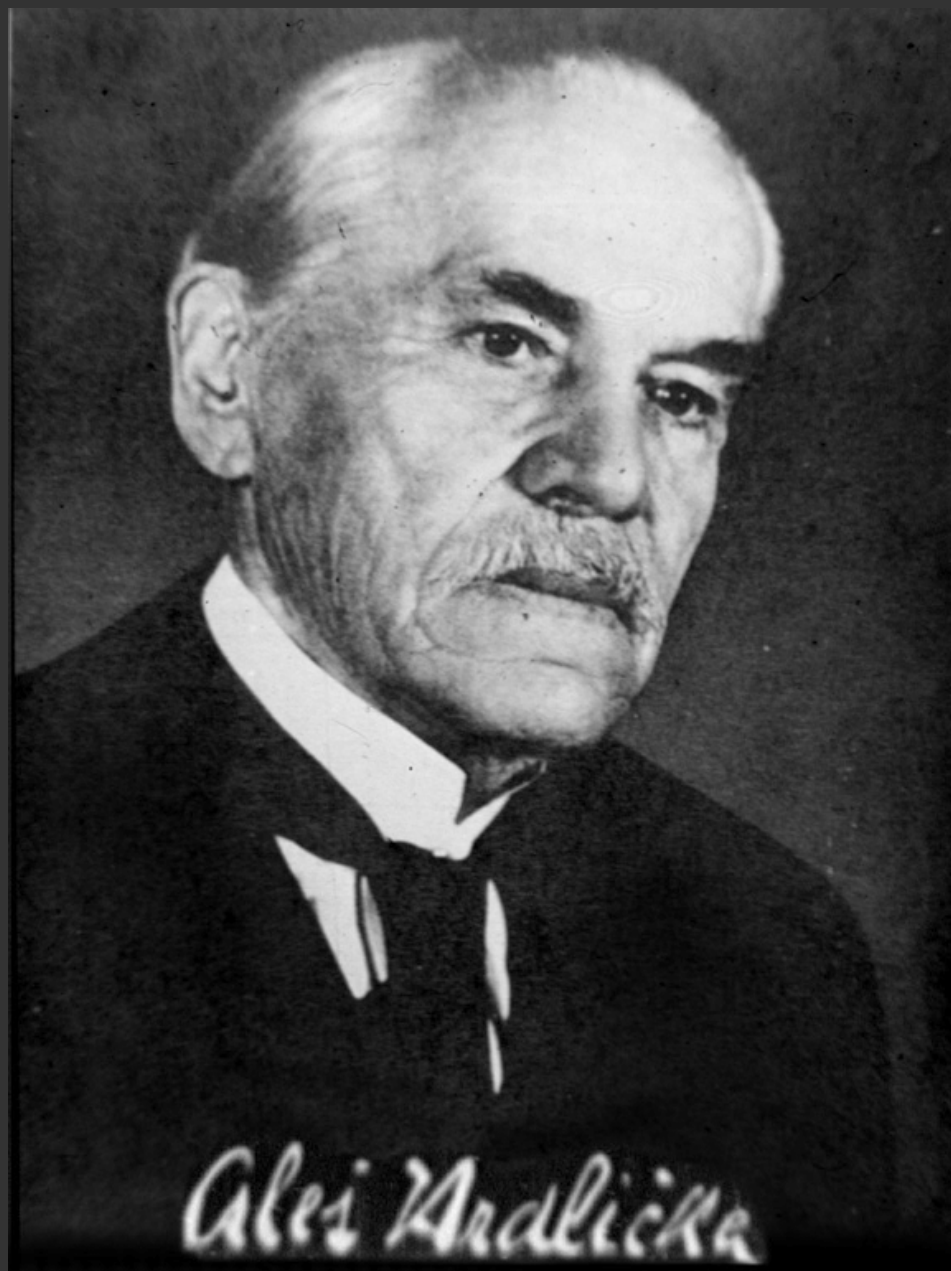


lower.....higher

8 Million Active
TB Cases

2-3 Billion
"Latent" TB





Tuberculosis (A. Hrdlička, 1909)

- endemic in Europe for centuries
 - change into epidemic in 18th century
 - industrial revolution
 - population change from rural to urban (crowded cities)
 - “Great White Plague”
 - genetic selection (25% of all deaths attributed to TB)
 - spread to Africa and Asia by European colonizers in 20th century (encampments, reservations)
-
- in 21st century, population of Africa and Asia remains much more susceptible to TB than Europeans

Twin studies of susceptibility to tuberculosis

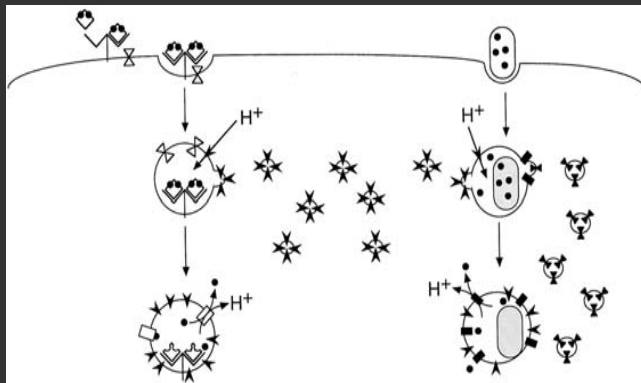
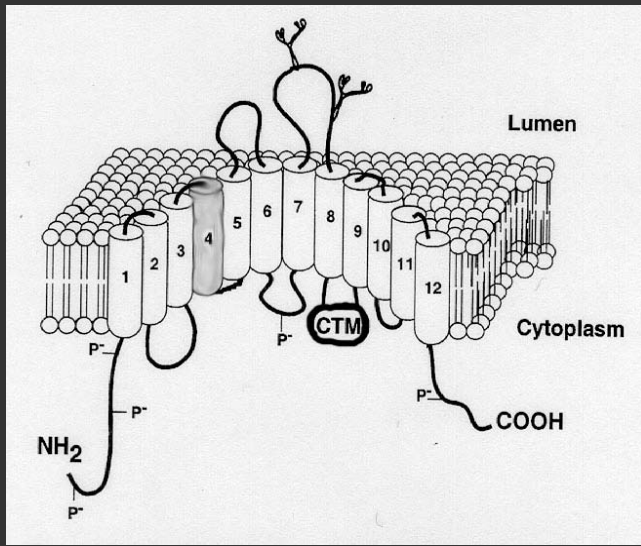
Tuberculosis

Concordance		Reference
Monozygous twins	Dizygous twins	
65%	25%	Diehl and Von Verschuer Beitr. Klin Kunsch 92: 275, 1936
62%	18%	Kallmann and Reisner, Am Rev Respir Dis 47, 549, 1942
32%	14%	Comstock, Am Rev Respir Dis 117, 621, 1978

Inbred Mouse Strains: Genetic Variation



Murine Nramp1



- Molecular correlate of the *Bcg(Lsh/Ity)* locus
- Expressed by mature tissue macrophages and targeted to late phagosomal vesicles
- Mutation attenuates phagosome acidification
- Wild-type protein is thought to be involved in trans-membrane iron flow

Why these mammals?

Role of congregate living

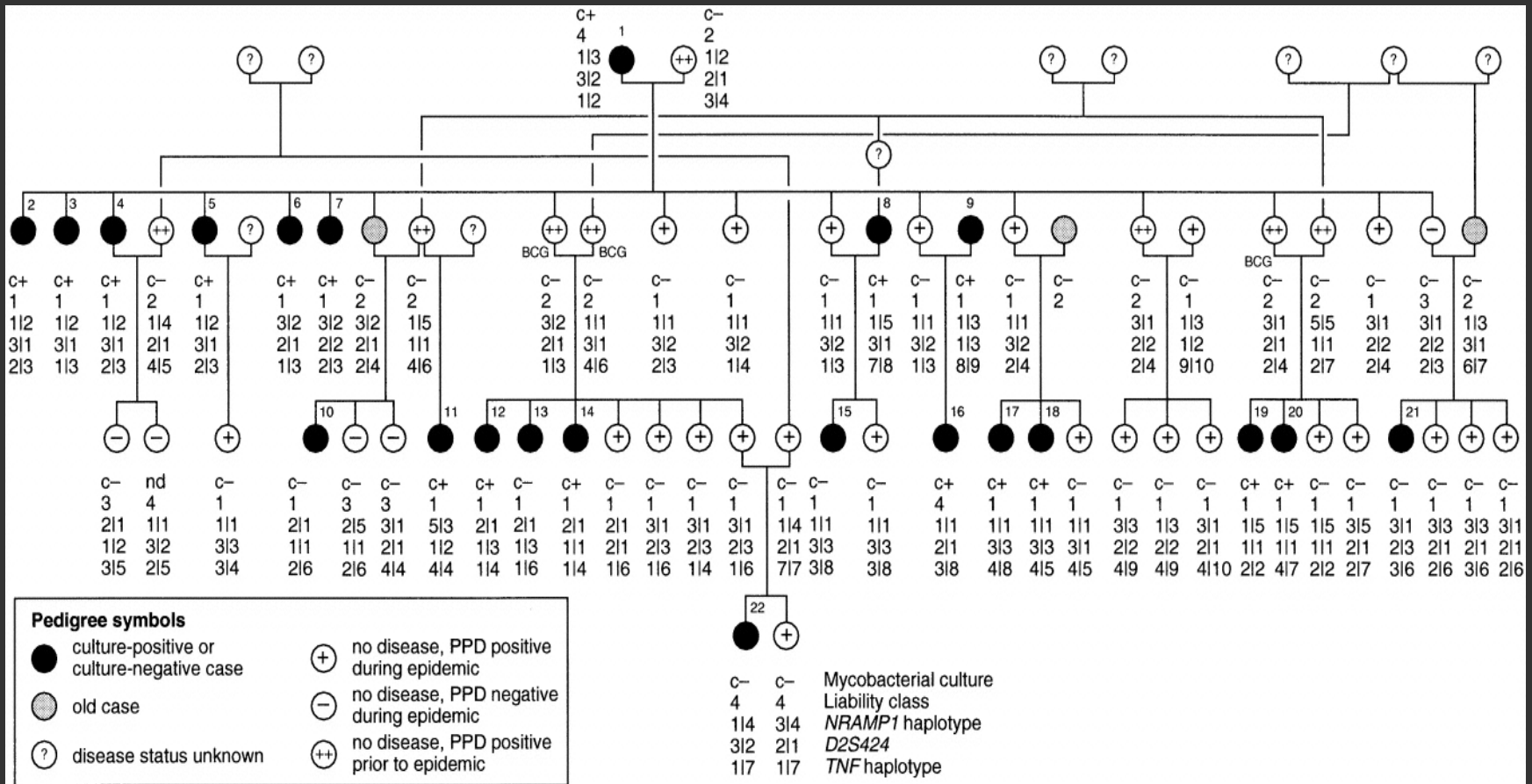


NRAMP1 and Tuberculosis Susceptibility

Tuberculosis Outbreak in a Canadian Aboriginal Community

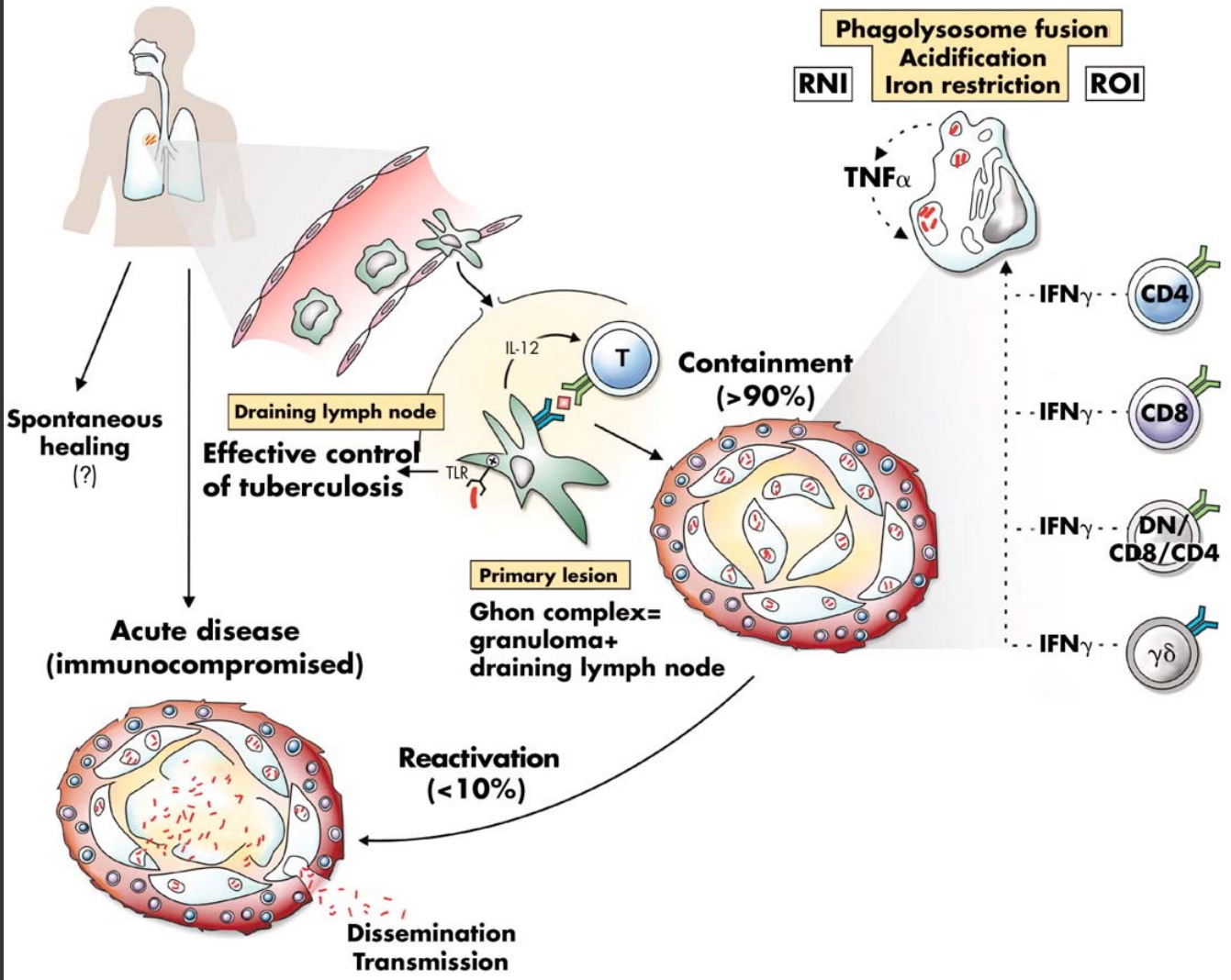


Pedigree of Extended Tuberculosis Family



Rising incidence of tuberculosis due to “civilization”

- HIV-AIDS (active TB in 50% of HIV-infected in countries without access to anti-retroviral Rx)
- in 2004, 50 million were newly infected with TB
- increased drug abuse
- increased immigration from countries with high prevalence of TB
- increase crowding among poor and other socioeconomic stresses
- homelessness, malnutrition, social deprivation
- airborne transmission in congregate settings (prisons, shelters)
- poor public health infrastructure
- multi-drug resistance



Asthma



Asthma - Disorder of Civilization?

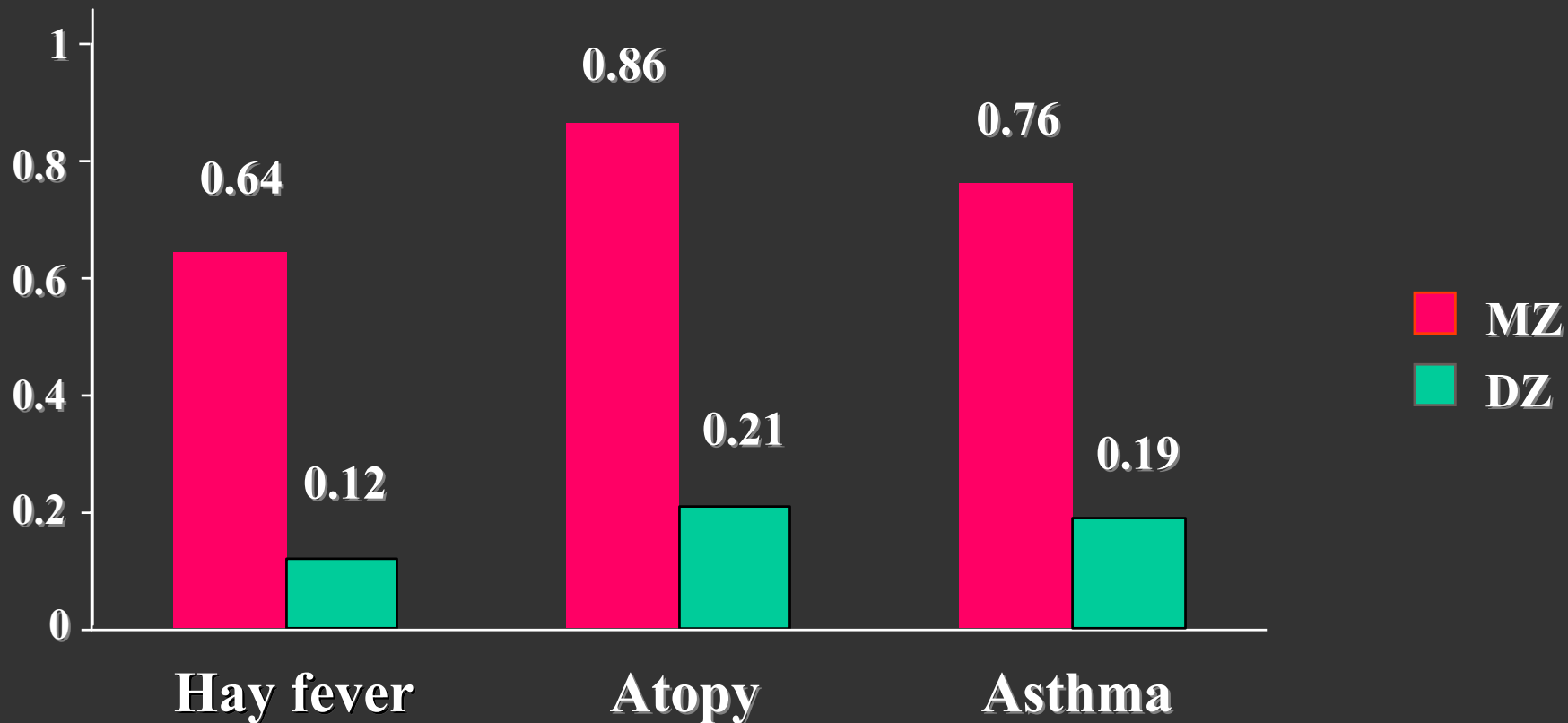
No Asthma	<ul style="list-style-type: none">✗ rural China✗ sub-Saharan Africa*✗ India✗ Malaysia
+++Asthma	<ul style="list-style-type: none">✓ Sweden✓ England✓ Australia✓ USA

*Note: African Americans have much higher rate of asthma than Caucasian Americans

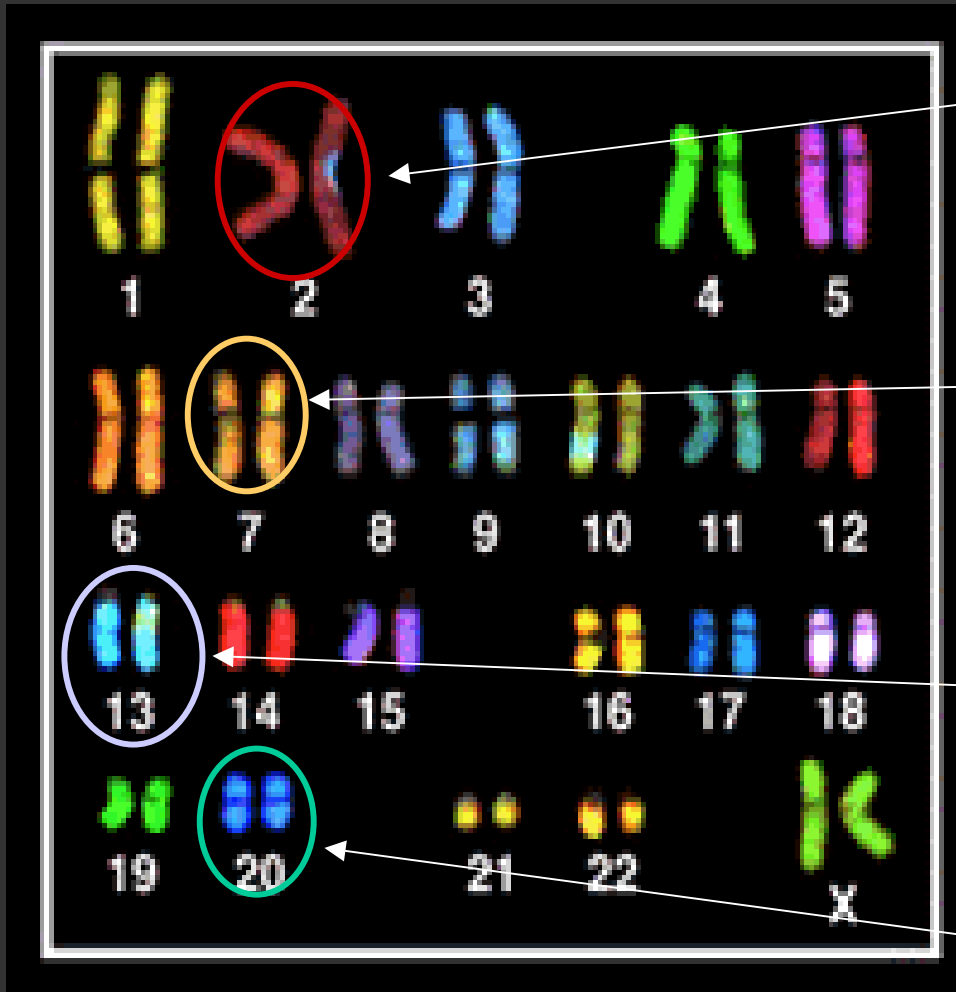
World Health Organization 2004 Statistics

- Incidence of asthma is rising by 50% every decade
- 150 million people suffer from asthma
- 180,000 people die from asthma every year
- direct and indirect annual costs:
 - \$6 billion (USA)
 - \$1.8 billion (England)
- asthma costs more than AIDS and TB combined
- major factor
 - urbanization
 - exposure to indoor allergens during infancy
 - family history of asthma

Australian Twin Studies : 3,808 Pairs



Cloned human asthma/atopy genes



2q14 – *DPP10*

dipeptidyl peptidase

? K⁺ channel transport in airway smooth muscle

7p14-15 - *GPRA*

G-protein-coupled receptor for asthma susceptibility
? Signal transduction

13q - *PHF11*

plant homeodomain finger protein 11
? Transcriptional regulation of immunoglobulin

20p13 - *ADAM33*

zinc dependent metalloproteinase
? Function in airway remodelling

Asthma - Nature vs Nurture

Asthma - permissive haplotypes

Hutterites (15%)
(South Dakota)

Chicago (15%)

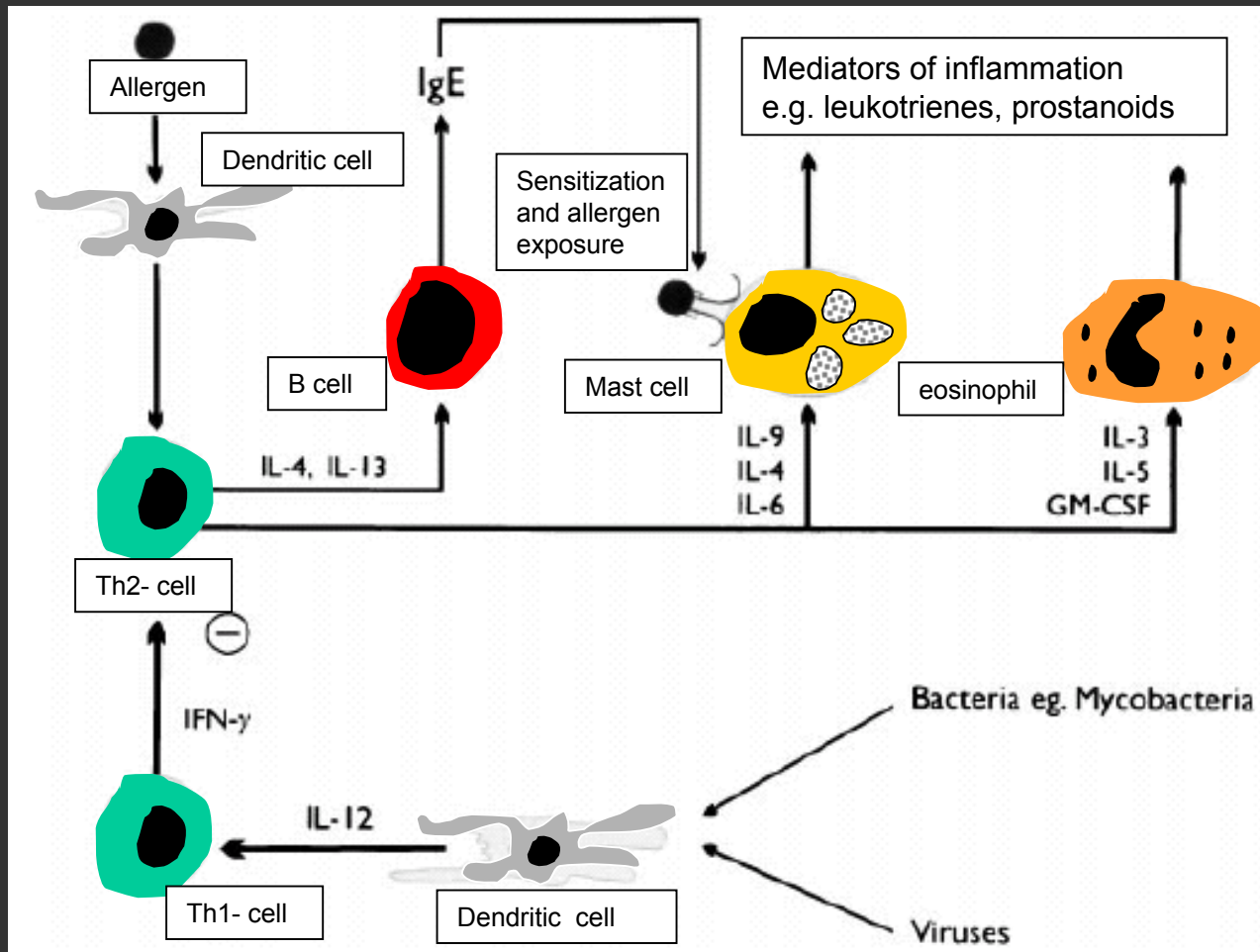
mild asthma

severe asthma



Asthma and civilization

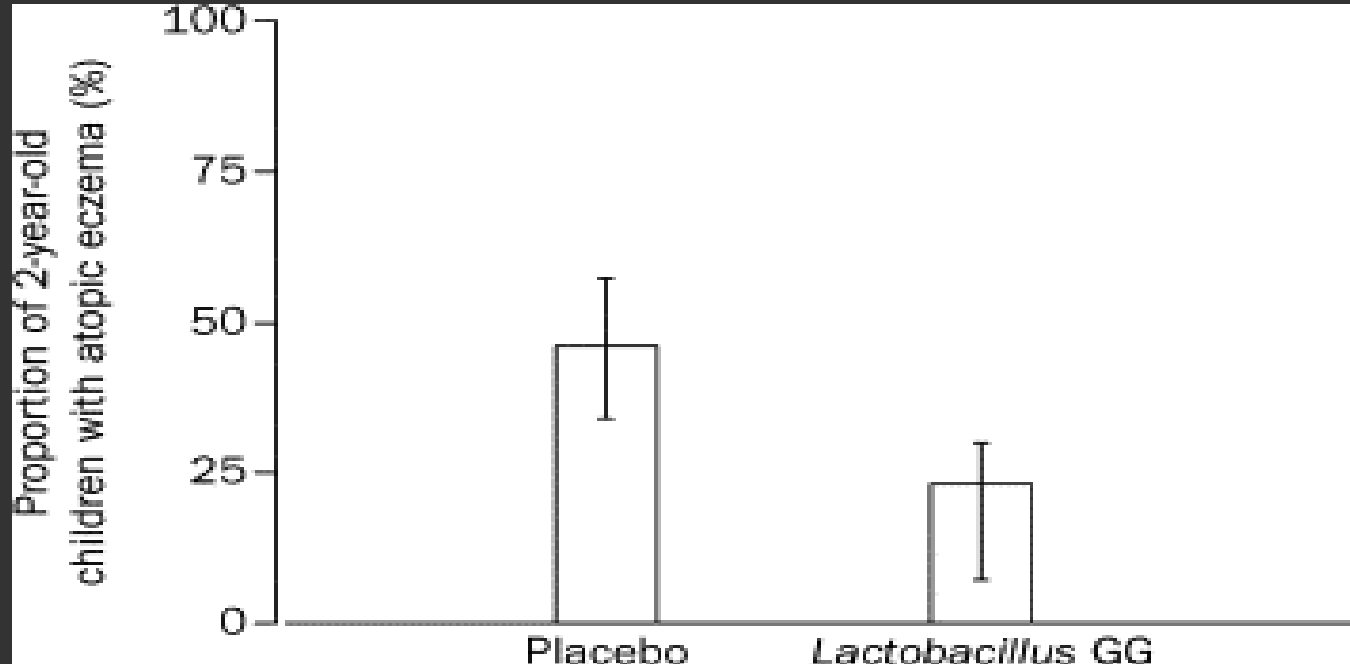
- Pollution? (not clear)
 - East Germany > West Germany
 - Cardiff (Scotland) > Isle of Skye
- Urbanization/tight houses
- Lack of infection
 - Japan: TB - > TB +



Role of intestinal flora in the development of allergy

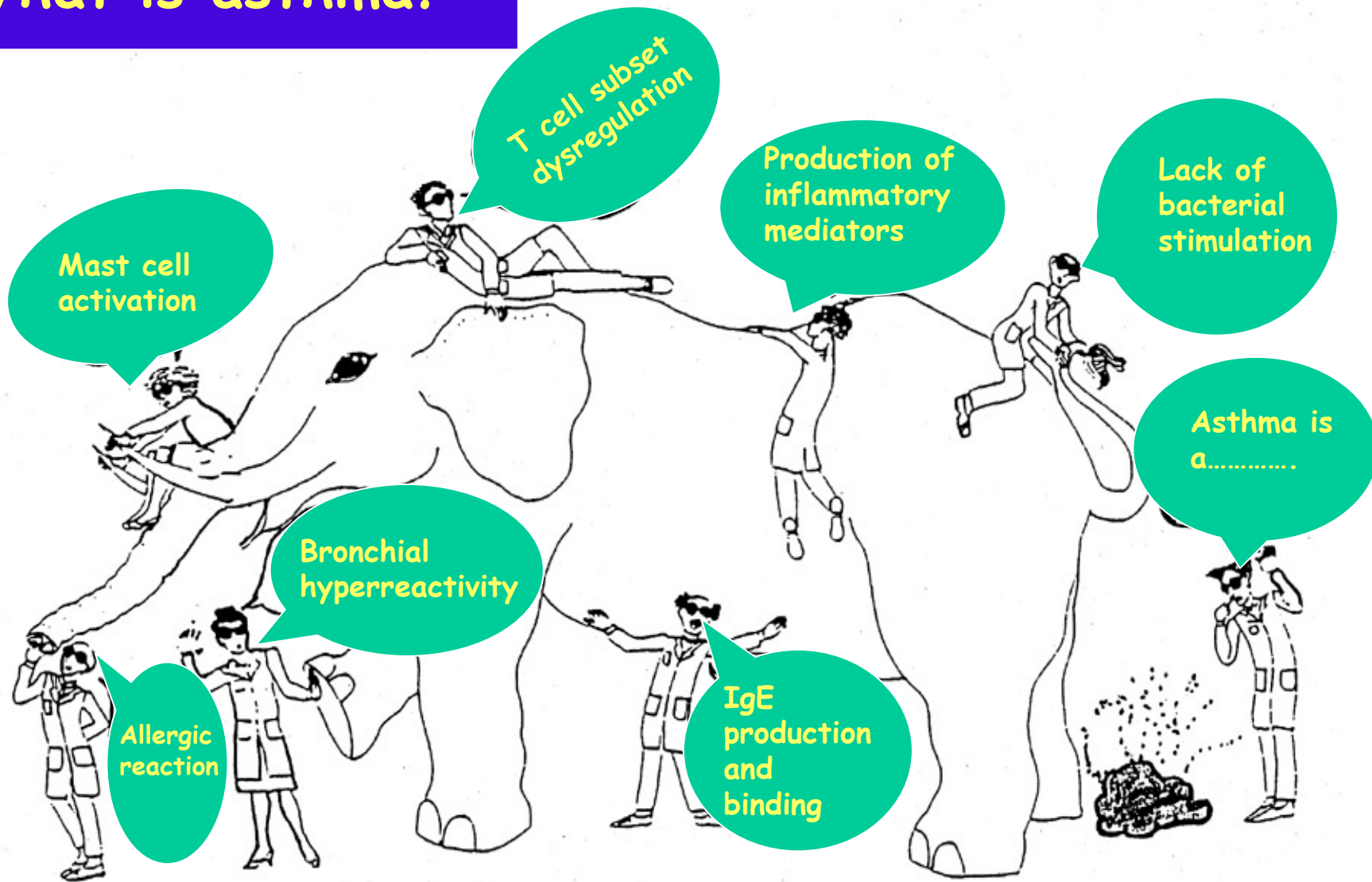
- pattern recognition receptors (TLR) in intestinal epithelial and antigen-presenting cells
- production of IL-10 and TGF- β
- host-microbe crosstalk in the gut is a delicate immunomodulator
- regulates maturation of naïve immune system

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



Treatment effect of *Lactobacillus* GG on atopic disease
[Bars are 95% CI]

What is asthma?



**GENOME IS JUST A
BLUEPRINT...**

**MANY OTHER FACTORS
SHAPE OUR DESTINY**



Charles University



McGill University