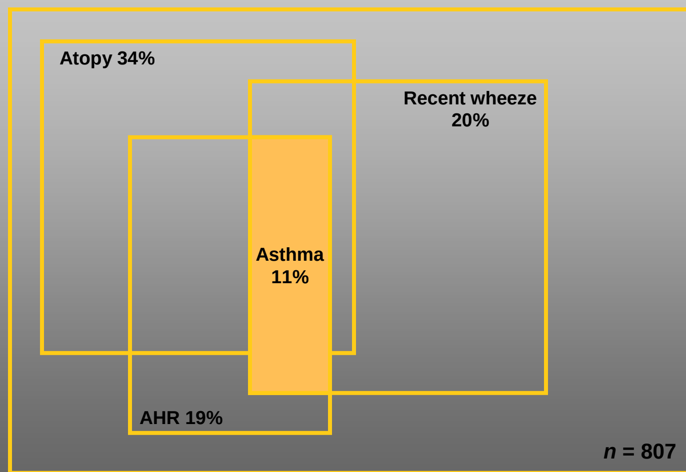
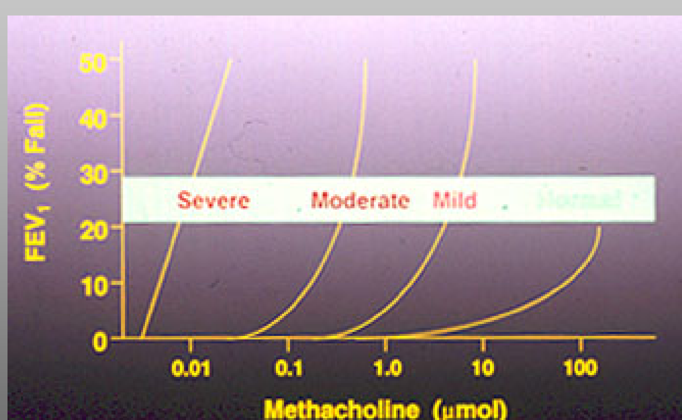
Defining Asthma: Clinical Criteria

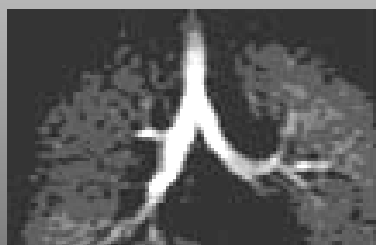


From: Woolcock, AJ. "Asthma" in *Textbook of Respiratory Medicine, 2nd ed.* Murray, Nadel, eds.(Saunders:Philadelphia) pp. 1288-1330, 1994

Defining Asthma: Bronchial Hyperresponsiveness



Impaired Ventilation in Asthma



Normal

Asthmatic

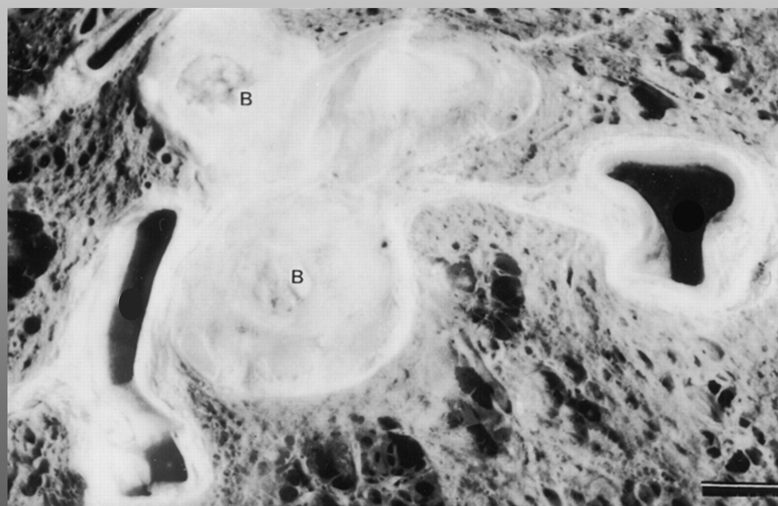
From: Klarreich, *Nature* 424:873, 2003

Dynamic Imaging of Asthma

Pre-treatment

Post-treatment

Mucus Plugging is a Prominent Feature of Moderate to Severe Asthma



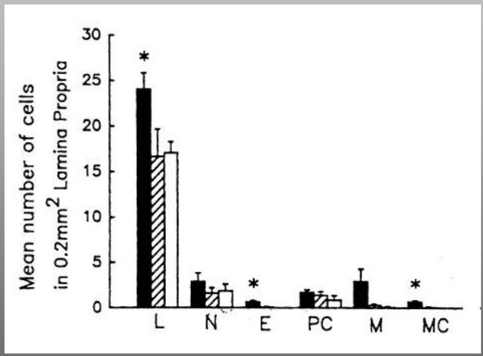
From: Bousquet et al., *Am. J. Respir. Crit. Care Med*., 161:1720, 2000

Some Landmarks in the History of the Immunology of Asthma*

1989: Early genetic mapping assigns chromosome 5q to the "cytokine gene cluster."
Early 1990s: Asthma is an inflammatory disease.
1990: Upregulation of ICAM-1 and LFA-1, adhesion molecules, in a primate model of asthma
1992: T_H2 bias of lymphocytes in asthma
1997: Experimental support grows for the "Hygiene hypothesis," first proposed in 1989.
2000: Role of Tregs in regulation of asthma

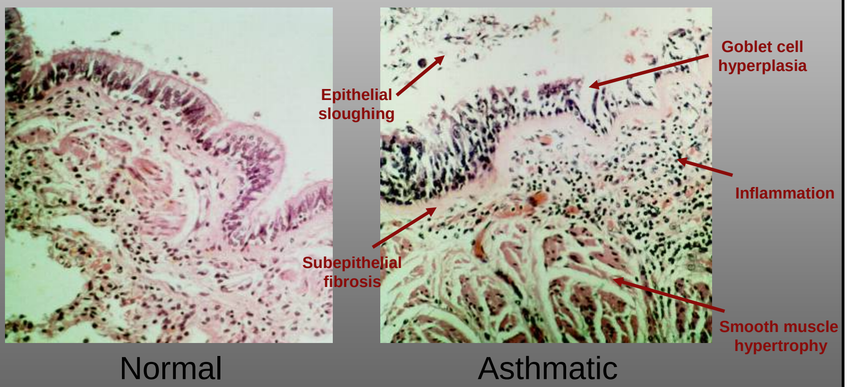
*Highly biased view; therefore, commit to memory

Nature of Inflammatory Cells in Biopsies From Airways of Asthmatics



From: Ollerenshaw and Woolcock., *Am. Rev. Resp. Dis.* 145:922, 1992

Defining Asthma: Pathological Features



From: Bousquet et al., *Am. J. Respir. Crit. Care Med.*, 161:1720, 2000

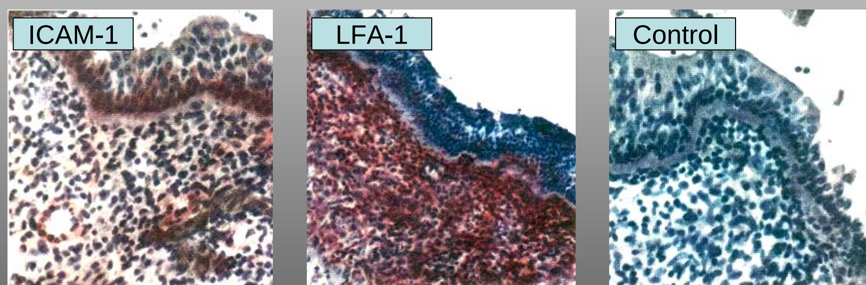
Pro-survival and Metaplatic Pathways to Goblet Cell Production

From: Cohn, *Am. J. Clin. Invest*, 116:306, 2006

Tissue “Compartments” in Asthma

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

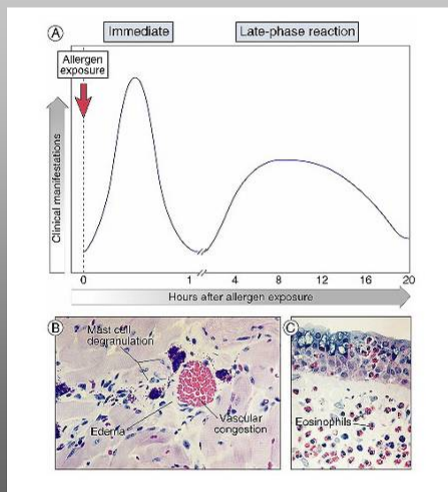
Adhesion Molecules ICAM-1 and LFA-1 in Experimental Asthma



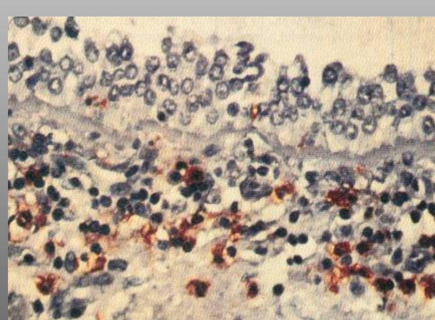
From: Wegner et al., *Science* 247:456, 1990

Asthma and the Immune Response

Early- and Late-phase Allergic Reactions



Presence of Degranulated Eosinophils in Asthmatic Airways



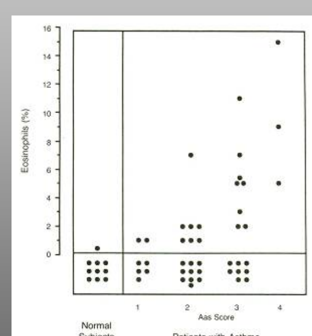


Figure 2. Percentage of Eosinophils in Bronchoalveolar-Lavage Fluid from Normal Subjects and Patients with Asthma.

From: Bousquet et al., *N. Engl. J. Med*. 323:1033, 1990

Eosinophils and Asthma

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

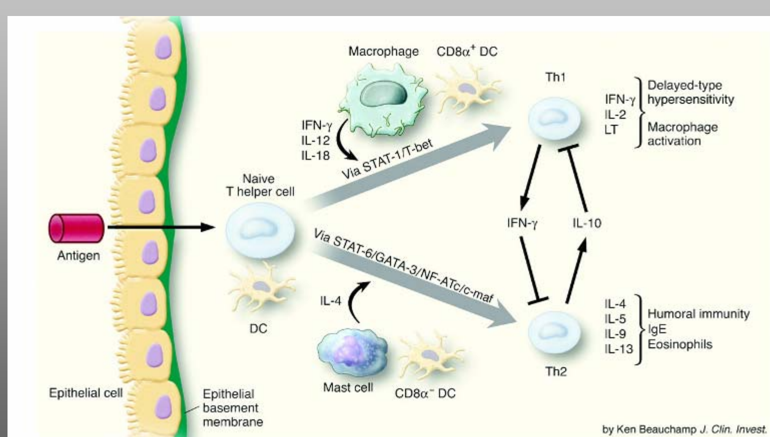
From: Wills-Karp and Karp, Science 305:1726-1729, 2004

Asthma as a T_H2-dominated Disease

First Recognition of a T_H2 Bias in Lymphocytes Obtained by BAL in Asthmatics

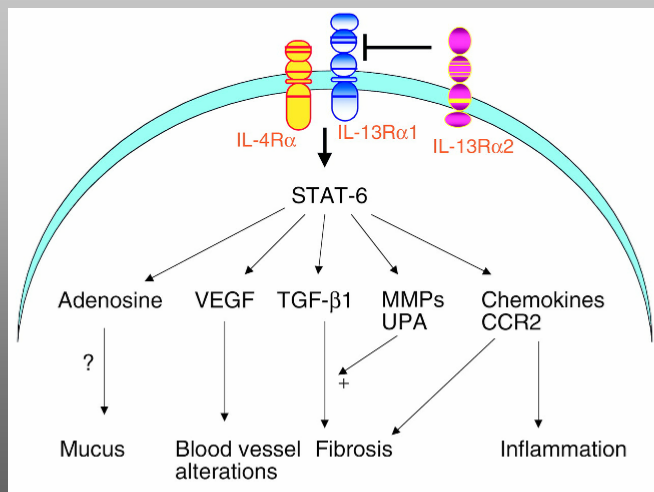
From: Robinson et al., *New Engl. J. Med.* 326:298,1992

Emergence of T_H1 and T_H2 Cells from Naïve Precursors



From: Elias et al., *J. Clin. Invest.* 111:291, 2003

STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype



From: Elias et al., *J. Clin. Invest.* 111:291, 2003

Defective Innate Immunity to Rhinovirus Infection in Asthmatics

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Wark and Gibson, *Thorax* 61:909, 2006

Potential Drug Targets in Asthma

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Understanding the Immunology of Asthma Leads to Insights Into Novel Therapeutics

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Who Gets Asthma?

4. M. Itoh et al., J. Cell Biol. 121, 491 (1993); E. Willott et al., Proc. Natl. Acad. Sci. U.S.A. 90, 7834 (1993).
5. C. P. Ponting and C. Phillips, Trends Biochem. Sci. 20, 102 (1995).
6. H. C. Kornau, L. T. Schenker, M. B. Kennedy, P. H. Seeburg, Science 269, 1737 (1995).
7. E. Kim, M. Niethammer, A. Rothschild, Y. N. Jan, M. Sheng, Nature 378, 85 (1995).
8. J. H. M. Cabral et al., ibid. 382, 649 (1996).
9. D. A. Doyle et al., Cell 85, 1067 (1996).
10. Z. Songyang et al., ibid. 72, 767 (1993).
11. A primary peptide library, KNXXXXXXX-COOH, where X indicates all amino acids except Cys and Trp, was first used to screen peptides that bind specifically to the glutathione-S-transferase (GST)–PDZ domains. All the peptides in the library end with free carboxylate, therefore orienting all binding pockets. The peptides that bound were sequenced as a mixture, and the selectivities for amino acids at a given position were determined by comparison to the sequence of control experiments with GST alone (10). Arg was not included in the calculation because of buffer contamination during sequencing. A secondary library, KNXXXXXX[S,T,Y]XX-COOH, where the −2 position was fixed with Ser, Thr, and Tyr, was used to further define the preference of some PDZ domains.
12. Peptide library synthesis was as described (10). Individual PDZ domains were expressed and purified as GST fusion proteins: murine hDlg PDZ-1 (186–282), PDZ-2 (281–377), PDZ-3 (428–518), and PDZ-1/2 (281–518); murine PTPbas PDZ-3 (1351–1445) and PDZ-5 (1756–1848); murine Tiam-1 PDZ; human LIN-2 PDZ (422–507); human erythroid p55 PDZ (1–164); and human AF-6 PDZ (983–1102). Glutathione beads (50 to 60 μl) saturated with GST-PDZ proteins were mixed with the peptide library (1 mg) in 300 μl of TSN buffer [40 mM triethylamine (pH 7.6), 150 mM NaCl, and 0.01% NP-40] containing bovine serum albumin (BSA, 1 mg/ml) and 1 mM dithiothreitol (DTT). After 45 min of constant shaking at 4°C, the beads were washed with TSN buffer. The peptides retained were eluted with 30% acetic acid, lyophilized, resuspended in distilled water, and sequenced on a Bio-Applied 477A sequencer.
13. Z. Songyang and L. C. Cantley, unpublished data.
14. T. Sato, S. Irie, S. Kitada, J. C. Reed, Science 268, 411 (1995).
15. P. Ruff, D. W. Speicher, A. Husain-Chishti, Proc. Natl. Acad. Sci. U.S.A. 88, 6595 (1991).
16. R. Hoskins, A. F. Hajnal, S. A. Harp, S. K. Kim, Development 122, 97 (1996); A. Brecher et al., in preparation.
17. G. G. Habets et al., Cell 77, 537 (1994).
18. R. Prasad et al., Cancer Res. 53, 5624 (1993).
19. G. Payne, S. E. Shoelson, G. D. Gish, T. Pawson, C. T. Walsh, Proc. Natl. Acad. Sci. U.S.A. 90, 4902 (1993).
20. H. T. Yu et al., Cell 76, 933 (1994).
21. Z. Songyang et al., data not shown.
22. J. S. Simske, S. M. Kaech, S. A. Harp, S. K. Kim, Cell 85, 195 (1996).
23. S. M. Marfatia et al., J. Biol. Chem., in press.
24. V. Hata, S. Butz, T. C. Sudhof, J. Neurosci. 16, 2488 (1996).
25. J. E. Brenman et al., Cell 84, 757 (1996).
26. B. Lipinska, M. Zylicz, C. Georgopoulos, J. Bacteriol. 172, 1791 (1990).
27. S. V. Shestakov et al., J. Biol. Chem. 269, 19354 (1994).

28. We thank M. Berne for peptide synthesis and sequencing, R. MacKinnon for structural coordinates of PSD-95-3, W. Boll and A. Nguyen for technical assistance, A. Couvillon for antibodies to GST, M. Oishi and T. Woodford-Thomas for the PTPbas cDNA, and A. Brecher for human LIN-2 PDZ. C.F. is a Lucille Markey Fellow. Supported by grants from American Cancer Society and Lucille P. Markey Charitable Trust (L.C.C.), NIH grants CA66263 and DK34989 (J.M.A. and A.S.F.), Pew Scholars Program (A.C.C.), and NIH grant CA66263 (A.H.C. and S.M.M.).

22 July 1996; accepted 23 October 1996

REPORTS

The Inverse Association Between Tuberculin Responses and Atopic Disorder

Taro Shirakawa, Tadao Enomoto, Shin-ichiro Shimazu, Julian M. Hopkin*

Human immune responses are heterogeneous and may involve antagonism between T helper (T_H) lymphocyte subsets and their cytokines. Atopy is characterized by immediate immunoglobulin E (IgE)-mediated hypersensitivity to agents such as dust mites and pollen, and it underlies the increasingly prevalent disorder asthma. Among Japanese schoolchildren, there was a strong inverse association between delayed hypersensitivity to *Mycobacterium tuberculosis* and atopy. Positive tuberculin responses predicted a lower incidence of asthma, lower serum IgE levels, and cytokine profiles biased toward T_H1 type. Exposure and response to *M. tuberculosis* may, by modification of immune profiles, inhibit atopic disorder.

Atopy is a state of allergic response, mediated by IgE, to largely innocuous, common environmental antigens (allergens) such as those derived from house dust mites and plant pollens (*1*); it underlies the clinical diseases of asthma, hay fever, and eczema (*2*). Atopy can be recognized by allergen-specific IgE in serum or by immediate-type hypersensitivity reactions to allergens upon intradermal skin testing. Heterogeneous genetic and environmental factors interact in the development of atopy (*3*); a set of cytokines—interleukin-4 (IL-4), IL-10, and IL-13 derived from the T_H2 subset of T lymphocytes—is central in mediating IgE production and the development of immediate hypersensitivity (*4*).

In recent decades there has been an increase in severity, and probably in prevalence, of atopic disorders in developed countries (*5*). Studies on migrants from developing to developed countries support the importance of etiological environmental changes associated with "Westernization" (*6*). The nature of these environmental changes is obscure, but speculation has focused on increased air pollution or other toxins in the environment, increased indoor exposure to dust mite antigens in less ventilated modern homes, and dietary changes (*7*). One factor temporally associated with the rise of atopy is the decline of many infectious diseases in developed countries as the result of improved living standards and immunization programs (*8*). Data on the risk of atopy according to sibship size and birth order (*9*) also support the possibility that diminished exposure to infection might, in some way, promote atopic responses. Childhood respiratory infections that might strongly modify the developing immune system, both systemically and within the lung, include measles, whooping cough, and tuberculosis. Some of these infections cultivate a T_H1 immunological environment with IL-12, interferon-γ (IFN-γ), and tumor necrosis factor (TNF) as predominant cytokines (*10*); because these cytokines inhibit T_H2 cytokine functions (*11*), the absence of such infections might release T_H2 immune mechanisms and thus promote atopic disorder.

In the case of tuberculosis, an important marker of T_H1-mediated acquired immunity (not synonymous with protection) is the development of delayed-type hypersensitivity. This can be tested by observing the reaction, after 48 hours, to the intradermal injection of tuberculin protein (*12*). There is likely a "J-shaped" relation between the degree of delayed hypersensitivity and the risk of tuberculous disease, in which people with moderate hypersensitivity are at least risk (*13*).

To test for clinical evidence of antagonism between delayed hypersensitivity to tuberculin and immediate atopic responses, we conducted an epidemiologic survey in a county of the Wakayama prefecture in southern Honshu, Japan, where there has been a long-established program of tuberculin testing and immunization with attenuated bovine M. tuberculosis vaccine [bacillus Calmette-Guérin (BCG)] after birth and at 6 and 12 years of age (*14*). From a population of approximately 1000 12- to 13-year-old schoolchildren attending the 18 junior high schools of the county in 1995, we studied 867 children with complete retrospective records of their tuberculin responses. We administered a

T. Shirakawa and J. M. Hopkin, Lung Research Laboratory, Osler Chest Unit, Churchill Hospital, Oxford OX3 7LJ, UK.
T. Enomoto, Department of Otolaryngology, Japanese Red Cross Society, Wakayama Medical Center, Wakayama, Japan.
S. Shimazu, Department of Pediatrics, National Wakayama Hospital, Wakayama, Japan.
*To whom correspondence should be addressed. E-mail: jhopkin@immsvr.jr2.ox.ac.uk

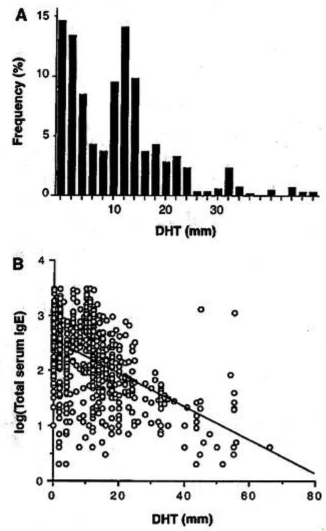


Fig. 1. Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE. **(A)** Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 867 Japanese schoolchildren. **(B)** Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492$, $P < 0.001$).

From: Shirakawa et al., *Science* 275:77, 1997

Table 1. History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

Measurement	Group 1 (*n* = 290)	Group 2 (*n* = 289)	Group 3 (*n* = 213)	Group 4 (*n* = 75)	Total (*n* = 867)
Tuberculin response					
At 6 years	−	−	+	+	
At 12 years	−	+	+	−	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
Number with IgE to *Ascaris*	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9‡‡	25.8‡‡	38.7	36.6
Atopy (present)	32.1	7.9‡‡‡	9.8‡‡‡	30.7	18.5
Asthma (past + present)	13.4	4.1‡‡	3.7‡‡	6.8	7.4
Rhinitis (past + present)	16.2	4.8‡‡	8.6‡	14.6	10.4
Eczema (past + present)	22.7	12.8‡‡	12.2‡‡	16.0	16.2
Geometric mean IgE (IU/ml)	208	149**	98***	178	154
Positive ASE (%)	55.8	43.9‡‡	41.8‡‡	53.3	48.2
Atopic (high IgE or positive ASE) (%)	65.5	54.0‡‡	49.2‡‡	61.3	57.3
Median cytokine level (pg/ml)					
IL-4	1.88	0.96†	0.92†	1.66	1.22 (10.2-UD)§
IL-13	18.3	10.2†††	7.8†††	19.1	14.2 (45.6-UD)
IL-10	5.9	3.1††	2.9††	5.9	3.9 (10.2-UD)
IL-12	UD	UD	UD	UD	UD
IFN-γ	7.8	11.0††	13.2††	6.4	10.5 (23.2-UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI	21.1	22.0	21.9	21.2	21.6

**$P < 0.01$, ***$P < 0.001$ on the basis of Student's test. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ on the basis of a median test. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ on the basis of χ^2 against group 1, respectively. §Maximum-minimum values.

From: Shirakawa et al., *Science* 275:77, 1997

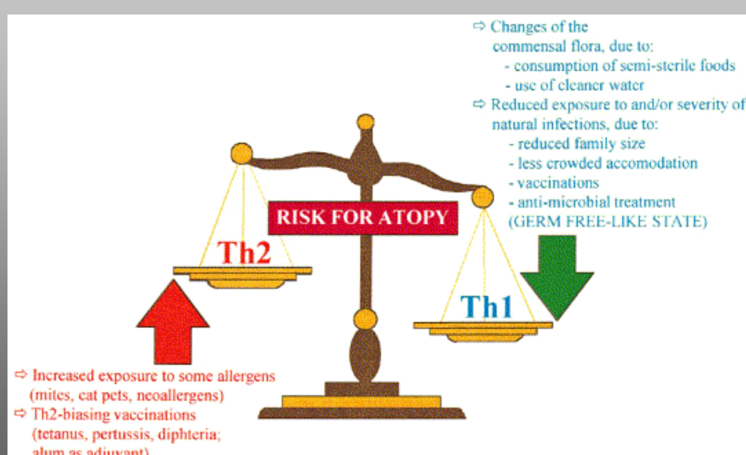
Table 2. Odds ratios for atopy and for occurrence and remission of atopic symptoms in positive versus negative tuberculin responders by age. Multiple logistic analysis was conducted with the SPSSX package, version 2.2. In all models, allowance was made for dichotomized variables including sex, life-style, nutritional status, environmental factors, and family history. Only significant values are shown.

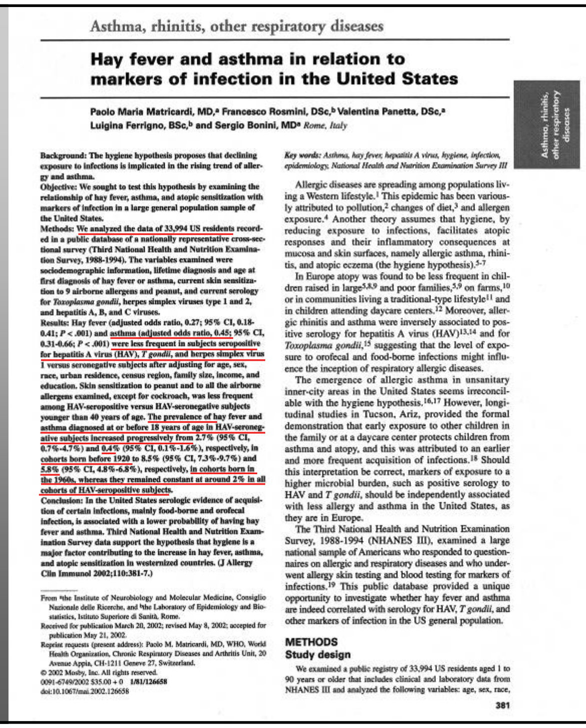
Tuberculin response	Odds ratio		
	Atopy	Atopic symptoms	
		Occurrence	Remission
Conversion to positive up to 6 years of age	0.50 (0.29 to 0.83)*	Asthma: 0.31 (0.22 to 0.45)* Eczema: 0.50 (0.33 to 0.91)*	Asthma: 8.2 (6.0 to 9.8)** Eczema: 1.6 (1.0 to 2.2)*
Conversion to positive between 6 and 12 years of age	0.43 (0.25 to 0.83)**	Asthma: 0.42 (0.24 to 0.56)*	Asthma: 6.0 (2.8 to 10.3)*** Eczema: 6.7 (4.8 to 11.4)*** Rhinitis: 9.0 (6.2 to 14.2)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$.

From: Shirakawa et al., *Science* 275:77, 1997

Environmental Influences and Asthma: The Hygiene Hypothesis





Hay fever and asthma in relation to markers of infection in the United States

Paolo Maria Matricardi, MD,[a] Francesco Rosmini, DSc,[b] Valentina Panetta, DSc,[a] Luigina Ferrigno, BSc,[b] and Sergio Bonini, MD[a] *Rome, Italy*

Asthma, rhinitis, other respiratory diseases

Background: The hygiene hypothesis proposes that declining exposure to infections is implicated in the rising trend of allergy and asthma.
Objective: We sought to test this hypothesis by examining the relationship of hay fever, asthma, and atopic sensitization with markers of infection in a large general population sample of the United States.
Methods: We analyzed the data of 33,994 US residents recorded in a public database of a nationally representative cross-sectional survey (Third National Health and Nutrition Examination Survey, 1988-1994). The variables examined were sociodemographic information, lifetime diagnosis and age at first diagnosis of hay fever or asthma, current skin sensitization to 9 airborne allergens and peanut, and current serology for *Toxoplasma gondii*, herpes simplex viruses type 1 and 2, and hepatitis A, B, and C viruses.
Results: Hay fever (adjusted odds ratio, 0.27; 95% CI, 0.18-0.41; $P < .001$) and asthma (adjusted odds ratio, 0.45; 95% CI, 0.31-0.66; $P < .001$) were less frequent in subjects seropositive for hepatitis A virus (HAV), *T gondii*, and herpes simplex virus 1 versus seronegative subjects after adjusting for age, sex, race, urban residence, census region, family size, income, and education. Skin sensitization to peanut and to all the airborne allergens examined, except for cockroach, was less frequent among HAV-seropositive versus HAV-seronegative subjects younger than 40 years of age. The prevalence of hay fever and asthma diagnosed at or before 18 years of age in HAV-seronegative subjects increased progressively from 2.7% (95% CI, 0.7%-4.7%) and 0.4% (95% CI, 0.1%-1.6%), respectively, in cohorts born before 1920 to 8.5% (95% CI, 7.3%-9.7%) and 5.8% (95% CI, 4.8%-6.8%), respectively, in cohorts born in the 1960s, whereas they remained constant at around 2% in all cohorts of HAV-seropositive subjects.
Conclusion: In the United States serologic evidence of acquisition of certain infections, mainly food-borne and orofecal infection, is associated with a lower probability of having hay fever and asthma. Third National Health and Nutrition Examination Survey data support the hypothesis that hygiene is a major factor contributing to the increase in hay fever, asthma, and atopic sensitization in westernized countries. (J Allergy Clin Immunol 2002;110:381-7.)

From [a]the Institute of Neurobiology and Molecular Medicine, Consiglio Nazionale delle Ricerche, and [b]the Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanità, Rome.
Received for publication March 20, 2002; revised May 8, 2002; accepted for publication May 21, 2002.
Reprint requests (present address): Paolo M. Matricardi, MD, WHO, World Health Organization, Chronic Respiratory Diseases and Arthritis Unit, 20 Avenue Appia, CH-1211 Geneve 27, Switzerland.

0091-6749/2002 $35.00 + 0 **1/81/126658**
doi:10.1067/mai.2002.126658

Key words: Asthma, hay fever, hepatitis A virus, hygiene, infection, epidemiology, National Health and Nutrition Examination Survey III

Allergic diseases are spreading among populations living a Western lifestyle.[1] This epidemic has been variously attributed to pollution,[2] changes of diet,[3] and allergen exposure.[4] Another theory assumes that hygiene, by reducing exposure to infections, facilitates atopic responses and their inflammatory consequences at mucosa and skin surfaces, namely allergic asthma, rhinitis, and atopic eczema (the hygiene hypothesis).[5-7]

In Europe atopy was found to be less frequent in children raised in large[5,8,9] and poor families,[5,9] on farms,[10] or in communities living a traditional-type lifestyle[11] and in children attending daycare centers.[12] Moreover, allergic rhinitis and asthma were inversely associated to positive serology for hepatitis A virus (HAV)[13,14] and for *Toxoplasma gondii*,[15] suggesting that the level of exposure to orofecal and food-borne infections might influence the inception of respiratory allergic diseases.

The emergence of allergic asthma in unsanitary inner-city areas in the United States seems irreconcilable with the hygiene hypothesis.[16,17] However, longitudinal studies in Tucson, Ariz, provided the formal demonstration that early exposure to other children in the family or at a daycare center protects children from asthma and atopy, and this was attributed to an earlier and more frequent acquisition of infections.[18] Should this interpretation be correct, markers of exposure to a higher microbial burden, such as positive serology to HAV and *T gondii*, should be independently associated with less allergy and asthma in the United States, as they are in Europe.

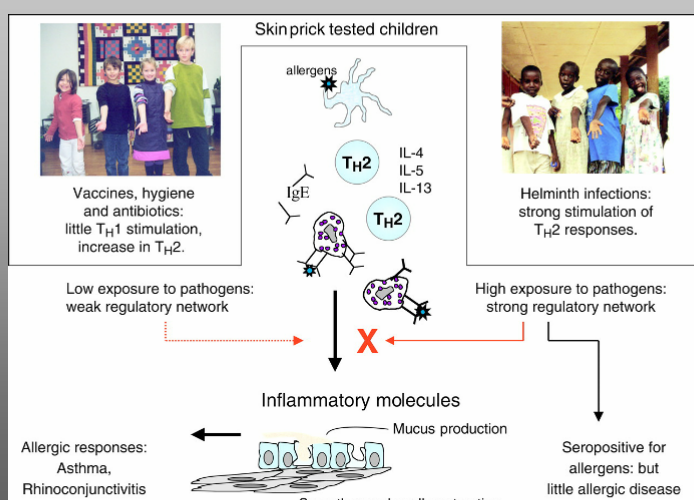
The Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III), examined a large national sample of Americans who responded to questionnaires on allergic and respiratory diseases and who underwent allergy skin testing and blood testing for markers of infections.[19] This public database provided a unique opportunity to investigate whether hay fever and asthma are indeed correlated with serology for HAV, *T gondii*, and other markers of infection in the US general population.

METHODS

Study design

We examined a public registry of 33,994 US residents aged 1 to 90 years or older that includes clinical and laboratory data from NHANES III and analyzed the following variables: age, sex, race,

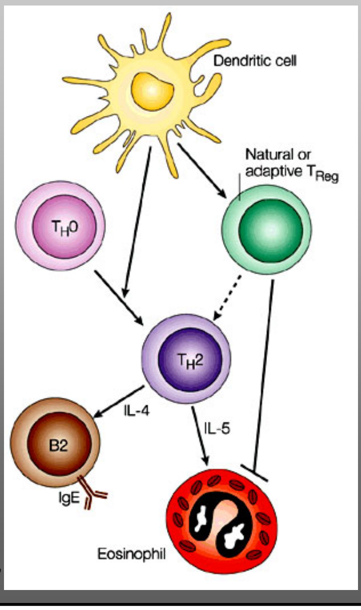
Paradox:
Why Does Chronic Infection with Helminths Not Predispose to Allergy?



From: Yazdanbakhsh et al., *Science* 296:490, 2002

An Alternative to the Hygiene Hypothesis: Regulatory T-cells

The Role of Regulatory T-cells in Modifying T_H2 Immunity



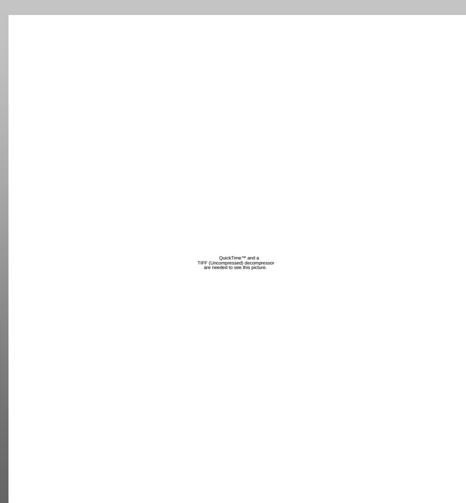
Modified from: Maizels & Yazdanbakhsh, *Nature Rev. Immunol.* 3:733, 2003

Immunotherapy of Atopic Diseases: a Role for Tregs?

Following 2-year grass pollen immunotherapy (closed circles), there were significant increases in (**A**) allergen-stimulated PBMC production of IL-10; (**B**) serum concentrations of grass pollen allergen-specific IgG4; and (**C**) serum inhibitory activity for allergen-IgE binding to B cells compared with controls (open circles). These changes were accompanied by a reduction in symptoms and inhibition allergen-induced late cutaneous response.

From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

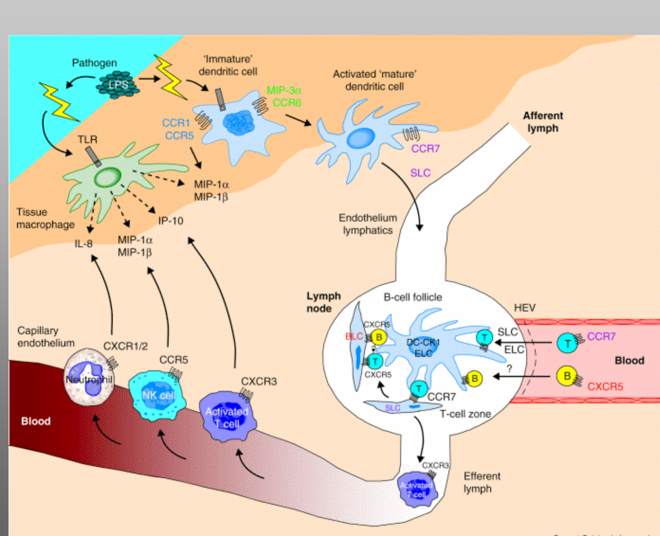
Regulatory T-cells (Tregs) in Asthma



From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

Chemokines: the Gatekeepers of Inflammation

Chemokines Direct Traffic



From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Chemokine Receptor Specificity in T_h2 Cells and Eosinophils

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

a
mpressor
cture.

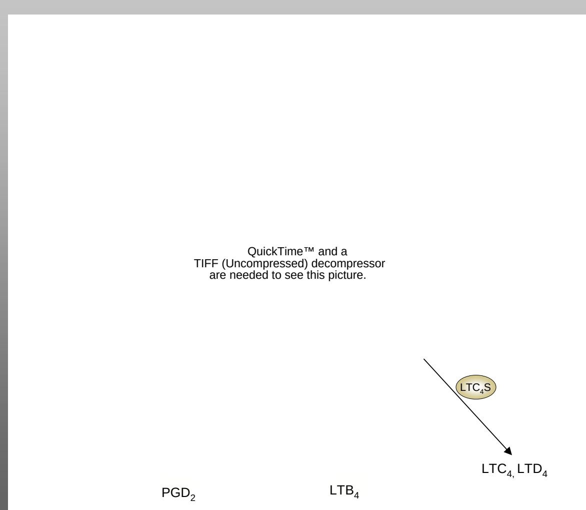
Potential Drug Targets in Asthma: Chemokines and their Receptors

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Inflammatory Mediators as Novel Drug Targets

Lipid Mediators in Asthma: LTB_4, PGD_2, LTC_4



From: Luster and Tager Nature Reviews Immunol. 4:711, 2004

Biological Activities of LTB_4 and PGD_2

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Tilley and Boucher J. Clin. Invest. **115**:13-16 (2005)

Adenosine Receptors as Drug Targets in Asthma

Pro- and Anti-inflammatory Activities of Adenosine in Asthma

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Tilley and Boucher
J. Clin. Invest. **115**:13-16 (2005)

Pharmacogenetics: The Future of Asthma Therapeutics?

Summary of Genes Associated With Atopy

Gene	Chromosome	Phenotype	Genetic variation	Association	Reference
IL10	1q31	Total IgE, eosinophils	Haplotypes	Yes	[23]
CHRM3	lq41	Atopy (cockroach)	Haplotype	Yes	[24]
IL1A	2q14	Atopy	4845G/T	Yes	[25]
CTLA4	2q33	Asthma severity	−318C/T	Yes	[26]
		BHR, asthma	−1147C/T	Yes	[27]
IL-4	5q31	AD	−590C/T	Yes	[28]
IL13	5q31	Atopy	Haplotype	Yes	[29]
IL13		Atopy	Arg130Gln	Yes	[30]
		AD	Arg130Gln	Yes	[31]
CD14	5q31	Atopy, asthma, BHR, IgE, AD, Allergic Rhinitis	−159C/T	No	[32]
UGRP-1	5q31-34	Asthma	−112G/A	Yes	[33]
B2AR	5q33-34		Arg16Gly	Yes	[34]
LTC4	5q33	Asthma	−444 (A/C)	No	[35]
		FEV_1%		Yes	
IL12B	5q33-34	Asthma severity	−4475ins	Yes	[36]
		AD	1188A/C	Yes	[37]
MHC	6p21	Asthma, total IgE	DRB1	Yes	[38]
		Atopy	DRB1, DQ	Yes	[39]
		Total, specific IgE	DRB1	Yes	[40]
		Atopy, specific IgE	DRB1	Yes	[41]
		Allergic asthma	DRB1	Yes	[42]
		Asthma	DRB1	Yes	[43]
TNF	6p21	Allergic asthma	−308G/A	No	[42]
		Allergic asthma	−308G/A	Yes	[43]
		Allergic asthma	−308G/A	No	[44]
		Childhood asthma	−308G/A	No	[45]
		Asthma	−857C/T	Yes	[46]
TCRG	7p14	Asthma, IgE		No	[47]
Eotaxin 2	7q11.23	Asthma	1265A/G	Yes	[48]
NOS3	7q36	Asthma	STR(intron 4)	Yes	[49]
		Total IgE			
NAT2	8p22	Allergic asthma	Slow acetylating allele	Yes	[50]
CC16	11q12	BHR	38A/G	Yes	[51]
		Asthma	38A/G	No	[52]
		BHR			
FCER1B	11q13	Asthma	Rsalex7	Yes	[53]
		Atopy			
GSTP1	11q13	FVC, FEV_1	Ile103Val	Yes	[54]
SART-1	11q12-13	Atopy	774C/T	Yes	[55[
			Gly485Ala		
STAT6	12q13	Allergy	2964C/A	No	[56]
			(CA)n intron 1	Yes	
			haplotype	Yes	
IFNG	12q21	Total IgE	(CA)n Intron 1	Yes	[57]
PHF11	13q14	Total IgE	Haplotype	Yes	[89]
IL4RA	16p12	Allergic asthma	Ile50Val	No	[58]
IL21R		Total IgE		Yes	[59]
CARD15	16q12	Allergic rhinitis	2104C/T	Yes	[60]
		Allergic rhinitis, AD	2722G/C	Yes	
		Atopy, total IgE	3020insC	Yes	
RANTES	17q21	Asthma (late onset)	−28C/G	Yes	[61]
		Asthma severity	−28C/G	Yes	[62]
Eotaxin-1	17q21	Total IgE	Ala23Thr	Yes	[48]
		Total IgE in AD	−426C/T	Yes	[63]
ADAM 33	20p13	Asthma	Haplotype	Yes	[94]

BHR, bronchial hyperresponsiveness; AD, atopic dermatitis; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

From: Halapi and Hakonarson, *Curr. Opin. Pulm. Med*. 10:22, 2003

Summary

1. Asthma is a chronic disease of the airways characterized by reversible airway obstruction, bronchial hyperreactivity, chronic inflammation, and mucus hypersecretion.
2. The allergic response is characterized by an early phase, dominated by degranulation of mast cells, followed by a late phase, involving T cells and eosinophils.
3. Asthma is accompanied by up-regulation of leukocyte adhesion molecules and the presence of multiple pro-inflammatory mediators, including chemokines, prostaglandins, leukotrienes, adenosine, and toxic products released from eosinophil granules.
4. Asthma is a prototypical Th2 disease, with increased production if IL-4 and IL-13, and STAT6 activation. The immunobiology of asthma is highly complex, but includes defects in the anti-viral response in airway epithelia.
5. The hygiene hypothesis states that asthma may arise from an imbalance in the Th1 and Th2 lymphocyte populations, possibly from differences in exposure to Th1-polarizing stimuli early in life.
6. An alternative view is that asthma arises from a defect in immune regulation. Insufficient production of Tregs may predispose to airway sensitization and atopy.
7. Future insights into the cellular immunology and genetics underlying asthma offer hope for future therapeutics.