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Official publication of the American College of Chest Physicians



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Chest 2008;133;100-106
DOI 10.1378/chest.07-1467

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A M E R I C A N C O L L E G E O F
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Absence of Relationships Between Tuberculin Responses and Development of Adult Asthma With Rhinitis and Atopy*

Jing Li, MD; Zhimin Zhou, MS; Jiaying An, MS; Chunqing Zhang, MD; Baoqing Sun, MS; and Nanshan Zhong, MD

Objective: To investigate the relationship between tuberculin skin responses and the development of adult asthma, rhinitis, and atopy.

Methods: Two hundred fourteen patients with mild-to-moderate asthma accompanied with rhinitis and 220 normal volunteers underwent a medical history, chest radiography, allergen skin-prick testing (SPT), bovine *Mycobacterium tuberculosis* vaccine (BCG) scar identification, purified protein derivative (PPD) tuberculin skin testing, serum-total and serum-specific IgE measurements, and bronchial provocation (provocative dose of histamine causing a 20% fall in FEV₁ [PD₂₀]).

Results: Thirty-one normal volunteers (14.1%) and 168 asthma-rhinitis subjects (78.5%) had one or more positive skin test results ($p < 0.0001$). Neither the presence of a BCG scar nor a history of BCG vaccination had a significant effect on atopy in either group. The rate of PPD positivity had no statistical difference between atopy and nonatopy in both groups. In multivariate logistic regression analysis, the odds ratio for tuberculin reactivity was not related to the level of serum-total IgE nor to the level of serum-specific IgE to *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farinae* (DF), skin response to DP and DF, and PD₂₀. Overall, no significant correlations were found between tuberculin skin reactivity and log serum-total IgE or PD₂₀.

Conclusion: There is no relationship between history of tuberculosis infection, tuberculin responses, and development of adult bronchial asthma, allergic rhinitis, and atopy. Our study suggests that the protection provided by intradermal BCG vaccination in infants to prevent atopic diseases may be limited in early childhood, when a substantial memory of cellular immune modulation still exists.

(CHEST 2008; 133:100–106)

Key words: adult; asthma; atopy; purified protein derivative skin test; rhinitis; tuberculosis infection

Abbreviations: BCG = bacille Calmette-Guérin; CI = confidence interval; DF = *Dermatophagoides farinae*; DP = *Dermatophagoides pteronyssinus*; OR = odds ratios; PD₂₀ = provocative dose of histamine causing a 20% fall in FEV₁; PPD = purified protein derivative; SPT = skin-prick test; Th1 = T-helper type 1; Th2 = T-helper type 2

The prevalence of allergic rhinitis and asthma has increased in many countries in recent decades.^{1–3} The reason for this increase is not clear but has been

largely attributed to environmental factors such as exposure to aerial pollutants^{4–5} and early life events, including the degree of exposure to infectious agents that might affect IgE production.⁶ Extensive evidence suggests that the decrease of bacterial and viral infection because of the improvement of living standard and reinforcement of vaccination may have contributed to the development of various allergic diseases.⁷ Allergic rhinitis and asthma are dominated by T-helper type 2 (Th2) lymphocyte responses when stimulated by allergens such as house dust mite, animal fur, and grass pollen in releasing interleukin-4, which promotes IgE production by B-lymphocytes.⁸

*From the First Affiliated Hospital of Guangzhou Medical School, Guangzhou Institute of Respiratory Diseases, Guangzhou, China. The authors have no conflicts of interest to disclose.

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Correspondence to: Jing Li, MD, The First Affiliated Hospital of Guangzhou Medical School, Guangzhou Institute of Respiratory Disease, 151 Yanjiang Rd, Guangzhou 510120, China; e-mail: jingli1016@vip.163.com

DOI: 10.1378/chest.07.1467

By contrast, T-helper type 1 (Th1) lymphocytes secrete interferon- γ and interleukin-2, which can inhibit B-cell production of IgE when stimulated by some respiratory infections or immunization with attenuated bacille Calmette-Guérin (BCG) vaccine.⁹ The absence of infections in childhood might, according to the microbial stimulation hypothesis, release Th2 immune mechanisms and thus promote allergic diseases.¹⁰

The tuberculin skin test with purified protein derivative (PPD) is a standard and simple test, and is still widely used to screen for tuberculosis. It is believed that a positive PPD response (5 to 15 mm of induration) indicates past tuberculosis infection, and that a strong PPD response (> 15 mm of induration) is highly suggestive of active tuberculosis. The PPD response is a delayed-type hypersensitivity reaction and is mediated primarily by a Th1 response and is supposed to be suppressed in atopic diseases. Shirakawa et al¹¹ reported an inverse association between tuberculin responses and atopic disorders in Japanese children. However, other studies^{12,13} have not observed a significant relationship between BCG vaccination during the first year of life and development of atopy in children and adults, assessed either by a questionnaire or by skin-prick testing (SPT) and measurement of serum-specific IgE antibodies. Norwegian investigators¹³ studied a group of young adults who had been vaccinated with BCG at the age of 14 years and reported no significant relationship between a positive tuberculin reaction and atopy. Although the evidence for an association between BCG vaccination and atopy is inconsistent, one could question whether the protection provided by BCG vaccination in preventing the development of allergy can extend to adulthood, or whether the memory of the immune system and capability of polarizing T-lymphocytes may be greater in early life and subsides gradually as one grows up.¹⁴

In China, the prevalence of tuberculosis infection is approximately 42 per 100,000 population, the second highest in the world. It is mandatory that BCG vaccination be administered within the first day of birth, and a scar forms later on the vaccination site. We can measure the size of the scar as an indicator of the effect of the BCG vaccination. One study showed that approximately 80% of the subjects had positive tuberculin reactions 3 months after BCG vaccination, which was reduced to 70% and 60%, respectively, 1 year and 10 years after BCG vaccination.¹⁵ We assume that the protection provided by BCG vaccination against tuberculosis infection and development of allergic diseases may be limited to populations immunized in early childhood when substantial modulation of the immune system

can occur. Therefore, we investigated the relationship between BCG scars, tuberculin skin responses, and the development of adult bronchial asthma, allergic rhinitis, and atopy.

MATERIALS AND METHODS

Study Subjects

The study was performed in the Allergy and Clinical Immunology Unit of Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical School. Two hundred fourteen patients with newly diagnosed uncontrolled mild intermittent to moderate persistent bronchial asthma¹⁶ accompanied with mild-to-moderate perennial rhinitis¹⁷ as an asthma-rhinitis group (105 men and 109 women; age range, 18 to 45 years) were enrolled in the study. All patients had symptoms of asthma and rhinitis for > 1 year. Asthma was defined by a history of recurrent dyspnea, wheezing episodes, positive airway reversibility testing (FEV₁ increasing $\geq$ 12% and 200 mL after inhalation of 400 mg of salbutamol), or positive airway responsiveness testing (FEV₁ decreasing $\geq$ 20% when $\leq$ 7.8 μ mol/L of cumulative dose of histamine is administered). Two hundred twenty healthy, sex- and age-matched subjects served as healthy group (116 men and 104 women). All subjects provided a health history, including history of BCG vaccinations and history of atopy and tuberculosis in the family, and underwent physical examination, chest radiography, peripheral eosinophil count, measurement of FEV₁, and measurement of airway responsiveness to histamine bronchoprovocation (provocative dose of histamine causing a 20% fall in FEV₁ [PD₂₀]). BCG scar identification in the deltoid region of the right arm was recorded at the study entry. Patients having an acute asthmatic attack or with any other active, acute, or chronic pulmonary diseases, and those with a history of corticosteroids use other than inhalation within the last 15 days were withdrawn from the study.

SPT

Each subject gave consent for SPT and were tested for sensitivity to 11 common aeroallergens: *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farinae* (DF), *Blomia tropicalis*, *Canis familiaris* (dog), *Felis domesticus* (cat), American cockroach, *Blatella germanica* (German cockroach), *Artemisia vulgaris*, *Ambrosia artemisiifolia*, and mold mix I and IV. Standardized allergen extracts and control solutions were obtained (ALK; Horsholm, Denmark). Histamine (10 mg/mL) and diluent were used as positive and negative controls. The weal reaction after 15 min was measured as the mean of the longest diameter and the length of the perpendicular line through its middle. The result was expressed as skin index (mean size of allergen weal/mean size of histamine weal), and a skin index $\geq$ 0.5 was considered positive. Subjects with one or more positive reactions were considered atopic.

Skin Test for PPD

PPD (0.1 mL of 0.05% PPD) [Shanghai Bioproduct Company; Shanghai, China] was administered intradermally on the volar surface of the forearm, and mean of the maximum diameter of vertical and horizontal readings of the indurations was recorded with a simple millimeter ruler after 72 h.

Serum IgE Analysis

For measurement of serum IgE, 10 mL of peripheral blood was obtained from each subject, coagulated at room temperature,

centrifuged, and stored at -20°C . Serum-total IgE, and serum-specific IgE against DP and DF levels were measured by fluorescent enzyme immunoassay (Pharmacia CAP System; Pharmacia; Uppsala, Sweden) described previously in detail.^{18–19} Serum samples were run in single determinations and evaluated against the stored calibration curve.

Spirometry and Histamine Bronchial Provocation Test

Spirometry was performed with a general spirometer linked to a computer (Gould 9000IV; Gould Recording Systems Division; Dayton, OH). Airway hyperresponsiveness was assessed using the rapid histamine inhalation provocation test in subjects whose initial FEV_1 was $> 70\%$ of the predicted value. Airway hyperresponsiveness was defined as FEV_1 decreasing $\geq 20\%$ of its baseline level when $\leq 7.8 \mu\text{mol/L}$ of cumulative dose of histamine was administered.

Statistical Analysis

All data were categorized and analyzed using the Statistical Package for the Social Sciences (Windows Release 13.0; SPSS; Chicago, IL). Serum antibody levels were log transformed in order to obtain a Gaussian distribution. Statistical analysis was performed using the Student t test, χ^2 test, and multiple logistic regression to examine the possible associations between tuberculin response (skin indurations $\geq 5 \text{ mm}$ and $\geq 10 \text{ mm}$) and the dependent variables such as serum-total IgE, serum-specific IgE to DP and DF, allergen skin response to DP and DF, as well as PD_{20} . The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). General linear regression was applied to compare continuous outcomes; $p \leq 0.05$ was considered significant. The study was approved by the Ethics Review Board of The First Affiliated Hospital of Guangzhou Medical School, and all subjects signed a consent form before entering the study.

RESULTS

The characteristics of the study and healthy control groups are presented in Table 1. By strictly adhering to the protocol of the study, the distribution of age and gender of subjects in both groups was similar. A significant higher proportion of asthma-rhinitis subjects had previous (45.8% vs 4.1%) and present (50.5% vs 2.7%) eczema as compared with healthy subjects. There were no differences between the two groups with regards to the percentage of subjects with a history of tuberculosis, focus of tuberculosis on chest radiography, and present and past cigarette smoking. Pulmonary function represented as FEV_1 was lower in asthma-rhinitis subjects, but the difference was not statistically significant, and they also had significantly lower PD_{20} values ($p < 0.001$). Peripheral eosinophil count was significantly greater in asthma-rhinitis subjects ($p < 0.001$).

Thirty one subjects (14.1%) in the healthy group and 168 subjects (78.5%) in the asthma-rhinitis group had one or more positive SPT results ($p < 0.0001$). Positive rates of SPT to DP, DF, and *B tropicalis* were 14.1%, 12.3%, and 10%, respectively, in healthy

Table 1—Characteristics of Healthy and Asthma-Rhinitis Subjects*

Characteristics	Healthy Subjects (n = 220)	Asthma-rhinitis Subjects (n = 214)	p Value
Male/female gender, No.	116/104	105/109	0.61
Age, yr	37.1 $\pm$ 3.5	38.0 $\pm$ 4.7	0.34
Previous eczema	9 (4.1)	98 (45.8)	< 0.001
Present eczema	6 (2.7)	108 (50.5)	< 0.001
BCG vaccination	218 (99.1)	211 (98.6)	0.78
History of tuberculosis	3 (1.4)	4 (1.9)	0.47
Focus of tuberculosis in chest radiograph	5 (2.3)	4 (1.9)	0.23
Present cigarette smoker	19 (8.6)	25 (11.6)	0.13
Past cigarette smoker	29 (13.3)	37 (17.3)	0.18
FEV_1 % of predicted	95.6 $\pm$ 9.8	87.2 $\pm$ 11.3	0.11
PD_{20} , $\mu\text{mol/L}$	10.8 $\pm$ 1.9	4.3 $\pm$ 2.5	< 0.001
Peripheral eosinophil count, $\times 10^6/\text{L}$	104.6 $\pm$ 63.5	289.4 $\pm$ 87.2	< 0.001

*Data are presented as No. (%) or mean $\pm$ SD unless otherwise indicated.

control subjects, while they were 65.9% (to DP or DF) and 59.3%, respectively, in asthma-rhinitis subjects ($p < 0.0001$). Skin sensitization rates to other allergens were also significantly higher in asthma-rhinitis subjects than in healthy subjects.

Table 2 shows the comparison of tuberculin responses between healthy and asthma-rhinitis subjects. The distribution of tuberculin responses did not differ between the two groups ($\chi^2 = 0.01$; $p = 0.9$). The mean tuberculin response was 7.8 mm (SE, 0.2) in healthy subjects and 8.1 mm (SE, 0.3) in asthma-rhinitis subjects ($F = 0.4$, $p = 0.5$), and it was 8.2 mm (SE, 0.2) mm in nonatopic subjects and 7.6 mm (SE, 0.3) in atopic subjects ($F = 0.1$, $p = 0.7$). The presence of BCG scar and history of BCG vaccination had no significant effect on atopy in both groups (Table 3). The rate of PPD positivity (induration $\geq 5 \text{ mm}$) had no statistical difference between atopy and nonatopy in healthy and asthma-rhinitis subjects. When adding the presence of BCG

Table 2—Comparison of Tuberculin Reactivity Between Healthy and Asthma-Rhinitis Subjects*

Induration size, mm	Healthy Subjects	Asthma-Rhinitis Subjects	χ^2	p Value
< 5	71 (32.3)	69 (32.2)	0.009	0.99
5–10	112 (50.9)	108 (50.5)	0.0002	0.99
10–15	29 (13.2)	29 (13.5)	0.16	0.70
15–20	6 (2.7)	5 (2.3)	0.07	0.79
> 20	2 (0.9)	3 (1.4)	0.23	0.62

*Data are presented as No. (%) unless otherwise indicated.

Table 3—Comparison of BCG Scars Between Atopic and Nonatopic Subjects in Healthy and Asthma-Rhinitis Groups*

Variables	Healthy		Asthma-Rhinitis	
	Nonatopic	Atopic	Nonatopic	Atopic
Total population	189	31	46	168
BCG scars				
Yes	168	25	38	138
No	21	6	8	30
χ^2		1.68		0.05
p Value		0.19		0.99

*Data are presented as No. unless otherwise indicated.

scars and/or history of tuberculosis exposure (any family member or friend with tuberculosis) to PPD positivity, again no statistically significant difference was found between atopy and nonatopy in the two groups (Table 4).

In multivariate logistic regression analysis, none of the interactions were statistically significant. The OR for tuberculin reactivity ≥ 5 mm or ≥ 10 mm was not related to the level of serum-total IgE nor to the level of serum-specific IgE to DP and DF, skin response to DP and DF, as well as PD₂₀ (Table 5). Again, no significant difference for coefficient of correlation was found in linear regression analysis

Table 4—Distribution of Tuberculin Reactivity (≥ 5 mm of Induration), BCG Scars, and Tuberculosis Exposure Between Atopic and Nonatopic Subjects in Healthy, Asthma-Rhinitis Groups*

Variables	Healthy		Asthma-Rhinitis	
	Nonatopic	Atopic	Nonatopic	Atopic
Total population	189	31	46	168
PPD ≥ 5 mm				
Yes	130	21	30	115
No	59	10	16	53
χ^2		0.01		0.17
p Value		0.87		0.73
PPD ≥ 5 mm with BCG scars				
Yes	78	14	16	62
No	52	7	14	53
χ^2		0.34		0.27
p Value		0.60		0.63
PPD ≥ 5 mm with BCG scars and tuberculosis exposure				
Yes	32	8	4	22
No	46	6	12	40
χ^2		1.25		0.62
p Value		0.25		0.45

*Data are presented as No. unless otherwise indicated.

between tuberculin skin reactivity and log serum-total IgE values as well as PD₂₀ (Fig 1).

DISCUSSION

This study demonstrates that the magnitude of tuberculin response was similar among asthma-rhinitis and healthy, atopic and nonatopic Chinese adults in the Guangdong area. There was no association between tuberculin response, presence of BCG scars, and asthma and rhinitis as well as atopy. These results were consistent in both the univariate and multivariate analyses.

We employed allergen SPT, serum-total, and serum-specific IgE levels as markers to indicate atopic status of our study subjects. These markers are widely used and well recognized and have been applied widely in many epidemiologic studies. A significant relationship between serum-total IgE and specific IgE as atopic markers in a randomly drawn population from Norway²⁰ indicates that serum IgE measurements are highly related to atopy in Western environments. One recent study²¹ also showed that serum-total IgE and serum-specific IgE correlated significantly with allergen SPT in Indian asthmatics with food allergy. We therefore believe that serum-total and serum-specific IgE, like allergen skin testing, are useful markers of atopy in our study.

Asthma and rhinitis patients were enrolled from our outpatient clinic, and age-matched healthy control subjects were selected from the subjects who came to our hospital for a routine health check-up. According to the report of Guangdong Centre of Disease Control and Prevention, the prevalence of tuberculous disease in Guangdong area has been approximately 42 per 100,000 population, which is much higher than in Western countries.²² The policy of BCG vaccination of all newborn children at 24 h or no later than 1 year after birth in China has long been established. The study subjects were born between 1960 and 1987, when $> 95\%$ of population had received BCG vaccination. During their 20 to 45 years of life, it is likely for them to be exposed to viral and bacterial infections including *Mycobacterium tuberculosis*. Therefore, it allowed us to investigate whether tuberculin responses, early BCG vaccination, and history of tuberculosis infection have an impact on the development of asthma and rhinitis, as well as atopic status in this group of adults. From history review and chest radiography, we could not find differences in the percentage of BCG vaccination (99.1% vs 98.6%), past tuberculosis infection (1.4% vs 1.9%), and pulmonary fibrous and calcified tuberculosis focus (2.3% vs 1.9%) between healthy and asthma-rhinitis subjects, which suggests that early BCG vaccination and tuberculosis infection do not influence the occurrence of allergic symptoms and diseases.

Table 5—Logistic Regression Analysis of Relationship Between Tuberculin Skin Reactivity and Serum-Total IgE, Serum-Specific IgE to DP and DF, Skin Response to DP and DF, as Well as PD₂₀ in All Subjects

Variables	PPD ≥ 5 mm			PPD ≥ 10 mm		
	OR	95% CI	p Value	OR	95% CI	p Value
Log serum-total IgE	0.771	0.308–1.934	0.581	1.071	0.505–2.276	0.859
Log serum-specific IgE to DP	0.362	0.031–4.183	0.432	0.536	0.051–5.586	0.602
Log serum-specific IgE to DF	0.620	0.208–3.026	0.471	0.427	0.126–6.182	0.774
SPT response to DP	0.941	0.728–1.218	0.645	0.790	0.639–1.697	0.092
SPT response to DF	1.200	0.728–1.218	0.086	1.227	0.836–1.452	0.081
PD ₂₀	1.211	0.954–1.536	0.105	0.890	0.735–1.078	0.234

The Th2 hypothesis for asthma states that atopy is caused by a relative increase in Th2 response in combination with a decrease in Th1 response. Shirakawa et al¹¹ observed an inverse association in

Japanese children between tuberculin responses and atopic disorders. They showed that a strongly positive PPD response was associated with a lower incidence of allergic disease, lower levels of serum

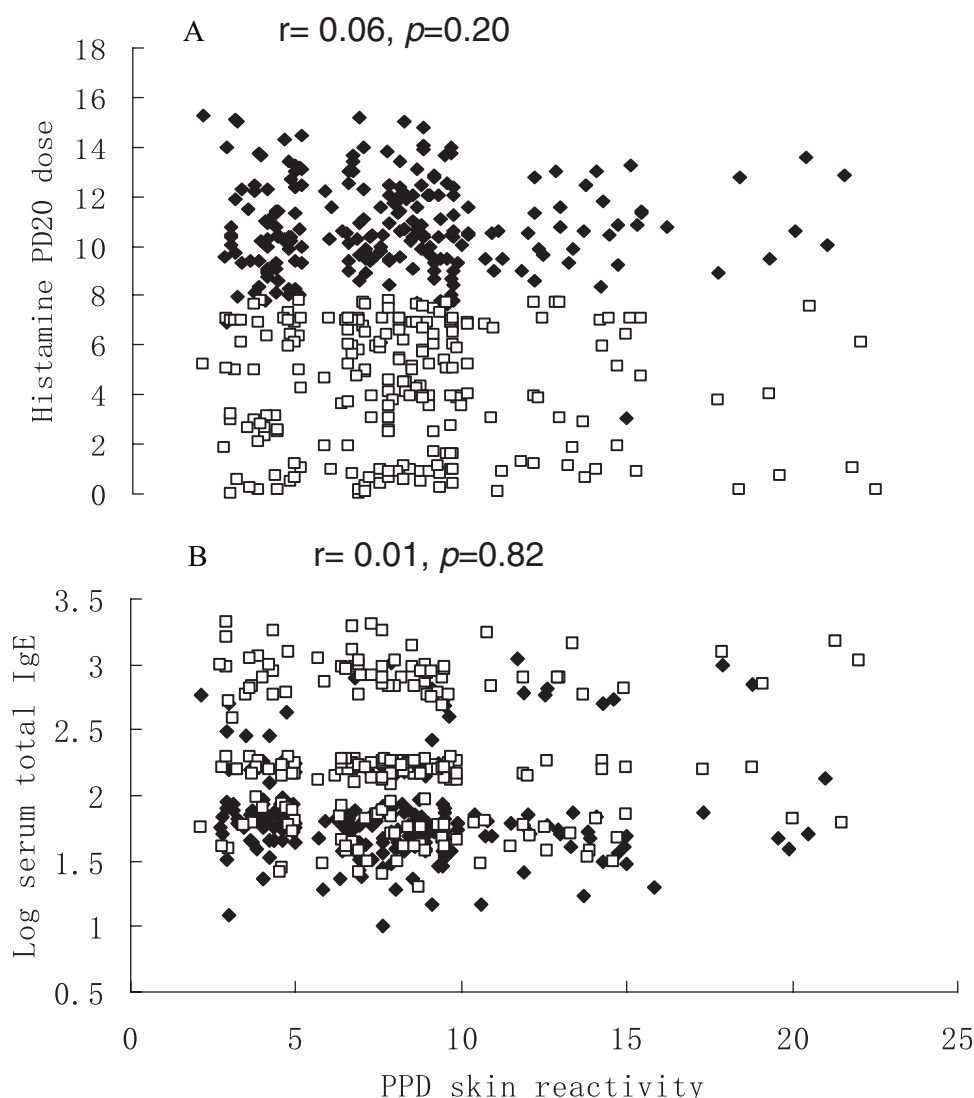


FIGURE 1. Linear regression between tuberculin skin reactivity and PD₂₀ (top, A) and serum-total IgE (bottom, B) from all subjects. Solid diamonds indicate healthy subjects; open squares indicate asthma-rhinitis subjects.

IgE, and higher levels of Th1 cytokines. However, other epidemiologic studies from areas with a low prevalence^{13,23–24} and high incidence^{25–27} of tuberculosis showed no differences between allergic and healthy children with respect to PPD induration and PPD positivity rates, which suggests that the Th1 response is not completely suppressed in atopic subjects. However, one study²⁸ in Turkey showed that PPD induration in atopic asthmatic children was statistically significantly greater than in healthy children, indicating that when the relationship between tuberculin response and atopy is studied in tuberculosis-prevalent countries, it should be taken into consideration that the PPD response can be stronger and overemphasized as an active infection in atopic asthmatic subjects.

The PPD response is variable and depends not only on BCG vaccination in early life, but also on tuberculosis infection later in life, or sensitization to environmental mycobacteria. The PPD response is mediated by primary Th1 response, which is expected to be suppressed in atopic asthmatics and rhinitis patients. However, we did not find any evidence that it induces less or weaker tuberculin responses or lower proportion of previous tuberculosis exposure and infection in our atopic subjects. Several factors could have accounted for this. A high prevalence of tuberculosis infection and ubiquitous exposure to mycobacteria in our environment could have diluted its effect on atopy, and one would expect to demonstrate its impact in settings with lower levels of exposure. It is also likely that the time and route of BCG vaccination or duration of exposure to mycobacteria might be critical in influencing the development of atopy.²⁹ It is speculated that the memory of cellular immunity induced by BCG vaccination in infancy in our study subjects was attenuated 20 to 45 years later, and did not provide enough protection for them from atopic diseases. Evidence obtained from animal models shows that vaccines administered via the mucosa are able to elicit neutralizing serum antibodies and cell-mediated immune responses as well as mucosal secretory IgA antibodies.³⁰ Thus, it is possible that vaccines delivered by mucosal surfaces would stimulate vigorous cell-mediated immune responses similarly in humans and efficaciously protect against tuberculosis infection as well as atopic diseases.³⁰ However, currently available BCG vaccination administered intradermally in humans has not shown any protective effect against atopic diseases.³¹ However, some studies^{32–33} showed that a progressive increase in type 1 diabetes, a Th1-related disease, in the face of increasing prevalence of atopy in developed countries suggests that the pathogenesis of atopy could be more complicated than only a shift in

Th1/Th2 balance. It has also been reported that there is an increased frequency of interferon- γ -producing CD4+ and CD8+ T-cells in asthmatics compared with normal subjects.³⁴ In contrast to the Th2 hypothesis, these results suggest that Th1 responses may have a role in atopy pathogenesis.

In conclusion, we did not observe significant relationships between history of tuberculosis infection, tuberculin responses, and development of adult bronchial asthma, allergic rhinitis and atopy. Our study suggests that the protection provided by BCG vaccination intradermally in infancy from atopic diseases may be limited in early childhood, when a substantial memory of cellular immune modulation still exists.

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Absence of Relationships Between Tuberculin Responses and Development of Adult Asthma With Rhinitis and Atopy

Jing Li, Zhimin Zhou, Jiaying An, Chunqing Zhang, Baoqing Sun and Nanshan Zhong

Chest 2008;133;100-106
DOI 10.1378/chest.07-1467

This information is current as of January 15, 2008

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