Immunological findings and respiratory function in cotton textile workers*

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Summary. Immunological parameters were studied in a group of 24 cotton textile workers. These were volunteers from a cohort of 106 (83 women and 23 men) previously studied textile workers. A group of 30 employees from a bottle packing plant served as a control for the immunologic studies. The subgroup of volunteers undergoing immunologic testing did not differ from the original cohort of textile workers in age, sex, smoking history, or prevalence of most chronic respiratory symptoms, nor were there any significant differences in baseline lung function or across-shift changes. The 24 cotton worker volunteers underwent skin testing with extracts of cotton dust and cotton seed. Eight of these 24 (33.3%) had positive tests, and 5 of the 8 had elevated serum immunoglobulin E (IgE) levels. Only one of the 8 skin-test-positive workers had symptoms of byssinosis. Only 1 of 30 control workers' skin tested with cotton extract reacted, and none had an increased serum IgE level ($P < 0.01$). Both baseline lung function and across-shift changes did not differ between workers with positive and negative skin test reactions or between workers with normal and elevated IgE levels. Additionally, we studied the response in vitro of nonsensitized guinea pig trachea to cotton bract extract and demonstrated a dose-dependent contractile response. These data suggest that while immunological findings are frequent in textile workers, they correlate poorly with respiratory symptoms and function and may not be the basis for the airway obstruction seen in this disease.

Key words: Cotton dust – Respiratory function – Allergy – Guinea pig

Introduction

Respiratory findings, particularly byssinosis, are associated with the inhalation of cotton and other textile dusts (Schilling et al. 1963; Merchant et al. 1973; Zuskin and Valic 1975; Bouhuys 1976; Zuskin et al. 1976; Beck et al. 1982). These symptoms are usually accompanied by acute reductions in lung function which may ultimately lead to chronic, irreversible changes. Recently, we have described a cohort of textile workers in a Yugoslav cotton textile mill (not the current one studied) seen over the past 10 years, illustrating the chronic effects of textile dust exposure in a group of cotton workers (Zuskin et al. 1991).

The mechanism by which textile dust causes bronchospasm is unknown, but pharmacologic intervention as well as in vitro models suggest a number of possible mechanisms (Hitchock et al. 1973; Ellisalde and Greenblatt 1979; Kutz et al. 1979; Schachter et al. 1981; Ainsworth and Neuman 1981). There are only a few reports examining the possibility of an allergic etiology of byssinosis and the accompanying lung function changes in textile workers. Cayton et al. (1952) reported no correlation between skin reactions to cotton dust extract and symptom of Monday chest tightness in textile workers. Massoud and Taylor (1964) described an antibody directed against an antigen present in the cotton plant. The amount of antibody was higher in cardroom workers than in controls, and it was highest in workers with byssinosis. Edwards and Jones (1973) demonstrated that "cotton antigen" extracted from cotton bracts nonspecifically precipitated 58% of immunoglobulin G (IgG), 54% of IgM, and 15% of IgA in human serum. The allergenic properties of cotton and flax spinning mill dust were studied by Fetisova et al. (1970), who suggested that the properties of these industrial dusts were due to the presence of bacteria and fungi in the dust. Similarly, O'Neil et al. (1983) proposed that an IgE-mediated hypersensitivity against cotton dust or a fungal compo-

nent of the dust may be important in the pathogenesis of byssinosis. Oehling et al. (1978) and Popa et al. (1969) also concluded that an allergic component contributed to the byssinosis.

The interaction of preexisting atopy and exposure to cotton dust in the bronchoconstrictor response was described by Jones et al. (1980) and Sepulveda et al. (1984). Salvagio et al. (1986) suggested that cotton-dust-induced respiratory disease may be due to preexisting or occupationally induced mold allergy and proposed that atopy predisposes to byssinotic reactions. Ig assays in textile workers showed high IgG values among workers with work-related symptoms, especially cough, but not among those with bronchitis symptoms. By contrast, a very low percentage of atopy (2%) was described by Petronio and Bovenzi (1983) in cotton textile workers. The data presented by Mundie et al. (1985) do not support an immune complex etiology for byssinosis. Finally, skin testing with an aqueous extract of cotton bract by Schachter et al. (1985) suggest that a nonspecific inflammatory reaction (and not an atopic one) initiated by mast-cell-derived mediators may be responsible for some of the airway effects observed in byssinosis.

As can be appreciated from the preceding, there is no consensus on the role of immune mechanisms in byssinosis and relatively few epidemiologic studies on this issue. In the present study, we investigated immunological status by skin testing with cotton dust and cotton seed extracts, bacteria, and fungi and measured the serum IgE levels in a cohort of cotton workers; these findings were correlated with the presence of respiratory symptoms and ventilatory capacity changes.

Subjects and methods

Epidemiological study

Subjects. Some 83 women and 23 men were initially studied in one cotton textile mill located in a community on the coast of Yugoslavia. They represented 90% of all the workers in the mill. Twenty-four of these textile workers underwent immunologic testing. The comparison between workers who were tested and those whe not are listed in Tables 1 and 2. A group of 30 workers not exposed to cotton dust (20 women and 10 men) of similar age and smoking habits employed in the packing of bottles of fruit juice was used as a control for comparing respiratory symptoms and immunological findings.

Textile workers were employed in the opening of bales and the operation of carding, spinning, and weaving machines. Opening bales and carding were performed in one large area, while spinning and weaving were located in a separate area. Both areas, however, were only partially separated, and workers frequently changed jobs from one area to the other.

Immunological studies. Cotton dust and cotton seed extracts were prepared using standard immunological techniques employing the dust collected from the workroom where workers were examined (Sheldon et al. 1967). In addition, workers were skin tested with histamine base (0.01 mg/ml) and antigenic preparations of bacteria, mold, *Dermatophagoides pteronyssinus,* as well as a buffer solution used as a control. Bacterial antigen was prepared from *Haemophilusa influenza, Streptococcus pneumoniae, Str. viridans, Str. pyogenes,* and *Staphylococcus aureus* in a concentration of 60×10^6 per ml. Mold antigen was prepared from a mixture of *Alternaria, Penicillium, Mucor, Cladosporium, Aspergillus niger,* and Asp.

fumigatus in 0.2% solution. The skin reactions were read after 20 min. A skin test was considered positive if the diameter of the observed wheal was > 3 mm.

The serum level of total IgE was determined by a reference laboratory PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden) using the direct radioimmunologic "sandwich" technique. Levels of IgE below 125 IU/ml were considered normal.

Respiratory symptoms. Chronic respiratory symptoms were recorded using the British Medical Research Council Committee (1960) questionnaire on respiratory symptoms with additional questions on occupational asthma (WHO 1986) and on byssinosis (Schilling et al. 1963). In all workers, a detailed occupational history as well as questions about their smoking habit were recorded.

The following definitions were used:

Chronic cough or phlegm: cough and/or phlegm production for at least 3 months per year

Chronic bronchitis: cough and phlegm for a minimum of 3 months a year and for not less than 2 successive years

Dyspnea grades: grade 3, shortness of breath when walking with other people at an ordinary pace on level ground; grade 4, shortness of breath when walking at their own pace on level ground

Occupational asthma: recurring attacks of dyspnea, chest tightness, and pulmonary function impairment of the obstructive type diagnosed by physical examination and spirometric measurements during exposure to dust at or following work

Byssinosis grades: grade 1/2, occasional chest tightness on Monday; grade 1, chest tightness and/or difficulty in breathing on Monday only; grade 2, chest tightness and/or difficulty in breathing on Mondays and other working days

Ventilatory capacity was measured in all cotton workers by recording maximum expiratory flow-volume (MEFV) curves using a portable flow-volume spirometer (Pneumoscreen, Jaeger, Germany). Measurements were performed on the first working day of the week (Monday) before (6 a.m.) and after (2 p.m.) the work shift. The forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and maximum flow rates at 50% and the last 25% of the control vital capacity were measured on these curves (FEF50 and FEF25). At least three MEFV curves were recorded, and the best value was used as the result of the test. The measured Monday preshift values of ventilatory capacity were compared with the expected normal values of the Commission des Communautes Européennes (1971) for FVC and the FEV1 and of Cherniack and Raber (1972) for FEF50 and FEF25.

Statistical analysis. The results of ventilatory measurements were analysed by using the t-test for differences of paired (across-shift) and unpaired (comparing baseline to predicted values) variables. The χ^2 test was used for testing differences in the prevalence of respiratory symptoms. Value of $P < 0.05$ was considered statistically significant.

Environmental dust measurements. Airborne dust in the cotton mill was sampled with Hexhlet horzizontal two-stage samplers during the 8-h workshift at the worksite of the examined workers. Airborne dust samples were collected in the areas where workers were examined. Dust concentrations were expressed separately for the total and respirable dust fractions.

Cotton bract extract assay

In order to investigate the potential of cotton dust to produce a contraction of unsensitized airway smooth muscle, we tested the bronchoconstricting potential of cotton bract extract on guinea pig trachea. Bracts were obtained after frost (and thus after senescence). Aqueous extracts were prepared and purified as previously described (Buck et al. 1983). After mixing pulverized bract with water and removing insoluble debris by centrifugation, the crude

extract thus obtained was sterilized by passage through a 0.45-μm filter. This preparation is used for routine airway challenge and for classifying subjects as responders and nonresponders. Further purification was obtained by precipitating polymeric material by the addition of methanol, removing negatively charged components by diethylaminoethanol (DEAE)-Sephacel chromatography, and removing lacinilenes by ether extraction to produce the DEAE-ether-extracted preparation.

We used the trachea of young Albino Hartly male guinea pigs (300–390 g) purchased from Perfection Breeders, Penn. Animals were sacrified by CO_2 asphyxiation for 2 min, and the trachea was removed within 3 min. The animal tissues were normally trimmed of excess fat and connective tissues. Four segments ("rings" each 4–6 mm wide) were cut from a single trachea, and each was suspended between two L-shaped stainless steel hooks mounted in a 20-ml organ chamber containing Krebs-Hanseliet buffer of the following composition (in μM): NaCl, 110.0; KCl, 4.80; $CaCl_2$, 2.35; $MgSO_4$, 1.20; KH_2PO_4, 1.20; $NaHCO_3$, 25.0; dextrose, 11.0; and Na_2-EDTA, 0.03 in glass-distilled water. The organ chambers were maintained at 36.5° ± 0.5°C and were continuously aerated with 95% O_2 and 5% CO_2 to maintain a pH of 7.5 ± 0.1. The tissue segments were initially set to 2 g of tension and were allowed to relax for approximately 1.5 h before the experiment began. During that period, the tissue was washed at 15-min intervals. After the relaxation period, the tension in each tissue segment was adjusted to 2 g for all subsequent assays. Isometric contractions were recorded using a Grass FTO3C force displacement transducer attached to a Grass polygraph recorder. Before and after the concentration-response assays with cotton bract extract were performed, a challenge with carbachol 10^{-5} M was performed. A dose-response curve with cotton bract extract was obtained by adding progressively increasing volumes of extract or Krebs solution (used as a control) into the tissue bath in progressive aliquots of 10, 30, 100, 300, and 1000 μl. The potency of the extract was determined by comparing the biological activity with the maximal contraction induced by carbachol (10^{-5} M) on the same tissue. The data are expressed as a percentage of the initial maximal carbachol contraction (10^{-5} M).

Results

Expidemiological study

Respiratory symptoms. Table 1 presents the prevalence of chronic respiratory symptoms in workers who were skin tested and in those who were not. There were no significant differences between these two groups of workers except among women for sinusitis (skin tested 27.8%; not skin tested 7.7%; $P < 0.03$) and for byssinosis (skin tested 50.0%; not skin tested 26.2%; $P < 0.05$).

Ventilatory capacity. The data on ventilatory capacity in female and male cotton workers is presented separately for those workers skin tested and those who were not (Table 2). While characteristic reductions for almost all ventilatory capacity parameters and across-shift changes were seen in female and male workers, no significant differences were noted between volunteers who were skin tested and those workers who were not. In relation to predicted values, the measured FEF25 showed the lowest percentage (range 90.5%–75.1%).

Immunological studies. Table 3 presents individual and summary data for 8 cotton workers with positive skin tests to at least one of the two cotton extracts. Among 24

Table 1. Prevalence of chronic respiratory symptoms in cotton workers

Sex	Group	Smoking habit	Age (years)	Exposure (years)	Chronic cough	Chronic phlegm	Chronic bronchitis	Dyspnea	Asthma	Nasal catarrh	Sinusitis	Byssinosis
F	Skin tested (n = 18)	5 / 27.8%	26	5	6 / 33.3% / NS	3 / 16.7% / NS	2 / 11.1% / NS	0 / 0% / NS	0 / 0% / NS	6 / 33.3% / NS	5 / 27.8% / <0.03	9 / 50.0% / <0.03
	Not skin tested (n = 65)	27 / 41.5%	27		9 / 13.8%	5 / 7.7%	3 / 4.6%	1 / 1.5%	0 / 0%	10 / 15.4%	5 / 7.7%	17 / 26.2%
M	Skin tested (n = 6)	3 / 50.0%	30	5	2 / 33.3% / NS	2 / 33.3% / NS	2 / 33.3% / NS	1 / 16.7% / NS	1 / 16.7% / NS	3 / 50.0% / NS	3 / 50.0% / NS	1 / 16.7% / NS
	Not skin tested (n = 17)	11 / 64.7%	31	4	5 / 29.4%	4 / 23.5%	4 / 23.5%	0 / 0%	0 / 0%	3 / 17.6%	2 / 11.8%	1 / 5.9%

NS, Difference not statistically significant ($P > 0.05$)

Table 2. Ventilatory capacity in cotton workers

Sex	Group	Measurement	FVC Before shift L	FVC Difference before–after shift Percentage	FVC P	FEV1 Before shift L	FEV1 Difference before–after shift Percentage	FEV1 P	FEF50 Before shift L/s	FEF50 Difference before–after shift Percentage	FEF50 P	FEF25 Before shift L/s	FEF25 Difference before–after shift Percentage	FEF25 P
F	Skin tested (n = 18)	Measured	3.98 ± 0.50	−4.1	<0.01	3.01 ± 0.40	−5.1	<0.01	4.56 ± 0.56	−5.5	<0.01	2.49 ± 0.70	−5.8	<0.01
		Percentage predicted	95.8			97.5			95.3			89.8		
	Not skin tested (n = 65)	Measured	3.84 ± 0.40	−3.2	<0.01	3.15 ± 0.39	−4.5	<0.01	4.43 ± 0.39	−7.0	<0.01	2.60 ± 0.70	−9.9	<0.01
		Percentage predicted	93.4			97.1			91.9			90.5		
M	Skin tested (n = 6)	Measured	5.07 ± 0.90	−2.5	NS	4.10 ± 0.70	−2.5	NS	5.68 ± 0.80	−7.1	<0.05	2.55 ± 0.60	−9.2	<0.05
		Percentage predicted	97.9			91.5			90.2			76.5		
	Not skin tested (n = 17)	Measured	5.18 ± 0.90	−2.0	<0.05	4.20 ± 0.68	−2.4	<0.05	5.90 ± 0.70	−8.3	<0.01	2.59 ± 0.71	−13.5	<0.01
		Percentage predicted	95.1			95.4			95.5			75.1		

Ventilatory capacity data are presented as mean ± SD

FVC, Forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF50, FEF25, maximum flow rates at 50% and last 25% of control vital capacity

Table 3. Ventilatory capacity in cotton workers with positive skin tests to cotton allergens

Subject	Age (years)	Exposure (years)	IgE (IU/ml)	Byssinosis grades	FVC Difference before–after shift (%)	FVC Percentage predicted	FEV1 Difference before–after shift (%)	FEV1 Percentage predicted	FEF50 Difference before–after shift (%)	FEF50 Percentage predicted	FEF25 Difference before–after shift (%)	FEF25 Percentage predicted
1	40	1	98	0	−6.2	108.0	−14.7	103.0	−25.6	75.4	−27.8	64.3
2	37	6	480	0	−3.2	82.0	−8.1	88.0	−8.5	87.7	−10.5	65.5
3	39	2	53	1	−2.0	90.4	−2.8	98.4	−2.3	100.0	−14.3	60.9
4	23	3	170	0	−9.4	89.0	−8.8	92.6	−6.2	78.7	−9.5	62.8
5	25	1	200	0	−0.7	112.9	−1.3	100.7	−3.2	63.9	−11.1	62.1
6	21	2	380	1/2	−1.5	109.9	−5.0	111.6	−10.6	90.4	−9.0	71.0
7	29	11	900	0	−0.3	100.0	−1.3	109.8	−8.6	104.2	−10.0	103.7
8	43	8	44	0	−8.5	102.4	−8.4	102.9	−16.3	95.5	−17.9	54.5
Mean ± SD	32 ± 8.6	4.3 ± 3.7	291 ± 291	0.2 ± 0.4	−4.0 ± 3.6	99.3 ± 11.1	−6.3 ± 4.6	100.5 ± 8.2	−10.2 ± 7.6	87.0 ± 13.6	−13.8 ± 6.4	68.1 ± 15.1
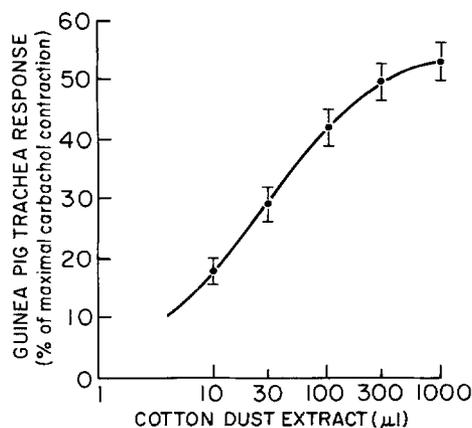
Fig. 1. Contractile responses of cotton bract extract in guinea pig trachea, expressed as a percentage of maximal carbachol (10^{-5} M) contraction (mean ± SE)

skin-tested cotton workers, 8 (33.3%) reacted to either cotton dust or cotton seed antigen. Four (16.7%) reacted to *Dermatophagoides*, 8 (33.3%) to bacteria, and none to fungi. Five among 8 workers (62.5%) with positive skin tests had an increased IgE serum level ranging from 170–900 IU/ml, while only 2 of 16 (12.5%) cotton workers with negative skin tests had an increased IgE serum level (155 IU/ml and 210 IU/ml; $P < 0.05$). Two workers among the 8 skin-test-positive workers (25.0%) had symptoms of byssinosis, and 8 of the 16 (50.0%) skin-test-negative workers had byssinosis (NS). All 8 workers with positive skin tests demonstrated across-shift decreases in ventilatory capacity, being particularly pronounced for FEF25 (range 9.5%–27.8%). The across-shift changes were, however, not in general greater than those in workers with negative skin tests. In comparison with predicted normal values, 1 out of the 8 workers had FEF50 and 6 workers had FEF25 below 70% of predicted normal values. This was similar to workers with negative skin tests. By contrast, among 30 control workers only 1 (3.3%) reacted to cotton dust and also to cotton seed and bacteria. None had an increased serum IgE level ($P < 0.01$).

Cotton bract extract assay

The mean data for the effect of cotton bract extract on isolated (unsensitized) guinea pig tracheal smooth muscle are shown in Fig. 1. A total of 17 guinea pigs were studied and the contractile response to 10, 30, 100, 300, and 1000 µl of cotton bract extract were tested. The results are presented as a percentage of an initial maximal contraction produced by stimulation with 10^{-5} M carbachol. This demonstrates the dose-response data of the water-soluble cotton bract extract, which caused an average increase of basal tension of up to 53% of the maximal carbachol contraction. A control Krebs solution added in the same volume to control tissues did not cause changes in the basal tone of the guinea pig tracheal rings.

Discussion

Our data support previous studies which have demonstrated that chronic respiratory symptoms and changes in lung function characterize workers in the textile industry (Christiani et al. 1986a, b; El Karim et al. 1986; Elwood et al. 1986; Kamat et al. 1981). Immunology tests in 24 of the textile workers studied suggests a high prevalence of immunologic responses in the form of specific skin test reactions and elevated IgE levels. The latter two were highly correlated in this group. By contrast, there was no association between respiratory symptoms and lung function abnormalities and the immunologic changes.

The etiology of lung disease in cotton workers has been attributed to many causes and has recently been reviewed (O'Neil et al. 1982; Butcher et al. 1983). These can be grouped under three primary headings: (1) pharmacologic, which includes a nonspecific mediator release and/or a direct action of dust components on smooth muscle; (2) microbiologic, which involves bacteria and/ or their metabolic products (notably endotoxin); (3) immunologic, including humoral antibody production. None of these models is entirely satisfactory. Our data suggest that immunological responses are frequent in cotton workers. Among 24 textile workers skin tested, 8 (33.3%) reacted positively to cotton dust or cotton seed extracts, a rate which was significantly greater than among control workers (3.3%) ($P < 0.01$). Furthermore, in our study IgE was increased in a majority of cotton workers with positive skin tests to cotton allergens (62.5%), while only 2/16 (12.5%) of skin-test-negative workers and of control workers had increased IgE levels. Nevertheless, these immunologic findings were not related to clinical disease.

Rylander and Haglind (1986) argue that the bacterial contamination of cotton and the prevalence of symptoms among exposed workers are related. Such a relationship would be compatible with the findings of the current study. However, Buck et al. (1985) found that aqueous extracts of cotton bract contain agent(s) other than endotoxin were capable of causing airway constriction in healthy volunteers. The role of endotoxin cannot be addressed directly from our data.

The data of Witek et al. (1988) suggest that an inflammatory reaction may be involved in the effect of cotton dust, accounting for changes in airway reactivity. As in the case of Popa et al. (1969), the skin tests described were delayed. Our study did not document any delayed response to skin testing. Possible differences in antigen preparation may account for these variations.

The present studies on isolated guinea pig trachea suggest a model for the clinical findings obtained in workers. Such data indicate that cotton bract extract has component(s) that can induce nonimmunologic airway constriction by a direct action on the guinea pig airway smooth muscle. The guinea pigs used in these experiments were not presensitized to cotton dust. A number of other investigators have demonstrated the ability of cotton dust as well as of bract extract to produce airway constriction in various animal preparations both in vivo and in vitro (Davenport and Patton 1962; Russell et al.

1982; Buck et al. 1986). The importance of these observations in the current context is to emphasize the nonimmunologic nature of the response to this environmental agent.

The mean total dust concentration in this cotton mill was 3.69 mg/m³ with a respirable fraction of 1.01 mg/m³. These levels are within the maximum concentrations for vegetable dust allowed by Yugoslav occpuational standards (total dust 5 mg/m³; respirable fraction 1 mg/m³). However, they are higher than those allowed by American standards and may be associated with the high prevalences of immunologic responses as well as the clinical findings.

Byssinosis continues to be a major occupational problem in those countries where high dust concentrations persist in the work environment. Many lines of evidence suggest that some of the clinical findings in byssinosis are due to a nonspecific inflammatory responses rather than specific immunologic reactions. While immunologic findings were frequent in these workers employed under conditions of high dust exposure, our study failed to demonstrate a strong association between the respiratory findings and allergic indices. The data from both our clinical and in vitro studies are compatible with a nonallergic basis for byssinotic findings.

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