Cotton Dust and Endotoxin Exposure-Response Relationships in Cotton Textile Workers[1-4]

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SUMMARY Endotoxin exposure has been implicated in the etiology of lung disease in cotton workers. We investigated this potential relationship in 443 cotton workers from 2 factories in Shanghai and 439 control subjects from a nearby silk mill. A respiratory questionnaire was administered and pre- and postshift forced expiratory volume (FVC) and flow in one second (FEV_1) were determined for each worker. Multiple area air samples were analyzed for total elutriated dust concentration (range: 0.15 to 2.5 mg/m^3) and endotoxin (range: 0.002 to 0.55 μg U.S. Reference Endotoxin/m^3). The cotton worker population was stratified by current and cumulative dust or endotoxin exposure. Groups were compared for FEV_1, FVC, FEV_1/FVC%, % change in FEV_1 over the shift (ΔFEV_1%), and prevalences of chronic bronchitis and byssinosis, and linear and logistic regression models were constructed. No dose-response relationships were demonstrated comparing dust concentration to any pulmonary function or symptom variable. A dose-response trend was seen with the current endotoxin level and FEV_1, ΔFEV_1%, and the prevalence of byssinosis and chronic bronchitis, except for the highest exposure level group in which a reversal of the trend was seen. The regression coefficients for current endotoxin exposure were significant ($p < 0.05$) in the models for FEV_1 and chronic bronchitis but not in the models for ΔFEV_1% (i.e., acute change in FEV_1) or byssinosis prevalence. The coefficient for dust level was never significant in the models. We conclude that exposure to increasing levels of airborne endotoxin is associated with an increased risk of pulmonary abnormalities among cotton workers, although those workers exposed to the highest levels may represent a "survivor population." The fact that we failed to show a significant relationship between exposure and acute change in FEV_1 suggests that other etiologic factors may also be important.

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Introduction

Lung disease among cotton textile mill workers is not a new problem, but the etiology of the acute and chronic lung response is still not determined.

It is widely accepted that some component of the bract of the cotton plant or an associated contaminant is responsible for the acute response (1, 2). In addition, higher dust levels have been shown to correlate with an increased risk of acute symptoms (3, 4). The dose-response relationship for chronic functional impairment is less evident, although there is some evidence demonstrating an association with increasing length of employment (3, 5). However, there is also increasing experimental evidence that dust from various cottons are not equally potent in producing an acute response (6).

Several recent investigations have focused on the hypothesis that microorganisms or their constituents (notably gram-negative bacterial endotoxin) may be key factors in the etiology of cotton dust lung disease (7-9). In an experimental study, Castellan and coworkers (7) found that an acute drop in FEV_1 correlated highly with endotoxin level among volunteers specifically selected for reactivity to cotton dust with high endotoxin content. The correlation with endotoxin was much greater than that to dust level alone.

We sought to further investigate this potential relationship in the working population of two Chinese cotton textile mills. A cross-sectional study carried out in these mills in 1981 revealed mild byssinosis among 8% of the workers and increased pulmonary symptoms and acute cross-shift decrements in FEV_1 compared with control silk mill workers (10, 11). Area-specific dust levels in the two cotton mills were similar; however, subsequent endotoxin analysis of the dust filters revealed significantly different levels in airborne endotoxin (12). Thus, these mills provided an opportunity to assess the relative roles of dust and endotoxin in the production of breathing disorders in cotton workers in a workplace environment.

Methods

Details of the population studied, questionnaires, and pulmonary function testing have been reported previously (10, 11). These are summarized below.

Population

We studied 443 workers in the yarn preparation areas of 2 Shanghai cotton mills and a control population of 439 workers from a nearby silk mill who denied previous exposure to cotton dust or to cotton-silk blends.

Workers in all 3 mills were comparable with respect to income status and residence. The 2 cotton mills were built in the 1920s and current ventilation systems were installed in the late 1950s.

Questionnaires and Pulmonary Function Testing

Questionnaire administration and pulmonary function testing were carried out on each worker before entering the workshop after a 48-h rest period. Function tests were repeated at the end of the shift.

A standardized respiratory questionnaire (13) was modified to include work related symptoms for the classification of byssinosis

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(according to Roach and Schilling (14)) as well as past employment histories. This was administered by trained interviewers using the local dialect.

Because of unusual work-shift schedules the classic Monday morning pattern for byssinosis was difficult to assess. Thus, byssinosis was defined as definite work-shift related chest tightness or shortness of breath, which improved away from work (10). Chronic bronchitis was defined as cough or sputum from the chest for at least 3 months per year for 2 or more consecutive years.

Function testing was performed using a Collins 8L. Stead-Wells spirometer under the direction of one technician, according to the American Thoracic Society (ATS) criteria for spirometric techniques for epidemiologic studies (15). The values used were the highest of at least 3 acceptable blows. Function tests not meeting the ATS criteria for reproducibility (15) were not included in the analyses.

Environmental Assessment

Airborne dust was collected using vertical elutriators (General Metal Works Inc.) designed to collect particles less than 15 μ aerodynamic diameter. Multiple area samples were collected from each of the 6 different work areas in the 2 mills, on at least 2 different days for each area. Collection time varied from 3 to 7 h per sample, and 130 samples were collected. Procedures were in accordance with the National Institute for Occupational Safety and Health (NIOSH) recommended guidelines (16), except that the height of the elutriators was set between 1.35 and 1.4 meters to compensate for the shorter height of the work force.

Samples were collected on 5 μ polyvinyl chloride hydrophobic filters and weighed to an accuracy of 10^{-5} g. The filters were then wrapped individually (dust face down) in parafilm (Parafilm M, American Can Co., Greenwich, CT) and sent to the United States for endotoxin analysis. Dust samples were not obtained from the silk mill.

Endotoxin Analysis

The procedures for endotoxin analysis of bulk samples and filters have been described in detail elsewhere (12). The samples were extracted from both filters and parafilm wrappers using sterile nonpyogenic water and duplicate analyses of the supernatant fluids were quantified using a Limulus amebocyte lysate gel test (Pyrostat-50). Results were compared to a standard curve and reported in nanograms of U.S. Reference Endotoxin. The values for each filter and its corresponding parafilm wrapper were summed and further converted from ng/ml to μg/m³ air using the air-flow rate of the sampler and the sampling time.

Endotoxin analysis was carried out on 40% of the filters collected. This reduction in data was due to inadvertent destruction of several samples and to loss during transport.

Statistical Analysis

Prediction formulas for pre- and postshift FEV_1, FVC, and FEV_1/FVC were derived from the silk worker population using age, age², height, and pack-years in the models. The acute change in FEV_1 over the work shift was expressed as

$$\frac{\text{preshift } FEV_1 - \text{postshift } FEV_1}{\text{preshift } FEV_1} \times 100 = \Delta FEV_1\%.$$

Cumulative exposures to dust and endotoxin were estimated for each worker by assigning an exposure level to each work area and summing the product of exposure level times years employed in that area for all work areas reported by the worker. Thus, cumulative dust exposure and cumulative endotoxin exposure were differently weighted sums of combinations of years exposed in various work areas, based on the assumption that current exposure levels were a fair representation of historic levels since 1950. The natural log transformation of these values was used for regression analyses.

Dose-response relationships were analyzed first by stratifying on exposure (current or cumulative) and second by using linear and logistic regression models.

The stratified analysis was done as follows: workers were divided into 4 groups based on the median endotoxin exposure level in their current work area and into 4 different groups according to the median current dust levels (Table 1). The population was also stratified into 5 groups based on cumulative endotoxin exposure and 5 different groups based on cumulative dust exposure (with approximately equal numbers in each group).

Strata were compared for percent-predicted pulmonary function, $\Delta FEV_1\%$, and for the prevalence of byssinosis and chronic bronchitis. These latter prevalences were standardized for sex and smoking habits by the direct method, using the characteristics of the silk population as the reference, in order to compare across strata.

Multivariate linear and logistic regression models were constructed to relate measured function parameters and symptom prevalences to current or cumulative dust or endotoxin exposure separately (as continuous variables), controlling for sex, age, height, and pack-years of smoking.

TABLE 1

COTTON DUST AND ENDOTOXIN CONCENTRATIONS IN AREA SAMPLES COLLECTED BY VERTICAL ELUTRIATORS

	Dust (mg/m³)		Endotoxin (μg/m³)	
	Plant 1	Plant 2	Plant 1	Plant 2
Opening*	1.83† (1.65 to 2.14)‡ 4§ / Group‖ 4	1.15 (0.42 to 2.50) 27 / Group 3	0.24 (0.13 to 0.46) 4 /Group 3	0.11 (0.05 to 0.18) 27 / Group 2
Blowing	1.06 (0.59 to 2.32) 24 / Group 3		0.50 (0.28 to 0.92) 24 / Group 4	
Carding	1.17 (0.73 to 2.26) 44 / Group 3	1.83 (0.48 to 2.47) 37 / Group 4	0.53 (0.32 to 0.71) 44 / Group 4	0.22 (0.08 to 0.55) 37 / Group 3
Drawing	0.49 (0.21 to 1.16) 35 /Group 1	1.58 (0.46 to 2.21) 26 / Group 4	0.10 (0.02 to 0.24) 35 / Group 2	
Combing	0.31 (0.19 to 0.41) 26 / Group 1	0.66 (0.19 to 0.98) 48 / Group 2		0.07 (0.05 to 0.11) 48 / Group 2
Roving	0.43 (0.15 to 0.61) 54 / Group 1	0.46 (0.42 to 0.61) 39 / Group 1	0.23 (0.07 to 0.41) 54 / Group 3	
Fine spinning*		0.59 (0.28 to 0.80) 79 / Group 2		0.002 (0.001 to 0.02) 79 / Group 1

* Plant 1: Fine spinning not tested; Plant 2: Opening and blowing combined.
† Median.
‡ Range.
§ No. of workers in area.
‖ Exposure groupings for stratified analysis based on current exposure level.

Results

Population

A total of 448 cotton workers and 439 silk workers participated in the study. This represented a 90% participation rate for daytime workers in areas sampled in both industries. Five cotton workers were subsequently excluded because they had not worked regularly in any one work area and thus could not be assigned exposure levels. There were 39 cotton workers and 67 silk workers with missing or nonreproducible function testing. These were excluded from the analysis of lung function parameters but included for the analysis of symptoms. Although Eisen and colleagues (17) have shown that such exclusion of subjects with function test results which do not meet the ATS criteria for reproducibility tends to exclude a more diseased subset of individuals, we were unable to include even maximal test results for these workers as the data were no longer readily available.

Workers in all three mills were comparable for age, height, and sex distribution but differed in the number of smokers and the years of employment patterns (table 2). There was only 1 ex-smoker and only 8 female smokers (4 in Cotton Plant 1, 3 in Cotton Plant 2, 1 silk worker). Over one half (58.2%) of the cotton workers had not changed jobs during the course of their employment, and only 6.1% (27 workers) had held more than two different jobs.

Environmental Data

The results of the area sampling for both respirable dust (< 15 μ) and endotoxin are shown in table 1. To assess the importance of the filters lost before endotoxin analysis could be carried out, we recalculated the mean area dust concentrations based only on those filters which had both dust and endotoxin analysis. Comparison of these results with the original calculations showed no significant difference in any of the mean values. We concluded that the endotoxin levels as calculated from the reduced number of filters were representative of the actual values.

The range of dust concentrations was similar in the two cotton mills: 0.15 to 2.34 mg/m³ in Plant 1 and 0.19 to 2.50 mg/m³ in Plant 2. There was approximately a sixfold difference in the mean levels for different work areas (0.31 to 1.83 mg/m³). The U.S. standard for yarn preparation is 0.2 mg/m³.

The endotoxin concentration range differed between the two cotton mills: 0.02 to 0.92 μg/m³ in Plant 1; 0.002 to 0.55 μg/m³ in Plant 2. There was a 250-fold difference in the area mean levels.

The estimated cumulative exposure variables for dust and endotoxin reflected these range differences. Cumulative dust exposure correlated highly with years exposed ($r = 0.82$), whereas cumulative endotoxin exposure did not ($r = 0.27$). Cumulative endotoxin exposure correlated well with current exposure ($r = 0.70$). The correlation coefficients relating current exposure level and years exposed were −0.06 for dust and 0.08 for endotoxin.

Stratified Exposure-Response Analysis

The mean FEV_1 (% predicted), mean $\Delta FEV_1\%$, and prevalence rates of chronic bronchitis and byssinosis for the 4 current endotoxin exposure groups and 4 current dust exposure groups are shown in figure 1.

Mean FEV_1 measured preshift decreased in relation to increased current endotoxin exposure. The mean FEV_1 levels in the two highest current endotoxin exposure groups (95.9 and 97.7% of predicted) were significantly less than FEV_1 in the lowest exposure group (102.1% of predicted) ($p < 0.05$). When the groups were stratified according to current dust exposure they did not differ significantly with respect to FEV_1.

The FVC and $FEV_1/FVC\%$ did not differ significantly across exposure groups using either stratification scheme.

No significant differences were found across exposure groups for the acute change in FEV_1 over the work shift. The within-group variance in $\Delta FEV_1\%$ was high in every group (total variance = 51.8%), and the differences in group means were comparatively small (2 to 5%); thus the power to detect significant differences was very low. The results shown in figure 1A do suggest, however, a dose-response trend for $\Delta FEV_1\%$ in relation to current endotoxin exposure except in the highest exposure group in which a reversal of the trend is seen.

The prevalence of chronic bronchitis increased with increasing current endotoxin exposure level (prevalence = 12.6, 16.5, 23.0, 24.5% in strata 1 to 4, respectively; χ^2 test for trend, $p < 0.001$, see figure 1B). Byssinosis prevalence showed a similar dose-response trend in relation to the 3 lower endotoxin exposure categories (prevalence = 2.5, 6.4, 9.5% in strata 1 to 3, respectively). However, the prevalence of byssinosis in the highest endotoxin exposure category was the lowest overall (prevalence = 1.8%). This group was comprised solely of carders and blowroom workers in Cotton Plant 1.

We regrouped the cotton worker population into five strata based on cumulative endotoxin exposure and five strata based on cumulative dust exposure. The only significant dose-response trend seen was an increase in the prevalence of chronic bronchitis in relation to increased cumulative dust exposure (prevalance = 12.9, 13.5, 20.4, 16.9, 27.2% in strata 1 to 5, respectively).

Finally, we compared the group with the lowest current endotoxin exposure (i.e., Cotton Plant 2, fine spinning department) with the silk worker population. For this analysis we excluded 9 workers from the spinning department who had

TABLE 2

DEMOGRAPHIC, SMOKING, AND EMPLOYMENT DATA FOR EMPLOYEES STUDIED AT 2 COTTON TEXTILE PLANTS AND A SKILL MILL*

	Cotton Plant 1 187 (*n*)	Cotton Plant 2 256 (*n*)	Silk Mill 439 (*n*)
Male	47%	48%	42%
Age (yr)	36.2 ± 10.8	38.1 ± 10.3	35.7 ± 10.7
Height (cm)	164.4 ± 7.5	163.6 ± 7.4	162.6 ± 7.2
Smokers			
Males	74%	69%	55%
Females	4%	2%	0.4%
Pack-years†	8.8 ± 9.4	9.4 ± 10.5	9.1 ± 9.9
(median)	(5.0)	(4.0)	(4.9)
Years employed	14.7 ± 10.6	17.8 ± 9.7	16.7 ± 11.9
(range)	(1 to 41)	(4 to 42)	(1 to 49)
Workers employed for < 5 yr	29%	2%	18%
Workers employed for ⩾ 25 yr	29%	34%	28%

* Values are mean ± SD.
† For smokers only.

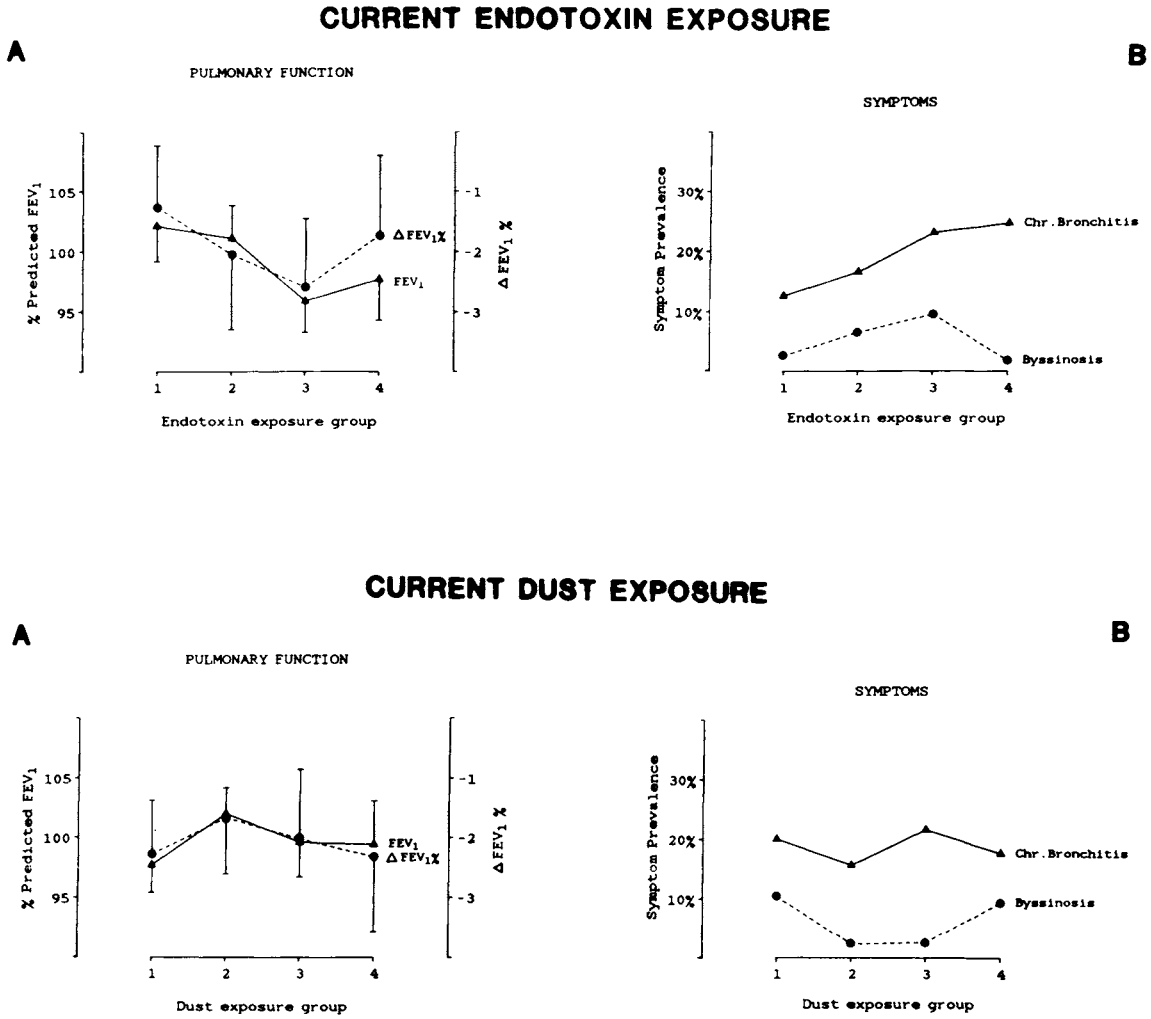

Fig. 1A. Mean values (± 95% C.I.) for preshift percent predicted FEV_1 (▲———▲) and cross-shift change in FEV_1 (ΔFEV_1% ●- - - -●), stratified according to current exposure to endotoxin or dust. B. Group mean prevalence rates (%) for chronic bronchitis (▲———▲), and byssinosis (●- - - -●), stratified according to current exposure to endotoxin or dust, standardized for sex and smoking status to the silk worker population. Note: Connecting lines drawn between points for clarity in viewing only.

previously worked elsewhere in Cotton Plant 2. Pulmonary function and symptom prevalence data are displayed in table 3. There were more male smokers in the cotton group than in the silk group (42.8% versus 23%, $p < 0.01$), so the symptom prevalences for the cotton workers were standardized for sex and smoking status to the silk worker population. The cotton group had a significantly larger cross-shift drop in actual FEV_1 (mean FEV_1 drop = 386 ml compared with 7 ml in the silk workers $p < 0.05$); the difference in ΔFEV_1% was marginally significant ($p = 0.06$). We found no other pulmonary function differences between the two groups. An increased prevalence of chronic bronchitis and byssinosis was present in this group of cotton workers relative to the silk workers.

Regression Analysis

The coefficients and their significance levels for smoking and exposure variables derived from linear and logistic regression models for FEV_1, ΔFEV_1%, chronic bronchitis prevalence, and byssinosis prevalence are shown in tables 4 and 5. Since the stratified analysis indicated the possibility that the carders and blowroom workers from Cotton Plant 1 may represent a healthier group due to self-selection (i.e., compared to next highest exposure group, these workers had a higher FEV_1, a smaller ΔFEV_1%, and the lowest byssinosis rate of all groups), we repeated the regression analyses after excluding these workers. The results from both sets of analyses are included in tables 4 and 5.

TABLE 3

COMPARISON OF LOWEST ENDOTOXIN EXPOSURE GROUP TO CONTROL SILK POPULATION*

	Silk Workers ($n = 439$)	Plant 2 Fine Spinners ($n = 70$)
Age	35.7 ± 10.7	40.4 ± 9.7†
Years employed	16.6 ± 11.9	20.1 ± 9.9†
FEV_1 (% predicted)	100.0 ± 12.5	101.6 ± 12.8
FVC (% predicted)	100.0 ± 10.8	99.3 ± 10.7
FEV_1/FVC%	100.0 ± 8.5	102.5 ± 9.4
ΔFEV_1 (L)	−0.0007 ± 0.144	−0.0386 ± 0.129†
ΔFEV_1%	+0.29 ± 6.7%	−1.14 ± 4.7%
Byssinosis	0	3.1%
Chronic bronchitis	7.1%	14.1%†

* Values are mean ± SD. Symptom prevalences for cotton workers directly standardized for sex and smoking status to silk population.

† Differs from silk workers ($p < 0.05$)

TABLE 4

REGRESSION COEFFICIENTS FOR SMOKING (PACK-YEARS) AND EXPOSURE (DUST OR ENDOTOXIN) IN PULMONARY FUNCTION MODELS*

		Current Exposure		Cumulative Exposure	
Pulmonary Function	Smoking/ Exposure	All Workers ($n=317$)	Excluding Plant 1 Carders and Blowers ($n=257$)	All Workers ($n=317$)	Excluding Plant 1 Carders and Blowers ($n=257$)
FEV_1 (preshift)	Pack-years	−0.010†	−0.008‡	−0.010†	−0.009‡
	Endotoxin	−0.242§	−0.778†	−0.018	−0.018
	Dust	+0.023	−0.059	+0.031	+0.037
$\Delta FEV_1\%$	Pack-years	−0.021	−0.078	−0.019	−0.086
	Endotoxin	−0.150	−4.960	−0.160	−0.261
	Dust	−0.026	+0.207	−0.236	+0.002

* General models: (1) FEV_1 pre = $\beta_0 + \beta_1$ (age) + β_2 (sex) + β_3 (height) + β_4 (pack-years) + β_5 (exposure) + ε. (2) $\Delta FEV\% = \beta_0 + \beta_1$ (age) + β_2 (pack-years) + β_3 (exposure) + ε.
† $p < 0.01$.
‡ $p < 0.05$.
§ $p < 0.10$.

TABLE 5

REGRESSION COEFFICIENTS FOR SMOKING (PACK-YEARS) AND EXPOSURE (DUST OR ENDOTOXIN) IN LOGISTIC REGRESSION MODELS FOR CHRONIC BRONCHITIS AND BYSSINOSIS*

		Current Exposure		Cumulative Exposure	
Symptom	Smoking/ Exposure	All Workers ($n=326$)	Excluding Plant 1 Carders and Blowers ($n=271$)	All Workers ($n=326$)	Excluding Plant 1 Carders and Blowers ($n=271$)
Chronic bronchitis	Pack-years	0.075†	0.044‡	0.073†	0.040§
	Endotoxin	1.700‡	2.232	0.141§	0.110
	Dust	−0.009	−0.053	0.001	0.044
Byssinosis	Pack-years	0.036	0.026	0.045	0.041
	Endotoxin	0.443	4.730§	0.078	0.140
	Dust	−0.147	−0.036	−0.170	−0.167

* General model: $\ln [p/(1-p)] = \beta_0 + \beta_1$ (age) + β_2 (sex) + β_3 (pack-years) + β_4 (exposure) + ε.
† $p < 0.01$.
‡ $p < 0.05$.
§ $p < 0.10$.

TABLE 6

PULMONARY FUNCTION TEST RESULTS, COMPARING SMOKERS AND NONSMOKERS STRATIFIED BY INCREASING LEVEL OF CURRENT ENDOTOXIN EXPOSURE*

	Current Endotoxin Exposure Groups			
	1 (0.002 μg/m³)	2 (0.10 μg/m³)	3 (0.23 μg/m³)	4 (0.52 μg/m³)
FEV_1 preshift (% predicted)				
Smokers	101.7 ± 12.6	100.3 ± 13.0	94.3 ± 12.0	97.3 ± 14.3
Nonsmokers	102.4 ± 12.6	101.4 ± 13.6	96.7 ± 12.7	98.5 ± 10.9
$\Delta FEV_1\%$				
Smokers	−2.21 ± 2.9	−2.53 ± 6.5	−3.24 ± 4.9	−1.67 ± 4.8
Nonsmokers	−0.72 ± 5.2	−1.86 ± 6.1	−2.26 ± 5.5	−1.85 ± 5.9

* Values are means ± SD.

The results indicate a dose-response relationship between preshift FEV_1 and current endotoxin exposure but not between FEV_1 and dust level. When the highest endotoxin exposure category was excluded, the coefficient associated with current endotoxin level increased from −0.242 L per μg/m³ ($p < 0.10$) to −0.778 L per μg/m³ ($p < 0.01$).

In the models for $\Delta FEV_1\%$, none of the exposure or smoking variables was significant, although excluding the high exposure group again resulted in a very large change in the coefficient for current endotoxin exposure (from −0.150% per μg/m³ to −4.96% per μg/m³).

Chronic bronchitis prevalence increased significantly with current endotoxin exposure ($\beta = 1.70$, $p < 0.05$), whereas dust exposure level was not found to be significant in the model. Exclusion of the Plant 1 carders and blowroom workers made little change in the model for chronic bronchitis. The model for byssinosis prevalence, however, did not include smoking or exposure as significant variables in either analysis. The coefficient for current endotoxin exposure changed from 0.433 to 4.73 ($p = 0.06$) with the exclusion of the workers in the high exposure area.

When estimated cumulative exposure was entered into the regression models in place of current exposure, no exposure variable was significant in relation to pulmonary function or symptom prevalence. This suggested that current endotoxin exposure level was a better predictor for chronic bronchitis and a reduced FEV_1 than cumulative exposure. To test this possibility, the models were reanalyzed after entering the current and cumulative exposure variables simultaneously. In every case, these two exposure variables negated each other's effect, indicating that we could not distinguish the significance of one over the other.

Smokers versus Nonsmokers

Mean values for preshift FEV_1 and for the cross-shift drop in FEV_1 were compared for smokers and nonsmokers in the four strata determined by current endotoxin levels (table 6). Smokers had consistently lower preshift FEV_1 values and a greater cross-shift decrement than did nonsmokers, but the dose-response trend of a greater functional decrement with increased exposure levels for Strata 1, 2, and 3 and a reversal of the trend for Strata 4 was still seen in both groups. Regression analyses for preshift FEV_1 and $\Delta FEV_1\%$ were repeated using categorical variables for smoking (smoker or nonsmoker), current endotoxin exposure (Categories 1 to 4), and an interaction term between smoking and exposure. The significance level of the interaction term was greater than 0.40 in every case.

The prevalence of byssinosis was 6.7% among smokers and 8.2% among nonsmokers ($p > 0.50$).

Discussion

Our results support the hypothesis that a decline in lung function and an increase in symptom prevalence among cotton workers correlate more closely with endotoxin levels than with the mass of elutriated cotton dust.

We hypothesized that cumulative exposures would correlate better with baseline lung function and symptom prevalence than would current exposure levels. However, we were unable to

distinguish clearly between the effects of current and cumulative endotoxin exposure.

Our estimates of cumulative exposure assumed that past exposure levels were similar to current ones. This is difficult to establish, particularly because other investigators have shown that the endotoxin content of cotton varies greatly with its grade, handling procedure, and geographic source (12, 18). We were unable to confirm that the two cotton mills in this study received cottons of consistent grade or from the same locations in the past. It is not surprising, then, that we could not determine whether cumulative or current exposure was a better predictor of lung function and symptom prevalence.

We also hypothesized that cross-shift change in FEV_1 may relate best to current endotoxin exposure level. This was not supported by the results, in contrast to the experimental studies of Castellan (7) and Rylander (8) that demonstrated a positive correlation between an acute FEV_1 drop and endotoxin exposure. However, Castellan and colleagues specifically selected subjects with a large cross-shift positive response to high endotoxin cotton, and in Rylander's study, only the mean responses for groups were correlated with endotoxin exposure. Similarly, when our subjects were divided into exposure groups the mean values indicated a dose-response trend in the lower exposure categories; however, the considerable variation within groups precluded finding any significant exposure component in the regression model. These studies suggest that the wide degree of individual variability in cross-shift change in FEV_1 perhaps obscures dose-response tendencies when a general population rather than a reactive population is studied.

Our results also showed that the workers in the highest endotoxin exposure category (i.e., Plant 1 carders and blowroom workers) had less byssinosis, a smaller cross-shift change in FEV_1, and better baseline function than those workers in the next highest exposure category. Given the dose-response relationships observed across exposure Strata 1 to 3, this strongly suggests that the high exposure group had either become less reactive as a result of repeated high exposures (i.e., tolerance) or that the group was a survivor population. The latter is more likely, given that baseline function in the highest exposure group was, on the average, better than expected. Company officials confirmed that, several years before our study, older workers were encouraged to retire early to provide jobs for younger workers, and there was also an active program of medical removal for workers with "asthma."

However, the dose-response relationship observed for chronic bronchitis and current endotoxin exposure did not spare workers in the highest exposure areas, suggesting that the presence of either an acute drop in FEV_1 over the shift or the symptoms of byssinosis (i.e., chest tightness or shortness of breath at the beginning of the shift) were more likely to result in job transfer or resignation, whereas an increased amount of cough and phlegm could be tolerated as long as baseline function had not deteriorated substantially. The continued upward trend in chronic bronchitis at the highest exposure levels, in the absence of byssinosis, suggests that the two symptom complexes – acute airway response (byssinosis) and chronic cough and phlegm (chronic bronchitis) – may be independent pathologic responses to cotton dust.

Further evidence that these responses may be independent is provided by the fact that smoking status and pack-years were not related to byssinosis prevalence, whereas smokers did have more chronic bronchitis and a greater functional decrement at all endotoxin exposure levels.

Animal data reported by Kutz and colleagues (19) also supports the concept of a different pathogenesis for the acute and chronic responses to endotoxin aerosols. They found a reversible increase in arterial-alveolar O_2 gradient 1 h after exposure but a nonreversible decrease in arterial O_2 level at 5 and 24 h after exposure.

The histologic picture reported in animals exposed to cotton extract or endotoxin aerosols includes an influx of polymorphonuclear leukocytes to small airway walls 6 to 24 h after exposure (20, 21) followed by a chronic inflammatory response including lymphocytes and macrophages (19, 20). This response is similar to that seen in experimental animals following cigarette smoke exposure (22, 23) and in human smokers (24). Cosio and associates (24) have suggested that such small airway inflammation may be the primary event in the pathogenesis of chronic air-flow obstruction. Similarly, it is possible that airway inflammation in response to endotoxin may lead to chronic air-flow obstruction among cotton workers. The relationship of this process to the acute response is unclear both in experimental and epidemiologic studies. Rylander and coworkers (9) and Haglind and Rylander (25) have not found any consistent relationships in human volunteers, among endotoxin exposure level, acute FEV_1 response, and an increase in peripheral blood leukocyte count (9, 25). Recent experimental evidence that washing of cotton may reduce the cross-shift drop in FEV_1 (26) needs to be clarified in terms of its impact on the development of chronic lung impairment.

Finally, we attempted to assess the presence of a threshold level of endotoxin exposure by comparing the silk workers with cotton workers who had always worked in an area with very low endotoxin levels (< 20 ng/m^3). We found no difference in baseline spirometry, but the increased prevalence of byssinosis and chronic bronchitis and the augmented cross-shift change in FEV_1 suggest that even exposure to endotoxin at 1 to 20 nanograms per cubic meter constitutes an "adverse respiratory health effect" as defined by the American Thoracic Society guidelines (27).

In conclusion, the results of this study support the hypothesis of a dose-response relationship between endotoxin levels in cotton dust and chronic lung impairment among cotton workers. However, the difference in the prevalence pattern between byssinosis and chronic bronchitis and the failure to show a significant relationship between the acute FEV_1 drop and endotoxin level are not explained by this hypothesis. The potential importance of other exposure factors cannot be ruled out, and further research seems warranted to identify other biologically active agents in cotton dust.

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