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Skin testing with an aqueous extract of cotton bract

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Airway challenge with cotton bract extract (CBE) causes reversible bronchospasm in most volunteers never before exposed to CBE or the textile industry. Lung function abnormalities develop slowly after inhalation with a maximum effect reached within 2 hours and lung function slowly improving thereafter. When CBE was injected intradermally in three naive subjects with negligible airway response to CBE, we observed an initial wheal-and-flare reaction within minutes followed by erythema and subsequent induration that persisted for 24 to 48 hours. Microscopic examination of skin biopsy specimens obtained during the course of these reactions revealed edema in the early phase followed by perivascular infiltration of a mixed cellular nature in the subsequent stages of the reaction. Degranulation of mast cells was noted throughout the course of the reaction. These findings indirectly suggest that a nonspecific inflammatory reaction initiated by mast cell-derived mediators and sustained by the presence of infiltrating cells may be responsible for some of the airway effects observed in byssinosis. (J ALLERGY CLIN IMMUNOL 76:481-7, 1985.)

Byssinosis is an occupational lung disease associated with the inhalation of cotton and other textile dusts.¹⁻⁴ Early manifestations of this disease are characterized by reversible symptoms such as chest tightness and shortness of breath that accompany exposure to cotton dust, particularly early in the work week.

Abbreviations used

CBE: Cotton bract extract
MEF: Maximal expiratory flow
DEAE: Diethylaminoethyl

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These symptoms are usually accompanied by changes in lung function that slowly abate after exposure.⁵

The symptoms and physiologic changes of early byssinosis can be reproduced in healthy, naive subjects never before exposed to cotton dust by the inhalation of an aerosol of a water-soluble extract of cotton bracts.⁶ Although most healthy subjects will show some decrease in lung function after exposure

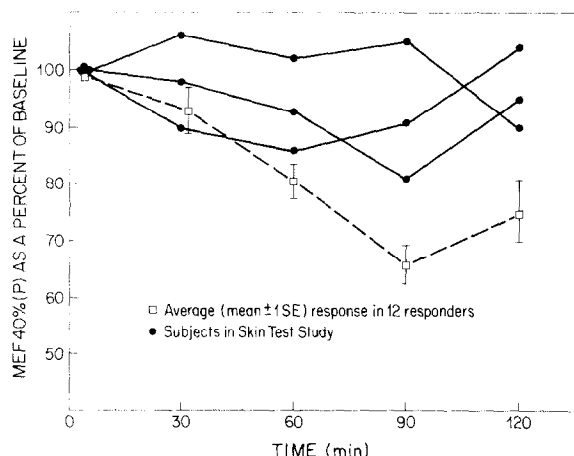


FIG. 1. Response of MEF 40%(P) over time in three subjects undergoing skin testing. Group of responder subjects ($n = 12$) is illustrated for comparison.

to such an aerosol, the magnitude of the response to a standardized dose varies. These differences have allowed us to classify subjects into responder and non-responder groups.⁷ This spectrum of severity in airway reactivity may possibly explain why some individuals develop clinically important disease.

The mechanism by which CBE causes bronchospasm is unknown, but pharmacologic intervention as well as in vitro models suggest a number of possible mechanisms⁸⁻¹³ (Table I). Intradermal injection of airway irritants (e.g., histamine and antigens) has proved useful in studying the inflammatory mechanism of such agents.^{14, 15} To date only limited experience is reported with skin testing by use of extracts derived from cotton dust.¹⁶ We describe here observations of the macroscopic and microscopic skin response to intradermal injections of CBE.

MATERIAL AND METHODS

Bracts from cotton (Paymaster 111 variety) were obtained from Texas cotton fields in 1979. These samples were obtained after frost (and thus after senescence). Aqueous extracts were prepared and purified as previously detailed.¹⁷ After mixing pulverized dried bracts with water and removing insoluble debris by centrifugation, the crude extract thus obtained was sterilized by passage through a 0.45 micrometer 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 addition of methanol, removing negatively charged components by DEAE sephacel chromatography, and removing lacinilenes by ether extraction to produce the DEAE ether-extracted preparation. This preparation was used for our skin testing experiments. Airway challenge with this extract demonstrates that it retains >50% of the bronchoconstricting activity of the crude ex-

TABLE I. Postulated mechanisms for CBE-induced bronchospasm

- (1) CBE contains antigenic components that trigger an antibody-dependent reaction
- (2) CBE contains mediator compounds
- (3) CBE contains compounds that trigger an inflammatory response

Such a reaction may involve:

Chemotactic factors
Complement
Cyclic nucleotides
Mast or other cells

tract. A single large quantity of the crude CBE was prepared. The crude extract was freeze-dried for storage and reconstituted for individual challenges. This approach was used to assure standardization of concentration for the active agent(s). Skin testing material (DEAE ether-extracted preparation) was prepared from this standard crude extract.

Each dose of CBE was reconstituted to its original concentration in 10 to 12 cc of buffered solution. For airway challenge, this solution was subsequently aerosolized by use of a Dautrebande D-30 nebulizer. The nebulizer is attached to the subject's mouthpiece via a J valve. A reservoir tubing was attached to the valve to ensure uniform concentration. The aerosol nebulizer was powered by compressed air under a constant pressure of 20 psi. Under such circumstances the output of the nebulizer is constant, and the particle size delivered has been measured to be less than 1 μ m in diameter, ensuring delivery of aerosol beyond large airways. Subjects inhaled the aerosol under conditions of normal tidal breathing for a total of 10 minutes.

A pneumotach integrator system¹⁸ was used to measure lung function and to define responder status. Flow was plotted against volume. Partial and MEF volume curves were obtained. The maneuver consisted of an initial inspiration to approximately 70% of vital capacity followed by a forced exhalation to residual volume. The subject next inspired to total lung capacity and once again exhaled forcefully to residual volume. These maneuvers generated partial and maximal flow volume curves. The flow rate at 60% of the baseline vital capacity below total lung capacity was measured on partial curves. This flow rate, the MEF40%(P), has been found to be particularly sensitive to small degrees of bronchospasm.¹⁹ Responders to CBE are designated as individuals whose MEF40%(P) falls more than 20% following CBE inhalation. Similar significant changes are observed with the FEV₁, but the changes are smaller. Our experience with >100 healthy volunteers demonstrates that approximately half fall into the responder category. It should be noted however, that this distribution is continuous and normal, not bimodal, suggesting that response to CBE is ubiquitous in the healthy population, but responder status represents one end of the distribution.⁶

This study examined the histopathologic effects of intradermal injections of CBE. In three healthy volunteers, 0.1

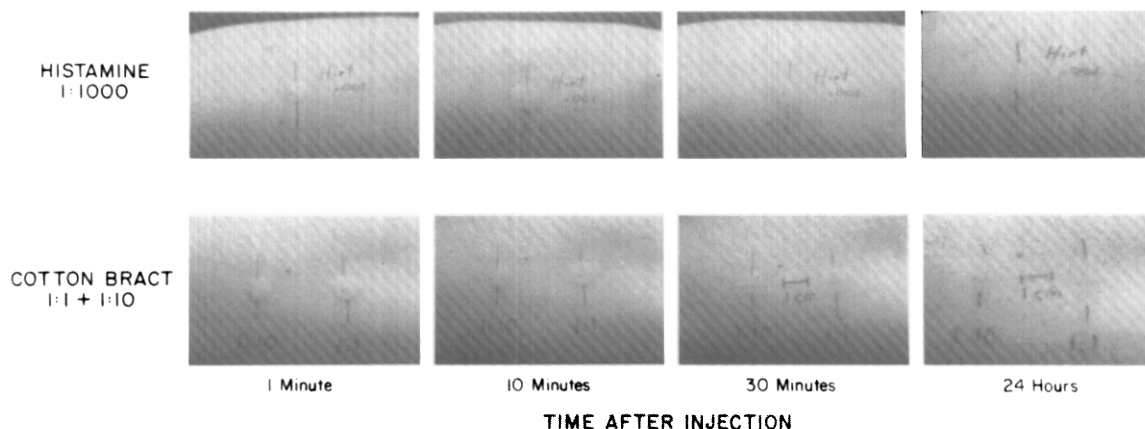


FIG. 2. Skin test response (*macroscopic*) to intradermal injection of CBE at dilutions of 1:1 and 1:10. Response to histamine 1:1000 illustrated for contrast. Histamine was injected in the right forearm. The two dilutions of CBE are injected in the left forearm.

cc of CBE was injected intradermally by use of a tuberculin syringe in the volar surface of the forearm. Two dilutions of CBE in normal saline were injected 1:1 and 1:10. On the volar surface of the contralateral arm, 0.1 cc of histamine in a dilution of 0.001 mg/cc was also injected for comparison.

In the same three individuals 0.1 cc of the undiluted DEAE ether extract was injected intradermally by use of a tuberculin syringe at three different sites of the buttocks. Skin biopsies were performed at 15 minutes, 3 hours, and 24 hours after injection. Biopsy was performed at one site at each point in time in each of the three subjects. The biopsy material was fixed in Karnovsky's solution and imbedded in methacrylate. The specimen was cut into 0.5 μ m sections and was stained with a Wright's-Giemsa stain.²⁰ The types of infiltrating cells were assessed by differential counts of dermal fields. Criteria for cellular identification were similar to those described by Mitchell et al.²¹ Mast cells were elongated fusiform cells, each with a single oval nucleus and fine granules. Basophils were not detected in these specimens. Because the infiltrates were comprised of focal perivascular aggregates, the quantitative method of Mitchell et al. was not used. The number of perivascular fields required to count 200 cells served as an assessment of the relative intensity of cellular infiltration.

Although the classic late-phase reaction is generally maximal at 6 hours, the microscopic events characterizing this reaction form a continuum of cellular infiltrative changes that can be demonstrated as early as 1 hour after injection. We chose 3 hours for our intermediate biopsy because we were attempting to sample early infiltrating cells, and we reasoned that the 24-hour biopsy would be representative of late events.¹⁵

RESULTS

Reactor status was determined in the three subjects, and changes in MEF 40% (P) as a percent of baseline are illustrated in Fig. 1. The average (mean $\pm$ 1 SE)

changes in MEF 40% (P) in 12 responder subjects studied in a separate investigation are illustrated for contrast. It can be observed that all three individuals' airways were relatively resistant to the bronchoconstricting effect of CBE and fell into the nonresponder category. All three individuals were healthy non-smokers with no atopic history; the average age was 39 years.

Examination of skin test sites revealed similar responses in all three subjects. The course and nature of the skin test site changes are illustrated in Fig. 2 and Table II. These data demonstrate that the response is initially a wheal-and-flare reaction identical to that produced by intradermal injection of histamine; however, the histamine reaction disappeared within 1 to 2 hours, but the CBE injection site remained inflamed after the wheal-and-flare response subsided and was replaced by induration and erythema. The latter persisted at 24 and 48 hours. Of interest is the dose response characteristic of the cutaneous response. The size of the reaction to the 1:1 strength CBE agent was approximately 1.5 to 2 times the size of the 1:10 dilution (Table II).

Examination of histologic sections of the reaction obtained 15 minutes, 3 hours, and 24 hours after injection of the full strength CBE paralleled the qualitative clinical changes observed in skin reactions macroscopically. Fig. 3 illustrates various characteristic features of this reaction. The sections are displayed from top to bottom at different times in the skin reaction, and sections illustrated from left to right go from low power to high power views. These sections were obtained from representative fields in all three individuals. They demonstrate that early in the reaction there is primarily edema with relatively few cells

TABLE II. Comparison of skin test reactions to histamine and CBE (dilutions 1:1 and 1:10) in three subjects

	Histamine (0.001 mg/cc)			CBE					
	W	R	I*	1:1			1:10		
				W	R	I	W	R	I
0 minutes				Injection					
10 minutes	10 to 12	25 to 90	0	10 to 11	30 to 39	0	6 to 8	9 to 15	0
30 minutes*	12 to 20	38 to 70	0	12 to 15	35 to 60	11	5 to 8	20 to 31	9
60 minutes	10 to 13	32 to 50	0	0	30 to 60	10 to 15	0	10 to 16	8 to 12
120 minutes	0	0 to 30	0	0	12 to 35	10 to 11	0	8 to 12	6 to 10
24 hours	0	0	0	0	12 to 50	5 to 12	0	6 to 15	4 to 8
48 hours	0	0	0	0	3 to 5	3 to 5	0	0	0

The range for the reaction size is expressed in millimeters.

W = wheal; R = redness; I = induration.

*In one subject induration occurred. In the other two subjects wheals were noted.

TABLE III. Morphologic characteristics of dermal cellular infiltrates

Time	Subject	MNC*	PMN*	MAST*	Fieldst	Cells counted‡
15 minutes	1	—	—	§	slide	—
	2	62	15	22	slide	45
	3	58	31	10	slide	170
3 hours	1	60	35	5	3	200
	2	63	32	5	5	200
	3	90		10	5	200
24 hours	1	83	8	9	2	200
	2	93	2	4	2	200
	3	87	9	3.5	3	200

*Percentages of apparent mononuclear cells (MNC), polymorphonuclear neutrophils (PMN), and mast cells (MAST).

†Fields of perivascular cellular infiltrate that were counted. Slide indicates review of all perivascular areas in the specimen.

‡Number of cells counted for differential percentage estimate.

§The biopsy specimen from subject 1 obtained after 15 minutes contained some perivascular mast cells that appeared to be degranulating. No other inflammatory cells could be identified.

||The biopsy specimen from subject 3 obtained after 3 hours and all specimens obtained at 24 hours contained "nuclear dust", suggesting destruction of cells, presumably polymorphonuclear neutrophils.

in the dermis. The morphologic appearance of the skin test suggests that this relatively acellular phase corresponds to the wheal that lasts approximately ½ hour. Some perivascular accumulation of cells was however already noted in two specimens, and induration was noted macroscopically in one subject at 30 minutes (Table I). As the lesion develops the dermis becomes progressively more cellular, and perivascular concentrations of cells increase. This cellular invasion is observed at 3 and 24 hours. The cells include both polymorphonuclear cells and mononuclear cells. No eosinophils were observed. Degranulating mast cells were also detected both in the early and late phases

of the reaction (Fig. 3). Quantitative analysis of the cellular infiltrate is described in Table III. These findings suggest that mononuclear cells predominate throughout the course of the reaction; however, initially polymorphonuclear cells make up almost one third of the inflammatory cells; this proportion decreases markedly at 24 hours. The proportion of mast cells also appears to decrease with time.

DISCUSSION

This study documents for the first time the unique histopathology and the evolution over time of the inflammatory response to intradermal injections of

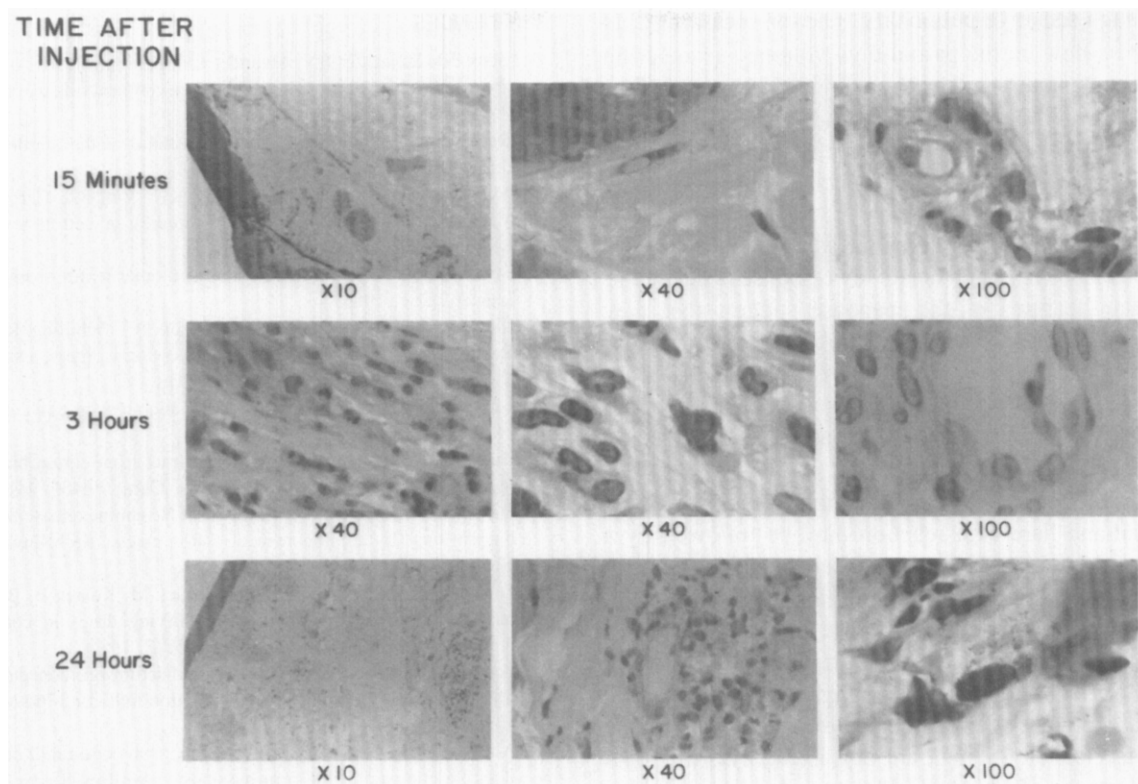


FIG. 3. Skin test response (*microscopic*) to intradermal injection of CBE. Injections are made at the level of the pelvic rim at three separate sites for each of the biopsies at the three time points. *Microscopic sections* are from the three subjects. Degranulating mast cells are noted in the *second midpower* (original magnification $\times 40$) view at 3 hours and in the high-power (original magnification $\times 100$) view at 24 hours.

aqueous CBE. The findings suggest that this response is biphasic with an early edematous wheal-and-flare reaction similar to that observed with histamine followed by an exudative phase characterized by a mixed cellular infiltrate migrating from perivascular areas. The presence of degranulating mast cells throughout the course of the reaction suggests that mediator release from these cells may be involved in the mechanism of this response. Previous work has demonstrated that disodium cromoglycate partially inhibits the airway response to CBE, whereas the (H_1) anti-histamine chlorpheniramine does not. This would suggest that mediators other than histamine are involved in this effect and could explain the sustained response both in the skin and airways.⁹

The documentation of this reaction in naive individuals never before exposed to the cotton industry or its waste products suggests that the response is probably a nonspecific inflammatory reaction not conditioned by previous exposure to a specific antigen. Although we have only documented a response in three nonreactors, it is likely that this response would also occur in reactors since (at least in terms

of their airways) these individuals are more responsive to the irritative effects of CBE. The skin response is thus probably common to most of the population at large. Our observation may however be due to the dose of CBE injected intradermally (i.e., lower doses may distinguish airway responders and non-responders).

Airway reactivity to CBE has been characterized extensively.^{6, 7, 9, 17} Reaction to the inhalation of an aerosol of this extract is widespread in the healthy, nonatopic population and occurs in naive individuals never exposed to cotton dust extract. Characteristically, the response may begin immediately after exposure and may manifest itself as progressive airway obstruction that becomes maximum approximately 2 hours after exposure, gradually subsiding thereafter.⁶ In workers exposed to dust in the cotton textile industry, gradual across-shift loss of lung function occurs and slowly returns to baseline after the worker leaves the mill.⁵ Differences in the time course of the worker response and response to CBE challenge may reflect dosage differences as well as the fact that the industry exposure continues through the shift. Finally,

although sensitive pulmonary function measurements such as flow on the partial flow volume curve permit us to separate our healthy subjects into responders (Δ MEF 40% [P] > 20%) and nonresponders (Δ MEF 40% [P] < 20%), virtually all subjects will demonstrate some mild bronchoconstriction after challenge.⁶

The relation between the intradermal inflammatory response to CBE and the airway response is unknown. Certain features of the response suggest that they may be related. In particular the lack of pre-sensitization common to both responses and the reactivity in the normal population suggest that both organ systems may be responding in a similar nonspecific manner.

It has been known for some time that an immediate wheal-and-flare skin reaction may be followed by a delayed late-phase reaction. Microscopic evaluations of such reactions^{15, 22-24} indicate that mast cell degranulation may initiate this response and lead to a mixed infiltrate of neutrophils, lymphocytes, and monocytes with variable numbers of eosinophils. This attraction of inflammatory cells is mediated by mast cell granule release.²⁵ Our findings are consistent with this evolution of the chronic late-phase reaction. The presence of nuclear dust in the biopsy specimen implies the degeneration of participating neutrophils. This is typical of the late-phase reaction. Fibrin was not observed on Giemsa-stained specimens. Unfortunately, the tissue was not frozen for cryostat sections as described by deShazo et al.,^{23, 26} and, therefore, we cannot further examine the controversy concerning the contribution of the coagulation cascade to the late-phase reaction.

Recent observations in subjects that were characterized by the severity of their airway response to CBE suggests that lymphocytes in alveolar lavage fluid may be associated with the airway response to CBE inhalation.²⁷ Involvement of mononuclear cells including lymphocytes in the skin reaction is suggested by our histologic analysis of reactions to intradermal injections of CBE (Table III).

In conclusion, we have demonstrated that intradermal injections of CBE results in a biphasic inflammatory response. The early phase is edematous and similar to that observed with histamine injection. The later phase is exudative and is characterized by a mixed cellular infiltrate. Further definition of this reaction may be useful in understanding the mechanisms by which CBE causes inflammation. Finally, it is possible that skin testing may serve to identify workers at risk of developing byssinosis.

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A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma

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Three hundred seventy-four patients with asthma were entered into a year-long, double-blind, double-placebo controlled study comparing the prophylactic effect of ketotifen (229 patients), theophylline (73 patients), and placebo (72 patients). The ketotifen group was larger to allow the accumulation of additional long-term safety data. The primary measure of therapeutic effect was a decrease in concomitant medication without a significant increase in symptomatology or a decrement in pulmonary functions. A patient daily diary was used to document symptoms (cough, shortness of breath, and wheeze) and concomitant medications taken during the 2-week baseline and the subsequent 12 monthly periods. After 2 months of study-drug therapy, the ketotifen patients had a greater decrease in both concomitant medication and symptomatology than either of the other groups. This delay in the onset of therapeutic activity has been observed in other studies and is characteristic of this compound. The principal side effect observed with ketotifen is initial sedation, which was found to be self-limiting and of little concern to the patient after the first month. (J ALLERGY CLIN IMMUNOL 76:487-97, 1985.)

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