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Effects of Histamine Aerosol in Byssinotic Subjects

ALY A. E. MASSOUD¹, R. E. C. ALTOUNYAN², J. B. L. HOWELL, and R. E. LANE

From the Departments of Occupational Health and Medicine, University of Manchester

The changes in symptoms and lung function tests of 26 cotton cardroom workers were investigated before and after inhalation of histamine aerosols. Three subjects with no chest symptoms and 11 with uncomplicated byssinosis showed no evidence of any pulmonary reaction, but 12 bronchitic byssinotic subjects showed evidence of the pulmonary hypersensitivity found in patients with chronic bronchitis alone.

These findings cast doubt on the possible role of non-antigenic histamine liberators in the mechanism of production of 'return-to-work' tightness in byssinosis.

Any theory of the pathogenesis of byssinosis must take into account two facts. First, only a percentage of subjects exposed to cotton dust develop the condition, and secondly, those who do, do so usually only after exposure for a number of years.

One theory which has gained acceptance is that cotton dust contains a non-antigenic histamine liberator (Haworth and MacDonald, 1937) and the existence of such a liberator was reported by Antweiler (1961) and Bouhuys (1963).

Such a theory is only tenable if it can be shown that the affected subjects have developed an increased pulmonary sensitivity to the liberated histamine, otherwise it does not account for either the selectivity or the delay in the onset of symptoms. This study was undertaken to investigate this possibility.

Materials and Methods

Subjects Twenty-six cardroom workers, who had worked all their lives in mills spinning coarse cotton in Lancashire, were chosen for this investigation. Three workers with at least 10 years' exposure had no chest symptoms and are classified as group 0. The results of tests on them are included with those of the subjects with uncomplicated byssinosis in Table I. The remaining 23 workers were divided into two groups according to their chest symptoms (Massoud, 1964):

1. *Pure byssinotic subjects* (without evidence of chronic bronchitis): this group consisted of 11 subjects (Table I) who were diagnosed as grade $\frac{1}{2}$, I, and II byssinosis, *i.e.*,

they complained only of a sensation of tightness and had no clinical evidence of chronic bronchitis.

2. *Bronchitic byssinotic subjects*: this group consisted of 12 subjects (Table II) who were diagnosed as byssinosis grade II+, *i.e.*, in addition to a sensation of tightness, they had a chronic productive cough with or without shortness of breath on exertion.

Estimation of F.E.V._{1.0} and F.V.C. A closed-circuit spirometer³ of 9 litres capacity was used for the estimation of the volume of gas expelled from the lungs during the first second of a forced expiration from total lung capacity (F.E.V._{1.0}) and the forced vital capacity (F.V.C.). Measurements were made with the subjects seated. An F.E.V._{1.0} and F.V.C. estimation was obtained every minute for a minimum of five minutes during the control period and at intervals after each aerosol inhalation for a period of 10 minutes. All volumes were corrected to B.T.P.S. (body temperature, atmospheric pressure, and saturated with water vapour).

Subjective Symptoms Each subject was asked to comment on any symptoms before and after each inhalation.

Aerosol Administration All aerosol drugs were administered from Wright nebulizers operating with compressed air (8 l./min.) led into a loosely fitting face mask. Separate rooms were used for each type of aerosol to avoid the risk of cross-contamination.

The aerosols used were (1) distilled water; (2) histamine acid phosphate 0.03% (histamine base); (3) histamine acid phosphate 0.1% (histamine base); and (4) isoprenaline sulphate 1%.

Results

Pure Byssinotic Subjects The inhalation of a 0.1% histamine aerosol for one or two minutes

¹Present address: Director, Industrial Medicine, National Research Centre, Dokki, Cairo, Egypt, U.A.R.

²Research Department, Fison's Pharmaceuticals Ltd., Holmes Chapel, Cheshire.

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³Pulmonet, Godart, De Bilt, Holland

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TABLE I
CHANGES IN F.E.V._{1.0} AND F.V.C. OF PURE BYSSINOTIC SUBJECTS BEFORE AND AFTER THE INHALATION OF DISTILLED WATER, 0.1% HISTAMINE, AND 1% ISOPRENALINE

No.	Age (yrs.)	Exposure (yrs.)	Cigarettes/day	Byssinosis Grade	Predicted V.C. (ml.)	Spirometric Measurements							
						Control		Distilled Water		0.1% Histamine		1% Isoprenaline	
						% Change		% Change		% Change		% Change	
						F.E.V. _{1.0} (ml.)	F.V.C. (ml.)	F.E.V. _{1.0}	F.V.C.	F.E.V. _{1.0}	F.V.C.	F.E.V. _{1.0}	F.V.C.
1	30	10	15	0	5,450	5,340	6,600	Nil	Nil	Nil	Nil	Nil	Nil
2	36	12	10	0	4,650	3,340	4,970	Nil	Nil	Nil	Nil	Nil	Nil
3	32	11	20	0	5,200	3,570	5,580	Nil	Nil	Nil	Nil	Nil	Nil
4	45	18	20	$\frac{1}{2}$	4,550	4,140	5,200	Nil	Nil	Nil	Nil	Nil	Nil
5	37	7	0	$\frac{1}{2}$	4,250	3,530	4,270	Nil	Nil	Nil	Nil	Nil	Nil
6	40	20	10	$\frac{1}{2}$	4,550	2,480	3,940	Nil	Nil	Nil	Nil	Nil	Nil
7	46	23	10	I	4,300	2,980	3,880	Nil	Nil	Nil	Nil	Nil	Nil
8	43	22	10	I	4,500	2,430	3,800	Nil	Nil	Nil	Nil	Nil	Nil
9	38	10	15	II	4,500	3,540	4,540	Nil	Nil	Nil	Nil	Nil	Nil
10	50	20	10	II	4,400	3,070	4,340	+9	+4	+13	+4	+15	+12
11	42	24	10	II	4,600	3,840	4,660	Nil	+3	Nil	Nil	+4	Nil
12	38	21	10	II	5,800	4,410	5,490	Nil	Nil	Nil	Nil	Nil	Nil
13	54	30	5	II	3,750	1,680	1,940	-6	-3	-5	-6	+7	+3
14	58	44	10	II	4,000	2,200	2,680	+3	Nil	Nil	+3	Nil	Nil

Predicted V.C. is according to Miller, W. F., Johnson, R.L., Jr., and Wu, N. (1959).

Nil represents less than 2% change, which was the range of reproducibility of five successive control measurements.

TABLE II
CHANGES IN F.E.V._{1.0} AND F.V.C. OF BRONCHITIC BYSSINOTIC SUBJECTS BEFORE AND AFTER THE INHALATION OF DISTILLED WATER, 0.03% HISTAMINE, AND 1% ISOPRENALINE

No.	Age (yrs.)	Exposure (yrs.)	Byssinosis Grade	Predicted V.C. (ml.)	Spirometric Measurements							
					Control		Distilled Water		0.03% Histamine		1% Isoprenaline	
					% Change		% Change		% Change		% Change	
					F.E.V. _{1.0} (ml.)	F.V.C. (ml.)	F.E.V. _{1.0}	F.V.C.	F.E.V. _{1.0}	F.V.C.	F.E.V. _{1.0}	F.V.C.
15	50	20	II+	3,800	1,960	3,830	+4	-3	-18	-13	+8	+4
16	47	30	II+	3,300	1,810	2,500	-5	-7	-28	-30	+8	Nil
17	60	33	II+	2,950	1,440	1,720	-5	-4	-12	-8	+3	+3
18	62	40	II+	3,200	1,380	1,920	Nil	Nil	-18	-13	Nil	Nil
19	61	36	II+	3,050	1,150	1,860	Nil	Nil	-10	-16	+13	+13
20	68	35	II+	3,500	1,120	2,800	-3	-17	-26	-26	+10	Nil
21	65	34	II+	3,300	1,040	2,080	-8	Nil	-35	-35	-10	-10
22	59	29	II+	3,000	990	1,540	Nil	Nil	-36	-22	+15	+19
23	53	39	II+	3,200	700	1,540	Nil	Nil	-29	-19	+10	+16
24	65	38	II+	2,900	610	1,170	-8	-3	-42	-44	-8	Nil
25	54	30	II+	4,500	3,300	4,430	Nil	Nil	-10	-6	Nil	Nil
26	61	37	II+	3,200	1,450	2,400	-5	-6	-59	-58	+14	+23

Abbreviations as for Table I.

did not produce chest symptoms of any sort, nor did it cause any detectable reduction in the F.E.V._{1.0} and F.V.C. in 13 of the 14 subjects, despite the occurrence in some subjects of systemic symptoms such as flushing or headaches. Furthermore, there was no marked change ($< 2\%$) in the F.E.V._{1.0} and F.V.C. of these subjects when the histamine inhalation was followed by the inhalation of isoprenaline 1% (Table I). Subject 13 showed a 5% fall in F.E.V._{1.0} after histamine and a 6% fall after water. This subject, although denying symptoms of chronic bronchitis, had evidence of diffuse airways obstruction in the control period. Subject 10 showed an increase in both F.E.V._{1.0} and vital capacity after all types of inhalation.

Bronchitic Byssinotic Subjects Inhalation of the weaker solution of histamine (0.03%) for one minute caused a number of respiratory symptoms, such as wheezing, choking, and breathlessness. None of the subjects was able to identify these symptoms with the tightness experienced in the cardroom. In addition to their subjective response, histamine induced a fall in the F.E.V._{1.0} and F.V.C. which is highly significant ($P < 0.001$). Inhalation of isoprenaline aerosol resulted in the relief of symptoms and the return of the F.E.V._{1.0} and F.V.C. to their original levels or above.

Discussion

The results of this investigation show that cotton cardroom workers, who complained of a sensation of tightness only, *i.e.*, non-bronchitic byssinotic subjects, did not show any evidence of an abnormal pulmonary sensitivity to histamine.

By contrast, the subjects classified as having byssinosis and bronchitis showed a significant degree of hypersensitivity to histamine and in this respect

are similar to chronic bronchitic patients who had never been exposed to industrial cotton dust (Altounyan, 1964). Their bronchial hyper-reactivity to non-specific irritants also is shown by the change in F.E.V._{1.0} which sometimes followed the inhalation of distilled water. Although the mean age of the bronchitic group is higher than that of the non-bronchitic group, the overlap of their ages and the striking difference between the two groups makes it highly improbable that age could be responsible for the results. It is therefore necessary to exclude those subjects with byssinosis complicated by bronchitis when examining the theory of the development of histamine sensitivity in byssinosis.

The failure to demonstrate an increased histamine sensitivity in uncomplicated byssinotic subjects casts doubt on the role of non-antigenic histamine liberators in the genesis of byssinosis.

However, selectivity and delay in the onset of byssinosis can be explained by the development of an antibody to a component of the cotton dust (Massoud and Taylor, 1964). Although it is possible that histamine may be released in these circumstances, the failure of histamine aerosol in dosage sufficient to cause systemic effects to reproduce the symptoms of byssinosis suggests that some other mediator is more important.

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