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BYSSINOSIS

James A. Merchant

> . . . those who hackle in the flax and hemp to prepare it for being spun and wove, afford frequent instances of the unwholesomeness of their trade; for there flies out of this matter a foul mischievous powder, that entering the lung by the mouth and throat, causes continual coughs and gradually makes way for an asthma. . . but at the long run if they find their affliction grows upon them they must look out for another trade; for 'tis a sordid profit that's accompanied with the destruction of health.
>
> Bernardino Ramazzini, 1705 (142)

INTRODUCTION

Exposure to textile vegetable dusts is a major occupational hazard of global dimension. Of the three natural fibers associated with respirable dust exposure during processing, cotton (Gossypium species) is the predominant textile fiber, followed by flax (Linum usitatissinum) which is woven into linen, and soft hemp (Cannabis sativa), traditionally used for rope and net making, but now largely replaced by synthetic fibers.

Both developed and underdeveloped countries are dependent upon cotton as the staple of their textile economy. The U.S.S.R. leads in annual production of cotton with over 11 million bales, followed closely by the People's Republic of China and the United States. China consumes over 12 million bales annually followed by the U.S.S.R., the United States and India (52). Several underdeveloped countries are heavily dependent upon the cotton industries with significant proportions of their populations dependent upon cotton for their livelihood—Syria (16.0%), Guatemala (19.3%), Nicaragua (35.4%), Chad (71.4%) (51). With several million workers occupationally exposed to vegetable dusts worldwide, and with little evidence that cotton will be replaced by synthetic fibers, respiratory disease arising from exposure in these industries is clearly a world-wide public health problem.

DEFINITION

Byssinosis is the generic name applied to acute and chronic airways disease among those who process cotton, flax, and hemp fibers. The acute response to dust exposure is characterized by a sensation of chest tightness upon return to exposure following a holiday or weekend break. This symptom is often accompanied by a cough, which may become productive with time, and occasionally by shortness of breath. Measurement of lung function upon return to exposure often reveals modest decreases in expiratory flow rates over the working shift. For most affected individuals, these findings will diminish or disappear on the second day of work. With prolonged exposure, both the symptoms and functional changes become more severe. Dyspnea becomes the prominent complaint while decrements in expiratory flow rates over a work shift are often marked, and clear clinical and physiological evidence of chronic obstructive lung disease emerges.

CAUSATIVE AGENTS

A great deal of interest and research has been focused on identification of the etiological agent(s) of byssinosis. The specific etiology and mechanism of this disease, however, is still not fully understood. It is generally accepted that there are three definite exposures which cause byssinosis: cotton dust (largely bract, leaf, and stem), flax dust (stem), and soft hemp dust (stem). There is some evidence that dust arising from the processing of the hard fibers, sisal (stem) and jute (stem), may occasionally result in byssinosis.

COTTON AND FLAX INDUSTRIES AND POPULATION AT RISK

Based upon 1977 Bureau of Labor Statistics figures, estimates of the total U.S. population potentially at risk to cotton dust exposure have been made (50). Taking into account all industrial processes where cotton dust exposure may occur, including over 200,000 in knitting mills where risk is considered very low, the estimated total population at potential risk is 559,700 (see Table VI-1). Perhaps half this number is significantly exposed.

It is more difficult to estimate the number of workers exposed to flax dust. The weaving of linen cloth is not a major industry in the United States, yet flax is used in a number of special textile applications. It is estimated, based upon anecdotal information, that no more than 5,000 workers are exposed. The little information available on exposure indicates that dust concentration may be marked (138). There is virtually no soft hemp, sisal, or jute processed in the United States.

EPIDEMIOLOGY

Early Observations

Observations regarding respiratory disease among those exposed to vegetable dust associated with the manufacturing of textiles began with the writings of Ramazzini. "One may see these men always covered with dust from the hemp, pasty-faced, coughing, asthmatic, and blear-eyed"(143). Following their development in Italy, textile industries flourished in France and then in England and Ireland. Shortly after the introduction of this industry to northern England, the first observations of its influence on the health of the workers were made by Jackson in 1818 (84). He observed that "...few attain their fiftieth year...there is something preys on the man thus to induce premature old age." Patissier (1822) made similar observations in France and commented that workers "must often change their work in order to prevent phthisis" (136). Thackrah, who studied the cotton textile industry in Leeds, wrote in 1831, "Workers handling cotton, as well as people working in dusty places of such plants, are not healthy as a rule. Cough and difficulties of breathing persist, and advance gradually sometimes over months, often over years" (166). J.D. Kay, also writing in 1831, observed that workers employed in the early processes were more affected and that coarse cotton caused greater frequency of disease than cleaner material. He noted "...the cough is at length very frequent during the day, and continues even after its employments have ceased, disturbing the sleep, and exhausting the strength of the patient.... The patient is easily affected with acute bronchitis on exposure to its exciting causes, and this disease often succeeds the previous complaint." Kay further observed that symptoms are severe after returning to employment. "I have found it necessary to insist that the patient should abstain from his ordinary employment, for some time after his apparent convalescence. When this injunction has been disregarded, immediate relapse has generally followed; the most severe symptoms have reappeared"(88).

The respiratory disease suffered by textile workers was initially referred to as "tracheal phythisis" by Gerspach in 1836 (73). Credit for coining the term "byssinosis" belongs to Adrien Proust.* The term has not been used uniformly; the disease has frequently been referred to as "stripper's asthma or stripper's and grinder's asthma" (48)(49).

Mareska and Heyman studied 2,000 cotton workers in Ghent, Belgium, in 1845 and first described the periodicity of Monday chest discomfort (cited by Tuypens (168)). Greenhow (1861) also noted that symptoms were more severe at the beginning of the workweek and provided a lucid clinical picture of the disease (75).

In addition to the frequently mentioned chronic bronchitis, many of the early descriptions of workers severely affected are clinically consistent with emphysema (48). Among the signs in common with emphysema are weight loss, cough productive of only scanty amounts of sputum, wheezing respiration, and a quiet chest to auscultation.

In 1932, the British Home Office established a Departmental Committee on Dust in Cardrooms in the Cotton Industry. Its report described the disease as respiratory in nature with three stages (145): (A) The stage of irritation; (B) The stage of temporary disablement or incapacity; (C) The stage of total disablement or incapacity.

*The word byssinosis is derived from the Greek *Bυσσος* or Latin *byssus*, defined by *The Shorter Oxford Dictionary*, 1962, as "an exceedingly fine and valuable textile fiber and flax, but used also of cotton, silk, etc.

Table VI-1
WORKERS EXPOSED TO COTTON DUST BY INDUSTRY SECTOR

Industry Sector/Title	Sic. No.	Exposed Workers[a] (000)
Agricultural		
Cotton ginning	0724	92.6[b]
Classing	9641	0.3[c]
Cotton compresses and warehouse	4221	10.8[d]
Cottonseed oil mills	2074	4.0
Yarn Manufacturing		
Broad woven fabric mills, cotton	2211	86.6
Broad woven fabric mills, fiber, and silk[e]	2331	47.0
Circular knit fabric mills	2257	1.0
Yarn spinning mills	2281	34.4
Texturizing, throwing, twisting, and winding mills	2282	13.9
Thread Mills	2384	3.6
Tire cord and fabric	2296	1.6
Fabric Manufacturing		
Broad woven fabric mills, cotton	2211	16.2
Broad woven fabric mills, man-made fiber, and silk	2221	8.8
Narrow fabrics	2241	4.5
Knitting mills	225	200.7
Textile Waste		
Paddings and upholstery fillings	2293	4.9
Processed waste	2294	3.7
Mattresses and bedsprings	2515	25.1
		559.7

[a]Except as noted, the estimates of exposed workers were developed from 1977 data for production workers obtained from the Bureau of Labor Statistics.

[b]During the 1974-75 growing season, 92,647 W-2 forms were issued (Docket exhibit No.88d—Cotton Dust Hearing, Department of Labor, 1977).

[c]Source: U.S. Department of Agriculture, Raleigh, North Carolina.

[d]Docket exhibit No. 95b (Cotton Dust Hearing, Department of Labor, 1977).

[e]Cotton-synthetic blend mills.

Source: U.S. Department of Labor (50)

Schilling, who rediscovered byssinosis when he inquired into excess cardiovascular deaths among Lancashire textile workers (152), developed a grading scheme for byssinosis based on the typical stages. It is the standard definition used in epidemiological surveys today. The grading scheme is based entirely on symptomatology (147), and has been incorporated into the British Medical Research Council Respiratory Questionnaire (109)(158):

Grade 0 — No symptoms of chest tightness or breathlessness on Mondays.

Grade ½ — Occasional chest tightness on Mondays, or mild symptoms such as irritation of the respiratory tract on Mondays.

Grade 1 — Chest tightness and/or breathlessness on Mondays only.

Grade 2 — Chest tightness and/or breathlessness on Mondays and other days.

Mortality Studies

A good deal of anecdotal information regarding mortality is available from early writings. In 1818, Jackson observed that few cotton workers "attain their fiftieth year" (84). Thackrah (1831) commented on those employed in flax rippling: "... most of the men doing this work are young. Very few of them reach the age of 30 if they stay on the job"(166). Greenhow studied workers exposed to flax and cotton dust in 1861 and found evidence of increased mortality (75). Similarly, Pardon (1873) recorded excess mortality among flax workers as compared to other classes in the community of Belfast (135). Barbero studied 100 consecutive deaths among hemp workers and compared the results with 100 consecutive deaths among farm workers from the same region in Spain for the years 1938 to 1943 (6). The mean age of death for hemp workers was 39.6 years, that for farm workers 67.6 years. Barbero found cardiorespiratory disease listed as a cause of death twice as frequently among hemp workers and noted that hemp workers aged 30 appeared to be 40 to 50.

The most complete mortality data for those exposed to cotton dust is found in the Decennial Supplements to the Annual Report of the Registrar General of Births, Deaths, and Marriages in England and Wales between the years 1880 and 1932. Caminita reviewed these reports and found (excluding pulmonary tuberculosis) an increased mortality from respiratory disease, particularly bronchitis and pneumonia (40). Later reports emphasized that the excess mortality from respiratory disease occurred chiefly among cardroom and blowing room operatives and strippers and grinders, rather than other cotton workers.

Schilling reanalyzed the Registrar General data between 1910 and 1932 (154)(155). All showed excess mortality from respiratory and cardiovascular causes among strippers and grinders over age 55 compared with cotton operatives and all males over that age. Schilling was able to explain the excess cardiovascular deaths by showing that a substantial proportion of cardiovascular deaths should have been classified as respiratory deaths. They were not because, with multiple certification, cardiovascular and renal disease was given preference over respiratory disease as cause of death prior to 1939. He concluded that "mortality from byssinosis has been underestimated in the past"(152).

Mortality data among textile workers in the United States is limited. Clark and Gage reported mortality by cause of death for communities in Massachusetts for the years 1896 to 1910 (47). They found 111% as many deaths from tuberculosis and 163% as many deaths from pneumonia and bronchitis in cotton mill communities as compared to shoe manufacturing communities.

More contemporary studies of cotton textile workers' mortality have not revealed consistent excesses in overall mortality. Assessment of respiratory mortality has been difficult because of a lack of adequate work history data in one study (62) and relatively small cohorts in two other studies (53)(132). Enterline studied 6,281 white male textile workers employed in Georgia mills (62). He found their overall mortality experience was similar to that of asbestos building product workers and asbestos friction material workers, while that for asbestos textile workers was clearly increased. There was, however, no evidence of excess respiratory disease deaths among all cotton workers, when cause-specific-rates were compared to U.S. white male mortality rates. Daum investigated a cohort consisting of a South Carolina local union membership employed between 1943 and 1949 (53). Initially, these mills processed cotton, but later a cotton synthetic blend. In this small cohort, moderate increases in respiratory deaths were found among male carders with 10 to 20 years of exposure and

among female spinning room workers with greater than 20 years of exposure. Evidence of self-selection out of mill work by those with poorer health was noted. Similarly, a recent mortality study of two mills in North Carolina found a trend toward an increase in respiratory mortality with increasing duration of exposure, but no overall increase in respiratory mortality (132). These authors also reported some significant increases in cardiovascular mortality and suggested methodological considerations which may in part explain these findings.

Morbidity Studies

Probably the first epidemiological study of morbidity among textile workers was conducted by Jackson in 1818 (84). As indicators he used sickness compensation and a control population of nontextile members of "Sick-Societies." "From the aggregate of ten extensive cotton-factories, the workmen [who are members of Sick-Societies] have received, upon an average . . . the relief to the amount of 11 s 6 d each per annum; other mechanics, &c. to the amount of 4 s each, per annum." Mareska and Heyman (1845) (as cited by Caminita (40)) studied 1,000 male and 1,000 female cotton workers with respect to occupational, economic, and social factors and were perhaps the first to measure dust levels. They found hospital admissions for pulmonary afflictions twice as frequent among cotton workers as other workers. Malcomb (1856) studied 2,078 flax workers in Belfast and found 12.1% of 262 preparers, 4.1% of 1,281 spinners, 0.9% of 457 reelers and 0.8% of 78 weavers to have diseases of the chest (104). Edgar Collis studied 126 strippers and grinders exposed to three grades of cotton by three stages of severity (48). Those exposed to coarse cotton were most frequently (91.3%) and most severely (56%) affected; those exposed to fine cotton were affected least often (61.9%) and had the lowest prevalence of severely affected workers (28.5%). Bradford Hill compared the incidence of illness among strippers and grinders with that of warehousemen and ringroom workers from 1923-27 (79). For disease other than respiratory there was little difference in rates, but after the age of 30, the rate for strippers and grinders was two to three times that for warehousemen and ringroom workers, exposed to less dusty areas. In the United States in 1933, Britten and colleagues found cotton workers to be underweight and to have reduced vital capacities and chest expansion. Carders had over double the sickness rate found in spinners (38).

Schilling's studies of the Lancashire cotton textile industry (reported in 1951 and 1952) heralded a new era of inquiry into respiratory disease among textile workers (154)(155). Although he was primarily concerned with increased cardiovascular mortality, his surveys of Lancashire mills revealed that respiratory disease, specifically byssinosis, was the major health hazard. He initially studied 131 carding and blow room workers and classified their complaints into three grades of byssinosis: 66% were found to have Monday chest tightness (Grade 1); 11% were judged, in addition, to have some permanent disability with effort intolerance when not at work (Grade 3) (155). In 1955, Schilling extended his observations of cardroom operatives to ringroom workers and male spinners which he found to have byssinosis prevalence rates of 4% and 12%, respectively (157). He and his colleagues tested the reliability of his questionnaire and found that two observers agreed as to byssinosis grade in 14% of the subjects, but disagreed as to the presence or absence of byssinosis in only 7% (156). The grading scheme was then validated by studying "indirect" maximum voluntary ventilation (MVV). Progressively higher grades of byssinosis were found to have progressively lower MVV's when compared to nonexposed controls and exposed nonbyssinotics.

Since this study, ventilatory function has been used widely in epidemiological surveys of vegetable dust exposure, most notably by McKerrow and colleagues who first demonstrated that workers grouped by progressively higher grades of byssinosis could be expected to have progressively greater decrements in expiratory flow rate on Mondays thereby providing an independent validation of Schilling's grading scheme (98). Following these studies by Schilling and McKerrow, investigations have been made into the respiratory effects of a variety of vegetable dusts under many work conditions in countries around the world. Indices of health effects have most commonly included the prevalence of byssinosis, the prevalence of chronic cough and phlegm or chronic bronchitis, the prevalence of weekend dyspnea, and measures of ventilatory capacity. Risk factors including level of dust exposure, smoking, duration of dust exposure, air pollution, age, and sex have been examined and

will be reviewed in the following pages.

Indices of Health Effects

Byssinosis Prevalence, Cotton

The greatest number of morbidity surveys have been carried out in the cotton textile industry, where byssinosis has been found to be most prevalent. Recent epidemiological studies of byssinosis prevalence began with Schilling's Lancashire study of 1955 (see Table VI-2). A strikingly high prevalence of Grade 1 and 2 byssinosis was found, especially among those in dustier jobs. Subsequent British surveys have established that byssinosis occurs among spinners (68) (110) and winders and among those who work with waste cotton (54). Similar observations have been made in prevalence surveys in other countries (see Table VI-2).

Studies of textile workers in the United States did not begin until after 1960 when McKerrow and Schilling visited cotton mills in Alabama where they found some workers with histories typical of byssinosis (101). In 1965, Heaphy and Kilburn studied 10 hospitalized patients with previous cotton exposure and characteristic histories of byssinosis (78). In 1967, Bouhuys and associates studied 22 southern textile workers with chronic respiratory disease and found 14 to have histories consistent with byssinosis (26). Epidemiological studies of the U.S. textile industry began with two studies conducted in 1967 by Schrag and Gullet (159) and by Bouhuys and associates (36) (see Table VI-3). Since then, several other prevalence surveys have been completed, including two reporting the results of company-wide surveillance programs. When results are categorized by work area, similar byssinosis prevalence patterns are observed among these studies (see Table VI-3).

Several inquiries have been made into cotton dust exposure in processes other than those directly dealing with the manufacturing of textiles. Batawi, in two surveys, found 28.4% and 33% of Egyptian cotton gin workers to have symptoms typical of byssinosis (8)(11). Two cotton seed pressing plants were also investigated and 52.6% found to be affected. Gilson reported decreased expiratory flow rates among workers in Ugandan cotton gins (74). Khogali studied 323 cotton gin workers in the Sudan and found 20.0% with byssinosis; among 35 workers in the farfara process, the prevalence was 48.6% (89). Kondakis studied 70 gin workers in Greece exposed to low levels of cotton dust (91). He found no typical case of byssinosis but evidence of "subclinical" effects of cotton dust on pulmonary function. Palmer and colleagues studied 203 U.S. gin workers and 260 controls and found no cases of byssinosis by questionnaire, but did find evidence of greater functional impairment among ginners as determined by spirometric testing (134). Noweir studied 147 employees of two Egyptian cottonseed oil extraction plants and found 30% of the 110 exposed to cotton dust in the delinting operation to have byssinosis, while no such diagnosis could be made among the 37 working in the oil extraction (130). Similarly, Simpson has reported significant biological activity as judged by decrement in expiratory flow among those in the Australian delinting and garnetting industries (161)(162). Jones and colleagues studied 172 workers in 4 U.S. cottonseed mills (86). Just over 2% were found to have byssinosis while a greater prevalence of functional abnormalities was observed.

Byssinosis Prevalence, Flax

Several studies of flax workers have been reported with results similar to those exposed to cotton dust. Mair and colleagues studied the Dundee textile industry where they found 15.7% of 242 flax workers to have mild symptoms of byssinosis (102). Bouhuys studied small populations of flax workers in the Netherlands and reported byssinosis in 67% of those exposed to biologically retted flax; those exposed to dust from chemically retted flax had no byssinosis (25)(35). Batawi and Hussein conducted a random survey of family heads in an Egyptian village where they found 92.5% of those who beat flax in their home, 75% of those who worked regularly in the plant, and 48.4% overall had typical byssinosis; 2.6% were judged to be disabled (10). Ferris and colleagues studied 161 flax mill workers in New England and found no typical cases of byssinosis, but did find an increase in nonspecific lung disease (65).

A small cross-sectional study of flax dust exposure at a paper manufacturing plant in North Carolina, however, revealed 3 of 27 exposed workers to have Monday chest tightness, together with significant declines in expiratory flow rates among those with high dust exposure (138). The most extensive flax survey was conducted in Northern Ireland (41)(60)(61). The

Table VI-2

BYSSINOSIS PREVALENCE
SELECTED STUDIES OF COTTON TEXTILE WORKERS

Year	*Investigator*	*Industry Process*	*Prevalence*	*Notes*
Great Britain				
1955	Schilling (157)	Carders/Setters/Fitters	42.5	Grade 1 & 2
		Strippers/Grinders/Blowroom	65.3	"
1960	Roach & Schilling (147)	Coarse Mills		
		Cardroom		
		Men	63.0	Grade ½ & 1 & 2
		Women	48.0	"
		Spinning Rooms		
		Men	11.0	"
		Women	1.0	"
		Fine Mills		
		Men	7.0	"
		Women	6.0	"
1964	Lammers (94)	Lancashire Mills		
		Cardroom	13.5	Fine Mills
		Spinning	1.5	"
		Dutch Mills		
		Cardroom	17.0	"
		Spinning	1.6	"
1966	Dingwall-Fordyce (54)	Waste Cotton	30.0	Grade ½ & 1 & 2
		Raw Cotton	62.0	"
1967	Mekky (110)	Winders		
		Men	13.8	Grade ½ & 1 & 2
		Women	18.8	"
1970	Molyneux & Tombleson (123)	Cotton		
		Men	78.3	Grade ½ & 1 & 2
		Women	25.6	in 10 occupations
		Man-Made Fiber		
		Men	4.1	All had previous
		Women	4.6	cotton dust exposure
1973	Fox (68)	Blow and Cardroom	83.8	Men-Grade ½ & 1 & 2
		Ring Spinning	5.5	M & F "
		Winding	13.4	M & F "
Belgium				
	Tuypens (168)	Cotton Workers	11.0	
		Severely affected	1.0	

Table VI-2

BYSSINOSIS PREVALENCE
SELECTED STUDIES OF COTTON TEXTILE WORKERS (Continued)

Year	*Investigator*	*Industry Process*	*Prevalence*	*Notes*
Egypt				
1962	El Batawi (8)	Carders	26.6	
1964	El Batawi & Shash (11)	Strippers and Grinders Waste Cotton Washed Cotton	35.7 26.7	
1964	El Batawi (11)	Blow Room Cardroom	18.0 43.0	
Sweden				
1965	Belin (13)	Carders in Four Mills	25-60%	
Australia				
1965	Gandevia & Milne (72)	Cotton Operatives	14%	Mild symptoms
India				
1966	Siddhu (160)		9%	
1967	Viswanathan (177)		8.4%	
Yugoslavia				
1971	Valich & Zuskin	Women Cotton	21.0	Nonsmokers
1972	(171)(173)	Operatives	88.3	Nonsmokers

study included 3,052 workers over the age of 35 and exposed primarily to flax, although other fibers were considered as well. Pre-preparers were found to be most frequently affected (54.1%), followed by preparers (26.6%), finishers (1.8%), others (4.2%), and wet finishers (0.5%). Valic and Zuskin studied 30 nonsmoking women flax workers in Yugoslavia and found 30% to have typical histories of byssinosis (173).

Byssinosis Prevalence, Soft Hemp

Fewer studies have been conducted in mills processing hemp, but results are similar to those for cotton and flax. Barbero and Flores described chronic respiratory disease among Spanish hemp workers (6) who were further studied by Bouhuys and colleagues (22). Seventy-seven percent of the male workers in one plant and 33% of males in a second plant were found to have histories typical of byssinosis. Twenty retired hemp workers were examined and 80% found to have far advanced byssinosis. In a later study, 91% of those workers over the age of 50 gave a history of Monday dyspnea (23). Valic et al. studied hemp workers in Yugoslavia and found 40.6% to be affected by byssinosis (174). During that study, three of the investigators developed byssinosis symptoms associated with reductions in expiratory flow rates. In a later study, Valic and Zuskin reported a byssinosis prevalence of 39% among 102 nonsmoking women exposed to soft hemp dust (173).

Byssinosis Prevalence, Rope, Sisal, and Jute

It is now recognized that exposure to dust during the manufacturing of rope and other products from the hard fibers of sisal and jute is rarely associated with typical byssinosis but can result in decreases in ventilatory function and symptoms of nonspecific respiratory disease. McKerrow et al. studied 44 workers exposed to vegetable dusts of Manila and St. Helena hemps and sisal used to make rope; no byssinosis was found but moderate and significant falls in $FEV_{1.0}$ and FVC were found (99). Munt et al. studied 82 workers who were manufacturing rope from the

Table VI-3

BYSSINOSIS PREVALENCE
UNITED STATES STUDIES OF BYSSINOSIS PREVALENCE

Year	*Investigator*	*Industry*	*N*	*Prevalence*	*Notes*
1968	Bouhuys (36)	Cotton Mill			
		Carders	214	26	Many exposed less
		Spinners		29	than one year
1968	Schrag & Gullet (159)	Cotton Mill			
		All Studied	509	12	
		Carding		29	
		Spinning		10	
		Winding		13	
		Weaving		10	
1969	Zuskin (182)	Cotton Mill			
		Carders	59	25	
		Spinners	99	12	
1970	Merchant (114)	Cotton/Synthetic	441		Grade 1 & 2
		Carders		20	"
		Other Jobs		2	"
1973	Merchant (118)	Cotton Mills			
		Preparation			
		Men	208	38.4	Grade ½ & 1 & 2
		Yarn Processing			
		Men	231	12.9	"
		Women	208	15.9	"
		Slash/Weave			
		Men	224	15.4	"
		Women	140	11.1	"
		Cotton/Synthetic			
		Preparation			
		Men	142	21.9	"
		Women	21	16.8	"
		Yarn Processing			
		Men	103	2.1	"
		Women	246	6.5	"
		Slash/Weave			
		Men	87	6.7	"
		Women	65	4.5	"
		Synthetic/Wool			
		Men	433	1.1	"
		Women		0.0	
1973	Braun (37)	18 Cotton Mills			
		Carders	611	21.7	"Any Tightness"
		Noncarders	284	5.4	"
1973	Imbus (82)	Company Wide Surveillance Program	10,133	4.6	Grade ½ & 1 & 2
		Cotton Preparation		26.2	"
		Cotton/Synthetic Spinning		2.0	"

Table VI-3

BYSSINOSIS PREVALENCE

UNITED STATES STUDIES OF BYSSINOSIS PREVALENCE (Continued)

Year	*Investigator*	*Industry*	*N*	*Prevalence*	*Notes*
		Winding		2.0	"
		Twisting		2.0	"
1976	Martin & Higgins (105)	Company Wide Surveillance Program	6,631	3.0	Grade ½ & 1
		Preparation	661	15.9	"
		Yarn Processing	1,284	1.4	"
		Weave/Other	3,443	1.1	"

same fibers (127). Although no byssinosis was found, rope workers had significantly more nonspecific chest tightness than controls and small drops in expiratory flow. In another study in which rope workers were exposed to flax (35%) and soft hemp (65%) dusts, symptoms of byssinosis were found in 10% of all studied and 37.5% of those in high dust areas (163).

Mair et al. reported no evidence of byssinosis, increased bronchitis prevalence or decreased ventilatory capacity in jute workers compared with controls (102). Gilson et al. studied workers in a Kenya sisal factory and an English jute mill and found little evidence of biological activity based on measurement of expiratory flow over a work shift (74). In this study, in which cotton was also considered, the authors suggested the order of biological dust activity, from greatest to least, was cotton > flax > sisal > jute. Valic and Zuskin studied five groups of nonsmoking women (173). Each group was exposed to a separate vegetable dust. Duration of exposure to dust was controlled; total dust levels were less well controlled and ranged between 16.23 (hemp) and 1.92 (sisal) mg/m^3 for the five groups (respirable levels were not available for all groups). Based on this study—in which significant decrements in expiratory flow but no cases of byssinosis were found among sisal and jute workers—Valic and Zuskin concluded the proper order of biological activity was soft hemp > flax > cotton > sisal > jute. Further studies of sisal workers confirmed these observations for this dust exposure (164) (180). Similarly, Gandevia and Milne, who studied 46 men exposed to sisal dust in the Australian felt and wadding industry, found no typical byssinosis but did find a productive cough to be common, particularly among smokers (72).

Chronic Cough and Phlegm, Chronic Bronchitis Prevalence

Increased rates of chronic cough, phlegm, and chronic bronchitis have been repeatedly observed among workers exposed to high dust levels and those with symptoms typical of byssinosis. Most surveys have used the British Medical Research Council respiratory disease questionnaire (109) to identify workers with cough and phlegm and those with bronchitis, (usually defined as the production of phlegm on most days for at least three months out of a year). Because nearly all surveys in the textile industry have been cross-sectional, conditions defined via a time factor are necessarily more affected by outward migration than conditions such as byssinosis which are strongly associated with current dust levels (60)(114). Other risk factors, such as age and smoking (known to be important in chronic bronchitis), must also be considered and have frequently made interpretation of data difficult, particularly in small populations.

Because initial surveys were conducted in the Lancashire area where chronic bronchitis is common, possible associations between cotton dust exposure, cigarette smoking, air pollution, byssinosis, and chronic bronchitis were of particular interest. To assess the role of climate and air pollution in contributing to respiratory disease among cotton workers, Lammers and colleagues studied Lancashire and Dutch cotton workers with similar cotton dust and tobacco smoke exposure (94). The prevalence of byssinosis between the two areas was similar, but a

clear excess of chronic bronchitis was observed among English workers and was attributed to atmospheric pollution. This study also suggested that chronic bronchitis *per se* does not influence the prevalence of byssinosis. Gilson studied textile workers in Africa where chronic bronchitis is uncommon. He found evidence suggestive of byssinosis, and concluded that chronic bronchitis is not necessarily associated with early stages of byssinosis (74). Batawi studied cotton gin workers in Egypt and found no more chronic bronchitis among those exposed to cotton than among controls despite a byssinosis prevalence of 38.4% among the gin workers (8). He concluded that there was no necessary link between byssinosis and chronic bronchitis, but differences in smoking habits between the two populations could not be ruled out. Similarly, Mair and colleagues found no increase in bronchitis prevalence among flax workers when compared to controls, but found that flax workers smoked less and suggested that flax exposure may discourage smoking (99)(102). Gandevia and Milne found 8% of their 50 cotton workers to have bronchitis—considered low for Australia (71). However, based on the pattern of expiratory flow over a workweek, they concluded it was likely that there was a closer association between byssinosis and chronic bronchitis than generally appreciated.

Review of other surveys tend to support this concept. Several surveys of cotton processes have reported elevated rates of chronic cough and phlegm or chronic bronchitis among those with heavy cotton dust exposure compared to those with lesser exposure or control subjects (89)(159)(173)(182). Others have examined the prevalence of bronchitis among cotton workers with symptoms of byssinosis and have found a uniformly strong association in addition to an increased bronchitis prevalence among those at risk (36)(68)(82)(114)(119)(123). Similar observations have been made in the well-controlled studies of flax workers in Northern Ireland (41)(60)(61). Studies of those exposed to hemp provide further evidence of the frequency of bronchitis in these populations. Bouhuys found chronic bronchitis to be particularly common among retired hemp workers (22)(23). Valic found a significant association between chronic bronchitis and byssinosis, but not between the severity of the two conditions (174). Studies of workers exposed to Manila and St. Helena hemp, sisal, and jute have revealed no convincing evidence that chronic cough and phlegm is more common than would be expected in inert dust exposure. Mair found no increase in bronchitis in jute workers compared with controls (102). Similar conclusions have been reached in other studies of hard fibers (127)(171)(173)(180). Gandevia and Milne concluded that productive cough among jute workers was most closely associated with smoking (72).

Dyspnea Prevalence

Indices of dyspnea have been less frequently considered in cross-sectional surveys, perhaps because as a late manifestation of respiratory disease, it is more likely to be influenced by selection and outward migration. Like bronchitis, assessment of dyspnea has most often depended upon the MRC questionnaire of respiratory symptoms (which provides increasing grades of severity for shortness of breath on the weekend when away from exposure). Using this approach, Elwood reported a marked association between dustier occupational groups and increased dyspnea grade, as well as a significant increase in shortness of breath, among those with Grade two and three byssinosis (61). Bouhuys et al. found significantly more dyspnea among hemp workers than control farm workers and also found dyspnea to be a common finding in retired hemp workers (22)(23). Valic and Zuskin have found increased dyspnea prevalence consistently in their studies of nonsmoking Yugoslavian women (171)(172)(173)(179).

United States surveys of cotton mills have also found increased dyspnea prevalence among byssinotics (36)(114)(159) and among carders compared with spinners (182). An indirect indication of dyspnea among American textile workers is the Social Security proportional morbidity ratio for emphysema, chronic bronchitis, and other respiratory diseases, exclusive of tuberculosis and cancer. Ratios of 1.40 to 2.22 have been quoted for male and female textile workers under age 65 relative to all workers for the period 1959 to 1962 (H.E. Ayer, as cited by Zuskin (182)). Similar ratios, particularly for U.S. textiles workers in preparation areas, have been observed upon recent review of this data (131).

Ventilatory Function Tests

Like other indices, studies of ventilatory function have been done primarily among survivor populations as represented in cross-sectional

studies. Retirement due to disability among female cotton textile workers in Finland has shown a slight increase in disability due to respiratory diseases with evidence of selection out of employment prior to pensionable disability (92). A variety of pulmonary function parameters have been used and will be considered more completely in the section dealing with physiological aspects of vegetable dust exposure. The tests most commonly used in epidemiological studies have been measures of expiratory obstruction—initially the $FEV_{0.75}$ and its derivative, the indirect maximal breathing capacity (IMBC), and later the $FEV_{1.0}$ together with FVC. Two major effects of vegetable dusts on ventilation have been consistent. The first is a chronic effect characterized by airways obstruction with reduction in $FEV_{1.0}$, FVC, and the $FEV_{1.0}$/FVC ratio. The second one is an acute effect characterized by significant airways obstruction developing over a few hours of dust exposure, particularly following an absence from exposure of two or more days.

The chronic effect of vegetable dust exposure has most often been judged by measuring pulmonary function prior to work on Monday, at which time any persisting acute effects have been dissipated. Decreased rates of expiratory flow and FVC have been consistent findings in those with byssinosis compared to those without byssinosis; in those with heavy vegetable dust exposure compared to those with no dust exposure; and in those who smoke compared to those who do not. Cross-sectional studies have, however, resulted in some paradoxical observations. Bouhuys and colleagues reported significantly higher $FEV_{1.0}$ levels among active 50 to 60-year-old hemp workers who were moderate to heavy smokers compared with those who were nonsmokers or light smokers of the same age and exposure (32). Twenty-six percent of the hemp workers were former smokers; self selection was probably responsible for this unexpected observation.

Schilling et al. first observed that workers with typical symptoms of byssinosis had lower expiratory flow rates than those without Monday symptoms (157). This observation has been confirmed by several investigators (11)(22)(23)(43)(159). Zuskin and Valic reported chronic changes in ventilatory capacity occurred primarily in workers with a history of byssinosis with prolonged dust exposure, as opposed to those with byssinosis but short exposure to vegetable dust (179). Others have also found expiratory flow rates to be reduced among byssinotics and, in addition, have reported that chronic cough and phlegm, together with Monday chest tightness, can be expected to result in a further lowering of pulmonary function (82)(94)(174). Although the size of study populations has precluded controlling for smoking habit in some of these studies, Imbus and Suh studied a population large enough to categorize by smoking habit and sex (82). Among nonsmoking men and women and smoking women, those with byssinosis and bronchitis had lower mean $FEV_{1.0}$ levels than byssinotics alone. Those with byssinosis had lower $FEV_{1.0}$ levels than those with bronchitis alone, and the latter had lower levels than those with neither condition. Among male smokers, the order was the same with the exception of those with byssinosis alone and those with bronchitis alone who had the same mean $FEV_{1.0}$. Those exposed to high concentrations of respirable dusts, particularly those working in preparation work areas, have been found to have lower levels of ventilatory capacity. Carey and colleagues found that byssinotic preparers had lower mean $FEV_{1.0}$ and FVC levels than nonbyssinotic preparers and nonpreparers independent of age, height, and smoking (43). They also found that nonbyssinotic preparers had a lower $FEV_{1.0}$ than nonbyssinotic nonpreparers. Bouhuys found significantly reduced flow rates among populations exposed to cotton (21), flax (35), and hemp (22)(23) than nonexposed control groups. Batawi and colleagues, studying workers exposed to cotton dust in Egypt, found those with heavy dust exposure had the lowest flow rates; unexposed controls had the highest (11). Merchant and colleagues found reduced $FEV_{1.0}$ and FVC occurred particularly among current smokers exposed to higher dust levels (114)(117).

McKerrow et al. first observed the acute reduction in expiratory flow. It was most marked after an absence from exposure, among those with higher grades of byssinosis, and among those exposed to higher dust levels (98). Based on these observations, they suggested that symptoms of Monday chest tightness and dyspnea might be explained by the rate of reduction in flow—a hypothesis that has been questioned by others because the degree of reduction, although significant in grouped data, is often not marked (12). Others have confirmed the finding that

Table VI-4

RECOMMENDATIONS FOR CLASSIFICATION AND MANAGEMENT OF WORKERS EXPOSED TO COTTON DUST

Functional Severity	FEV 1* (% of predicted)	FEV 1** (%)	Interpretation of FEV 1	Recommendations for Employment
F0	>80 (No evidence of chronic ventilation impairment)	(a) -4 to 0; or more	(a) Minimal or no acute effect of dust on ventilatory capacity	No change; annual FEV 1, and questionnaire
		(b) -9 to -5 or more	(b) Moderate acute effect of dust on ventilatory capacity	No change; 6 mo. FEV 1, and questionnaire
		(c) -10 or more	(c) Definite and marked acute effect of dust on ventilatory capacity	Move to lower risk area; 6 mo. FEV 1, and questionnaire
F1	60-79 (Evidence of slight to moderate irreversible impairment of ventilatory capacity)	(a) -4 to 0; or more	As (a) above	No change; 6 mo. FEV 1, and questionnaire
		(b) -5 or more	As (b) above	Move to lower risk area; 6 mo. FEV 1, and questionnaire
F2	<60 (Evidence of moderate to severe irreversible impairment of ventilatory capacity)	—	—	Work requiring no cotton dust exposure, detailed pulmonary examination, and questionnaire

*FEV 1 in absence of dust exposure (2 days or longer).

**Difference between FEV 1 before and after 6+ hours of cotton dust exposure on a first working day.

Derived from Organizing Committee of National Conference on Cotton Dust and Health, (133).

Source: National Institute for Occupational Safety and Health (128).

those with higher grades of byssinosis, when categorized, have the greatest reduction in expiratory flow (35)(41)(42)(71)(113). Bronchitics and byssinotics tend to have greater decrements in expiratory flow than those with byssinosis or bronchitis alone (82)(174). Based upon the association between byssinosis grade and decrease in expiratory flow, Bouhuys first proposed a functional grading scheme for byssinosis (later modified—see Table VI-4) (133) which employed both pre-exposed $FEV_{1.0}$ and decreased $FEV_{1.0}$; exposure was defined as significant if greater than 200 cc (24). Subsequent reports have shown that in individual cases the relationship between Monday fall, when so defined, and byssinosis is not strong: an appreciable proportion of non-byssinotics have a large Monday decrement while many byssinotics do not show a significant decline (12)(82)(123).

Because expiratory flow can be easily measured in untrained subjects and provides an objective indicator of biological effect, it has been widely used to assess the degree of biological effect in populations exposed to vegetable dusts (7)(22)(23)(36)(82)(114)(117). Those exposed to cotton, soft hemp dust, and flax usually have greater decrements in expiratory flow than those exposed to similar dust levels from hard fibers (74)(172). Those exposed to higher dust levels consistently been found to have more marked decrements in expiratory flow; a linear dose response relationship has also been described (11)(115)(118). Based on decrements in expiratory flow among those who smoked heavily and were exposed to moderately high concentrations of cotton dust, McKerrow and Schilling suggested that heavy smoking may potentiate the flow rate response (101). Imbus and Suh reported no greater decrement in $FEV_{1.0}$ among smokers than nonsmokers, but Merchant et al. found significant reductions in $FEV_{1.0}$ and FVC occurred only in smokers with no significant reduction in flow among nonsmokers (117).

Three prospective studies have considered reduction in $FEV_{1.0}$ over time (14)(116)(172). In each of these studies, conclusions were based upon a survivor population with attrition of the original population exceeding 25%. In addition, variance of annual decline measurements has been found to exceed the decline itself (16). A study of 28 workers exposed to fine cotton in Yugoslavian mills over a nine-year period revealed no greater decline than would be expected for aging alone (172). Berry et al. reported roughly twice the annual decline among cotton workers than occurred among those working with synthetic fibers (14). The decline attributable to cotton dust exposure was slightly greater but similar to that attributable to smoking. The authors found no evidence of a greater decline among survivors with a history of byssinosis, but they did find some evidence of greater annual declines among those in dustier work areas and among those exposed for 0-4 years, compared to those exposed over a longer period. Merchant and colleagues similarly found workers, many of whom were new employees, exposed to high levels of cotton dust had annual declines greater (>200 cc/yr) than those exposed to lower dust levels (>60 cc/yr), but who also had a longer duration of dust exposure (116). Zorach studied workers before employment and following several weeks of exposure in a dusty cotton mill and found preshift $FEV_{1.0}$ declines in excess of 10% were not uncommon (personal communication).

Estimation of Risk

Estimation of respiratory disease risk among those exposed to vegetable dust and identification of factors which predictably influence risk has been limited by the type of data available. No prospective study has been completed that was not greatly affected by high rates of outward migration—leaving a survivor population from which to estimate risk. Available data is largely cross-sectional which necessarily affects risk estimations and may differentially affect risk, depending upon the indicator utilized. Indicators of biological effect expected to be least affected are byssinosis prevalence and change in expiratory flow rate over a work shift, both of which are strongly associated with current dust levels. Indices such as cough, sputum, and ventilatory capacity before exposure (which are more affected by duration of dust exposure) are expected to be less accurate indicators of risk since more outward migration from high risk areas often occurs (32)(60)(114)(147). Indices such as dyspnea, although most relevant to impairment and disability, represent late manifestations of respiratory disease. Hence, they are poorer indicators of biological effect because of their long developmental period, over which outward migration may occur. Consequently, risk

estimations have depended on parameters which provide the best correlation with current working conditions, byssinosis prevalences, and changes in expiratory flow rates over a work shift.

Dust Concentration

There are strong *a priori* reasons for suspecting a predictable dose-response relationship of byssinosis to dust exposure. Roach and Schilling were the first to relate byssinosis prevalence to dust quantity (147). They studied cardrooms and spinning rooms in mills processing coarse and fine cotton and measured three fractions of dust: a fine fraction below 7 μ in aerodynamic diameter, a medium fraction measuring 7 μ to 2 mm in size, and total lint and dust. They further determined levels of the three main constituents of dust (cellulose, protein, and ash) and computed correlation coefficients by dust levels and constituents of cotton dust. A stong linear association between byssinosis prevalence and total dust ($r = .93$) was found; they suggested a reasonably safe level of dust exposure was 1.0 mg/m^3 total lint and dust. Batawi studied four groups of cardroom workers in Egyptian cotton mills and found a strong linear association between total dust and decrement in expiratory flow over a working shift ($r = .95$) which supported the suggested safe total dust level of 1 mg/m^3 (11). Elwood and colleagues in their study of flax operatives, considered the relationship between dust level and byssinosis and bronchitis prevalence among preparers over a relatively narrow range of dust exposure. These authors combined men and women exposed to flax alone or exposed to flax with synthetic fibers and found significant association between dust level and byssinosis prevalence, which was more marked with the respirable fraction of dust (60). The absence of a significant association between dust level and bronchitis prevalence was attributed to the confined range of dust exposure, factors related to the definition of bronchitis, its multifactorial etiology, and the opportunity for outward migration in the study population. Because a marked and significant association had been found between bronchitis prevalence and occupational group, the investigators concluded the relationship between dust exposure and byssinosis and chronic bronchitis differ in degree but probably not in nature (60).

Molyneux and Berry developed dose-response relationships between dust exposure and byssinosis prevalence, simple bronchitis among nonsmokers, and Monday cough among non-byssinotic, nonsmokers (122). All showed strong linear associations with cotton dust, but only Monday cough appeared to have a true threshold (0.2-0.4 mg/m^3 respirable dust—modified Hexhlet). Their data further suggested that respirable and medium fractions of dust had greater biological significance than previously appreciated. Others also observed that total dust levels, particularly in areas such as spinning and winding where higher concentrations of lint were found, did not correlate with the decrease in byssinosis prevalence (114). As a result, the vertical elutriator cotton dust sampler was developed and has been found to be a reasonable method to sample a biologically active fraction of cotton dust 15 μ and less in aerodynamic diameter (95). Studies of American cotton textile workers, in which this sampling method was used, resulted in strong linear associations between lint-free cotton dust and prevalence of byssinosis and decrement in $FEV_{1.0}$ over six hours of dust exposure (118). Separate dose-response relationships have been developed by byssinosis grade, smoking status, and work area (see Figure VI-1). Strong linear associations were consistent findings; regressions for smokers and nonsmokers suggested smokers had a significantly greater prevalence at all dust levels. Similarly, the dose-response relationship between all grades of byssinosis and lint-free dust among those working in slashing and weaving compared with those employed in preparation and yarn processing (spinning, winding, twisting) found consistently lower prevalence rates at all dust levels among the former, presumably because biologically inert sizing contributed to the dust concentration. No threshold effect was evident among the preparation and yarn workers where a dust level of 0.2 mg/m^3 was associated with an expected byssinosis prevalence of 12.7% by probit analysis. Among those exposed to slashing and weaving dust, a prevalence of 0.6% was expected at 0.2 mg/m^3 exposure and a prevalence exceeding 12.7% was not found until dust levels approached 1 mg/m^3.

Fox and colleagues reported correlations between cotton dust (medium and fine fractions less fly) on 1,140 subjects employed in 11 Lancashire mills (69). Again a linear dose-response relationship was observed and found to be im-

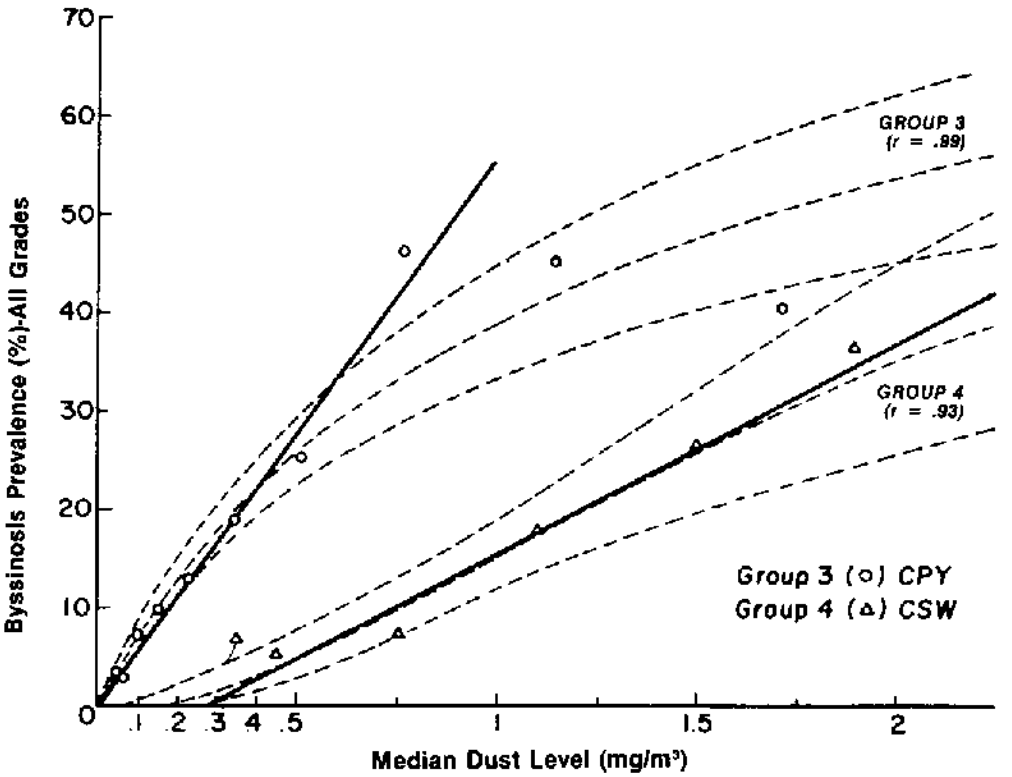

Figure VI-1. Dose-response relationships: Byssinosis prevalence by median dust level among cotton preparation and yard area workers and cotton slashing and weaving workers: linear regressions and fitted probit dose-response curves and their 95% confidence limits. North Carolina, 1970-71.

Source: Merchant, et al. (118)

proved by taking duration of exposure into account. Correlations between bronchitis prevalence and time-weighted dust measurement was not greater among cotton operatives than a separately studied population of control subjects. Regressions for smokers as opposed to nonsmokers for byssinosis prevalence and $FEV_{1.0}$ (percent of predicted) suggested that smokers developed abnormalities more rapidly with increasing dust exposure than did those who did not smoke (69).

A number of recent studies have been reported on botanical analysis of cotton trash in various nontextile segments of the cotton industry. These studies have confirmed that cotton bract is the major trash component, but that cotton leaf and noncotton weed material were also major components in most raw cottons (125). Using these analytical techniques, Morey and colleagues have provided an indicator to assess the effectiveness of cleaning processes (124) and to register differences in dust composition in various sectors of the industry such as cottonseed oil mills and the cotton garnetting industry (126). The limited epidemiological data available suggest that dose-response relationships may well be different than those observed in the primary textile industry (86)(169).

Smoking

Evaluation of the contribution of smoking to respiratory disease among textile workers has been hampered by several methodological problems. Among these are failure to account for a possible smoking effect; inadequate numbers to categorize by smoking status and consumption; lack of control populations unexposed to dust; and outward migration from dust and/or tobacco smoke exposure. Therefore, precise evaluation of the relationship between smoking, vegetable dust, and other factors associated with respiratory disease is difficult.

Additionally, there is evidence that selection out of smoking populations also occurs among workers exposed to vegetable dusts. Mair noted the proportion of smokers among flax workers was lower than among controls and suggested that flax work may discourage smoking (102).

This phenomenon has appeared in other studies (22)(35): higher proportions of *former* smokers have been observed in dusty areas (36)(114)(117). Results of two studies suggested that smoking was clearly a more important factor than dust exposure in relation to indices of respiratory disease, but environmental exposure was not well defined, nor was a control population unexposed to vegetable dust considered in either of these studies. Bouhuys and colleagues, utilizing a non-exposed control population and considering retired as well as active hemp workers, concluded that hemp dust exposure was more deleterious, as judged by symptoms of chronic respiratory disease and ventilatory capacity, than was tobacco smoking (23). Similar conclusions have been reached by Bouhuys in his more recent study of a cotton textile community in South Carolina (33).

Merchant et al. studied a large population of cotton workers as well as synthetic and wool exposed controls, and found both cotton dust exposure and smoking to be important factors with cotton dust having a more consistent and significant effect on all pre-shift and shift measures of ventilatory capacity than cigarette smoking (117)(119). Although some smaller studies have not found that smoking contributed to the prevalence of byssinosis (13), studies of larger populations have found byssinosis prevalence to be significantly greater among smokers than nonsmokers (36)(82)(114)(117). When grade of byssinosis was used as an index of severity, statistical analyses have revealed a positive dust exposure and cigarette smoking interaction (111)(114)(117)(119). Smoking is well known to be associated with increased rates of bronchitis, a finding which has also been a feature in most studies of textile workers.

Age and Duration Of Dust Exposure

Factors of age and duration of exposure are considered together since they are usually well correlated in homogeneous populations of textile workers who frequently spend their working years in this trade. Inconsistencies between study populations may be imposed by selection factors such as contraction of the industry, labor competition, wages, and job availablilty, as well as adverse working conditions. These factors are not detectable in prevalence studies.

No consistent association between age and byssinosis prevalence was found in the study of Northern Ireland flax workers after accounting for the effects of smoking and duration of flax exposure in sex specific analyses (59). Molyneux and Tombleson, after accounting for duration of cotton dust exposure, mill type and sex, found that byssinosis prevalence increased until age 25 and then remained stable until age 50, after which it slowly declined (123). Other large studies, in which the association between age unadjusted for other factors and byssinosis prevalence has been considered, suggest a weak positive association. Although no evidence of an age association with byssinosis was found in an initial study (114), with a better defined and larger population Merchant found a marginally significant association with age (117). Similarly, the data of Imbus and Suh suggest a higher byssinosis prevalence over age 40 among both smokers and nonsmokers (82). Fox et al. found crude byssinosis prevalence increased with age from 15 to 30 and then stabilized (68).

Although Ferris and colleagues found no association between age and an index of nonspecific lung disease among flax workers (65), others have found evidence of an aging effect on persistent cough and phlegm among populations of cotton workers (94)(114). Bouhuys et al. found that hemp workers showed progressively lower $FEV_{1.0}$ levels than nonexposed controls with increasing age (23). Others who have considered measures of expiratory flow by age have observed increased flow rates among those in the highest age categories (82)(157), a finding generally attributed to outward migration of those with low ventilatory capacities in these age categories. There is no evidence to suggest that aging affects the acute decrease in expiratory flow that occurs with dust exposure, or that the rate of annual decline in $FEV_{1.0}$ increases with age category *per se* among workers exposed to vegetable dust (14).

Most studies have found a positive association between duration of vegetable dust exposure and prevalence of byssinosis, although this has not been uniformly observed. Schilling found a progressive increase in byssinosis prevalence over 30 years of dust exposure in his 1955 study of Lancashire cotton operatives (157). Elwood found little evidence of an association with duration of flax exposure among male operatives, but did find a significant association among women independent of smoking and age (59). No evidence of progression from Grade ½ to 2 byssin-

osis was found in this study. Molyneux and Tombleson found byssinosis prevalence increased over the first 24 years of exposure following adjustment for age, mill type, and sex (123). Imbus and Suh (82) and Fox et al. (68) both reporting crude byssinosis prevalence, presented data that suggested an increase in byssinosis prevalence over a 20 to 24 year duration of cotton dust exposure. Bouhuys and colleagues, in a study of a mill with a rapid labor turnover, found that workers exposed to cotton dust for less than a year had a byssinosis prevalence similar to those exposed for longer periods: nearly a quarter of each group had some grade of byssinosis (36). There is some evidence that those relatively new to vegetable dust exposure may have larger shift decrements in $FEV_{1.0}$ (71), and that their annual decline in $FEV_{1.0}$ may be greater than survivors working in vegetable dust for longer periods (14)(116).

Air Pollution

Atmospheric pollution is well known to be associated with increased incidence of chronic cough and phlegm and was thought to be a contributing factor in producing pulmonary disease in Lancashire, where air pollution was significant. Therefore, a study was designed to compare prevalence of respiratory disease in Lancashire and Dutch cotton textile workers exposed to similar concentrations of cotton dust but living in areas where air pollution differed (94). No difference in byssinosis prevalence between the two populations was detected, but the prevalence of chronic cough and phlegm among Lancashire workers was greater than that among Dutch workers. Dutch workers in the town of Almela had more cough and phlegm than workers who lived in the country. These differences could not be accounted for by differences in smoking habit or other characteristics and were attributed to differences in atmospheric pollution. It was also found that Lancashire workers had lower expiratory flow rates, and it was suggested that byssinosis was more disabling when combined with air pollution effects.

Elwood and colleagues considered flax mill locations but found no significant difference in byssinosis prevalence between mills located in urban and rural areas (59). Batawi studied flax workers in an Egyptian town where byssinosis was common yet found little disabling disease (10). He concluded that lack of atmospheric pollution may have been a factor in the low prevalence of severe disease (10) (153). Bouhuys et al., however, studied Spanish hemp workers in a rural community with negligible air pollution and found disabling pulmonary disease to be common (24)(27). Berry et al., in a study of Lancashire workers between 1963 and 1966, found an "air pollution index" had no relation to annual decline in $FEV_{1.0}$ in this population (14). Air pollution has not been considered a risk factor in American textile mills. The vast majority are located in rural areas of the southeastern United States where air pollution is negligible (111).

Sex, Race, Ethnic Group

Available data suggest no difference in byssinosis prevalence between men and women after other risk factors such as dust level and smoking habit are considered (14)(114)(147). No data is available concerning race in relation to byssinosis prevalence or change in expiratory flow rate with dust exposure. The comparative study of English and Dutch textile workers suggests no difference between these two populations exposed to similar dust levels (94). Similarly, comparison of byssinosis prevalence in large studies of British (68)(123) and American (82)(117) cotton workers suggests that byssinosis prevalence is similar at given dust concentrations in the two populations.

PATHOLOGY

Although a limited amount of anatomic pathological data is available on byssinosis, a good deal of experimental research has been done. This has largely involved clinical pathophysiology, investigations searching for etiological agents, and experimental pathological studies.

Pathophysiology

Clinical observations on the pathophysiology of respiratory dysfunction associated with vegetable dust exposure may be summarized under four headings: pattern of flow rate response, other effects on ventilatory function, radiographic observations, and cellular responses. Studies have utilized small panels of textile workers or volunteers, yet have produced important observations.

Pattern of the Expiratory Flow Response

Previous subject exposure to vegetable dust is not necessary for subsequent significant decre-

ments in expiratory flow rate over a work shift of exposure. McKerrow studied 15 subjects with little or no previous exposure to cotton dust and found 9 developed chest tightness and a marked drop in expiratory flow rate, with a single exposure of 3½ hours (100). Hamilton, who has a childhood history of asthma, studied his own response to cotton dust after minimal previous exposure and observed a dramatic symptomatic and flow rate response (76). (His response, however, was more typical of the immediate response found in asthma in that a significant decrement was observed within 15 minutes and the entire decrement of $FEV_{1.0}$ occurred in 30 to 45 minutes.) The response typical of byssinosis occurs more slowly over two to eight hours of exposure and tends to be linear over this duration (98) (115). The pattern of response varies with the grade of byssinosis both over a day and a week of exposure. Two basic patterns have been described (71). The first pattern is that observed in those with histories typical of Grade 2 byssinosis by Schilling's criteria (157). These workers' expiratory flow decreased each day of exposure, with the greatest reduction on Monday following a two-day weekend. These workers tended to recover their Monday morning flow rate between days of exposure. This tendency toward full recovery after a significant Monday decrement has also been observed among workers without chest tightness (71)(113) (Figure VI-2). A second pattern has been observed in workers with intermediate grades of byssinosis and is characterized by a lack of the Monday morning flow rate recovery after a significant Monday decrement. This is typically greater than that of asymptomatic workers but less than that of the Grade 2 byssinotics (35)(42)(71)(113). Despite small numbers of subjects, these observations have been made by several independent investigators and suggested an interesting paradox to Gandevia (70)(71). Why, in a disease thought to progress through grades, would a pattern of physiological response emerge that suggests workers begin with one type of response, then develop the second type of response, and then revert to the first? Epidemiological studies, (14)(59) as well as the observations of McKerrow (99) and Bouhuys (34), suggest the pattern of response does not necessarily progress through grades. McKerrow

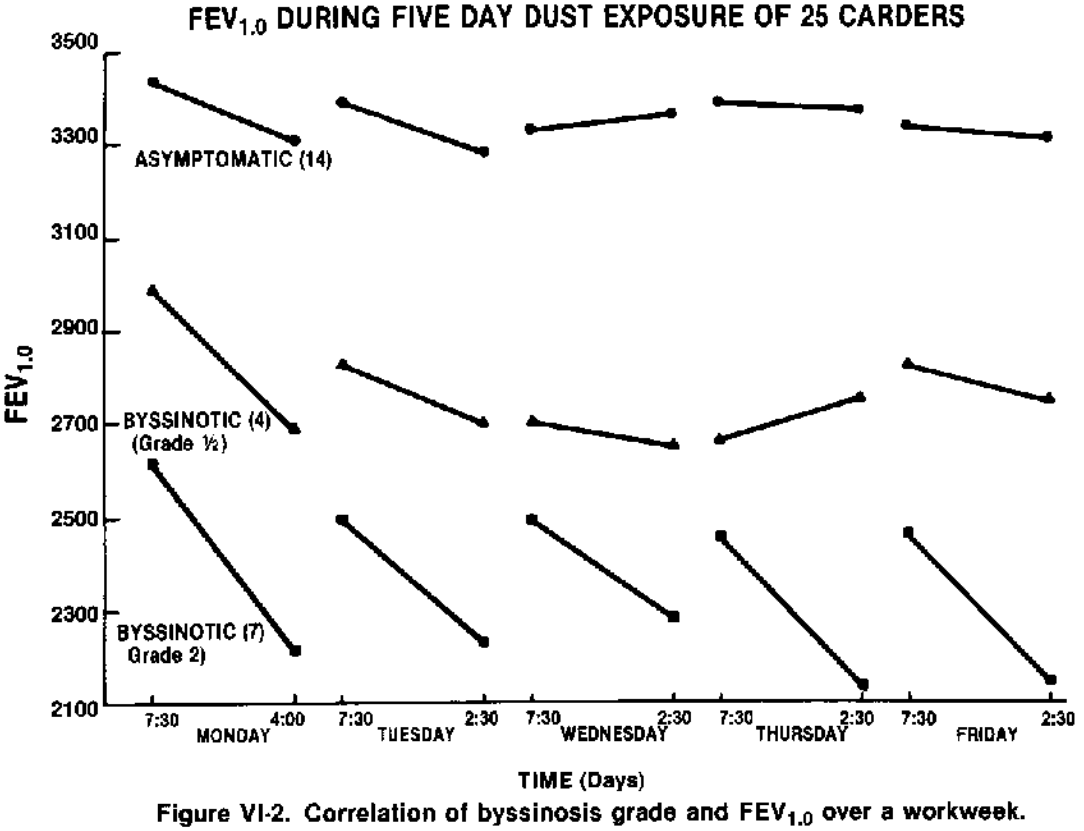

Figure VI-2. Correlation of byssinosis grade and $FEV_{1.0}$ over a workweek.

Source: Merchant, et al. (113)

has further observed that workers with heavier dust exposure tend to have a greater Monday fall in expiratory flow following a two week holiday than after a weekend break, and that byssinotics tend to have a significantly higher $FEV_{1.0}$ after the two week holiday than do nonbyssinotics, who have a significantly lower $FEV_{1.0}$ after the post-holiday Monday exposure compared to other Mondays following a weekend break (99)(100).

Other Parameters of Ventilatory Function

A variety of more sophisticated techniques have been used to study the acute physiological response to vegetable dust. $FEV_{.75}$, frequently reported as indirect maximal breathing capacity (IMBC or MVV) in earlier studies, has been replaced by $FEV_{1.0}$ as the most commonly used test to detect this response. Bouhuys has studied respiratory mechanics with vegetable dust exposure and has advocated the use of flow volume measurements as more sensitive methods of detecting airways narrowing (27)(30)(34)(36). This has been found to be true particularly of partial flow volume curves and maximal flow volume curves at a constant volume (e.g., 60% of the control total lung capacity). Others have also studied a variety of tests in order to determine the most sensitive. McKerrow studied the acute response among rope workers using $FEV_{1.0}$, FVC, PEFR, FEF_{25-75}, FEF_{50-75}, and FEV_{mid} and concluded that flow measurements provided a slight increase in sensitivity, but that the coefficients of variation for flow measurements were two to three times higher than those for $FEV_{1.0}$ and FVC (97). Merchant and colleagues observed similar differences in variation when comparing $FEV_{1.0}$ and several other parameters including MEFV curves and closing volume (CV) and closing capacity (CC) (112). In this study, $FEV_{1.0}$ provided the most consistent and statistically significant differences over six hours of exposure, largely due to its relatively small variance. CV and CC did not increase significantly, a finding consistent with the view that these tests depend primarily upon elastic properties of the lung which have been found not to change over a few hours of cotton dust exposure (57)(63).

Detailed plethysmographic studies of workers exposed to vegetable dust showed marked increases in FRC and RV and, in some subjects, small but significant increases in TLC together with decreased $FEV_{1.0}$ and FVC (34)(57)(175). The same authors have reported significant increases in airways resistance. Bouhuys found a decrease in conductance or "conductance response" in the absence of the "flow rate response" (34). Both responses were abolished by bronchodilating drugs, and it was suggested the individual differences may reflect sympathetic innervation patterns of the lung (18). These investigators also found propranolol potentiates the "flow rate response," while atropine inhibits the response. McDermott studied the acute effects of cotton dust, washed cotton dust, coal dust, cigarette smoke, and histamine aerosol on airways resistance as measured by volume plethysmography (96). Airways resistance increased with raw cotton but not with washed cotton. Coal dust concentrations reached 20 times that of cotton dust before resistance increased significantly. Recovery time was delayed following cotton dust exposure while recovery was as rapid as after coal dust following cigarette smoke, histamine, and SO_2.

Evidence that small airways are significantly affected by vegetable dust exposure is supported by studies which have shown nitrogen washout to be reduced (28) and dynamic lung compliance to become more frequency dependent (30)(57). Changes in ventilation/perfusion ratios, with small airways closure, has been the mechanism suggested as the most likely explanation of hypoxemia, which may be marked following a few hours of dust exposure (76)(112)(120). Changes in $FEV_{1.0}$ and increased frequency dependent dynamic compliance were found to last for several days following cotton dust exposure (57). Neither the lung's elastic properties nor diffusing capacity have been found to be affected by acute exposure (57).

Workers exposed to vegetable dust for several years—particularly those with histories of byssinosis—often have pre-exposure ventilatory function indicating airways obstruction, hyperinflation or relative hyperinflation, and hypoxemia (22)(35)(77).

Cellular Responses

Bouhuys first observed that workers exposed to biologically retted flax developed a peripheral leukocytosis over four to six hours of dust exposure and concluded that this may be produced by products of metabolism to bacteria and fungi used in the retting process (35).

Bomsky and co-workers also observed a leukocytic response and a decrease in thrombocytes among some workers exposed to cotton dust (16). Merchant et al. found segmented neutrophils increased significantly in the blood during cotton dust exposure and corresponded temporally with symptoms of chest tightness and decreases in expiratory flow in the panel as a whole, but not in individuals (112). These findings are consistent with leukocytosis observed in experimental animals following tracheal instillation of a cotton dust extract (90)(137). However, the relevance of the leukocyte response in byssinosis *per se* remains to be shown.

Radiographic Observations

Roentgenographic studies of textile workers are notable for their lack of specific findings. Schilling studied 45 age-matched workers, 15 with byssinosis, 15 nonbyssinotic textile workers, and 15 normal controls (156). No significant difference in chest x-ray findings between the groups was observed, except that the byssinotic group had a significantly smaller diaphragmatic excursion. The only other radiographic findings were those found in chronic bronchitis and emphysema. Others have reached similar conclusions in radiographic surveys of cotton workers (58), flax workers (41), and jute workers (102). Although an early American study reported 52 of 88 cotton textile workers to have x-rays suggesting "more fibrosis than usual," pulmonary fibrosis must be considered a rare manifestation of vegetable dust exposure (38). Bolen reported two cases of cotton workers with byssinosis who had radiographic evidence of marked fibrosis together with signs of emphysema (15). Effat reported pulmonary opacities only among workers exposed to cotton with a significant mineral content. The author has seen four workers with long exposures to cotton dust and typical histories of byssinosis, who had fine nodular densities, predominantly in the lower lung zones. All four workers had physiological evidence of airways obstruction with relative hyperinflation. One was found to have sarcoid at open lung biopsy; another was found to have lymphocytic leukemia, which was probably responsible for his opacities.

Apical fibrosis, without evidence of pulmonary tuberculosis, was found in four of 37 workers with long exposure to sisal dust (164). Patchy fibrosis was confined to apical and posterior segments of the upper lobes and tended to also involve subpleural zones.

Vaskov studied 67 textile workers with obstructive airways disease and/or signs of right-sided heart failure compared to 35 healthy controls (176). Radioisotopes were used to measure circulation times to the pulmonary artery and to the pulmonary vein. Pulmonary function tests showed those with occupational exposure to have evidence of moderate to marked airways obstruction, with a relative increase in residual volume. The venous part of the central pulmonary circulation time was not increased, even among those with right-sided failure, but the earlier part of the circulation time was significantly increased among workers with marked airways obstruction with or without right-sided failure. Pulmonary scintigrams suggested either a generalized or localized loss in pulmonary vasculature, consistent with emphysema, in many of the disabled workers.

Pathogenesis

Critical to experiments dealing with the etiology of byssinosis is agreement on the biological end-point for such studies. Because byssinosis has been defined by a pattern of symptoms, objective criteria such as increased airways resistance or decreased expiratory flow rate have been used to indicate response to cotton dust. A mechanism for chest tightness has been inferred from such findings. However, a hypothesis for respiratory disease arising from vegetable dust exposure must explain Monday chest tightness, associated bronchoconstriction, and ultimately chronic airways obstruction. Although it was once thought that this hypothesis should account for a latent period of several years between first exposure and the onset of typical byssinosis, recent evidence suggest that there may be a short or no latent period at all (23)(36). There is strong evidence, however, that a greater proportion of workers become affected with time (59)(123). Because byssinosis has been defined by acute respiratory symptoms which reflect airways narrowing, attention had been focused on modeling the acute events, with little emphasis on developing experimental models of the chronic process. Although many hypotheses have been advanced, they fall into three mechanisms: a pharmacological mechanism, a microorganism etiology, and an immunological mechanism. All offer an explanation for the Monday phenom-

enon, all overlap in many respects, but not all account for the chronic phase of the disease.

Pharmacologic Mechanism

Similarities between asthma and byssinosis suggested to early investigators that byssinosis may be secondary to histamine and/or histamine-like substances, which were subsequently found in small quantities in vegetable dust (103)(133). It was suggested that dust might release histamine from the lung following accumulation of histamine stores over the weekend (away from dust exposure). With release of histamine, Monday chest tightness would occur but disappear following consumption of the stored histamine (19)(29). To examine this hypothesis, several investigations have assessed histamine release from animal and human chopped lungs *in vitro* and isolated smooth muscle preparations, as well as change in flow rates among affected textile workers or volunteers exposed to various aqueous dust extracts. Using these techniques as assays, extracts have been found to contain contractor substances which are water soluble, dialysable, resistant to boiling, steam volatile, unstable in strong acids and alkali, not destroyed by proteolytic enzymes, and exhibit some pyrogenic activity (77)(80). In addition to small amounts of histamine, serotonin and a kinin-like substance have been identified in cotton dust extracts (3). Paper chromatography of extracts has lead some to conclude that polypeptides are the causal agents for histamine release (2). Methyl piperonylate has been identified as one component of cotton bract which is capable of histamine release (80). Although there is now a great deal of evidence that a nonimmunological pharmacological mechanism is involved with bronchoconstriction resulting from vegetable dust exposure, it does not necessarily explain the chest tightness which often occurs independent of measurable changes in flow rates, nor does it provide a good explanation of the disease's chronic stage. Therefore, pharmacological events are probably only part of the mechanism of byssinosis.

Immunological Mechanism

The known relationship between skin reactivity and asthma led several early investigators to suggest allergy to some component of cotton dust might be involved in the etiology of byssinosis. Skin testing, often with crude extracts, has yielded highly variable results which have not contributed to our understanding of byssinosis (45)(139)(140). A classical immunological mechanism unrelated to skin reactivity was proposed by Massoud and Taylor (106)(108). Finding precipitating antibodies to a condensed polyphenol in the serum of textile workers, especially carders and byssinotics, led them to suggest byssinosis might represent an atypical Type III pulmonary disease similar to farmers' lung. Although it was appreciated that granuloma formation, typical of farmers' lung was not a feature of byssinosis, it was suggested this may be attributable to altered "handling" of the inhaled dust (165). Examination of condensed polyphenols by Edwards later showed the precipitin observed by Taylor, et al. was likely explained as a nonspecific precipitation of IgG mediated by the polyphenolic polymer (55). Antweiler found little liberation of histamine with the polyphenolic materials (4).

Although the serum precipitins to Taylor's condensed polyphenol may well be nonspecific, double blind trials with byssinotic cardroom workers and nonexposed controls remain to be explained. In these clinical trials, Taylor and colleagues found that aerosol exposure to condensed tannin produced typical Monday chest tightness in those with byssinosis, but not among textile workers without these symptoms, nor in unexposed controls. Although concomitant changes in spirometry were not observed, it is of particular interest that these experimental exposures blocked or markedly diminished byssinosis symptoms upon return to mill work the following day (165).

Microorganism Etiology

Both bacterial and fungal microorganisms have been extensively studied as possible etiological agents. They are found in substantial quantities in textile mill air (45). The occurrence of mill fever and the description of mattress maker's fever, thought to be caused by endotoxins, suggested to early investigators that microorganisms and/or their products may play an important role in byssinosis pathogenesis. Early studies of bacterial and fungal species however, have shown that only rarely are textile workers infected. Attention then turned to endotoxin produced by gram-negative bacteria in mill dust as a possible etiological candidate (137)(14). Among the biological features common to endotoxin and

byssinosis are: tachyphylaxis; pyrogenic properties; leukocytosis; anaphylaxis in lab animals; liberation of histamine; decrease in circulating platelets; fever and tachypnea in rabbits "sensitized" with both cotton dust extract and endotoxin; and cross-reactivity between the two (137) (148). Pernis concluded that byssinosis may therefore be due to the protracted inhalation of small amounts of endotoxin which he interpreted as a condition of "immunological hypersensitivity" (137). Antweiler, however, pointed out that the small amount of endotoxin found in vegetable dust was incapable of releasing histamine; that the smooth muscle constricting substance(s) were stable with boiling; that the endotoxin hypothesis could not explain quantitative differences with different plant parts; and finally, that the clinical picture of byssinosis was not consistent with "hypersensitivity" or an endotoxin effect, fever being conspicuously absent (1).

Nevertheless, recent attention has again focused on endotoxin or enzymes contained in gram-negative organisms as possible etiological agents. Braun, Rylander, and Cinkotai and colleagues have recently shown that the prevalence of byssinosis is roughly correlated with the number of airborne gram-negative bacteria or their products in mill air (37)(46)(149). These relationships have, however, not been as strong as those for nonspecific respirable dust. Because of the stronger association between fine cotton dust and byssinosis prevalence, it is probable that dose-response relationships observed with gram-negative organisms are secondary associations, because these organisms are highly associated with the vegetable dust from which they arise. Although often consistent both epidemiologically and experimentally with certain characteristics of respiratory disease resulting from cotton dust exposure, endotoxin causality has not been established.

Recently, experimental animal studies focused on acute airways changes have been stimulated by the observations of Kilburn who found polymorphonuclear (PMN) cell recruitment to airways surfaces with exposure to raw cotton dust (90). Studies of chemotaxis in Boyden chambers suggest that complement is not necessary for the leukocyte response to occur (William S. Lynn, personal communication). Anecdotal studies of affected workers during dust exposure have shown no change in complement levels.

Studies of complement activation *in vitro* are of particular interest in regard to PMN recruitment and other pharmacological events. Kutz and colleagues have shown that human complement is consumed by the alternate pathway *in vitro* by both cardroom dust and, to a lesser degree, by treated (washed and extracted) cardroom dust (93). They further showed that nanogram quantities of endotoxin found in cardroom dust could not explain the complement consumption, which would have required microgram quantities of endotoxin. They concluded that other unidentified active substances are involved and speculated that antibody-independent complement activation could explain the accumulation of PMN's in the airways— secondary to complement cascade releasing chemotactic factors, which may induce airway changes via the release of histamine and other pharmacologically active mediators. Similarly, Kilburn noted PMN's are rich in lysosomal enzymes, among which are collagenases and elastases (90); both may play an important role in producing airways narrowing and the chronic airways changes found among severely affected workers.

Experimental Pathology

In earlier studies of experimental pathology, Jotten placed nine rabbits in cages behind carding engines with dust levels from 7.6 to 13.90 mg/m^3 (cited by Caminita (40)). Subsequent autopsies revealed diffuse levels of dust and cotton fiber deposits and reactive inflammatory manifestations throughout the rabbit's lungs.

Prausnitz exposed 40 guinea pigs to cotton dust 3 to 4 hours per week for 36 weeks (140). Tachypnea was commonly observed after exposure. Three guinea pigs died of intercurrent pneumonia at 14,16, and 30 weeks; 3 died but had no pulmonary pathology, and the remainder were sacrificed at 3 to 36 weeks. Those sacrificed after two months had pitted, mottled, and greyish-black pleural surfaces, particularly along the anterior borders of the middle and inferior lobes. The lungs were fixed in inflation and sectioned. Animals that had been dusted for one month had scattered peribronchial nodules, patent alveoli but thickening of alveolar walls with infiltration by polymorphonuclear leukocytes, and edema. Animals dusted for six months showed similar changes with involvement of the entire lung and evidence of a chronic pneumonia. High magnification revealed thickened alveolar walls containing large numbers of polymorphonuclear

leukocytes, large numbers of dust particles in alveolar walls, a small to moderate number of "dust cells," and slight traces of fibrosis. It was concluded that "cotton dust has a great power of penetrating into the deepest parts of the lungs and of producing in them very extensive irritative changes."

Prausnitz also reported histological findings from intradermal injection in his arm of cotton dust protein (prepared by precipitation with ammonium sulfate) (140). After one hour, slight dilatation of capillaries was observed in the papillary region of the dermis with a polymorphonuclear leukocytic infiltration confined to the sweat glands, ducts, and hair follicles. After 16 hours, capillaries were more dilated and there was leukocytic infiltration throughout the dermis and some edema of collagen bundles. There were no plasma cells and only an occasional mast cell. This inflammatory reaction was not observed with intradermal injection of histamine. Prausnitz concluded that the pathology caused by cotton dust inhalation was most likely caused by soluble proteins in dust; that hypersensitivity (based on skin test results) was acquired; and that the pathological changes observed were consistent with chronic bronchitis and emphysema. Alveolar septal thickening was thought to explain dyspnea and to ultimately produce emphysema.

Cavagna and colleagues reported histopathology in rabbits which had inhaled extracts of cotton dust combined with purified *E. coli* endotoxin over a 20 week period (44). All rabbits had bronchitis and bronchiolitis, "bronchial cell exfoliation, endobronchial secretion and parabronchial lymphocyte infiltrates." Alveolar septa were thickened in most animals. Since bronchitis did not appear until after the appearance of endotoxin reacting antibodies, it was concluded it was due to "hypersensitivity" to endotoxin rather than to primary toxicity.

Kilburn et al. studied the effects of cotton dust inhalation (90); condensed complex polyphenols as prepared by Taylor et al. (165); the polyphenolic monomer quercetin; silica flour; barium sulfate; ferric chloride aerosol; and carbon dust. Both guinea pigs and hamsters were exposed and their lungs fixed with intratracheal osmium tetroxide suspended in fluorocarbon. This prevented recruited cells from washing into alveoli from the trachea and from bronchial surfaces. Polymorphonuclear leukocyte recruitment of airways surfaces was observed, particularly with crude extract and Taylor's material within four hours of exposure. It became most prominent at 6 hours of exposure and gradually resolved over 24 hours, at which time there was still an increased polymorphonuclear to epithelial cell ratio. At two hours, polymorphonuclear leukocytes lined the basal lamina of small airways and a few such cells were found between airway epithelial cells. By four hours leukocytes were observed between many airway epithelial cells, beneath the basal lamina, and upon luminal surfaces. Careful study of airway epithelial cells showed no signs of injury such as vacuolation, swelling, crenation, or mitochondrial or nuclear swelling. Alveolar cells and spaces also showed no morphological changes. There was a greater response with one-tenth the concentration of the Taylor material than with the crude extract. Exposure to cotton trash and quercetin dust also resulted in leukocyte recruitment, but not to the degree observed with extracts. Despite massive exposure to carbon dust, there was no evidence of leukocyte recruitment with control dusts.

Rylander has conducted similar aerosol exposure studies in guinea pigs and confirmed Kilburn's observations by counting the number and type of cells lavaged from the lungs following exposure (148). Similarly, Hudson and Halprin have observed marked increases in numbers of leukocytes lavaged from several species of experimental animals after instillation of cotton dust extracts (81). They have also observed a peripheral leukocytosis following an initial relative leukopenia as previously reported by Pernis (137). The time course of these experimentally induced leukocyte responses in animals and leukocytosis observed in exposed human subjects has been consistent with the characteristic delay of one to four hours in onset of symptoms of chest tightness and decreased expiratory flow in textile workers (35)(112).

Anatomic Pathology

Schilling reviewed the pathological observations on lungs of workers with long cotton dust exposure made by several investigators and concluded the pathology was that of nonspecific chronic bronchitis and emphysema (151). The report of Dunn and Sheehan is notable in that good occupational (although not smoking) his-

tories were available, and in that the lungs were fixed in inflation (151). Of the 10 autopsies performed, evidence of pulmonary disease was found in 9, all of whom had worked in dusty areas of cotton mills for over 20 years. All nine showed evidence of chronic bronchitis and/or emphysema which was most marked among the five with histories of stripping and grinding carding machines. These five and two others also had evidence of right ventricular hypertrophy; four of these seven were judged to have died from cor pulmonale. Schilling also described pathological observations made by Gough and Woodcock on lungs of workers with histories of byssinosis (151). Both described emphysema as a prominent lesion. Gough described inflammation of the bronchi with squamous metaplasia and emphysema which was generalized, but somewhat more pronounced in relation to dust deposits. The lungs were further described as having some increase in dust content which appeared to be mainly carbonaceous and only slightly fibrogenic. Gough also described "byssinosis bodies" which consisted of a core of black dust surrounded by a yellowish material which stained positively for iron. These "bodies" were characteristically round or oval and varied in size up to 10 micron. There is at least one pathology case report that suggests pulmonary fibrosis may occur with cotton dust inhalation (144).

The most extensive pathological study of byssinosis has been recently published by Edwards, et al. (56). Lungs from 43 patients who had long exposure to cotton dust, and had been receiving industrial benefits for byssinosis, were distended with formalin at necropsy. Gross examination revealed 27 (63%) with no significant emphysema, 10 (23%) with varying degrees of centrilobular emphysema, and 6 (14%) with panacinar emphysema. Most cases showed heavy black dust pigmentation, often associated with centrilobular dilation of distal air spaces. Microscopic examination showed no evidence of fibrosis, granuloma formation, or vascular abnormality. There was, however, significantly more mucous gland hyperplasia and hypertrophy of smooth muscle in the upper and lower lobar bronchi and significantly less connective tissue and cartilage than in controls. "Byssinosis bodies" were observed in seven cases but thought to be of little significance. Ventricular weights revealed no significant evidence of left or right ventricular hypertrophy. Although 17 of the 43 were known to be cigarette smokers and all subjects were from the Lancashire area, this study did not assess the possible influence of smoking and/or air pollution.

CLINICAL DESCRIPTION

Clinical Signs, Symptoms and Natural History

The hallmark of byssinosis is the characteristic symptom of chest tightness which typically occurs following a weekend away from work. Although the onset of chest tightness after dust exposure is variable, it is most often observed two to three hours after exposure. This time interval is one important feature distinguishing byssinosis from asthma which usually has an immediate onset with exposure or a later onset (six to eight hours or longer) (17)(20). Affected individuals often compare the feeling of chest tightness to that of a "chest cold". Frequently, chest tightness will be accompanied by a nonproductive cough, especially prominent on Monday. A history of chronic, often productive cough is frequently obtained. In older workers who have been exposed to cotton dust for many years, a history of exertional dyspnea is a common finding. Among those severely affected, chest tightness and dyspena occur on all work days with relief only on weekends and holidays, if then.

All symptoms become more severe if the period away from cotton dust exposure is prolonged; i.e., the affected individual appears to lose exposure tolerance. Conversely, Monday symptoms do not occur if exposure occurs seven days per week. Symptoms are often more severe and more frequent among smokers. Occasionally a worker will report that his symptoms of Monday chest tightness disappeared when he stopped smoking, even though his dust exposure did not change.

There are no typical or characteristic signs to be found upon physical examination of byssinotic subjects who are not severely affected. While the subject will frequently exhibit a productive cough, on auscultation of the chest it is usually relatively quiet except for occasional rhonchi. Wheezing is not commonly found early in the course of the disease. Among those severely affected, all of the physical findings of advanced chronic bronchitis or emphysema may be observed.

A number of nonspecific symptoms are experienced by those exposed to cotton dust, with or without byssinosis. Cotton dust is an irritating material which dries and inflames mucous membranes resulting in mild conjunctival irritation, sneezing, and hoarseness. Chronic cough and phlegm and exertional dyspnea are also observed among cotton workers who have not smoked and recall no typical history of byssinosis. Whether these individuals merely forgot they once had symptoms on Monday or developed these nonspecific symptoms without the typical periodicity is not well understood. Available data suggest the latter.

New workers and those who first go into dusty cotton processing areas for a period of a few hours may experience "mill fever" (5) which has been also called "weaver's fever, cardroom fever, dust chills, dust fever, cotton cold, cotton fever," and among flax workers "heckling fever" (35). Symptoms, which occur within 12 hours of exposure, consist of chills, headache, thirst, malaise, sweating, nausea, and vomiting accompanied by a transient fever. Without further exposure these symptoms subside spontaneously within a day or two. With repeated exposure, such as that experienced by a new worker, these symptoms may occur for several days until the worker is "seasoned" (5) or develops tolerance. Another common complaint of new workers or visitors to mills is tobacco intolerance following exposure to higher concentrations of cotton dust. These symptoms are not often observed at lower dust exposures and are, therefore, becoming less common as dust control improves within the cotton processing industries.

A second group of febrile syndromes associated with cotton processing includes "Mattress-Makers' Fever" and "Weavers' Cough". These conditions occur among experienced workers and are characterized by a high attack rate, a clear-cut febrile episode, severe cough, and dyspnea. Most of these epidemics have been attributed to mildweed yarn. An endotoxin containing gram-negative bacillus, *Aerobacter cloacae*, has been isolated and was thought to be the likely etiological agent in one of these outbreaks (129).

Clinical Laboratory Investigations

Clinical laboratory evaluation of workers affected by textile vegetable dust usually does not occur until function has become impaired. At that point, a thorough pulmonary evaluation, including chest x-ray and spirometry, are indicated. Although the chest radiograph can produce no specific information to associate impairment with occupational exposure, it is important to eliminate other pulmonary pathology such as tuberculosis, lung cancer, and pulmonary fibrosis. If a worker is significantly impaired, this will usually be clear from spirometry assessment. In cases where symptomatology and functional changes do not coincide, a fuller assessment of lung function, including diffusing capacity and lung volumes, may be useful. The most direct route to determining impairment is assessment of arterial blood gases at rest and, if necessary, with exercise. This invasive procedure is not indicated except in borderline cases where the level of impairment or other abnormality is not clear (see section on "Criteria for Assessing Impairment").

Treatment

Research on byssinosis therapy has been confined to acute events. Clinical trials have relied almost exclusively on changes in flow rates among active workers as indicators of effect. While propranolol has been shown to increase bronchoconstriction with hemp dust exposure, antihistamines and ascorbic acid have been found to protect against this effect (172)(174). Similarly, it has been found that inhaled bronchodilators (salbutamol, insoprenaline, and orciprenaline) will prevent or reverse flow rate changes (64)(87)(173)(181). Finally, it has been found that pre-exposure treatment with disodium chromoclycate tends to block bronchoconstriction (64)(178). Inhaled beclamethazone also appears to decrease the flow rate response (64). It must be emphasized that the beneficial effects observed were functional, without similar documentation in regard to symptomatology. Although the bronchoconstriction effects of these dusts (which is usually not severe) may be blocked or reversed, there is no evidence that use of these drugs will necessarily suppress byssinosis symptoms or retard the progression of cotton dust-induced obstructive airways disease: they cannot be considered preventive measures. Among those who are severely affected, therapy is that for chronic bronchitis and emphysema (see section on "Chronic Airways Obstructive").

Prognosis

The prognosis of the worker affected by textile vegetable dusts is highly dependent upon the stage at which the effect is identified and upon subsequent exposures. Workers often select themselves out of dusty areas which they perceive to affect their respiration. This is particularly true of asthmatics and others with "twitchy airways" who will often transfer out of dusty areas within days or weeks of first exposure. As a result, the likelihood they will develop chronic impairment is slight. Similarly, those without symptoms but with functional changes observed over a work shift may be identified through medical surveillance. If their baseline function is normal and they transfer out of dust exposure, their prognosis should be excellent. If they continue to be exposed, available evidence suggests that their lung function may be expected to decline at an accelerated rate (14)(116). This is particularly true for those who are exposed at higher dust concentrations and for those who smoke (67) (116). Smokers who stop smoking have been found to revert to a normal rate of annual decline in function, but will not recover the function loss already sustained (67).

Whether this is also the case among those affected by vegetable dusts is not known. It is known that lung function will continue to improve over a period of at least ten days away from dust exposure, but that function is largely recovered following only a weekend away (111). These observations have been made among active workers with reasonably normal baseline lung function. It is probable workers with significant airways obstruction may recover some functional loss over a longer period of time. In the one study which assessed former flax workers, a number of interesting observations were made (unfortunately, lung function measurements were not available): Older men, with a history of byssinosis or high flax dust exposure, were more likely to give exertional dyspnea as the reason for leaving the mill. Several with symptoms of byssinosis stated their symptoms improved after leaving exposure, but two with severe byssinosis reported they continued to become progressively worse (59). These observations are consistent with the clinical experience of the author.

As has been observed in other studies of chronic airways obstruction, prognosis is closely tied to level of impairment as measured by spirometry. When this level of impairment is marked and cannot be improved by avoiding dust and cigarette smoking exposure or by bronchodilation or steroids, spirometry has proven to be the best single prognostic sign (39)(85)(146)(167). There is no reason to believe this is not also true for chronic airways obstruction produced by the textile vegetable dusts.

DIAGNOSTIC CRITERIA

The criteria used in assessing the health effects of textile vegetable dusts are dictated by their application. For epidemiological studies, Schilling's criteria (see page 536) has proven to be reliable and valid. These criteria are, however, entirely subjective, making them less useful for surveillance programs which may involve a recommendation to retire or transfer a worker to another job. Criteria based on functional changes have been introduced (see Table VI-4). These criteria offer the advantages of objectivity and replication, which is important because of inherent variability in individual spirometric measurements. Using this scheme, corporation-wide surveillance programs may be carried out which may both describe the prevalence of functional changes and provide a mechanism for management of currently employed workers (105).

Neither of these classifications (which have been used extensively among currently employed workers) are by themselves suitable for disability evaluation. Schilling's classification is subjective and defines only part of the biological effect. Bouhuy's functional classification is dependent upon in-mill exposures and measurements, and defines only part of the biological effect. Both classifications, however, provide useful information to physicians assessing impairment and disability.

Probably no area in chest medicine suffers as much confusion as does the terminology of chronic obstructive diseases (66). Included in this group are chronic bronchitis, emphysema, asthma, and byssinosis. Physicians frequently disagree in diagnosing these diseases which are multifactorial in etiology and overlap functionally, pathologically, and by available definitions (66). A good deal of effort has been given to deriving acceptable definitions for these entities. Except for emphysema, which has been defined pathologically but not well clinically, we still have no uniform, acceptable international definitions. Because of the Schilling and Bouhuys classifications, there are probably more uniformly applied definitions for byssinosis than these other en-

tities. Yet, they do not provide adequate diagnostic criteria to assess impairment and disability among textile workers. At the same time it has been estimated there are several thousand textile workers who are severely impaired, at least in part because of their exposure to cotton dust (33).

To deal with this, based upon epidemiological data, allocation of risk may be applied to individuals for whom risk factors have been measured. No physician can measure the effect of cotton dust, cigarette smoke, infection, ambient air pollution, or genetic constitution in an individual. With detailed knowledge of these factors he may be able to draw a reasonable opinion, but it is doubtful that another physician with the same information would come to the same conclusion.

Among those exposed to the textile vegetable dusts, there are two overwhelming risk factors associated with respiratory symptoms and impaired function—dust exposure and cigarette smoking. Large cross-sectional studies, as well as some prospective studies, have shown both to be important. Further, it is known that although those with byssinosis symptoms and acute functional changes may progress more rapidly, others also progress at accelerated rates, depending on dose of dust and smoking. Therefore, all individuals with a significant dust exposure could justifiably be allocated at increased risk and presumed to have acquired at least some of their impairment from their occupational exposure.

The first important determination is to define "significant exposure" in order to distinguish those eligible for such allocation. The British require five years employment in an area of cotton textile preparation and yarn exposure (121). Based on cross-sectional and prospective data, it is unlikely that significant irreversible impairment would occur over a shorter period. There is American data which would support inclusion of cotton textile workers in the areas of preparation, yarn processing and weaving.

The second important determination is objective assessment of airways obstruction (see "Criteria for Assessing Impairment"). Spirometry will usually provide an excellent indication of impairment. If necessary, arterial blood gases at rest or with exercise will better define cases with borderline spirometry. Medical history, physical examination, and other laboratory tests should provide a clinical picture compatible with chronic obstructive lung disease and also serve to eliminate other medical conditions or diseases such as tuberculosis, lung cancer, hypersensitivity pneumonitis, etc. These entities do not arise from employment in cotton mills but may result in pulmonary impairment.

PREVENTION

Given our current state of knowledge about the etiology of byssinosis and lack of an environmental biological assay, risk assessment is dependent upon assessment of dust concentrations (31). Similarly, prevention is dependent largely upon dust control in the workplace. Significant improvements in exhaust ventilation control technology and application have recently resulted in reduced risk in many areas of textile mills in the United States. A second control technology, which appears promising experimentally, is washing cotton (9)(115). Although this procedure has been found to reduce symptoms and functional changes, largely through removal of fine dust, it is not yet clear whether cotton washing is technically feasible on a large scale. Cotton steaming studies have shown equivocal results (83)(116).

While dust control is the foundation of a respiratory disease prevention program in the cotton processing industries, medical surveillance and employee education also play important roles. Smoking and the interaction between smoking and cotton dust exposure are clearly important risk factors in respiratory disease among textile workers. Therefore, it is essential that information about the adverse effects of smoking, particularly in combination with cotton dust exposure, be provided to those exposed. Similarly, it is essential that work practices which affect individual dust exposure be stressed. Periodic medical examinations designed to detect those acutely affected and those with chronic lung disease are important and can be effective. Through the use of a standard questionnaire, it is possible to ascertain a sound occupational and smoking history, and screen for byssinosis, bronchitis, dyspnea, and other medical complaints. Simple spirometry, routinely applied, will identify many of those acutely affected and nearly all with significant impairment.

All of these prevention provisions—allowable dust concentrations, work practices, and medical surveillance—are detailed in the Depart-

ment of Labor Cotton Dust Standard promulgated in 1978 (170). Compliance with the provisions of that standard would largely eliminate byssinosis and prevent significant occupationally related pulmonary impairment among United States cotton textile workers.

RESEARCH NEEDS

Research is needed to fill gaps in vegetable dust exposure epidemiology, lung injury mechanisms, and control technology. Other organic dusts, such as grain dust, pose problems similar to the textile vegetable dusts; therefore, appropriate research will have far-reaching consequences.

Epidemiological Research

1. Cross-sectional studies of the nontextile cotton industries to establish dose-response relationships.
2. Prospective and community studies to account for outward migration, and to better quantitate risk factors and their interactions on prognosis.
3. Studies targeted at former workers to better establish their impairment and reversibility levels after leaving employment.
4. Dose-response studies of flax dust exposure.

Mechanism Research

1. Development of a reliable animal model of chronic airways effects to facilitate research on etiological agents and to more fully assess toxicological properties of dust from various sectors of the cotton industry.
2. *In vivo* and *in vitro* studies of mediators, complement and their interactions as related to lung injury arising from exposure to textile vegetable dusts.
3. *In vivo* and *in vitro* studies targeted at the interaction of vegetable dusts and cigarette smoke to interpret the mechanisms by which smoking increases susceptibility.
4. To relate *in vitro* and *in vivo* studies to clinical byssinosis, controlled trials involving human subjects are essential.

Control Technology Research

1. Textile machinery research to develop desirable alternatives to processes such as spinning frames (i.e., open end spinning) to achieve more efficient processing together with good dust control.
2. Research into the feasibility and effectiveness of cotton washing or other treatment to eliminate respirable dust and/or "detoxify" dust which may remain. Prospective epidemiological studies would establish the medical effectiveness of such a process.
3. Development of closed-boll growing, harvesting, and processing of cotton to preclude contamination of the cotton fiber with cotton trash.
4. Development of basic ventilation exhaust systems for certain nontextile cotton processes found to be associated with hazardous dust levels.

REFERENCES

1. Antweiler, H.: Histamine liberation by cotton dust extracts: evidence against its causation by bacterial endotoxins. Br J Ind Med *18:*130-132, 1961.
2. Antweiler, H.: Observations about a histamine liberating substance in cotton dust. Ann Occup Hyg *1:*152-156, 1960.
3. Antweiler, H.: The histamine retaining capacity of cotton dust extracts inhaled by guinea pigs. Ann NY Acad Sci *221:*136-140, 1970.
4. Antweiler, H. and Pallade, S.: Polyphenolic actions on guinea pig smooth muscle and mast cell in the rat. Ann NY Acad Sci *221:*132-135, 1974.
5. Arlidge, J. T.: The Hygiene Diseases and Mortality of Occupations. London: Percival and Company, 1892.
6. Barbero, A. and Flores, R.: Dust disease in hemp workers. Arch Environ Health *14:*529-532, 1967.
7. Barnes, R. and Simpson, G.R.: Ventilatory capacity changes on exposure to cotton dust. Med J Aust *1:*897-900, 1968.
8. Batawi, M.A. El-: Byssinosis in the cotton industry of Egypt. Br J Ind Med *19:* 126-130, 1962.
9. Batawi, M.A. El- and El-Shash, S.: An epidemiological study on aetiological factors in byssinosis. Int Arch Fur Gewerbepatholgie und Gewerbehygiene *19:*393-402, 1962.
10. Batawi, M.A. El- and Hussein, M.: Endemic byssinosis in an Egyptian village. Br

J Ind Med *21:*231-234, 1964.
11. Batawi, M. A. El-, Schilling, R.S.F., Valic, F., and Wolford, J.: Byssinosis in the Egyptian cotton industry: changes in ventilatory capacity during the day. Br J Ind Med *21:*13-19, 1964.
12. Bates, D.V., Macklem, P.T., and Christie, R.V.: Respiratory Function in Disease, 2nd Edition. Philadelphia: W.B. Saunders Company, 1971.
13. Belin, L., Bouhuys, A., Hoeskstra, W., Johansson, M.-B., Lindell, S.-E., Pool, J.: Byssinosis in cardroom workers in Swedish cotton mills. Br J Ind Med *22:*101-108, 1965.
14. Berry, G., McKerrow, G.B., Molyneux, M.K.B., Rossiter, E.C., and Tombleson, J.B.L.: A study of the acute and chronic changes in ventilatory capacity of workers in Lancashire cotton mills. Br J Ind Med *30:*25-36, 1973.
15. Bolen, H.L.: Byssinosis: report of two cases and review of literature. J Ind Hyg Tox *25:*215-224, 1943.
16. Bomsky, H., Otawski, J., and Bomska, H.: Hematologische und serologische untersuchungen bei Byssinose- ge- fahrdeuten arbeitern. Int Arch Arbeitsmed *27:*309-323, 1971.
17. Bouhuys, A.: Asthma and byssinosis. Rev Allergy *22:*473-476, 1966.
18. Bouhuys, A.: Byssinosis. Arch Environ Health *23:*405-407, 1971.
19. Bouhuys, A.: Experimental studies in byssinosis. Arch Environ Health *6:*56-61, 1963.
20. Bouhuys, A.: Response to inhaled histamine in bronchial asthma and in byssinosis. Am Rev Respir Dis *95:*89-93, 1967.
21. Bouhuys, A. L.: The forced expiratory volume ($FEV_{0.75}$) in healthy males in textile workers. Am Rev Respir Dis *87:* 63-68, 1963.
22. Bouhuys, A., Barbero, A., Lindell, S.-E., Roach, S. A., and Schilling, R. S. F.: Byssinosis in hemp workers. Arch Environ Health *14:*533-544, 1967.
23. Bouhuys, A., Barbero, A., Schilling, R. S. F., and van de Woestijne, K.P.: Chronic respiratory disease in hemp workers. Am J Med *46:*526-537, 1969.
24. Bouhuys, A., Gilson, J.C., and Schilling, R. S. F.: Byssinosis in the textile industry. Arch Environ Health *21:*475-478, 1970.
25. Bouhuys, A., Hartogensis, F., and Korface, H. J. H.: Byssinosis prevalence and flax processing. Br J Ind Med *20:*320-323, 1963.
26. Bouhuys, A., Heaphy, L. J., Schilling, R. S. F., and Welborn, J. W.: Byssinosis in the United States. New Engl J Med *277:* 170-175, 1967.
27. Bouhuys, A., Hunt, V. R., Kim, B. M., and Zapletal, A.: Maximum expiratory flow rates in induced broncho-constriction in man. J Clin Invest *48:*1159-1168, 1969.
28. Bouhuys, A., Jonsson, R., Lichtneckert, S., Lindell, S.-E., Lundgren, C., Lundin, G., and Ringquist, T. R.: Effects of histamine on pulmonary ventilation in man. Clin Sci *19:*79-94, 1960.
29. Bouhuys, A., Lindell, S.-E., and Lundin, G.: Experimental studies in byssinosis. Br Med J *1:*324-326, 1960.
30. Bouhuys, A., and Nicholls, P. J.: The effect of cotton dust on respiratory mechanics in man and in guinea pigs. In Inhaled Particles and Vapors. New York: Pergamon Press, Inc., Vol. 2, pp. 75-85, 1966.
31. Bouhuys, A., Peters, J. M.: Control of environmental lung disease. New Engl J Med *283:*573-581, 1970.
32. Bouhuys, A., Schilling, R. S. F., and van de Woestijne, K. P.: Cigarette smoking, occupational dust exposure, and ventilatory capacity. Arch Environ Health *19:*793-797, 1969.
33. Bouhuys, A., Schoenberg, J. B., Beck, G. J., and Schilling, R. S. F.: Epidemiology of chronic lung disease in a cotton mill community. Lung *154:*167-186, 1977.
34. Bouhuys, A. and van de Woestijne, K.P.: Respiratory mechanics and dust exposure in byssinosis. J Clin Invest *49:*106-118, 1970.
35. Bouhuys, A., van Duyn, J., and van Lennep, H. J.: Byssinosis in flax workers. Arch Environ Health *3:*499-509, 1961.
36. Bouhuys, A., Wolfson, R. L., Horner, D. W., Brain, J. D., and Zuskin, E.: Byssinosis in cotton textile workers. Ann Int Med *71:*257-269, 1969.

37. Braun, D.C., Scheel, L. D., Tama, J., and Parker, L.: Physiological response to enzymes in cotton dust. JOM *15:*241-244, 1973.
38. Brittten, R. H., Bloomfield, J. J., and Goddard, J. C.: The health of workers in textile plants. U.S. Public Health Bulletin No. 207, Washington, DC., 1933.
39. Burrows, B. and Earle, R. H.: Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. New Engl J Med *280:*397, 1968.
40. Caminita, B. H., Baum, W. F., Neal, P. A., and Schneiter, R.: A review of the literature relating to affection of the respiratory tract in individuals exposed to cotton dust. Public Health Bulletin No. 297, U.S. Government Printing Office, Washington, DC., 1949.
41. Carey, G. C. R., Elwood, P.C., McAulay, J. R., Merrett, J.D., and Pemberton, J.: Byssinosis in flax workers in Northern Ireland. A report of the Minister of Labour and National Insurance, the Government of Northern Ireland. Belfast: HMSO, 1965.
42. Carey, G. C. R. and Merrett, J. D.: Changes in ventilatory capacity in a group of flax workers in Northern Ireland. Br J Ind Med *22:*121-127, 1965.
43. Carey, G. C. R., Merrett, J. D., Elwood, P. C., Pemberton, J., and McAulay, J. R. Ventilatory capacity in flax workers in Northern Ireland. Br J Ind Med *22:* 109-120, 1965.
44. Cavagna, G., Foa, V., and Vigliani, E. C.: Effects in man and rabbits of inhalation of cotton dust or extracts and purified endotoxins. Br J Ind Med *26:*314-321, 1969.
45. Cayton, H. R., Furness, T., and Maitland, H. B.: Studies on cotton dust in relation to byssinosis. Br J Ind Med *9:*186-196, 1952.
46. Cinkotai, F. F., Lockwood, M. G., Rylander, R.: Airborne microorganisms and prevalence of byssinosis symptoms in cotton mills. Am Ind Hyg Assoc J *8:*554-559, 1977.
47. Clark, H.W. and Gage, S. de M.: A study of the hygienic condition of the air in textile mills with reference to influence of artificial humidification. Am J Pub Health *3:*1176, 1294, 1913.
48. Collis, E.L.: Annual report of the chief inspector of factories for 1908. London: HMSO, 1908, pp. 203-205.
49. Collis, E. L.: Industrial pneumoconioses with special reference to dust phthisis (Milroy Lectures, 1915). Public Health *28:*252-253, 1915; *29:*11-20, 37-44, 1916.
50. Cotton Dust: Review of alternative technical standards and control technologies: U.S. Department of Labor, 1979.
51. Cotton's importance to the developing world. International Institute for Cotton, Brussels, 1976.
52. Cotton-World Statistics. International Cotton Advisory Committee, Washington DC., 30(12), Part II, 1977.
53. Daum, S.: Proceedings of the A.C.G.I.H. Conference on Cotton Dust. Atlanta, GA 1975.
54. Dingwall-Fordyce, I. and O'Sullivan, J.G.: Byssinosis in the waste cotton industry. Br J Ind Med *23:*53-57, 1966.
55. Edwards, J. H. and Jones, B. M.: Immunology of byssinosis: A study of the reactions between isolated byssinosis "antigen" and human immunoglobulins. Ann NY Acad Sci *221:*59-63, 1974.
56. Edwards, C., MacArtney, J., Rooke, G., and Ward, F.: The pathology of the lung in byssinotics. Thorax *30:*612-623, 1975.
57. Edwards, J., McCarthy, P., McDermott, M., Nicholls, P.J., and Skidmore, J. W.: The acute physiological, pharmacological and immunological effects of inhaled cotton dust in normal subjects. J Physiol *208:*63P-64P, 1970.
58. Effat, H.: Radiological changes in byssinosis and pneumoconioses. Alexandria Med J. *9:*292-297, 1963.
59. Elwood, P.C.: Respiratory symptoms in men who had previously worked in a flax mill in Northern Ireland. Br J Ind Med *22:*38-42, 1965.
60. Elwood, P. C., McAulay, J.R., McLarin, R.H., Pemberton, J., Carey, G. C. R., and Merrett, J. D.: Prevalence of byssinosis and dust levels in flax preparers in Northern Ireland. Br J Ind Med *23:* 188-193, 1966.
61. Elwood, P.C., Pemberton, J., Merrett, J.

D., Cary, G. C. R., and McAulay, J. R.: Byssinosis and other respiratory symptoms in flax workers in Northern Ireland. Br J Ind Med *22:*27-37, 1965.
62. Enterline, P. E. and Kendrick, M. A.: Asbestos-dust exposures at various levels and mortality. Arch Environ Health *15:*181-186, 1967.
63. Fairman, R. P., Hankinson, J., Imbus, H., Lapp, N.L., and Morgan, W.K.C.: Pilot study of closing volume in byssinosis. Br J Ind Med *32:*235-238, 1975.
64. Fawcett, I. W., Merchant, J. A., Simmonds, S.P., and Pepys, J.: The effect of sodium cromoglycate, beclomethasone diproprionate and salbutamol on the ventilatory response to cotton dust in mill workers. Br J Dis Chest *29:*29-38, 1978.
65. Ferris, B. G., Anderson, D. O., and Burgess, W. A.: Prevalence of respiratory disease in a flax mill in the United States. Br J Ind Med *19:*180-185, 1962.
66. Fletcher, C. M.: Terminology in chronic obstructive lung disease. J Epid & Comm Health *32:*282-288, 1978.
67. Fletcher, C. and Peto, R.: The natural history of chronic airflow obstruction. Br Med J *1:*1645-1648, 1977.
68. Fox, A.J., Tombleson, J.B.L., Watt, A., and Wilke, A. G.: A survey of respiratory disease in cotton operatives. Part I. Symptoms and ventilation test results. Br J Inc Med *30:*42-47, 1973.
69. Fox, A. J., Tombleson, J.B.L., Watt, A., and Wilke, A.G.: A survey of respiratory disease among cotton operatives. Part II. Symptoms, dust estimations, and the effect of smoking habit. Br J Ind Med *30:* 48-53, 1973.
70. Gandevia, B.: Current studies in Australia. Transactions of the National Conference on Cotton Dust and Health. Chapel Hill, NC, University of North Carolina, pp. 63-64, 1970.
71. Gandevia, B.: Milne, J.: Ventilatory capacity changes on exposure to cotton dust and their relevance to byssinosis in Australia. Br J Ind Med *22:*295-304, 1965.
72. Gandevia, B. and Milne, J.: Ventilatory capacity on exposure to jute dust and the relevance of productive cough and smoking to the response. Br J Ind Med *22:* 187-195, 1965.
73. Gerspach, J.: Considerations sur l'influence des filatures do coton et des tissages sur la soute des ouvriers. Paris, 1827.
74. Gilson, J.C., Stott, H., Hopwood, B.E.C., Roach, S.A., McKerrow, C.B., and Schilling, R. S. F.: Byssinosis: the acute effect on ventilatory capacity of dusts in cotton ginneries, cotton, sisal and jute mills. Br J Ind Med *18:*9-18, 1962.
75. Greenhow, E. H.: Report of Medical Officer of the Privy Council, with Appendix, 1860. Third Report, Appendix VI, pp. 172-176, London: HMSO, 1861.
76. Hamilton, J. D., Germino, V. H., Merchant, J. A., Lumsden, J. C., and Kilburn, K. H.: Byssinosis in a nontextile worker. Am Rev Respir Dis *107:* 464-466, 1973.
77. Hamilton, J.D., Halprin, G. M., Kilburn, K. H., Merchant, J. A., and Ujda, J. R.: Differential aerosol challenge studies in byssinosis. Arch Environ Health *26:* 120-124, 1973.
78. Heaphy, L. and Kilburn, K. H.: Byssinosis: a model of airway reactivity in man. Am Rev Respir Dis *92:*329, 1965.
79. Hill, A. B.: Sickness amongst operatives in Lancashire cotton spinning mills (with special reference to the cardroom). Rep Industr Hlth Res Bd Rep No. 59, London: HMSO, 1930.
80. Hitchcock, M.: *In vitro* histamine release from human lung as a model for the acute response to cotton dust. Ann NY Acad Sci *221:*124-131, 1974.
81. Hudson, A., Halprin, G., Kilburn, K. H., and Pratt, P. C.: Time course of blood and airway leukocyte responses to cotton dust extract. Abstract No. 3385, Fed Proc 32, 1973.
82. Imbus, H. R. and Suh, M. W.: Byssinosis: a study of 10,133 textile workers. Arch Environ Health *26:*183-191, 1973.
83. Imbus, H. R. and Suh, M.W.: Steaming of cotton to prevent byssinosis—a plant study. Br J Ind Med *31:*209-219, 1974.
84. Jackson, J.: On the influences of the cotton manufactories on the health. The London Medical and Physical *39:*464-466, 1818.

85. Jones, N. L., Burrows, B., and Fletcher, C. M.: Serial studies of 100 patients with chronic airway obstruction in London and Chicago. Thorax *22:*327, 1967.
86. Jones, R. N., Carr, J., Glindmeyer, H., Dieur, J., and Weill, H.: Respiratory health and dust levels in cottonseed mills. Thorax *32:*281-286, 1977.
87. Kamat, S. R., et al.: Bronchodilator trials in byssinosis. Ind J Med Sci *29:*208-212, 1975.
88. Kay, J. P.: Trades producing phthisis. The North of England Medical and Surgical Journal *1:*358—363, 1831.
89. Khogali, M.: A population study in cotton ginnery workers in the Sudan. Br J Ind Med *26:*308-313, 1969.
90. Kilburn, K. H., Lynn, W. S., Tres, L.L., and McKenzie, W. N.: Leukocyte recruitment through airway walls by condensed vegetable tannins and quercetin. Lab Invest *28:*55-59, 1973.
91. Kondakis, X. G. and Pournaras, N.: Byssinosis in cotton ginneries in Greece. Br J Ind Med *22:*291-294, 1965.
92. Koskela, R. S., Luoma, K., Hakkinen, I.: Mortality, disability and turnover of cotton mill workers. Tyotervey-slaitoken Tutkimuksia *150:*47-54, 1979.
93. Kutz, S. A., Olenchock, S. A., Elliott, J. A., Pearson, D. J., and Major, P. C.: Antibody-independent complement activation by cardroom cotton dust. Environ Res *19:*405-415, 1979.
94. Lammer, B., Schilling, R. S. F., and Wolford, J.: A study of byssinosis, chronic respiratory symptoms, and ventilatory capacity in English and Dutch cotton workers, with special reference to atmospheric pollution. Br J Ind Med *21:* 124-134, 1964.
95. Lynch, J. R.: Air sampling for cotton dust. Transactions of the National Conference on Cotton Dust and Health. Chapel Hill, NC, University of North Carolina, pp. 33-43, 1970.
96. McDermott, M.: Lung airways resistance changes due to the inhalation of dusts and gases. Respiration *26:*242-243, 1969.
97. McKerrow, C. B., Gilson, J. C., Schilling, R. S. F. and Skidmore, J.W.: Respiratory function and symptoms in rope workers. Br J Ind Med *22:*204-209, 1965.
98. McKerrow, C. B., McDermott, M., Gilson, J. C., and Schilling, R. S. F.: Respiratory function during the day in cotton workers: a study in byssinosis. Br J Ind Med *15:*75-83, 1958.
99. McKerrow, C.B. and Molyneux, M.K.B.: The influence of previous dust exposure on the acute respiratory effects of cotton dust inhalation. Proceedings of an International Conference on Respiratory Diseases in Textile Workers. Alicate, Spain, pp. 95-101, 1968.
100. McKerrow, C. B., Roach, S. A., Gilson, J. C., and Schilling, R. S. F.: The size of cotton dust particles causing byssinosis: an environmental and physiological study. Br J Ind Med *19:*1-8, 1962.
101. McKerrow, C. B. and Schilling, R. S. F.: A pilot inquiry into byssinosis in two cotton mills in the United States. JAMA *177:*850-853, 1961.
102. Mair, A., Smith, D.H., Wilson, W.A., and Lockhart, W.: Dust diseases in Dundee textile workers. Br J Ind Med *17:*272- 278, 1960.
103. Maitland, H.B., Heap, H., and MacDonald, A. D.: The presence of histamine in cotton dust. Appendix VI in Report of the Departmental Committee on Dust in Card Rooms in the Cotton Industry. London: HMSO, 1932.
104. Malcolm, A.G.: The influence of factory life on the health of the operative as founded upon the medical statistics of the class in Belfast. J R Statist Soc *19:* 170, 1856.
105. Martin, C. and Higgins, J.E.: Byssinosis and other respiratory ailments. JOM *18:*455-462, 1976.
106. Massoud, A. A.: The origin of the term "byssinosis". Br J Ind Med *21:*162, 1964.
107. Massoud, A. A. E., Altounyan, R. E. C., Howell, J. B. L., and Lane, R. E.: Effects of histamine aerosol in byssinotic subjects. Br J Ind Med *24:*38-40, 1967.
108. Massoud, A. and Taylor, G.: Byssinosis: antibody to cotton antigens in normal subjects and in cotton cardroom workers. Lancet *2:*607-610, 1964.
109. Medical Research Council Committee on Aetiology of Chronic Bronchitis. Standardized questions on respiratory symptoms. Br Med J *2:*1665, 1960.
110. Mekky, S., Roach, S. A., and Schilling, R.

S. F.: Byssinosis among winders in the cotton industry. Br J Ind Med *24:*123-132, 1967.

111. Merchant, J. A.: Epidemiological studies of respiratory disease among cotton textile workers, 1970-1973, (dissertation), University of North Carolina, 1973.
112. Merchant, J. A., Halprin, G. M., Hudson, A. R., Kilburn, K. H., McKenzie, W. N., Bermanzohn, P., and Hurst, D. J.: Evaluation of clinical indicators of biological responses to cotton dust. Arch Environ Health *30:*222-229, 1975
113. Merchant, J. A., Halprin, G. M., Hudson, A. R., Kilburn, K. H., McKenzie, W. N., Bermanzohn, P., Hurst, D. J., Hamilton, J. D., Germino, V. H.: Evaluation before and after exposure—the pattern of physiological response to cotton dust. Ann NY Acad Sci *221:* 38-43, 1974.
114. Merchant, J. A., Kilburn, K.H., O'Fallon, W. M., Hamilton, J. D., and Lumsden, J. C.: Byssinosis and chronic bronchitis among cotton textile workers. Ann Intern Med *76:*423-433, 1972.
115. Merchant, J. A., Lumsden, J. C., Kilburn, K. H., Germino, V. H., Hamilton, J. D., Baucom, D., Byrd, H., and Lynn, W. S.: Preprocessing cotton to prevent byssinosis. Br J Ind Med *30:*237-247, 1973.
116. Merchant, J. A., Lumsden, J. C., Kilburn, K. H., O'Fallon, W. M., Germino, V. H., McKenzie, W. N., Baucom, D., Currin, P., and Stilman, J.: Intervention studies of cotton steaming to reduce biological effects of cotton dust. Br J Ind Med *31:*261-274, 1974.
117. Merchant, J. A., Lumsden, J. C., Kilburn, K. H., O'Fallon, W. M., Ujda, J. R., Germino, V. H., and Hamilton, J. D.: An industrial study of the biological effects of cotton dust and cigarette smoke exposure. JOM *15:*212-221, 1973.
118. Merchant, J. A., Lumsden, J. C., Kilburn, K. H., O'Fallon, W. M., Ujda, J. R., Germino, V. H., and Hamilton, J. D.: Dose response studies in cotton textile workers. JOM *15:*222-230, 1973.
119. Merchant, J. A., O'Fallon, W.M., Lumsden, J. C., Kilburn, K. H., Copeland K., Ujda, J. R., Germino, V. H., Hamilton, J. D.: Determinants of respiratory disease among cotton textile workers. Proceedings of the ACGIH Conference on Cotton Dust, Atlanta, GA, 1975.
120. Merino, V. L., Lombart, R. L., Marco, R. F., Carricero, A. B., Guillen, F. G., and Bouhuys, A.: Arterial Blood gas tensions and lung function during acute responses to hemp dust. Am Rev Respir Dis *107:* 809-815, 1973.
121. Ministry of Social Security Pneumoconiosis and Allied Occupational Chest Diseases. London: HMSO, 1974.
122. Molyneux, M. B. K. and Berry, G.: The correlation of cotton dust exposure with the prevalence of respiratory symptoms. Proceedings of an International Conference on Respiratory Diseases in Textile Workers. Alicante, Spain, pp. 177-183, 1968.
123. Molyneux, M. K. B. and Tombleson, J. B. L.: An epidemiogical study of respiratory symptoms in Lancashire mills, 1963-1966. Br J Ind Med *27:*225-234, 1970.
124. Morey, P. R., Bethea, R. M., Wakelyn, P. J., Kirk, I.W., and Kopetzky, M. T.: Botanical trash present in cotton before and after saw-type tint cleaning. Am Ind Hyg Assoc J *37:*321-328, 1976.
125. Morey, P. R., Sasser, P. E., Bethea, R.M., and Kopetsky, M. T.: Variation in trash composition in raw cottons. Am Ind Hyg Assoc J *37:*407-412, 1976.
126. Morey, P. R., and Wakelyn, P.J.: Plant trash in linters and willowed picker: materials used in the cotton garnetting industry. Am Ind Hyg Assoc J *37:*413- 417, 1976.
127. Munt, D. F., Gauvain, S., Wolford, J., and Schilling, R. S. F.: Study of respiratory symptoms and ventilatory capacities among rope makers. Br J Ind Med *22:* 196-203, 1965.
128. National Institute for Occupational Safety and Health: Criteria for a recommended standard—Occupational Exposure to Cotton Dust. Cincinnati, NIOSH 75-118, 1974.
129. Neal, P. A., Schneiter, R., and Caminita, P. H.: Report on acute illness among rural mattress-makers using low grade, stained cotton. JAMA *119:*1074-1082, 1942.
130. Noweir, M. H., El-Sadek, Y., and El-Dak-

hakhry, A. A.: Exposure to dust in the cottonseed oil extraction industry. Arch Environ Health *19:*99-102, 1969.
131. Ortmeyer, C.: Disability awards to textile workers for specified respiratory conditions. Social Security Administration. Data Report 1970-1973, NIOSH, 1977.
132. Ortmeyer, C. E. and Merchant, J. A.: Mortality of employees of two cottonmills in North Carolina by dust-exposure category of job, 1940-1975. Chest, *79:*4, April, 1981 Supplement.
133. Organizing Committee. The status of byssinosis in the United States. Arch Environ Health *23:*230-234, 1971.
134. Palmer, A., Finnegan, W., Herwitt, P., Waxweiler, R., and Jones, J.: Byssinosis and chronic respiratory disease in U.S. cotton gins. JOM *20:*96-102, 1978.
135. Pardon, C. D.: The Mortality of Flax Mill and Factory Workers as Compared with Other Classes of Community. Belfast: Adair, 1873.
136. Patissier, P. H.: Traite des Malaidies des Artisans, etc. Paris: J. B. Bailliere, 1822.
137. Pernis, B., Vigliani, E. C., Cavagna, C., and Finulli, M.: The role of bacterial endotoxins in occupational diseases caused by inhaling vegetable dusts. Br J Ind Med *18:*120-129, 1961.
138. Piccirillo, R. E. and Roper, C. P.: U.S. Department of Health, Education, & Welfare, National Institute for Occupational Safety and Health. Health Hazard Evaluation Determination, Report No. 75-104, 1976.
139. Popa, V., Gavrilesca, N., Preda, N., Teculescu, D., Plecias, M., and Cirstea, M.: An investigation of allergy in byssinosis: sensitization to cotton, hemp, flax, and jute antigens. Br J Ind Med *26:*101-108, 1969.
140. Prausnitz, C.: Investigation on respiratory dust disease in operatives in the cotton industry. Privy council, Medical Research Council Special Report Series, No. 212 London: HMSO, 1936.
141. Proust, A. A.: Traite d'Hygiene Publique et Privee. Paris: G. Masson, 1877.
142. Ramazzini, B.: DA Treatise of the Diseases of Tradesmen. London: Bell, 1705.
143. Ramazzini, B.: Diseases of Workers, 1713. Translation by George Rosen, M.D., Ph.D. New York: Hafner Publishing Company, 1964.
144. Rattner, J. R., Spycher, M. A., and Engeler, M. L.: Pulmonary fibrosis induced by cotton fiber inhalation. Pathol Microbiol (Basel) *32/1:*1-14, 1968.
145. Report of the Departmental Committee on Dust in Cardrooms in the Cotton Industry. London: HMSO, 1932.
146. Renzetti, A. D., McClement, J. M., and Lilt, B. D.: The Veterans Administration cooperative study of pulmonary function III. Mortality in relation to respiratory function in chronic obstructive pulmonary disease. Am J Med *41:*115, 1966.
147. Roach, S. A. and Schilling, R. S. F.: A clinical and environmental study of byssinosis in the Lancashire cotton industry. Br J Ind Med *17:*1-9, 1960.
148. Rylander, R. and Nordstrand, A.: Pulmonary cell reactions after exposure to cotton dust extract. Br J Ind Med *31:*220-223, 1974.
149. Rylander, R., Nordstrand, A., and Snella, M.: Bacterial contamination of organic dusts. Arch Environ Health *30:*137-140, 1975.
150. Rylander, R. and Snella, M.: Acute inhalation toxicity of cotton plant dusts. Br J Ind Med *33:*175-180, 1976.
151. Schilling, R. S. F.: Byssinosis in cotton and other textile workers. Lancet *2:*261-265, 319-324, 1956.
152. Schilling, R. S. F.: Byssinosis in the British cotton textile industry. Br Med J *17:* 52-56, 1950.
153. Schilling, R. S. F.: Epidemiological studies of chronic respiratory disease among cotton operatives. Yale J Biol Med *37:* 55-74, 1964.
154. Schilling, R. S. F. and Goodman, N.: Cardiovascular disease in cotton workers: Part I. Br J Ind Med *8:*77-90,1951.
155. Schilling, R. S. F., Goodman, N., and O'Sullivan, J. G.: Cardiovascular disease in cotton workers: Part II. A clinical study with special reference to hypertension. Br J Ind Med *9:*146-153, 1952.
156. Schilling, R. S. F., Hughes, J.P.W., and Dingwall-Fordyce, I.: Disagreement between observers in an epidemiological study of respiratory disease. Br Med J *1:*65-68, 1955.
157. Schilling, R. S. F., Hughes, J. P. W., Dingwall-Fordyce, I., and Gilson, J. C.: An epidemiological study of byssinosis

among Lancashire cotton workers. Br J Ind Med *12:*217-227, 1955.
158. Schilling R. S. F., Vigliani, E. C., Lammers, B., Valic, F., and Gilson, J. C.: A report on a conference on byssinosis. Excerpta Medica International Congress Series 62(11):1963.
159. Schrag, P. E. and Gullet, A. D.: Byssinosis in cotton textile mills. Am Rev Respir Dis *101:*497-503, 1970.
160. Siddhu, C. M. S., Kedar, N., and Mehrotra. R. K.: Byssinosis amongst cotton and jute workes in Kanpur. Ind J Med Res *54:*980-994, 1966.
161. Simpson, G. R.: Exposure to dust in the cotton-garnetting industry. Med J Aust *1:*1151-1152, 1970.
162. Simpson, G. R. and Barnes, R.: Cotton dust exposure during lint removal. Arch Environ Health *17:*807-810, 1968.
163. Smith, G. F., Coles, G. V., Schilling, R. S. F., and Wolford, J.: A study of rope workers exposed to hemp and flax. Br J Ind Med *26:*109-114, 1969.
164. Stott, H.: Pulmonary disease amongst sisal workers. Br J Ind Med *15:*23-37, 1958.
165. Taylor, G., Massoud, A. A. E., and Lucas, F.: Study on the aetiology of byssinosis. Br J Ind Med *28:*143-151, 1971.
166. Thackrah, C. T.: The effects of Arts Trades, and Civic States and Habits of Living on Health and Longevity. London: Longmans, 1831.
167. Traver, G. A., Cline, M. G., and Burrows, B.: Predictors of mortality in COPD: A 15-year follow-up study. Am Rev Respir Dis *119:*895-902, 1979.
168. Tuypens, E., Byssinosis among cotton workers in Belgium. Br J Ind Med *18:* 117-119, 1961.
169. U.S. Department of Health, Education, and Welfare. Public Health Service, National Institute for Occupational Safety and Health. Health Hazard Evaluation Determination, Stearns and Foster, Company. Report No. 76-73-523, September 1978.
170. U.S. Department of Labor, National Institute for Occupational Safety and Health. Cotton dust. Title 29 Code of Federal Regulations, Part 1910.1043.
171. Valic, F. and Zuskin, E.: A comparative study of respiratory function in female non-smoking cotton and jute workers. Br J Ind Med *28:*364-368, 1971.
172. Valic F. and Zuskin, E.: Byssinosis-a follow up study of workers exposed to fine grade cotton dust. Thorax *27:*459-462. 1972.
173. Valic F. And Zuskin, E.: Effects of different vegetable dust exposures. Br J Ind Med *29:*293—297, 1972.
174. Valic, F., Zuskin, E., Wolford, J., Kersic, W., and Paukovic, R.: Byssinosis chronic bronchitis, and ventilatory capacities in workers exposed to soft hemp dust. Br J Ind Med *25:*176-186, 1968.
175. van de Woestijne, K. P., Douglas J. S., and Bouhuys, A.: Pathophysiology of byssinosis. Clin Res *16:*376, 1956.
176. Vaskov, L.S.: Use of radioisotopes in the study of textile workers with byssinosis and chronic lung damage. Br J Ind Med *30:*37-41, 1973.
177. Viswanathan, R., Damodarah, V. N., Sabramanian, T. A. V., Chakravarty, S., Sandhu, R. S., Gupta, S. N., Chandraskhar, S., and Sen, A. K.: Report of the inquiry on byssinosis in cotton textile workers. Ind J Med Res *55:*185-192, 1967.
178. Zuskin, E. and Bouhuys, A.: Protective effect of disodium cromoglycate against airway constriction induced by hemp dust extract. J Allergy Clin Immunol *57:*473-479,
179. Zuskin, E. and Valic, F.: Respiratory symptoms and ventilatory function changes in relation to length of exposure to cotton dust. Thorax *27:*454-458, 1972.
180. Zuskin, E. and Valic, F. L.: Respiratory symptoms and ventilatory function in sisal dust exposure. Int Arch Arbeitsmed *30:*105-111, 1972.
181 .Zuskin, E., Valic P., and Bouhuys, A.: Byssinosis and airway responses are to exposure to textile dust. Lung *154:*17-24, 1976.
182. Zuskin, E., Wolfson, R. L., Garpel, G., Welborn, J. W., and Bouhuys, A.: Byssinosis in carding and spinning workers. Arch Environmental Health *19:*666-67, 1969.