Byssinosis: a review

R McL Niven, C A C Pickering

Over the past two decades the cotton industry in the United Kingdom has suffered from a major recession. Cheaply produced and subsidised imported cotton has decimated a major industry which was responsible for much of the industrial wealth in the north west of England. With the diminishing industry, we are also losing one of the most studied but least understood occupational diseases, byssinosis. Our own study of the working population of the remaining Lancashire textile mills is now in its seventh year, with up to 1500 workers having been seen each year (although the recession has reduced this to 1000 in the last two years). Of the original 10 mills included in the study, only two remain in production.

The early reports of the health of cotton workers describe a “work-related cough associated with a sensation of uneasiness beneath the sternum” and later the unusual periodicity of the disease “all the workers have told us that the dust bothered them much less on the last days of the week than on Monday or Tuesday”. The workers attributed this to the interruption of work making them lose, in part, their habituation to the dust.1

Over a century later Sir Richard Schilling performed the first substantial epidemiological studies of cotton workers and described and classified the specific features recognised in the UK as byssinosis.2 Over recent years new terminology has been introduced, dividing byssinosis into “acute” and “chronic” forms. Acute byssinosis refers to the acute airways response which occurs in approximately a third of volunteers exposed to cotton dust for the first time. Substantial falls in FEV1 exceeding 30% have been reported in artificial cardroom exposures to cotton dust in cotton naive subjects.3 This type of response may account for the substantial labour turnover observed during the first year of employment in cotton spinning mills. A study of Finnish cotton spinning mills reported that one in 10 employees left within two weeks and one in four within three months of taking up employment.4 The pathophysiological process underlying this response is unknown, but probably represents a mixture of acute irritant or toxic reactions following exposure to cotton dust. Chronic byssinosis is applied to the symptoms and disability described in the early epidemiological studies which may develop after 20–25 years exposure to cotton dust. The term byssinosis in this article will relate to the disease as described in these early epidemiological studies.

Symptoms
The classical form of byssinosis is characterised by a feeling of chest tightness and difficulty in breathing which the worker experiences as being most severe on the first day of the working week after a period of absence from work. The symptoms continue after the individual has finished work and may even progress during the evening. However, they are perceived as being less troublesome on subsequent days. The reason for this lessening of symptoms remains unknown.

The affected worker will not experience the symptoms until he or she has worked for many years in the industry; indeed, it may be seen for the first time 25 years after starting to work in the industry and is rare in individuals continuously exposed for less than 10 years. This clearly distinguishes it from occupational asthma, and makes specific sensitisation an unlikely cause.

The duration and frequency of the symptoms are used as the basis for the original classification of the disease, which was later updated to include impairment of lung function.5 The classification included clinical grades C1/C2 to C3 and functional grades F0 to F3, based on symptoms and ventilatory impairment, but this grading system had important limitations. The clinical grades did not take into account the acute irritant effects of exposure to cotton dust or the changes in lung function which may occur in the absence of symptoms.

It was traditionally accepted that the disease progressed from one grade to another, presumably as a result of continuing exposure. However, two longitudinal studies have shown that this is unlikely to be the case as, in both studies, individuals were seen to commence at grade 2 or 3 byssinosis without passing through the preceding grades. Individuals have also been seen whose symptoms have remitted and who have therefore gone down grades despite continuing exposure to cotton dust.

Symptoms other than those described by Schilling are seen in workers with byssinosis. In our own study workers with byssinosis have reported other symptoms, including cough and wheeze. Other workers describe cough and wheeze to be most severe on the first day of the working week but in the absence of chest

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WHO grading system for byssinosis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Grade 0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>Byssinosis:</td>
<td>Chest tightness and/or shortness of breath on most of first days back at work</td>
</tr>
<tr>
<td>Grade B1</td>
<td>Chest tightness and/or shortness of breath on the first and other days of the working week</td>
</tr>
<tr>
<td>Grade B2</td>
<td>Persistent phlegm initiated or exacerbated by dust exposure</td>
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Respiratory tract irritation:

| Grade RTI 1 | Cough associated with dust exposure |
| Grade RTI 2 | Persistent phlegm (i.e. on most days during 3 months of the year) initiated or exacerbated by dust exposure |
| Grade RTI 3 | Persistent phlegm initiated or made worse by dust exposure either with exacerbations of chest illness or persisting for 2 years or more |

Lung function:

- Acute changes: A consistent decline in FEV₁, of less than 5% or an increase in FEV₁, during the work shift.
- Mild effect: A consistent decline of 5–10% in FEV₁, during the work shift.
- Moderate effect: A consistent decline of 10–20% in FEV₁, during the work shift.
- Severe effect: A decline of 20% or more in FEV₁, during the work shift.

- Chronic changes: FEV₁, 80% of predicted value
- Mild to moderate effect: FEV₁, 60–79% of predicted value
- Severe effect: FEV₁, less than 60% of predicted value

* A decline occurring in at least three consecutive tests made after an absence from dust exposure of two days or more.
* Predicted values should be based on data obtained from local populations or similar ethnic and social class groups.
* By a preshift test after an absence from dust exposure of two days or more.

and by our own field experience of asthmatic subjects entering the industry and having to leave due to increasing asthmatic symptoms.

Respiratory physiology

Changes in lung function have frequently been demonstrated in cotton workers — both acutely, across shift, and chronically — as estimated from cross sectional and prospective longitudinal studies. Some of these studies have shown across shift falls which are larger on the first working day of the week than on later days. The findings support the symptom periodicity of the disease. However, in one study of byssinotic subjects, while the across shift fall was largest on the first day of the working week, the forced expiratory volume in one second (FEV₁) after the shift was lowest on the last day of the week and the across shift falls became progressively smaller during the study week.

It may be that the extent of change in lung function associated with the working shift determines the severity of symptoms, perhaps combined with a degree of habituation or conditioning to a lower level of lung function.

While most studies have concentrated on forced expiratory volumes, some studies have shown larger changes in the calibre of the small airways which have led to the suggestion that the disease process starts in the smaller peripheral airways. Changes are greater for workers diagnosed as having byssinosis or chronic bronchitis than in asymptomatic workers and this is not affected by the smoking status of the individual.

No changes in gas transfer have been demonstrated in workers exposed to hemp, flax, or cotton, but in a challenge study of previous mill workers changes in arterial gas tensions were found and correlated to falls in FEV₁ after exposure to hemp dust.

While several studies have shown that cotton workers as a cohort have lower lung function than predicted, few have successfully observed a decline in lung function. One recent study in the USA has demonstrated that specific groups of cotton workers experience an excess decline in lung function compared with control workers with a mean annual decline of 57.4 ml in the smoking/high dust exposure group. Both this study and our own have been hampered by the realisation that the chosen control population of man-made fibre workers, while relatively asymptomatic, have also been shown to have an excess decline in lung function, particularly in terms of vital capacity.

In addition to changes in lung function, cotton workers have changes in airways reactivity. Fishwick and Pickering demonstrated that byssinosis was associated with increased bronchial reactivity in 78% of workers with byssinosis and 37% of those with non-specific work related symptoms, in comparison to a matched (age, sex, ethnic origin, smoking status, and workplace) group of asymptomatic workers in whom increased bronchial reactivity was identified in only 17%. The changes in both reactivity and small airway calibre have given rise to the
suggestion that byssinosis is an asthma-like condition of the small airways.\textsuperscript{24}

Warburton \textit{et al} recently continued this work by observing the changes in bronchial reactivity across a working week. Bronchial reactivity was demonstrated as being greatest after the end of the first shift of the week in workers with byssinosis but not in those with non-work-related lung disease such as chronic bronchitis.\textsuperscript{25}

Modest across shift decrements in FEV\textsubscript{1} have recently been shown to be strongly predictive of long term impairment of lung function in cotton workers.\textsuperscript{26}

Pathology
The pathological features of byssinosis have not been clearly defined, partly because of the difficulty in making specific diagnoses in life and also because of the presence of confounding features such as cigarette consumption which influence pathological changes. In the studies performed, insufficient numbers of never smoking byssinotic workers have been studied to distinguish between the non-specific features of smoking related pulmonary disease and any specific pathology associated with byssinosis.

A number of contradictory findings have been reported. Firstly, in a study by Edwards \textit{et al} evidence of mucous gland hyperplasia and smooth muscle hypertrophy were demonstrated.\textsuperscript{27} These features are non-specific and can be seen in patients with both chronic bronchitis and asthma.\textsuperscript{28} A later study confirmed the finding of increased mucous gland hyperplasia\textsuperscript{29} but, in addition, suggested that the changes occurred irrespective of whether the individual had ever smoked (the numbers were unfortunately small and exposure not satisfactorily documented). Both studies failed to show a relationship between byssinosis and emphysema or interstitial lung fibrosis.

These studies investigated necropsic changes within a variable time period between cessation of exposure to cotton dust and death. No studies have yet been performed in which either bronchial biopsy or bronchial lavage specimens have been taken from individuals with a well substantiated diagnosis of chronic byssinosis.

Bronchoalveolar lavage studies have been performed after exposure of both animals and human volunteers to cotton dust or dust extracts. Unfortunately these have been done predominantly on volunteers rather than individuals with chronic byssinosis. Variable changes have been identified, but neutrophil recruitment appears to be the most consistent finding.\textsuperscript{30} Whether such neutrophil recruitment is a feature of chronic byssinosis is unknown.

There remains doubt as to whether byssinosis is associated with any excess mortality and morbidity once exposure has ceased. Early studies suggested that there was no effect on survival in cotton workers.\textsuperscript{31} Such studies have been flawed by low response rates and by a lack of comparison between workers with and without respiratory symptoms. More recently, Hodgson achieved a response rate of over 90% and, while confirming an expected "healthy worker" effect, he also identified an increased mortality in workers who were diagnosed as having byssinosis.\textsuperscript{32}

Epidemiology
Epidemiological studies have shown that the prevalence of the disease in the UK has been falling continuously since the original studies of Schilling recorded a rate of around 50% in workers in the dustiest parts of the cotton spinning process.\textsuperscript{33} More recent studies have reported prevalence rates of 10% amongst these high risk workers,\textsuperscript{34} while current rates from our own prospective study suggest an overall prevalence of 3%.

While the reduction in prevalence of the disease has been explained by a reduction in dust exposure, there is little evidence to confirm a continued fall in dust levels. Indeed, it appears that, as the industry has striven to survive in a period of recession, increased machine running speeds to increase productivity have been achieved at the expense of increased dust exposures.\textsuperscript{35} Whether the increased use of respiratory protection will counterbalance the recent increase in dust levels remains to be seen, but it is unlikely that the disease will disappear from the working population in the UK as it has in the USA where technological improvements have resulted in much lower exposures to dust.\textsuperscript{36}

Similar prevalence rates of byssinosis as experienced in the UK in the 1950s and 1960s are now being experienced in the developing countries where cotton production is increasing. Prevalence rates of byssinosis of 30% in Indonesia,\textsuperscript{37} 37% in Sudan,\textsuperscript{38} 40% in Ethiopia,\textsuperscript{39} and up to 50% in India\textsuperscript{40} have been reported, although the same criteria for diagnosing byssinosis have not been used in all these studies. However, it appears that, while the disease is disappearing from the UK as a result of both lower dust exposures and because of industrial recession, it is becoming epidemic in parts of the world where cheap labour can be exploited.

Studies of workers exposed to flax and hemp have suggested that these dusts have a similar propensity to cause disease.\textsuperscript{41,42} The so called hard fibres of jute and sisal, while historically having been considered as unable to produce byssinosis,\textsuperscript{43} may have a low capacity to produce the disease.\textsuperscript{44}

Mechanisms of disease induction
Where the actual pathophysiology of a disease remains incompletely resolved, it is not surprising that the mechanisms of disease induction are similarly uncertain. Byssinosis is not a disease of exposure to inert dust. Studies have shown that washed cotton, while producing very similar dust exposure levels, has a reduced ability to produce physiological changes in affected individuals.\textsuperscript{45} In addition, while cotton contains a certain amount of histamine, the concentrations are too low to produce bronchoconstriction in man.\textsuperscript{46} An allergic
IgE mediated mechanism, while plausible from the highly antigenic composition of cotton dust and its contaminants, is unlikely as there is no relationship between atopy and disease. A non-IgE immunological mechanism has certain evidence to support it and remains plausible. Precipitating IgG antibody to an antigen in cotton is present in cotton workers and exposed controls. Its titres are highest in byssinotic workers and are greater at the beginning of the working week than at the end. Unfortunately, challenge with the identified compound failed to produce any pulmonary change to support the theory.

Complement activation has been reported from both arms of the cascade. Polymorphonuclear recruitment and activation has also been demonstrated in challenges with cotton dust extract on experimental animals and in the nasal passages of current workers. Activation of the arachidonic cascade has also been described and, while these mechanisms are plausible, no single explanation is satisfactory.

Aetiological agents

The airborne environment of the cotton mill is a milieu of different biochemical and microbiological agents capable of producing pulmonary reactions. It is certain that byssinosis is not a simple reaction to inert dust but is a response to one or a combination of these compounds.

Bract is the part of the cotton harvest which is not cotton fibre itself. It is predominantly dried leaf or plant debris collected during harvesting, but may also contain some soil. It contains a mixture of polyphenolic compounds with immunological activity and microbiological flora. Exposure of cotton workers to bract extracts causes bronchoconstriction. However, no good epidemiological data have been gathered to demonstrate a relationship between bract extract and disease. Such data are vital to identify a causal link with a disease of such prolonged development.

Tannins are present in cotton dust and have been shown to occur at levels capable of producing airway smooth muscle and epithelial changes in experimental animals. Tannins are also considered to be the cause of a byssinosis-like disease of herbal tea workers who experience symptoms on the first working day similar to those of cotton workers. There is, as yet, no clear mechanistic role for tannins, however, and no epidemiological studies have included measurement of tannins.

Much of our own work has focused on the microbiological contaminants of cotton dust. Fungi, with antigenic properties and thermophilic actinomycetes capable of producing alveolitides, have been reported in significant concentrations. No relationship was identified between fungal exposure and disease in a study by Cinkotai and Whittaker, but a strong relationship was found between bacteria (both Gram positive and Gram negative) and byssinosis. These findings have been confirmed by our own study where strong relationships were found between measures of all Gram positive and Gram negative bacteria and fungal exposures and chronic byssinosis. Unfortunately, it is apparent that, where the conditions favour the high exposure to one microbiological agent, then all are prevalent. The relationships are strongest for Gram negative bacteria but it was statistically impossible to confirm whether this was causal or related to co-association.

Endotoxin is a name given to a heterogeneous group of lipopolysaccharides which have been shown to be the cause of toxic reactions in Gram negative septicaemia. Inhalation of endotoxin causes both bronchoconstriction and, in animal models, an inflammatory response including polymorphonuclear recruitment. After chronic exposure, changes compatible with chronic bronchitis have been demonstrated histologically. In acute exposure studies in humans challenged with cotton dust, endotoxin levels were measured and correlated most closely with bronchoconstriction compared with the other hygiene exposure parameters. In our own epidemiological study there is a very close correlation between current levels of endotoxin exposure and the prevalence of byssinosis. However, exposure to endotoxin is known to occur in a number of other industries where organic dust is present – for example, swine confinement buildings, poultry farms, and hay handling – but workers in these industries, while potentially at greater risk of respiratory disease, do not suffer a byssinosis-like syndrome. A dose effect has been suggested as a possible explanation for this as existing studies have failed to compare exposure levels in different industries. Recent work in our centre has shown that, in some of these industries, exposure to endotoxin is much greater than in the cotton industry. If endotoxin were to explain all the features of byssinosis, it would have to relate to the chronicity of exposure or to an effect of mixed exposures.

Treatment and prevention

The treatment for affected individuals is similar to that for patients with occupational asthma. Prevention of further exposure, while preferred, has not been regularly achieved – partly because of the uncertainty as to the long term prognosis of the disease even if exposure continues, and partly because affected workers are unable to change to alternative employment. Cessation of exposure in an occupational disease should be recommended, particularly as recent studies have shown increased mortality in workers with byssinosis.

Both bronchodilators and anti-inflammatory agents can be used to ameliorate symptoms and inhaled steroids are probably more potent than sodium cromoglycate in the chronic form of the disease. The long term aim must be to prevent the disease by a reduction in dust exposure or exposure to the specific agent once this has been identified. As has been demonstrated by the cotton industry in the USA, technological
investment can bring both improved productivity with reduced incidence of the disease.16

Conclusions
It is clear that short term exposure to cotton dust for some workers is associated with acute respiratory symptoms and long term exposure is still associated with the classical form of byssinosis. The disease is characterised by small airways changes, both physiologically and histo-
logically, and by increased bronchial reactivity. Exposure to cotton dust is also associated with an excessive decline in lung function, irrespective of the presence of byssinosis itself. The unusual periodicity of chronic byssinosis remains the most specific feature of the disease which otherwise might be quite indistinguishable from occupational asthma/ bronchitis. The underlying mechanisms are un-
certain, but probably involve an inflammatory reaction secondary to an immunological or endotoxin induced process. While it will be a rare occurrence for many physicians in the UK, the disease will have worldwide relevance for many years to come.

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