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by [Rylander R](#)

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Organic dusts and lung reactions — Exposure characteristics and mechanisms for disease

by Ragnar Rylander, MD¹

RYLANDER R. Organic dusts and lung reactions — Exposure characteristics and mechanisms for disease. *Scand J Work Environ Health* 11 (1985) 199–206. Exposure to organic dusts has been related to pulmonary occupational disease in a variety of environments. These dusts contain several different agents, but the microbial contamination is always important, particularly regarding molds and Gram-negative bacteria. In the lung, organic dusts cause a series of reactions ranging from irritation with neutrophilic invasion to the initiation of cell mediator release and the development of antibodies. For certain diseases, such as byssinosis, the relation between the cell reactions and the disease is relatively well established; for others, such as allergic alveolitis (hypersensitivity pneumonitis) with fibrosis, more research is needed before the pathogenesis can be established. An understanding of the specific agents causing the disease and the cellular reactions behind its development is essential for its prevention.

Key terms: bacteria, lung disease, macrophages, molds, neutrophils.

Exposure to organic or nonmineral dusts has been known to cause pulmonary disease for several centuries. A disease caused by cotton dust was first described by Ramazzini in his *De Morbus Artificum*, published in 1713 (31). The recognition of a lung disease caused by moldy hay among humans and cattle also goes back several hundred years. Increased awareness of occupational disease, the development of sensitive lung function tests, and appropriate epidemiologic techniques have subsequently demonstrated that the problem is more widespread than previously thought.

In this presentation, I concentrate on two aspects of organic dust-related disease of particular relevance for today's physician, namely, *exposure conditions* in different environments and *cellular mechanisms* behind the development of the various diseases encountered. Knowledge of different risk areas will increase the accuracy of diagnosis, and insight into the cellular mechanisms responsible for the disease will improve treatment and prevention.

To describe the kind of exposure I am dealing with, the term "organic dusts" is often used. Sometimes the word "nonmineral" dust is applied. In a recent working document from the World Health Organization (WHO), the term "vegetable and other natural fibers" was used. Another derivative of this definition is "dusts of vegetable and animal origin."

The definition of "organic" given in the Oxford dictionary is: "existing as constituent of organized bodies or formed from bodies so existing, containing carbon in its molecule." According to this definition,

the term "organic dusts" quite adequately covers the types of environment that are considered in the following discussion.

Characteristics of organic dust exposure

Any organic dust has the potential to cause lung disease if (i) the particle size allows penetration into the lung and/or the alveoli, (ii) the agents are water- or lipid-soluble, and (iii) reactions occur at realistic concentrations of the agent as evaluated either in provocation tests with human subjects or in animal experiments.

Microbial contamination is an important factor determining the biological reaction. Organic dusts are contaminated with Gram-positive and Gram-negative bacteria and fungi/molds. The number of such organisms is of importance for the possible health hazards. Normal air contains from 10^3 to 10^4 fungi or bacteria/m³. The defense mechanisms of the respiratory apparatus against this normal environmental exposure are efficient, and adverse reactions usually occur only when the defense system is compromised.

In addition to viable and dead microorganisms in organic dusts, toxins from microorganisms have received increasing attention over the last several years. Gram-negative bacteria contain a compound known as endotoxin in their outer cell wall. This is a lipopolysaccharide which is present between the protein molecules of the cell wall. Endotoxins cause a series of important biological effects. They induce inflammation, attenuate the immune system, and interfere with the coagulation of blood.

Mycotoxins are probably also important although little is known about their occurrence or how exposure to them relates to lung diseases. One study

¹ Department of Environmental Hygiene, University of Gothenburg, Göteborg, Sweden.

Reprint requests to: Dr R Rylander, Department of Environmental Hygiene, University of Gothenburg, Box 33031, S-400 33 Göteborg, Sweden.

suggested that exposure to a fungal toxin in moldy hay may impair motor neuron function (personal communication, B Lembke, 1984).

Environments contaminated by organic dusts

The definition previously given to organic dust implies that exposure may take place in a variety of different environments. The most common sites from which patients come are industries in which vegetable fibers are handled and the agricultural environment. The processing of vegetable products and exposure to aerosols of contaminated waters represent additional areas of importance.

A list follows of some environments where exposure to organic dusts occurs:

Industry

- processing of vegetable fibers, eg, cotton
- saw mills, wood chips
- enzyme production
- laboratory animal handling

Agriculture

- hay handling
- grain handling
- pigsties
- poultry houses

Water

- sewage treatment
- sludge processing
- humidifiers

Dusts from *cotton and flax* handling and processing industries have been intensively studied regarding their chemical and microbiological characteristics. The particle size of the aerosol allows for deposition deep in the lung. Many specific chemical compounds have been isolated and tested in animal and human exposures in an effort to assay their importance for the development of the symptoms found after exposure to cotton or flax dust.

There are several naturally occurring compounds in cotton and flax plants which protect them from insects and diseases. Examples of such compounds are phenols, gossypols, flavonoids, and tannins.

From a microbiological point of view, cotton and flax dusts are characterized by their large content of Gram-negative bacteria and low numbers of molds and fungi. Among the Gram-negative bacteria, *Enterobacter agglomerans* is very common according to data from European, Australian, and American cotton mills. The amount of airborne endotoxin may reach several micrograms per cubic meter when cotton is carded.

The bacterial contamination of cotton is influenced by weather conditions during its growth. Cotton from areas with irrigation and a dry climate such as California and Australia have a considerably lower number of bacteria than cottons grown in

humid and rainy areas such as parts of Texas and Greece (34). Water-retted flax has a high bacterial contamination, whereas in chemically-retted flax bacterial contamination is low.

Regarding other vegetable fibers such as soft hemp and sisal, less information is available.

The air in *saw mills* processing moldy timber or in storehouses for *wood chips* contains large amounts of thermophilic molds, particularly *Rhizopus species* (1). Gram-negative bacteria are also present, and airborne endotoxin levels of up to $0.35 \mu\text{g}/\text{m}^3$ have been measured.

In industries processing bacterial enzymes, particularly those from *Bacillus subtilis*, airborne levels of enzymes can be important. During the handling of laboratory animals, organic dusts are also created: skin epithelium, hair from furs, and proteins from the fecal material and urine.

The agricultural environment often gives rise to lung disease due to organic dusts. WHO has paid particular attention to occupational health in agriculture. In the proceedings from a workshop on occupational health care in agriculture (41) attention was drawn to the problem of large quantities of dusts generated by the stirring of the soil, the manipulation of the crop, or mechanized animal feeding.

The microbiological contamination in agricultural environments has been extensively documented by Dutkiewicz (11, 12, 13). He measured concentrations of viable organisms, ranging from 2.0×10^5 to $1.3 \times 10^6/\text{m}^3$ in rooms contaminated with grain dusts and slightly lower concentrations where contamination with flour dusts was present. On animal farms, the number of bacteria was particularly high in pigsties and in poultry houses.

Most of the information available on agricultural environments and lung disease has been obtained in connection with the handling of *moldy hay*. Molds and Gram-positive and Gram-negative bacteria are present on fresh growing grass. The following list provides an overview of the types of common fungi and actinomycetes sampled in the air over growing grass (19).

Fungi

- Absidia species*
- Aspergillus fumigatus*
- Humicola lanuginosa*
- Penicillium piceum*

Actinomycetes

- Thermoactinomyces vulgaris*
- Micropolyspora faeni*
- Streptomyces species*

When the hay is cut and stored without being dried properly, fermentation increases its temperature. The temperature reached during storage is related to water content. Hay containing less than 15 % water will not heat, and no mold growth occurs. Up to 20 % water causes the temperature to rise to 30—

35°C, which favors the growth of *Aspergillus*. At about 30 % water, the temperature reaches 40°C, and *Aspergillus fumigatus* will grow.

A microorganism commonly cited to be present on moldy hay is *Micropolyspora faeni*. This was earlier believed to be the microorganism responsible for farmer's lung, an allergic alveolitis. It is now evident however that this disease appears in a multitude of organic dust environments where *M faeni* is not present. A good illustration of this point is given in a recent report describing allergic alveolitis due to *Aspergillus fumigatus* in compost workers. When serum precipitins were measured, no indications of any exposure to *M faeni* were found (38).

In addition to viable microorganisms, large amounts of endotoxins have sometimes been found in aerosols generated from moldy hay. Levels up to 2 µg/m³ — nearly equal to those present in cotton cardrooms — have been measured.

Apart from the handling of moldy hay, other agricultural environments have lately received increased attention. Measurements have been made in grain silos (40) where large amounts of different molds (*Aspergillus* and others) have been detected. These environments also contain high numbers of bacteria, particularly Gram-negative bacteria. Data on endotoxin levels are scarce. In one study (Rylander & Warren, unpublished) dust levels of up to 39 µg/g dust were found; in another study (9) levels of up to 188 µg/g were reported. The importance of this contamination is difficult to assess until measurements of airborne endotoxin and the particle size distribution have been made.

Several studies have investigated organic dust exposure in swine confinement buildings. The microbiological contamination has been characterized by a relatively high level of *Enterococci* (10⁵–10⁶/m³) originating from the fecal flora of the pigs. The numbers of Gram-negative bacteria and endotoxins are usually relatively low. Concentrations of molds may be high, particularly in connection with dry feeding operations, which are usually very dusty (5, 8, 35). However, most of the bacteria-carrying particles in this environment are not in the respirable size range. A considerable part of the respirable dust is believed to be protein from animal skin, although precise data are not available. The presence of proteins from the urine of pigs is of particular interest for the development of occupational asthma (18).

A few studies have been made in poultry processing plants. Large numbers of bacteria were isolated, particularly in connection with the loading and unloading of chickens/hens into cages (36). Among Gram-positive organisms *Bacillus* and *Corynebacterium* were particularly abundant. The Gram-negative flora contained *Escherichia coli* and *Actinobacter* species. Airborne endotoxin levels were as high as a few micrograms per cubic meter of air (13,

20, 29, 36). Similar conditions seem to prevail in turkey confinements (7).

In sewage water processing, the number of airborne bacteria is high, particularly in areas where water is sprayed or agitated, eg, with pumps, or where sludge is pressed to decrease its water content (21). The microbial flora is mainly composed of Gram-negative bacteria with a relatively low proportion of *E coli*. Few molds are present. The number of *B subtilis* may sometimes be important.

In treatment processes of sewage water sludge such as composting, large amounts of *Aspergillus* are found (6). Levels of up to 10⁶–10⁷/m³ of air have been recovered at sites where the compost is shifted. This dust is usually low in Gram-negative bacteria and airborne endotoxin. However, in special processing plants where the sewage sludge is dried, high concentrations of airborne endotoxins have been found (22).

It has long been known that contaminated waters in humidifiers contain a variety of microorganisms. Most of the emphasis has been on the identification of different molds, but interest in contamination with Gram-negative bacteria and endotoxin has recently increased. Among Gram-negative species isolated from contaminated water, *Flavobacterium* (33) and *Cytophaga* species (15) have been reported. In 30 samples of water from episodes with humidifier fever, 23 contained endotoxin in excess of 0.1 µg/ml, which, if aerosolized under appropriate conditions, would result in airborne amounts in excess of those required to cause fever in humans (Rylander, unpublished).

In summary, the characterization of some of the most important environments with organic dust exposure demonstrates the presence of a multitude of agents, both of nonmicrobial and of microbial origin. Levels of viable bacteria can be high, and, if the amount of dead microorganisms is taken into account, the exposure exceeds that present in the general environment by many orders of magnitude.

Diseases caused by organic dusts

The following list summarizes the various kinds of pulmonary diseases which have been related to exposure to organic dusts. [Diseases caused by infections (microorganisms multiplying in the lung) have been disregarded.]

- Byssinosis syndrome
- Occupational asthma
- Allergic alveolitis
- Toxin fever
- Bronchitis
- bronchial hyperreactivity
- chronic bronchitis

The byssinosis syndrome is a series of separate symptoms, encountered particularly after exposure

to cotton and flax dust, although these symptoms have also been observed among persons exposed to air humidified by contaminated water. A subjective feeling of chest tightness and slight dyspnea, which commonly occurs on Mondays or on days after an absence from work, are hallmarks of the disease. In parallel, but sometimes unrelated to this symptom, one can detect an airflow limitation caused by bronchoconstriction, which gradually develops over the first hours of the first workday of the week. The patient may also complain of tiredness and an increased airway irritation, provoked by a variety of agents. The symptoms are more pronounced in smokers, and some data suggest that they are more common among males than among females. There is a complete absence of specific radiographic changes in the lung, as well as pathology on autopsy. After several years of exposure chronic bronchitis develops.

Occupational asthma involves a bronchoconstriction with a rapid or delayed onset, provoked by exposure to a particular type of dust, often in small amounts. Occupational asthma is known to be caused by a variety of substances, many of which are organic dusts such as wool, furs, wheat grain, red cedar wood, and garlic powder. Among the several mechanisms discussed as responsible for this bronchoconstriction are particle irritation, mediation through immunologic mechanisms, induction by pharmacological agents, or the presence of inflammation (16). The symptoms are usually characterized by a gradual onset over the years during a continuous exposure to the responsible agent. The reaction occurs early during the workday and is sometimes quite violent. Likely sufferers are those with a previous history of atopy — smokers and nonsmokers seem to be affected to an equal degree.

Allergic alveolitis (hypersensitivity pneumonitis) is characterized by an acute onset of respiratory symptoms, often in combination with cough, as well as chills, fever, headache, nausea, and pain in the joints and muscles. The onset of the disease may resemble that of pneumonia. The disease occurs after repeated exposure to the same agent, eg, moldy hay, but often in connection with an unusually heavy exposure. The clinical stage lasts for several days to weeks, with persisting fever and respiratory symptoms. When the exposure ceases, the symptoms generally disappear. In some cases, chronic lung fibrosis will develop, particularly in patients who have experienced several acute episodes.

Lung radiographs may show small nodular infiltrates in the acute stage, resembling pneumonia or miliary tuberculosis. Lung biopsy in the initial phase demonstrates an accumulation of neutrophil granulocytes, phagocytes, edema, and cell disintegration in the alveolar cell walls. Collagen may be deposited and giant cells appear later in the process. The disease is more common among nonsmokers than among smokers (39).

I would like to suggest *toxin fever* as a new entity among diseases caused by organic dusts, although the term has been used by previous authors. In the afternoon, or the evening after a workday exposure, the patient develops fever accompanied by chills, joint pains, and other signs resembling influenza. Clinical examination reveals leucocytosis, but the radiographic finding is negative. The patient usually recovers within 24 h. If repeated exposure takes place, the fever response gradually disappears. This symptom appears after exposure to airborne endotoxins, but other agents may also elicit the reaction.

Exposure to organic dusts may also cause nonspecific *bronchitis*. Two stages can be distinguished: bronchial hyperreactivity and chronic bronchitis. Bronchial hyperreactivity is characterized by an onset of smooth muscle contraction in the upper airways after exposure to a specific agent, often of a particle nature, although distinct chemical compounds in vapor form may also provoke the reaction. Clinically, the presence of bronchial hyperreactivity can be evaluated in a metacholine provocation test. The patient often complains about respiratory difficulties in specific environments and also in the presence of general air pollution, tobacco smoke, or household dust. Chronic bronchitis is characterized by an increase in the goblet cell number, an increase in mucous production, and a change in the characteristics of the mucus toward a more sticky consistency. Next airway obstruction develops. The patients complain of persistent cough, and the condition is often aggravated by repeated upper respiratory infections, particularly in wintertime.

This short overview of the different diseases related to exposure to organic dusts demonstrates that the clinical picture resulting from the exposure can be extremely diverse.

The clinical case encountered often presents a mixture of the different symptoms, such as a worker in the cotton industry who, apart from symptoms of chest tightness and a decrement in forced expiratory volume in 1 s (FEV_{1,0}) over the workshift, may also suffer from symptoms of chronic bronchitis and, occasionally, when the exposure level is high, toxin fever. Cases of allergic alveolitis are seldom as clear as this typical case. Radiographic changes in the lungs may be absent, a fever resembling toxin fever may be present, and bronchial hyperreactivity may develop. Occupational asthma may resemble classical intrinsic asthma, but delayed reactions may be present. This symptomatology is sometimes similar to that encountered in byssinosis, but the symptoms are not confined to exposure on Mondays.

It is futile to believe that generalized reactions like those described are provoked by one or two specific agents occurring in organic dusts. On the contrary, they probably represent reactions elicited in the lung

by a variety of agents, alone or in combination, where exposure conditions, particularly dose levels and host factors, determine the development of clinical disease.

This concept casts doubt on the possibility to associate one particular agent with an observed disease in a provocation test. A patient's reaction to a given agent may only represent a nonspecific reaction and may not be related to the actual exposure which initiated the disease. The complexity of the exposure and the different reactions should also be considered in cases of compensation. That a patient does not present a textbook picture of a defined disease does not mean that he is not suffering medically from his environmental exposure.

Lung cell reactions after organic dust exposure

The major emphasis on cell reactions after organic dust exposure was previously on the development of antibodies and their demonstration in peripheral blood (precipitins). It is now generally agreed that, apart from occupational asthma with a rapid onset, antibodies are mainly indicators of exposure and probably not related to mechanisms of disease. In recent years, research has shifted towards the study of cell reactions in the lung itself. These studies have been greatly facilitated by the introduction of the lung lavage technique, first developed for experimental animals and later applied in clinical use.

The basic concepts regarding the cell reactions in the lung after exposure to organic dusts are outlined in figure 1. Dust particles which deposit on the respiratory epithelium are, to a large extent, cleared from the lung within a few hours after exposure. Should the particles contain toxic substances, such as mycotoxins or endotoxins, or should the clearance mechanisms be impaired, for instance by a prior exposure to chemical agents or a viral infection, contact times will be longer and the risk for cell damage will consequently increase.

At the alveolar level, the alveolar macrophage is the primary target cell. Alveolar macrophages approach and engorge all kinds of particles deposited in the lung. Subsequently, the material may be presented to immune competent cells for transformation into antibody secreting cells. The alveolar macrophages also influence other cells. Through the secretion of chemotactic substances an influx of neutrophils and platelets occurs, particularly after exposure to endotoxin-containing dusts. Monocytes also migrate into the lung for later development into alveolar macrophages.

All of the cells mentioned may themselves be activated and turn into secretory cells. By far the most versatile of these is the alveolar macrophage itself, which has been shown to produce a wide range of biologically active agents after appropriate stimulation. Particle stimulation in general brings about an

Figure 1. Basic concepts for lung cell reactions after organic dust exposure.

increase in the production of lysosomal enzymes. Cotton dust and endotoxins cause alveolar macrophages to increase the production of specific lysosomal enzymes (23, 32).

Neutrophils which have migrated into the lung may be activated and discharge their intracellular content of oxidizing agents, particularly after phagocytosis. The oxygen radicals so secreted are capable of causing endothelial cell injury, which facilitates the penetration of further cell elements from the blood into the lung and also causes tissue edema. Due to their content of endotoxin, cotton and flax dusts are particularly potent inducers of neutrophil migration into the lung.

Platelets are also powerful secretory cells. They are known to release serotonin (which causes bronchoconstriction), acid hydrolases (which may act on C5 in plasma) and a platelet permeability factor which produces a leucocyte activation that is independent of histamine. Extracts of cotton dust have been shown to activate platelets.

Several of the substances secreted by individual cells are chemotaxins, leading to a further assembly of cells at the site of injury. Many of the cells involved in the inflammatory response secrete mediators for further reactions. Traditional mediators are histamine and serotonin. The role of histamine in the bronchoconstriction seen in the byssinosis syndrome has been extensively investigated. Using lung preparations in vitro, some researchers have reported histamine liberation following the application of cotton dust extracts. In vivo conditions are quite dif-

Figure 2. Formation of mediators from cell membrane phospholipids.

ferent. The slow onset of the bronchoconstriction does not correspond to a typical histamine release reaction. The present belief is that, although histamine may be involved in the later stages of the inflammatory process following cotton dust inhalation, it does not act as a primary mediator for the reaction.

During recent years a series of new mediators has been detected (28). These originate from phospholipids in the cell membrane, and through external insults the phospholipids are transformed by phospholipase A_2 into three major groups of mediators (figure 2).

Following arachidonic acid synthesis, cyclooxygenases form prostaglandins and thromboxanes. The latter are potent bronchoconstrictors. Lipoxygenases transform arachidonic acid into lipo-peroxides and leukotrienes; one of the latter is identical to the earlier known slow reacting substance. Through acetylation, the cell membrane phospholipid can be transformed into the platelet-activating factor (PAF-acether), a potent inflammatory and bronchoconstricting agent.

Some information exists on the relation between organic dust exposure and the aforementioned mediators. One study (25) shows that thromboxane A_2 is present in lung lavage in rabbits after the inhalation of cotton dust extract. Other data demonstrate that extracts of cotton dust in vitro induce the production of thromboxane.

A specific mediator-induced reaction is the release of endogenous pyrogen from alveolar macrophages, the result being fever (10). Endogenous pyrogen is also secreted by human neutrophils although macrophages may produce at least 10 to 15 times more (2). Some data suggest that endogenous pyrogen is identical to the lymphocyte-inhibitory factor secreted by macrophages.

The presence of such a variety of potential inflammatory mechanisms as has been described requires shut-off mechanisms. Some of these are related to the secretion of the active substances themselves.

PAF-acether has been shown to act as an inhibitor of neutrophil activation (27). The neutrophils themselves produce a neutrophil-inhibitory factor. Activated macrophages have been shown to phagocytize neutrophils and render them innocuous (26). Alveolar macrophages are also a source of antioxidant defense enzyme systems such as catalase, superoxide dismutase, and glutathione peroxidase.

This review of cell reactions after organic dust exposure demonstrates the variety of pathways through which the diseases described earlier could develop. Other mechanisms not dealt with are the complement system, mast cells, and lymphocytes, particularly as regulators of other cells.

Connection between cell reactions and disease

It is apparent that a multitude of cellular effects may be elicited after exposure to organic dusts. However, only for a few of the diseases earlier described are the pathways established through which the disease develops.

The mechanism behind the appearance of fever, caused by endotoxin-containing dust, is fairly certain. The typical febrile response in humans after inhalation challenges starts 4 to 6 h after the inhalation, and the fever reaches a peak a few hours thereafter. The minimal pyrogenic dose of *E coli* endotoxin in humans is 0.1 to 0.5 ng/kg by injection (14). No dose-response relationships for inhalation have yet been defined, but the reaction was found to occur in 8 of 10 subjects inhaling 10 μ g of *E coli* LPS (17).

Dose levels in some environments have been shown to be sufficient for the fever reaction, and fever reactions have been produced in challenge experiments (4, 17, 24). The release of endogenous pyrogens from activated alveolar macrophages can thus be considered responsible for the mill fever episodes seen among cotton and flax workers, the typical fever responses seen in cases of humidifier fever, and some of the fever cases seen among grain handlers. However, not all cases of humidifier fever can be explained by the presence of endotoxin. Two cases of allergic alveolitis have been reported which were apparently caused by contamination by *Cephalosporium* (30). The environment in one case was repeated flooding of the home with sewage water and in the other case a contaminated humidifier. There is no discrepancy in these observations, as agents other than endotoxin can probably activate alveolar macrophages and cause the release of endogenous pyrogen.

After repeated exposure, tolerance to pyrogenic activity appears. Tolerance is characterized by a reduction in the febrile response of humans with an increasing number of exposures. This occurrence explains the disappearance of mill fever. If the reticuloendothelial system is blocked, the uptake of endo-

toxin is prevented, and the febrile reaction reappears, although this reversal may only be partial.

As far as the byssinosis syndrome is concerned, the situation is more complex. In cotton workers, neutrophils and platelets migrate to the lung on Mondays. Several mechanisms, such as an increased airway sensitivity due to the presence of neutrophils and reactions related to the release of mediators from platelets, may play a role in the byssinosis syndrome. At present no definite information is available.

The mechanisms responsible for the development of allergic alveolitis are also unclear. A critical review of the literature (3) shows that there is very little evidence for its classification as a type III (antibody-antigen) reaction. Much interest has been connected to the presence of an increased number of suppressor T-cells, which are found in lung lavages from persons suffering from the disease. How this change in lung-cell pattern relates to the development of an alveolitis in exposed workers is unclear.

The fibrosis which sometimes follows allergic alveolitis has been related to activated macrophages, but the exact circumstances under which this reaction occurs after exposure to organic dusts is yet unclear. The role of the neutrophil in this connection is interesting. An absence of neutrophils has been shown to aggravate the fibrotic response after silica inhalation (37). The absence of fibrosis in the lungs of cotton mill workers exposed to endotoxins — which recruit neutrophils into their lungs — further suggests a role for the neutrophil in this response.

Occupational asthma represents a mixed group of a variety of symptoms. It is likely that the traditional type I reaction involving sensitization to immunoglobulin E antibodies, as well as type III reactions and macrophage/lymphocyte activation, all play a role depending upon the type of exposure agent. The role of mediators derived from cell membranes, such as prostaglandins, leukotrienes or PAF-acether, has not yet been explored.

Bronchial hyperreactivity has recently been related to the presence of neutrophils in the respiratory epithelium. Apart from this occurrence, other mechanisms, such as an increased permeability of the epithelium, which is particularly pronounced after exposure to tobacco smoke, may also play a role. Changes in receptor function of the nerve endings with sensitization towards a specific agent may also be involved.

Chronic bronchitis is a result of a chronic insult to the respiratory epithelium. Examples of agents capable of such insults are sulfur dioxide and particles. Some evidence suggests that endotoxins may play a role in the development of this effect in organic dust exposures.

In conclusion a plethora of cell mechanisms exists which can be related to the development of clinical lung disease seen after exposure to organic dusts. More research is needed to define which of the

postulated mechanisms are relevant. Such experiments need to be done using in vivo animal models, and clinical studies on normal subjects and those with the disease need to be carried out. Continued research in this field will hopefully be able to prevent lung disease resulting from the inhalation of organic dusts.

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References

1. Belin L. Clinical and immunological data on "wood trimmers disease" in Sweden. *Eur J Respir Dis* 61 (1980); suppl 107, 169—176.
2. Bodel P. Studies on the mechanism of endogenous pyrogen production: III Human blood monocytes. *J Exp Med* 140 (1974) 954—965.
3. Burrell R, Rylander R. A critical review of the role of precipitins in hypersensitivity pneumonitis. *Eur J Respir Dis* 62 (1981) 332—343.
4. Cavagna G, Foa V, Vigliani, EC. Effects in man and rabbits of inhalation of cotton dust or extracts and purified endotoxins. *Br J Ind Med* 26 (1969) 314—321.
5. Clark CS, Rylander R, Larsson L. Airborne bacteria, endotoxin and fungi in dust in poultry and swine confinement buildings. *Am Ind Hyg Assoc J* 44 (1983) 537—541.
6. Clark CS, Rylander R, Larsson L. Levels of Gram-negative bacteria, *Aspergillus fumigatus*, dust and endotoxin at compost plants. *Appl Environ Microbiol* 45 (1983) 1501—1505.
7. Cravens RL, Harry MS, Beaulieu J, Buchan RM. Characterization of the aerosol in turkey rearing confinements. *Am Ind Hyg Assoc J* 4 (1981) 315—318.
8. Curtis SE, Drummond JG, Grunloh DJ, Lynch PB, Jensen AH. Relative and qualitative aspects of aerial bacteria and dust in swine houses. *J Animal Sci* 41 (1975) 1512—1520.
9. DeLuca AJ, Godshall MA, Palmgren MS. Gram-negative bacterial endotoxins in grain elevator dusts. *Am Ind Hyg Assoc J* 45 (1984) 336—339.
10. Dinarello CA. Molecular mechanisms in endotoxin fever. *Agents Actions* 13 (1983) 470—486.
11. Dutkiewicz J. Exposure to dust-borne bacteria in agriculture: I Environmental studies. *Arch Environ Health* 33 (1978) 250—259.
12. Dutkiewicz J. Exposure to dust-borne bacteria in agriculture: II Immunological survey. *Arch Environ Health* 33 (1978) 260—270.
13. Dutkiewicz J. Keimflora der Luft in verschiedenen Geflügelzucht- und Verarbeitungsanlagen. *Z Gesamte Hyg Ihre Grenzgeb* 26 (1980) 45—54.
14. Elin RJ, Wolff SM, McAdam KP, Chedid L, Audibert F, Bernard C, Oberling F. Properties of reference *Escherichia coli* endotoxin and its phthalylated derivative in humans. *J Infect Dis* 144 (1981) 329—336.
15. Flaherty DK, Deck FH, Cooper J, Bishop K, Winzenburger PA, Smith LR, Bynum L, Witmer WB. Bacterial endotoxin isolated from a water spray air humidification system as a putative agent of occupation-related lung disease. *Infect Immun* 43 (1984) 206—212.

16. Gandevia B. Occupational asthma. *Med J Aust* 2 (1970) 332—372.
17. Haglind P, Bake B, Rylander R. Effects of endotoxin inhalation challenges in humans. In: Wakelyn PJ, ed. Eighth cotton dust research conference, Atlanta, Georgia, January 9—10 1984. National Cotton Council, Memphis, TN 1984, pp 105—106.
18. Harries MG, Cromwell O. Occupational asthma caused by allergy to pigs' urine. *Br Med J* 284 (1982) 867.
19. Lacey J. Potential hazards to animals and man from microorganisms in fodders and grain. *Trans Br Mycol Soc* 65 (1975) 171—184.
20. Lenhart SW, Olenchock SA, Cole EC. Viable sampling for airborne bacteria in a poultry processing plant. *J Toxicol Environ Health* 10 (1982) 613—619.
21. Lundholm M, Rylander R. Work related symptoms among sewage workers. *Br J Ind Med* 40 (1983) 325—329.
22. Mattsby I, Rylander R. Clinical and immunological findings in workers exposed to sewage dust. *J Occup Med* 20 (1978) 690—692.
23. Mörlund B, Mörlund J. Selective induction of lysosomal enzyme activities in mouse peritoneal macrophages. *J Reticuloendothel Soc* 23 (1978) 469—477.
24. Muittari A, Rylander R, Salkinoja-Salonen M. Endotoxin and bath water fever. *Lancet* 2 (1980) 89.
25. Mundie TG, Ainsworth SK. Changes in pulmonary lavage contents following acute inhalation of cotton dust extracts in rabbits. In: Wakelyn PJ, Jacobs RR, ed. Seventh cotton dust research conference. National Cotton Council, Memphis 1983, pp 104—105.
26. Newman SL, Henson JE, Henson PM. Phagocytosis of senescent neutrophils by human monocyte-derived macrophages and rabbit inflammatory macrophages. *J Exp Med* 156 (1982) 430—442.
27. O'Donnell MC, Siegel JN, Fiedel BA. Platelet activating factor: An inhibitor of neutrophil activation. *Clin Exp Immunol* 43 (1981) 135—142.
28. O'Flaherty JT. Biology of disease: Lipid mediators of inflammation and allergy. *Lab Invest* 47 (1982) 314—329.
29. Olenchock SA, Lenhart SW, Mull JC. Occupational exposure to airborne endotoxins during poultry processing. *J Toxicol Environ Health* 9 (1982) 339—349.
30. Patterson R, Fink JN, Miles WB, Basich JE, Schleuter DB, Tinkelman DG, Roberts M. Hypersensitivity lung disease presumptively due to *Cephalosporium* in homes contaminated by sewage flooding or by humidifier water. *J Allergy Clin Immunol* 68 (1981) 128—132.
31. Ramazzini B. Diseases of workers. Translated from the Latin text *De Morbis Artificum* of 1713 by Wright WC. Hafner Publishing Company, New York, NY 1964, p 257.
32. Rylander R, Fogelmark B, Sjöstrand M. Free lung cell phagocytosis and lysosomal enzyme activity after inhalation of lipopolysaccharide in guinea pigs. *Agents Actions* (in press).
33. Rylander R, Haglind P, Lundholm M, Mattsby I, Stenqvist K. Humidifier fever and endotoxin exposure. *Clin Allergy* 8 (1978) 511—516.
34. Rylander R, Lundholm M. Bacterial contamination of cotton and cotton dust and effects on the lung. *Br J Ind Med* 35 (1978) 204—207.
35. Thedell TD, Mull JC, Olenchock S. A brief report of Gram-negative bacterial endotoxin levels in airborne and settled dusts in animal confinement buildings. *Am J Ind Med* 1 (1980) 3—7.
36. Thelin A, Tegler Ö, Rylander R. Lung reactions during poultry handling related to dust and bacterial endotoxin levels. *Eur J Respir Dis* 65 (1984) 266—271.
37. Thrall RS, Phan SH, McCormick JR, Ward PA. The development of bleomycin-induced pulmonary fibrosis in neutrophil-depleted and complement-depleted rats. *Am J Pathol* 105 (1981) 76—81.
38. Vincken W, Roels P. Hypersensitivity pneumonitis due to *Aspergillus fumigatus* in compost. *Thorax* 39 (1984) 74—75.
39. Warren CPW. Extrinsic allergic alveolitis: A disease commoner in non-smokers. *Thorax* 32 (1977) 567—569.
40. Warren CPW, Manfreda J. Respiratory symptoms in Manitoba farmers: Association with grain and hay handling. *Can Med Assoc J* 122 (1980) 1259—1264.
41. World Health Organization. Workshop on occupational health care in agriculture, Geneva, 6—12 November 1979. Geneva 1979, pp 1—31.