Review
Scand J Work Environ Health 1977;3(2):53-72
doi:10.5271/sjweh.2790

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Corrections
See 1977;3(2):0 for a correction.

Key terms: airway disease; allergic and nonallergic mechanisms; allergic mechanism; asthma; bronchial asthma; nonallergic mechanism; obstructive airway disease; occupational asthma; review

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/329409
Bronchial asthma of occupational origin

A review

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Bronchial asthma is a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli; it is manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy (3). Occupational asthma is a respiratory disorder characterized by reversible obstruction of the airways and caused by the inhalation of substances or materials which are manufactured or directly used by a worker or are incidentally present at the work site (84). This definition encompasses a variety of airway disorders, regardless of the action, and includes processes which result from both an immunologic and nonimmunologic basis. Occupational asthma is manifested clinically by chest tightness, cough, wheezing and shortness of breath and physiologically by temporal alterations in pulmonary mechanics. While airway obstruction is initially intermittent and reversible, continued exposure to the inciting agent may, in some instances, lead to irreversible obstructive airway disease and chronic respiratory symptoms.

While the diagnosis of bronchial asthma is based largely on clinical and physiological characteristics, it must be differentiated from other obstructive pulmonary diseases such as chronic bronchitis. This latter disorder is characterized clinically by excessive production of bronchial mucus and is manifested by chronic productive cough (3, 22). For epidemiologic purposes "chronic" refers to the presence of these symptoms on most days for at least three months of the year during two or more successive years. Physiologically, chronic bronchitis is associated with irreversible obstruction of the airways. Emphysema, another type of chronic obstructive pulmonary disease, is defined in terms of its pathological characteristics as an abnormal and permanent enlargement of respiratory air spaces (the structure beyond the terminal bronchiole) that is accompanied by destructive changes (3). Bronchial asthma, chronic bronchitis, and emphysema can occur together, and many patients with chronic airway obstruction have combined features of two or even all three of the diseases. When chronic bronchitis and bronchial asthma occur together, the resultant clinical syndrome is often called "asthmatic bronchitis." Bronchial asthma and emphysema can also be encountered together, especially in older patients. A rational formulation of
diagnosis, therapy and prognosis for an individual suspected of having airway obstruction of occupational origin requires precise identification of the disorder or the combination of disorders afflicting the worker.

**EPIDEMIOLOGY**

According to the results of a health interview survey conducted by the National Center for Health Statistics (89), 6,031,000 persons in the United States were afflicted with bronchial asthma in 1970. This number represents approximately 3 to 3.5 % of the population.

The prevalence of occupational asthma is hard to determine. Bernstein reported that, in a recent survey of the United States, occupational asthma was not recognized as a reportable entity in a single state (8). In 1970 the state of California noted that the designation “noninfectious chronic respiratory disease” accounted for 4 % of all reported occupational diseases (8). Thirty per cent of these respiratory conditions could be attributed to agents capable of causing obstructive pulmonary disease. The incidence of respiratory symptoms due to wood and paper dusts was 4 %, isocyanates 4 %, various chemicals 8.8 %, and proteolytic enzymes 3 %. An estimate of the prevalence of specific types of occupational asthma in the United States for the years 1969—1970 indicated that in the cotton industry the prevalence of byssinosis was approximately 25 % among the workers in the carding process and 12 % among spinning workers (8).

About 5 % of the workers exposed to volatile isocyanates develop asthma. The prevalence of asthma among workers exposed to proteolytic enzymes was estimated to be between 10 and 45 %. Epidemiologic studies of workers exposed to grain dust, including millers and bakers, have reported asthma prevalences between 2 and 40 % (84).

It is clear, however, that in any individual plant or industry, prevalence depends on factors such as type, source and concentration of occupational exposure, work conditions, industrial hygiene factors, climactic influences, and individual characteristics of host response. Wada et al. reported on approximately 2,000 oyster workers from 500 plants in the Hiroshima Bay and found 18.1 % with bronchial asthma (129). Nakashima conducted a questionnaire survey which included 66.2 % of the 9,326 residents of Saka town in Japan, where 70 oyster shops were located, and found a history of bronchial asthma in 2.7 % of the males and 2.6 % of the females (88). The results strongly suggest that the presence of bronchial asthma in Saka town was influenced by the particular type of asthma prevalent among cultured oyster workers.

In certain instances especially high percentages of persons exposed to an occupational inhalant can develop asthma. For instance, it has been reported that almost every worker in the power plants along the Mississippi River eventually becomes sensitized to river flies (31). Approximately 70 % of flight crews dispersing irradiated sterile male screwworm flies develop allergic symptoms (43).

In some cases prevalence may be influenced by economic factors. Ishizaki et al. were able to demonstrate an association between the numbers of reported cases of allergic symptoms in workers exposed to western red cedar dust and the quantity of western red cedar imported into Japan (51). Up to 1960, as little as 10,000 m³ of western red cedar had been imported into Japan and the imports were limited mainly to the Tokyo and Yokohama-Kawasaki ports. By 1968 imports had increased to 440,000 m³ and the wood was widely distributed among various ports throughout Japan. Coincidentally with the wide distribution of the wood, cases of western red cedar asthma were reported from all over Japan.

**IMMUNOLOGY OF BRONCHIAL ASThma**

The term “atopy” was first introduced by Coca and Cooke in 1923 to describe a population of patients in which disorders such as allergic rhinitis, asthma, and atopic dermatitis were common (23). Atopic patients were found to have a unique response to intranasal immunizations with certain protein and carbohydrate antigens. They produced high concentrations of
skin-sensitizing antibodies which resulted in an immediate type response to skin testing with these antigens (64, 105, 106, 107, 108, 109, 110). Such a reaction was rarely observed in normal (nonatopic) subjects immunized by the same schedule. When the same antigens were given parenterally, both atotics and controls had similar serum antibody responses. Atopic individuals seem more likely to develop allergy to many industrial materials, e.g., enzymes of *B. subtilis* and gum acacia, than nonatopic subjects. On occasion, however, nonatopics may be more susceptible to sensitization (20).

The critical role of immunoglobulin E (IgE) in the pathogenesis of many cases of asthma has been demonstrated by surveys of patients with allergic asthma who show significantly elevated concentrations of IgE, whereas serum IgE is often normal in patients with rhinitis without asthma (49, 53, 54, 61, 64, 65, 119). In 1966 Reid and associates reported skin-fixing antibody activity in the IgG fraction of the sera of several atopic patients (103). It appears that some allergic patients possess a non-IgE antibody which may contribute to tissue changes noted in chronic allergic reactions. It is not clear, however, if they are directly related to acute asthmatic reactions.

Immunologic reactions have been classified into four types (44). In type I, or anaphylactic reaction, IgE antibody binds by its Fc fragment to specific receptor sites on the surface of the mast cell or basophil. Antigen reacts with the cell-bound antibody to form bivalent complexes, and these in turn trigger a series of enzymatic reactions that ultimately result in the release of mediators such as histamine, serotonin, the slow-reacting substance of anaphylaxis (SRS-A), and the eosinophil chemotactic factor of anaphylaxis (ECF-A), which causes the asthmatic reaction. Type II, or cytotoxic type reaction, is mediated by a reaction of the antibody with the surface antigen of cells and the formation of an immune complex. There is no evidence to suggest that this type of immunologic reaction takes place in asthma. Type III, or Arthus reaction, involves circulating antibodies and depends on the presence of immune complexes capable of activating the complement system and generating certain chemotactic fragments. It is not clear what role this type of reaction has in the pathogenesis of occupational asthma. Type IV, delayed hypersensitivity or "tuberculin reaction," is cell-mediated immunity. This type of immunologic mechanism may play some role in certain types of occupationally induced asthma (14).

Different types of asthmatic reactions can be observed following bronchial provocation conducted with specific antigens and under carefully controlled conditions (96, 97). The types of reaction fall into three main groups: immediate; nonimmediate or late; and dual or combined reactions, during which both immediate and late reactions occur (fig. 1). To date at least two forms of immediate and three forms of late asthmatic reaction have been described. The immediate reactions are rapid in development (within 15—30 min) and are relatively short in duration. The immunologic mechanisms regarded as responsible for immediate asthmatic reactions are type I, IgE (long-term homocytotropic) and type I, IgG (short-term homocytotropic) antibody-mediated allergy. The three types of nonimmediate or late asthmatic reaction consist of a reaction beginning about 1 h after antigen challenge and lasting for 2—3 h, (b) a reaction starting after about 3—4 h, maximal 5—8 h, and lasting about 24—36 h, in which there is evidence of a type III precipitating antibody, immune-complex allergic reaction, and (c) a reaction beginning early in the morning which can be recurrent for several days after the challenge even though measurements of forced expiratory volume in 1 s return to pretest levels during the day. These various patterns of late reaction occur in the absence of IgE antibody. The responses of immediate and late asthmatic reactions to therapeutic agents are different. Isoproterenol inhalation causes reversal of the immediate reactions. Corticosteroids have little effect on immediate asthmatic reactions, whether given systemically or by inhalation, but they are effective in inhibiting late asthmatic reactions. Disodium cromoglycate inhibits immediate asthmatic reactions and may also inhibit certain late reactions or those associated with immediate asthmatic reactions.
BRONCHIAL SMOOTH MUSCLE TONE AND HYPERREACTIVE AIRWAYS

Bronchial smooth muscle tone is maintained through a regulatory mechanism involving the adrenergic and cholinergic nervous pathways. One proposed theory for the development of bronchial asthma suggests the presence of partial or complete blockage (acquired or inherited) of the beta-adrenergic nervous system with resultant bronchoconstriction from unopposed alpha-adrenergic and cholinergic innervations (2, 122). Cholinergic innervation through the vagus seems to have the most influence over normal bronchial smooth muscle tone (17). The increased airway resistance produced in sensitized dogs challenged with allergen can be prevented by blockage of either the efferent or afferent nerves of the vagus (45).

Stimulating various receptors causes a striking reflex effect in bronchial motor tone. Damage to the bronchial epithelium, by toxic gases or chemicals, has been shown to expose sensory nerves of airways and result in a lowering of the threshold for activation of their sensory nerve endings (87). Inhaling certain chemicals (e.g., TDI), gases (e.g., SO₂), or chemically inert dust or mechanically stimulating the mucosa of the airways may stimulate subepithelial (irritant) receptors and cause reflex bronchoconstriction which can be abolished by or prevented by cutting the vagus nerves of animals or by administering atropine sulfate to healthy human subjects (86, 87). Histamine also produces bronchial smooth muscle contraction which is abolished by ganglionic blockade or by atropine; this action suggests that cholinergic mechanisms are involved (45, 87). Bronchoconstriction will develop to proportionally smaller concentrations of certain inhaled chemicals such as methocholine and histamine in asthmatics than in healthy individuals (45, 87, 92, 93). It has been suggested that increased sensitivity of the “irritant” receptors could be the cause of airway hyperreactivity and it may continue even after exposure has ended. Paine and associates reported evidence of bronchial hyperreactivity in some patients with occupational asthma (94). Seven patients with asthma induced by either western
red cedar or isocyanate fumes were greatly
benefited by removal from their occupa-
tional exposure. Reexamination, however,
after a period of up to three years of free-
dom from exposure showed that their
response to the inhalation of methacholine
aerosol was still abnormal. This finding
indicated persistent hyperreactive airways
that were similar to "nonoccupational" asthma.

**INTRACELLULAR NUCLEOTIDES**

The beta-adrenergic receptor is closely
associated with adenyl cyclase, an enzyme
which is present in the plasma membrane
of many cells and which indirectly con-
trols processes such as active secretions,
transport and the storage of carbohydrate
(5, 57). Evidence suggests that stimulating
the beta-adrenergic receptor results in a
series of intracellular biochemical events
which involve the activation of the recep-
tor enzyme, adenyl cyclase, and the pro-
duction of adenosine 3', 5' monophosphate
(cyclic AMP) from adenosine triphosphate
(ATP). Cyclic AMP levels are regulated by
another enzyme, phosphodiesterase, which
degrades cyclic AMP to adenosine 5'
monophosphate.

It has been proposed that asthmatic pa-
tients do not respond normally to beta-
adrenergic stimulating agents (5, 122). Con-
sequently, they have lower levels of in-
tracellular cyclic AMP that result in the
release of mediators which cause the
asthmatic reaction. Additionally, in vitro
studies demonstrate cholinergic receptors
which regulate a different intracellular
cyclic nucleotide pool, cyclic guanosine 3',
5' monophosphate (cyclic GMP) (5). Cho-
linergic agents such as carbachol or meth-
acholine cause mediator release by aug-
menting intracellular concentrations of cy-
clic GMP without any concurrent effect on
cyclic AMP. Thus the balance of smooth
muscle tone is maintained by the recipro-
cal activity of the sympathetic and para-
sympathetic nerve pathways and is in-
fluenced by intracellular homeostasis me-
diated by two different intracellular cyclic
nucleotide pools, one being influenced by
adrenergic stimulation, the other by cho-
linergic stimulation. Fig. 2 is a summary
of the mechanisms which enhance me-
diator release.

**DISPOSITION AND CLEARANCE OF
PARTICLES FROM THE LUNG IN
ASTHMA**

The site at which aerosol particles con-
tact responding tissue is an important
determinant of the nature and severity of
resulting damage. With particles 20 \( \mu \) in
diameter, deposition takes place mainly in
the upper respiratory tract and secondary
bronchi primarily by inertial deposition.
Particles 5 \( \mu \) in diameter are deposited

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![Fig. 2. Mechanisms involving intracellular nucleotides which influence the release of the mediators responsible for acute asthmatic attacks.](image-url)
nearly evenly between the upper respiratory tract and bronchi, sedimentation by gravity being important in the deeper penetration. Tracheobronchial depositions of particles 1—5 μ in diameter were found to be higher in asthmatic and bronchitic patients than in nonsmoking subjects, and most of the increase was found in airways distal to the trachea (66). Studies on healthy subjects and subjects with chronic bronchitis have demonstrated that inhaled particles 5 μ in diameter penetrate deeper in healthy subjects than in bronchitic subjects (125). The nose, with its narrow tortuous passages, is ideally constructed to remove larger aerosol volumes. For particles larger than 10 μ nasal deposition can approach nearly 100 % provided that flow rate is greater than 18 l/min (48). It has been estimated that there is also a substantial removal of particles in the 2—5 μ range. In the larger bronchi, the mucociliary blanket propels particles toward the mouth. Inhaled particles resting on alveolar surfaces are engulfed by macrophages and are passively transported into this film (48). Other lung clearance mechanisms have also been described (48, 125).

In asthma the site of deposition of inhaled particles depends on the degree of airway obstruction that is present at any time. In the presence of bronchospasm, airway radius decreases and the deposition is more by impaction, which results in a net effect of more central deposition of all inhaled material. As bronchial constriction subsides, the particles reach more peripheral airways. During an asthmatic attack the normal pulmonary defenses may be impaired by environmental and occupational agents such as cigarette smoke, air pollution chemicals, and dust. This phenomenon could result in the persistence of antigen within the lung.

MECHANISMS PROPOSED FOR OCCUPATIONAL ASTHMA

Patients with occupational asthma may have wheezing and bronchospasm on the basis of nonallergic as well as allergic processes. Either type of mechanism will cause the airways to become hyperreactive. This airway hyperreactivity can persist for a variable period of time even after termination of exposure to the offending substance. The development of airway hyperreactivity by nonallergic mechanisms has been documented. For instance, Boushey reported that preexposure to the thermal degradation products of polyvinyl chloride meat-wrappping film resulted in hyperreactivity in subsequent challenges to histamine aerosol (11).

Occupational asthma on an allergic basis may develop in an atopic worker with preexisting nonoccupational asthma. Once occupational exposure is terminated in this individual, symptoms will improve, but because of the underlying disease they may not disappear completely. On the other hand, symptoms of nonatopic workers who have no underlying disease and develop asthma at work usually disappear when exposure is terminated. The time frame for the disappearance of clinical and physiological changes may depend on the duration of airway hyperreactivity which was part of the original asthmatic response. Asthma on a nonallergic or irritant basis (mechanical, chemical, reflex, pharmacological) can occur in both atopic and nonatopic individuals (38, 84). Terminating exposure will lead to cessation of asthma in this group after some period of time.

Clinically, occupational asthma can be present in one of several forms. (a) Purely allergic asthma occurs paroxysmally but is usually associated with symptom-free intervals. The attacks are precipitated by exposure to specific allergens in the workplace and may be immediate, late or dual reactions. (b) Nonallergic asthma is caused by reflex, pharmacological or inflammatory mechanisms (38, 84). (c) Complicated asthma includes pulmonary processes such as emphysema or chronic bronchitis in a patient with occupational asthma. There may be other medical complications such as cardiac disease or chronic cor pulmonale. In complicated asthma there is, in addition to reversible airway obstruction, a significant irreversible component. (d) Preexisting nonoccupational asthma may be aggravated by nonspecific irritants at work. (e) Status asthmaticus is a severe form of asthma which does not respond to usual treatment and may lead to acute respiratory insufficiency. It is a medical emergency and requires hospitalization.
PULMONARY PHYSIOLOGY

Pulmonary function testing is essential for the diagnosis of obstructive airway disease. One of the most common tests for measuring changes in expiratory air flow is forced vital capacity (FVC), or the volume of air that can be expired with a forced expiration after a deep inspiratory vital capacity maneuver is made. The volume of air that is expired by the first second is the forced expiratory volume at 1 s (FEV$_1$). Both FEV$_1$ and FVC are decreased with obstructive airway disease. FEV$_1$ and FVC may also be decreased in restrictive lung disease, but because of a generalized decrease in lung volume and not because of a reduction in air flow. For this reason, FEV$_1$ must be related to FVC (FEV$_1$/FVC %). FEV$_1$/FVC % is decreased with airway obstruction, but is "normal" in restrictive lung disease. In general most subjects show a FEV$_1$/FVC % of 75 % or greater. This figure may vary with age so that older individuals may have values between 70 and 75 % and younger individuals may have values between 80 and 85 %. Forced expiratory flow rates are decreased with both interluminal disease of the airways such as asthma and bronchitis and disease associated with the loss of lung elasticity such as emphysema.

Recent evidence suggests that physiological tests which detect airflow changes in the small airways (less than 2 mm internal diameter) may be useful in identifying early disease (69). The resistance of airways smaller than 2 mm in diameter is a small fraction of the total pulmonary resistance, and considerably increased resistance must be present in these airways before any significant change in FEV$_1$ and FVC occurs. Measuring airflow during the latter part of vital capacity has been reported to aid in detecting small airway disease (75). A spirogram formed from these events suggests that the traditional measurement most likely to be affected would be the maximum midexpiratory flow (MMF), since it is a measure of flow taken at a relatively low lung volume (fig. 3). The screening tests of 53 smokers showed the only abnormal values to be a reduced MMF and an increased residual volume (75). Airway resistance, specific conductance, FEV$_1$, total lung capacity, and maximum expiratory flow rates were

![Fig. 3. Change in pulmonary function tests taken before and after work from a patient with occupational asthma. (See text for explanation)](image-url)
within predicted norms. Other tests used for detecting small airway disease have included measurements of expiratory flow volume curves, closing volumes, and expiratory flows utilizing different density gases (16, 70).

The sine qua non of bronchial asthma is the reversibility of airway obstruction. The degree of reversibility is assessed by inhalation of a bronchodilator. Reversibility is defined as at least a 15% improvement in the FEV₁, as compared to the baseline value.

**OCCUPATIONAL ASTHMA WITH AN ALLERGIC BASIS**

Many allergenic substances in the work environment cause sensitivity and are associated with reversible obstructive airway disease. Most of these substances are organic in nature and include animal and vegetable compounds. Inorganic chemicals are usually primary irritants in nature, but they can become allergenic perhaps by acting as haptenes. While the exact cause may be identified, the relative importance of specific agents on the overall incidence of occupational asthma is scant. It is likely that many cases are either unrecognized or unrecorded.

*Substances of animal origin*

Workers may come in contact with substances of animal origin that result in asthma (table 1). These substances include animal hair, epidermal squamae, mites, small insects, molds, dander, bacteria, and protein dust (50, 79, 84, 102).

Workers such as shepherds, farmers, jockeys, laboratory and research technicians, animal handlers, veterinarians, and grooms who come in contact with animals, particularly in poorly ventilated areas, may develop asthma on an allergic basis (4, 36, 47, 79, 84). Animal hair and dander or epidermal squamae in themselves can be the causal agents, but mites and other small insects, as well as mold, in the work environment have been implicated (84). Voorhorst reported on a group of workers with human dander allergy (128). Some of these individuals worked as hairdressers. A detailed examination of five subjects indicated that all reacted to human dander and two had a positive nasal provocation test to human dander extract. There was a good correlation between the degree of skin reactions in patients and peripheral eosinophilia. Positive skin reactions to human dander, even in high dilutions, appeared more frequently in atopic patients, about as frequent as to house dust. There appeared to be no cross-allergy with danders derived from dogs, cats, and other animals.

Occupational asthma to proteolytic enzymes have been documented in a variety of workers (32, 35, 52, 83, 90, 95, 98, 115, 130). Proteases (subtilisins or subtilopetidases) obtained from strains of *B. subtilis* exhibit enzyme activity over a wide pH and temperature range and are therefore ideally suited for incorporation into household cleaning agents. Occupational exposure may occur among workers handling drums or paper sacks

| Occupation                      | Industrial exposure                        |
|---------------------------------|--------------------------------------------|
| Animal handlers                 | Hair, epidermal squamae, mites, small insects, danders |
| Apiarists                       | Bee toxin, squamae from bees, hair, chitin |
| Antibiotic workers              | Penicillin, ampicillin                      |
| Cheese workers                  | Penicillium casei                          |
| Culture oyster workers          | Marine organisms                           |
| Detergent industry or laundry workers | *B. subtilis*                                |
| Feather workers                 | Uncleaned feathers, mites, moths            |
| Hairdressers                    | Human hair                                  |
| Mushroom workers                | Thermophilic molds                          |
| Morticians                      | Molds                                       |
| Silkworm cutters                | Silk hair, butterfly squamae, silk glue (sericin) |
of the enzyme and during the preparation or packing of the powders, and the risk of sensitization may also be present during industrial and, rarely, domestic use (7, 95). Asthma caused by sensitization to these substances is associated with positive scratch and interdermal tests to the enzyme extract and the presence of specific IgE antibodies (35, 84, 95). In some studies between 40 and 50 % of workers with moderate to heavy exposure to enzyme dust have become sensitized according to positive scratch or interdermal skin tests. Atopic individuals more often develop asthma or positive skin tests to enzyme extract, but symptoms also occur in non-atopic individuals and those who do not develop skin test reactivity (130).

No evidence of permanent lung damage, as revealed by pulmonary function tests, has been detected in exposed workers whether sensitized or not, but some reduction of gas transfer for carbon monoxide and an increase in alveolar-arterial oxygen tension, supposedly due to small airway obstruction, has been described in a small group of workers (35, 95). Recently Musk and Gandevia have reported a loss of pulmonary elastic recoil in workers formerly exposed to proteolytic enzyme (alcalase) in the detergent industry (85).

Adequate dust suppression and preventive measures reduce the prevalence of respiratory symptoms in sensitized workers (131). There is a clear relationship between sensitization and the level of exposure to the powder (90, 112). When the condition is recognized, changes in production techniques are indicated. Dust sources can be enclosed, ventilation must be increased, and vacuum cleaning should be used instead of sweeping. Effective respirators have been provided for exposed workers and have substantially reduced the frequency of sensitization.

Inhalation of papain, another proteolytic enzyme, causes emphysema in experimental animals (18). Milne and Brand investigated four food technologists who were occupationally exposed to heavy concentrations of papain dust and developed asthma (80). In two subjects an immediate asthmatic reaction occurred following exposure and symptoms persisted for some months. Pulmonary function tests of the four subjects 1.5 years later showed that two had minimal abnormalities related to bronchial reactivity and the distribution of ventilation.

Other substances of animal origin

A variety of insects such as mushroom fly, aphid, bedbug, locust, bee, housefly, moth, daphnia, Mexican bean weevil, and sewage filter flies have been implicated as causing rhinitis and bronchial asthma (4, 30, 31, 33, 43, 47, 79, 84, 127). Sensitizing materials include scales and hair which have been rubbed off in flight from the wings or body and have become airborne. Occupational exposure to insect emanations occurs for entomologists, beekeepers, laboratory workers, and mushroom workers. In some instances the majority of workers exposed to insect products can be sensitized. This was the case for workers in power plants along the Mississippi River; they became sensitized to river flies and developed rhinitis or asthma (31).

Sensitization to irradiated male screw-worm flies have been reported in 70 % of the flight crews dispersing the flies into infested areas (43). Other sources of occupational exposures include weevils in grain dust, moths in fish bait, mites in house dust, and trypsin dust (33, 34, 67, 120, 127, 134). Asthma from primitive organisms which live in the sea and attach themselves to the surfaces of oyster shells has been reported in seasonal workers who crush oyster shells in order to obtain the meat (88, 129).

Substances of vegetable origin

Substances of vegetable origin (table 2) are probably the most commonly reported causes of reversible obstructive airway disease in industry. Sensitization occurs to materials such as wood or wood products, cotton, flax, hemp, grain, flour, maiko, mold, castor and green coffee beans, and kapok (9, 10, 20, 24, 29, 39, 46, 62, 72, 76, 77, 78, 79, 81, 82, 84, 91, 95, 101, 112, 114, 117, 133). Asthma from primitive organisms which live in the sea and attach themselves to the surfaces of oyster shells has been reported in seasonal workers who crush oyster shells in order to obtain the meat (88, 129).

Carpenters, joiners, and sawmill workers can be sensitized to sawmill dust, fungal spores, and substances used to treat wood. Particularly implicated wood
Table 2. Causes of occupational asthma of vegetable origin.

| Occupation                         | Industrial exposure                      |
|-----------------------------------|-----------------------------------------|
| Bakers, millers, grain workers    | Flour, grain dust, grain weevil          |
| Brewers of farmers                | Hops                                    |
| Celery pickers                    | Pink-rot-fungus                         |
| Coffee workers                    | Green coffee dust                       |
| Cotton, flax, hemp workers, weavers, textile workers | Cotton, flax, hemp |
| Oil extractors/crushers and processors of beans and seeds | Castor bean meal, linseed, cotton seed |
| Paprika splitters                 | Molds                                   |
| Soybean workers                   | Soybean flour and dust                  |
| Sausage makers                    | Garlic powder                           |
| Tea makers                        | Tea fluff                                |
| Tobacco workers                   | Tobacco                                 |
| Wood workers                      | Wood dust                                |

Dusts include cedar, oak, mahogany, iroko, keejat, and western red cedar (4, 84, 112).

The clinical picture of western red cedar asthma has received a great deal of attention. Western red cedar is characteristically different from other woods in its unusually high content of water soluble compounds, including a variety of materials such as tannin, dyes, pitch, resins, and lignins (20). Plicatic acid, a major fraction, is a unique component of western red cedar and has not been identified in any other wood. In provocation tests, plicatic acid produces bronchial reactions similar to that produced by the whole extract and is probably the causative agent (20).

Usually the exposed worker first complains of eye and nose irritation with rhinorrhea and nasal obstruction. After some weeks, a cough develops which is usually worse at the end of the day or at night. Subsequently there may be episodes of nocturnal cough or wheezing. Characteristically the symptoms, especially those occurring at night, persist for days or weeks after the cessation of exposure. Symptoms may recur on the first day or evening after return to work but sometimes they do not reappear for a week or more. Diagnosis may be more difficult for workers who have continued exposure with a clinical picture of persistent airway obstruction showing no change over weekends and only partial recovery during absences of 2–4 weeks from work. Diagnosis is not aided by skin testing since immediate and delayed skin reactions to cedar extracts have been inconsistent (40). At present, inhalation tests are the best method for confirming the diagnosis.

Asthma due to grain allergy is found principally in millers and bakers, although it may occur in farm workers handling grain (4, 62, 67, 84, 91, 95, 101). Outbreaks of asthma have occurred in people exposed to a prevailing wind carrying grain dust from neighboring mills (95). The specific antigens responsible for wheat allergy are not known, although it may be a component of the wheat, parasitic fungi such as smut or rust, saprophytes such as aspergillus, or organisms such as wheat weevil and the mite (84, 95). Many mill workers have positive skin reactions to mixed flour or weevil extracts but only a minority complains of asthma and a few react to inhalation with weevil extract (95). Prevalence of asthma has ranged from 2.1% in a study from The Netherlands to 30% in Yugoslavian employees of a mill and some bakeries (84). Other studies have indicated rates of sensitization up to 50%. Often asthma is sufficiently mild to allow workers to continue work. Since in almost 50% symptoms improve or even disappear, spontaneous desensitization may occur. Pepys has reported dual types of asthmatic reactions in two bakers (96, 97). These patients were given immediate prick tests and had serum precipitin antibodies.

Cotton

Byssinosis represents a complex of respiratory symptoms due to exposure to the dust of cotton, flax, or soft hemp; it may vary clinically from acute dyspnea and chest tightness on one or more days of
a work week to chronic and permanent obstructive airway disease (8, 10, 39, 77, 78, 84, 95, 101, 112). The chief sources of dust occur in the ginnery where seeds are removed from the cotton after it has been picked, in the "mixing room," during the opening of cotton bales, in the "blow room" where the cotton is beaten and blown for the elimination of dust and short fibers, and in the "card room" where carding engines comb the fibers and remove dirt and defective materials (95). Other dusty operations are "stripping," which consists of removing dust and cotton fibers adherent to the wire teeth of the carding engine, and "grinding" the teeth. Respiratory problems are noted in industries employing flax in the manufacture of linen and yarn for rope or in the manufacture of rope, twine, thread, hose pipes, tarpaulins, fishing nets, and clothing (95). Jute is used in the manufacture of carpets, felt, wadding, and in combination with flax for various types of cloth. Sisal is employed chiefly in rope manufacturing. The diagnosis of byssinosis rests on (a) a history of occupational exposure to cotton or dust of related material, (b) a typical history of chest tightness or shortness of breath, particularly on the first day of the work week, and (c) a fall in FEV$_1$ during the workday or work week (84). The prevalence of the symptom complex seems to be related to dust level and, in particular, to the coarse protein particles rather than to the mineral or cellulose portion of the cotton (84). While it is not clear whether an immunologic response is working in this type of occupational asthma, a pharmacologically active substance which causes constriction of smooth muscles in animal preparations has been identified (29, 72, 84).

Substances of chemical origin

A variety of chemicals, both simple and complex, is associated with occupational asthma (table 3). In general those with molecular weights of less than 1,000 (micromolecules) are included, for example, paraphenylenediamine, formalin, chloramine, formaldehyde, and sulfathiazole (84). Other substances are pesticides, chromium, vanadium, platinum, tannic acid, gum arabic, tragacanth, karaya aliphatic polyamines, piperazine, ethylene diamine, penicillin, ampicillin, spiramycin, phenylglycerine, phthalic anhydride, epoxy resins, and isocyanates.

Table 3. Causes of occupational asthma of chemical origin.

| Occupation                   | Industrial exposure          |
|------------------------------|------------------------------|
| Chemical workers             | Paraphenylenediamine, piperazine, formaldehyde, phenol, chloramine, sulfathiazole, chromium, sulfonechloramide, tannic acid |
| Cobalt refinery or alloy workers | Cobalt dust                  |
| Cosmetic workers and hairdressers | Constituents of powders, orris root |
| Dye users                    | Phenylendiamine, P-phenylendiamine |
| Electricians                 | Aluminum soldering flux with aminoethyl-ethanolamine |
| Insecticide makers           | Pyrethrins                    |
| Metal workers                | Acrolein, vanadium trioxide, tungsten carbide |
| Mineral ore processors       | Vanadium pentoxide            |
| Nickel workers               | NiSO$_4$                      |
| Polyurethane manufacturers, paint, linoleum workers | Isocyanates |
| Plastic workers              | Pthalic anhydride, epoxy resins, isocyanates, formaldehyde |
| Platinum refiners            | Complex platinum salts        |
| Precision casters            | Chromium                      |
| Printers                     | Gum arabic, tragacanth        |
| Spice workers                | Spices                        |
Isocyanates. Isocyanates are widely used in the production of polyurethane, which has application in the manufacture of plastics, foam, surface coating and elastomers, adhesives, and fibers (6, 14, 15, 26, 63, 84, 95, 100, 110, 113, 123, 124). The four most common isocyanates are toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), naphthalene diisocyanate (NDI), and hexamethylene diisocyanate (HDI). Occupational exposure to TDI, by far the most significant commercially and toxicologically, may occur during its production in the vicinity of foam-producing machines, during spraying and molding operations, from accidental leakage or spillage of liquid TDI, during bulk or drum handling or drum emptying or leakage from pumps, during disposal of TDI waste, the welding of polyurethane covered wires, the burning of polyurethane products or during the use of polyurethane floor varnish with a TDI activator (95). Exposure to high concentrations, which may occur with accidental spillage, is irritating and causes shortness of breath, chest tightness, cough, wheezing, and occasionally rales. Usually low concentrations are encountered in industry. The mechanism for the development of asthma has not been demonstrated, and it is not completely clear whether the reaction is mediated by a true allergic mechanism, although it seems likely. There does not appear to be any correlation between atopic status and the development of clinical sensitivity. Both reaginic and complement fixing antibodies have been reported in affected subjects, and specific lymphocyte transformation to TDI has been demonstrated (14, 63, 123). Pepys has described an immediate, late and dual response in workers. The late bronchial reaction was inhibited by cromolyn sodium (96).

Apart from the asthmatic reactions in apparently sensitized subjects, a progressive fall in FEV\textsubscript{1} and FVC through the week and over periods of up to two years has been shown in workers exposed to levels of TDI below the threshold limit value of 0.02 ppm (100, 112). In addition, a high prevalence of cough and sputum production has been demonstrated in workers exposed both acutely to high concentrations and repeatedly to low concentrations (112).

Other chemicals. Phthalic anhydride is an essential chemical reagent in the manufacturing process of a variety of industrial products which include plasticizers, epoxy resins, and paints (59, 68). Although the prevalence of sensitization to this chemical is unknown, the occurrence of asthma in exposed workers is cited as an important toxic effect by chemical safety data sheets issued by the Manufacturing Chemists Association (71). Maccia and coworkers reported on clinical sensitization in a worker who developed symptoms of rhinorrhea, lacrimation, and wheezing after exposure to this chemical (68). Positive immediate skin tests and bronchial challenge to phthalic anhydride, as well as a high serum titer of specific IgE (by the radioallergosorbent test), corroborated clinical hypersensitivity.

Metals

Chromium, a potent sensitizer that is used in the manufacture of pigments and in tanning, has been reported to cause bronchial asthma (19, 27, 56, 84, 116). The hexavalent compound is the most active one chemically and the most widely encountered in occupational health problems. Complex salts of platinum, used in the manufacture of catalysts, in electroplating, in the production of fluorescent screens, in work with jewelry, and in platinum refinery operations, can cause a syndrome of asthma, urticaria, and rhinitis that is known as “platinosis” (37, 112). The asthmatic reaction may be immediate, late, or dual in type and it can be reproduced by inhalation challenge tests (Skin prick tests with low concentrations of chloroplatinates give immediate positive reactions, and late asthmatic reactions are inhibited by cromolyn.) Asthma resulting from nickel sulfate has been reported in nonatopic workers involved in nickel plating (74). The inhibition of tanned red cell hemoagglutination reactions indicated the presence of a specific antibody in the patient’s serum.
ASTHMA WITH NO ALLERGIC BASIS

Occupational asthma may occur on a non-allergic basis, either by reflex, pharmacological or inflammatory mechanisms (38, 84). Extracts of cotton, hemp, sisal, and flax contain an active bronchoconstrictor or histamine-releasing substance (84, 95, 112). Histamine-releasing agents and other vasoactive substances have been identified in wheat dust (38, 84). Histamine liberation has been proposed as one mechanism by which proteolytic enzymes produce clinical effects (84). Acute bronchospasm as a result of reflex or inflammatory mechanisms has been noted following occupational exposures to sulfur dioxide, ammonia, hydrochloric acid, ozone, nitrogen dioxide, hydrogen sulfide, piperazine, and thermal degradation products of polyvinyl chloride meat-wrapping film (12, 38, 84). Boushey et al. noted increased bronchial reactivity to histamine aerosol in subjects preexposed to polyvinyl chloride pyrolysis products (11). After a severe inflammatory reaction to an irritating gas such as chlorine, attacks of bronchospasm may occur on subsequent days after exposure to very low concentrations of this gas (74). Other substances causing bronchoconstriction include urea formaldehyde, used in molding sands in metal foundries, and organic phosphate insecticides.

DIAGNOSIS OF OCCUPATIONAL ASTHMA

A careful history is essential for the diagnosis of occupational asthma. Clues for suspecting the possibility of a work-related disease include the abrupt onset of asthma in an adult with no previous history of allergic disease. The worker may note that asthma tends to develop toward the evening and is often better by the next morning. Sometimes the symptoms are only nocturnal, and the clockwork regularity of a nocturnal symptomatology is frequently the only clue. The subject generally improves over the weekend or during vacations. Although the patient may be aware of substances at work that affect him and fellow workers, in some industries complex chemical and engineering processes may liberate substances which the worker is unaware of.

The fact that other workers are not symptomatic does not, in itself, differentiate between a direct irritant effect and an allergic phenomenon. It is helpful to differentiate between an irritant and allergic process. Asthma on an allergic basis more often appears after repeated exposure to the offending allergen. There is a delayed period of exposure at work which lasts several months or several years before the onset of asthma. Only a small proportion of exposed workers is affected if the process is allergic in basis. Once sensitization has occurred, reactions are elicited with very small concentrations of the substance, below those which produce irritation and below those noted for threshold limit values. There may be difficulty in diagnosing a late asthma reaction since the time lapse between development of symptoms and exposure to the provoking agent may obscure the relationship and lead to a diagnosis of nonoccupational asthma or bronchitis.

Physical examination of the worker in the office may not be helpful, but examination at work during exposure can lead to the diagnosis. The patient complains of tightness in the chest, and inspiratory and expiratory wheezes become audible shortly after exposure begins. It is important to remember that chest examination may be normal, particularly for workers whose only symptoms are cough and chest tightness and whose exposure took place several hours previously.

The chest X-ray is usually normal in a vast majority of subjects with occupationally induced asthma. The most frequent positive findings that are not related to complications include hyperaeration, changes in thoracic configuration, decrease in size of heart associated with attenuation of peripheral pulmonary vessels, and prominence of the main hilar arteries.

Peripheral blood or sputum eosinophilia are useful for diagnosis. When airway obstruction becomes chronic, the presence of eosinophilia is helpful in confirming obstructive airway disease on an allergic basis. In a study of patients in a respiratory disease clinic with peripheral blood eosinophil counts greater than 400 cells/
ml³ all the patients showed some reversibility of airway disease with bronchodilator drugs and corticosteroids (50). Those with eosinophil counts below 400 cells/ml³ had a variable response. Peripheral blood eosinophilia is also present in bronchial asthma caused by nonoccupational sources. Physicians have applied the stop-resume work test in trying to differentiate occupational from nonoccupational causes. After several days away from work the offending allergen will result in a decrease in total blood eosinophil count. This occurrence can be coupled with pulmonary function tests so that the diagnosis will be more definitive. Sputum eosinophils can be recognized rapidly and reliably on unstained specimens (21). It has been reported that bronchial asthma is characterized by 15 % or more of all cells in the sputum being eosinophils (28). In general the presence of eosinophils in the sputum indicates an allergic process, and the numbers possibly bear a rough relationship to the severity of the attack.

Pulmonary function testing is an essential laboratory means for confirming the diagnosis of obstructive airway disease. FVC and FEV₁ can be measured on several days while the patient is asymptomatic and not working. Measurements after a work exposure, particularly one associated with wheezing or dyspnea should show a decrement of 10 % or more in FVC or FEV₁ in order to be considered positive, i.e., if a stable base line has been observed. Measurements before and after a work shift, particularly on Mondays or after an absence from work, is frequently revealing. The diurnal variation of FEV₁ is small, perhaps not more than 2—3 %. Decreases of 200 ml or more, however, are often seen from 0800 to 1600 in cases of occupational asthma. Malingering can usually be excluded by multiple measurements which vary by less than 50 ml, provided that the test is performed by an experienced technician with a well-calibrated spirometer. Response to bronchodilators such as isoproterenol is also helpful in confirming reversible obstructive airway disease. A 15 % or more improvement in FEV₁ following the administration of bronchodilators suggests reversible airway obstruction. Patients with no significant response to bronchodilators generally have an irreversible obstructive pulmonary disease such as chronic bronchitis or emphysema. Thus the bronchodilator response is also helpful in the diagnosis of occupational asthma. In some cases the FEV₁ measured before and after work only slightly differs (less than 200 ml). Then a greater change may be noted in MMF. Some investigators feel however that at least a 20—25 % improvement in MMF after bronchodilators is necessary before the diagnosis of reversible airway disease can be confirmed.

Immunologic studies are often not available for specific occupational allergens. It is helpful to establish whether the subject is atopic or not and whether immunologic mechanisms are involved. It may thus be useful to perform skin tests to common allergens such as house dust, danders, grasses, and trees. Skin tests for specific occupational allergens are often unreliable and may result in false positive or false negative results. These latter studies are often more useful as corroborative evidence of exposure rather than as specific proof of the etiology of the asthma. Immunologic studies such as a positive Prausnitz-Kustner reaction in the case of castor bean exposure or the demonstration of elevated levels of specific IgE in the presence of pthalic anhydride provides strong confirmation of the allergic nature of the work related asthma (68, 76). Complement fixation tests, precipitating antibodies, and lymphocyte studies are other tests reported to be helpful in confirming sensitization (6, 123). Unfortunately these may not always be available and are often only performed in university centers.

In cases of doubt, inhalation challenge tests with carefully controlled aerosol concentrations of a suspected agent will establish the diagnosis (1, 62, 97, 118). These tests should be made under hospital conditions when the patient is symptom-free, and a very careful control of dosage is necessary if dangerous bronchial reactions are to be avoided. It is important that the investigator use a reliable control aerosol prior to the administration of a specific occupational allergen in order to assess the contribution of nonspecific bronchoconstriction.
Methacholine challenges may be useful in assessing the bronchial reactivity of symptom-free individuals with occupational asthma. In order to identify workers with underlying hyperreactive airways, one could use a provocation test employing methacholine to screen workers who may be exposed to known asthma-provoking hazards (38, 94). Methacholine hyperreactivity, by itself, should not be regarded as disqualifying, however, since some subjects with asthma can work with allergenic agents without difficulty. The demonstration of exaggerated bronchial reactivity in individuals removed from industrial exposure could indicate a latent asthmatic state and may indicate a need for long-term follow up.

TREATMENT AND PREVENTION

Individuals found to have occupational asthma on an allergic basis should be removed from work since even low concentrations below the threshold limit value can provoke an asthmatic reaction. In addition, repeated exposure can, in some cases, lead to irreversible obstructive airway disease. High concentrations of allergen could result in acute severe asthmatic reaction and death. Therefore, once sensitization occurs, an individual should be removed from work and have no further exposure. Industrial hygiene considerations are important. Attempts to follow threshold limit values are extremely important to the reduction or prevention of sensitization. It is imperative that safety measures concerning handling procedures, avoidance of spills, protective equipment, and good housekeeping procedures be instituted. Increasing the effective control of environmental inhalants by modern industrial hygiene techniques makes it possible for many workers to remain in an improved occupational environment.

Engineering dust and vapor suppression is the most effective way of lowering the average concentration of the incriminated inhalant. The most difficult exposure to control is a short, intermittent, peak level which generally results from some equipment or occupational malfunction. While respiratory protection is useful, in some instances it is difficult to apply prior to the time that such an exposure occurs. The cotton industry provides an important example of how experimental alterations of manufacturing processes, such as washing and steaming the cotton prior to its early processing, can have an important modifying effect on the production of disease and can lead to its prevention. Changes in product formulation can be used in reducing exposure to inhalants. This method has been employed by the detergent industry where the proteolytic enzyme portion of the product was made less dusty by encapsulation procedures.

Since some agents such as isocyanates can produce a decrease in pulmonary function with chronic exposure, periodic medical surveillance which includes respiratory questionnaires, pulmonary function testing and, possibly, eosinophil counts are necessary for the identification of early disease or individuals with few or no symptoms.

The drug treatment of occupational asthma is similar to the treatment of non-occupational asthma. Oral and aerosol bronchodilators such as theophylline and isoproterenol are the mainstay. Several new beta-adrenergic agents such as terbutaline and allupent are effective. Corticosteroids may be helpful for the treatment of an acute severe reaction. Cromolyn has proven effective in certain instances.

SUMMARY

There are immediate benefits when one can establish the diagnosis of occupationally induced asthma. It is a man-made disease and is thus reversible. Diagnosis depends on knowledge of the source and types of exposure which can be correlated with the clinical, physiological and immunologic patterns of affected workers. The discovery of one case can often lead more readily to recognition of others. Individuals with asthma of an occupational origin should be removed from work. Equally as important is the initiation of proper industrial hygiene procedures which would improve the occupational environment and periodic medical sur-
veillance of workers for the identification of early disease or individuals with few or no symptoms.

ACKNOWLEDGMENT

This work was supported in part by funds from Grant ES00159 from the Center for Study of the Human Environment, U.S. Public Health Service.

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Received for publication: 1977-02-08