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Occupational Asthma: Coming of Age

ALTHOUGH Bernadino Ramazzini described wheezing among grain sifters in the beginning of the 18th century (1), the significance of asthma as an industrial disease was not generally recognized until the middle of this century. This prolonged information gap was due to a proportionately greater focus on structural lung damage mediated by inorganic and organic dusts, and less concern about possible long-term disability as an aftermath of reversible obstructive airways disease. However, as the occurrence of occupationally related asthma increased in several high technology industries (such as chemical, plastics, and pharmaceutical) after World War II, there developed a general consensus among government, management, and workers' representatives that more emphasis should be placed on seeking solutions to this problem. The special talents of clinical immunologists, physiologists, and asthma specialists were sought by the occupational health team—a trend that has accelerated during the past 3 decades. These collaborative efforts have established scientific ground rules upon which the diagnosis and management of occupational asthma should be based.

The prevalence of asthma after occupational exposure is difficult to define because national or international statistics are not available. In part, this is due to under-reporting of occupationally related diseases in general, but probably is also a reflection of the uncertainty many industrial safety and medical officers have in distinguishing between the chief varieties of obstructive airways disease (2). Moreover, in a recent survey of workers' compensation regulations in the United States, occupational asthma was not recognized as a reportable disease in any of the 50 states (3).

Work-related bronchospasm may be induced by nonimmunologic or immunologic mechanisms. Reflex bronchoconstriction may be produced by exposure to irritant or toxic pollutants present in the work environment (4). Inflammatory bronchial smooth muscle reactions may be caused by direct toxic effects or by activation of the classic or alternate pathways of serum complement with subsequent generation of biologically active components of complement (5). Other industrial asthmogens appear to exert direct pharmacologic activity on specific receptors in bronchial epithelium or smooth muscle (6). There is also some evidence that certain occupational substances may function as beta receptor blocking agents (7).

Immunologically induced asthmatic reactions are most often mediated by IgE reaginic antibody. Reaginic antibodies have high affinity for membrane receptors in tissue-fixed mast cells. In lung tissue, some sensitized mast cells are present intraluminally but most are present within interepithelial and submucosal tissues. The tissue and serum concentrations of specific IgE antibody are dependent on allergenic determinants in occupational allergens, the duration of exposure, the route and amount of stimulation, the susceptibility of the worker, and complex cellular factors regulating interactions between macrophages, helper and suppressor T cells, and IgE-producing B cells. Multivalent allergenic determinants may be present in a

wide assortment of naturally occurring or synthetic substances including peptides, proteins, glycoproteins, and polysaccharides. Chemicals of small molecular weight are imperfect antigens or haptens but they may become potent allergens after combination with one or more somatic carrier proteins. Reaginic sensitization may also be mediated by an IgG4 reagin that is also capable of sensitizing tissue mast cells. Much less is known about the significance of IgG4 reaginic reactions in occupational asthma. It is possible that this alternate method of sensitization could be involved in situations where clinical sensitivity is suspected but specific IgE antibodies cannot be detected by available techniques (8).

The number and variety of occupational-asthma-inducing agents have grown extensively in the past 3 decades. Recently, these agents have been classified on the basis of their chief pathophysiologic effects (9). Some major occupational causes of reflex bronchoconstriction include exposure to cold air, subtoxic concentrations of sulfur dioxide, fluorocarbons, and various inert dusts. Toxic gases, such as sulfur dioxide, the halogens, ammonia, acid fumes, and solvent odors cause inflammatory bronchoconstriction. Occupational substances that mimic the dose-dependent effects of pharmacologic agonists include histamine releasing agents in the bracts of cotton dust, organic acids in wood dusts, diisocyanates, and anticholinesterase chemicals (9). The greatest number of occupational agents causing asthma have known or suspected allergenic properties. In this group the most significant sensitizing agents are proteins derived from various animal sources, enzymes, grain and cereal dusts, legumes, seeds, and vegetable gums. The incidence of asthma induced by small-molecular-weight inorganic chemicals is also expanding. Representative examples of this group include antibiotics, sulfonechloramide, diisocyanates, platinum salts, and a number of reactive anhydride compounds.

The first conclusive evidence that low-molecular-weight compounds in the workplace could also be immunogenic was the demonstration of specific IgE antibody against a human serum albumin conjugate of phthalic anhydride (10). Later, similar findings were shown in workers exposed to hexahydrophthalic anhydride and trimellitic anhydride (TMA) (11, 12). Clinical responses to phthalic and hexahydrophthalic anhydrides were classically those of IgE-mediated allergic asthma. However, in the case of trimellitic anhydride, three distinct syndromes have been seen (12). The first syndrome was typical asthma that occurred after a suitable latent or sensitization interval. The second syndrome was not only associated with cough and wheezing but also included systemic symptoms of arthralgias, myalgias and fever. This has been termed "TMA flu." The third clinical presentation appeared after heavy exposure to trimellitic anhydride for relatively short periods and was characterized by symptoms of epistaxis, rhinorrhea, cough, dyspnea, and wheezing. It was therefore postulated that several different mechanisms could be involved in the pathogenesis of airways obstructive symptoms induced by TMA.

The concept that occupational asthma could be multifaceted had previously been suggested by investigations of asthma induced by toluene diisocyanate (TDI), which occurs in 5% to 10% of workers after a latent period of exposure. Thus, TDI airways hyperreactivity has been attributed to stimuli causing reflex, pharmacologic, beta adrenergic blockade, and specific IgE effects (7, 13, 14). Several investigators have also obtained evidence of specific blastogenic and lymphokine leukocyte inhibitory factor responses in susceptible workers (15, 16).

The identification of individual cases is clearly the responsibility of the primary care physician. A careful and detailed history of past and present occupational experience is the most essential element in the diagnosis of occupational asthma. Smoking, preexistent airways disease, and the degree of atmospheric pollution in the area may be important predisposing factors. Certain clinical characteristics may serve to distinguish allergic and nonallergic asthma. In the case of allergic asthma, workers with family or personal histories of allergy may be more susceptible to sensitization. There is a latent period between first exposure and subsequent development of symptoms. Repeat exposures to small concentrations of the allergen typically elicit symptoms and reexposure to the offending agent after weekend absences or vacations results in prompt recurrence of symptoms that are often more intense (anamnesis). In contrast, agents causing reflex, toxic, or pharmacologic bronchoconstriction tend to affect workers without regard to allergic predisposition, with no sensitization or latent period, and an obvious dose-response effect.

Confirming the diagnosis of occupational asthma may require skin testing, measurement of pulmonary function, evaluation of nonspecific and specific bronchial hyperreactivity, and other in-vitro methods. Direct skin tests and baseline pulmonary function measurements can be done as office procedures. Other techniques, such as preparation of hapten-protein conjugates, serial pulmonary function monitoring, and specialized bronchial challenge testing, are most complex and should be referred to specialists of the occupational health team.

Reliable and practical in-vitro methods are the ultimate goals for early diagnosis and prevention of occupational asthma. Significant progress in this regard has been made by immunologic tests that distinguish between allergic and nonallergic asthma (9). Specific IgE tests have been developed for many occupational protein and vegetable gum allergens. Similar tests have also been developed for a number of chemical occupational problems. Specific IgE assays for the entire family of anhydride compounds (phthalic anhydride, hexahydrophthalic anhydride, trimellitic anhydride) and some platinum salts are currently available. A small subset of diisocyanate asthma patients may have positive radioallergosorbent tests to a para-tolyl monoisocyanate protein conjugate. There is also a single case report of a positive radioallergosorbent test to diphenylmethanediisocyanate (17). Recently, positive radioallergosorbent tests to a plicatic acid—human serum albumin conjugate have been reported in workers exposed to western red cedar. The specificity of all specific IgE reactions should be confirmed by the radioallergosorbent inhibition technique.

Proper epidemiologic assessment of occupational asthma requires a team effort and this should include the combined expertise of an epidemiologist, chemist, toxicologist,

aerosol systems engineer, industrial hygienist, physiologist, and clinical immunologist (9). It is also essential that there be good rapport between labor, management, and government regulatory agencies. This rapport may not always be possible, and probably accounts for the fact that the literature on occupational asthma chiefly consists of individual case reports. However, in recent years, because of the economic impact of occupational asthma upon productivity in the workplace, there has been a shift to a more collaborative spirit with the occupational health science team.

In most cases of occupational asthma, removal of the worker from all future respiratory contact with the offending agent is mandatory. In some instances, it may be possible to transfer the worker to another part of the plant where there is no apparent exposure to the causative substance. However, possible exposure to cross-reacting chemicals should always be considered. Management of asthma symptoms should be predicated on the same pharmacologic principles used in the treatment of nonoccupational asthma. Under certain conditions, cromolyn sodium may have short-term efficacy in preventing asthmatic responses after exposure to various allergenic or reflex causes of asthma. Although there are a few preliminary reports of successful immunotherapy in cases of bakers' and laboratory animal asthma (18), the immunologic aproach to long-term management of occupational asthma cannot be recommended in most cases.

The duration of disability resulting from occupationally induced asthma is usually temporary with respect to active airways obstruction. However, to what extent this state of hyperactive airways can persist in later life is unknown at the present time. There are several reports that indicate that hyperactive airways may persist for years after removal from further exposure to diisocyanates and western red cedar (19).

As Ramazzini had forecast, occupational asthma is becoming a major occupational health problem. Reversal of this trend is possible and can be implemented by special attention to several recommendations. Better record-keeping should be encouraged by labor, management, and government agencies. More research support should be allotted for development of valid susceptibility profiles and objective diagnostic techniques that might be useful for prescreening purposes and early diagnosis. When warranted by specific occupational conditions, serial physiologic and immunologic monitoring should be done and encouraged by both management and labor.

If one reflects that the modern era of occupational asthma is barely 30 years old, considerable progress has been made in defining the problem and developing new methods of detection. Internists should keep abreast of future advances in this field because workplace-acquired asthma may be an ideal clinical investigative model of spontaneous asthma. (I. LEONARD BERNSTEIN, M.D.; *University of Cincinnati Medical Center, Cincinnati, Ohio)*

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