

REVIEW ARTICLE

*Ind. J. Tub., 1986, 33, 171*IMMUNOLOGY OF OCCUPATIONAL LUNG DISEASES CAUSED BY DUST:
AN OVER VIEW

K.V. THIRUVENGADAM*, V. KUMARASWAMY* AND S. KPISHNAN***

SUMMARY : The lungs are exposed to numerous injurious substances. Such injury may be the result of immunological or non-immunological mechanisms. The lung clears itself of inhaled particles by means of ciliated cells lining the airways and the macrophages. The latter play an important role in the immune process as well. Inorganic particles are ingested by macrophages and if found inert are transported for eventual expulsion. Particles such as silica are poorly handled by macrophages, they not only damage the macrophages but also impair their function. Others, such as asbestos, may stimulate fibrosis. Endogenous factors such as the presence of auto-antibodies (rheumatoid factor or anti-nuclear factor) alter the response of the host to inhaled particles. The pathological changes caused by handling inorganic dusts include interstitial fibrosis, nodular fibrosis or macule formation leading to emphysema. Occupational asthma occurs when individuals are exposed to dusts during the course of their work. The lung responds differently to organic dust. T cells and complement are important elements in handling organic dust. The role of inhaled steroids which have no significant systemic effects in the prevention of certain occupational asthmas is worth evaluating, apart from control measures which minimise the exposure.

The lungs occupy a vulnerable position in the body both structurally and functionally. Since they have to exchange gases they are necessarily exposed to a wide variety of environmental agents such as smokes, fumes, organic and inorganic dusts etc. In fact, next to the skin, the lungs are exposed to the maximum insult from environmental factors. Exposure to such agents may have several consequences. These particles may interfere with the defense mechanisms of the lung or may lead to pulmonary damage as a consequence of an immunological reaction. Further, as the lungs receive the entire cardiac output, they are often the seat of disease when circulating antigens or immune complexes are deposited in the pulmonary capillary bed.

Pulmonary injury is more likely to occur in individuals engaged in occupations which entail exposure to dusts, usually over prolonged periods of time. Host factors also influence the effects of inhaled agents. Genetic determinants clearly influence ciliary action clearance rates of inhaled particles and macrophage function. Afzelius et al, 1989. In addition HLA antigens have been linked to certain occupational lung diseases e.g. HLA B-27 and asbestosis. Airway geometry and breathing patterns, as also the effect of smoking, have recently begun to be recognised as important factors that influence the development of an occupational lung disease (Chamber Ian et al, 1983). Needless to say the immunological make up of the individual by factors such as the presence of an allergic diathesis also play an

important role in the etiology of disease. Individuals with a personal or family history of atopy are liable to hypersensitivity to inhaled antigens in the course; of occupational exposure (e.g. baker's asthma on exposure to wheat flour). However, occupational asthma can also develop in non-atopic individuals as occurs in exposure to Isocyanate which is a powerful sensitizer. Disability due to airflow limitation may be precipitated or aggravated in individuals with hyperreactive bronchi such as asthmatics on exposure to non-allergic environmental factors like inorganic dust.

Defense mechanisms of the lung

Most of the larger inhaled particles (5µm or greater) are deposited in the nose or in the dead space proximal to the respiratory bronchioles. Particles less than 3 µm tend to reach the gas exchanging part of the lung.

The lung clears itself of inhaled particles by means of ciliated cells lining the airways. In addition, inhaled harmful agents which reach the lung are also cleared by the aggregates of lymphoid tissue and their effector cells. Within the alveoli, clearance is to a large extent the function of the alveolar macrophage. These highly specialized cells, after ingesting particles, can transport them to the level of the terminal bronchioles from where they can be expelled by the use of the mucociliary escalator. Currently, opinion is divided as to whether such transport occurs along the surface or as a consequence

*Retired Professor of Medicine, Madras Medical College.

**Senior Research Officer, Indian Council of Medical Research, Tuberculosis Research Centre, Madras.

***Formerly Honorary Medical Officer, VHS Medical Centre.

of the macrophage transiting through the interstitium to reach the terminal bronchiole.

Immunoglobulins A (IgA) and E (IgE) are associated with secretions and it is not surprising that they play an important role in the defence of the respiratory tract. In fact, secretory IgA (a specialised form of IgA, with a secretory piece) and IgE are the antibodies involved in the primary defence of the lung and they are capable of being synthesised locally by specialized B lymphocytes. On the other hand, T lymphocytes mediate delayed type hypersensitivity reactions which are characterised by granulomata. Such reactions are the hallmark of disorders like tuberculosis and sarcoidosis. Phagocytes and complement complete the rest of the components which make up the defense system of the lung.

It is important to remember that while immune mechanisms play a crucial role in the pathogenesis of occupational lung diseases due to dust, both inorganic and organic, nonimmunological pathways could also initiate occupational lung disease.

Response of the lung to inorganic particles

In the gas exchanging part of the lung, inorganic particles are ingested by alveolar macrophages. The response of the macrophage depends on the type of particle ingested. For example, coal dust and haematite which are inert are sequestered within macrophages which transport them to other sites for expulsion. But a particle like silica causes macrophage dysfunction. Silica is readily ingested by the macrophage but is poorly handled thereafter. This leads to lysosomal injury either by bonding of silica to the membrane or by activation of membrane phospholipases (de shazo RD 1982). The end result is autolysis of the macrophage leaving the particle free to attack a fresh macrophage. This impairment of macrophage function renders the cell incapable of handling other agents such as mycobacteria.

Asbestos has a different effect on the macrophage. Asbestos fibres cause the release of powerful enzymes within the macrophage and also stimulate arachidonic acid metabolism. In addition, they promote the release of fibronectin (a substance which promotes fibrosis) and increase the number of surface receptors such as Fc (for immunoglobulins) and C_a (for complement) suggesting an enhanced macrophage activity (Kagan E, 1981). A postulated defect of antigen presentation by macrophages in certain occupational lung diseases awaits confirmation.

It has also been shown that the immunological

background of the host also influences the handling mechanisms. For example, rheumatoid factor (RF) and antinuclear factor (ANF) have been found in individuals with occupational lung diseases more often than in normals (Turner Warnick, 1979). Rheumatoid factor is found frequently in silicosis, asbestosis and coal worker's pneumoniosis. The relationships of these autoantibodies to occupational lung disease is not clearly defined. While it would appear, on one hand; that the increased incidence of RF is due to the adjuvant effect of silica (Pernis and Paronetto, 1962) other evidence also shows that RF itself is an important factor in the production of silicosis (DeHoratius and Williams, 1972): In addition, depressed responses to Concanavalin A have been observed among silicotics suggesting loss of suppressor T-cells. This might explain the appearance of autoantibodies described in silicosis (Schulyer et al, 1977). The occurrence of these autoantibodies and the immunoglobulin type vary with the type of dust ingested.

Antinuclear factor is a good indicator of the prevalence and severity of disease in coal workers (CWP) and asbestosis. This is based on observations which suggest a high degree of correlation between ANF and the extent of radiological abnormalities and its more frequent occurrence in disease than RF (Lippman et al, 1973).

The pathological changes seen as consequence of handling inorganic dust can be broadly grouped as under.

(a) *Interstitial fibrosis:* This occurs when fibrosis of the alveoli is associated with thickening of the alveolar capillary membrane. This is commonly seen in exposure to dusts such as asbestos, beryllium and cobalt.

(b) *Nodular fibrosis:* is commonly seen in silicosis. Silica is transported by macrophages to the interstitium and lymph nodes where autolysis leads to liberation of enzymes and development of fibrosis. This occurs away from the gas exchanging part of the lung near the respiratory bronchioles.

(c) *Interstitial and nodular fibrosis:* A combination of the above two occurs in exposure to diatomaceous earth.

(d) *Macule formation and emphysema:* When minimally fibrogenic materials such as coal are ingested by macrophages, effective clearance occurs as long as the macrophages are not overwhelmed by the number of particles. When the burden exceeds the capacity of the macrophages, dust particles are deposited around

the respiratory bronchiole. This leads to atrophy of smooth muscle leading to emphysema.

Response of the lung to inhaled organic dust

Initially when immunological mechanisms were involved to explain the pathogenesis of organic dust induced pulmonary disease, it was believed that organic dust induced the production of IgG antibodies (precipitin) which complexed with the inhaled antigens to form immune complexes. It was also believed that the deposition of immune complexes in the lung resulted in complement activation and consequent pulmonary damage (Pepys et al, 1959).

It is now recognised that this may not be the actual event obtaining in extrinsic allergic alveolitis induced by exposure to organic dust.

In these disorders the predominant cell type in most lesions is the lymphocyte and granulomata and giant cells are a predominant feature of such an exposure. Such lesions are characteristic of T-cell mediated immune injury. In addition, however, complement activation occurs either by the classical or by the alternate pathway. It would thus appear that both antibodies (Type III) and cells (Type IV) are involved in the handling of organic dusts (Burrell and Rylander 1981).

A large number of occupational lung diseases, exemplified by disorders such as farmer's lung are caused as a result of such immune mechanisms operating. This usually results in the production of occupational asthma, or alveolitis.

Occupational asthma: Liberation of a variety of mediators from sensitized mast cells and basophils leads to bronchial narrowing resulting in asthma. The usual trigger for such a release is the IgE molecule which on contact with the appropriate antigen initiates a sequence of membrane perturbations culminating in the release of mediators. Some of the mediators are histamine while others such as leukotrienes are synthesized de novo and the release of mediators is controlled by cyclic AMP levels in the mast cells.

Large molecule proteins such as grains, animal derived dust and wood dust provoke asthma which is similar to allergic asthma. It is likely that atopic individuals by their inherent capacity to produce more IgE are affected more often than non-atopic subjects. However, isocyanates resins which have a low molecular weight are capable of inducing occupational asthma in both atopic as well as non-atopic individuals.

Non-IgG mediated histamine release is known to occur in certain occupational disorders. Methyl piperonylate a substance found in cotton bract, is considered to cause by histamine release, symptoms and signs of byssinosis. Adrenergic blockade, which results in lowering of cyclic AMP levels, is probably another mechanism by which occupational asthma can be induced by agents such as toluene di-isocyanate.

An understanding of these mechanisms is likely to help in the prevention and management of some of the occupational lung diseases. For example, since the airways narrowing that occurs in certain occupational asthmas is immune mediated, it has been suggested that prophylactic use of either membrane stabilizing agents such as cromolyn sodium or steroids may prevent or minimise the occurrence of the airways narrowing. The role of inhaled steroids in the prevention of occupational asthmas particularly those based on immunological mechanisms is worth evaluating, besides strict measures for minimising occupational exposure to the agents concerned for e.g. baller's asthma. Prior inhalation of Betamethasone aerosol or taking of an antihistamine orally before entering the work spot has minimised the fall in FEV₁ through the work shift in textile workers (Thiruvengadam et al 1971). In other occupational lung diseases, the development of fibrosis is an important event in the pathogenesis of the disease. Methods to diminish or to prevent the progression of fibrosis are currently under experimental study. This includes the use of Vitamin A analogues in certain occupational lung diseases (Mossman et al. 1980). Clearly, further studies with particular emphasis on the cellular aspects of the tissue response to organic and, as well as inorganic dust injury would help in the development of more effective strategies to combat these disorders.

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