INTERSTITIAL LUNG DISEASE **MEDICAL APPENDIX**
(DIFFUSE PARENCHYMAL LUNG DISEASE)

DEFINITION

1. This term denotes the effect of a very wide variety of disorders upon the lung. Although of diverse pathology and aetiology (at least 180 causes have been described) these conditions share the uniting feature that they cause profound effects on the tissues lining the smallest blood vessels (capillary endothelium), the air sacs (alveolar epithelial lining cells), and the small airways.

2. The hallmark of interstitial lung disease is the proliferation of cells (fibroblasts) which produce fibrous tissue and the consequent abnormal deposition of this material in the above sites in the lungs. Another uniting feature is the fact that the pathological changes are diffusely distributed throughout the lungs.

CLINICAL MANIFESTATION

3. Collectively the causative conditions produce a wide range of clinical features and often present significant diagnostic difficulty.

4. The most marked features of interstitial lung disease are gradually progressive shortness of breath and cough. Other signs and symptoms may be determined by disease processes outside the respiratory system, e.g. joint pain and stiffness in the rheumatological diseases, dysphagia and Raynaud's syndrome in systemic sclerosis and ocular symptoms in sarcoidosis.

5. Similarly, the progression of the condition will be determined by the nature of the underlying cause. For example some, such as asbestosis and pulmonary lymphoma are progressive in the absence of treatment; others pursue a more chronic relapsing and remitting course, such as extrinsic allergic alveolitis and pulmonary eosinophilia.

6. Routine investigations may yield normal results in these patients, although in most cases there is a restrictive defect with reduced vital capacity, total lung capacity and carbon monoxide transfer factor. A normal or increased ratio of forced expiratory volume in 1 second:forced vital capacity - is usual.

7. However more intensive investigations will generally be required to reveal the true nature of the underlying pathological process. Thus bronchoalveolar lavage and lung biopsy may be needed, although high-resolution computed tomography has been a major advance in the diagnosis of the condition.

AETIOLOGY

8. The following are examples of the groups of conditions which may underlie interstitial lung disease; the list is by no means exhaustive.

9. **Occupational or other inhalant-related conditions:**

9.1. **Pneumoconioses** The principal dust-related diseases typically occur after sustained exposure, which may be direct, due for example to the use of drills and grinders, or indirect, due to secondary exposure to such material. They include many conditions, such as coal worker's pneumoconiosis, asbestosis, siderosis, etc.

9.2. **Hypersensitivity pneumonitis (extrinsic allergic alveolitis)** This spectrum of interstitial lung diseases results from repeated inhalation of, and sensitisation to, a wide variety of organic aerosols which may be:

Microbial agents (Bacteria, fungi, amoebae)

Animal proteins (Avian, fish meal, wheat weevil, etc.)

Chemical sensitisers e.g. isocyanates, acid anhydrides, etc.

10. **Drug-related causes** A drug history is important in the assessment of patients with interstitial lung disease as respiratory symptoms may appear weeks to years after the drug has been discontinued. Relatively little is known of the mechanisms of drug injury to the lungs but more than 200 drugs are known to affect the lungs adversely. Interstitial lung disease has been linked to the following but apart from the last group the association is rare:

10.1. **Antibiotics** e.g. furantoin, sulphasalazin

10.2. **Anti-arrhythmics** e.g. amioderone, tocamide, propanolol

10.3. **Anti-inflammatory drugs** e.g. gold, penicillamine, methotrexate, phenylbutazone

10.4. **Anticonvulsants** e.g. dilantin, phenytoin, carbamazepine

10.5. Dietary supplements e.g. L-tryptophan

10.6. **Oral hypoglycaemic agents** e.g. tolbutamide, chlorpropamide.

10.7. **Chemotherapeutic agents** These drugs are more frequently responsible for interstitial lung disease and include bleomycin, busulfan, cyclophosphamide etc.

11. **Physical agents and toxin** Examples include Paraquat, which is unique in its ability to induce an accelerated pulmonary fibrosis, and radiation injury. The latter is encountered in the setting of therapy for solid tumours in the chest and mediastinum, especially cancers of the lung, breast, and oesophagus, where doses of 40 to 55 Gy may be given; and whole body radiation therapy prior to bone marrow transplantation. Cocaine inhalation and intravenous drug abuse are also implicated in some cases of interstitial lung disease.

12. **Connective tissue diseases** The lungs may be involved in almost all the connective tissue diseases. The involvement may be imperceptible, and its true extent masked by exercise limitation due to musculoskeletal features of the connective tissue disease e.g. rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc.

    12.1. Patterns of lung involvement are diverse, and the picture may be complicated further both by drug-induced pulmonary reaction and opportunistic infections secondary to immunosuppressive treatment for the lung disease.

13. **Autoimmune conditions** Diffuse fibrotic lung disease may occur in such autoimmune conditions as inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, etc.

14. **Primary diseases** Most conditions in this group are genetically determined and include sarcoidosis, amyloidosis, neurofibromatosis, tuberous sclerosis, etc. Interstitial lung disease may occur in association with all of these diseases.

15. **Neoplastic diseases** Interstitial lung disease may occur in association with a number of neoplastic conditions such as lymphangitic carcinomatosis, bronchoalveolar cell carcinoma, etc.

16. **Vasculitis-related diseases** This group of conditions is characterised by a pathological process involving inflammation and necrosis of the wall of blood vessels. Blockage of the affected vessels may occur, compromising blood flow to the organ supplied. The process is due to abnormalities in immune mechanisms which vary from one variety to another. They include Wegener's granuloma, giant-cell arteritis, polyarteritis nodosa, etc. Interstitial lung disease may be associated with these disorders.

17. **Haemodynamic disorders** Interstitial lung disease of acute or chronic progression may accompany conditions where there is fluid overload, e.g. in left ventricular failure and renal failure.

18. **Alveolar filling diseases** Alveolar filling diseases occur when air spaces distal to the terminal bronchiole are filled with blood, lipid, protein, water, or inflammatory cells. They include alveolar proteinosis, microlithiasis, lipoid pneumonia, etc. Virtually all of these varieties may ultimately result in interstitial lung disease.

19. **Idiopathic fibrotic disorders** This group encompasses a number of diseases whose aetiology is as yet imperfectly understood. Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) includes familial idiopathic pulmonary fibrosis, acute interstitial pneumonia, cryptogenic organising pneumonia, nonspecific interstitial pneumonitis, bronchiolitis obliterans organising pneumonia (BOOP), etc.

    19.1. These disorders have a prevalence of some 5 per 100,000 population and they are typically diagnosed between the ages of 40 and 60.

19.2. The inciting factors are as yet unclear. The present widely-held hypothesis is that idiopathic pulmonary fibrosis (IPF) occurs in susceptible individuals after some as yet unknown stimulus. This inciting agent initiates a cascade of events that involve inflammation, immune and fibrotic processes in the lung. Environmental, viral, immunological and genetic factors appear to play a complex and important role.

19.3. Long term exposure to metal or wood dust appears to be an independent risk factor for IPF, and occasionally patients date the onset of their condition to an influenza-like illness. There is however no convincing cultural or serological evidence for persistent viral infection.

19.4. Cigarette smoking is also thought to be an independent risk factor for the development of IPF and fibrosing alveolitis is more common in patients who have a history of cigarette smoking. In Langerhans cell histiocytosis a history of cigarette smoking is obtained in more than 90% of patients.

CONCLUSION

20. Interstitial pulmonary fibrosis is the term given to the widespread formation of fibrous tissue in the capillaries, terminal bronchioles and alveoli of the lung, causing destruction of functioning pulmonary tissue.

21. The condition pursues a variable course, depending on the nature of the underlying disorder and it is usually marked by cough and breathlessness.

22. It may be caused by a wide variety of drugs, toxic agents and inhaled materials, and may be associated with a large number of constitutional disease; primary, inherited and idiopathic.

REFERENCES

Burton J and Evans A. Diffuse lung diseases: Approach to diagnosis. In: (Eds) Albert R, Spiro S and Jett J. Comprehensive respiratory medicine. Basildon. Mosby. 1999. p44.1-44.8.

Schwarz M I, King T E and Cherniak R M. Principles of and approach to the patient with interstitial lung disease. In: Murray J F and Nadel J A (Eds). Textbook of Respiratory Medicine. 3rd Ed. Philadelphia. W B Saunders Company. 2000. p1649-70.

Du Bois R M et al. Interstitial lung disease. In: (Eds) Weatherall D J, Ledingham J G and Warrell D A. Oxford Textbook of Medicine. 3rd Ed. Oxford. Oxford University Press. 1995. p2779-2861.

Toews G B. Interstitial lung disease. In: Goldman L and Bennett J C (Eds). Cecil Textbook of Medicine. 21st Ed. Philadelphia. W B Saunders Company. 2000. p410-20.

Baumgartner K B, Samet J M, Stidley C A et al. Cigarette Smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1997;155:242.

Ryu J H, Colby T V, Hartman T E and Vassallo R. Smoking -related interstitial lung diseases: a concise review. Eur Respir J. 2001;17(1):122-32.

British Thoracic Society. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Thorax. 1999;54(Suppl 1):S1-14.

American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000:161(2 Pt 1):646-64.

August 2002