Diffuse lung disease: combined clinical and laboratory studies

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Fibrosing alveolitis

The group of diseases collectively known as the diffuse (interstitial) lung diseases continues to present a formidable challenge to the practising physician. There are more than 200 different varieties, approximately one in 3,000–4,000 of the population suffers from a diffuse lung disease, and about 3,000 of such individuals die each year [1]. Current management strategies are uncoordinated and minimum standards of care have not been defined.

Fibrosing alveolitis is the most depressing of the diffuse lung diseases. The annual mortality from this disease in England and Wales approaches 1,500, with a median survival from diagnosis of just over four years and a poor response to treatment [2–4].

Over the last 5–10 years considerable advances have been made in the understanding of the mechanisms of diffuse lung disease. This has been made possible by new forms of imaging, particularly high-resolution computed tomography (CT) and molecular biology methodology. The lung lends itself to these new approaches as the whole organ can be imaged from apex to base and can be repeatedly accessed with the bronchoscope to harvest inflammatory cells from the lower respiratory tract for cellular and molecular analyses.

The purpose of this review is to illustrate how these modern technologies can be harnessed to define key factors in the pathogenesis, evolution and prognosis of fibrosing alveolitis, the most life-threatening of the diffuse lung diseases. These factors will be compared with studies of a homogeneous population of patients suffering from the type of fibrosing alveolitis which occurs in the context of systemic sclerosis (FASSc), a complication of systemic sclerosis which affects some but not all individuals with this disease. The degree of lung involvement is variable, and the pulmonary component of the disease is identified earlier than in most diffuse lung diseases because diagnosis is often first made as the result of the manifestation of disease in organs other than the lung at a time when pulmonary symptoms are minimal or absent. It is clinically, radiologically, functionally and histopathologically indistinguishable from lone fibrosing alveolitis, but because FASSc can be studied at various stages of disease it has allowed key factors in the pathogenesis of fibrosing alveolitis to be identified.

Role of imaging in diagnosis, prognosis and management

High resolution computed tomography

CT has been used in fibrosing alveolitis to answer four questions. Is CT able to:

- improve the sensitivity of diagnosis and diagnostic accuracy in fibrosing alveolitis?
- predict the relative degrees of cellularity and fibrosis within the lung parenchyma, an assessment that is usually determined from histological examination of lung biopsy samples?
- improve the assessment of likely response to treatment and prognosis?
- identify change in disease extent, particularly change which is not identifiable using more traditional indices?

Sensitivity and accuracy of computed tomography in diffuse lung disease

Numerous studies have shown that CT is more sensitive and accurate than plain chest radiography in identifying diffuse lung disease [5–9]. Our studies compared chest radiography with CT in 86 individuals, 41 of whom had fibrosing alveolitis and 45 other diffuse lung diseases [9]. CT provided an accurate diagnosis in 88% of cases compared with 76% with chest radiography alone, and the sensitivity of diagnosis was higher (89%) than with chest radiography (71%).

Computed tomography as a predictor of histopathology

One of the major advantages of CT over other forms of imaging is that much more precise anatomical definition can be obtained and effectively the whole of the lung can be 'sampled'. In fibrosing alveolitis, there are two patterns of disease: a 'reticular' pattern (Fig 1a) and a 'ground-glass' pattern (Fig 1b). Previous studies related a reticular pattern on CT to predominantly fibrotic histopathological appearances, and a ground-glass pattern to cellularity. These reports, however, concentrated on 'pure' patterns only [10–12]. There have been no studies of the assessment of the *relative* degrees of reticular and ground-glass patterns on CT of the whole lung as predictors of the relative degrees

of cellularity and fibrosis in lung biopsies, but this is the best predictor of likely response to treatment and therefore of survival.

The predictive value of CT against biopsy appearance has been formally analysed in 24 biopsy samples from 12 patients with systemic sclerosis, from each of whom two lung sites were sampled [13]. The relative degrees of reticular and ground-glass change were assessed for CT; pathological grading of lung biopsies was undertaken independently. CT appearances were scored as 'predominantly reticular' (suggesting predominant fibrotic disease) or 'at least equivalent amounts of a reticular and ground-glass pattern'. Biopsies were graded as showing predominant fibrosis, equal amounts of cellularity and fibrosis, or predominant cellularity. If the radiologist predicted predominant fibrosis, this was histologically confirmed in 12 out of 13 cases, giving a positive predictive value of 92%. If at least equivalent amounts of cellularity and fibrosis were predicted, the accuracy fell to 57%.

There are two possible explanations for this discordance. First, the degree of resolution of CT is not good enough to distinguish between fine fibrosis and cellularity. Thus, in the absence of established fibrosis, the relative amounts of cellular infiltration will be overestimated. Secondly, CT is being compared with a small peripheral segment of biopsied lung. Biopsy may not be the best 'gold standard' against which to judge the relative degrees of cellularity and fibrosis in the lung as a whole, so it might be argued that CT provides more global information. Studies of larger numbers of patients will be required to elucidate this fully.

Role of computed tomography in predicting prognosis

Studies of clinical and investigational indices which predict a good prognosis are confusing because the factors analysed were often different and involved both treated and untreated patients. Two of the larger studies, however, reached similar conclusions [4,14]. In the Royal Brompton series [4], 220 patients were studied, 77 of whom had received no therapy. Factors which predicted better survival in the untreated group were female sex and younger age at either presentation or onset of symptoms. Chest radiography and histology were not predictors of survival except in the treated group, in whom less dyspnoea, less radiographic abnormality and a more cellular lung biopsy were associated with corticosteroid responsiveness and better survival (median nine years). Tukiainen *et al.* also found better survival of patients who had an early response to corticosteroids [14].

In the series of Carrington *et al.* [15], patients were allocated to groups according to the predominant histopathological abnormality: a mixed pattern of cellularity and interstitial fibrosis (UIP), and a virtually pure cellular pattern with almost no fibrosis (DIP). Survival in the DIP group at five years was 95% compared with 55% for UIP, and at 10 years 70% and 29%,
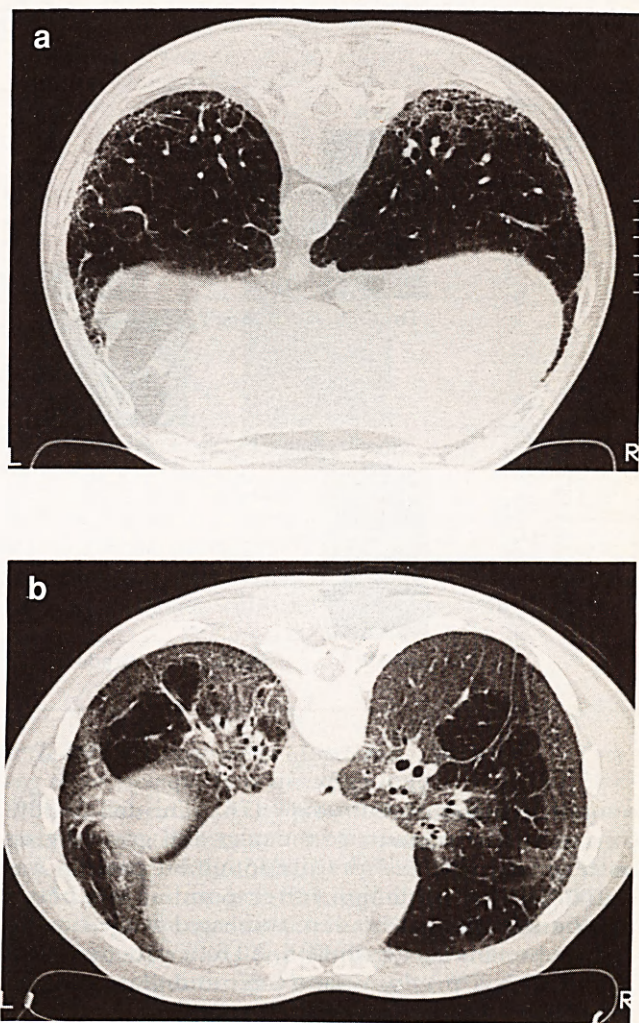

Fig 1. *High resolution computed tomography of a patient with fibrosing alveolitis showing: (a) a predominantly reticular pattern of abnormality associated with a more fibrotic lung biopsy; (b) a ground-glass pattern associated with a more cellular lung biopsy. The disease process in both (a) and (b) is peripheral.*

respectively. However, correlations between biopsy appearance and indices such as survival are difficult to interpret, particularly on an individual basis, because the disease is patchy and it is never possible to be certain that a biopsy represents the overall lung picture.

CT has the advantage over biopsy of being non-invasive, of 'sampling' the whole lung and of providing individual information on prognosis. The pattern of abnormality on CT can predict both the likely response to therapy and actuarial survival (Fig 2). In our study, if the predominant CT abnormality was of a ground-glass pattern (predictive of a more cellular biopsy), 43% of all individuals obtained a significant
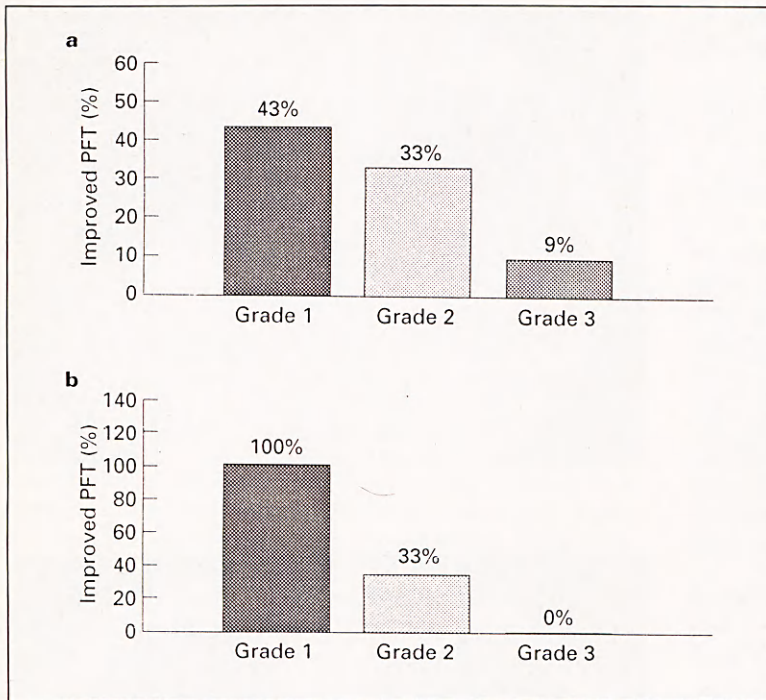
Fig 2. *Relationship between computed tomography (CT) pattern and response to therapy, showing the percentage of patients who obtained significant (>15%) improvement in lung function (vital capacity ± gas transfer) in response to therapy related to the grade of CT appearance: (a) all patients; (b) previously untreated patients.* Grade 1 = ground-glass pattern (indicative of predominant cellularity) > reticular pattern (indicative of predominant fibrosis); grade 2 = equivalent amounts of ground-glass and reticular patterns; grade 3 = reticular pattern > ground-glass.

(> 15%) improvement either in vital capacity or in gas transfer in response to therapy [16]. This fell to 33% for equivalent amounts of reticular and ground-glass pattern and to 9% if the predominant pattern was reticular. The prediction for responders was better when only patients who were untreated at the time of first assessment were evaluated. All four patients in this group with a predominantly ground-glass pattern showed significant response to therapy.

CT can be as good as an open lung biopsy in predicting survival. Previous studies [17] of actuarial survival have shown that all patients whose histology was predominantly inflammatory were alive at four years, whereas half those with a mixed histological appearance and those whose histopathology was predominantly fibrotic had died by the end of the four-year period. Identical conclusions are drawn from actuarial data on groups of patients subdivided on the basis of CT rather than biopsy: 100% survival at 50 months if CT predicts a predominantly cellular biopsy, and a much poorer outcome if the pattern is mixed or predominantly reticular [16].

In consequence of these observations using CT both for diagnosis and for prognosis, lung biopsy is now used much more selectively than in the past. A decision to perform open lung biopsy depends upon an assessment of the individual case. A patient over the age of 65, with poor lung function, especially with hypoxia at rest, is a poor risk for any operative procedure. In these circumstances, it is reasonable to make a clinical diagnosis of fibrosing alveolitis particularly if the CT shows a predominantly reticular pattern, in which case biopsy will add nothing to the accuracy of

either diagnosis or prognosis. Biopsy remains a powerful investigative tool, to be used where diagnosis is unclear or when there is reasonable doubt that a more ground-glass pattern may be due to 'fine' fibrosis rather than cellularity, particularly in younger patients. In these circumstances, when a prolonged period of immunosuppressant therapy is contemplated, lung biopsy is still recommended for staging purposes. CT-guided indications for biopsy have modified the Royal Brompton Hospital use of open lung biopsies. A fairly stable number of biopsies was performed between 1984 and 1987; numbers then began to fall as CT use increased.

Computed tomography as a monitor of disease

CT can give a semiquantitative assessment of the extent of lung involvement in fibrosing alveolitis by estimating the extent of abnormal lung at five different levels of the thorax (at the origin of the great vessels, mid arch of aorta, carina, pulmonary venous confluence, and 1 cm above the diaphragm), using a weighting factor to adjust for lung volume at each level. A value (to the nearest 5%) can then be derived for the amount of disease in the lung as a whole. This quantification can be repeated to assess change, especially in situations where traditional indices of change such as chest radiography and lung function tests show no significant change.

Based on a number of studies of response to treatment, it is generally accepted that there is a significant objective response to therapy (defined as better than 10–15% improvement in vital capacity or gas transfer
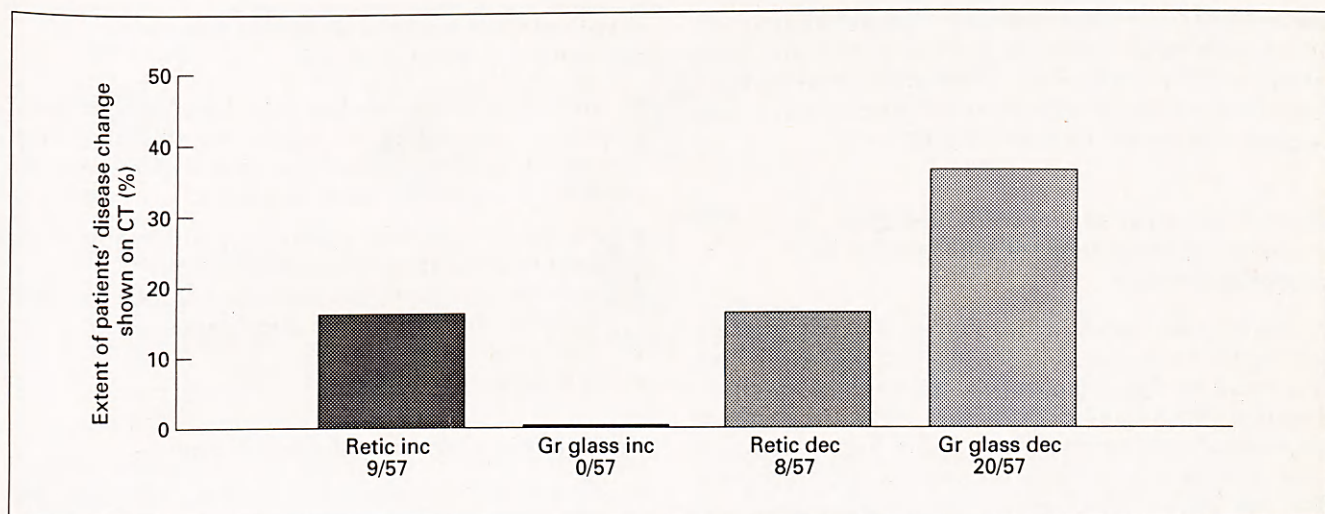
Fig 3. *Change in extent of disease in fibrosing alveolitis assessed by serial computed tomography (CT) at an interval of one year, showing the percentage of patients whose CT showed a change in disease extent.* retic = reticular pattern; gr glass = ground-glass; inc = increased; dec = decreased. Note that it is only the ground-glass (cellular) component which decreases; the extent of the reticular component never decreases.

(DLCO) or improvement in chest radiography) in only about 25% of unselected patients. One possible explanation is that in a process which progresses slowly there is already considerable fibrosis and injury to the lung before diagnosis is made. At this point, the relative proportion of reversible inflammatory disease process to irreversibly fibrotic, destroyed lung is low. Any response to therapy, therefore, is unlikely to produce a *significant* improvement in pulmonary function. Less striking changes in pulmonary function cannot be considered to be statistically significant. However, subtle changes in disease extent in response to therapy may be visualised using high-resolution CT. Using CT together with lung function as indices of change in disease, and comparing this combination with the more traditional indices of change (chest radiograph and lung function), we have shown that combining CT with pulmonary function tests enables a definite statement to be made about change in 35 of 43 cases compared with only 21 of 43 where chest X-ray and lung function tests were combined, and 13 of 43 where chest X-ray alone was used as the index of change.

It was striking that a reticular pattern did not decrease in extent in any of 57 paired observations (Fig 3) [18]. Thus, once reticular disease has extended to produce symptoms, therapy which cannot reduce the degree of reticular (fibrotic) change is much less likely to improve either symptoms or function than if the disease is more cellular. If treatment has any hope of arresting the more reticular form of fibrosing alveolitis, therefore, it needs to be commenced before sufficient lung function has been lost for little reserve to remain, and when any, even small, further reduction in function results in symptoms.

^{99m}Tc-DTPA measurement of epithelial clearance

99m-Technetium (Tc)-labelled diethylenetriamine pentacetate (DTPA) (a 500 Da compound) clearance is a measure of epithelial permeability and has been used as an index of inflammation in various diffuse parenchymal lung diseases, including extrinsic allergic alveolitis, sarcoidosis and fibrosing alveolitis [19–21]. After four minutes tidal breathing of ^{99m}Tc-DTPA via a nebuliser, gamma camera recordings are made over the thorax for 45 minutes. Rates of clearance from the lung are then derived and plotted either in terms of half-time clearance or percentage clearance from the lung per unit time. It is a highly sensitive technique, although it is not specific for diffuse parenchymal lung disease and is abnormal in current smokers. In fibrosing alveolitis and FASSc, rapid rates of clearance can be demonstrated in the absence of any other evidence of disease including high-resolution CT [19].

Although CT can provide prognostic information both on likely improvement in response to therapy and on survival, it cannot predict likely disease progression. Serial measurements of DTPA can be used to subdivide patients into groups, predicting those whose disease will remain stable and those who fall into a high-risk group for deterioration. In one study, clearance was measured on two occasions at annual intervals in 54 patients suffering from either fibrosing alveolitis or FASSc [22]. Approximately 40% of individuals whose clearance was abnormally rapid on both occasions suffered a fall of more than 15% in pulmonary function over the subsequent 21 months. In striking contrast, 12 individuals whose clearance remained normal and eight whose clearance, having started abnormal,

reverted to normal had no further deterioration in pulmonary function. Interestingly, individuals in the latter group were more likely to show an improvement in pulmonary function (six of eight) subsequent to the second measure of clearance (Fig 4).

Role of molecular biology methodology in defining key components of pathogenesis in fibrosing alveolitis

Inflammatory mechanisms responsible for disease pathogenesis are controlled in the local micro-environment and involve complex cell/cell interactions either through direct contact or by the release of chemical mediators such as cytokines. These highly complex mechanisms are shared by the vast majority of chronic inflammatory diseases occurring within the lung and other organs. It is crucial, therefore, to attempt to identify key factors in individual diseases which would enable therapeutic approaches to be targeted more appropriately.

Molecular biology as a tool

Molecular biological techniques provide the tools for identifying genes and gene products involved in these key mechanisms, but they must be considered in the context of other means of identifying pathogenetic mechanisms, including immunohistological and biochemical investigations.

*Use of molecular biology to identify key areas in pathogenesis of fibrosing alveolitis*

In individuals who are likely to have an immuno-genetic predisposition to developing fibrosing lung disease, the pathogenesis of fibrosing alveolitis may be considered under four major headings:

- an *insult* to alveolar epithelium and/or the adjacent endothelium, followed by
- an *immune response,* the trafficking of inflammatory granulocytes into disease sites, producing
- local *injury,* and
- a *fibrogenic repair* process [23].

Predisposition to disease and epithelial injury

The currently accepted paradigm of disease pathogenesis is shown in Fig 5. The initiating event which triggers the development of fibrosing alveolitis involves injury to the epithelium and/or the endothelium which, in predisposed individuals, results in progressive disease. There is good evidence from an analysis of major histocompatibility genes in our studies of systemic sclerosis to suggest that the predisposition to the development of fibrosis has an immunogenetic basis [24]. Chromosome 6 includes a 3 kb segment on its short arm (Fig 6). This segment contains class I, II, and III major histocompatibility complex (MHC) molecules which are in turn associated with pro-inflammatory genes. The haplotype of MHC and other immune response gene expression can be determined

Fig 4. *Value of serial* ^{99m}*Tc-DTPA in predicting likely deterioration of pulmonary function, showing the percentage of patients whose lung function deteriorated about two years after the second DTPA measurement.* AA = persistently abnormal clearance; AN = abnormal clearance reverting to normal; NN = persistently normal clearance; CFA = cryptogenic fibrosing alveolitis; SSc = systemic sclerosis.
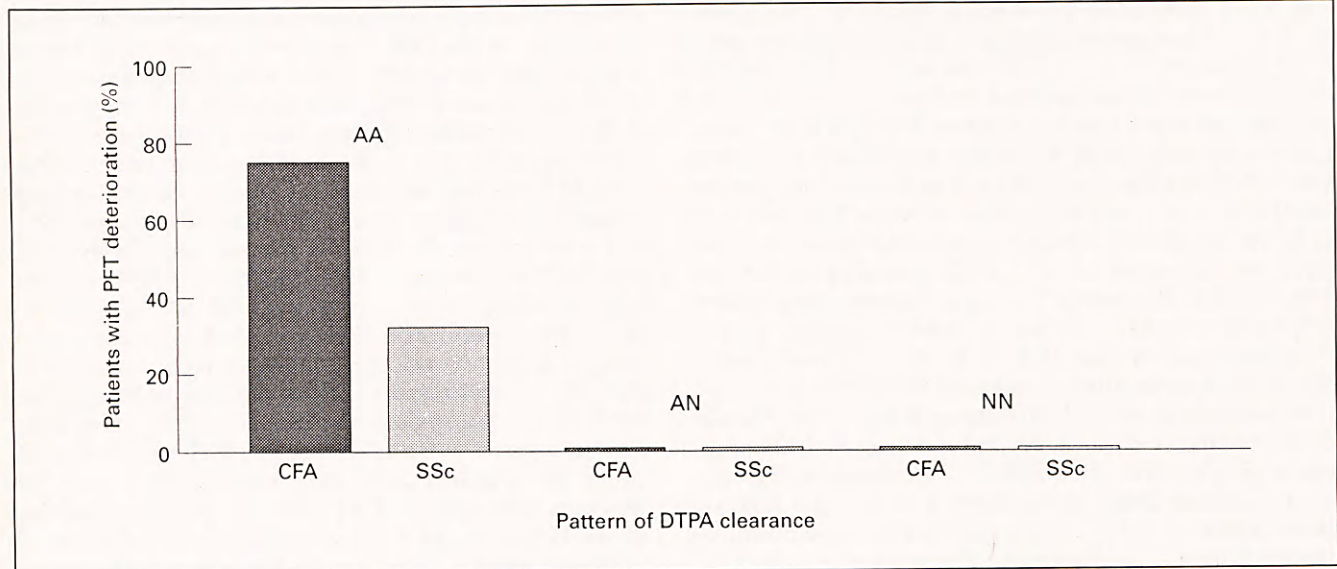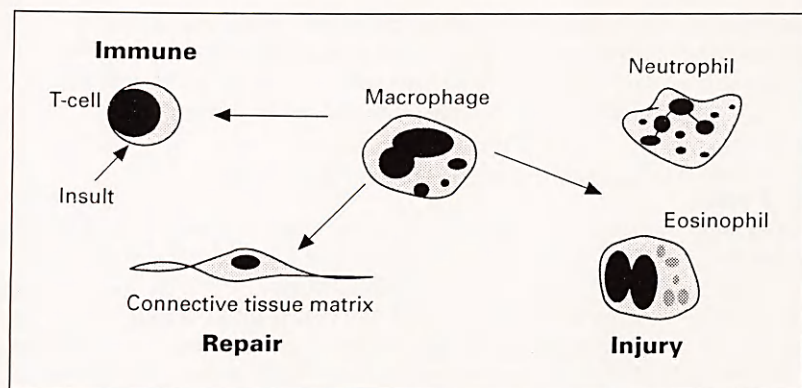
Fig 5. *Pathogenesis of fibrosing alveolitis, showing the three major components of pathogenesis which follow the initiating insult (immune response, injury and fibrogenesis) and the central role of the alveolar macrophage.*

by gene analysis using either the polymerase chain reaction (PCR) and specific primer pairs selectively to amplify individual alleles, or a combination of PCR and product identification with oligonucleotides complementary for specific alleles.

In patients with systemic sclerosis the presence of the class II MHC HLA DR3/52a haplotype carries a much higher risk of pulmonary fibrosis. Taken together with the presence of the diffuse cutaneous systemic sclerosis-associated autoantibody Sc170, the relative risk of developing pulmonary fibrosis in the context of systemic sclerosis for individuals with either the HLA DR3/52a haplotype or the presence of Sc170 is 16.7 fold greater than in individuals without either of these indices. The implications of this study are that this association can identify individual susceptibility to fibrosis and that it is likely to depend on an immune response gene.

Immunological responses

Histological evaluation of lung biopsies from patients with fibrosing alveolitis has demonstrated the presence of abundant lymphoid follicles and large numbers of T

Fig 6. *Schematic representation of the short arm of chromosome 6 which contains the loci for MHC class I, II and III genes and also a number of genes which play an important role in chronic inflammation.* C^1 = complement; HSP = heat shock protein; MHC = major histocompatibility complex; TNF = tumour necrosis factors α and β.
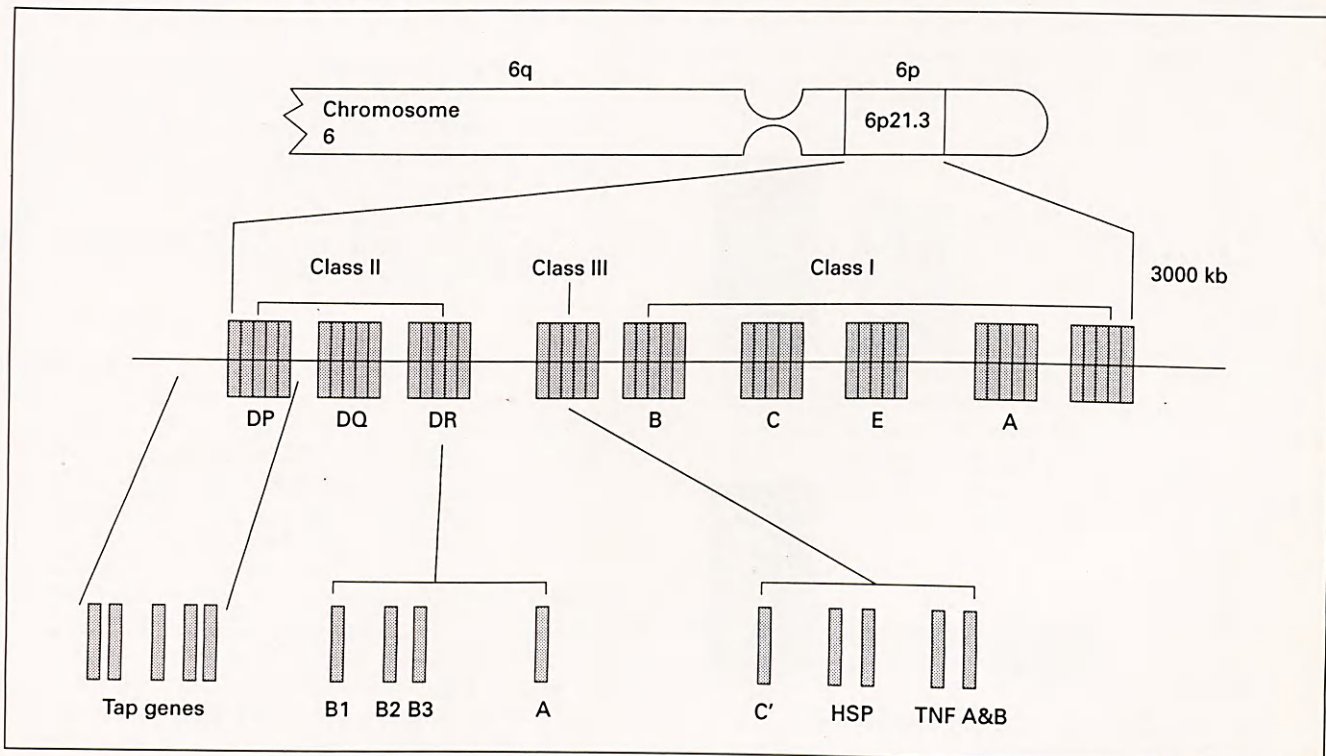
cells within the interstitium [25,26]. These lymphoid follicles have the immunohistological features of secondary follicles with true germinal centres, indicating that they are actively producing antibody.

The T cells within the interstitium are predominantly CD4+ helper/inducer cells and they are CD45R0+, the phenotype which marks them as T cells of the committed, 'memory' subset [27]. To attempt to determine whether these cells have been exposed to a common antigen, evidence of clonality was sought within the population of T cells accumulating at disease sites [28]. The majority of mature T cells express the T cell antigen receptor which consists of α and β chains. Each chain, in common with the immunoglobulin molecule, has constant and variable regions and there are families of α and β chains. Antigen specificity of T cell response resides within the variable regions. Clonality of T cells at disease sites can be defined by determining the relative frequencies of expression of specific families of T cell antigen receptors responsible for antigen recognition, and which are expressed on the surface of the cells.

Our studies, using a panel of primer pairs specific for the variable regions of 18 α-chain (Vα) families, are consistent with the concept that the normal lung is an active immune organ, and that at disease sites in fibrosing alveolitis the T cell response within the lower respiratory tract is also broad based, defined by Vα family expression [28]. However, limited oligoclonality within or across Vα families could still be masked by an approach which was not designed to quantify messenger RNA (mRNA) transcription products of individual T cell receptors. Further experiments are needed to sequence in detail multiple cDNA clones from mRNA isolated from each biopsy and to quantify the degree of homology in order to confirm the clonality of T cell accumulation at disease sites.

Functional status of T cells at disease sites

Despite their presence in large numbers at disease sites, little is known about the function of lymphocytes in pathogenesis. In addition to their role in antigen presentation, T cells have a repertoire of cytokine products which can augment and amplify the inflammatory response. *In situ* hybridisation experiments have shown that the cells within the interstitium express at the mRNA level a number of cytokines with pro-inflammatory activity such as interleukin (IL) 4, IL-5 and interferon (IFN) gamma [29]. This pattern of cytokine production does not fall neatly within the classically defined T helper (TH) 1 and TH2 subsets of T cells, indicating that it is not always possible to divide T cell response in man into inflammatory (TH2; IL-4, IL-5) or delayed hypersensitivity (TH1; IL-2, IFN-gamma) types. The situation may therefore be more complex in humans than in the mouse in which the TH1, TH2 subsets were first defined.

Inflammatory response

Granulocytes, especially neutrophils, are the primary cause of lung injury in fibrosing alveolitis and FASSc. They release oxidant species, and their granules contain proteases, cathepsins, major basic protein and eosinophil cationic protein. CT in combination with
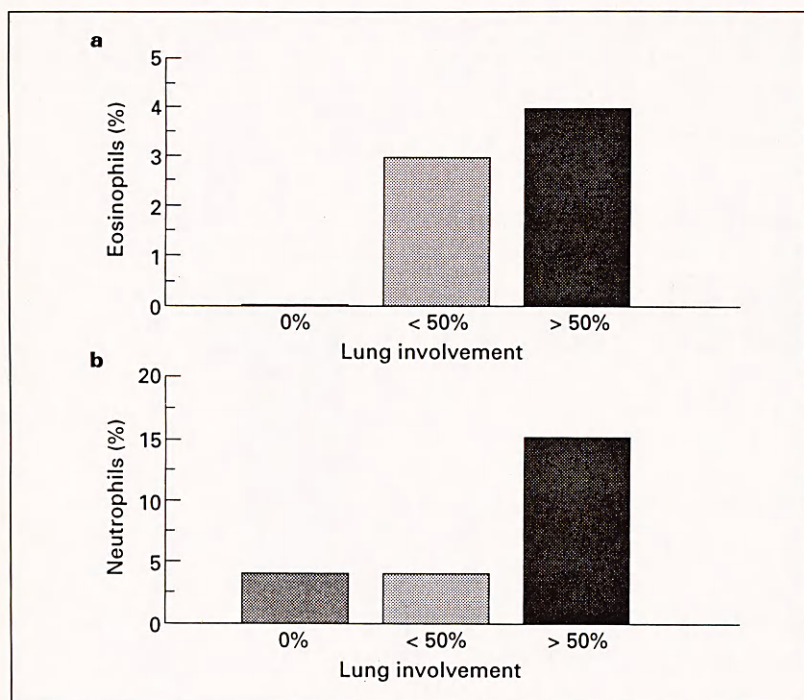

Fig 7. *Relationship between inflammatory cells in the lower respiratory tract assessed by bronchoalveolar lavage and extent of disease in the lavaged lung lobe assessed by computed tomography (CT).* (a) ordinate: percentage of eosinophils; abscissa: extent of lung involvement on CT; (b) assessment of neutrophil numbers.
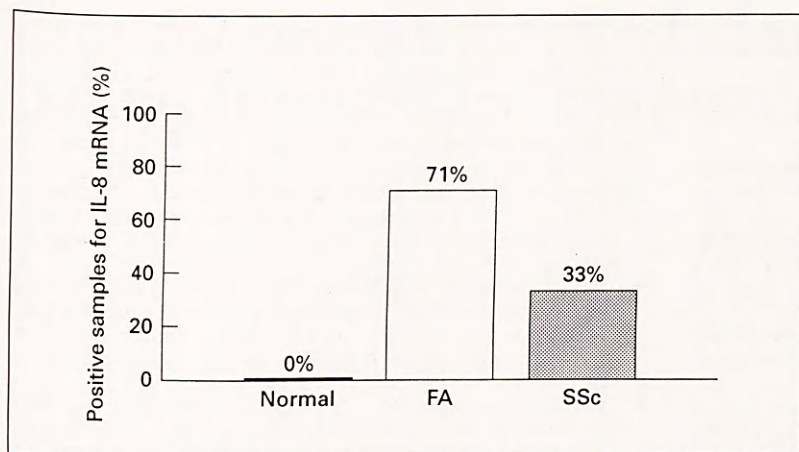
Fig 8. *The presence of mRNA for IL-8 in bronchoalveolar lavage cells obtained from patients with fibrosing alveolitis occurring alone or in the context of systemic sclerosis, showing the percentage of samples positive for IL-8. FA = fibrosing alveolitis; IL = interleukin; SSc = systemic sclerosis.*

bronchoalveolar lavage (BAL) can be used to determine the relationship of inflammatory cell traffic with disease stage. In a recent study we have compared the extent of disease in the right middle lobe of lung assessed by CT with the cell returns from BAL of the same lobe [30]. The results showed that eosinophils and neutrophils migrate separately to disease sites (Fig 7). If the CT of the lavaged lobe showed no evidence of abnormality, no eosinophils were present; however, in individuals whose CT showed up to 50% of disease involvement in that lobe, eosinophils were present in abnormal numbers—comparable to the numbers seen when more than 50% of the lobe was involved (median 3%; range 0–9%). By contrast, although normal lobes contained a few neutrophils, the greatest numbers were observed in patients whose lobe showed more than 50% involvement, at which stage neutrophils were always found in excess numbers (median 17%; range 5–55%). These studies suggest a pattern of inflammatory cell traffic to the lungs, and that increased neutrophil migration to the lungs is associated with more extensive disease and results in amplification of the extent of lung injury by releasing proteolytic enzymes and generating oxidant radicals.

Granulocyte traffic

What attracts granulocytes to disease sites in fibrosing alveolitis has not yet been fully elucidated. However, the observation of IL-5 mRNA expression by cells at disease sites using *in situ* hybridisation is consistent with the knowledge that IL-5 is a potent eosinophil chemotactant and activator, and is the most likely explanation for the presence of eosinophils within the lower respiratory tract.

The expression of IL-8 (neutrophil attractant protein 1) by alveolar macrophages is almost certainly responsible for the traffic of neutrophils [31,32]. IL-8 is an 8.4 kDa protein of the chemokine family and is the most potent naturally occurring neutrophil chemotactant yet described. The concentration of IL-8 in epithelial lining fluid obtained from patients with fibrosing alveolitis is greater than in those with FASSc, and both contain more IL-8 than fluid from normal individuals. Lavage cells obtained from these patients contain IL-8 mRNA, identified by Northern analysis and PCR of reverse transcription products. Importantly, IL-8 mRNA is found only in individuals with FASSc; in the absence of fibrosis, no IL-8 mRNA is identified (Fig 8).

The number of neutrophils present in the lower respiratory tract is strikingly greater in the presence of higher lavage fluid IL-8 concentrations. IL-8 is predominantly expressed by cells within the air spaces, identified using *in situ* hybridisation and IL-8 specific probes. This suggests that neutrophils are preferentially attracted to the air spaces and may explain why relatively few neutrophils are seen within the interstitium (ie there is a chemotactant gradient from vessels to air space).

Conclusion

By identifying critical determinants of the immune and inflammatory phases of fibrosing alveolitis, it should be possible to target therapy to these components and prevent the development of irreversible fibrotic changes. Molecular approaches to identify predisposing immunogenetic markers, the clonality of lymphocytes at disease sites and the mechanisms of recruitment of inflammatory cells can all be harnessed to high technology imaging to identify lung disease at an early stage and predict prognosis. These approaches should enable us to develop more rational ways of treatment.

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