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Idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia should stay separate

To the Editors:

We read with interest the recent perspective by MAHER *et al.* [1], challenging the current definition of idiopathic pulmonary fibrosis (IPF). Questioning dogma is critical to progress in science and the authors should be commended for doing so.

We agree that the relationship between disease entity (*i.e.* clinical diagnosis) and histopathological pattern is more complex than simply equating IPF with usual interstitial pneumonia (UIP), and that distinguishing idiopathic UIP from idiopathic nonspecific interstitial pneumonia (NSIP) can sometimes be difficult, even for expert clinicians, radiologists and pathologists [2]. Indeed, the American Thoracic Society/European Respiratory Society Consensus Statement made these points quite deliberately [3].

However, we disagree with the authors' contention that "idiopathic UIP and idiopathic NSIP, sharing a common clinical phenotype, form a spectrum of disease with a common pathogenesis" [1]. This blanket statement assumes a homogeneity to idiopathic NSIP and idiopathic UIP that is contrary to the evidence. The idea of a distinct clinical phenotype for idiopathic NSIP is supported by demographic, serological and survival differences seen when IPF and idiopathic NSIP patients are compared [4–6], and by the differences, not similarities, seen in gene expression profiles (six of 10 published NSIP profiles are distinct from UIP while four are similar) [7, 8].

It is our belief that idiopathic nonspecific interstitial pneumonia represents a collection of conditions including occult connective tissue disease, hypersensitivity pneumonia and, perhaps, truly idiopathic cases, and should not be lumped together clinically with idiopathic pulmonary fibrosis. We share the hope of MAHER *et al.* [1] that new and emerging methods of categorising disease will allow us to better understand the relationship of histopathology to pathogenesis and to refine future definitions and diagnostic criteria.

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STATEMENT OF INTEREST

None declared.

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From the authors:

We appreciate the comments of H.E. Collard and T.E. King on our article [1]. The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification has been important in advancing clinical understanding of the idiopathic interstitial pneumonias [2]. In that document, the clinical entity of nonspecific interstitial pneumonia (NSIP) was proposed as a provisional term only. As we have argued, we believe that using histological appearances alone to define separate clinical entities is unhelpful [1]. Different histological patterns may occur in the same patient [3]. Furthermore, conditions with a defined aetiology (*e.g.* hypersensitivity pneumonitis, connective tissue disease or familial pulmonary fibrosis) may give rise to either usual interstitial pneumonia (UIP) or NSIP in different patients [4–6].

By associating the histological lesion of NSIP with a clinical diagnosis of NSIP, the ATS/ERS consensus classification has blurred the distinction between idiopathic and secondary NSIP in the minds of many clinicians. This has led some to consider NSIP as a single disorder. We agree strongly with H.E. Collard and T.E. King that many cases of NSIP are due to either connective tissue disease or hypersensitivity pneumonitis. However, when reviewing the clinical data in such cases there are often ancillary features that point to the underlying diagnosis [7]. Once secondary cases are excluded, there remains a large subgroup of NSIP patients who have a clinical phenotype that overlaps substantially with that of UIP/idiopathic pulmonary fibrosis (IPF). This group of patients have a sex distribution, smoking-exposure history, mode of clinical presentation, distribution of clinical signs and bronchoalveolar lavage cell

differential that mirrors that of IPF/UIP [2, 8, 9]. The distribution of disease on high-resolution computed tomography is also strikingly similar [10].

We therefore propose that idiopathic UIP and idiopathic NSIP, sharing a common clinical phenotype, form a spectrum of disease with a common pathogenesis. The pathogenetic mechanisms involved in the development and progression of IPF are complex and are likely to involve abnormalities in a number of the multiple pathways of normal wound healing [1]. It seems likely that the balance of abnormalities in each of the key wound-healing pathways may vary between individuals. This variation is likely to be responsible for the range of clinical, radiological and pathological phenotypes observed in IPF.

Like H.E. Collard and T.E. King, we hope that future clinical and scientific research will further clarify these issues, as advances in our understanding of idiopathic pulmonary fibrosis can only be to the benefit of patients with this devastating and currently untreatable disease.

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None declared.

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