# Five simple reasons to discard DIP, or why we should stop calling dolphins big fish

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## ABSTRACT

The aim of this review is to explain why the term 'desquamative interstitial pneumonia' (DIP) should be discarded and replaced with modern terminology. Reason 1: DIP is a misnomer. Within a few years after the term was coined, it was shown that the airspace cells in DIP are macrophages not desquamated pneumocytes. Reason 2: As a result of overly simplistic and poorly defined histologic criteria, DIP is currently a mixed bag of smoking-related diseases and unrelated processes in never-smokers. Reason 3: DIP obfuscates the modern concept that smoking causes some forms of parenchymal lung disease. Despite the fact that >80% of cases of DIP are caused by smoking, it is currently classified as a 'smoking-related idiopathic interstitial pneumonia', an oxymoron. Reason 4: The premise that the presence of numerous macrophages within airspaces defines an entity creates problematic histologic overlap with other lung diseases that may feature prominent airspace macrophages. Reason 5: DIP is outdated. It was coined in 1965, when many entities in interstitial lung disease had not been described, smoking-related interstitial lung disease was an unknown concept, computed tomograms of the chest had not been introduced and immunohistochemistry was unavailable. We suggest a way forward, which includes eliminating the term DIP and separating smoking-related lung abnormalities (including accumulation of pigmented airspace macrophages) from cases characterised by numerous non-pigmented macrophages in never-smokers. The laudable goal of smoking cessation is not served well by muddying the relationship between smoking and lung disease with inaccurate, outdated terminology.

## INTRODUCTION

The term desquamative interstitial pneumonia (DIP) was introduced by Liebow *et al* in 1965.[1] Over the following half century, electron microscopy, immunohistochemistry, the creation of better-defined entities in interstitial lung disease and the increasing recognition of smoking as a cause of interstitial lung disease have chipped away at the raison d'être of this entity. The aim of this review is to make the case that this outdated misnomer should be discarded.

Perhaps presaging the future, Liebow *et al* described their term as 'cumbersome but descriptive'. Their manuscript defined DIP as follows: 'the most striking feature of DIP was the lining and filling of the lumens of thickened distal air spaces by masses of what here will be called 'large alveolar cells'. Evidence that these were predominantly granular pneumocytes rather than phagocytic pneumocytes will be discussed'.

This key concept, on which the term DIP was based, was soon shown to be incorrect.

## THE INTRA-ALVEOLAR CELLS IN DIP ARE MACROPHAGES NOT DESQUAMATED PNEUMOCYTES

Within a few years after the term DIP was coined, studies using electron microscopy suggested that the cells filling the airspaces were macrophages not desquamated pneumocytes. In 1969, Shortland and colleagues[2] showed the presence of lysosome-rich macrophages among the intra-alveolar cells. A year later, Farr *et al*[3] showed by electron microscopy in one case of DIP that 'the cell population within the alveoli was composed predominantly of macrophages…'. In 1977, Tubbs and colleagues[4] determined, based on electron microscopy of five cases of DIP, that 'macrophages were the predominant type of cells within the alveolar spaces, identified by abundant lysosomes and pseudopodia'. In the same year, Valdivia *et al*[5] studied 30 lung biopsies and 3 necropsies including one case from Liebow's original series and concluded '…the accumulation and aggregation of alveolar macrophages must be considered the primary phenomenon of DIP…'. Further evidence came from immunohistochemistry. In 1998, Mutton *et al*[6] showed that in three cases of DIP, the major intra-alveolar cell population stained positively with the macrophage marker CD68.

## DIAGNOSTIC CRITERIA FOR DIP ARE OVERLY SIMPLISTIC AND POORLY DEFINED

Many of the problems the plague DIP stem from its diagnostic criteria, which have been defined differently by various authors over the years (table 1).[7–16] In 2002, a document published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) redefined diagnostic criteria for several entities in interstitial lung disease based on the opinions of a consensus panel.[7] Among the redefined entities was DIP. As shown in table 1, the criteria laid down for this entity by the ATS/ERS document differed from prior definitions used by Liebow *et al*[1] and Carrington *et al*.[9]

Discomfort with the term DIP is clearly expressed in the ATS/ERS document: 'the term DIP is retained in this document but it presents several problems. The name originated from the belief that the dominant histologic feature was desquamation of epithelial cells. However, this is now recognised to be intra-alveolar macrophage accumulation rather



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**Table 1** Diagnostic criteria for DIP*

| Reference | Year | Diagnostic criteria |
|---|---|---|
| Liebow *et al*[1] | 1965 | 1. Massive proliferation and desquamation of large alveolar cells. 2. Slight thickening of the walls of distal air spaces. 3. Absence of necrosis. 4. Minimal loss of tissue. |
| Gaensler *et al*[8] | 1966 | Not defined. |
| Carrington *et al*[9] | 1978 | 1. Relative uniformity of the lesion throughout the tissue sample. 2. Sparse interstitial cellular infiltrate, including an appreciable proportion of plasma cells and eosinophils. 3. Prominent lining of alveoli by large rounded cells. 4. Abundant mononuclear cells filling many small air spaces. 5. Little if any proteinaceous exudate in air spaces or interstitium. |
| Yousem *et al*[10] | 1989 | Not defined. Distinction between RBILD and DIP 'is based primarily on the patchiness, bronchiolocentricity, and nonuniform airspace filling by finely pigmented macrophages in RB/ILD and the more extensive, diffuse and uniform changes in DIP'. |
| Hartman *et al*[11] | 1993 | 'The diagnosis of DIP was based on numerous macrophages that filled the airspaces, relatively mild fibrosis, and uniformity of the histologic features from field to field'. |
| Hartman *et al*[12] | 1996 | Not defined. 'Biopsy specimen-proved DIP'. |
| Heyneman *et al*[13] | 1999 | Not defined. 'All pathology specimens were reexamined by experienced pulmonary pathologists who were aware of the histologic distinctions among the three entities'. |
| Travis *et al*[14] | 2000 | Not defined. |
| ATS, ERS | 2002 | 1. Uniform involvement of lung parenchyma. 2. Prominent accumulation of alveolar macrophages. 3. Mild to moderate fibrotic thickening of alveolar septa 4. Mild interstitial chronic inflammation (lymphoid aggregates). |
| Craig *et al*[15] | 2004 | Not defined. Refers back to 2002 ATS/ERS document: 'the criteria for distinguishing histological patterns of DIP and RB are now well defined by consensus in the recently published ATS/ERS classification for idiopathic interstitial pneumonias'. |
| Ryu *et al*[16] | 2005 | DIP was defined by the presence of pigmented macrophages diffusely involving alveolar spaces in at least one low-magnification field (×40) without a bronchiolocentric distribution and accompanied by diffuse alveolar septal thickening due to alveolar septal inflammation with or without fibrosis. |

*Articles listed in this table are the 10 most cited publications on DIP as of July 18, 2020 (Google Scholar) and the 2002 ATS/ERS consensus guidelines.
ATS, American Thoracic Society; DIP, desquamative interstitial pneumonia; ERS, European Respiratory Society; RBILD, respiratory bronchiolitis-interstitial lung disease.

than desquamation of epithelial cells as originally thought by Liebow and Carrington' and '…the panel seriously considered changing this term to alveolar macrophage pneumonia'. Table 2 of the ATS/ERS guideline suggests that pathologists should diagnose the 'histologic pattern' DIP, which—by adding clinical and radiologic information—transforms into the 'clinical-radiologic-pathologic' diagnosis of DIP. Neither the minimum histologic criteria nor the mandatory clinical and imaging features that enable this transformation are defined clearly, leaving readers to fill in the blanks. Table 14 of the ATS/ERS document lists four 'Key Histologic Features': uniform involvement of lung parenchyma, prominent accumulation of alveolar macrophages, mild to moderate fibrotic thickening of alveolar septa and mild interstitial chronic inflammation (lymphoid aggregates) without specifying which of these are mandatory. The reader might ask: what degree of alveolar filling is required to consider involvement of lung parenchyma 'uniform' and accumulation of macrophages 'prominent'? The text states 'the DIP pattern is characterized by diffuse involvement of the lung by numerous macrophage accumulations within most of the distal airspaces'. Since 'most' could be interpreted as anything from 50% to 99% of alveoli in the sample, this allows a wide range of interpretations. Similarly, it is not specified how many macrophages are required per alveolus or whether fibrotic or inflammatory thickening of alveolar septa are mandatory. Can cases with 'prominent accumulation of alveolar macrophages' but no fibrotic thickening of alveolar septa be classified as DIP? Indeed, one could argue that without some degree of interstitial thickening, the word 'interstitial' in DIP is inaccurate.

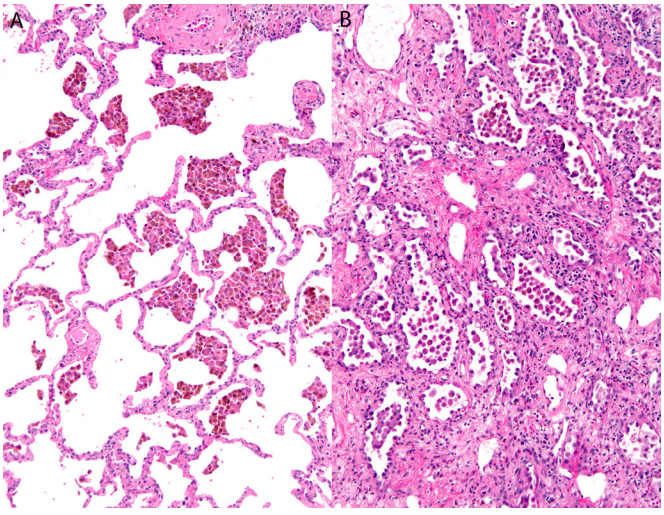


**Figure 1** Desquamative interstitial pneumonia-like areas in (A) pulmonary Langerhans cell histiocytosis and (B) usual interstitial pneumonia.

Perhaps more problematic in practice is the fact that the document does not specify the essential clinical or imaging findings required to transform a 'DIP pattern' into DIP, making the final diagnosis an arbitrary decision where clinicians have complete leeway to reject or accept a histologic 'DIP pattern' as DIP at their whim. The 2013 update of the ATS/ERS guidelines does not clarify these criteria.[17]

The overly simplistic premise that the presence of alveolar macrophages within most airspaces defines a discrete entity causes problems for pathologists in practice. Defined thus, DIP overlaps with non-specific interstitial pneumonia (NSIP; which also features mild interstitial chronic inflammation and fibrosis), usual interstitial pneumonia (UIP; some cases of which contain numerous intra-alveolar macrophages), pulmonary Langerhans cell histiocytosis (most cases of which feature numerous intra-alveolar pigmented macrophages, a feature that has been termed 'DIP-like') and respiratory bronchiolitis-interstitial lung disease (RBILD).[18] Figure 1 shows examples of DIP-like areas in other entities.

Most significantly, the recently described entity smoking-related interstitial fibrosis (SRIF) effectively replaces some cases that would previously have been termed DIP in smokers because it places emphasis on the presence and quality of

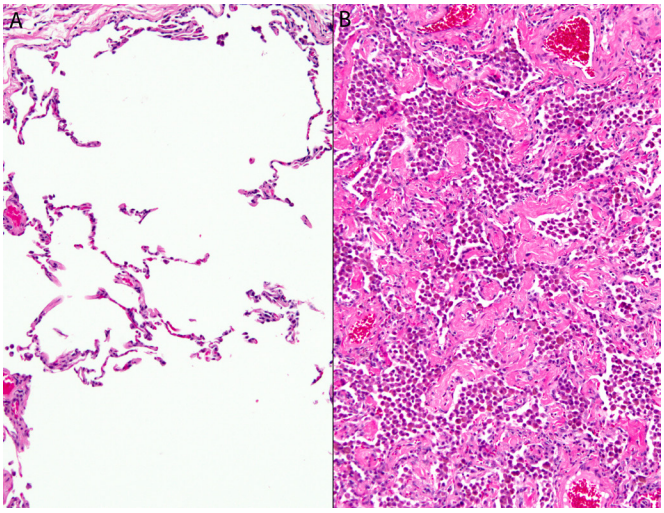


**Figure 2** Surgical lung biopsy from a heavy smoker with clinical features of interstitial lung disease. (A) This field shows emphysema without alveolar filling by macrophages or interstitial fibrosis. (B) In an adjacent field from the same slide, most airspaces are filled by numerous pigmented macrophages, and the interstitium is mildly expanded by ropy collagen. In such cases, the term smoking-related interstitial fibrosis better describes the histologic findings and aetiology than desquamative interstitial pneumonia (DIP). Criteria for DIP are not met since most airspaces are not filled by macrophages.

interstitial fibrosis rather than the extent of intra-alveolar pigmented macrophages.[19] A case where SRIF is clearly a better term than DIP is illustrated in figure 2. This issue was addressed in 2013 by Dr Anna-Luise Katzenstein, a pioneer who described several entities in the field of interstitial lung disease, including NSIP, acute interstitial pneumonia, RBILD and SRIF. Writing in this journal,[20] Dr Katzenstein summarised the case against DIP as follows: 'although some cases of SRIF have, in the past, been included under the rubric of DIP, SRIF should be separated from that entity because it differs pathologically and also because it is not a type of idiopathic interstitial pneumonia. Furthermore, recognition of SRIF as a specific entity suggests that the time may have come to eliminate DIP from interstitial lung disease terminology altogether. DIP is a misnomer, and the term has been applied indiscriminately and incorrectly to several unrelated entities when they occur in smokers, including UIP, NSIP and LCH, for example. Intra-alveolar macrophage accumulation, although often a striking finding in those conditions as in SRIF, simply reflects the fact that the patient is a cigarette smoker, and it is unrelated to the underlying disease'.

## DIP IS CLASSIFIED AS A 'SMOKING-RELATED IDIOPATHIC INTERSTITIAL PNEUMONIA', AN OXYMORON

In 2020, it is widely accepted that most cases of DIP occur in smokers. The proportion of smokers in most series of DIP is greater than 85% (table 2); a recent review puts this estimate at 81%.[21] When Liebow *et al* coined the term DIP, the concept of smoking-related interstitial lung disease did not exist. In fact, key entities linking smoking to parenchymal lung disease were only described later, including 'respiratory bronchiolitis' by Niewoehner *et al* in 1974,[22] and 'respiratory bronchiolitis causing interstitial lung disease' (RBILD) by Myers *et al* in 1987.[23] The obvious overlap between these entities and DIP was noted by several observers—starting with Yousem *et al* in 1989[10]—leading to the concept of smoking-related interstitial lung disease.[16 24–26] Currently, this concept is widely accepted, and the extensive overlap between DIP and RBILD is well-recognised.[27] Hence, it is puzzling that DIP continues to be classified as a 'smoking-related *idiopathic* interstitial pneumonia',[17] an oxymoron that has caused considerable confusion over the years.[28 29] We hope the reader will agree that a disease caused by cigarette smoking is not idiopathic. Imagine a physician telling a patient that they have been diagnosed with DIP. If the patient were to ask 'what causes this disease, doctor?', the physician might reasonably respond 'smoking cigarettes'. But if the patient were to read about DIP and find that it is classified as 'idiopathic' and that idiopathic means 'of unknown cause', would this make sense to him? Would he believe that his doctor is correct when she says that his lung problems are related to smoking? Would he quit smoking for a disease that experts have deemed 'idiopathic'? To those who respond that DIP in smokers is caused by smoking, and rare cases of DIP in never-smokers are idiopathic, we would suggest that the time has come to explicitly label the former as 'smoking-related' and separate them clearly from the latter. While doing this, we must discard the outmoded descriptor 'desquamative', which is incorrect in both settings.

The occasional occurrence of DIP in never-smokers is an enduring source of confusion. Why does RBILD occur almost exclusively in smokers while DIP can occur in never-smokers? The explanation lies in the way these entities are defined. The definition of RBILD mandates the presence of respiratory bronchiolitis on histology,[22] which in turn rests on the presence of lightly pigmented macrophages within airspaces, a fairly reliable marker of smoking status.[30] Since RBILD is defined more stringently than DIP—taking macrophage morphology into account—it has a virtually perfect association with cigarette smoking. On the contrary, since DIP does not take macrophage morphology into account—allowing any type of macrophage as long as 'most' alveoli are filled—it is a hodgepodge of smoking-related diseases and examples of macrophage accumulation in never-smokers in diverse, etiologically unrelated settings.[21]

## IS DIP IN SMOKERS RESPONSIVE TO CORTICOSTEROIDS?

One argument for retaining the term DIP is that—unlike RBILD—it is corticosteroid responsive. The 2002 ATS/ERS consensus document states 'most patients improve with smoking cessation and corticosteroids'.[7] But what is the evidence to support this assertion?

Table 2 summarises the literature on this issue. There has never been a randomised controlled trial of corticosteroids in DIP (let alone smoking-related DIP), so the data on this question are without exception anecdotal. Even if we accept scattered case reports claiming responses to corticosteroids in never-smokers with DIP, this still leaves the larger group of smoking-related DIP.

The sole study cited by the 2002 ATS/ERS document as a reference for responsiveness of DIP to corticosteroids dates back to 1978, a testament to the absence of modern literature on this question.[9] Like Liebow's original series, the Carrington study is from the pre-CT era, and even a cursory review of this paper shows that the entity labelled as DIP by Carrington *et al* was a far more heterogeneous entity than candidates for this diagnosis in 2020. Some patients in Carrington's series (12.5%) had collagen vascular disease, and 12.5% even showed honeycombing on chest X-rays! Carrington *et al* state: 'Almost two thirds of those with DIP improved as compared with only three with UIP'. 'The patients with DIP who were treated and improved fell into two groups. One group, including the acutely and most seriously ill, responded dramatically to a long course of corticosteroids and

**Table 2** DIP, smoking status and response to corticosteroids

| Reference | Year | Number of patients with DIP | Smoking status | Treatment with corticosteroids and follow-up |
|---|---|---|---|---|
| Liebow *et al*[1] | 1965 | 18 | Not mentioned | Most patients received steroid therapy. Two became free of dyspnoea, two showed 'marked clinical improvement' (in one, withdrawal of steroids was associated with 'distressing increase in dyspnoea'), three showed 'less spectacular clinical improvement' (with no striking change in imaging in two of these), three showed 'ultimate stabilisation'. |
| Gaensler *et al*[8] | 1966 | 12 | Not mentioned | Six patients were given corticosteroids. One died after the first visit. Five showed '+++improvement'. One patient with no therapy was well 10 years later, another was 'entirely unchanged' without therapy 10 years later. |
| Carrington *et al*[9] | 1978 | 40 | 36 of 40 (90%) were smokers | See text for detailed description. |
| Yousem *et al*[10] | 1989 | 36 | 30 of 33 (91%) were smokers | Most were treated with corticosteroids. Of 25 with follow-up, 14 improved, 3 were stable and 8 were worse or died as a consequence of progressive fibrosis despite such therapy. |
| Hartman *et al*[11] | 1993 | 22 | Not mentioned | No data on corticosteroid therapy. |
| Hartman *et al*[12] | 1996 | 11 | Not mentioned | No data on corticosteroid therapy. On follow-up, parenchymal abnormalities decreased (6), or showed no interval change (3), or increased (2). |
| Heyneman *et al*[13] | 1999 | 16 | 12 of 14 (86%) were smokers | No data on corticosteroid therapy. No follow-up provided. |
| Travis *et al*[14] | 2000 | 16 | 14 of 14 (100%) were smokers | No data on corticosteroid therapy. 100% 10-year survival. No respiratory deaths. |
| Craig *et al*[15] | 2004 | 20 | 12 of 20 (60%) were smokers | No data on corticosteroid therapy. All patients for whom follow-up was available survived. |
| Ryu *et al*[16] | 2005 | 23 | 20 of 23 (87%) were smokers | 21 patients with DIP and 11 with RBILD underwent a trial of corticosteroid therapy. Symptomatic improvement was noted in 5 patients with DIP (24%) and 6 with RBILD (55%). Objective improvements were seen in 7 (33%) with DIP and 7 (64%) with RBILD. However, these positive responses tended to be transient with a not uncommon worsening of their condition back to baseline values seen (ie, DIP, 3 patients; RBILD, 2 patients) with tapering and discontinuation of prednisone treatment. This regression back to the baseline status occurred even in the absence of smoking (DIP, 2 patients; RBILD, 2 patients). |

*Articles listed in this table are the 10 most cited publications on DIP as of July 18, 2020 (Google Scholar).
DIP, desquamative interstitial pneumonia; RBILD, respiratory bronchiolitis-interstitial lung disease.

has remained well since. The other group required maintenance therapy and usually had functional and radiographic residua. Four patients with DIP progressed relentlessly in spite of therapy, and death was due to cardiopulmonary failure or fibrothorax in three'. Again, we emphasise that this description of acutely and seriously ill patients responding to corticosteroids does not fit with the modern concept of smoking-related DIP, in which most patients have an indolent clinical course and an excellent long-term prognosis.[14 16]

If one were to accept the argument that randomised controlled trials of corticosteroid therapy in smoking-related DIP will never be feasible and that anecdotal reports should suffice, it is not unreasonable to demand—at a minimum—that such reports use modern histologic criteria for diagnosis of DIP, document smoking status, illustrate the histologic findings and radiologic responses to therapy, and document which aspects of the clinical picture improved with corticosteroid therapy. The reader will find that—with the exception of the 2005 study by Ryu *et al*—not a single report in the literature meets these modest expectations (table 2). Even in the Ryu study, responses to corticosteroids were seen only in a minority of smokers with DIP (one-third or less), were transient (the few patients who responded regressed to baseline after corticosteroids were tapered) and occurred in RBILD as well as DIP. In fact, contrary to current dogma, objective responses were more frequent in RBILD (64%) than DIP (33%). Many of these patients also stopped smoking, making it difficult to determine whether improvements were attributable to smoking cessation or corticosteroids. We remain unconvinced that responsiveness to corticosteroids is a characteristic feature of smoking-related DIP, or that it supports the separation of DIP from RBILD, or justifies retention of this inaccurate term.

## OTHER PROBLEMS WITH CURRENT TERMINOLOGY OF SMOKING-RELATED LUNG ABNORMALITIES

As pointed out by Franks and Galvin,[31] some smoking-related abnormalities are not interstitial at a histologic level but consist entirely of collections of pigmented macrophages within airspaces. Therefore, one could argue that 'smoking-related interstitial lung disease' is inaccurate as an umbrella term because it does not apply to pure airspace macrophage accumulation without interstitial thickening. We also agree with Konopka and Myers[27] that the current mishmash of terminologies for smoking-related lung disease is confusing and suffers from a high degree of overlap. DIP is not the only problematic term in the realm of smoking-related lung abnormalities. 'Respiratory bronchiolitis' also creates confusion because the hallmark of this entity—pigmented airspace macrophages—is not restricted to respiratory bronchioles and does not require a true 'itis' (chronic inflammation involving lymphocytes or plasma cells).[30] As with other outdated terms, this one also has historical roots,[23] was created to support a hypothesis that has outlived its utility and is

**Table 3** Suggested terminology in pathology reports of smoking-related lung abnormalities

| Findings | Current terminology | Smoking status known to pathologist | Smoking status not known to pathologist |
|---|---|---|---|
| Pigmented airspace macrophages* in respiratory bronchiole and adjacent alveoli | RB | Pigmented airspace macrophages (smoking-related)* | Pigmented airspace macrophages* |
| Pigmented airspace macrophages within ANY alveoli (airspaces) | Unclear | Pigmented airspace macrophages (smoking-related) | Pigmented airspace macrophages |
| Pigmented airspace macrophages in 'most' alveoli | DIP | Pigmented airspace macrophages (smoking-related) | Pigmented airspace macrophages |
| Emphysema+any number of pigmented airspace macrophages+ropy alveolar septal collagen | DIP, SRIF, RBILD, emphysema, NSIP | SRIF | SRIF† |
| Sheets of Langerhans cells forming lung nodules | Pulmonary Langerhans cell histiocytosis | Pulmonary Langerhans cell histiocytosis (smoking-related) | Pulmonary Langerhans cell histiocytosis (smoking-related)† |
| Numerous macrophages within 'most' alveoli, non-pigmented | DIP | Numerous intra-alveolar macrophages | Numerous intra-alveolar macrophages |

*In this table, the description 'pigmented airspace macrophages' assumes that the macrophages are not hemosiderin-laden (coarsely granular), a distinction that is straightforward in most cases.
†The qualifier smoking-related could be applied in these situations even if the pathologist does not have access to smoking status if numerous pigmented macrophages or SRIF are present in the background lung.
DIP, desquamative interstitial pneumonia; NSIP, non-specific interstitial pneumonia; RB, respiratory bronchiolitis; RBILD, respiratory bronchiolitis-interstitial lung disease; SRIF, smoking-related interstitial fibrosis.

discordant with the true histologic picture seen under the microscope. Perhaps the biggest problem with current terminology of smoking-related lung abnormalities is that none of the terms in use—RB, RBILD, DIP—clearly implicate smoking in the aetiology of the changes. If one contrasts this ambiguous nomenclature to terms such as 'asbestosis', 'silicosis', 'coal-workers' pneumoconiosis', 'talc granulomatosis',[32] 'hot tub lung'[32] and 'e-cigarette or vaping product use-associated lung injury',[33] one wonders why pulmonologists, radiologists and pathologists are willing to explicitly name other agents that cause lung injury in their diagnoses but hesitate to do so when it comes to smoking, arguably more dangerous and far more common.

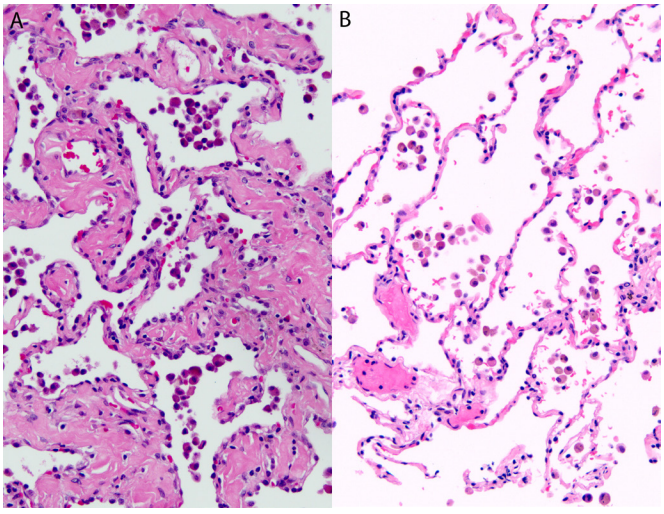


**Figure 3** Terminology of smoking-related lung abnormalities. (A) The ropy eosinophilic paucicellular alveolar septal fibrosis seen here is diagnostic of smoking-related interstitial fibrosis (SRIF), regardless of the number and distribution of intra-alveolar macrophages. (B) This field features pigmented airspace macrophages without interstitial abnormalities. Such cases neither meet criteria for SRIF nor for desquamative interstitial pneumonia (DIP). Respiratory bronchiolitis is also an unsuitable term in this situation, as the cells are located within alveoli, not respiratory bronchioles. We propose using the term 'pigmented airspace macrophages' if no history is available or 'pigmented airspace macrophages, smoking-related' if the history of smoking is available to the pathologist.

## THE WAY FORWARD: CONCEPTUALLY ACCURATE TERMINOLOGY OF SMOKING-RELATED LUNG ABNORMALITIES

What terminology would we use if we were to discard the term DIP altogether? In table 3, we propose terminology that reflects our current understanding of the lung pathology of smoking and explicitly labels smoking-related lung abnormalities as such. The proposed terminology is easy to use on the basis of histologic features alone (figure 3) and can be refined if the patient's smoking status is known to the pathologist. Although the importance of a history of cigarette smoking in classifying lung disease as 'smoking-related' is obvious, this terminology demonstrates how histology can play a role in deciding whether a given case of parenchymal lung disease is truly smoking-related. Specifically, airspace macrophages with finely granular brown pigment and ropy alveolar septal collagen are well-recognised histologic manifestations of exposure to cigarette smoke, and their identification helps to label a case as smoking-related.[19 20 30] The recently described entity SRIF, being defined on the basis of a constellation of three smoking-related features (emphysema, pigmented airspace macrophages, ropy alveolar septal collagen), is highly specific for smoking and can be diagnosed as smoking-related even in the absence of knowledge of smoking status.[34] Similarly, the vast majority of cases of pulmonary Langerhans cell histiocytosis occur in smokers and can be reliably labelled as smoking-related even without a history of smoking, especially when numerous lightly pigmented airspace macrophages or SRIF are present in the background lung.

Using an analogy from the marine world, figure 4 summarises the transition from a conceptually inaccurate mixed bag to better defined conceptually accurate entities.

## WHAT TERMINOLOGY SHOULD BE USED FOR SMOKING-RELATED LUNG ABNORMALITIES BY CLINICIANS?

This issue obviously requires input from pulmonologists and radiologists, since any change in clinical terminology will need buy-in from the professionals who will use these terms. Given the overlap between various smoking-related histologic findings

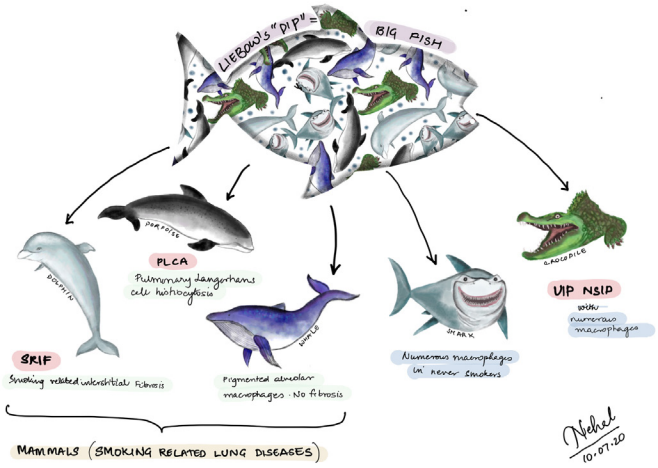


**Figure 4** Cartoon illustrating the problems associated with the term DIP and a possible solution. In this illustration, the term 'big fish' is analogous to DIP. It is clearly a misnomer and a mixed bag that groups together various unrelated animals (three mammals, a shark and a crocodile) based on the erroneous concept that all large swimming animals are 'big fish'. In the bottom half of the figure, we illustrate how the term 'big fish' could be discarded and replaced with modern terms. One of the 'big fish', for example, would be termed a dolphin (SRIF), another would be termed a porpoise (pulmonary Langerhans cell histiocytosis) and the third would be called a whale (pigmented airspace macrophages without fibrosis). The three mammals in the modern grouping are analogous to smoking-related lung abnormalities. The shark corresponds to macrophage accumulations in never-smokers. The crocodile represents other interstitial lung diseases that occasionally feature numerous macrophages. DIP, desquamative interstitial pneumonia; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; Illustrator: Dr Nehal Rahate.

and the fact that several smoking-related histologic abnormalities (pigmented airspace macrophages, 'RB', 'DIP', SRIF) can be present in the same biopsy, we suggest that an umbrella term such as 'smoking-related parenchymal lung disease' could be used to categorise most cases that would have been previously labelled RB, RBILD or DIP or that are currently labelled SRIF (ie, all the categories in table 3). We favour 'smoking-related *parenchymal* lung disease' over 'smoking-related *interstitial* lung disease' because the former term is accurate whether or not interstitial involvement is present histologically. Since many patients with these histologic abnormalities are asymptomatic, it is reasonable that the decision of whether to consider these findings incidental or to label them as a 'disease' should be based on clinical and imaging features.

## THERE IS PRECEDENT FOR DISCARDING MIXED BAG TERMINOLOGY

In 2011, the term bronchioloalveolar carcinoma was discarded for many of the same reasons that we have described above for DIP.[35] The term was poorly defined and was a mixed bag of good prognosis and poor prognosis entities with different pathologic features. The solution to this problem was not simply to rename bronchioloalveolar carcinoma but to discard the term entirely and create a modern framework where entities were named based on current concepts. We hope the same approach can be taken with DIP.

**Box 1 5 Reasons to discard DIP**

**Misnomer**
The intra-alveolar cells in DIP are macrophages, not desquamated pneumocytes.

**Mixed bag**
Lumps together smoking-related lung abnormalities with diseases caused by numerous other etiologies in never-smokers.

**Misleading**
Underemphasises the fact that smoking is clearly the cause of a subset of cases of parenchymal lung disease; the entity is classified as 'smoking-related idiopathic interstitial pneumonia', an oxymoron.

**Poorly defined**
Diagnostic criteria are vague and do not take macrophage morphology into account, creating overlap with many other entities.

**Outdated**
Modern entities replace most cases that would have been diagnosed as DIP in the 1960s and 1970s, including UIP, NSIP, PLCH, RBILD and SRIF.

DIP, desquamative interstitial pneumonia; NSIP, non-specific interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; RBILD, respiratory bronchiolitis interstitial lung disease; SRIF, smoking-related interstitial fibrosis; UIP, usual interstitial pneumonia.

## CONCLUSION

This review outlines five reasons to discard the term DIP (box 1). DIP is an outdated misnomer that obfuscates the role of smoking in the aetiology of parenchymal lung abnormalities. More than 80% of cases currently classified as DIP are caused by smoking (ie, are not idiopathic) and feature pigmented airspace macrophages or ropy alveolar septal collagen, well-known histologic manifestations of smoking. We propose terminology to diagnose such cases explicitly as being 'smoking-related' and hope that this will help patients recognise that smoking is deleterious to their health. The pathology community—which has long been instrumental in the recognition of the relationship between smoking and lung disease—should no longer muddy the waters.

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