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## Inflammation-associated remodelling and fibrosis in the lung – a process and an end point

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### Summary

Fibrosis by common usage in the pathological and clinical literature is the end result of a healing process and synonymous with scarring. We would argue that its use to describe a dynamic series of events which may be reversible is unhelpful and that the term 'lung remodelling' is a better description for this process as it reflects changes in tissue organization that may or may not progress to 'fibrosis' as a final fixed point. Resolution, through reversal of active lung remodelling, by therapeutic intervention is possible providing the alveolar architecture remains intact. If the lung architecture is lost then healing by permanent fibrosis with loss of organ function is inevitable.

**Key words:** fibrosis, inflammation, injury, lung, remodelling

### Introduction

To pathologists and chest physicians 'What is pulmonary fibrosis?' may seem a straightforward question. Pulmonary fibrosis is the presence of scarring in the alveolar compartment of the lung where gas exchange occurs. This may be localized, for example following tuberculous infection (Dheda *et al.* 2005), or more diffuse such as in patients with interstitial lung disease (ILD) (Leslie 2005). Fibrosis can involve other areas of the lung as well, such as the bronchi (Vignola *et al.* 2000) and the pleura (Jantz & Antony 2006), but in general the unqualified term pulmonary fibrosis

usually indicates alveolar pathology. The presence of symptoms will depend on the extent of the process and whether it is static or progressive. Typically when lung fibrosis is extensive and diffuse it results in a restrictive ventilatory defect with hypoxia and in some cases pulmonary hypertension, cor pulmonale and death (Zisman *et al.* 2005). More localized areas of fibrosis may be associated with distortion of the lung anatomy and secondary conditions such as bronchiectasis and chronic respiratory infection (Dheda *et al.* 2005).

In more recent years the terms 'lung remodelling' and 'fibrosis' have been used, at times almost interchangeably, to

describe a range of processes in the lung where the architecture is altered up to, and including, the formation of permanent, fixed scar tissue. Some authors, however, suggest that 'fibrosis' is, or could be reversible (Marshall *et al.* 1998; Bellingan 2002; Lawson *et al.* 2005). This clearly is a different view of 'fibrosis' from the traditional clinico-pathological understanding of the term. This article aims, in the context of human lung disease, at considering various scenarios where the lung's response to inflammation is associated with different outcomes (Figure 1). We hope to convince the reader that the use of the term 'fibrosis' in the context of inflammation-associated lung injury should define one possible outcome of the repair process which is characterized by the replacement of pre-existing alveolar structure by permanent fixed scar tissue. As such it should be regarded as synonymous with scar tissue. We suggest that the term 'lung remodelling' should be used as a descriptor for the dynamic repair multi-step process that occurs in the lung following inflammatory injury. This process may either be reversible with resolution and return to the pre-existing structure, or progress to the point of irreversible fixed fibrosis.

In order to understand what is occurring at the tissue level in the lung and what factors might dictate whether or not an inflammatory process is likely to lead to permanent fixed fibrosis or a more labile potentially reversible form of remodelling it is useful to look at different patterns of lung injury and outcome. Before this, however, it is necessary to consider the structure of the normal alveoli (reviewed by Hasleton & Curry 1996; Travis *et al.* 2002a). These are arranged in functional groups termed 'acinar units' which are all supplied by a single respiratory bronchiole and resemble a bunch of grapes at the end of a stalk. The alveoli are predominantly lined by thin attenuated type I epithelial cells which sit on a basement membrane. Within the alveolar wall are capillary loops lined by endothelial cells. They too have a basement membrane that is extensively fused to the basement membrane of the alveolar epithelial cells. Also within the alveolar wall is a supporting network of collagen and elastic fibres that in effect forms the supporting skeleton of the lung with scattered resident fibroblasts and tissue macrophages.

### Acute inflammation and alveolar injury

It is well established that the lung can be subjected to intense inflammatory reactions and return to its pre-inflammatory state. Bacterial pneumonia with organisms such as *Streptococcus pneumoniae* cause an intense acute inflammatory process in the lung with the alveolar spaces becoming filled with neutrophils admixed with a fibrinous exudate

(reviewed by Macfarlane 1995; Travis *et al.* 2002b). Providing the patient survives the acute septic episode the lung returns to its previous state with no significant fibrosis or alteration in the pre-existing architecture (Macfarlane 1995). We would term this type of repair 'resolution'.

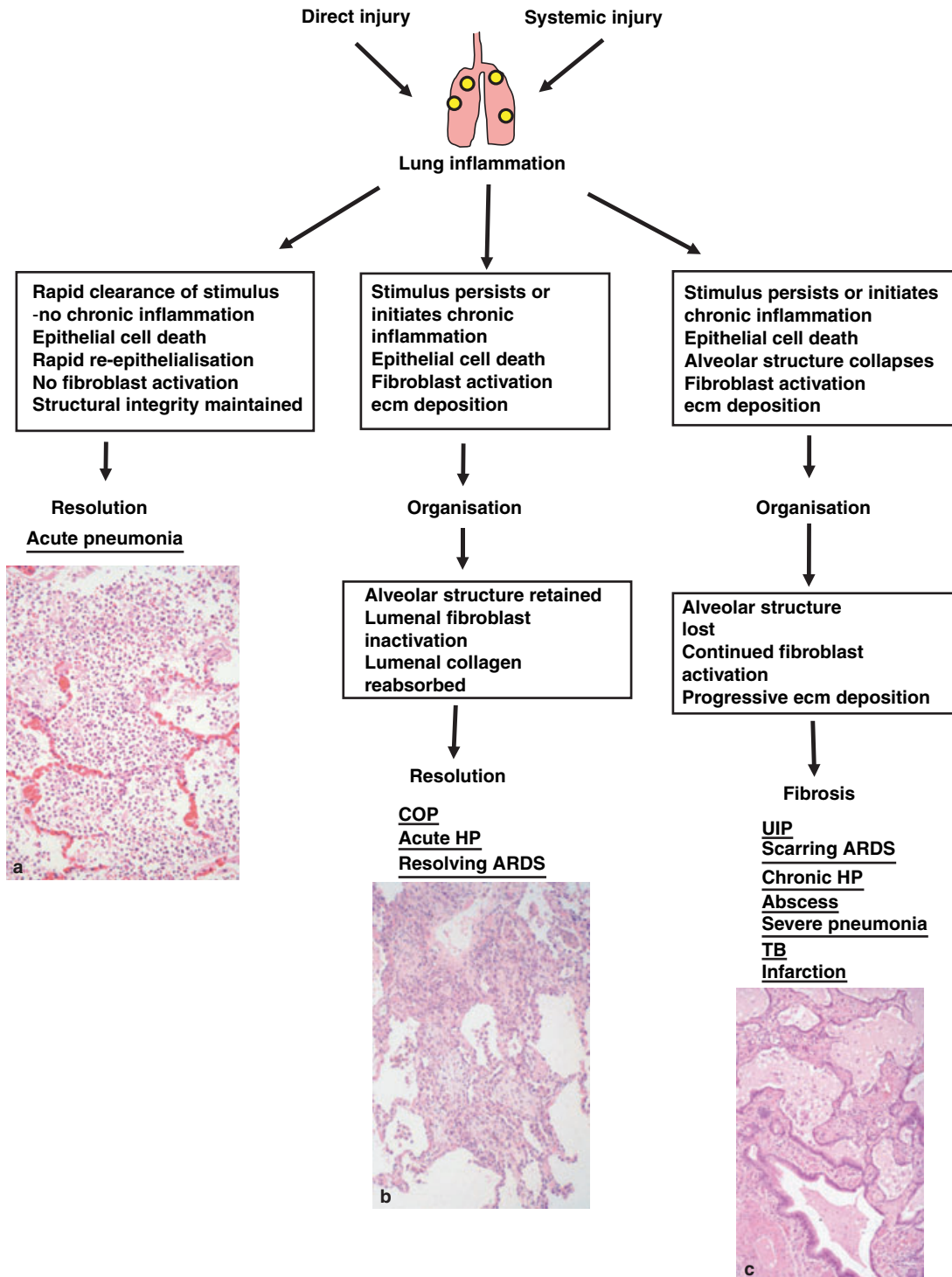
Animal models indicate that there is damage to the alveolar epithelium in acute pneumonia (McElroy *et al.* 1995) and a key factor in allowing the desirable outcome of resolution in such a setting is that the triggering agents, in this case the bacteria, are rapidly cleared (Clegg *et al.* 2005). Ultrastructural studies in animal models show that the basement membrane is retained and undamaged (McElroy *et al.* 1995) allowing rapid re-epithelialization to occur (Clegg *et al.* 2005) and we know from studies in animals that this inhibits the proliferation of mesenchymal cells (Adamson *et al.* 1988, 1990).

We would suggest therefore that the desirable outcome of resolution in acute pneumococcal pneumonia occurs because the inflammatory reaction is very limited in duration and there is no chronic inflammation or ongoing lung injury. In contrast, infections with organisms associated with a sustained chronic inflammation, such as tuberculosis, where there is ongoing tissue injury are not associated with resolution but result in remodelling and fibrosis (Dheda *et al.* 2005).

### Chronic inflammation and alveolar injury

Chronic inflammation by definition is associated with, or will result in, tissue damage and inevitably this is associated with attempts by the tissue to repair itself (Kumar *et al.* 2005a). In most instances, especially if the chronic inflammatory process is ongoing the tissue damage and repair will be seen occurring in tandem. The traditional pathological perspective is that scarring, or fibrosis, is the end result of damage in a tissue not capable of regeneration and is fixed with no possibility of a return to the pre-existing structure (Kumar *et al.* 2005b). Chronic inflammation in the alveolar compartment of the lung can be associated with a wide range of aetiologies: infection (bacterial, mycobacterial, viral and atypical agents such as mycoplasma) (Travis *et al.* 2002b), systemic immunological processes (such as systemic sclerosis) (Nicholson *et al.* 2002a; Crestani 2005), allergic processes (such as hypersensitivity pneumonitis) (Mohr 2004), toxins (including drugs) (Kehrer & Kocew 1985; Camus *et al.* 2004), dusts (Glazer & Newman 2004) and radiation (Camus *et al.* 2004), although in many clinical situations the aetiology remains unknown (Leslie 2005).

The lung's response to such a diverse range of potentially damaging agents is relatively limited and as such similar



**Figure 1** Schematic representation of possible outcomes following inflammation-associated lung injury with clinical examples. (a) Photomicrograph of acute bacterial pneumonia showing alveolar filling by neutrophils and fibrin. (b) Photomicrograph of cryptogenic organizing pneumonia showing the nodular buds of organizing exudates in airspaces. (c) Photomicrograph of usual interstitial pneumonitis showing extensive fibrosis with loss of the pre-existing alveolar architecture. ecm, extracellular matrix; COP, cryptogenic organizing pneumonia; HP, hypersensitivity pneumonitis; ARDS, adult respiratory distress syndrome; UIP, usual interstitial pneumonitis; TB, tuberculosis.

patterns of response may be seen clinically and pathologically in patients with differing aetiologies (Nicholson 2002b). It is also important to appreciate that while an external stimulus may trigger chronic inflammation, once this is initiated the inflammatory process itself may result in further 'by-stander' tissue damage. An example of this would be the florid type IV hypersensitivity reaction that characterizes post primary tuberculous infection (Dheda *et al.* 2005).

Ideally tissue injury would be associated with a healing process that resulted in restoration of the pre-existing structure. While this may occur in some tissues such as bone (Gerstenfeld *et al.* 2003) and liver (Taub 2004) most tissues, including the lung, are not capable of organ regeneration and tissue damage leads to repair characterized by the formation of scar tissue (Kumar *et al.* 2005b).

Tissue injury at the alveolar level associated with chronic inflammation could have a variety of potential outcomes. There could be injury and loss of the alveolar epithelial cells, damage or loss of the basement membrane, endothelial cell loss/injury and at the most severe end of the spectrum a complete collapse of the collagen and elastic support framework of the alveoli. The exact ultra-structural patterns of injury may depend on the nature of the insult. Systemically mediated lung injury may be more associated with endothelial injury (Fujita *et al.* 1998), although necrosis appears to be unusual (Hasleton 1996; Menezes *et al.* 2005). Direct pulmonary insults may show more prominent epithelial injury (Menezes *et al.* 2005). The common effect, however, would appear to be that a protein-rich exudate leaks out into the alveolar space and this is associated with migration of myofibroblasts from the interstitium resulting in the formation of organizing immature collagenous tissue (Chau *et al.* 2005).

If the stimulus for the chronic inflammatory process is removed and the basement membrane, collagen and elastic structure of the alveolus remains intact re-epithelialization could still theoretically occur in tandem with removal of the immature intra-luminal collagenous tissue in the lumen by the fibrinolytic system (Idell 2003) and apoptosis of the myofibroblasts (Kuwano *et al.* 2004) (resolution). Alternatively, either because of persistence of the chronic inflammatory process or the severity of the tissue damage, there could be loss of tissue integrity and alveolar collapse or even complete destruction.

This is clearly seen in patients with localized destructive processes such as necrotizing pneumonias (Travis *et al.* 2002b), type IV hypersensitivity reactions with mycobacterial infection (Dheda *et al.* 2005) and pulmonary infarcts (Corrin 2000) where by definition there is extensive loss of tissue. This situation by necessity precludes any return to the

pre-existing tissue architecture. There would be organization of the immature fibrinous exudate with neovascularization, proliferation of myofibroblasts, deposition of increasing amounts of extracellular matrix components and the development of scarring (Kumar *et al.* 2005b) which, depending on the pattern of injury, could be localized or diffuse and, in the case of continuing chronic inflammation, progressive (fibrosis).

## Remodelling in interstitial lung disease

The ILDs represent a group of lung conditions characterized by inflammation and remodelling of the alveolar compartment of the lung (Leslie 2005) that help to illustrate some of these potential consequences of inflammatory-associated lung injury. In most instances the aetiology of this group of conditions is unclear but it is apparent that a wide range of triggering events appear to give rise to a very limited and rather stereotyped pattern of reaction in the tissue (Nicholson 2002b). At least in the case of idiopathic ILD, clinical progress and prognosis is closely related to the histological pattern (Monaghan *et al.* 2004; Tansey *et al.* 2004). Examination of some of these patterns of lung disease provides some support for our hypothesis that resolution of a chronic inflammatory-associated lung injury without permanent fibrosis may be dependent on the nature of injury to the lung structure induced either by the injurious agent itself or the chronic inflammation.

Idiopathic pulmonary fibrosis (IPF) is the commonest clinical form of ILD. The typical pattern of lung pathology associated with this is usual interstitial pneumonia (UIP). IPF has a very poor prognosis and no pharmacological intervention has been shown to alter this (Walter *et al.* 2006). The pathogenesis is unclear but it appears associated with an acute on chronic interstitial inflammatory process in the distal lung (Campbell *et al.* 1985; Leslie 2005) with evidence of type I alveolar epithelial cell injury (Corrin *et al.* 1985). This is associated with foci of organizing exudates, identifiable as 'fibroblastic foci', composed of myofibroblasts and rather loose oedematous extracellular matrix (Nicholson 2002b). These fibroblastic foci are believed to be the sites of active remodelling with deposition of matrix proteins (Wallace *et al.* 1995). Morphological studies suggest that these represent foci of epithelial injury and subsequent alveolar collapse (Myers & Katzenstein 1988a). Although this is less gross than in the examples of necrotizing pneumonia, mycobacterial infection or infarction discussed above, the ultimate effect is the same. The loss of the normal alveolar structure precludes resolution and commits the lung to healing by fibrosis. From what we have suggested before, given that UIP is

characterized by ongoing inflammation, injury and architectural collapse, it would be unsurprising that the condition is progressive and associated with extensive lung scarring leading to the clinical features that a clinician would recognize as pulmonary fibrosis.

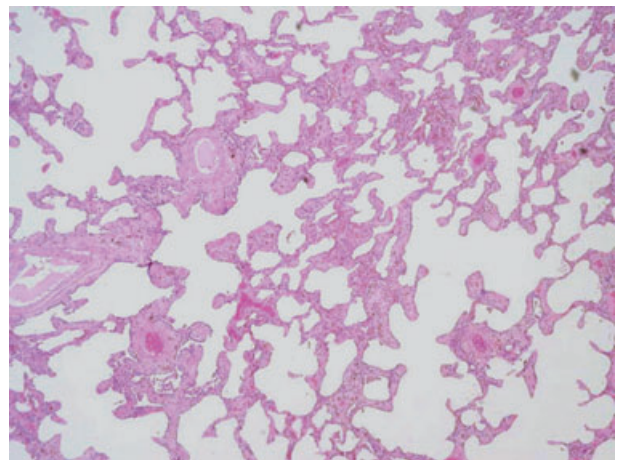
In contrast to UIP, cryptogenic organizing pneumonia (COP) is another pattern of ILD with a wide range of potential aetiologies characterized by interstitial inflammation and the formation of intraluminal buds of organizing exudates composed of myofibroblasts and loose myxoid stroma (Nicholson 2002b; Cordier 2004). Morphologically the appearance of these buds is not dissimilar to that of the organizing fibroblastic foci described above in UIP. Despite this, the clinical progress of the disease is completely different and resolution is usually seen with steroid therapy. In the majority of cases the lung returns to its previous architecture rather than becoming fibrotic, although in a minority of cases this may occur (Schlessinger & Koss 2005). At the ultrastructural level in COP there is alveolar epithelial injury but the alveolar structure appears to be retained rather than collapsing (Myers & Katzenstein 1988b). This preservation of the alveolar architecture may therefore account for the ability of this pattern of injury to undergo resolution rather than fibrosis.

Given the hypothesis we are putting forward it would seem possible that a chronic inflammatory condition could result in a pattern of lung injury where the alveolar architecture was retained and therefore potentially capable of resolution. If the lung injury then became more severe it could result in either localized or more diffuse damage to the alveolar architecture of the lung resulting in areas where healing by fibrosis becomes inevitable. This may be the case in diffuse alveolar damage syndrome, a pattern of lung injury associated with the adult respiratory distress syndrome (ARDS) (Nicholson 2002b).

The ARDS can result from direct lung injury (for example with pneumonia, inhalation of gases or aspiration) or indirect injury (for example from systemic sepsis or in association with pancreatitis or extrapulmonary trauma) (Hudson *et al.* 1995). The early histological features are of oedema with leakage of fibrin-rich fluid into the alveolar spaces. After 48–72 h this material starts to form immature plugs of organizing exudates in the airspaces, termed the fibro-proliferative phase, with myofibroblasts and loose immature oedematous stroma (Wallace & Donnelly 2002). Many patients develop extensive pulmonary fibrosis with replacement of the normal alveolar architecture by collagenous tissue (Bellingan 2002). Some patients who survive may be left with evidence of variable pulmonary fibrosis but a small number appear to develop severe ARDS that resolves

(Bellingan 2002). The mechanisms regulating the outcome of the fibro-proliferative phase are unclear but we would suggest that collapse of the alveolar structure of the lung would be one event whereby fibrosis, rather than resolution, becomes an inevitable outcome. Some ultrastructural studies have certainly indicated that alveolar collapse does occur in some patients with ARDS (Hoelz *et al.* 2001). A similar mechanism might be applicable in other conditions such as hypersensitivity pneumonitis, where acute exposures to the triggering agent may not result in scarring whereas chronic exposures may lead to extensive pulmonary fibrosis (Travis *et al.* 2002c).

Up until this point we have argued that in situations where the structural integrity of the tissue is retained there is a capacity for the tissue to return to its pre-existing architecture. However, there are conditions where the alveolar architecture appears to be largely retained but there is evidence of progressive scarring. As discussed above most patients with idiopathic ILD have a histological pattern of lung injury that we recognize as UIP. A group of patients with idiopathic ILD have, however, been recognized in the last few years to have a different pattern of disease termed non-specific interstitial pneumonia (NSIP) (Katzenstein & Myers 2000). Histologically this is characterized by a relatively diffuse and even inflammatory or fibrous expansion of the alveolar walls but with the architecture retained (Figure 2). The process is described as temporally homogeneous and areas of immature fibroblastic tissue are not identifiable (Katzenstein & Myers 2000; Nicholson 2002b). These patients in general have a better prognosis than those with



**Figure 2** Photomicrograph of a biopsy showing the typical even pattern with fibrous expansion of alveolar walls typical of non-specific interstitial pneumonia. No histological evidence of organizing intra-luminal exudates is identifiable (haematoxylin and eosin, original magnification  $\times 100$ ).

idiopathic UIP (Daniil *et al.* 1999). The pathogenesis of NSIP is uncertain but morphologically it appears that fibrous tissue is laid down progressively and uniformly on the pre-existing alveolar structures. There is typically marked type II alveolar epithelial cell proliferation but no histological features suggesting organizing exudates within the alveoli (Katzenstein & Myers 2000; Nicholson 2002b). One possible explanation could be that this is evidence of a true 'interstitial fibrosis' with the process being limited to within the alveolar walls rather than representing fibrosis created by organizing fibrinous material which has leaked into the airspaces as described above.

### Interpretation of results in animal models of lung fibrosis

Over the last 30 years or so a wide range of animal models have been developed to study the processes of chronic inflammation and repair in the lung. The majority of these, induced by, for example, bleomycin (Thrall & Scalise 1995) and silica (Lemaire 1995) are what can be termed toxic models that generate inflammation and lung damage.

Intra-tracheal bleomycin is perhaps the most widely used model for studying 'fibrosis' in the lung (Thrall & Scalise 1995; Chau *et al.* 2005). This model produces intense lung injury with an inflammatory infiltrate in the lung, leak of proteinaceous fluid into the airspaces and organization with the ultimate development of focal established fibrosis. This is principally seen around the airways and variably in the peripheral lung (Thrall & Scalise 1995; Chau *et al.* 2005). Studies appear to suggest that permanent fixed fibrous tissue becomes established between day 14 and 21 after exposure (Izbicki *et al.* 2002). This established fixed fibrosis is, however, much more localized than the inflammation/organization seen at earlier time points. Studies using interventions in such models may modulate lung injury and organization but not necessarily lung 'fibrosis', unless sufficiently late time points are included. This is not to suggest that these models cannot give us useful information on the regulatory process of lung injury but it could be misleading to suggest that they can show amelioration or prevention of 'lung fibrosis' unless appropriate studies at late time points are included after the remodelling process is finally complete.

### What are we aiming to treat – remodelling or fibrosis?

One of the current major objectives behind research into 'fibrotic' lung disease whether clinically or in animal models

is the search for new therapeutic strategies and pharmacological agents. Much of this is clearly aimed at modulating the remodelling that occurs with inflammation and injury in the lung. Such approaches could be thought of as either preventing the development of fibrosis by promoting complete resolution of the remodelling process or in the more common clinical situation preventing progression and the development of further fibrosis.

This inevitably raises the question over whether 'fibrosis' is reversible. It is at this point that the need for clear, unambiguous terminology becomes apparent. Do we mean 'preventing or reversing the dynamic remodelling fibro-proliferative/remodelling process' or actually 'replacing established fibrotic lung tissue with new functioning alveolated lung'? From the discussion above the first goal is potentially achievable by therapeutic intervention but the second would require extremely complex targeted tissue engineering to recreate alveoli whose structure has been lost and replaced by the fibrosis. Such potential confusion indicates the need for consistency and clarity in the terminology used by pathologists, physicians, radiologists and scientists working in the field, especially given the ready access that patients now have to the medical and scientific literature.

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