

# If it was good enough for Aristotle.....

Toby M Maher,<sup>1,2,3</sup> Athol U Wells<sup>1,2</sup>

'If you want to understand today you have to search yesterday' wrote the American novelist Pearl Buck, and such is the challenge facing those who hope to disentangle the pathogenesis of idiopathic pulmonary fibrosis (IPF). The disease is characterised by the insidious but progressive development of fibrosis that culminates in respiratory failure and death, usually within 5 years of diagnosis. Despite recent advances in pathogenetic understanding, IPF remains a disease in need of effective treatments.

Following the reclassification of the idiopathic interstitial pneumonias 10 years ago,<sup>1</sup> our understanding of the natural history of IPF has increased exponentially. Yet there remain lacunae in our knowledge of the disease: what does the earliest lesion of IPF look like and, even more importantly, what triggers its development and early progression? In most cases of IPF, extensive fibrosis is already established at the time of diagnosis. Much in the same way that cosmologists strive to infer the origins of the universe from modern-day movements of stars and planets, researchers hoping to understand the initiating events in pulmonary fibrosis have to do so by studying events that occur in established disease.

At a molecular level, IPF is characterised by the apparently unopposed activation of multiple profibrotic pathways involved in wound healing.<sup>2</sup> The purpose of the normal wound healing process is to restore tissue integrity, structure and function following injury. In early wound healing, tissue expansion is associated with migration to the site of injury of fibroblasts that then proliferate, transform into myofibroblasts and rapidly synthesise extracellular matrix.<sup>3</sup> In healthy individuals, the profibrotic phase of tissue repair then switches off and resorption of the

extracellular matrix, with fibroblast apoptosis and architectural remodelling of tissue, occurs. In IPF, in contrast, several strands of evidence point strongly to a pivotal role for repetitive alveolar epithelial injury, resulting in an imbalance between profibrotic and antifibrotic mediators.<sup>2-4</sup> Cigarette smoke, pollutants, dusts and infectious agents are all plausible causative factors for this imbalance, and epidemiological studies have thrown up other possible environmental triggers.<sup>5,6</sup> However, until relatively recently, the possible pathogenetic role of recurrent microaspiration from gastro-oesophageal reflux (GER) has been largely overlooked in IPF.

Large volume aspiration of gastric contents causes chemical pneumonitis that can progress to the development of acute lung injury and acute respiratory distress syndrome (ARDS).<sup>7</sup> In a rodent model of chronic gastric content aspiration, animals develop lymphocytic infiltrates, obliterative bronchiolitis and interstitial fibrosis.<sup>8</sup> These pulmonary changes are associated with increased levels of the profibrotic cytokines transforming growth factor  $\beta$  (TGF $\beta$ ) and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) in bronchoalveolar lavage fluid. In *in vitro* experiments using primary human airway epithelial cells, Perng *et al* demonstrated that exposure to bile salts resulted in increased epithelial cell expression of TGF $\beta$  and this, in turn, caused enhanced proliferation of fibroblasts grown in bile acid-exposed epithelial cell-conditioned culture media.<sup>9</sup> Clinical observations also lend some credence to the pathogenetic importance of GER in some patients. Linkage between GER, hiatus hernia and idiopathic fibrosing lung disease was first suggested 35 years ago.<sup>10</sup> More recently, Raghu and co-workers performed 24 h pH monitoring in 65 patients with IPF and showed that GER occurred in 87%, with proximal reflux to the throat in half of the cases. Further, they found that GER was often resistant to medical treatment.<sup>11</sup>

It would be tempting to design a definitive prospective study, in which symptoms and measures of GER are quantified, to establish that the presence and severity of reflux are indeed linked to the severity

of IPF. However, there is a poor symptomatic correlation with the severity and volume of GER that is found on oesophageal pH monitoring and this applies especially to IPF in which, among patients with significant acid reflux on oesophageal studies, only half report symptoms suggestive of GER.<sup>11</sup> The reproducibility of 'objective' measures of GER is not known, either in identifying GER or in quantifying its severity. More importantly, association is not synonymous with cause. Is there an increased incidence of GER in IPF because microaspiration of gastric contents is an important trigger or does increased GER simply reflect larger negative swings in intrathoracic pressure in IPF, as an inevitable consequence of reduced pulmonary compliance? Is GER merely a marker of more severe pulmonary fibrosis?

Perfect quantification of GER would not resolve this question. However, in *Thorax*, Tcherakian and colleagues report striking indirect evidence for the pathogenetic role of GER in a subgroup of patients with IPF.<sup>12</sup> The authors have explored the observation, hitherto dismissed as little more than a curiosity, that a minority of patients with IPF have marked asymmetry of their lung disease on high-resolution CT (HRCT). Careful characterisation of these patients has provided compelling indirect evidence that the microaspiration of gastric contents is a key trigger in some patients with IPF, and is of particular relevance to acute exacerbations of the disease. In this patient group (examined against a group of IPF 'control' patients with symmetrical disease on HRCT), there was a truly striking increase in the prevalence of acute exacerbations, seen in half of the cases, occurring in the more extensively involved lung and associated with a significant increase in reflux symptoms. Remarkably, there was a very strong concordance with the choice of sleeping position, with the more extensively involved lung being the dependent lung in 94% of interrogated patients able to state a preference.

The study was—shock, horror—a retrospective study and the authors are suitably contrite for any distress that this might have caused. Retrospective it might be, but the data provide indirect 'narrative' pathogenetic evidence which is more powerful, perhaps, than might be achievable by a prospective study, however carefully designed. Of course, it is essential that these findings should now be confirmed or refuted. However, without the ideas stimulated by this retrospective study, it is inconceivable that a suitable

<sup>1</sup>Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK; <sup>2</sup>National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, London, UK; <sup>3</sup>Centre for Respiratory Research, University College London, Rayne Institute, London, UK

**Correspondence to** Athol U Wells, Interstitial Lung Disease Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; athol.wells@rbht.nhs.uk

prospective evaluation would have been conceptualised.

In reality, this is usually the way. What ground-breaking thoughts have ever emerged from prospective studies? The large ideas have been distilled from observation—often quirky observation, at that—whether of the Newtonian apple, the Archimedean bath, the accidental contamination of culture dishes by *Penicillium* mould or the recognition of the pathogenetic role of *Helicobacter pylori* in peptic ulcer disease.<sup>13</sup> Great thinkers can draw inspiration from a grain of sand. The rest of us must refine the act of observation by the analysis of clinical databases and the construction of robust scoring systems. Often, an iterative approach is required. In a vigorous defence of the importance of careful clinical observation, Sir Keith Peters has argued that ‘the reality of much clinical research is that the starting point is a series of observations in which the astute clinical observer notices something exceptional’.<sup>14</sup> But the starting point is not, of itself, sufficient. The observation must then be explored further, with a sifting of available data, and a search for internal consistency in a larger sample, in order to distil a conclusion that makes sense and can be subjected to further evaluation. Allied to creative but disciplined thought, the ‘retrospective’ approach, amounting to a careful and critical study of available data, is the lifeblood of clinical science, without which progress cannot be made by properly focused prospective studies.

Yet, in the current climate, to describe a study as ‘retrospective’ is to damn it as second rate, without further thought. In the words of AJ Munro, ‘we have convinced ourselves that the talismanic words ‘randomised’ and ‘systematic’ are guarantees of scientific worth and that any activity to which the word ‘observation’ is attached is of dubious merit and that the adjective ‘mere’ should automatically be attached to it’.<sup>15</sup> By an act of prestidigitation, the confirmation of a hypothesis is exalted as the supreme part of the scientific process because it is prospective. Retrospective work is praised

faintly as a ‘hypothesis-forming exercise’, as though the disciplined distillation of a coherent hypothesis from observed data is something other than the heartbeat of the scientific process. Finding the right ideas is the hard part—the rest is procedural.

Certainly, the retrospective evaluation of databases is open to abuse, with chance findings emerging due to the promiscuous evaluation of multiple relationships. Scientific integrity is needed in order to address any question with rigour, but this is equally true of prospective studies—in which all kinds of abuses can and do occur. Bad work is bad work, and cheating is cheating, whether data are retrospective or prospective. The shoddy and purposeless evaluation of accumulated data for its own sake does not in any way diminish the critical importance of meticulous observation and thought in scientific progress. To dismiss retrospective evaluation in its entirety is to dismiss the act of observation itself.

In this regard, Tcherakian and colleagues have embraced the scientific precepts of the ancients. They take as their starting point the existence of an outlying patient group with asymmetric IPF. Their study amounts to careful observation, a comparison with a control group, the formulation of a hypothesis and the refining of that hypothesis with a key ancillary question in a subgroup of patients. As a result of this retrospective study, the likelihood that a definitive study of reflux treatment will be performed in IPF has probably risen significantly. Observe; compare; hypothesise: a fair summary of the essence of Aristotle. The Mrs Grundys of the research world would, it seems, prefer Aristotelian science without observation, comparison or the formulation of hypothesis. Long story short, this dismissive approach leaves us with nothing. As Parmenides once said, ‘nothing comes from nothing’.

**Competing interests** None.

**Provenance and peer review** Commissioned; not externally peer reviewed.

Published Online First 13 January 2011

*Thorax* 2011;66:183–184.

doi:10.1136/thx.2010.149096

## REFERENCES

1. **American Thoracic Society**, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277–304.
2. **Maher TM**, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? *Eur Respir J* 2007;30:835–9.
3. **Desmouliere A**, Chaponnier C, Gabbiani G. Tissue repair, contraction, and the myofibroblast. *Wound Repair Regen* 2005;13:7–12.
4. **Selman M**, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001;134:136–51.
5. **Hubbard R**. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. *Eur Respir J Suppl* 2001;32:119s–21s.
6. **Vannella KM**, Moore BB. Viruses as co-factors for the initiation or exacerbation of lung fibrosis. *Fibrogenesis Tissue Repair* 2008;1:2.
7. **Matthay MA**, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. *Annu Rev Pathol* Published Online First 15 January 2010. PMID: 20936936.
8. **Appel JZ 3rd**, Lee SM, Hartwig MG, *et al*. Characterization of the innate immune response to chronic aspiration in a novel rodent model. *Respir Res* 2007;8:87.
9. **Perng DW**, Chang KT, Su KC, *et al*. Exposure of airway epithelium to bile acids associated with gastroesophageal reflux symptoms: a relation to transforming growth factor-beta1 production and fibroblast proliferation. *Chest* 2007;132:1548–56.
10. **Mays EE**, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. A study of the frequency of hiatal hernia and gastroesophageal reflux in interstitial pulmonary fibrosis of obscure etiology. *Chest* 1976;69:512–15.
11. **Raghu G**, Freudenberger TD, Yang S, *et al*. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006;27:136–42.
12. **Tcherakian C**, Cottin V, Brillet PY, *et al*. Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. *Thorax* 2011;66:226–31.
13. **Robin Warren J**, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983;321:1273–5.
14. **Peters K**. Harveian Oration: exceptional matters. *Lancet* 2004;364:2142–51.
15. **Munro AJ**. The conventional wisdom and activities of the middle range. *Br J Radiol* 2005;78:381–3.