EDITORIAL

Drug history and remote exposure to drugs. A cause of lung disease?

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In this issue of the *European Respiratory Journal*, HUBBARD *et al.* [1] present the results of their study relating a history of exposure to antidepressant drugs with the development of "idiopathic" pulmonary fibrosis (IPF). In a cohort of well-defined IPF patients, they reported on a modest positive effect of prior exposure to antidepressants as a whole on the likelihood of developing pulmonary fibrosis. Only for amitriptyline, however, was the likelihood somewhat higher and statistically significant. According to these authors, reverse causation (*i.e.* the fact that the psychological strain of IPF required antidepressants, instead of these drugs causing the disease) may have played a role. It is of note that their earlier findings of an increased risk of pulmonary fibrosis associated with a history of exposure to imipramine or dothiepin [2] were not reproduced in this current study. Accordingly, they concluded that recent exposure to antidepressant drugs is unlikely to be associated with or cause pulmonary fibrosis. Likewise, they have reported formerly that exposure to β -blockers, anticonvulsants, antibiotics or nonsteroidal anti-inflammatory drugs is also unlikely to increase the risk of pulmonary fibrosis [2]. These studies on the possible role of exposure to drugs form part of other elegant studies by this group that are directed at the elucidation of what may cause IPF [2–5].

HUBBARD *et al.* [1] were aware of and even discussed, several weaknesses inherent to their study. To the knowledge of the present author, there was no control for ethnicity, socioeconomic status or presence of aero-contaminants in the home. More importantly, there was no control for occupation. These potential confounders may independently have influenced either the likelihood of developing pulmonary fibrosis (*e.g.* dusty environments [6, 7]) or, conceivably also, the need for antidepressant therapy. Also, no data were available regarding current or remote exposure to any of the thirty, or so, drugs other than antidepressants that are already known possibly to cause pulmonary fibrosis [8]. This is of importance as, for drugs such as amiodarone, chemotherapeutic agents or nitrofurantoin, the likelihood of developing pulmonary fibrosis is substantial. Conversely, in order to rule out reverse causation, the prescription of furosemide was used as a marker of IPF severity [1]. Indeed, furosemide was prescribed with increasing frequency, as a function of time, in patients with IPF, but a

cause and effect relationship remains to be established. It is of note that odds ratios for furosemide exposure were consistently >2 (*i.e.* greater than the odd ratios for any of the antidepressants studied), in the 4 yrs preceding diagnosis of IPF. This even raises the possibility that furosemide may also cause IPF.

With these limitations in mind, however, the study of HUBBARD *et al.* [1] is of great importance in several respects regarding drug-induced respiratory disease, on the one hand, and the elucidation of possible causes of chronic unexplained interstitial lung disease, on the other. To the present author, the terms "cryptogenic" or "idiopathic" in cryptogenic fibrosing alveolitis or IPF (used interchangeably) reflect more the current inability to identify the underlying cause(s) of the disease than the real absence of cause(s) for it. Therefore, the varied attempts by HUBBARD and coworkers [1, 2, 6] to elucidate possible inciting agents underlying apparently "idiopathic" pulmonary fibrosis should be complimented and encouraged.

To date, it has been relatively easy for pulmonologists to associate respiratory disease with current exposure to drugs, mainly because there has been close temporal association between the two events. Indeed, this is true of the vast majority of case reports on drug-induced respiratory diseases in the literature [8]. It is of note that, although the time to onset of the pulmonary adverse effect may vary greatly, from minutes for drug-induced bronchospasm/anaphylaxis [9, 10] to many years for amiodarone pneumonitis [11], the vast majority of patients were still on the drug at the time the adverse reaction developed. A further argument in favour of drugs as a cause is that, especially in patients with acute/subacute changes (*e.g.* subacute cellular (nonspecific) interstitial pneumonias, pulmonary oedema or pleural effusions), cessation of exposure to the offending drug leads to definite improvement or resolution of the respiratory abnormalities.

In contrast, few studies have insisted that adverse drug reactions in the lung can develop months to years after cessation of exposure to the drug [12–15]. Significant and illustrative clinical/radiographic patterns include: pneumonitis/fibrosis induced by thoracic [16, 17], cranial [18] or infused radiation therapy [19]; pneumonitis/fibrosis induced by the chemotherapeutic agents cyclophosphamide or nitrosoureas [20–23], or amiodarone [14]; pulmonary fibrosis in young adults who had received nitrosoureas for brain tumours in childhood [24]; pulmonary vascular disease and hypertension due to the intake of older [25] or more recent anorectics [15, 26–28];

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irreversible bronchiolitis obliterans due to repeated intake of dietary Asian shrub leaves [29]; or pleural fibrosis due to ergoline compounds [30].

All these latter patterns developed long after cessation of exposure to the inciting agent, and are predominantly fibrotic and irreversible, as opposed to the reversible inflammatory changes mentioned above. Amiodarone is a notable exception, in that the drug may induce reversible pneumonitis or other adverse effects, weeks to a few months after cessation of exposure [14, 31, 32]. The very long retention time profile of that drug in lung tissues is probably an explanation [33]. In this connection, several antidepressants are also sequestered in lung tissues of rodents and humans [34], as also pointed out by HUBBARD *et al.* [1]. Whether chronic lung diseases such as IPF can be induced by the prolonged storage of excessive quantities of drug in the lung currently remains unknown. It should be noted, however, that, for two approximately equally sequestered drugs (namely amiodarone, and imipramine), the pulmonary toxicity profile is very different [35, 36]. This tends to suggest that storage of drugs in the lung is neither the prerequisite nor the only determinant of pulmonary toxicity.

As exemplified above, the fact that pulmonary sequelae of delayed onset may follow exposure to drug or radiation therapy by many years is in keeping with the rationale of the study of HUBBARD *et al.* [1]. This may fuel further research in that area, especially with longer periods of observation and examination of the possible role of other drugs. A number of questions remain unanswered. 1) What is the recent drug history (*e.g.* which drugs have been given and/or stopped within the last year) of patients with clinical patterns such as bronchiolitis obliterans organizing pneumonia, accelerated interstitial lung disease, unexplained adult respiratory distress syndrome or sarcoidosis? Observational case histories indeed suggest that amiodarone [37–39], antibiotics [40], antirheumatic agents [41], interferons [42, 43] or statins [44] may cause such patterns of involvement, but firm epidemiological data are lacking. Similar reasoning applies to subsets of oncology patients treated with several chemotherapeutic agents (notably busulphan) who develop the so-called "idiopathic pulmonary syndrome", a form of protracted and severe nonspecific chronic fibrosing interstitial pneumonia [23, 45, 46]. The exact role of the various drugs and their association or sequence of use all remain to be clarified. 2) What is the exact remote drug history (*e.g.* in the last 20 yrs) of patients with IPF, or with other forms of chronic respiratory fibrosis (*e.g.* lupus erythematosus with pleuropulmonary involvement, bronchiolitis obliterans, chronic pulmonary hypertension or pleural fibrosis)? Careful examination of the drug history of a cohort of patients with IPF, as in the study of HUBBARD *et al.* [1], or with any of the chronic aforementioned patterns of involvement is required, with, initially, particular attention to the commonly fibrogenic drugs amiodarone, nitrofurantoin or chemotherapeutic agents [8]. It is necessary to examine drug prescription over long periods of time as very remote exposure to a toxicant drug may conceivably lead to fibrosis of the lungs many years later. It should also be emphasized that the number of drugs known to be capable of causing respiratory problems has considerably increased with time. The author's continuously updated Pneumotox® database currently details 318 causative

drugs, in comparison with 204 in 1997 [47]. Thus drugs with currently unrecognized fibrogenic potential may have to be screened in the future.

The work of HUBBARD *et al.* [1] raises other questions in addition to these. 1) Are there differences in pulmonary susceptibility among different ethnic groups, as already suggested for other drugs [48, 49]? 2) Are medicinal herbs really harmless to the lung? Reports and concerns regarding these compounds have recently emerged [29, 50–55], and the present author is of the opinion that a history of herb intake/exposure should be obtained exactly as is done for drugs. 3) Since the myocardium [56–59] and heart valves [60–63] may be damaged by drugs, drug history taking may also be of relevance in the cardiology field regarding patients with "idiopathic" cardiomyopathies.

To conclude, the idea behind the study of HUBBARD *et al.* [1], is likely to change conceptual views on iatrogenic lung disease. Indeed, physicians are well aware that the drugs they use daily may cause lung disease during the time they are given. They are also aware that some drugs may cause fibrosing alveolitis/pulmonary fibrosis during the prescription period, or relatively soon thereafter. If, in addition, some drugs can trigger "cryptogenic" fibrosing alveolitis/"idiopathic" pulmonary fibrosis, to be discovered many years later, then it would be extremely useful to know which drugs can do so, and the duration of exposure or drug associations that may put patients at risk, in order to formulate preventive and safety guidelines early during life. The cohort followed by British general practitioners and by HUBBARD *et al.* [1] may help solve these questions. Then and only then will it be possible to formulate pathophysiological questions aimed at elucidating additional risk factors, be they related to ethnicity, pharmacogenetics or the eminently variable pulmonary inflammatory/immune response to toxicants [64, 65].

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