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EDITORIAL

Respiratory disease induced by drugs

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Adverse effects from drugs on the respiratory system have emerged as a significant topic in pulmonology, and represent a sizeable proportion of patients seen in pulmonary practice nowadays. Under the impetus of a French study group on drug-induced respiratory disease (DIRD), known as the Groupe d'Etudes de la Pathologie Pulmonaire Iatrogène (GEPPI), a comprehensive table of drugs initiating adverse respiratory reactions has been drawn up, and is presented in this issue of the Journal [1]. This table was designed to make it possible to determine rapidly: whether a given drug may induce respiratory problems; what pattern of involvement can be expected; an estimate of frequency of the adverse reaction, and significant references from a database of nearly 2,650 papers on DIRD. It was hoped that this table would become a companion document, at the bedside.

In addition to this hardcopy, a continuously upgraded list of drugs with typical chest radiograph(s), computed tomography (CT) scan(s) and pathology slide(s) is available on e-mail at http://www.epidaure.com/lungdrug, where cases may be notified confidentially. We may also be reached at: pneumo.dijon@planetb.fr whenever additional information is needed.

DIRD is a group of diseases that has changed markedly, mainly during the past 25 yrs. This is demonstrated by the growing literature on the topic, the output of which averages 100 clinical articles per year (fig. 1). Collectively, of approximately 2,650 clinical articles published so far, 32% are related to chemotherapeutic agents: bleomycin (226 papers); busulphan (58); cyclophosphamide (75); methotrexate (129); and nitrosoureas (46). Adverse pulmonary effects from: amiodarone (214 articles); ergolines (54); gold salts (133); minocycline (35); nitrofurantoin (135); nonsteroidal anti-inflammatory drugs (NSAIDs) (58); and sulphasalazine (22) point to all these drugs as being common offenders of the respiratory system, in addition to angiotensin-converting enzyme (ACE) inhibitors. On this basis, a brief historical perspective on DIRD is warranted.

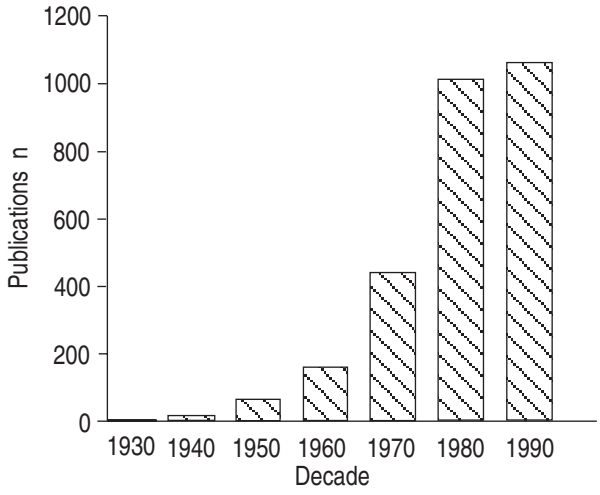

Fig. 1. – Number of publications on drug-induced respiratory disease (per decade) as a function of time. The current decade is an estimate.

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The first notice of adverse effects of drugs on the respiratory system dates back to the years 1920–1930, when it was realized that aspirin could induce severe asthma attacks and even death [2].

In the 1940s, the then newer antibiotic drugs were associated with allergic pneumonia with or without eosinophilia or angiitis [3, 4], and gold was linked to the development of interstitial lung disease [5], although most of the literature on "gold lung" was published later [6–8].

The 1950s was an innovative decade, with the description of such varied and important drug-induced patterns as: lipoid pneumonia [9]; allergic pneumonia from para-aminosalicylic acid [10]; other anti-tuberculosis agents [11]; or nitrofurantoin [12]; the lupus erythematosus syndrome induced by hydralazine [13]; acute allergic pulmonary oedema from salicylates [14]; mediastinal lymphadenopathy or lymphoma from anticonvulsants [15]; and a severe diffuse pattern of organizing pneumonia, very reminiscent of what is now called diffuse bronchiolitis obliterans organizing pneumonia (BOOP), in patients exposed to hexamethonium [16].

The 1960–1969 decade was dominated by an overwhelming number of reports on nitrofurantoin lung. In addition, a worrisome picture of medication-induced pulmonary hypertension emerged, and an epidemic of this devastating illness in young females was ascribed to the appetite-suppressant, aminorex, which was withdrawn from the market [17]. For the first time, it became clear that one drug could induce more than one pattern of respiratory reactions. In the case of nitrofurantoin, these patterns included: acute allergic pneumonia, with or without eosinophilia in the blood [18]; subacute/chronic interstitial pneumonia, with or without a desquamative or eosinophilic pattern at histology [19–21]; bronchospasm [22]; anaphylaxis [23]; and pleural effusion [24]. In that decade also, alkylating agents [25], other antineoplastic drugs, including bleomycin [26] and methotrexate [27], imipramine [28], and sulphasalazine [29] emerged

as novel causative drugs for DIRD. Newer drug-induced patterns of involvement were reported, and included ergoline-induced pleural fibrosis [30] and hydrochlorothiazide-induced pulmonary oedema [31].

The 1970s elapsed against a background of continuing interest in nitrofurantoin, gold or bleomycin pneumonia and drug-induced bronchospasm. However, novel offenders, such as nitrosoureas [32], cyclophosphamide [33], mitomycin [34], azathioprine [35], chlorambucil [36], melphalan [37], NSAID [38], and tetracycline/minocycline [39], progressively emerged. In addition, new and occasionally worrying patterns of DIRD were described, such as: penicillamine-induced bronchiolitis obliterans [40]; interstitial pneumonia [41]; and alveolar haemorrhage [42]. A study showed development of pulmonary oedema in parturients when high-dose *i.v.* β_2-agonists were used to retard term [43]. A transient picture of pulmonary oedema following blood transfusion was coined the "transfusion-related lung injury syndrome" [44]. A disturbing syndrome of generalized hypersensitivity with associated multiorgan failure and neurological symptoms was ascribed to salycilates [45] and, later, to phenytoin and carbamazepine [46]. Due to its propensity to induce pleural/pericardial fibrosis and because of additional extrapulmonary problems [47], practolol was taken off the market during these years.

Amiodarone became the most durable drug of the 1980s, soon after the first report of amiodarone pneumonitis in 1980 [48]. This was followed by a surge of publications, which has since substantially decreased (fig. 2). It appeared that amiodarone could induce several distinctive clinicopathological patterns of involvement, including lung fibrosis [49], BOOP [50], and acute respiratory distress syndrome (ARDS), probably because of the potentiating effect of exposure to oxygen in some patients [51]. At the same time, treatments with nilutamide [52], and intravesical Bacille Calmette-Guérin [53] were associated with the development of interstitial lung disease. Low-dose methotrexate, as employed in the long-term treatment of rheumatoid arthritis, was also associated with severe pneumonia [54]. Novel patterns of DIRD continued to be described, such as: multiple lung nodules following exposure to bleomycin [55]; cough during treatment with ACE inhibitors [56]; the haemolytic and uraemic syndrome with renal failure in patients exposed to mitomycin [57]; and pulmonary veno-occlusive disease following treatments with variegated chemotherapeutic agents [58]. A syndrome of fluid retention, pleural effusion and possibly ARDS was described in females during ovarian hyperstimulation [59, 60], and déjà-vu concerns arose from the resurgence of drug-induced pulmonary hypertension, following exposure to the then newer appetite depressant, fenfluramine [61].

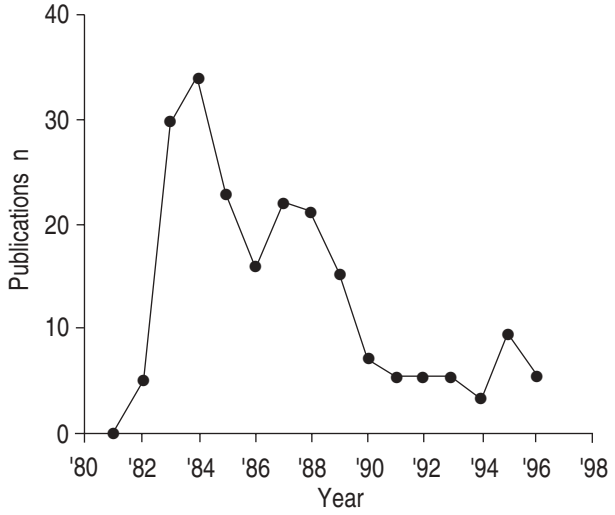

Fig. 2. – Number of clinical publications on amiodarone pneumonitis between the time of publication of the first case report (1980) and the time of writing (1996). Following an initial surge, the number of publications of adverse effect from many drugs tends to diminish with time. Thus, the information from cases that do not reach the stage of publication is epidemiologically lost.

The present decade has also brought substantial clinically relevant information to the area of DIRD. Drugs, such as fluoxetine [62], paclitaxel [63], ACE inhibitors [64], the cytokines interferon [65], granulocyte or granulocyte/monocyte colony-stimulating factor [66, 67], have been associated with interstitial pneumonia. Penicillamine-induced bronchiolitis obliterans remained almost restricted to the patient with rheumatoid arthritis, but tiopronin [68] and gold salts [69] have been shown to induce the syndrome as well. Newer clinical pictures emerged, such as the retinoic acid syndrome [70], and L-tryptophan-induced pulmonary eosinophilia, with occasional pulmonary hypertension, skin changes and fasciitis [71, 72], which almost reached the stage of an epidemic. Sadly, fenfluramine-induced pulmonary hypertension continues to be a problem, mainly in young females [73, 74], and this may lead to severe restriction of the use of this drug in the close future [75]. In addition to amiodarone, the causative role of which was amply confirmed [76], BOOP was related to radiation therapy [77] and to treatments with minocycline [78] or penicillamine [79]. It was also realized that disabling fibrosis could be detected years after the end of treatment with nitrosoureas [80].

In addition to laboratory work, which is clearly needed to further elucidate the fine mechanisms of drug-induced lung disease [81], is there capacity for further clinical research into DIRD? Indeed, several avenues may be explored. Little is known about the epidemiology of DIRD. As shown in figure 2, once a drug leaves the forefront, and many do so sooner or later, the number of publications drops significantly, whilst the incidence of pneumonia to that drug remains little changed. Thus, most new cases of pneumonitis to the drug are "lost", epidemiologically speaking. We therefore need an improved method of collecting this information. Moreover, there are clinical settings in which we lack adequate information on DIRD. As examples, it is unclear whether cytokines potentiate the pneumotoxicity of chemotherapeutic agents, and this issue is debated [82]. It is also unclear whether mesalamine (5-aminosalicylic acid) should be stopped when pulmonary opacities develop in a patient with inflammatory bowel disease exposed to this drug [83]. Indeed, cases have been reported where pulmonary opacities have disappeared, even though the drug was maintained [84]; continuation of mesalamine may protect the patient from a flare-up of the bowel disease a few weeks later. Currently, we have no response to this question, and a prospective trial may be warranted before mesalamine is definitively blamed. We also lack

sufficient data on methotrexate rechallenge, which has been performed harmlessly after methotrexate pneumonitis in a few patients with rheumatoid arthritis [85]. If a negative rechallenge could safely be predicted, then rheumatologists may reuse this excellent compound, and improve joint disability without the patient undergoing undue risk. We also lack epidemiological data on the prevalence of pleural changes in elderly persons exposed to ergolines, a curious and poorly-known syndrome that has recently been revisited [86].

Finally, we also need a warning system with a short time-constant, in order to rapidly detect potential questions raised by exposure to certain drugs, especially the newer ones. In this way, European pulmonologists may point more purposefully and with considerably more pertinent data than that available from isolated case reports, to almost any new drug-induced clinical problem. In addition to methotrexate and mesalamine, fluoxetine, recombinant cytokines and simvastin are now potential candidates for such an inquiry.

I believe that novel drug-induced lung diseases will relentlessly continue to emerge, as they have done in the past, and this is likely to fuel a strong level of interest in this area of pulmonology in the foreseeable future. We all need to be familiar with drug-induced respiratory disease in order to improve our own diagnostic accuracy and quality of care. Hopefully, the Groupe d'Etude de la Pathologie Iatrogène table and Web page will help us to advance in into that direction.

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A French version of the GEPPI table in now available [87].

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