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EDITORIAL

Asbestos, ergot drugs and the pleura

P. De Vuyst*, P. Pfitzenmeyer+, Ph. Camus+

In this issue of the Journal, two groups of researchers with established experience in asbestos-induced respiratory disease, independently report on patients with prior occupational exposure to asbestos, who developed exudative pleural effusion and/or pleural thickening, while being treated with bromocriptine for Parkinson's disease [1, 2]. Ultimately, the pleural changes were largely reversible following drug withdrawal. Both groups prudently stressed that, since no control group was included, the interaction of, and possible potentiation between asbestos and ergot drugs currently remains speculative [1, 3]. Despite the lack of definitive epidemiological evidence that bromocriptine and asbestos act synergistically to induce pleural thickening, fibrosis or effusion, the Editorial Board of the Journal decided to have these papers published, as a possible warning sign in occupational/iatrogenic respiratory disease.

The following pleural lesions are associated with asbestos exposure: hyaline or calcified plaques of the parietal pleura; diffuse pleural thickening or fibrosis involving the visceral pleura; benign exudative or haemorrhagic effusions; and the malignant mesothelioma [4–7]. The typical radiographic manifestations of asbestos-induced pleural lesions are distinctive [5, 6], but the diagnosis of early mesothelioma in patients with pleural thickening may be difficult. Classically, folding and shrinking of the lung, and rounded atelectasis [8–12] are ascribed to fibrosis of the visceral pleura. Benign asbestos pleural effusion may be followed by pleural thickening or fibrosis, but rarely by the development of pleural mesothelioma [13].

Ergot drugs such as methysergide, ergotamine, dihydroergotamine, bromocriptine, nicergoline, pergolide, and dopergine, collectively known as ergolines, are utilized to treat symptoms or syndromes such as cluster headache, migraine, Parkinson's disease, or the organic brain dysfunction syndrome [14, 15]. When administered in the long term, ergolines can also induce distinctive pleuropulmonary changes in a few patients, including parietal [14, 15] or visceral [15] pleural thickening, pleural effusion [14–17], rounded atelectasis [14], and fibrosis of the lung adjacent to pleural lesions [15, 18, 19]. Of note, and in contrast to what is seen in asbestos-related diseases [5], pleural changes induced by ergolines rarely, if ever, calcify [14], possibly because they develop over shorter periods of time. A marked elevation of the erythrocyte sedimentation rate (ESR) is common in association with ergoline-induced pleural changes, occasionally with figures over 100 mm in one hour [14, 15].

The histological transcript of radiographic pleural thickening or plaques is pleural fibrosis, whether ergolines or asbestos are the cause [4, 14, 15]. Thus, these two terms may be used interchangeably in this text. As we shall discuss below, only ergoline-induced pleural thickening/fibrosis is reversible.

The exact aetiological diagnosis is difficult to establish when pleural thickening with or without effusion develops during treatment with bromocriptine (or another ergoline) in a patient with prior asbestos exposure [1, 2, 14], except perhaps in the rare circumstance where the pleural lesions develop in association with retroperitoneal fibrosis [20–22], a hallmark of ergolines. Evidence in favour of pure asbestos-induced, as opposed to ergoline-induced, changes are proposed in table 1. Key elements to differentiate between the two aetiologies include the rate at which the pleural disease develops, which is usually far more rapid with ergolines, and the presence of calcifications, which clearly weighs in favour of asbestos-related disease (provided that the patient has not developed tuberculosis in the past [14]). In fact, the major difference lies in the outcome following drug withdrawal, which is definitely favourable if ergoline is the cause:

1) In ergoline-induced pleural thickening, withdrawal of the drug is quickly followed by remarkable improvement of chest discomfort and of the ESR. Radiographic improvement lags behind by a few weeks or even months, and some pleural thickening will usually persist indefinitely [1, 14]

2) The issue is more complicated in cases with pleural effusion. Chest pain and cellular analysis of the pleural fluid, when present, are not specific enough to enable discrimination between asbestos- and ergoline-induced pleural manifestations. The possible merit of histopathology in differentiating asbestos- from ergoline-induced pleural fibrosis is unclear. Withdrawal of the drug leads to improvement of the effusion, and similarly, benign asbestos pleural effusion usually improves spontaneously within a few weeks or months [13, 23]. As a consequence, segregating the iatrogenic from the occupational cause for pleural effusion in the context of treatments with ergolines and past asbestos exposure may be difficult, but ways exist to circumvent this difficulty (see below).

Often, the ESR is increased to a greater extent in ergot-induced [14, 15], as opposed to asbestos-induced, pleural changes [24] (55.0 *versus* 25.7 mm in the series by PFITZENMEYER *et al.* [14] and HILLERDAL [24], respectively) (table 1), but a significant overlap probably exists. How-ever, only in ergoline-induced pleural changes, will the rise in ESR

*Service de Pneumologie, Hôpital Erasme, Brussels, Belgium. +Service de Pneumologie et de Réanimination Respiratoire, Centre Hospitalier Universitaire, Dijon, France. Correspondence: P. De Vuyst, Service de Pneumologie, Hôpital Erasme, Route de Lennik, B-1070 Bruxelles, Belgium.

Table 1. – Schematic characteristics of ergoline- and asbestos-induced pleural changes

	Ergoline-induced	Asbestos-induced
Pleural thickening/fibrosis		
Onset*	Subacute	Slow
Chest symptoms*	Common	Unusual
Systemic symptoms*	Common	Unusual
Raised ESR*	Common†	Occasional
Pleural calcifications	Never reported	Common
Asbestos exposure*	No	Yes#
Asbestos bodies in the BAL*	No	Often
Outcome drug continued*	No improvement	No improvement
Outcome drug discontinued*	Improvement	No improvement
Pleural effusion		
Onset	Subacute	Subacute
Chest symptoms	Common	Common
Characteristics of pleural fluid	Lymphocytic exudate	Lymphocytic exudate; haemorrhage§
Raised ESR	Common†	Quite common
Pleural calcifications	No	Common
Asbestos exposure*	No	Yes#
Asbestos bodies in the BAL	No	Often
Outcome drug continued	Persistence	Improvement common
Outcome drug discontinued	Improvement	Improvement
Spontaneous+ recurrence*	Not described	Common (in about 33% of patients)

*: Characteristic more suggestive of one aetiology than the other, which may be used to favour one aetiology in patients exposed to both causes; +: *i.e.*, without re-exposure to the ergoline drug; †: usually the erythrocyte sedimentation rate (ESR) is greater in ergoline-induced than in asbestos-induced pleural changes (see text); #: may require confirmation by occupational inquiry and mineralogical analysis of bronchoalveolar lavage (BAL) or lung tissue; §: there may occasionally be eosinophilia in both situations.

improve (within a few weeks) following drug withdrawal [1, 14].

In some patients, additional procedures may prove useful to substantiate past exposure to asbestos, essentially when the occupational history is not reliable (*i.e.* for short, indirect, remote or forgotten exposures). Mineralogical analysis of the bronchoalveolar lavage (BAL) fluid and/or of lung tissue (if available) evaluates the lung retention of asbestos fibres and bodies [25, 26]. However, such analyses may show only low fibre burdens in lung tissue, and very few, if any, asbestos bodies in the BAL in roughly 30% of patients with pleural plaques, despite definite prior exposure [25]. Pleural plaques can indeed develop after low-dose cumulative exposures to asbestos, and fibres may still be found in pleural tissue, whereas they have been cleared from the alveolar compartment [27]. It is generally agreed that both the level of exposure and the fibre counts in BAL and lung tissue are greater in those workers with pleural thickening or effusion, as opposed to those with simple plaques [28]. Asbestos fibres and bodies are very rarely detected in the pleural fluid, and should not routinely be looked for there.

In former asbestos workers on ergolines, the clinician may be faced with four situations, which are specified below:

Pleural plaques (hyaline or calcified). Plaques with sharp margins on computed tomography (CT)-scan examination are almost specific for asbestos exposure [5, 6]. They have not been described following treatments with ergolines, which induce a more diffuse and uniform pattern of pleural thickening [14]. Thus, one can confidently ascribe such well-demarcated plaques to prior exposure to airborne asbestos.

Chronic pleural thickening with calcifications. As stated above, the diagnosis of asbestos-related pleural disease should be favoured, unless pleural thickening is shown to progress rapidly (*i.e.* within a few months), which would suggest a dual aetiology (asbestosis and ergolines). In such cases, close follow-up should establish whether, and to what extent, the radiographic changes, and a possible concomitant rise in the ESR are reversible upon withdrawal of the ergoline.

Indolent pleural thickening without calcifications. Again, the diagnosis of asbestos-related pleural disease should be favoured, because ergolines usually induce a subacute (over months to weeks), not a chronic (over years) illness. Rounded atelectasis and lung shrinking (crow's feet) may be associated with both aetiologies [9, 14]. Thoracoscopy is probably unnecessary in any of the three situations above.

Pleural effusion. Here, the work-up is most difficult, because, as stated above, onset, clinical-radiographic presentation and characteristics of the pleural fluid cannot usually discriminate between asbestos and ergolines as a cause [13, 14] (table 1). Benign asbestos pleural effusion tends to resolve spontaneously, but may recur in up to a third of the cases [13]. In contrast, ergoline-induced effusion will not improve unless the drug is discontinued, and has never been shown to recur [14].

Thus, in cases with mild chest or systemic symptoms, pleural fluid should be taken for analysis and a closed-chest pleural biopsy may be performed to rule out (within the limits of this procedure) mesothelioma or a chance association. Many clinicians favour thoracoscopy and directed biopies at this stage, because of the superior sensitivity of this technique. Bromocriptine (or the ergoline) may be continued for 1–2 months, while the patient is closely observed. If the effusion improves, it may tentatively be ascribed to asbestos. However, further follow-up

is warranted, because ipsilateral or contralateral recurrence of benign asbestos pleural effusion is common [13, 23]. If the pleural disease does not improve, or even worsens, within that time frame, the causative role of bromocriptine (or the ergoline) should be favoured, and the drug should be withdrawn. Lack of improvement of pleural effusion and of the ESR within a few weeks after drug cessation requires additional investigations (including thoracoscopy if not performed earlier) to determine other causes, such as pleural mesothelioma. It must be born in mind that early pleural mesothelioma may be heralded by totally reversible pleural effusion, and the exact diagnosis may be established only months to a few years later. Thus, close follow-up of any effusion in patients previously exposed to asbestos is warranted, and thoracoscopy with directed biopsies should be prompted at the slightest doubt

In patients with severe constitutional or chest symptoms at the outset, the neurologist should be consulted as regards therapeutic options other than bromocriptine for Parkinson's disease (for other ergolines, the rationale for treatment should also be critically re-evaluated). The role of thoracoscopy at this stage is still unclear. Early drug withdrawal may lead to rapid clinical-radiographic improvement, at the expense of possible deterioration of the underlying neurological illness. It should be noted that early drug withdrawal may make it impossible to ultimately determine the respective responsibility of asbestos and the ergoline at the origin of the pleural effusion. Only if ipsilateral or contralateral recurrence develops some months later, will the diagnosis of benign asbestos pleural effusion eventually be settled, provided biopsies of the pleura *via* thoracoscopy rule out the diagnosis of mesothelioma at this time.

It is noteworthy that, despite their frequent utilization, steroids have demonstrated no unequivocal beneficial effect in asbestos- or ergoline-induced pleural changes. We feel that the critical analysis of drug- or asbestos-induced nature of the disease will be easier if steroids are not used, because they may obscure the exact temporal relationships between drug withdrawal on the one hand, and outcome of the effusion on the other.

Although conceivable, there is currently neither clear explanation as to whether ergolines and asbestos act synergistically to induce pleural disorders nor experimental support for it. When injected locally into the pleural space, minerals such as talc, or certain drugs (bleomycin, tetracyclin) will induce pleural fibrosis, and this forms the basis for chemical pleurodesis [29]. Thus, a synergy is possible between agents capable of inducing pleural fibrosis after inhalation and translocation to the pleura (asbestos), and following intake *via* the oral route (ergolines). It should be pointed out that the pharmacokinetics of ergolines in the pleural fluid or tissue is unknown, and consequently, toxicity resulting from serosal sequestration of these compounds cannot be ruled out at the moment. Incidentally, exposure to the two agents need not be simultaneous, since it has been demonstrated that asbestos fibres may remain in some areas of the parietal pleura for decades [27]. Why ergoline-induced changes are reversible, and asbestos-induced changes are not, is unclear. Tentatively, the irreversible nature of asbestos-induced changes may relate to the biopersistence of mineral fibres within the pleura, whereas ergolines will clear up after discontinuation. By virtue of pleural changes or discrete lesions of the lymphatic network of the parietal pleura and/or lung tissue [27], asbestos might also impair the draining capacity of the pleura, and thus favour all causes of pleural effusion. In this connection, it has been reported that pleural effusions, regardless of their cause, are more common in persons previously exposed to asbestos [13]. This may point to an increased susceptibility of the pleura in such persons, and explain why ergolines are more often the cause in this setting. Serotoninergic mechanisms may also play a role, since some ergolines have anti-serotoninergic properties [14], and the carcinoid syndrome may also lead to pleural fibrosis [30, 31]. Regardless of the exact causative mechanism(s), the fibrogenic potential of asbestos and ergolines on the serosal surfaces is intriguing, as is the essentially reversible nature of ergoline-induced pleural fibrosis [14].

Epidemiological proofs are indeed awaited to demonstrate whether asbestos and ergolines act in concert to damage the pleura. In the meantime, any progressive pleural thickening or pleural effusion in a patient with former asbestos exposure should encourage pulmonologists to look for secondary causes with potential reversibility, and among such causes are treatments with ergolines. In this regard, European pulmonologists may be willing to inform their neurology colleagues, that closer attention should be directed to the pleura, whenever the latter plan to institute treatments with ergolines in a patient with occupational history of exposure to asbestos.

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