had a slightly elevated mean amosite/crocidolite content of 470,000 fibres vs. 210,000 for the controls.

In the Green et al. (18) study, the lung cancer cases on which fibre burden analysis was carried out were not representative of the cohort as a whole (e.g. autopsies were carried out on only about 10% of all deaths in the cohort, and the mean lifetime cumulative exposure for the 10 lung cancer cases was 94.6 fibre-years in comparison to 67 fibre-years for male lung cancer cases across the whole cohort (18, 39)). There are even greater concerns about the representativeness and comparability of the cases on which fibre burden analysis was carried out by Sébastien et al. (43) and, therefore, Case et al. (42) (i.e. no more than 5.56% of the South Carolina lung cancers studied; > 10 years difference in the mean age at death; substantial over-representation of asbestos-related disorders in the Thetford autopsies (42%) in comparison to the cohort as a whole (7%); median interval of 20 years after cessation of exposure for the textile workers vs. 8 years for the miners/millers; and differences in estimated exposures, especially when fibre clearance is taken into account). In addition, the total amphibole content (amosite/crocidolite + tremolite) was significantly higher in the miners/millers. Finally, the difference in the amosite/crocidolite content seems too small to account for the K difference.

The Weiss review

In 1999, Weiss (44) reviewed multiple cohort studies on the relationship between asbestosis exposure and lung cancer, and supported the view that excess lung cancer risk occurs only among those cohorts where asbestosis also occurs. He concluded that "asbestosis is a much better predictor of excess lung cancer risk than measures of exposure and serves as a marker for attributable cases." However, this review was the subject of critical comment by Banks et al. (45) in the same issue of the Journal.

In addition, the following comments on the Weiss review (44) can be adduced:

- This review specifically excludes case-control studies, autopsy investigations, and fibre burden analyses, and it confines itself largely to the English-language literature.

- The review is confined to studies and reports published up to January 1997 only.

- For Weiss' review of the Hillerdal study on patients with pleural plaques (46), Banks et al. (45) point out that Weiss' calculated RR for workers aged 40–69 years appears to be in error, because age was mistaken for years from first exposure.

- The Weiss review also contains data that undermine its own conclusions. For example, Table 4 (Lung cancer specific mortality ratios among Quebec miners and millers by chest radiograph status) records an SMR of 3.11 for workers with radiological small opacities (an X-ray marker for asbestosis; 95% CI 2.14–4.39). However, the SMR was also elevated at 3.30 (95% CI 2.32–4.62) in workers with radiographic abnormalities other than small opacities; Banks et al. (45) point out that 11 out of 37 in this category had a "large opacity" (not feature of asbestosis), so that the SMR for

lung cancer was increased among those with radiological abnormalities other than asbestosis.

- In Table 10 (Association between cumulative asbestosis mortality rate and cumulative excess lung cancer mortality rate in one study), the excess lung cancer death rate was 8.48 among 884 workers with light/moderate exposure lasting ≤ 2 years (likely to be insufficient to produce asbestosis, so that the asbestosis death rate in the same Table was zero); the figure of 8.48 was based on an observed number of 24 vs. an expected number of lung cancer deaths of 16.5, with an SMR of 1.45 (95% CI 0.93–2.16). However, if one assumes that the excess lung cancer death rate = 0 when there is no asbestos exposure (zero exposure, zero effect; SMR = 1.0), and notes that the excess lung cancer death rate is 19.49 among those with light/moderate exposure lasting > 2 years (when the asbestosis death rate = 3.61), then it appears that a trend to an increase in lung cancer SMR is evident even at light/moderate exposure ≤ 2 years (no asbestosis), and χ^2_1 (trend) = 163.9.

- Even if one sets aside, for the moment, all of these criticisms of the Weiss review and others outlined by Banks et al. (45), a fundamental problem remains. Weiss argues that increased death rates or risks of lung cancer occur in cohorts where asbestosis also occurs. But this does not mean – and one should not jump to the conclusion – that the asbestosis and lung cancer must occur in the same individual. All the data indicate is that lung cancer death rates are raised in cohorts where asbestosis occurs in some individuals. This observation is equally explicable by a dose-response effect for both asbestosis and lung cancer whereby they are not pathogenetically linked.

Asbestos-attributable lung cancer remains under-recognized

Although higher percentage figures are given for some countries, it has been estimated that about 3–5% of lung cancers can be related to asbestos. However, there seems to be little doubt that the role of asbestos as a contributory factor for many lung cancers goes unnoticed. The 1998 Report of the NSW Dust Diseases Board (DDB) is of interest in relation to the proportions of lung cancer cases relative to mesotheliomas: the Medical Authority considered 2,338 claims during 1997–98 (2,665 in 1996–97), with the following certifications:

1. The 238 certificates of disablement for 1997–98 included 96 mesotheliomas (97 in 1996–97) in comparison to 9 asbestos-induced carcinomas of the lung (10).

2. The 138 certificates for deaths (1997–98) included 104 mesotheliomas (101) vs. 14 lung cancers (13).

Some 1,509 workers were "certified to have not contracted a dust disease ...". In other words, the mesothelioma:lung cancer ratio was almost 10–11:1 (disablement) or 7.5–8:1 (death). These ratios stand in contrast to – and are the reverse of – those reported in epidemiological studies for other nations, where there are estimated to be about 1–10 asbestos-related lung cancers for every mesothelioma. There are a number of possible explanations for this apparent discrepancy of about two orders of magnitude:

1. The ratios reported elsewhere are incorrect and the NSW DDB figure is accurate.

2. The ratios reported elsewhere are correct and so is the NSW DDB ratio. In this case there must be something peculiar about the aetiology of lung cancer in NSW, but we are not aware of any evidence that this is so.

3. Both ratios are incorrect.

4. The NSW DDB ratio embodies an under-estimate of the number of lung cancers relative to mesotheliomas: this might be explicable by lung cancer patients not seeking compensation – i.e. they never came to the attention of the DDB – or, alternatively, by rejection of their claims, or both. It would be of interest to ascertain the numbers of lung cancers in the 1,509 claims that were rejected for 1997–98.

Some problems encountered with application of *The Helsinki Criteria*

In practice, there are cases where there is a disparity between the asbestos body vs. the uncoated fibre concentration in lung tissue, so that one or the other conforms to *The Criteria*, whereas the other does not. Alternatively, the count is occasionally high in one lobe of the lung and within normal values at another site. (According to Thimpont and de Vuyst (19), only one of the Belgian criteria need be satisfied.)

Again, *The Criteria* do not provide clear guidelines on how to handle a case where the amphibole concentration in lung tissue is elevated but does not reach the threshold figure, whereas there is an additional burden of chrysotile fibres – e.g. 3 million amphibole fibres > 1 micrometer in length per gram dry lung tissue, together with 3 million chrysotile fibres. Taking into account the lack of convincing evidence for a difference in carcinogenic potency between the amphiboles and chrysotile for lung cancer, can one simply add the chrysotile and amphibole content together, or is it better to base attribution on estimated cumulative exposures?

How does one resolve the issue if there are conflicting estimates of cumulative doses of asbestos, or if the occupational histories are too fragmentary for methodical assessment? For example, we have seen one case where one occupational hygienist assessed cumulative exposure at up to 90 fibre-years, but another came up with a figure of < 1 fibre-year. With a difference of this magnitude, the assumptions underlying each exposure estimate require critical re-evaluation (e.g. interpolation of data from a similar facility), because one or other estimate will not withstand scrutiny; when the estimates are closer but one fulfils *The Criteria* and the other does not, this introduces a diminished confidence level.

Screening for lung cancer in asbestos-exposed cohorts

In a recent review, Mulshine (47) gives a useful summary of trends in screening for lung cancer in order to improve therapeutic outcomes. Evaluation of screening programs is usually carried out on groups with an extremely high risk of lung cancer – e.g. males ≥ 45 years of age who are heavy cigarette smokers or cigarette-smoking tin miners in Yunnan, China, exposed also to arsenic and radon (48, 49). Cigarette smokers among

asbestos-exposed cohorts represent another group suitable for the evaluation of screening programmes.

Screening is based on the observation that surgical resection appears to be curative in a high proportion (up to 70%) of small stage I lung cancers and that thin-section or spiral CT can detect non-calcified lung nodules as small as ≤ 5 mm in diameter (e.g. see 50 and 51).

In the past, screening programmes have usually involved:

- Serial (e.g. annual) chest radiographs; *and/or*
- Serial sputum cytology examinations.

Using these modalities, some studies have returned disappointing results, presumably because of lack of sensitivity of the diagnostic techniques. However, others have been more encouraging. Midori et al. (52) found significantly increased lung cancer incidence and mortality in a radiation-exposed group screened biennially by plain X-ray compared to a non-screened but exposed group, but a lower mortality/incidence in the screened group, suggesting a benefit of earlier detection on outcome. This was a large study (1,799 screened; 8,735 not screened) and had been carried out since 1958. In another study from Japan, Okamoto and Tanaka (53) found that CT scanning was more cost-effective than plain X-ray screening: even though CT costs are higher they are more than balanced by the increased benefits of early detection. Encouraging results have also been reported by Sone et al. (54) in Japan, and in the Early Lung Cancer Action Project (ELCAP) in the US (50, 55).

Recent developments also indicate that the following techniques are worth investigation, including:

- Spiral CT examination of the thorax.
- The use of immunocytochemistry to detect biomarkers expressed early during the development of bronchogenic carcinoma. For example, one monoclonal antibody used for this purpose (703D4) recognizes a heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 and in the Yunnan tin miners (48, 49) this monoclonal antibody was found to be two to three-fold more sensitive for the detection of early disease in comparison to standard chest radiographs and sputum cytology examinations. (Screening for antibodies to nuclear auto-antigens also offers promise for the early detection of mesothelioma: Robinson et al. [56] found 93% of mesothelioma cases had antibodies to TOP11 antigen and 14% had antibodies to U2AF.)
- Perhaps more promising is the detection of oncogenes – e.g. K-ras (57) – in sputum, BAL fluid, or blood.

Two problems remain:

1. It needs to be shown that the techniques employed will lead to improvement in clinical outcomes in the cancers detected by screening programmes and that they are applicable to other high-risk groups.

2. Although well defined groups of asbestos-exposed individuals are suitable for the evaluation of screening programmes, screening becomes more problematical for the far more numerous workers who are exposed at various points of asbestos end-use, because many such individuals do not identify themselves as asbestos workers and it is difficult to recruit them into screening programmes.

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