Editorial

Silica, silicosis, and lung cancer*

Until recently few physicians or epidemiologists concerned with dust diseases would have given much thought to the possibility that exposure to silica might be linked with lung cancer. The general view was expressed in 1982 by Parkes as follows: "Bronchial carcinoma occasionally occurs in silicotic lungs but there is no evidence of a causal relationship between it and silicosis or siliceous dusts; indeed, the incidence of lung cancer in miners with silicosis is significantly lower than in non-silicotic males."¹ The NIOSH criteria document of 1975 that recommended a reduction in the occupational exposure standard for crystalline silica to 50 $\mu\text{g}/\text{m}^3$ made no reference to carcinogenicity for man or animals.² The same is true of the WHO report of 1986 that proposed a health based limit of 40 $\mu\text{g}/\text{m}^3$ without mention of cancer.³ In that same year, 1986, however, there appeared a book entitled *Silica, silicosis, and cancer* edited by Goldsmith *et al* which brought together new information that has become the subject of major controversy.⁴

In 1986 an IARC working group met in Lyon to review all the findings then published on the subject. The final evaluation by this group was that sufficient evidence existed for the carcinogenicity of crystalline silica to experimental animals, but that for man the evidence was *limited*.⁵ In IARC terminology "sufficient" evidence in experimental animals requires an increased incidence of malignant tumours either (a) in multiple species, (b) in multiple experiments, or (c) in some unusual way. In man "limited" evidence implies that although a causal interpretation is credible, other explanations such as chance, bias, or confounding cannot be excluded. So far as experimental animals are concerned the IARC conclusions were based on a significant increase of carcinoma of the lung in rats after inhalation or intratracheal instillation and on the production of malignant lymphomas after intrapleural or intraperitoneal injection. Animal studies will not be considered further here; instead, the epidemiological evidence will be examined concentrating on the 20 or more occupational cohort and case

referent studies, all but one⁶ of which were reviewed by the IARC working group.⁵ Simple case series, studies of proportional mortality, and studies of cancer morbidity will not be considered as, scientifically, they tend to carry less weight.

Of nine cohorts of mining and quarry workers, four based on large numbers showed moderately raised SMRs for lung cancer, ranging from 127 to 156.⁶⁻⁹ In only one of these, in Finland,⁶ was any allowance made for cigarette smoking and in none can the possible contribution of radon or other occupational exposures be confidently excluded. Of four negative studies, that of Higgins *et al* had too few deaths from lung cancer for interpretation¹⁰; that of Lawler *et al* was peculiar in that, although their large cohort was probably exposed to ore containing at least 8% silica, it experienced significantly lower mortality from respiratory disease and tuberculosis than expected.¹¹ Three studies were of men employed in a large gold mine in South Dakota. Suggestive findings initially reported by Gillam *et al*,¹² based on a small and probably unrepresentative sample of miners, was not confirmed in the much larger surveys of McDonald *et al*¹³ and Brown *et al*¹⁴ that followed. The strength of their negative conclusion was emphasised by Brown *et al*, as follows: "The number of expected deaths in this cohort allows for a very powerful analysis; we had a 90% probability of detecting a true relative risk of 1.5 for lung cancer, based on a one sided test. When the cohort was restricted to those with at least 15 years latency there was still an 88% probability of detecting the same risk, and when restricted to at least 15 years latency and at least five years employment underground, there was still a 76% probability of detecting the risk."¹⁴ To this may be added the fact that mortality in these cohorts from silicosis and silicotuberculosis were both substantial and related to exposure.¹⁵ The great majority of men in these cohorts, however, did not die of these diseases; probably many, if not most, had some degree of silicosis and remained at risk from lung cancer. In other types of occupation the SMRs for lung cancer show similar variation. New York tunnel workers studied by Selikoff suffered badly from silicosis and tuberculosis and had also an excess of lung cancer, but there may have been exposure to

*Based on a presentation at the VIIth International Pneumoconioses Conference, Pittsburgh, 1988.

radon.¹⁶ The probability of additional exposure to other carcinogens also confounds the studies of foundry workers.¹⁷⁻¹⁹ The exposure of refractory plant workers, studied by Puntoni *et al*, may have been relatively pure but smoking habits were not evaluated.²⁰

There have also been several cohort studies of men with silicosis with observed deaths from lung cancer and other causes compared with those expected from various reference populations.²¹⁻²⁵ In all of them the SMRs for lung cancer were raised substantially, by some two to fourfold. Westerholm *et al* obtained their expected deaths from a similar follow up of men in the Swedish silica exposure registry who did not have silicosis.²⁴ In the remaining studies mortality in the general population was the basis for comparison. Apart from the study of Zamboni *et al*,²⁵ no account was taken of smoking habits and in none was consideration given to the possible effect of other exposures. The association between lung cancer and both silica exposure and silicosis has been investigated in a few case-referent studies of varying quality. Except for the study by Steenland and Beaumont,²⁶ adjustments were made for age and smoking but in this study and that of Vutuc,²⁷ comparability of the control groups is open to question. The studies of Forastiere *et al*²⁸ and of Hessel and Sluis-Cremer²⁹ did not have these problems but gave opposite answers. Although tightly designed, the latter study for reasons of size had only limited power. In the slightly larger Italian study lung cancer was significantly associated with both exposure to silica and silicosis in the ceramics industry but not in quarries.²⁸

In any assessment of the evidence in a question of cause and effect it is useful to consider the time honoured criteria of consistency, strength, specificity, time relation, dose response, and biological plausibility. If there is truly "sufficient" evidence for the carcinogenicity of silica in experimental animals the last mentioned criterion is met. With the possible exception of time relations, however, none of the others is. The epidemiological findings are not consistent, risk estimates are generally low, exposure response has not been studied, and the possibilities for confounding by other carcinogens, including tobacco, are many. Men employed in the pottery and ceramics industries may also have been exposed to fibrous talc, in foundries to asbestos and polycyclic hydrocarbons, and in mines to radon. Levels of silica exposure have fallen in most industries in the past 40-50 years and it is thus anomalous that as silicosis has become less prevalent, lung cancer should become more so.¹⁸ In underground miners this lack of correlation may be explained by exposure to radon daughters.³⁰ The studies of lung cancer in silicotic subjects raise several other questions, in particular as

to the manner in which cases were selected for study. Except in the investigations of Hessel and Sluis-Cremer²⁹ and Kurpa *et al*,²³ where the results were conflicting, silicosis implied compensation for this disease. Compensation depends largely on disability and therefore on smoking; there is certainly no assurance that such cases had not also been exposed to fibrosis silicates or radiation or, indeed, that lung cancer was not already present and contributing to the disability. The use of mortality in the general population for comparison with that in compensated silicotic subjects must also be questioned. The evidence reviewed in the present paper has been confined to cohort studies of mortality and to case-referent studies of similar reliability. It is only fair to add that there have been many reports on case series, on proportional mortality studies, and on epidemiological studies based on cancer registry diagnoses⁵ that generally support the association between silica, or silicosis, and lung cancer. Such studies are less convincing, however, and more likely to be published if positive than negative.

Evidence for the carcinogenicity of crystalline silica to man is indeed limited; although credible, alternative explanations such as chance, bias, or confounding have not been adequately excluded. The credibility of the hypothesis rests largely on a few animal experiments that are themselves difficult to interpret (JC Wagner, personal communication). Without more and better evidence it is premature to conclude that exposure to crystalline silica has caused lung cancer in man.

J C McDONALD

*Department of Clinical Epidemiology,
National Heart and Lung Institute,
Brompton Hospital,
London SW3 6HP.*

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