NEWER CONCEPTS IN SILICA AND SILICATE LUNG DISEASE

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Pulmonary disease may be caused by exposure to free silica and a wide variety of nonfibrous silicates. The pulmonary disease caused by chronic exposure to free silica is usually referred to as silicosis or classical silicosis. The lesion typical of silicosis is said to be the silicotic or classical silicotic nodule. Classical silicotic nodules are rounded, whorled, well demarcated very fibrotic lesions clearly demarcated from the background lung. Microscopically they have a narrow rim of dust containing macrophages admixed with randomly oriented collagen fibres, an intermediate zone of concentrically arranged collagen and a central collagenous core which may be variably hyalinised and calcified. On the other hand the mixed duet fibrotic nodule is stellate and microscopically is composed of a central zone of collagen with a periphery of linearly and radially arranged collagen admixed with dust laden macrophages.[1] The latter is said to be characteristic of pulmonary disease caused by exposure to free silica in combination with less fibrogenic dusts such as kaolin,iron oxide or carbon.[1-3]

The occurrence of pneumoconiosis consequent to pure nonfibrous silicate exposure is debatable since commercial silicates are often contaminated by other minerals of known fibrogenicity. Relatively few cases have been described and in many of these no accurate analytical data is available.

When examining histopathological specimens of lungs from cases of so-called classical silicosis I have often been struck by the frequency of lesions other than the classical silicotic nodules. For example in a study of the lungs from North Wales slate workers, who were exposed to dust containing between 30 and 35% free silica, "mixed dust" fibrotic nodules and interstitial fibrosis were noted in a considerable proportion of the cases as well as the classical silicotic nodules.[4] It is probably not surprising in view of the fact that slate contains considerable quantities of mica and other minerals such as chlorite, iron salts and titanium in addition to free silica. On further reflection it will be obvious that there are few if any situations where pure exposure to free silica occurs and it is nearly always accompanied by exposure to combined silicates. There is experimental evidence that the toxic effects of free silica on the lung can be modified by the presence of other minerals such as mica, haematite and coal probably by modifying the surface activity of the free silica particles but the results are difficult to predict.[5,6] At present the precise conditions of dose, duration of exposure, mineral composition and physicochemical properties for the development of classical silicotic, mixed dust fibrotic nodules and interstitial fibrosis in humans are not fully understood. Other factors also appear to be important such as subject variation and complicating disease.[7]

In this presentation I would like to outline the results that my colleagues and I have obtained from a study of autopsy lungs from a group of Cornish china clay workers since it sheds some light upon how these lesions develop.[8] It is also one of the few studies of a pure nonfibrous silicate pneumoconiosis in which good pathological and analytical data are available.

The Cornish china clay industry is largely confined to a small geographical area located around St. Austell in the South West of England. The industry started in the 18th century when china clay and china stone deposits were worked and the products used in British pottery production. Since then the industry has expanded by increasing the production of china clay but china stone usage has ceased.

The lungs from 62 subjects who had worked in the Cornish china clay industry had been referred to the MRC Pneumoconiosis Unit between 1968 to 1981. These were studied both pathologically and mineralogically and occupational histories and chest radiographs, available in 39 cases, were obtained. As the study proceeded it became apparent that there was good agreement between the occupational histories and the mineral content of the lungs. Indeed mineralogical analysis often proved more accurate than the initial occupational history.

On the basis of the mineralogical findings three groups could be distinguished:

1. "China clay" group–kaolinite > 90%, quartz < 1.1% and feldspars < 1% by mass.
2. "China clay and china stone" group–kaolinite < 90%, quartz > 0.9%, feldspars > 1.0% by mass.
3. "Miscellaneous" group–did not meet conditions for groups 1 and 2; it was considered probable that there was exposure to other minerals.

Each lung was graded histopathologically for nodular and interstitial fibrosis and the size of any PMF lesion noted. When the histopathogical gradings were compared with the mineralogical values the following conclusions were reached:

a. Nodular fibrosis correlated better with quartz concentrations than kaolinite
b. Interstitial fibrosis correlated better with kaolinite concentration than nodular fibrosis
c. In the majority of cases it was relatively easy to separate the china clay cases from the china clay and china stone cases histologically.

This study shows that a pneumoconiosis may result from nonfibrous silicates in the absence of free silica, in this case kaolin, and interstitial fibrosis is the predominant lesion. Further studies of this type are necessary to comprehend the toxic effects of free silica and nonfibrous silicates on the human lung.

REFERENCES

1. Craighead, J.E., Kleinerman, M.D., Abraham, J.L., Gibbs, A.R., Green, F.H.Y., Harley, R.A., Ruettner, J.R., Vallyathan, V., Juliano, E.B.: Diseases associated with exposure to silica and non-fibrous silicate minerals. *Arch. Pathol. Lab. Med.* In Press.
2. McLaughlin, A.I.G.: Pneumoconiosis in foundry workers. *Br. J. Dis. Chest* 4:297-308 (1957).
3. Nagleschmidt, G.: The relation between lung dust and lung pathology in pneumoconiosis. *Br. J. Ind. Med.* 17:247-259 (1960).
4. Gibbs, A.R., Craighead, J.E., Pooley, F.D., Wagner, J.C.: The pathology of slate workers' pneumoconiosis in North Wales and Vermont. In: *Inhaled Particles VI.* In Press.
5. Heppleston, A.G., Morris, T.G.: The progression of experimental silicosis. *Am. J. Pathol.* 46:945-958 (1965).
6. Le Bouffant, L., Daniel, H., Martin, J.C., Bruyere, S.: Effect of impurities and associated minerals on quartz toxicity. *Ann. Occup. Hyg.* 26:625-634 (1982).
7. Koskinen, H.A., Tiilikainen, A., Nordman, H.: Increased prevalence of HLA-Aw19 and of the phenogroup Aw19,B18 in advanced silicosis. *Chest* 83:848-852 (1983).
8. Wagner, J.C., Pooley, F.D., Gibbs, A.R., Lyons, J., Sheers, G., Moncrieff, C.B.: Inhalation of china stone and china clay dusts: the relationship between the mineralogy of the dust retained in the lung and pathological changes. *Thorax* 41:190-196 (1986).

SILICA—IS IT A CARCINOGEN IN THE RESPIRATORY TRACT?

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The role of silica in the causation of bronchogenic carcinoma in man is a contemporary question of great public health importance.[1,2] Should silica be found to contribute to the pathogenesis of bronchogenic carcinoma, without question, rigorous controls for its use in industry must be introduced. However, my evaluation of the contemporary epidemiological, experimental and medical information at present does not permit me to conclude that the scientific evidence implicates silica in the causation of this neoplastic disease. Not only is the epidemiological information inadequate for reasons which will be discussed below, but the experimental work in animal models is deficient. In the absence of more convincing evidence, it can be stated with conviction that restrictions on the use of crystalline silica in industry should not be introduced for the sole purpose of eliminating its alleged role in cancer. There are countless studies in the medical literature which attest to the contribution of silica in the pathogenesis of pulmonary parenchymal fibrosis, but even in this area, differences of opinion exist based on the interpretation of the scientific information.[3]

In a widely quoted publication, Sir Bradford Hill, a noted English epidemiologist, proposed nine general criteria which should be employed in assessing the possible role of an environmental pollutant in the causation of a disease process.[4] The evaluation of the scientific information recommended by Dr. Hill is an appropriate basis for this analysis. In brief, Hill expressed the view that a cause and effect relationship is improbable if epidemiological associations cannot be demonstrated consistently in different studies conducted by different investigators in various population groups. He also emphasized the importance of the strength of the association, for weak, but statistically significant associations can often be due to confounding factors unrelated to the issue under investigation. The plausibility and specificity of the association (i.e. the reproducible characteristics of the disease process) and the intensity of the exposure, (i.e., dosage effects) are also matters for consideration. And, finally, Hill pointed out the key role that experimental studies might have in establishing causative relationships.

Human Epidemiology: (i.e. consistency and strength of the association)

Ideally, prospective longitudinal studies of worker populations exposed to silica would provide definitive information on cancer risks, but this often is obviously not possible. Accordingly, it is necessary for epidemiologists to conduct cross-sectional analyses to determine the prevalence of a disease in a population associated with an alleged environmental pollutant. By comparing the prevalence of lung cancer in a dust-exposed population with members of a comparable subset of a non-exposed population group, (presumably individuals having similar demographic characteristics) the potential risk of a disease can be established. Although a large number of systematic investigations of this type have been carried out on workers employed in a number of different industries, the results fail to conclusively implicate silica. With regard to bronchogenic carcinoma, it is imperative that considerations of tobacco smoking be employed in any analysis, since it is clearly the major risk factor in the development of the disease. In addition, among industrial workers, environmental pollutants possessing known carcinogenic properties, should also be considered and appropriately evaluated.

It is clear from a review of the published literature that the prevalence of bronchogenic carcinoma in a number of silica.exposed worker groups exceeds the prevalence in the control population.[1-3] However, in these studies, with one exception, cigarette smoking and exposure to toxic, potentially carcinogenic inhalants in the workers' environment have not been taken into consideration. Thus, these studies *de facto* cannot be used in a definitive analysis of the question. Admittedly, this is a difficult problem to address because of the widespread use of tobacco products among so-called "blue-collar workers." In a concerted effort to address these problems, Hessel, P.A., et al.[5] studied South African gold miners with autopsy-proven pulmonary silicosis. In this investigation, a statistically significant increase in the prevalence of bronchogenic carcinoma was *not* found when environmental pollutants such as smoking were excluded as an alternate pathogenic consideration. This investigation was clearly superior in design to many others in view of the fact that the worker population had pathologically demonstrable silicosis. The observations referred to above contrast with the results of a study in Ontario in which applicants for workers' compensation were evaluated.[6] In this investigation, the silica-exposed population exhibited a significant increase in bronchogenic carcinoma when the effects of cigarette smoking were controlled. However, human factors, including the potential benefits of compensation, may well have influenced and possibly biased the makeup of the cohort group. A recent epidemiological study of ceramic workers came to a similar conclusion.[7]

Exposure Criteria: (i.e. biological gradient and temporality)

Should silica dust play a role in bronchogenic carcinoma, one might expect that individuals with severe degrees of silicotic

pulmonary disease would exhibit a higher prevalence of bronchogenic carcinoma than those claiming exposure but exhibiting no evidence of silica-induced disease. There have been only two reported studies which suggest such a relationship;[8,9] thus, a dosage effect has not been demonstrated convincingly. This is an important shortcoming of the existing epidemiological evidence.

Exclusion of Artifactual Influences: (i.e. specificity and plausibility)

Consideration of cigarette smoking has been referred to above, but pyrolysis products in several different industries and radon pollution among miners have generally not been considered in epidemiological investigations. For example, both soot and coke oven products are recognized and accepted respiratory carcinogens and radon (in hard rock miners) has been increasingly incriminated in the causation of bronchogenic carcinoma.[10,11] Both of these general classes of carcinogens are potential confounding factors among worker populations exposed to silica dust. The role of such foreign substances as asbestos has also not been accorded reasonable consideration.[12]

Animal Studies: (i.e. experimental observations)

Three types of animal investigations have been carried out which are said to demonstrate a carcinogenic role of silica. Wagner, M.M.F. and his colleagues[13,14] first reported that certain forms of silica possess the capacity to induce histiocytic lymphomas when inoculated into the pleural and peritoneal cavities of rats of certain specific strains. These lesions are clearly neoplastic and the phenomena is reproducible, but unexplained. Whatever the mechanism, this form of experimentation in no way can be implicated as a major consideration in assessing whether or not silica plays a role in bronchogenic carcinoma in man.

In the second type of study, animals were exposed to silica in large amounts, either by intratracheal instillation or in aerosols. In the experiments of Stenbeck, et al.,[15] the silica dust was instilled with benzo-a-pyrine, a recognized respiratory carcinogen. Bronchogenic neoplasms developed. As might be expected, bronchogenic carcinomas also were found in animals exposed to foundry dust containing silica and chemical carcinogens.[16] This type of investigation is similar to the pathfinding experimental work of Saffiotti and his associates carried out years ago.[17] This work demonstrated the effect of mineral dusts on the uptake of carcinogens and the subsequent development of respiratory tract neoplasms in animals.

In the third type of study, rats were exposed to large amounts of dust either by intratracheal instillation or aerosol and the animals maintained until death.[18-22] It is clear from these investigations that proliferative lesions develop in the lung parenchyma among animals with fibrotic changes attributable to the silica dust. The malignant nature of these cellular lesions, however, is questionable, for in only a single instance[20] was an extrapulmonary metastatic lesion demonstrated. It is important to evaluate these studies critically, since adenomas and adenomatosis, as well as squamous metasplasia, occur commonly in the lungs of dust-exposed experimental animals as a non-specific cellular response to foreign particulates. Although these lesions mimic malignancy at times, they do not exhibit most of the biologic properties of malignancy. Although the investigators claim that adenocarcinomas and squamous carcinomas developed in exposed animals, their conclusions can be faulted for the following reasons. Firstly, detailed descriptions documenting the morphologic features of malignancy were not provided in the publications and a critical unbiased review of the tumors by a pathologist, expert in the diagnosis of lung cancer was not conducted. Secondly, no apparent attempt was made to demonstrate the biologic malignancy of these lesions by transplantation into alternate hosts such as syngenic animals or nude, athymic mice. And, thirdly, metastases. the critical measure of malignancy, were demonstrated in only a single animal. Investigators working in the area of respiratory carcinogenesis are well acquainted with the adenomatosis and squamous metasplasia which sometimes mimics carcinomas in animals. In the absence of evidence, more concretely establishing the biologic nature of the lesions described, it is difficult to conclude *de facto* that malignancies developed in experimental animals consequent to silica dust exposure.

Pathogenetic Construct: (i.e. plausibility, coherence and analogy)

Experimental studies have not provided a basis for hypothesizing a mechanism of carcinogenesis in man or animals. Silica has not been shown convincingly to be a genotoxic substance and there is no convincing evidence that it serves as a foreign body carcinogen or induces cancer as a result of chronic irritation. Thus, one has little basis for hypothesizing how silica might act, were one to accept the evidence implicating silica in neoplastic disease in experimental animals or man.[23]

CONCLUDING REMARKS

In summary, the experimental evidence in animals, suggesting a possible role of silica in the pathogenesis of bronchogenic carcinomas, is incomplete. I also conclude that the epidemiological studies in humans provide insufficient evidence to permit one to conclude that man is at increased risk of developing carcinoma of the lung as a result of silica dust exposure. My comments in no way exclude silica from consideration as a cause of bronchogenic carcinoma, but only point out the inadequacies of the contemporary scientific information and emphasize the need for additional, carefully designed systematic studies. In the light of the existing information, regulations designed to eliminate the alleged potential of silica in the causation of cancer of the lung are premature.

REFERENCES

1. Silica-exposed workers. In: *The Health Consequences of Smoking. Cancer and Chronic Lung Disease in the Workplace.* A report of the Surgeon General. 1985, pp. 321-54.
2. Goldsmith, D.F., Guidotti, T.L., Jonston, D.R.: Does occupational exposure to silica cause lung cancer? *Amer. J. Indust. Med.* 1982, 2:423-440.
3. Craighead, J.E., Kleinerman, J., Abraham, J.L., et al: Diseases associated with exposure to silica and nonfibrous silicate materials. *Arch. Pathol. Lab. Med.* 1988, 112:673-720.

4. Hill, B.: The environment and disease: association or causation? *Proc. Royal. Soc. Med.* 1965, 29S-30.
5. Hessel, P.A., Sluis-Cremer, G.K., Hnizdo, E.: Case-control study of silicosis, silica exposure, and lung cancer in white South African gold miners. *Amer. J. Indust. Med.* 1986, 10:57-62.
6. Finkelstein, M.M., Liss, G.M.: *Proceedings of the Third International Conference of Environmental Lung Disease*, October 15-18, 1986.
7. Forastiere, F., Lagorio, S., Michelozzi, P., et al: Silica, silicosis and lung cancer among ceramic workers: A case-referent study. *Am. J. Ind. Med.* 1986, 10:363-370.
8. Mur, J.M., Meyer-Bisch, C., Pham, Q.T., et al: Risk of lung cancer among iron ore miners: A proportional mortality study of 1,075 deceased miners in Lorranie, France. *J. Occup. Med.* 1987, 29:762-768.
9. Swaen, G.M.H., Passier, P.E.C.A., van Attekum, A.M.N.G.: Prevalence of silicosis in the Dutch fine-ceramic industry. *Int. Arch. Occup. Environ. Health* 1988, 60:71-74.
10. *Fourth Annual Report on Carcinogens. Summary 1985.* U.S. Department of Health and Human Services. Public Health Service.
11. NIOSH Recommendations for Occupational Safety and Health Standards 1988. *Morbidity and Mortality Weekly Report.* U.S. Department of Health and Human Services. Public Health Service.
12. Craighead, J.E., Mossman, B.T.: The pathogenesis of asbestos-associated diseases. *NEJM* 1982, 306:1446-1455.
13. Wagner, M.M.F., Wagner, J.C., Davies, R. et al.: Silica-induced malignant histiocytic lymphoma: Incidence linked with strain of rat and type of silica. *Br. J. Cancer* 1980, 41, 908.
14. Wagner, M.M.F., Wagner, J.C.: Lymphomas in the wistar rat after intrapleural inoculation of silica. *J. Natl. Cancer. Inst.* 1972, 49:81-91.
15. Stenback, F., Wasenius, V.M., Rowland, J.: Alveolar and interstitial changes in silicate-associated lung tumors in Syrian hamsters. In: *Silica, Silicosis and Cancer*, eds. Goldsmith, Winn, and Shy, 1986, pp. 199-213.
16. Niemeier, R.W., Mulligan, L.T., Rowland, J.: Cocarcinogenicity of foundry silica sand in hamsters. In: *Silica, Silicosis and Cancer*, eds. Goldsmith, Winn, and Shy, 1986, pp. 215-27.
17. Saffiotti, U., Stinson, S.F., Keenan, K.P., et al: Tumor enhancement factors and mechanisms in the hamster respiratory carcinogenesis model. In: *Carcinogenesis—A Comprehensive Survey. Cancer of the Respiratory Tract: Predisposing Factors.* eds. Mass, M.J., Kaufman, D.G., Siegfried, J.M., Steele, V.E., Nesnow, S. 1985, 8:63-92.
18. Groth, D.H., Stettler, L.E., Platek, S.F., et al.: Lung tumors in rats treated with quartz by intratracheal instillation. In: *Silica, Silicosis and Cancer*, eds. Goldsmith, Winn, and Shy, 1986, pp. 243-86.
19. Harvey, J.J., Wagner, M.M.F., Edwards, A., et al.: Tumors induced experimentally by silica: Establishment and characterization of malignant cell lines *in vitro*. In: *Silica, Silicosis and Cancer*, eds. Goldsmith, Winn, and Shy, 1986, pp. 229-42.
20. Dagle, G.E., Wehner, A.P., Glark, M.L. et al.: Chronic inhalation exposure of rats to quartz. In: *Silica, Silicosis and Cancer*, eds. Goldsmith. Winn, and Shy, 1986, pp. 266-66.
21. Holland, L.M., Wilson, J.S., Tillery, M.I. et al.: Lung cancer in rats exposed to fibrogenic dusts. In: *Silica, Silicosis and Cancer*, eds. Goldsmith, Winn, and Shy, 1986, 267-79.
22. Johnson, N.F., Smith, D.M., Sebring, R. et al.: Silica-induced alveolar cell tumors in rats. *Amer. J. Indust. Med.* 1987, 11:93-107.
23. Heppleston, A.G.: Silica. pneumoconiosis, and carcinoma of the lung. *Amer. J. Indust. Med.* 1985, 7:285-94.