particles in humans and laboratory species. Health Effects Institute Res. Report No. 10. Health Effects Institute. Cambridge, MA.
31. POTT, F. 1989. A hypothesis for explaining the syncarcinogenic effect of cigarette smoke and asbestos. *In* Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke. Proceedings of an International Symposium/Workshop held at the Battelle Seattle Conference Center, April 10–14, 1988 Seattle, Washington. Werner, A. P. & D.-L. Felton, Eds.: 51–62. Battelle Press. Columbus, OH.
32. OBERDÖRSTER, G. 1988. Lung clearance of inhaled insoluble and soluble particles. J. Aerosol. Med. **1**: 289–330.
33. BRODY, A. R. & L. H. HILL. 1982. Interstitial accumulation of inhaled chrysotile asbestos fibers and consequent formation of microcalcifications. Am. J. Pathol. **109**: 107–114.
34. POTT, F. 1984. On the problems of experimental carcinogenicity studies with fibrous dusts administered intraperitoneally, intratracheally, and by inhalation. *In* Problems of Inhalatory Toxicity Studies. Grosdanoff, P., R. Bass, U. Hackenberg, D. Henschler, D. Müller & H.-J. Klimisch, Eds.: 211–220. MMV Medizin Verlag. Munchen.
35. CHOUROULINKOV, I. 1989. Experimental studies on ingested fibres. *In* Non-occupational Exposure to Mineral Fibres. J. Bignon, J. Peto & R. Saracci, Eds. IARC Scientific Publ. No. **90**: 112–126. International Agency for Research on Cancer. Lyon.
36. POTT, F. 1987. Problems in defining carcinogenic fibres. Ann. Occup. Hyg. **31** (No. 4B): 799–802.
37. POTT, F., U. ZIEM, F.-J. REIFFER, F. HUTH, H. ERNST & U. MOHR. 1987. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp. Pathol. (Jena) **32**: 129–152.
38. STANTON, M. F., M. LAYARD, A. TEGERIS, E. MILLER, M. MAY, E. MORGAN & A. SMITH. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J. Natl. Cancer Inst. **67**: 965–975.
39. WAGNER, J. C., G. BERRY & V. TIMBRELL, 1973. Mesotheliomata in rats after inoculation with asbestos and other materials. Br. J. Cancer **28**: 175–185.
40. POTT, F., M. ROLLER, U. ZIEM, F.-J. REIFFER, B. BELLMANN, M. ROSENBRUCH & F. HUTH. 1989. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. *In* Nonoccupational Exposure to Mineral Fibres. J. Bignon, J. Peto & R. Saracci, Eds. IARC Scientific Publ. No. **90**: 173–179. International Agency for Research on Cancer. Lyon.
41. POTT, F., H.-W. SCHLIPKÖTER, M. ROLLER, R. M. RIPPE, P.-G. GERMANN, U. MOHR & B. BELLMANN. 1990. Carcinogenicity of glass fibres with different durability [in German]. Zeutralbl. Hyg. **189**: 563–566.

Comparability of Mesothelioma in Humans and in Experimental Animal Studies

Y. SUZUKI

Division of Environmental and Occupational Medicine
Department of Community Medicine
Mount Sinai School of Medicine of the
City University of New York
New York, New York 10029

IMPORTANCE OF EXPERIMENTAL ANIMAL STUDIES IN THE UNDERSTANDING OF MALIGNANT MESOTHELIOMA

Three major asbestos-related diseases—pulmonary asbestosis, lung cancer, and malignant mesothelioma—can be experimentally induced in laboratory animals.[1] Malignant mesothelioma can be easily induced by asbestos and other fibrous minerals following inhalation or intraperitoneal and intrapleural injection in various animals.[1-5]

The results of these animal studies have suggested a number of factors that influence the induction of malignant mesothelioma.[2,3] In particular, fiber shape, length (>8 μm), diameter (<1.5 μm), and durability were found to be more important than chemical composition in causing cancer. Further, the animal inhalation studies strongly suggested that retention and/or clearance of intrapulmonary asbestos fibers was not the same for chrysotile and the amphiboles, the latter accumulating in the lung far more readily than does chrysotile.[1]

The animal data alluded to above are important to our understanding of asbestos carcinogenicity in humans.

ETIOLOGIC FACTORS IN MALIGNANT MESOTHELIOMA

In human malignant mesothelioma, asbestos is considered to be virtually the exclusive carcinogen, although erionite (a type of zeolite, similar to asbestos in respect to shape and durability)[6] and radiation[7,8] have also been suggested as etiologic agents, albeit with much lower incidence than that seen with asbestos. On the other hand, in animal experiments, various other agents, such as erionite, fibrous glass, brucite, sepiolite, radiation and chemicals (including ethyelene dibromide, ethylene oxide, *N*-methyl-*N*-nitrosurea and diethylstilbesterol) were able to induce malignant mesothelioma.[9,10]

SIMILARITIES OF THE LATENCY BETWEEN HUMAN AND ANIMAL MESOTHELIOMA

It is well accepted that the latency period (from first exposure to the development of the tumor) is quite long for asbestos-induced human malignant mesothe-

lioma: generally, it takes 20 years or more for tumors to appear.[11] The same situation can be seen in animal mesothelioma. In mice, it takes 7 months and longer (the murine life span is approximately 2 years),[12] in rats (which have a 2- to 4-year life span) 1 year and longer,[1,2] and in baboons[13] (with a 30–35-year life span), 6 years and 2 months and longer. In a previous study in our laboratory, comparison of the latency period for mesothelioma in mice induced by a single intraperitoneal administration of asbestos or erionite did not show any notable differences between the fibers, although the dose of each was different.[12] We have also studied the neoplastic effects of inhaled vinyl chloride, a chemical carcinogen, with special reference to the induction of lung tumor (alveologenic tumor).[14]

Unlike the case with mineral fibers, when the dose was increased, the incidence of tumors was higher, and the latency period was inversely related to dose.[14]

COMPARABILITY OF HISTOPATHOLOGY BETWEEN HUMAN AND ANIMAL MESOTHELIOMA

As with human malignant mesothelioma, animal mesotheliomas induced by asbestos vary by cell type. Epithelial, biphasic and fibrous cell types have been identified.

In human mesothelioma, the ratio of the incidence of these three cell types was found to be 65% epithelial, 25% biphasic, and 10% fibrous.[9] In contrast, mouse mesothelioma induced by an intraperitoneal administration of asbestos and erionite was noted to be 1% epithelial, 11% biphasic, and 88% fibrous.[12] The reason for this remarkable difference is not known. However, the dose of the mineral fibers was quite high in the mouse experiments, and it would be interesting to know whether the proportions would change if the dose were much smaller. Further, the incidence of cell type in the tumors induced by inhalational exposure to asbestos should be examined.

TYPE OF ASBESTOS ASSOCIATED WITH THE INDUCTION OF MALIGNANT MESOTHELIOMA

Although it is generally accepted that all types of asbestos can induce human malignant mesothelioma, the incidence of human malignant mesothelioma is said to vary among asbestos types. Some epidemiologists[15,16] have reported that crocidolite has a much greater capacity to induce human malignant mesothelioma, although for animals, all types of asbestos could induce the tumor without notable differences in incidence.

ASBESTOS TISSUE BURDEN STUDY IN MALIGNANT MESOTHELIOMA

A number of asbestos tissue burden studies have been done to evaluate the level of exposure to asbestos in humans. At first, the number of asbestos bodies (ferruginous bodies) in 1 wet gram of lung were used as the marker for the level of asbestos. Later the type, number, and size distribution of intrapulmonary asbestos fibers were determined by analytical electron microscopy. These data have been used to understand the pathogenicity of human asbestos-related diseases.

In this symposium, a new concept, the translocation of intrapulmonary asbestos fibers into other tissues, has been introduced by Dodson and his associates[17,18] and Kohyama and Suzuki.[19] The former investigators discovered that unlike amphiboles, intrapulmonary chrysotile asbestos could move into the pleura and the regional lymph nodes. The latter have found that, unlike amosite, chrysotile could be translocated from the lung into the pleura and the peritoneum. In tissue samples from asbestos-insulation workers, the hyaline plaque, pleural mesotheliomatous tissues, and peritoneal mesotheliomatous tissues contained chrysotile fibrils almost exclusively, although concomitant intrapulmonary asbestos was predominantly amosite with smaller numbers of chrysotile fibers.

Stanton's hypothesis, that the most dangerous fibers are those >8 μm in length and <1.5 μm in diameter, was based upon the observed size distributions of asbestos fibers that were used for direct innoculation into the rat pleural cavity, producing mesothelioma. However, it may now be necessary to test this hypothesis by inducing mesothelioma in animals by inhalation rather than by direct inoculation. It will be interesting to know whether the size distribution of the fibers is similar among three different samples: the preinhalation asbestos fiber (the standard asbestos sample used for inhalation), the post-deposition fibers in the lung (intrapulmonary asbestos fibers), and the translocated fibers in the pleura or the peritoneum (intramesotheliomatous asbestos fibers).

REFERENCES

1. WAGNER, J. C., G. BERRY, J. W. SKIDMORE & V. TIMBRELL. 1974. The effects of the inhalation of asbestos in rats. Br. J. Cancer 29: 252–269.
2. STANTON, M. F. & C. WRENCH. 1972. Mechanisms of mesothelioma induction with asbestos and fibrous glass. J. Natl. Cancer Inst. 48: 797–821.
3. STANTON, M. F., M. LAYARD, A. TEGERIS, E. MILLER, M. MAY & E. KENT. 1977. Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimention. J. Natl. Cancer Inst. 58: 587–603.
4. POTT, E., F. HUTH & K. H. FRIEDRICKS. 1974. Tumorigenic effect of fibrous dusts in experimental animals. Environ. Health Perspect. 9: 313–315.
5. POTT, F. 1980. Animal experiments on biological effects of mineral fibers. *In* Biological Effects of Mineral Fibers. Vol 1. J. C. Wagner, Ed., 261–269. IARC Sci. Pub. No. 30. Lyon, France.
6. BARIS, Y. I., A. A. SAHIN, M. OZLMI, I. KHSE, E. OGEN, B. KOI ACAN, M. ARTVINLI & A. F. GOKTEPELI. 1978. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgrup in Anatolia. Thorax 33: 181–192.
7. STOCK, R. J., Y. S. FU & J. R. CARTER. 1979. Malignant peritoneal mesothelioma following radiotherapy for seminoma of the testis. Cancer 44: 914–919.
8. BABCOCK, T. L., D. H. ROWELL & R. S. BOTHWELL. 1976. Radiation-induced peritoneal mesothelioma. J. Surg Oncol. 8: 369–378.
9. SUZUKI, Y. 1981. Pathology of human malignant mesothelioma. Sem. Oncol. 8: 268–282.
10. PETERSON, J. T., D. GREENBERG & P. A. BUFFLER. 1984. Non-asbestos-related malignant mesothelioma. Cancer 54: 951–960.
11. SELIKOFF, I. J., E. C. HAMMOND & H. SEIDMAN. 1980. Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 46: 2736–2740.
12. SUZUKI, Y. & N. KOHYAMA. 1984. Malignant mesothelioma induced by asbestos and zeolite in the mouse peritoneal cavity. Environ. Res. 35: 277–292.
13. GOI DSTEIN, B. & F. S. J. COETZEL. 1990. Experimental malignant mesothelioma in baboons. S. Afr. J. Sci. 86: 89–93.

14. SUZUKI, Y. 1983. Neoplastic effect of vinyl chloride in mouse lung: Lower doses and short-term exposure. Environ. Res 32: 91–103.
15. NEWHOUSE, M. L. & K. R. SULLIVAN. 1989. A mortality study of workers manufacturing frictions materials. 1941–86. Br. J. Ind. Med. 46: 176–179.
16. ACHESON, E. D., M. J. GARDNER, E. C. PIPARD & L. P. GRIME. 1982. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40 year follow-up. Br. J. Ind. Med. 39: 344–348.
17. DODSON, R. F., M. G. WILLIAMS, C. J. CORN, A. BROLLO & C. BIANDIE. 1990. Asbestos content of lung tissues, lymph nodes, and pleural plaques from former shipyard workers. Am. Rev. Resp. Dis. 142: 843–847.
18. DODSON, R. F. 1991. A comparison of asbestos burden in lung parenchymal lymph nodes, and plaques. Ann. N.Y. Acad. Sci. This volume.
19. KOHYAMA, N. & Y. SUZUKI. 1991. Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers. Ann. N.Y. Acad. Sci. This volume.
20. SUZUKI, Y. & N. KOHYAMA. 1991. Translocation of inhaled asbestos fibers into other organs. Am. J. Ind. Med. 19: 701–704.

Discussion: Part 8

DR. MORANDO SOFFRITTI (*Institute of Oncology, Bologna, Italy*): In this session three important items are addressed. The first is evidence that mesothelioma may occur in persons unexposed to asbestos, and that there may be a background occurrence due to other fibers or other reasons. And, while it is common experience that when a complete history is obtained, exposure to asbestos can be proved in nearly all cases, that still does not exclude the possibility that other causes can exist. The second item is the problem of the extent to which experimental bioassays can be predictive in assessing human risk. Finally, the third item is a consideration of the best experimental approaches to reach optimal results.

DR. BARRY CASTLEMAN (*Baltimore, Md.*): In my work with the Natural Resources Defense Council in dealing with the Environmental Protection Agency's proposed ban on asbestos, I found that Monsanto contributed information on a substitute product that they had developed—I believe that it was a soluble fiber-based phosphate.

SOFFRITTI: No; it was not soluble. After one year, 10 to 15 percent of the fibers were still present in tissues.

CASTLEMAN: So it produced tumors even though it was alleged to be soluble?

SOFFRITTI: Yes, but we aren't talking about solubility.

CASTLEMAN: Another point I would make is that some companies have dealt with the problem by developing substitute fibers that are too large to reach the deeper lung recesses, thereby avoiding the problem of whether or not the fibers will cause lung abnormalities. Since man-made fibers can be made whatever size you wish, by extrusion, this is a good way of dealing with respirable fibers.

DR. JACQUES DUNNIGAN (*University of Sherbrooke, Sherbrooke, Québec, Canada*): Dr. Suzuki mentioned that all fiber types in human studies have been shown to produce mesothelioma. He did acknowledge that crocidolite, of all fiber types, is much more potent. However, he said that in animal studies this was not so. All fiber types seem to be equally potent.

A paper in *Environmental Research* reported that if you inject equivalent mass doses of chrysotile and crocidolite you may indeed see an approximately equal tumor yield. But if you inject 1 mg of chrysotile, you are in effect injecting 1 billion fibers with lengths equal to or longer than 8 microns or 13 billion fibers with lengths of 75 microns. Whereas when you inject 1 mg of crocidolite, you are injecting 8 million fibers. Therefore, if you are going to report the tumor yield in experiments on a mass dose basis, I agree with your conclusion, but I think that it is more appropriate to report tumor yield per unit fiber. When you do this, you will see that crocidolite indeed is a far more potent inducer of mesothelioma. I would ask Dr. Davis and Dr. Pott and Dr. Suzuki: what is the impact of these considerations on future experimentation?

DR. YASUNOSUKE SUZUKI (*Mount Sinai School of Medicine, New York, N.Y.*): It is difficult to answer your question without knowing full size distributions and surface areas in addition to number.

DUNNINGAN: These were reported by Dr. Phil Cook of the U.S. Environmental Protection Agency. Somewhat similar data had been published in 1981 by Jean Bignon's group in Paris.

DR. VICTOR ROGGLI (*Duke University, Durham, North Carolina*): Dr. Mark, when you consider that in surgical pathology we tend to make diagnoses that are fashionable at the time, and when we consider the reluctance of a pathologist in

ANNALS OF
THE NEW YORK ACADEMY
OF SCIENCES

Volume 643

The New York Academy of Sciences
2 East 63rd Street
New York, New York 10021

THE THIRD WAVE OF ASBESTOS DISEASE: EXPOSURE TO ASBESTOS IN PLACE

PUBLIC HEALTH CONTROL