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March 15, 1943

Dr. Ludwig Hektoen, Chairman
Committee on Cancer Research
National Cancer Institute
Bethesda, Maryland

Dear Dr. Hektoen:

In analyzing the results of a recently completed inhalation experiment on asbestosis, I was startled to discover that a small group of 11 white mice that had been inhaling asbestos dust from 15 to 24 months showed an excessive incidence (81.8%) of pulmonary cancer. This experience was quite at variance with the results in all our previous long-term dust exposures which were summarized and published by Verwald and Karr in the American Journal of Pathology, January 1938. I would have attached little significance to this recent finding because of the small number of animals involved, but for the fact that the literature now contains some 10 reports of pulmonary cancer in cases of human asbestosis. Even these I have heretofore attributed to selection of material as we have found no cases of pulmonary tumor in surveys of employed asbestos workers. However, Gloyne, Merewether and other English observers contend that asbestos has a specific carcinogenic action on the lungs. The question is of considerable importance in industrial medicine because of the associated compensation aspects and from a scientific view point, it interests me a great deal.

In view of this recent finding I have reanalyzed the results of a large number of dust inhalation experiments that we have carried on during the past 25 years. The incidence of pulmonary tumors is shown in the appended table. It would appear that, except in mice, tumors have been generally uncommon in the strains of different species that we had used. Guinea pigs have shown occasional adenomas of the lung whose incidence is not influenced by dust exposure or by the type of dust involved. However, in white mice that survived for 15 or more months in our dust rooms, various forms of lung tumors were much more frequent. The average incidence of such tumors in a group of 143 mice exposed to 4 different quartz-containing dusts was 18.8% but this appears small in contrast to this incidence of 81.8% in the asbestos mice. In 51 younger mice that died or were killed after exposures of 10 or 11 months there was only one instance of pulmonary tumor. Therefore, either age duration of dust exposure must be important.

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None of these experiments was planned to study carcinogenic effects. Mice were only used as there was space in the dust rooms and many of these animals that died after short exposures were discarded without autopsy as they could not have developed a sufficient amount of dust reaction to be of interest. The strain of mice kept in the laboratory has changed from time to time by importation of new stock. At one time we did procure from Dr. Maud Slye some cancer susceptible stock but as these animals failed to react to inhaled quartz we lost interest in the subject.

Obviously under such conditions, the results with asbestos mean nothing but in view of the considerations which I have cited, I believe they should be checked. A decisive answer to this question would be of real practical value. From what we have learned about the action of asbestiform minerals in the living body, I would not be surprised to discover that their carcinogenic effects are different from those of other minerals. Their crystallographic structure is unique. They apparently act as mechanical irritants rather than chemically as is the case with quartz and other forms of free silica. On crushing or grinding, asbestos fibres loose practically all their irritating capacity; quartz on the other hand, becomes more irritating as the particle size decreases. Asbestos provokes fibrosis only in the lungs of certain species; quartz excites such reaction in any organ of any species of animal that we have tested. Asbestos seems to have no specific action upon pulmonary epithelium but in some species, it causes an unusual type of diffuse fibrosis which compresses and distorts the epithelial-lined respiratory bronchioles but often fails to obliterate them. However, this mechanism would not appear to be the one responsible for the mouse tumors for this is one of the species which develops no fibrosis on exposure. Possibly, the lack of reaction is due to superior upper respiratory protection against inhaled foreign bodies. The lungs of mice, exposed to asbestos dust for two years reveal relatively few fibre and all of these are short and coated to form that peculiar structure known as the asbestos body.

In order to verify our accidental discovery of possible carcinogenic action of fibrous asbestos, I would like to repeat the mouse inhalation experiment under properly controlled conditions. I would breed a large number of cancer susceptible mice, splitting each litter into three groups and keep a record of the ages of each. One third of the offspring would be kept in a normal atmosphere as a control; another third would be exposed to quartz dust as a second control and the other third would be exposed to asbestos dust.

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Would attempt to obtain 500 mice for each group. The exposures would apparently have to be continued for 15 to 24 months. Our routine in such experiments provides for dusting 8 hours a day, 6 days a week.

We have all the necessary equipment for such experiments and a trained laboratory personnel. Funds are lacking however. Our previous study of asbestosis which continued for a period of 7 years was financed by the Asbestos Association. Since this group of manufacturers has already invested $30,000, I cannot ask them for further contributions. I discussed the matter with Dr. Rhodes at the Memorial Hospital who favored and was of the opinion that it was worthy of consideration by your committee. I am therefore applying for a grant of $5,000 to cover the cost of the first year's expense.

I had told Dr. Rhodes that I would be willing to do the entire experiment for this amount and ordinarily I should. However, on my return from New York, I found two proposals for investigations of other industrial dusts each of which yield the Laboratory $5,000 a year. As I have only two dust rooms at the present time free for new work, I cannot afford to tie up one of them for two years for half the amount.

Should you be favorably impressed with this proposal I would appreciate any criticisms or suggestions.

Sincerely yours,

Leroy U. Gardner, M. D.
Director

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