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Editorial

Asbestos and Cancer: The International Lag¹

By the early 1940s, the question of whether asbestos caused lung cancer seemed to have been settled. Asbestosis, the fibrotic changes in the lung resulting from the inhalation of asbestos fibers, had been recognized for more than 40 years. In 1934 in England, Wood and Gloyne (1) reported 2 cases of lung carcinoma seen at autopsy in 43 cases of asbestosis, and in 1935 Gloyne (2) gave a complete description of these 2 cases. Also in 1935, Lynch and Smith (3) reported one case of lung cancer in an asbestosis case in the United States, and in 1936, Egbert and Geiger (4) reported a case—also from the United States. In Germany, Nordmann added 2 cases of lung cancer in 2 cases of asbestosis, thus making a total of 6, and concluded, "A cause-effect correlation must be present here, even if I had been the only observer. We are indeed facing an occupational cancer which affects asbestos workers" (5). German investigators quickly accepted Nordmann's views (6-8). They were reinforced by an animal study in which Nordmann and Sorge reported pulmonary carcinomas in 2 white mice as the result of asbestos dust inhalation (9). Other German researchers considered this the experimental evidence needed for proof and gave Nordmann credit for discovering the relationship between asbestos and lung cancer (10, 11). Meanwhile, in the United States, Hueper declared that, "Asbestosis cancer of the lung is the most recent newcomer among the occupational cancers of this organ" (12). In 1950, West Germany classified cancer of the lung, when associated with asbestosis (of any degree), an occupational disease.

And yet, in the United States the question of asbestos and lung cancer was debated for another 20 years. What prolonged the debate and prevented earlier acceptance of a relationship?

¹ Based on an unpublished manuscript: Asbestos and Cancer, The First Thirty Years.

First, Gloyne, to whom credit for the discovery should really have been given, was extremely cautious in interpreting his findings. In his report of 1935, Gloyne quoted Bridge and Henry (13) on conditions that must be fulfilled in order that cancer be classified as industrial in origin: (1) the incidence in the occupation under review should exceed significantly that in the general population, and (2) in the occupation concerned, there should be sufficient association of the workers with a substance proved experimentally to have carcinogenic properties. In Gloyne's lifetime, these conditions were not fulfilled. Nearly all of the evidence dealt with the association of asbestosis and cancer as seen at autopsy. In a paper published posthumously in 1951, Gloyne expressed concern for the selection obviously at work in picking cases for autopsy, pointing out that necropsy records at the London Chest Hospital showed 21.3 per cent primary lung cancer, whereas in the general population, only 2.4 per cent of deaths from all causes among persons 15 years of age and more were due to malignant disease of the lung.

Lynch, who actually received credit in the end, was no less skeptical. He was concerned not only with the problem of selection, but also with the lack of experimental evidence (14-19). Only Nordmann and Sorge claimed to have produced cancer experimentally with asbestos, whereas experiments by Vorwald and Karr (20), King and associates (21), Vorwald and co-workers (22), Behrens (23), and Hueper (24) had negative results. Moreover, W. E. Smith (25), in a review of work with asbestos and animals, concluded that the study by Nordmann and Sorge appeared to demonstrate that asbestos did not provoke lung tumors, because of the 2 tumors reported in animals exposed to asbestos, one was, on the basis of photographs presented, merely a squamous-cell metaplasia, whereas the other, asserted to be an adenocarcinoma, "is a type of tu-

mor that can arise spontaneously from the mouse adenoma." Even Hueper seemed to agree with this, and outside of Germany, Smith's views on Nordmann's work gained some acceptance (19, 26, 27).

Another problem in the United States was the attitude of leaders in the field of pneumoconiosis—particularly Vorwald, Lanza, and Gardner (20, 22, 28–32). Their expressed concern was the lack of experimental data. In addition, the possibility of a different relationship between asbestosis and lung cancer as compared to that between silicosis and lung cancer must have been disturbing. Lanza was also concerned about the English claims of an association in autopsied cases of asbestosis, and he wondered how many cases of lung cancer would be found if lungs from any sort of population were subjected to the same minute scrutiny (29).

The situation could have been resolved, from the American point of view, by a report by Merewether (33) who, in 1949, compared lung or pleural cancer in cases of asbestosis reported for compensation with lung or pleural cancer in cases of silicosis. This was clearly the most important single study in bringing about a consensus in Great Britain. In America, however, this seems to have given birth to a new idea: that there was a relationship between asbestosis and cancer in England and Germany, but not in the United States. This idea apparently originated with W. E. Smith; however, another Smith (K. W.) enlarged on this, stating that there was a difference due to the type of fiber used in England and Germany as compared to that used in the United States (34, 35). Italian writers picked this up as an argument for a difference between Italy and England (36, 37). The argument was also repeated by Eckhardt (38), Gilson (39), and Johnstone and Miller (40).

There was no answer to the question of fiber type (or fiber contamination), and it no doubt delayed acceptance by those who were uncertain as to whether a problem truly existed in the United States. There was, however, an answer to the question of selection that so bothered Gloyne and Lynch. In 1955, an epidemiologic study was reported of the type envisioned by Bridge and Henry in which it was shown that the incidence of lung cancer in a group of workers exposed to asbestos in England greatly exceeded that in a comparable group in the general population (41). This marked an end to a period when conclusions were based largely on pathologic and clinical observations, and opened the

door for contributions by biostatisticians and epidemiologists. It probably also set back acceptance of a relationship between asbestos and cancer in the United States by another decade.

The epidemiologists demanded epidemiologic evidence. In 1956, for example, Hammond and Machle (42) stated that with regard to a relationship between asbestos and lung cancer "... there are at present too few cases and too little epidemiologic data to establish a significant relationship." In 1958, the Committee on Occupational Cancer of the AMA Council on Occupational Health concluded that individual case reports contribute little to an understanding of occupational cancers and that "specific increases in age, sex, and site-specific cancer incidence above normal incidences for the same age, sex, and site represent the only reliable evidence for the existence of an occupational cancer hazard" (43).

The first 2 epidemiologic studies of this kind of workers exposed to asbestos in North America in 1958 and 1960 did not show a significant increase in lung cancer (44, 45). Thus, as recently as 1961, it could be said that "there is no epidemiological evidence [of an association between asbestos and lung cancer] among American workers" (46).

So what ended the debate in the United States? Probably 3 things: (1) positive results of epidemiologic studies in the United States in 1963 and 1964, (2) a widely read study of 1960 that showed that asbestos was associated with a rare tumor, malignant mesothelioma, and (3) experimental evidence in 1962 and 1964 that asbestos had carcinogenic properties (47–51). Thus, the kind of evidence demanded by Bridge and Henry, and which would have satisfied Gloyne, was finally developed 30 years after Gloyne made his initial observations, and more than 2 decades after the acceptance of a relationship between asbestos and lung cancer in Germany.

Clearly, the matter involved a question of what is acceptable and conclusive evidence. Perhaps special rules are needed for relationships such as that between asbestos and lung cancer where some other biologic response, such as asbestosis, can be used as evidence of significant exposure, and the rules proposed by Bridge and Henry were not appropriate after all. Many investigators were convinced of a relationship long before epidemiologic and experimental evidence was available. Aside from the high incidence of lung cancer in patients with asbestosis, they were impressed by the predominance of cancer in the

lower lobes, the time lapse between exposure and disease, the high incidence in women, and the young age of many of the patients seen. Moreover, there were reasonable theories concerning mechanisms by which asbestos could cause cancer.

In any event, the issue was definitely settled for the United States at a conference on the biologic effects of asbestos held in New York City in 1964 (52). At that conference, additional epidemiologic evidence was presented, and of 20 papers presented in which an opinion was expressed, none dissented from the view that asbestos is a cause of cancer.

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