Milestones... in Investigative Pathology

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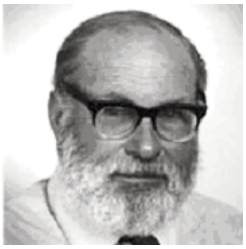
Asbestos and Mesothelioma

(1) Wagner JC, Sleggs CA, and Marchand P. Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province, *Brit J. Industr Med*, 1960, 17:260.



J.C. Wagner

As you endure another ad extolling the virtues of legal counsel for mesothelioma patients, you could assume that we've known since the Industrial Revolution that asbestos causes mesothelioma. Au contraire. We didn't know that asbestos pneumoconiosis was associated with increased risk of mesothelioma until Dr. Wagner suggested it in 1960. The above article[1], available at *http://imig.org/wp-content/uploads /2010/03/Wagner_Historic-Meso-Article_1960.pdf* is the first in a series of critical contributions that demonstrated the causal association of asbestos fibers and mesothelioma.

Pathologists of the 1930s and '40s were sorting out the biphasic morphologic potential of anecdotal cases of mesothelioma (reviewed in [2]). In these early case reports, etiology was not postulated, occupational history was not recorded, and ferruginous bodies were not described.

Industry was well aware of the insulation and fire-retardant qualities of asbestos, and used it extensively in construction and ship-building in WWII. One patient in our hospital remembered shipyard construction duty where "there was so much asbestos around that we had snowball fights with it."

J.C. Wagner was a pathologist working in South Africa from 1951-62. The story goes that the initial observation is traced to an autopsy on an asbestos miner in 1956, in which he identified asbestos fibers in a gelatinous pleural neoplasm (*http://imig.org/about/wagner-award-recipients-2/j-christopher-wagner-biography*). He sought out other cases of mesotheliomas, and reported a cluster of patients with mesothelioma who had been physically close to asbestos mining or milling. In this initial paper, he gives a history of asbestos mining and milling in South Africa, indicating a transition from manual separation of fibers ("cobbing") to automated milling in around 1915. 32 of the 33 patients he presented were either miners, millers, or children exposed to dusts from these industries 20-40 years prior. His initial paper[1] was observational, and hypothesized a higher-than-expected probability of mesotheliomas in individuals exposed to asbestos.

Dr. Wagner recognized the need to prove an etiologic relationship between asbestos and mesothelioma. He published data in 1962[3] on rats inoculated in the pleural space with suspensions of different types of asbestos. 3 of 50 (6%) rats receiving crocidolite ("blue" asbestos) or chrysotile ("white" asbestos) developed pleural mesotheliomas, said to show similar morphologies to human mesotheliomas. After moving to the UK in 1962, he published data in 1969[4] on rats inoculated in the pleural space with 20 mg of crocidolite, chrysotile, or amosite fiber suspension, then followed to natural death. 30-40% of amosite-exposed rats, and 50-70% of the crocidolite- and chrysotile- exposed rats, developed pleural mesotheliomata. None of the saline- inoculated controls rats developed mesotheliomas. Rats with mesotheliomas died at 500-750 days of age, whereas control rats died at around 1,000 days. (No statistical testing was performed on the datasets in either the Nature[3] or Br J Ca[4] papers, so take heart, you qualitative types out there.)

Dr. Wagner recognized that pleural inoculation experiments were unrealistic, so he followed up his pleural inoculation experiments with dust aspiration experiments[5]. Exposures mimicked 7 hour/5 day per week work hours. Amosite was the least fibrogenic of the three. As expected, increasing exposure led to increasing fiber load in the lungs. Interestingly, there were marked differences in steady-state fiber load following inhalation of similar amounts of crocidolite and chrysotile dust, indicating difference in dust clearance rates. Although chrysotile was cleared much better than crocidolite, the incidence of mesothelioma (6%) was similar to that seen with high-fiber burden crocidolite (6%). Most mesotheliomas developed after 6 months of dust exposure but, astoundingly, 2 rats exposed for only one day each (one to amosite and one to crocidolite) developed mesotheliomas. Assuming careful control of experimental conditions, these data beg the question of whether there is any risk-free exposure to asbestos dust.

Formal handling of asbestos exposure data in humans was sought by the NIH for a case-control study of mesothelioma patients presenting between 1975 and 1980 from three different populations (LA, NY, and the VA system)[6]. Dr. Wagner served as the study Pathologist. Their data showed that "90% of the incidences of pleural mesothelioma among men were directly attributable to past exposures to asbestos." They found an odds ratio of 27-fold for mesotheliomas in individuals with prior asbestos exposure. Statistical analysis confirmed what Dr. Wagner had suspected with that first autopsy.

In summary, Dr. Wagner made the initial association of occupational or environmental exposure to asbestos with subsequent risk for development of mesothelioma. This association required a prepared scientific mind in a region where there was high exposure to the etiologic agent. Following Koch's postulates, he showed that exposure of an animal model to the purified putative etiologic agent increased the incidence of a disease that was rare in the untreated control animals. His experimental work was confirmed by the exposure of humans involved in industries involving insulation and fire retardant materials. Careful history-taking was critical to making the observation, as the delay from exposure to signs/symptoms is measured in decades.

The scientific demonstration of asbestos as the major etiologic agent in mesothelioma prompted marketing of legal recourse to patients receiving this diagnosis. Asbestos has no medicinal value to the human, so our legal system recognized a skewed risk:benefit ratio to asbestos exposure, and proceeded to bankrupt the asbestos industry. Isn't this interesting, that we've witnessed destruction of a legitimate insulation/fire retardant materials industry because its dusty product leads to around 90% of the cases of a rare disease, when we've knowingly tolerated tax revenue subsidy of the growth, processing, and marketing of tobacco, whose dusty product leads to around 90% of the cases of the tobacco-associated common diseases, COPD and primary lung carcinoma?

References:

1. Wagner JC, Sleggs CA, and Marchand P. Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province, *Brit J. Industr Med*, 1960, 17:260.
2. Campbell WN. Pleural mesothelioma. *Am J Pathol* 1950; 26:473-487.
3. Wagner JC. Experimental production of mesothelial tumours of the pleura by implantation of dusts in laboratory animals. *Nature* 1962; 196:180-181.
4. Wagner JC, Berry G. Mesotheliomas in rats following inoculation with asbestos. *Br J Cancer* 1969; 23:567-581.
5. Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. *Br J Cancer* 1974; 29:252-269.
6. Spirtas R, Heineman EF, Bernstein L, et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994; 51:804-811.