the ideal area for these investigations, as the three main types of asbestos were produced in the same amounts by a similar labor force. In an international study, we set out to see whether the role of crocidolite could be confirmed in other countries. Over the years, our initial hypothesis has held. The vast majority of mesotheliomas are associated with exposure to crocidolite asbestos. A small number of cases have been recorded following exposure to other forms of amphibole asbestos: amosite, tremolite, and anthophylite. No mesotheliomas have been shown to have occurred in chrysotile-exposed workers, unless the exposure has been intense and for more than 20 years. In addition, there must be tremolite contamination of the chrysotile.

Two other facts are of great importance:

1. The majority of these tumors occurred following prolonged exposure to large quantities of fiber. This situation rarely exists today.

2. There is a "natural" incidence of these diffuse mesotheliomas. At least 10% of these diffuse mesotheliomas occur without exposure to asbestos dust, and sporadic cases of these tumors were reported before the widespread use of asbestos. □

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2. *Stayner and Colleagues Respond*

We thank Dr Wagner for his comments regarding our paper.[1] We do not believe our article misrepresented the evidence for an association between mesothelioma and asbestos exposure. We agree with Dr Wagner's main point, which is that the incidence of mesothelioma is greater in epidemiologic studies of workers exposed to crocidolite than either chrysotile or amosite, and recognized this fact in our paper. Interpretation of these epidemiologic findings is hampered by the lack of control for potential differences in exposure levels and fiber dimensions.

Nonetheless, ample evidence suggests that exposure to chrysotile is a risk factor for mesothelioma. As we reviewed in our paper, numerous cases of mesothelioma have been reported in several studies of workers exposed to chrysotile. In fact, Dr Wagner recognized in his early papers[2,3] that there were cases of mesothelioma in South Africa and Britain whose only known exposure was to chrysotile asbestos. Toxicologic studies, some of which were conducted by Dr Wagner,[4] also demonstrate an increase in mesotheliomas among animals exposed to chrysotile.

Dr Wagner suggests mesotheliomas occur in chrysotile-exposed workers only when there is tremolite contamination. While this statement is technically correct, it is virtually uninformative. Contamination by small percentages (<1%) of tremolite has been present in all of the reported epidemiologic studies of chrysotile-exposed workers. Unfortunately, studies of workers exposed to pure chrysotile have yet to be reported. In addition, this issue may be viewed as academic since workers are exposed to a mixture of fiber types and to commercial chrysotile containing tremolite.

A key point of our paper is that irrespective of mesothelioma, exposure to chrysotile asbestos should be viewed as a significant carcinogenic hazard. There is no serious disagreement in the scientific community that chrysotile asbestos exposure is causally associated with lung cancer and appears to be as potent a lung carcinogen as crocidolite or other forms of asbestos. The excess of lung cancer is generally far larger than the excess of mesothelioma in most epidemiologic studies of asbestos-exposed workers, a fact recognized in a recent review by Dr Wagner.[5]

Dr Wagner suggested that our paper and the accompanying editorial may have "confused readers." We hope that this letter will help to clarify any remaining confusion about exposure to chrysotile asbestos. Such exposure should be regarded as a serious potential public health hazard. □

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3. The Amphibole Hypothesis: Neither Gone nor Forgotten

Stayner et al.[1] and Cullen[2] failed to present the amphibole hypothesis in a developmental context that lent credence to their assertions that the hypothesis lacked scientific merit. Both indicated that chrysotile may be less potent than some amphibole asbestos minerals in causing mesothelioma. For crocidolite, the evidence is well beyond maybe. In 1964, Wagner[3] reported on a series of 120 mesotheliomas in the Republic of South Africa, (where the three major commercial asbestos fiber types—crocidolite, amosite, and chrysotile—were mined and milled). One hundred cases occurred in individuals exposed to the crocidolite mined and milled in the Cape Province; 10 cases occurred in industrial workers (9 exposed to crocidolite); 1 mesothelioma followed chrysotile exposure in Swaziland; and none followed exposure to amosite in the Transvaal. No exposure data are available for the remaining cases.

The geographic distribution of the mesotheliomas followed the original description of the disease in and around Kuruman.[4] The crocidolite hypothesis was introduced into the United States by Wagner at a meeting of the New York Academy of Sciences in 1964, and his assertions were supported by the clinical observations of Sluis-Cremer.[5]

In 1978, Webster reported on 712 mesothelioma cases confirmed by the South African Tumor Reference Pane.[6] Of these cases, 127 were associated with the mining and milling of asbestos. The pattern remained consistent with Wagner's earlier observations. Further, of 100 mesothelioma cases known to have occurred after environmental exposure, 93 were in persons who lived in and along the Cape crocidolite field, 2 in the area of the Pieterburg crocidolite mine and mill in the Transvaal, and 1 case in a person who lived within the Transvaal amosite field. No cases of environmental mesothelioma were known to have occurred in the chrysolite field of Swaziland. In the remaining 4 cases, the exposures were either uncertain or unknown. The pattern of disease led to the conclusion that crocidolite was a very powerful agent in the cause of human mesothelioma.

Other types of amphibole asbestos have been shown to cause mesothelioma as well. For example, 14 of 528 deaths among 820 former employees of an amosite asbestos factory in the United States were due to mesothelioma and accounted for 2.7% of the total mortality.[7] Miners and millers of Montana vermiculite were exposed to tremolite-actinolite asbestos among other fibrous minerals. Of the 165 deaths in the cohort, 4 mesotheliomas accounted for 2.4% of the total mortality. This confirmed reports of mesothelioma following environmental exposure to tremolite asbestos in Turkey, Greece, and Cyprus (see reference 8 for a review). As more data became available, the amphibole hypothesis emerged from the crocidolite hypothesis.

The activity of tremolite asbestos brings us to the issue of chrysotile asbestos and human mesothelioma. Among 20 cases of asbestosis from Canada, the lung content analyses revealed the presence of a high concentration of tremolite fibers.[9] Pooley hypothesized that fibrous minerals other than chrysotile could be agents in the induction of asbestosis. Later, this hypothesis was extended to include mesothelioma.[10] When the amphibole mineral tremolite is present in a chrysotile deposit, it is never homogeneously distributed throughout the ore. Therefore, exposure to tremolite would be expected to range significantly over time and among different geological locales.[11] When tremolite is present, it may or may not possess an asbestos habit.[12,13] This habit is crucial for imparting carcinogenic potency. Tremolite asbestos is a human and animal carcinogen, while the cleavage fragment is not.[8,14] The crocidolite and amphibole hypothesis has now further evolved into the tremolite hypothesis. While the relative potency of chrysotile as a lung carcinogen varies, its potency to cause mesothelioma is consistently much less than that of crocidolite.[15]

In the title of his annotation, Cullen stated that the amphibole hypothesis was "gone but not forgotten." We believe that he is half correct in that the hypothesis is not forgotten. Given the strength of the scientific evidence supporting the amphibole hypothesis,[3–15] surely it has not gone to wherever it is Cullen wishes it would go. On the other hand, we would not wish his annotation to be gone; for it simply to be forgotten would be sufficient. □

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4. The Hypothesis Is Still Supported by Scientists and Scientific Data

We respond here to the errors in an annotation by Cullen[1] to our *Science* article,[2] which espouses the amphibole hypothesis of mesothelioma. The underlying foundation of the amphibole hypothesis is a study by Wagner in 1960, which he has updated more recently[3] and which is still supported by studies showing increased risks of mesothelioma in a number of cohorts (gas mask workers, cigarette filter manufacturers, and others) exposed to crocidolite asbestos. Stayner and colleagues acknowledge, "The proportion of deaths due to mesothelioma are strikingly lower in chrysotile-exposed miners and millers than in crocidolite miners."[4(p184)] To state that our 1990 article in *Science*[2] was the first introduction of the amphibole hypothesis and to cite his 1987 review on asbestos-induced