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. □

Arthur M. Langer, PhD
Robert P. Nolan, PhD

The authors are with the Environmental Sciences Laboratory, Brooklyn College of The City University of New York, Brooklyn, NY.

Requests for reprints should be sent to Arthur M. Langer, PhD, Environmental Sciences Laboratory, Brooklyn College of The City University of New York, Brooklyn, NY 11210.

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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

lung cancers[5] as contributing to its demise are both wrong in view of the many original epidemiologic studies on mesothelioma by Wagner, the McDonalds, Liddell, Acheson and Gardner, deKlerk, Hughes and Weill and others that support this hypothesis. Moreover, the thrust of the amphibole hypothesis, as reemphasized recently by the McDonalds[6] and Wagner,[3] among others, is mesothelioma and *not* lung cancer. To allude to data from lung fiber burden studies, rodent toxicology, and lung cancer risks as primary bases for the advancement or refutation of the amphibole hypothesis is misconstrued. On the basis of recent mechanistic data, lung fiber burden studies, and some epidemiology, we suggested in our *Science* paper that chrysotile may be less pathogenic than crocidolite in the causation of lung cancer. However, given that smoking is a more powerful factor in lung cancer than asbestos exposure, it is more difficult to define the various roles of different types of asbestos fibers.

It is unfortunate for the readers that the "critical review" by Stayner and the accompanying postion paper by Cullen fail to cite recent proceedings and conclusions of international meetings and scientific panels endorsing the amphibole hypothesis.[7–11] Of the 72 references cited in the Stayner article, only 12 were published after 1991; half of these supported the amphibole hypothesis, but were dismissed for a rehash of earlier data previously considered by us and others.[2,7–11] Surely, the detection of mesothelioma in two individuals in Zimbabwe, a country where mesothelioma rates increasing in the general population are attributed to crocidolite,[9] is not evidence that "pure" chrysotile is the cause—especially in the absence of lung fiber burden studies.

Lastly, the section on "Mechanistic Studies" by Stayner et al. incorrectly states that experimental support for the increased pathogenicity of crocidolite is primarily derived from in vitro studies. Moreover, it fails to reference dozens of recent peer-reviewed papers by our laboratory and others (Faux, Kane, Kamp, Hei, Aust, Ghio, Weitzman, Gulumian, and others), as well as the proceedings of a conference organized by a scientist from their own institution.[12] All provide support for the role of active oxygen species in crocidolite-induced mutagenicity, protooncogene expression in mesothelial cells, and lung damage. These studies also show that crocidolite, in contrast to chrysotile at identical airborne concentrations, induces protooncogene expression in lungs and sustained proliferation of mesothelial cells after inhalation of fibers by rats,[13] thus providing a mechanistic framework for the amphibole hypothesis.

In view of these and other critical omissions by Cullen and Stayner, the "take-home" message is clear: "critical reviews" and annotations should be written by scientists with up-to-date knowledge of recent papers in the literature and in the mainstream of relevant panels and scientific meetings. Contrary to the annotation by Cullen, the amphibole hypothesis of mesothelioma was *not* dead on arrival in 1990, but is still viable. □

Brooke T. Mossman, PhD
J. Bernard L. Gee, MD

Brooke T. Mossman is with the University of Vermont College of Medicine, Burlington. J. Bernard L. Gee is with the Yale University School of Medicine, New Haven, Conn.

Correspondence should be sent to Brooke T. Mossman, PhD, Environmental Pathology Training, Department of Pathology, Medical Alumni Bldg, University of Vermont College of Medicine, Burlington, VT 05405-0068.

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5. *Cullen Responds*

I am delighted to see that Drs Mossman and Gee have appropriately narrowed the focus of the amphibole hypothesis to the question of mesothelioma. As their own letter makes clear, they had previously hinted widely of the possibility that chrysotile may be less pathogenic in the causation of lung cancer—a contention intriguing at the cellular level but absolutely unsupportable on the basis of incontrovertible population evidence. Such human evidence cannot and must not be confused by comments such as "given that smoking is a more powerful factor in lung cancer than asbestos exposure, it is more difficult to define the various roles of different types of asbestos fibers." Moreover, not all of the laboratory evidence of oncogenicity of one fiber compared with another can or should be used as a basis for avoiding the obvious: namely, that a strong dose–response relationship between cancer and chrysotile asbestos exposure is proven and that its slope appears to differ not at all from that of other fiber types. Period. Regarding the differences in pathogenicity of the various fibers in relationship to mesothelioma, I would concur that most reasonable people accept (as I made plain in my annotation) that chrysotile is of lower pathogenicity and may be without potential to cause this disease, although this remains unproven. The reader must be reminded, however, that in developed countries, 100 lung cancers occur for every case of mesothelioma, and despite the close association of the latter disease to asbestos, the public health concern about asbestos cannot be equated with or reduced to its role in causing an extremely rare disease, however scientifically interesting. □

Mark R. Cullen, MD

The author is with the School of Medicine, Yale University, New Haven, Conn.

Requests for reprints should be sent to Mark R. Cullen, MD, Yale University, Occupational and Environmental Medicine Program,