

EXECUTIVE SUMMARY

ARB Contract A9-076-31

NEW APPROACH FOR DETECTING HEALTH HAZARDS OF NO<sub>2</sub> INHALATION

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The presence of pollutants in the environment, especially those with carcinogenic properties, has been of great concern to environmental health scientists. In view of this, many studies have been carried out to isolate and to identify cancer causing agents in the environment. However, little attention has been paid to the possibility that inhalation of a noxious air pollutant could facilitate the spread and dissemination of cancer cells.

It is known that inhalation of ambient levels of nitrogen dioxide ( $\text{NO}_2$ ), a common air pollutant, can alter the structure and function of lung blood capillaries or very small blood vessels, as well as suppress the body's defense system. Moreover, several investigators have demonstrated that damage of blood capillaries or suppression of the defense system in general favors the development of secondary cancer masses or metastases in cancer patients. Thus, we have reasoned that the damage incurred in the lungs and/or in the defense system by inhalation of  $\text{NO}_2$ , could facilitate metastases development in lungs, particularly in the presence of circulating cancer cells. In order to test this new concept and see if the development of metastases could serve as an indicator for harmful  $\text{NO}_2$  effects, an animal model system, utilizing mouse cancer cells, was developed. In each experiment three groups of animals were used with 30 mice per group. One group was exposed to ambient levels of  $\text{NO}_2$ , the second group to filtered  $\text{NO}_2$  free air and the third group to ambient room air. The  $\text{NO}_2$  levels were continuously monitored. After designated periods of exposure all animals received cancer cells (mouse melanoma cells) which were prepared from in vitro cultures and were infused into the blood stream of the animals. Three weeks later the lungs were examined for development of cancer metastases.

The results have indicated that inhalation of 0.3, 0.4, or 0.8 parts per million (ppm) of  $\text{NO}_2$  for a period of 10 weeks or longer increases the frequency of cancer mass development in lungs from the circulating cancer cells. These small cancer masses, if permitted, continue to grow and eventually kill the animal. Of further significance is the finding that

animals inhaling ambient vivarium air for the same length of time also developed more lung metastases than the animals used as filtered air controls. Considering that most of the time vivarium air has levels of  $\text{NO}_2$  lower than 0.1 ppm, the observed results may be due to a combination of several low concentration pollutants frequently present in the ambient air. It is of interest that inhalation of  $\text{NO}_2$  (0.5 ppm) or ambient vivarium air for a shorter duration (8 weeks) did not show facilitation of cancer growth in the lungs. The later results suggest that the length of exposure to ambient levels of pollutants may be an important factor.

The mechanisms involved are not clear but it most likely reflects damage or alterations to lung capillary bed and/or the body's defense system. Moreover, these are the first reported studies where inhalation of an air pollutant ( $\text{NO}_2$ ) has been implicated in facilitation of cancer cell metastasis. Similar findings have been reported by other investigators who showed that inhalation of cigarette smoke facilitates cancer cell metastasis using a different experimental model. It should be pointed out that all our experiments were carried out under one specific condition, i.e. the nitrogen dioxide exposure always preceded the introduction of cancer cells into the circulation. However, there are several other conditions possible and further studies are needed to establish how inhalation of nitrogen dioxide affects those conditions. Studies where inhalation of  $\text{NO}_2$  is alternated with inhalation of clean air and inhalation of  $\text{NO}_2$  while cancer cells are in circulation would be of particular importance. Moreover, since the results of our studies also raise the question of whether similar events are happening in urban human population, epidemiological studies designed to detect the frequency of metastases development in cancer patients who have lived or are living in a polluted area versus those living in a clean air environment are urgently needed. Considering the fact that a significant segment of the population in the United States is already affected by cancer together with the probability that one in four individuals will develop cancer during their life time, the role of environmental pollutants in the dissemination of cancer cells and development of metastases becomes an important health issue. Even though the results of these studies are of a limited nature and come from experimental animal studies, we feel the findings are highly relevant to human health and to the setting of air quality standards.

The details of the research described have been published in Arch, Environ. Health 36:36, 1981 and J. Surg. Oncology 17:159, 1981.