EXECUTIVE SUMMARY

ARB Contract A2-128-33

The role of air pollutants in facilitation of cancer cell metastasis

Period: June 8, 1983 - December 31, 1984

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Date submitted: November 30, 1984

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Many studies have been carried out to isolate and identify cancer causing agents from the air we breathe. However, little attention has been paid to the possibility that inhalation of a noxious air pollutant could facilitate the spread and dissemination of already existing cancer cells. In recent years we have developed a novel biological probe-circulating cancer cells-to be used to detect the adverse effects of nitrogen dioxide (NO_2). This probe permits not only the detection of harmful effects, but it has important relevance to a highly significant disease process- the spread of cancer or metastasis.

Recent studies in our laboratory have indicated that inhalation of 0.3, 0.4 or 0.8 parts per million (ppm) of NO_2, a common air pollutant, for a period of ten weeks or longer, increases the incidence of blood borne cancer cell metastasis to the lungs, indicating adverse NO_2 effects. These small cancer masses, if permitted, continue to grow and eventually kill the animal. It should be pointed out that cigarette smoke inhalation has been linked to increased incidence of metastases development in the lungs in another experimental system and in an epidemiological study where human melanoma metastasis was evaluated. Of further significance was our finding that animals inhaling polluted ambient air also developed more lung metastases than the animals inhaling filtered clean air. The changes induced by NO_2 inhalation, which enhanced the dissemination of these cancer cells, are not known. Most likely it reflects damage or alterations in blood capillaries of the lung or cells of the defense system.

In view of the foregoing, the studies carried out under this contract were designed to accomplish the following: 1) to increase the sensitivity of the cancer cell probe; 2) to determine if inhalation of ozone (O_3) at concentrations encountered in the Los Angeles area would effect the spread of circulating cancer cells; 3) to determine the NO_2 effects on the growth and progression of "primary cancer" (cancer cell transplant) and 4) to carry out preliminary experiments towards the identification of specific lesions or mechanisms which may be associated with facilitation of cancer cell metastasis. We have had some success in all of these areas. The use of a

lower number of cancer cells in our biological probe has proved to be a more sensitive method for detecting adverse NO_2 effects. We have demonstrated not only the increased incidence of metastases in exposed animal lungs, but also increased number of animals with metastasis in the exposed animal group. The same probe was also used to study ambient level (0.15 ppm) O_3 effects. The results of this study showed an increase of 9% in the incidence of lung metastases in exposed animals, however, this difference was not statistically significant. This may mean that ozone affects animals differently than NO_2 with respect to cancer cell metastasis, but it does not mean that there were no adverse affects. In fact, the animals were affected adversely since the average body weight of the exposed animals was significantly lower than the body weight of animals breathing clean air.

The results were not conclusive in the experiment where the growth and spread of transplanted cancer cells was evaluated. The finding suggests that NO_2 inhalation may facilitate the growth and spread of cancer cells from the primary site. These observations would parallel our earlier studies where we have demonstrated increased early mortality from lung metastases in a subpopulation of NO_2 exposed animals.

The preliminary experiments evaluating effects on the body defense system, particulary the spleen, an organ where a number of defense cells reside, have indicated that the exposed animal defense cells from the spleen react differently to cancer cells than the same cells from animals breathing clean air. It appears that the spleen cell responses are very complex and many more experiments will be needed in order to properly understand and interpret the present findings.

In view of these findings we have to raise the question of whether the events described above are taking place in the urban human population. We do not have the answers at the present time. Some answers could come from epidemiological studies desinged to detect the incidence of metastasis in cancer patients who have lived or are living in polluted areas compared to those living in a clean air environment. 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 lifetime, the role air pollutants play in the dissemination of cancer and development of metastases becomes an important health issue. Most importantly, the data generated provide additional support for the need to improve air quality by reducing ambient air pollutants. Further studies are needed to evaluate other air pollutant effects on cancer metastasis and to identify the specific lesions and mechanisms involved.