Medical Hypotheses 12 : 159 - 165, 1983

GASTRIC CANCER IN COAL MINERS: AN HYPOTHESIS OF COAL MINE DUST CAUSATION

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ABSTRACT

An hypothesis is proposed to explain the elevated incidence of gastric cancer among coal miners. Inhaled coal mine dust, especially the larger particles, is cleared from the lung and tracheobronchial tree by mucociliary function, swallowed, and introduced into the stomach. Organic and/or inorganic materials in the dust can undergo intra-gastric nitrosation and/or interaction with exogenous chemicals to form carcinogenic compounds which in turn may lead to precancerous lesions, which may subsequently develop into gastric cancer. This sequence of events, however, depends upon occupational exposures as well as life-style features and individual genetic predisposition.

INTRODUCTION

Studies of the incidence and prevalence of gastric cancer among coal miners have been conducted by several investigators. Among United States coal miners, Enterline (1) found a nearly three-fold excess of gastric cancer mortality. More than a three-fold increase in gastric cancer incidence among coal miners was reported by Matolo et al. (2) for both Carbon and Emery counties in Utah. An excess risk for gastric cancer among coal miners has also been reported by Rockette (3) in a mortality follow-up study of U.S. coal miners and ex-miners. In Europe, Turner (4) and Stocks (5) have reported gastric cancer rates which were higher among coal miners than non-miners. Liddell (6), in England, found an excess only for other underground workers but not for face or surface workers. Rockette (7), reviewing coal miner mortality rates, concluded that elevated gastric cancer is the third most consistantly elevated cause of mortality among coal miners following accidents and pneumoconiosis. It is interesting to note that despite conflicting reports, increased lung cancer risk among coal miners has never been substantiated from epidemiological studies (8, 9, 10).

Although many risk factors for gastric cancer have been identified, the actual etiology of gastric carcinogenesis in humans is not known (11). While several

dusty trades have been identified as being at elevated risk of gastric cancer (12), the role of coal mine dust exposure as a gastric cancer risk is just begining to be tested. Several hypotheses to explain the increase in incidence of gastric cancer in coal miners (ranging from occupational exposures to life-style features to worker characteristics) have been formulated by Ames (13). Falk and Jurgelski (8) have suggested that gastric cancer risk is related to coal dust exposure. A close link between coal mine dust exposure and gastric cancer has been drawn by Jacobsen (14) who reported a positive relationship between gastric cancer mortality and pneumoconiosis progression. Pneumoconiosis progression is largely a function of coal mine dust exposure. Ames (15), in a case-control study of U.S. underground coal miners, found coal mine dust exposure to pose a gastric cancer risk only in long-term cigarette smokers. In this paper we propose an hypothesis to explain the elevated risk of gastric cancer in coal miners.

BACKGROUND OF THE HYPOTHESIS

Exposure of humans to airborne particles is primarily through inhalation. Deposition of inhaled particles in the respiratory tract depends upon particle size and other related factors. Smaller particles are deposited mainly in the alveoli and larger particles impact in the tracheobronchial region or higher. Inhaled particles cleared from the lung and tracheobronchial tree by mucociliary action can be swallowed, and introduced into the stomach. Dust can also be introduced in the stomach through food ingestion or simply swallowing dusty air. However, Meyer et al. (16) suggest that a greater stomach burden exists for inhaled dust than for ingested dust. They feel that inhaled carcinogens are more important than ingested carcinogens in the etiology of gastric cancer.

Many organic chemicals can be nitrosated under an acidic condition. Nitrite is the best known nitrosating agent in our environment. It is widely used in food coloring and preservation and is present in certain vegetables (17, 18). Therefore, nitrosation of organic materials by ingested nitrites, or ingested nitrates which are subsequently converted to nitrites, can occur within the stomach and carcinogenic compounds generated. The formation of mutagenic and carcinogenic N-nitrosamines from reaction of secondary amines and nitrite under acidic conditions has been documented both *in vitro* and *in vivo* (19, 20, 21, 22). Nitrosated mutagenic diazepam and hydroxyzine have been recovered from the stomach mucosa of patients treated with diazepam or hydroxyzine·HCl (23,24). It has been suggested that nitrosating enzymes in the mucosa are responsible for the formation of nitrosated mutagens (23, 24). Endogenous formation of N-nitroso compounds through bacterial nitrate reductase in the injured stomach is also possible (25). Many nitroso compounds are known to be carcinogenic; the linkage of nitroso compounds to human gastric cancer has been suggested by Mirvish (26).

Organic and inorganic compounds in the stomach through food ingestion, tobacco chewing, the use of tobacco snuff, and cigarette smoking may interact and generate or promote the generation of highly carcinogenic compounds. For instance, cigarette smoking could enhance nitrosation. Vogt et al. (27) found serum thiocyanate to be elevated as a consequence of cigarette smoking and

Boyland and Walker (28, 29) found thiocyanate to be a catalyst of nitrosamine formation.

AN HYPOTHESIS OF COAL MINE DUST CAUSATION

Coal mine dust can be introduced into the stomach of coal miners through food ingestion, swallowing of air, or inhalation followed by lung clearance as discussed in the previous section. Coal mine dusts per se are either noncarcinogenic or weakly carcinogenic. However, in the stomach environment, carcinogenic compounds are formed from coal dusts through enzymatic or nonenzymatic nitrosation processes or through other interactions with exogenous chemicals. The produced carcinogenic compounds attack epithelial cells and induce precancerous lesions in the stomach and are responsible for gastric cancer excess in coal miners (see Fig. 1).

FACTORS AFFECTING COAL MINE DUST CARCINOGENESIS

Generation of carcinogenic compounds from coal mine dust will depend upon the amount and type of coal dust exposure, the concentration of organic compounds, minerals, metals, and gases in the coal mine dust, and exposure to related mine dusts and gases such as particulate from blasting using ammonium nitrate. Additional factors likely to be involved include the lung clearance function, the condition of the stomach, and the availability of exogenous chemicals (nitrite, ascorbic acid, and α-tocopherol, chemicals from tobacco, etc.). For example, it is known that ascorbic acid and α-tocopherol can block the nitrosation process (30). Therefore, the greater the ascorbic acid intake the less the nitroso compounds which can be formed in the stomach from coal mine dust. Production of precancerous lesions by carcinogens in the stomach will depend upon the genetic predispositon of the exposed individuals and the availability of blocking agents. For instance, glutathion S-transferase, epoxyhydrase, certain phenols, lactone, aromatic isothiocyanate, indoles, and disulfiram can prevent carcinogens from reaching or reacting with target sites (31). While biochemical alterations may be repaired, the extent of repair is likely to vary from subject to subject. Whether precancerous lesions develop into gastric cancer depends upon the immune capability of the subject, the frequency of additional insults, and the presence of promoters.

SUPPORTIVE INDIRECT EVIDENCE FROM IN VITRO MUTAGENESIS STUDIES

Studies related to the proposed hypothesis have been conducted in our laboratory. We have found that organic solvent extracts of coal dust from different rank coals are either non-mutagenic or weakly mutagenic with microsomal activation. However, high mutagenic activities were found when extracts of bituminous, subbituminous and lignite coal dusts were reacted with nitrite under an acidic condition (32). Formation of mutagens by nitrosation of coal dust extracts was inhibited by the presence of ascorbic acid (33). The nitrosated coal dust mutagens induce gene mutations in bacteria and

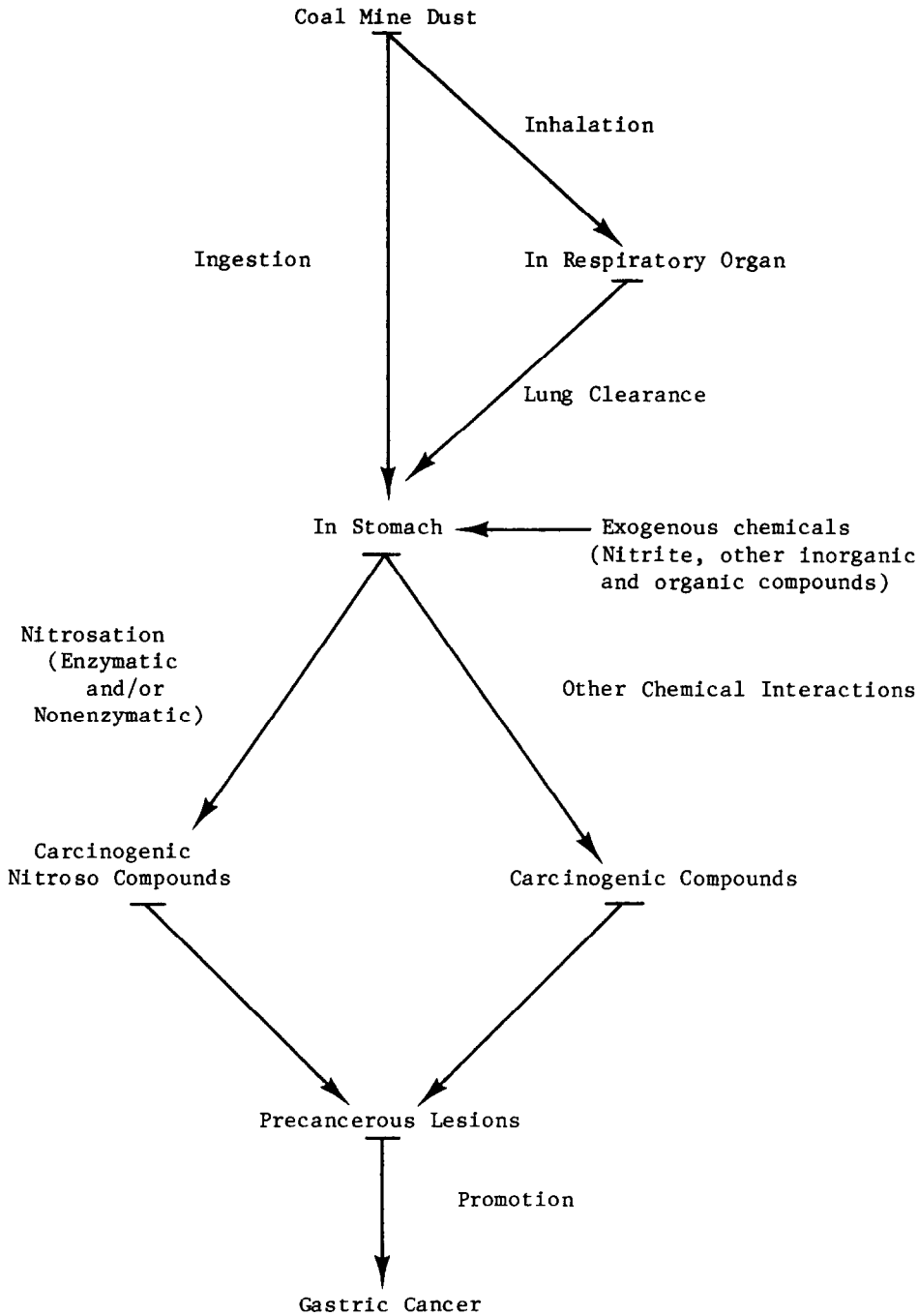

Figure 1. Causation of gastric cancer in coal miners: An hypothesis

mammalian cells, and induce sister chromatid exchanges and chromosomal aberrations in human peripheral lymphocytes (34). We have also found that mutagenic compounds can be formed by an interaction of coal dust and tobacco snuff extracts in an acidic environment (unpublished results). Since most carcinogens are mutagenic, the mutagens formed from coal dust in the in vitro studies may also be carcinogenic. Further in vitro and in vivo studies are in progress to identify the nitrosated mutagenic constituents and to specify the processes involved.

CONCLUSIONS

Based upon literature review and data from several NIOSH studies, an explanation for excess gastric cancer in coal miners is proposed. It is hypothesized that carcinogens produced in the stomach from coal mine dust, either through intra-gastric nitrosation or other chemical interactions, are responsible for the gastric cancer excesses in underground coal miners.

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