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Gastric Cancer in Coal Miners: Some Hypotheses for Investigation*

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Summary

Accumulating evidence suggests that US coal miners experience an elevated risk of gastric cancer. This increased risk rate should be investigated epidemiologically to determine if the risk is directly related to their occupation, indirectly related through social class, region, or other correlated lifestyle factors, or simply an artifact of the aggregation of high-risk individuals in the coal mining industry. Hypotheses in a continuum from most occupationally related to least occupationally related are presented to direct inquiry along these lines.

Introduction

Accumulating evidence suggests that US coal miners experience an elevated risk of gastric cancer. Enterline (1964) reported a standardized mortality ratio (SMR) of 275 for gastric cancer among coal miners, indicating a nearly three-fold excess. Matolo et al. (1972), in an analysis of male coal miners in two Utah mining areas, reported a standardized incidence ratio of 342 for gastric cancer in Carbon county and 338 in Emery county. A second study by Klauber and Lyon (1978), based on the earlier data plus five additional years, revised the estimates downward to 138 for Carbon county and 92 for Emery county. Rockette (1977) estimated the SMR for gastric cancer to be 138 from a follow-up of 22 998 male coal miners and ex-miners who were UMWA Health and Retirement Fund enrollees. Studies in other countries have also indicated excess risk for gastric cancer among coal miners—Turner (1938) and Stocks (1962). One study reported gastric cancer excesses for other underground workers but not for face or surface workers (Liddell, 1973). Coal miner mortality rates have been reviewed by Rockette (1980) who concludes that elevated gastric cancer mortality is the most consistent finding for coal miners other than accident and pneumoconiosis mortality.

An attempt to understand the cause of excess gastric cancer mortality among coal miners should question whether the increased risk is directly occupational, indirectly related through social class, region, or other correlative lifestyle risk, or an artifact of the aggregation of high-risk individuals in the mining industry.

Types of Gastric Cancer

Gastric cancer is reported to lack a characteristic clinical, radiological or pathological appearance (Haas and Schottenfeld, 1978). The search for similarities among gastric cancers has led to classifications by morphological type and by histological type. Lauren (1965) distinguished between diffuse and intestinal histological types of gastric cancer. In diffuse type the cancer is quite distinct from the surrounding tissue; usually solitary cells or small clusters of cells lacking a glandular structure. The adjacent mucosa rarely shows evidence of intestinal metaplasia. Tumours of the intestinal type have a glandular structure and resemble colon cancer. There may be intestinal metaplasia in the vicinity of the tumour. These two histological types differ epidemiologically and clinically (Lowenfels, 1973; Graham, 1975). Compared with the intestinal type, the diffuse type is more frequent in females, occurs on the average at

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younger ages, and has a lower survival rate (Haas and Schottenfeld, 1978; Ribeiro et al., 1981). It is felt that the diffuse type of gastric cancer has more genetic implications whereas the intestinal type has more environmental implications based upon the fact that increases or decreases in rates of gastric cancer between areas or over time appear to be primarily a function of changes in the intestinal type. Also, both intestinal type gastric cancer (Graham, 1975; Ribeiro et al., 1981) and intestinal metaplasia (Haas and Schottenfeld, 1978) are disproportionately prevalent in high gastric cancer rate areas.

Ming (1977) distinguished between an expanding and an infiltrative morphological type of gastric cancer based upon patterns of growth and invasiveness. The expanding type is defined as those whose cells grow en masse and by expansion. In the infiltrative type, the cells invade the stomach wall individually or in clusters. Ribero et al. (1981) found the histological and morphological bases of classification to be related, but not duplicates of each other. Each classification scheme had prognostic significance, but there was no added usefulness to joint classification. Ihamaki and Sipponen (1979) feel that the histological classification is the most epidemiologically useful basis of classification because it correlates with the epidemiological differences previously mentioned; these differences are not distinguished by the morphological basis of classification. It appears that gastric cancer is really more than one disease and that separate epidemiology for diffuse and intestinal gastric cancer ought to be developed. Unfortunately neither histological nor morphological type is recorded on a death certificate for retrospective analysis.

Risks for Gastric Cancer

Despite extensive description of potential risk factors (Wynder et al., 1963; Haas and Schottenfeld, 1978), actual identification of the specific cause or causes of gastric cancer in humans has not been made (Pfeiffer, 1979a). Both environmental and genetic causal factors are thought to be important. Support for environmental factors comes from epidemiological investigations which have shown gastric cancer to have many social correlates such as social class, nativity, area of residence, occupation, etc. Support for genetic causes rests primarily on family aggregation studies and clinical studies. Estimates of the genetic component vary. Graham and Lilienfeld (1958) suggest a two-fold increase in gastric cancer risk for relatives of gastric cancer probands while Videbaek and Mosbech (1954) suggest a four-fold increased risk. Ihamaki and Sipponen (1979), in a gastric cancer proband–relative study, report family aggregation for diffuse spreading gastric cancer, but not for intestinal type. A Danish twin study also reported familial aggregation for gastric cancer but did not differentiate between histological types (Harvald and Hauge, 1956). Patients with adult-type pernicious anaemia (Mosbech, 1954) and their first-degree relatives (Videbaek and Mosbech, 1954) have been reported to be at increased risk of gastric cancer. Clinical studies by Varis et al. (1978, 1979) found that members of the same family have similar morphology and immunology of the stomach. An hereditary component to gastric cancer is also indicated by the relationship which exists between blood type A and gastric cancer (Aird et al., 1953; Hoskins et al., 1965; Glober et al., 1971). Overall, the hereditary component to gastric cancer appears to involve correlations between achlorhydria, severe atrophic gastritis, pernicious anaemia, stomach polyps, intestinal metaplasia and epithelial atypia.

Not only are specific gastric cancer agents unknown, the exposure pattern of carcinogenic agents and incubation period for carcinogenesis is currently unknown. We are unable to answer such basic questions as: How long does the gastric mucosa have to be subjected to given levels of carcinogens? or: is a latency period required for tumour induction to take place? Since gastric cancer prevalence increases with age, the assumption has been made that either a long exposure pattern or a long incubation period is required for gastric carcinogenesis. Even in the absence of definable causes, it is clear that no single cause is likely to explain gastric cancer. In all probability, gastric cancer is multicausal and

involves interrelationships between environmental agents and individual susceptibilities (Pfeiffer, 1979a).

Hypotheses for Investigation

This paper offers a systematic presentation of formal hypotheses to explain gastric cancer excesses among coal miners which span the continuum from highly occupationally related through lifestyle hypotheses to hypotheses unrelated to occupation or lifestyle. The intent is to integrate what is already known about the risks and biology of gastric cancer. Each hypothesis is identified in terms of its relationship to occupation, correlated lifestyle, or miner characteristics, and examined from the perspective of its biological plausibility.

Hypothesis 1: The Greater the Exposure to Coal Mine Dust, the Higher the Risk of Gastric Cancer

Exposure to coal mine dust is an occupational hazard of coal miners.

Coal mine dust represents a biologically plausible relationship to gastric cancer. Coal is a mixture of hydrocarbons and mineral content. Analyses of coal (Green and Laqueur, 1980) indicate common mineral content to include: pyrite, quartz, calcite, calcium sulphate, dolomite, siderite, magnetite and a variety of other silicates. Common metals include: aluminium, calcium, iron, magnesium, potassium and sodium. Less common metals include: beryllium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickle and titanium. Organic compounds include: methane and other gases, benzenes, phenols, naphthalenes, acenaphthalenes, and 3-, 4- and 5- ring polynuclear aromatic hydrocarbons (PNA's, also called PAH's). Of these constituents, some of the trace metals are carcinogenic as are some PNA's. Benz (a) pyrene, usually chemically bound in the coal matrix, is a carcinogenic risk (Falk and Jurgelski, 1979).

Coal mine dust may adsorb PNA's. When coal mine dust is inhaled, particles are cleared via the bronchial mucus and cilia which elevate them to the pharynx where part is swallowed (Lippman et al., 1980). Much of the particulate will be engulfed by macrophages. It is possible that some precarcinogens will be activated by the P–450 mixed-function oxidase enzyme system (Strobel and Fang, 1981) within the pulmonary system. Thus the stomach may be exposed to raw coal mine dust, some of which may have adsorbed PNA's plus coal mine dust modified by residence in the lungs. Meyer et al. (1980) have postulated an important role for pulmonary clearance in gastric cancer etiology. Adsorbed carcinogenic precursors may be elutriated from particulate, thus allowing the intragastric production of carcinogens which may penetrate the mucosal defenses, attack the mucosal tissue and induce gastric carcinoma.

A less likely hypothesis is that the presence of blood serum in the stomach promotes the intragastric elutriation of PNA's adsorbed on soot or other particulate (Falk and Jurgelski, 1979). Blood serum in the stomach would result from bleeding ulcers or the breach of the mucosa due to excessive use of aspirins, or by other means. Occupational exposure is possible, although it seems unlikely. The sequence of events to provide a link to gastric cancer would have to include coal mine dust, or coal dust related disease, resulting in pulmonary release of blood serum which is then cleared, swallowed, and introduced into the stomach concurrently with PNA's adsorbed to particulate.

The hypothesis of coal mine dust as a risk factor for gastric cancer among coal miners deserves evaluation due to the fact that coal dust is a major factor discriminating between coal miners and other occupational groups and due to the presumption of biological plausibility. Indirect support to the hypothesis exists in the finding by Stocks (1962) that the higher the rank of coal mined, the higher the prevalence of gastric cancer mortality among coal miners. However, it should be noted that higher-ranked coals are associated with different mining environments including higher silica content of the mining dust. A position arguing against coal mining etiology for gastric cancer is taken by Creagan et al. (1974) based on an analysis comparing US coal mining counties with non-coal

mining counties which were matched on the basis of social status.

Hypothesis 2: The Greater the Exposure to Dust in General, the Higher the Risk of Gastric Cancer.

Some exposure to dusts could be occupationally related even though most exposures would fall under the general topic of air pollution. Possible occupational dust exposures just a step beyond coal dust per se include iron dust, iron oxides from welding, other metals found in coal, rock dust, particulate from blasting, asbestos dust from insulation and coal shuttle car brake linings, and diesel particulate if diesel equipment is used in the mining operation. Related lifestyle exposures might include soot from coal combustion from heating and/or cooking, proximity to nuisance dusts, or soil errosion dust.

Biological linkages between general dusts and gastric cancer are similar to that for coal mine dust. Inhaled particles are cleared by bronchial mucociliary action. Respirable particulate may be subject to macrophage scavanging, brought up through mucociliary clearance and swallowed, just as with the other inhaled particles. When the exact nature of the particle is unspecified, the precise link to gastric cancer becomes less plausible. As already noted, workers in certain dusty trades, such as quarrymen, have elevated rates of gastric cancer (Kraus et al., 1957). In addition to occupational exposures, gastric cancer has been shown to be more prevalent in persons exposed to higher levels of general air pollution (Hagstrom et al., 1967; Winkelstein and Kantor, 1969).

Hypothesis 3: The Greater the Exposure to Darkness, the Higher the Risk of Gastric Cancer

Additional darkness, beyond that normally experienced by night time, is an occupational exposure for underground coal miners.

Darkness is a biologically plausible risk factor for gastric cancer. *N*-nitrosamine formation in darkness has been demonstrated between secondary amines added to air containing 0·3 parts/10^6 NO_x, whereas another reaction pathway yielding nitramines, which are not carcinogenic, was observed in daylight (Pitts et al., 1978). It is possible that in earlier mining eras miners were not as cautious in ventilating mines following blasting operations and prior to re-entry, so that NO_x was allowed to accumulate in darkened corridors. Further substantiation to the general darkness risk factor is based upon the fact that geographical distributions of gastric cancer tend to show high rates in northern areas of countries (Wynder et al., 1963). However, it should be noted that the northern areas of countries in the Northern Hemisphere are usually colder and use more combustion heating.

Hypothesis 4: The Greater the Exposure to Soil and Moisture, the Higher the Risk of Gastric Cancer

Exposure to soil and moisture is an occupational exposure for coal miners.

From the standpoint of gastric cancer carcinogenesis, exposure to moisture and soils provides a biologically plausible link to gastric cancer as damp soils are likely to carry exposure to elaiomycin, a product of soil bacteria known to be carcinogenic (Lowenfels, 1973). Occupational exposure to elaiomycin might be exacerbated among miners as some miners are reported to drink water directly from the mine floor (R. Campbell, personal communication). Elevated risk for gastric cancer is found in other occupations with high contact with the soil, such as farmers and quarrymen (Turner, 1938; Kraus et al., 1957). However, findings arguing against the validity of this hypothesis include the facts that gastric cancer is not patterned after the distribution of farm land use in the United States (Seely, 1978), nor does gastric cancer coincide with the geography of coal mining in the United States. Finally, gastric cancer does not follow the distribution of humid areas in the United States (Seely, 1978). Therefore, exposure to moisture and soils is unlikely to be a tenable hypothesis even though it is a biologically plausible one.

Hypothesis 5: The Greater the Exposure to Raw Tobacco Juice, the Higher the Risk of Gastric Cancer.

Exposure to tobacco juice would be partially an occupational exposure and partially a lifestyle exposure. While the use of tobacco is a lifestyle choice, the alternative use of snuff and chewing tobacco is partially a constraint of mining which precludes the smoking of cigarettes underground. Persons who chew tobacco or use snuff inevitably ingest some tobacco juice.

Is the exposure to tobacco juice related to gastric cancer in a biologically plausible way? The answer is probably yes. Tobacco use has definitely been linked to cancers at sites of contact, such as the buccal cavity cancers (Hammond, 1975). Further, factors which promote the breakdown of the mucosal defence mechanisms would allow tobacco juice to attack the mucosal cells, possibly eventuating in gastric carcinogenesis.

Unanswered questions revolve around whether coal miners who use snuff or chew tobacco are at higher risk of gastric cancer that other labourers who also use tobacco in these forms. That is, does coal mine dust exposure or other mining exposure modify the risk of exposure to snuff or chewing tobacco?

Hypothesis 6: The Greater the Exposure to Nitrosamines, or their Precursors, or to Nitrosation Facilitators, the Higher the Risk of Gastric Cancer

Since nitrosamines are formed by the union of nitrites with secondary, tertiary, or other amines, any factor which would increase either the nitrites or their precursors, the amines or their precursors, or would catalyze the formation process, would be likely to increase the risk of gastric cancer. The increased risk of gastric cancer due to nitrosamine formation seems especially plausible in light of current belief that the carcinogenic target of nitrosamines is the stomach (Armijo et al., 1981b).

Two sub-hypotheses are suggested by this hypothesis. They will be discussed separately.

HYPOTHESIS 6A: THE GREATER THE DIRECT INTAKE OF NITROSAMINES OR THEIR PRECURSORS, THE HIGHER THE RISK OF GASTRIC CANCER

Some intake of nitrosamines may be occupational, such as those formed through release from coal by pyrolysis, NO_2, or other means. Other intakes of nitrosamines could be due to the correlated lifestyle factor of diet, such as the ingestion of smoked or salted fish, ham, or other similar foods.

Smoked foods contain benz (a) pyrene, a carcinogenic risk, while salted fish is a major source of nitrosamines (Berg, 1975). Supportive evidence of the linkage between dietary intake of nitrosamines and gastric cancer rests upon epidemiological international comparisons which show high gastric cancer rates in countries high in intake of smoked and salted fish, notably Japan and Iceland (Wynder et al., 1963). While coal miners are not likely to eat a great deal of salted or smoked fish, they may eat higher than average amounts of smoke and/or salted ham. In addition, nitrites are often used in the preservation of meats, especially bacon.

Since coal miners live, by and large, in more rural areas and have drinking water supplied by wells which might be contaminated by surface run-off, there is a suggestion that miners would be exposed to higher than average amounts of nitrates. Inhalation of particulate after blasting with nitroglycerine or ammonium nitrate might be an alternative avenue of occupational exposure to nitrates by coal miners. The relationships are plausible in light of several studies which have produced convincing, yet circumstantial, evidence to support the linkage between nitrate contamination of food and gastric cancer rates, especially in Chile (Armijo and Coulson, 1975), and the linkage of nitrate in well water to gastric cancer in Columbia (Cuello et al., 1976). More recent studies in Chile by Armijo et al. (1981a, 1981b) have cast doubt on a simple 'high nitrate–high gastric cancer' model and point to the possible co-factor involvement of arsenic and selenium.

HYPOTHESIS 6B: THE GREATER THE FACILITATION OF THE NITROSATION PROCESS, THE GREATER THE RISK OF GASTRIC CANCER

Nitrosation is enhanced by thiocyanate and

by colonization of the stomach by bacteria. Nitrosation enhancement could be partly occupationally related since the use of chewing tobacco or snuff by smokers is an alternative posed by the prohibition of underground cigarette smoking. Many correlated lifestyle variables could also enhance the nitrosation process. Bacterial contamination could come about due to sewage-polluted water supplies, poor dental health leading to bacteria growth in the mouth, or poor preservation and storage of food, all of which would be social class correlates.

The hypothesis of nitrosation facilitation is a biologically plausible hypothesis for gastric cancer. Poor dental health has been linked to buccal cavity cancer (Graham et al., 1977) and it has been speculated that poor dental health leads to increased risk of gastric cancer (Graham, 1975). One postulated sequence of events is that bacteria growing in the mouth facilitate the nitrosation process thus generating nitrosamines which are swallowed. Acute stomach irritation could lower the amount of gastric acid and allow colonization by bacteria. Lifestyle risks producing acute stomach irritation could be brought about by excessive use of aspirin, excessively hot beverages, or highly-salted or spiced foods.

Chronic gastritis also is associated with low stomach acid production and hypochlorhydria is related to intestinal metaplasia of the gastric mucosa (Siurala et al., 1977). Intestinal metaplasia, which is an adaptive response to cell injury, appears to be a precursor of the intestinal type of gastric cancer (Varis et al., 1973) although the causal sequence, precedent or concurrent, has always been difficult to define. Stomach injury, past history of achlorhydria, past gastric operations, etc. are predictive of lower levels of stomach acid (Siurala et al., 1974) which may in turn facilitate nitrosation or bacterial colonization and eventual carcinogenesis. Nitrosation and breach of mucosal defences are likely to be correlated events (Correa et al., 1975).

The biological potential for salivary thiocyanate to be involved in the pathogenesis of gastric cancer is very high as salivary thiocyanate is swallowed and becomes part of the stomach environment. Thiocyanate, which catalyzes the nitrosation reaction (Boyland and Walker, 1974a, 1974b), is enhanced by cigarette smoking. Many miners, or course, smoke cigarettes. It is not known to what extent miners are more likely to have elevated rates of salivary thiocyanate than other cigarette-smoking workers, nor is it known if chewing tobacco or the use of snuff elevates the level of thiocyanate in the stomach by inducing excessive salivation, or if chewing tobacco or snuff increases directly the level of salivary thiocyanate. In addition, nornicotine in tobacco smoke can be nitrosated in human gastric juice (Pfeiffer, 1979b).

A model for the production of *N*-nitroso compounds has been presented by Tannenbaum (1981):

> An injury to the gastric mucosa would lead to gastritis, progressing to atrophic gastritis, and then to intestinal metaplasia. The stomach then becomes gradually hypochlorhydric, leading to an elevation in fasting gastric pH. Above pH 5, there is extensive colonization of the stomach by bacteria, introduced either from saliva or by reflux from the small intestine. Many of these bacteria have nitrate reductase activity. Then, exposure to nitrate will lead to formation of nitrite and ultimately *N*-nitroso compounds.

Hypothesis 7: The Lower the Level of Antioxidants Ingested, the Higher the Risk of Gastric Cancer

The level of antioxidants ingested by coal miners varies by region and lifestyle.

Antioxidants are cancer protectives. Two modes of ingestion of antioxidants are: (1) trace elements in the water supply, such as selenium; and, (2) food additives, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). In addition, Vitamins C and E are antioxidants (Tappel, 1968; Berg, 1975), opening up the epidemiologist's pandora's box: diet. There is a suggestion that the Appalachian coal mining regions are selenium deficient areas (O. R. Bennett, personal communication). On the other hand, given the prevasive use of foods with antioxidant additives, there is no reason to believe that miners are deficient in their intake of these foods.

An hypothesis relating antioxidants to gastric cancer is biologically plausible and is

consistent with evidence from epidemiological studies and from experimental studies. Shamberger (1970) reports that 'antioxidants applied on or near the site of carcinogenesis may prevent peroxidation and attachment of the carcinogen to DNA'. Shamberger and Willis (1971) have demonstrated an inverse concordance between cancer rates generally in the areas in the US and selenium levels in plants, milk, and human blood. Finally, Shamberger et al. (1972) argue that the introduction of BHA and BHT as food additives in the United States in 1947 can explain the even steeper decline in the gastric cancer death rate from about 1947 onward.

Hypothesis 8: The Changes Which Have Been Occurring Nationally in Gastric Cancer Trends Have Been Occurring More Slowly Among Coal Miners Than for the Rest of the Population and, Therefore, the Elevated Risk for Coal Miners is Simply a Lag-effect Rather Than an Effect Due to Elevated Specific Exposures.

The lag-effect hypothesis for coal miners varies by region and lifestyle.

Biological assessment of the lag hypothesis is not possible in the same manner as the other hypotheses which have been discussed. However, it is a plausible hypothesis. Gastric cancer rates in the United States have been correlated with social factors such as race, social class, place of birth, and region (Wynder et al., 1963; Haas and Schottenfeld, 1978). Population composition changes in the United States over the last 50 years or so have included decreases in the proportion of the lower class, increases in the proportion of urban dwellers, increases in the proportion of black people. and decreases in the proportion of foreign-born people, among others. Concomitant downward changes have taken place in gastric cancer mortality. It is quite reasonable that the overall gastric cancer mortality trend has not been replicated by each sub-segment of the population. A lag-effect placing coal miners behind national trends is therefore likely and capable of explaining an elevated risk in the absence of elevations to any specific occupational exposures.

Hypothesis 9: The Greater the Aggregation of High Gastric Cancer Risk Persons in the Coal Mining Industry, the Higher the Apparent Risk of Gastric Cancer Among Miners

Elevated individual risks for gastric cancer need not indicate differential exposure to occupational or environmental risks. Personal risk for gastric cancer is enhanced by genetics and demographic characteristics.

Several individual risks are highly associated with gastric cancer. The strongest risk factor for gastric cancer is age. Gastric cancer is rare in persons under 30 years of age and increases monotonically by age (Haas and Schottenfeld, 1978). Males generally have higher rates of gastric cancer than females (Haas and Shcottenfeld, 1978). Blacks in the US currently have higher gastric cancer rates than whites, although the situation used to be reversed, while blacks in Africa have low rates of gastric cancer (Haas and Schottenfeld, 1978). Foreign-born people, especially those from central European countries, have higher rates of gastric cancer than native-borns (Haas and Schottenfeld, 1978). Persons born in high-risk areas tend to carry an elevated risk of gastric cancer even when they migrate to lower-risk areas (Haas and Schottenfeld, 1978; Armijo et al., 1981b). First-degree relatives of gastric cancer probands tend to have elevated rates of gastric cancer (Varis et al., 1979). Persons with pernicious anaemia or their first-degree relatives tend to have elevated risk of gastric cancer (Videbaek and Mosbech, 1954) as do persons with type A blood (Aird et al., 1953; Hoskins et al., 1965; Glober et al., 1971), stomach polyps, and past gastric surgery (Lowenfels, 1973).

Given the existence of so many genetic, personal, or host risk factors for gastric cancer, it is entirely possible that the reported elevated risk of gastric cancer among coal miners is simply an artifact of the aggregation of high-risk persons in the mining industry and non-statistical control for these factors in data analysis. If true, this hypothesis would implicate the genetic component of gastric cancer in the absence of increased occupational exposures. While age, sex, and race are always brought under control in epidemiological analyses, other factors such as blood type

seldom are. Given the fact that coal mining is associated with relatively isolated areas of the US, high father–son occupational transmission, and some inbreeding of subpopulations, the hypothesis of family clustering and clustering by national origin or other similar status deserves attention.

Concluding Comments

These few hypotheses do not exhaust potential cancer risk factors. The intent is to organize in a systematic way some of the gastric cancer risk factors which have been identified and point to linkages between them. Perhaps further research based on these hypothesis can help answer the question of whether or not the reported elevated gastric cancer risk among coal miners is one of their occupation or the mining lifestyle and what, if any, policy outcomes ought to be forthcoming.

REFERENCES

Aird I., Bentall H. H. and Roberts J. A. F. (1953) A relationship between cancer of the stomach and the ABO blood groups. *British Medical Journal* **1**, 799.

Armijo R. and Coulson A. H. (1975) Epidemiology of stomach cancer in Chile—the role of nitrogen fertilizers. *International Journal of Epidemiology* **4**, 301.

Armijo R., Orellana M., Medina E. et al. (1981a) Epidemiology of gastric cancer in Chile: I—case control study. *International Journal of Epidemiology* **10**, 53.

Armijo R., Gonzales A., Orellana M. et al. (1981b) Epidemiology of gastric cancer in Chile: II—nitrate exposures and stomach cancer frequency. *International Journal of Epidemiology* **10**, 57.

Berg J. (1975) Diet. In: Fraumeni J. (ed.) *Persons at High Risk of Cancer.* New York, Academic Press, pp. 201–224.

Boyland E. and Walker S. A. (1974a) Effect of thiocyanate on nitrosation of amines. *Nature* **248**, 601.

Boyland E. and Walker S. A. (1974b) Thiocyanate catalysis of nitrosamine formation and some dietary implications. In: Bogovski P. and Walker E. A. (eds.) *N-nitroso Compounds in the Environment.* Lyon, IARC, pp. 132–136.

Correa P., Haenszel W., Cuello C. et al. (1975) A model for gastric cancer epidemiology. *Lancet* **ii**, 58.

Creagan E. T., Hoover R. N. and Fraumeni J. (1974) Mortality from stomach cancer in coal mining regions. *Archives Environmental Health* **28**, 28.

Cuello C., Correa P., Haenszel W. et al. (1976) Gastric cancer in Columbia I. Cancer risk and suspect environmental agents. *Journal of the National Cancer Institute.* **57**, 1015.

Enterline P. E. (1964) Mortality rates among coal miners. *American Journal of Public Health* **54**, 758.

Falk H. L. and Jurgelski W. (1979) Health effects of coal mining and combustion: carcinogens and cofactors. *Environmental Health Perspectives* **33**, 203.

Glober G. A. Cantrell E. G., Doll R. et al. (1971) Interaction between ABO and rhesus blood groups, the site of origin of gastric cancers, and the age and sex of the patient. *Gut* **12**, 570.

Graham S. (1975) Future inquiries into the epidemiology of gastric cancer. *Cancer Research* **35**, 3464.

Graham S. and Lilienfeld A. M. (1958) Genetic studies of gastric cancer in humans: an appraisal. *Cancer* **11**, 945.

Graham S., Dayal H., Rohrer T. et al. (1977) Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. *Journal of the National Cancer Institute* **59**, 1611.

Green F. H. Y. and Laqueur W. A. (1980) Coal workers pneumoconiosis. In: Sommers S. C. and Rosen P. (ed.) *Pathology Annual,* Part 2, Vol. 15. New York, Appleton–Century–Crofts, pp. 333–410.

Haas J. F. and Schottenfeld D. (1978) Epidemiology of gastric cancer. In: Lipkin M. (ed.) *Gastrointestinal Tract Cancer* New York, Plenum Press, p. 173.

Hagstrom R. M., Sprague H. A. and Landau E. (1967) The Nashville air pollution study, VII. Mortality from cancer in relation to air pollution. *Archives of Environmental Health* **15**, 237.

Hammond E. C. (1975) Tobacco. In: Fraumeni J. (ed.) *Persons at High Risk of Cancer.* New York, Academic Press, pp. 131–138.

Harvald B. and Hauge M. (1956) Catamnestic investigation of Danish twins; preliminary report. *Danish Medical Bulletin* **3**, 150.

Hoskins L. C., Loux H. A., Britten A. et al. (1965) Distribution of ABO blood groups in patients with pernicious anemia, gastric carcinoma, and gastric carcinoma associated with pernicious anemia. *New England Journal of Medicine* **273**, 633.

Ihamaki T. and Sipponen P. (1979) Morphology and function of the gastric mucosa in first-degree relatives of probands with histologically different types of gastric carcinoma. *Acta Pathologica et Microbiologica Scandinavica Section A: Pathology* (*Copenhagen*) **87**, 457.

Klauber M. R. and Lyon J. L. (1978) Gastric cancer in a coal mining region. *Cancer* **41**, 2355.

Kraus A. S., Levin M. L. and Gerhardt P. R. (1957) A study of occupational associations with gastric cancer. *American Journal of Public Health* **47**, 961.

Lauren P. (1965) The two histological main types of gastric cancer: diffuse and so-called intestinal type carcinoma. *Acta Pathologica et Microbiologica Scandinavica* **64**, 31.

Liddell F. D. K. (1973) Mortality of British coal miners in 1961. *British Journal of Industrial Medicine* **30**, 1.

Lippman M., Yeates D. B. and Albert R. E. (1980) Disposition, retention, and clearance of inhaled particles. *British Journal of Industrial Medicine.* **37**, 337.

Lowenfels A. B. (1973) Etiological aspects of cancer of the gastrointestinal tract. *Surgery, Gynecology and Obstetrics* **137**, 291.

Matolo N. M., Klauber M. R., Gorishek W. M. et al. (1972) High incidence of gastric carcinoma in a coal mining region. *Cancer* **29**, 733.

Meyer M. B., Luk G D., Sotelo J. M. et al. (1980) Hypothesis: the role of the lung in stomach carcinogenesis. *American Review of Respiratory Disease* **121**, 887.

Ming S. C. (1977) Gastric carcinoma. A pathobiological classification. *Cancer* **39**, 2475.

Mosbech J. (1954) Pernicious anemia and cancer of the stomach. *Acta Medica Scandinavica (Stockholm)* **148**, 305.

Pfeiffer C. J. (ed.) (1979a) *Gastric Cancer.* New York, Gerhard Witzstrock.

Pfeiffer C. J. (1979b) Exogenous factors in the epidemiology of gastric carcinoma. In: Herfarth C. and Schlag P. (ed.) *Gastric Cancer* New York, Springer-Verlag.

Pitts J. N. jun., Grosjean D., Winer A. M. et al. (1978) Photochemistry of amine-NO_x mixtures in simulated urban atmospheres: formation of nitrosamines, nitramines, amides, and photochemical oxidant. Presented at the 13th Informal Photochemistry Conference. Clearwater Beach, Florida, 4–6 January.

Ribeiro M. M., Sarmento J. A., Sobrinho Simoes M. A. et al. (1981) Prognostic significance of Lauren and Ming classifications and other pathologic parameters in gastric carcinoma. *Cancer* **47**, 780.

Rockette H. (1977) Mortality among coal miners covered by the UMWA Health and Retirement Funds. Morgantown, National Institute for Occupational Safety and Health.

Rockette H. E. (1980) Mortality patterns of coal miners. In: Rom W. N. and Archer V. E. (ed.) *Health Implications of New Technologies.* Ann Arbor, Ann Arbor Sciences, pp. 269–81.

Seely S. (1978) The recession of gastric cancer and its possible causes. *Medical hypotheses* **4**, 50.

Shamberger R. J. (1970) Relationship of selenium to cancer. I. Inhibitory effect of selenium on carcinogenesis. *Journal of the National Cancer Institute* **44**, 931.

Shamberger R. J. and Willis C. E. (1971) Selenium distribution and human cancer mortality. *CRC Critical Reviews in Clinical Laboratory Sciences* **2**, 211.

Shamberger R. J., Tytko S. and Willis C E. (1972) Antioxidants in cereals and in food preservatives and declining gastric mortality. *Cleveland Clinic Quarterly* **39**, 119.

Siurala M., Lehtola J. and Ihamaki T. (1974) Atrophic gastritis and its sequelae. *Scandinavian Journal of Gastroenterology (OSPO)* **9**, 441.

Siurala M., Villako K., Ihamaki T. et al. (1977) Atrophic gastritis: its genetic and dynamic behaviour and its relations to gastric carcinoma and pernicious anemia. In: Farber E. et al. (eds.) *Pathophysiology of Carcinogenesis in Digestive Organs* Baltimore, University of Tokyo Press/University Park Press, pp. 135–50.

Stocks P. (1962) On the death rates from cancer of the stomach and respiratory diseases in 1949–53 among coal miners and other male residents in counties of England and Wales. *British Journal of Cancer* **16**, 592.

Strobel H. W. and Fang W. F. (1981) Role of cytochrome P-450 in the response of the colon to xenobiotics. In: Bruce W. R., Correa P., Lipkin M. et al. (eds.) *Gastrointestinal Cancer.* Cold Springs Harbor, Cold Springs Harbor Laboratory, pp 141–152.

Tannenbaum S. R. (1981) Endogenous formation of *N*-nitroso compounds. In: Bruce W. R., Correa P., Lipkin M. et al. (eds.) *Gastrointestinal Cancer.* Cold Springs Harbor, Cold Springs Harbor Laboratory, pp. 269–71.

Tappel A. L. (1968) Will antioxidants slow aging processes? *Geriatrics* **23**, 97.

Turner, H. M. (1938). An investigation into cancer mortality among males in certain Sheffield trades. *Journal of Hygiene* **38**, 90.

Varis K., Ihamaki T., Kekki M. et al (1973). Cancer-gastritis relationship. *Acta Hepato-Gastroenterologica* **20**, 513.

Varis K., Stennman U-H., Lehtola J. et al. Gastric lesion and pernicious anemia: a family study. *Acta Hepato-Gastroenterologica* **25**, 62.

Varis K., Ihamaki T., Harkonen M. et al. (1979) Gastric morphology, function, and immunology in first-degree relatives of probands with pernicious anemia and controls. *Scandinavian Journal of Gastroenterology* **14**, 129.

Videbaek A. and Mosbech J. (1954). The etiology of gastric carcinoma elucidated by a study of 302 pedigrees. *Acta Medica Scandinavica (Stockholm)* **149**, 137.

Winkelstein W. jun. and Kantor S. (1969) Stomach cancer. Positive association with suspended particulate air pollution. *Archives of Environmental Health* **18**, 544.

Wynder E. L., Kmet J., Dungal N. et al. (1963) An epidemiological investigation of gastric cancer. *Cancer* **16**, 1461.

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