

Research on Esophageal Cancer in China: a Review¹

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Abstract

Research on esophageal cancer in the People's Republic of China is reviewed. Massive epidemiological studies revealed the prevalence of this disease in China, especially in the Taihang Mountain range areas in the north. Gullet cancer in chickens was also observed in the high-incidence area of Linxian in Henan, suggesting the presence of cancer-causing substances in the environment. Research on the etiology of this cancer has been pursued extensively. Moldy food and pickled vegetables were shown to contain carcinogens. In chemical etiology, nitrosamines and their precursors have received the most attention. The possible roles of trace element deficiencies in the soil, nutritional deficiencies, fungal infection, polycyclic hydrocarbons, and other factors in contributing to the high cancer incidence have been studied. The esophageal cancer problem has also been investigated at the cellular and immunological levels. Mass cytological surveys allowed many cases of early cancer to be detected and treated. Precancerous changes and the use of interventive therapy have been studied in animal models and patients. Prevention, early detection, and early treatment of this cancer have been pursued vigorously in many areas of China.

Introduction

In contrast to most Western countries, cancer of the esophagus is a common disease in many areas of China, especially in the North. Historical records dating from 2000 years ago noted "dysphagia" syndromes among the inhabitants of Henan (Honan) Province. In Linxian (Linhsien)³ of Henan, *ge shi bing* or "hard of swallowing disease" has been an endemic disease for generations. The serious concern and fear of this disease in ancient times was reflected in the existence of the *Houwang Miao*, meaning "Throat-God Temple." The temple was destroyed by war in 1927.

In order to deal with this fearful disease, epidemiological studies on EC⁴ were initiated in 1959 in Linxian. Many clinical, laboratory, and field investigations have since been conducted by a great number of scientific and medical personnel. Most of the research work was carried out or organized by investigators in the Cancer Institute of the Chinese Academy of Medical Sciences in Beijing; the Tumor Prevention, Treatment, and Research Group of Henan Province; and Linxian Research

Team for the Prevention and Treatment of Esophageal Cancer. The Cancer Institute in Beijing is also the headquarters of the Coordinating Group for Research on Esophageal Cancer. Substantial accomplishments have been made. Some of the results were compiled in the book, *Collection of Papers for the 20th Anniversary of the Cancer Institute and Ritan Hospital* (11). Some of the information on this subject was published in the United States of America in the book *Cancer in China* (38), prepared by members of the American Cancer Delegation after a visit to China in 1977, and in a guest editorial by Miller (51).

The present paper reviews the recent research developments on EC in China. Special attention has been paid to the reports published in Chinese which were previously unavailable to scientists outside of China. Various aspects of the research have been discussed with many Chinese scientists. In this review, highlights on epidemiology, etiology, pathology, carcinogenesis in animals, laboratory investigations, and prevention are discussed.

Epidemiology

Prevalence of EC in North China. The epidemiological studies on cancer of the esophagus in North China began in 1959 in Linxian (18). The initial survey confirmed the suspected high incidence and mortality from EC in that county. From this starting point, many epidemiological surveys of EC were conducted. The largest survey encompassed 181 counties (cities) in the 3 North China provinces of Henan, Hebei (Hopei), and Shanxi (Shansi), all of which border on the Taihang Mountain range. The population of the total area surveyed was approximately 50 million. The annual mortality rate from EC of each county was mapped out systematically (Chart 1). The crude EC mortality rate for the area is 53.96/100,000. After age and sex adjustments, the figure is 37.39/100,000. The 2 counties with the highest rates are Yangcheng (135.16/100,000) and Hebi (139.80/100,000). The 2 counties with the lowest rates are Hunyuan (1.43/100,000) and Tatong (2.80/100,000). The relatively high mortality figures are all from the counties where the borders of the 3 provinces meet on the south side of the Taihang Mountain. From these high-incidence areas, extending outward on all sides, the figures gradually decrease, giving an impression of irregular concentric belts. The ratio between the highest mortality rates in the innermost belt and the lowest rates in the outermost belt is approximately 100:1 (Chart 1).

In Linxian, a registry for EC was started in 1959. Based on the data of 12 years (1959 to 1970), the adjusted average incidence rate is 108.56/100,000 and the mortality rate is 99.76/100,000. Deaths due to cancer of the esophagus amount to approximately 20% of the total deaths. In one survey in Linxian covering 20 production brigades with a total population of 31,126, 7,212 of 10,264 persons age 30 or above were examined for EC. The total number of EC's detected was 118, i.e., a prevalence rate of 379/100,000 (18).

Distribution of EC in the Population and Trends in Mortality

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³ Pinyin phonetics are used for all the Chinese names; the spellings used previously are shown in parentheses. The suffix "-xian" means county; therefore, Linxian is used instead of Linxian County. Linxian has an area of approximately 2,000 sq km and a population of about 750,000. It is divided into 15 "people's communes" and further divided into 526 production brigades.

⁴ The abbreviation used is: EC, esophageal cancer.

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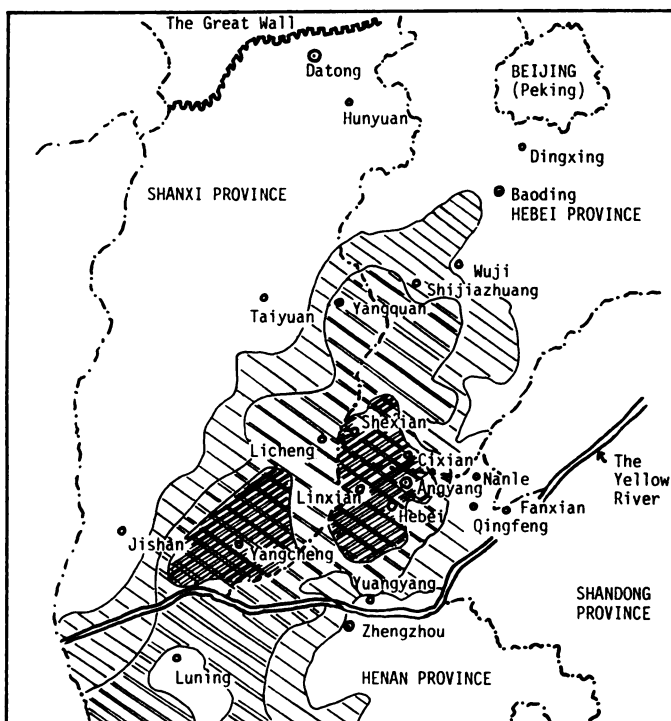


Chart 1. Distribution of EC in the triprovincial area of Hebei, Henan, and Shanxi in North China. Mortality: □, <20; ▨, 20 to 40; ▩, 40 to 80; ■, >80/100,000.

Rate. In North China, the ratio of male to female patients with EC is 1.6:1.0, ranging from 1.44:1 to 2.63:1 (18). The ratio is lower in areas with higher mortality rates and higher in areas of lower mortality rates. EC is not common among children and young adults. In Linxian, the incidence rate for those 25 years old is below 5/100,000. Above this age, the incidence gradually increases. At age 60, it is about 800/100,000. The highest mortality rate from EC is in the 60- to 69-year age group, accounting for 37 to 39% of the total death from EC. For those 50 to 59 years old and for those over 70, the values are 23 and 28%, respectively. The trend and actual figures for the prevalence rates are practically the same as the mortality rates. In areas of lower mortality rate, the occurrence of the cancer is usually delayed by several years; *i.e.*, the mortality curve is shifted to the right in a rate *versus* age plot (18).

In one area of Linxian with an approximate population of 110,000 persons over 30 years old, the yearly mortality rate due to EC averages 100 to 150/100,000. The value did not change significantly in the 30-year period from 1941 to 1970 (18) or in the period from 1971 to 1979.⁵ This relative "stability" in mortality rate is also found for the various age groups. Moreover, in the same county, the EC registry begun in 1959 also shows the same relative "stability" of incidence rate in a period of more than 10 years. This observation is suggestive of the possible presence of carcinogenic agents or factors inherent to the geographical area.

EC Mortality Patterns in China. A nationwide retrospective survey on mortality rates of cancer and 55 other diseases for the period 1974 to 1976 was accomplished recently; over 800 million people were surveyed. An atlas of cancer mortality of 2392 counties (from a total of 2429 counties in China) was

prepared (57). The survey showed that the national mortality rate of EC is 19.60 and 9.85/100,000 for males and females, respectively. Cancer of the esophagus accounts for 22.34% of the total cancer deaths, ranking second in prevalence, below stomach cancer (23.03%) and above liver cancer (15.08%). In addition to the Taihang Mountain triprovincial (Henan, Hebei, and Shansi) region, mortality due to EC is also high in the Dabie Mountain range between the provinces of Hubei (Hupeh) and Anhui, other areas of Henan and Hubei provinces, northern Jiangsu Province between the cities of Lianyungang and Nanjing (Nanking), northern Sichuan (Szechwan) Province, certain areas in southern Fujian (Fukien) Province, northeastern Guangdong (Kwangtung) Province, and the northern part of Xinjiang (Sinkiang) where the minority group, the Kazaks, resides. A high mortality rate is also seen in certain counties in the Provinces of Heilongjian, Gansu, and Qinghai as well as the Autonomous Regions of Neimenggu (Inner Mongolia) and Xizang (Tibet); however, the data may not be reliable due to the small number of inhabitants in these counties.

Research on Etiology

Extensive search for the causative factors of EC began in 1972 (11a). Various factors were compared in high- and low-incidence areas. The environmental factors which appear to have no correlation with EC mortality rate include rainfall, average temperature, altitude, types of soil, and types of crops (11a). On the other hand, correlations were found between EC and factors such as trace elements in the drinking water, food, and tissues; the nitrosamines and their precursors in the water and food; and the consumption of moldy foods. These and other factors are discussed in this section.

Trace Elements

Water and Food Samples. Initiated in 1972, a multiple correlation study was carried out on EC mortality and the content of trace elements in 686 drinking water and 909 food samples in 50 communes of 15 high-, medium-, and low-risk counties in Henan Province (10, 11a). The data showed an inverse correlation between EC mortality and contents of molybdenum, manganese, zinc, magnesium, silicon, nickel, iron, bromine, iodine, chlorine, potassium, sodium, phosphorus, and HCO_3 . Among the trace elements, molybdenum has received the greatest attention. It is a cofactor of the enzyme nitrate reductase which affects the nitrite and nitrate contents in plants. Low molybdenum content in soil and food has been suggested as a contributing factor to cancer of the esophagus in other areas (4). Moreover, zinc deficiency has been shown to increase nitrosamine-induced EC in rats (33).

Serum, Urine, and Hair Samples. In 1974, the molybdenum contents in serum, hair, and urine samples of male adults in high- and low-incidence areas were analyzed with catalytic polarography (11b, 11c). Molybdenum contents in the samples from Linxian were significantly lower than those from low-incidence areas of Yuxian and Xinyangxian. Low levels of molybdenum, similar to levels of the Linxian inhabitants, were found among the EC patients from Linxian and other areas who came to Linxian for treatment. However, the length of stay of the latter group of patients in Linxian was not recorded. It is not known whether the low molybdenum levels are due to the water and food in Linxian, their previous environment, or the cancerous state.

⁵ Linxian People's Hospital, unpublished results.

In 1973 and 1974, the trace elements in 871 male hair samples from 5 high- and low-incidence counties in the Provinces of Henan, Hebei, and Shanxi were analyzed by catalytic polarography and atomic absorption spectrophotometry (11d). An inverse correlation was found between EC mortality rate and the contents of magnesium, molybdenum, and zinc in the hair samples. The iron and copper contents in the hair appeared to be higher in Linxian than those in Yuxian (a low-risk area).

EC Patients. In one study in Henan, among 200 serum samples analyzed, the average level of zinc was lower in esophageal and cardiac cancer patients than in normal subjects, whereas the copper level was higher. No difference in serum magnesium was observed. Zinc content in overnight urine samples from EC patients was significantly higher than that of normal subjects. The magnesium content was lower in the urine of cancer patients than that of normal subjects (10). Molybdenum content was also examined in 44 EC tissues and in cut edges of resected esophagi from patients at the Linxian People's Hospital. Average content of molybdenum in cancer tissues was significantly lower than those in tissues of upper and lower cut edges of the esophagi (10).

Nitrosamines and Their Precursors

Since nitrosamines and other nitroso compounds are known to induce EC and other cancers in experimental animals (40, 48), the occurrence of these compounds and their precursors in water and food samples has been investigated extensively.

Nitrogenous Compounds in Drinking Water, Gastric Juice, and Saliva. In the mountainous regions of Linxian and other areas, water supply has historically been a serious problem. Although wells were available in certain areas, traditionally most people in Linxian relied on water from "dry wells" or man-made ponds. Dry wells or ponds were used to collect rain water and stored for use throughout the year. The water was infested with microorganisms and frequently contaminated with refuse from humans and domestic animals. Water was also stored in the home for several days in a *gang*, a large ceramic jar, often heavily contaminated. The nitrite content in "dry-well" and pond water was often much higher than in well water (65). In certain cases, the source of water has been considered as an important factor in determining the incidence rate of EC (65). The water supply conditions have improved since the construction of the Red Flag Canal in the 1960's and the "Water Improvement Campaign" in 1976. Nevertheless, water may have contributed and may still be contributing to the high incidence of EC. In 1976 and 1977, nitrate and nitrite were found in most of the drinking water samples from 495 wells in Yaocun Commune (a high-incidence area) of Linxian (11e, 23). The concentrations of nitrates and nitrites were especially high in the summer, ranging from 0 to 75 mg/liter (average, 12.65 mg/liter) and 0 to 2.63 mg/liter (average, 0.052 mg/liter), respectively. The concentration of nitrates in well water during the summer showed a positive correlation with the incidence rate of EC of each brigade. Similarly, a positive correlation was noted between the incidence rate of epithelial dysplasia of the esophagus and the nitrate levels in the spring and autumn water samples as well as the nitrite contents of the autumn samples. Moreover, the nitrites in drinking water were found to increase during storage or heating (64). For example, one study showed that the nitrite content was zero in well water,

0.074 mg/liter in *gang* water, 0.512 mg/liter in warm water heated and stored in iron pots, and 0.696 mg/liter in gruel, a very common food. In families with EC patients, the average nitrite nitrogen in *gang* water (29 samples) was 0.106 mg/liter and the ammonia-ammonium nitrogen content was 0.567 mg/liter, 7 and 30 times higher, respectively, than samples from families with no EC patients. Contamination by microorganisms has been suspected as the reason for the high nitrite and ammonia contents in water (64).

Nitrates and nitrites were detected in human gastric juice and saliva in Linxian. The salivary nitrites in patients with marked epithelial dysplasia or carcinoma of the esophagus were significantly higher than in the normal controls (23). The salivary nitrite contents of normal people in Linxian, however, were not higher than those in Xinyangxian, a low incidence area of EC (45).

Nitrosamines and Their Precursors in Food Samples. Food samples (wheat, corn, millet, millet bran, dried sweet potato, and pickled vegetables) from high- and low-EC-incidence areas in Henan Province were analyzed for nitrosamines by thin-layer chromatography (11f). Of the 124 food samples from Linxian, 29 were "positive" in the nitrosamine assay, whereas only one of 86 samples from Fanxian (low-incidence area) was positive. The presence of diethylnitrosamine and dimethylnitrosamine in some of the food samples was confirmed by gas chromatography. The "positive" compound detected in pickled vegetable samples, previously believed to be methylbenzyl nitrosamine (11f), was later identified as dimethylthiotetranitrosodiiron (Roussin's red) (10). Levels of secondary amines, nitrites, and nitrates in 8 varieties of grain and vegetable samples from these counties were also compared. Among the 111 samples from Linxian, the average secondary amine content was 2.29 mg/kg, significantly higher than the corresponding value of 1.94 mg/kg in 91 samples from Fanxian. Likewise, a difference was observed in the nitrite contents of food samples (11g). Soil composition (e.g., deficiency of molybdenum) and mold contaminations are suspected contributing factors for the elevated levels of nitrosamines and their precursors in food.

Formation of Nitrosamines in the Stomach. When methylbenzylamine, piperazine, and sarcosine were given together with sodium nitrite to rats by gastric gavage, the corresponding methylbenzyl nitrosamine, nitrosopiperazine, and nitrososarcosine were formed in the stomach after 60 to 90 min (23, 50). If pigs were fed with food containing methylbenzylamine or methylphenylamine and sodium nitrite, the corresponding nitrosamine was formed after 1 to 2 hr in the stomach if the pH was between 3.5 and 4.0. Between pH 4.0 and 4.5, methylphenyl nitrosamine was not formed. Diethylnitrosamine was not formed from the precursors even at pH 3.5 to 4.0, probably because of the strong basicity of diethylamine.

After human gastric juice was incubated with secondary amines and sodium nitrite at 37° for 2 hr, methylbenzyl nitrosamine was formed at pH 2.5 to 7.0, but dimethylnitrosamine and diethylnitrosamine were formed only at a pH below 3.0. When the secondary amines, extracted from bran of millet or flour of sweet potato from Linxian, were allowed to react with sodium nitrite either *in vitro* or in rat stomach, dimethylnitrosamine and diethylnitrosamine also formed readily (11h, 23). When vitamin C was fed to rats before methylphenylamine and sodium nitrite, it inhibited the synthesis of nitrosamine in the stomach (14).

Formation of Nitrosamines in Fungus-infested Food. In areas where EC is prevalent, foodstuffs are frequently contaminated with fungi. In order to simulate these conditions, steamed corn bread was kept at room temperature or 26–30° for 3 to 5 days to allow mold growth. During this process, the concentration of secondary amines was increased by 4-fold and the contents of nitrate and nitrite were also raised (50). Similar results were observed by inoculating cornmeal with a pure culture of several strains of fungi isolated from grains in Linxian (49, 50). Furthermore, nitrosamines were detected in the stomach contents of rats fed moldy corn bread, but not in those fed un moldy corn bread (50). The formation of nitrosamine in *Aspergillus niger*-inoculated cornmeal has also been reported (32).

It was observed that several species of fungi such as *Fusarium moniliforme*, *Geotrichum candidum*, *Aspergillus versicolor*, *Penicillium brevi-compactum*, and *Penicillium lividum* could reduce nitrate to nitrite (10). Fungal contamination also raised the amount of secondary amines in food and promoted the synthesis of nitrosamines from their precursors. When corn bread was tainted with the commonly occurring fungi, *F. moniliforme*, *Aspergillus flavus*, *G. candidum*, *Penicillium chrysogenum*, or *Cladosporium herbarum*, the content of secondary amines increased after several days of incubation. The greatest increase, 17-fold, was with *F. moniliforme*. When sodium nitrite was added to the moldy corn bread, dimethylnitrosamine, diethylnitrosamine, and methylbenzyl nitrosamine were produced (39). A new compound, *N*-1-methylacetyl-*N*-3-methylbutylnitrosamine, was found to be present at 0.2 to 0.3 ppm (47). The structure has been confirmed by comparison with a chemically synthesized standard. The carcinogenicity of this nitrosamine is under active investigation. In addition to the formation of nitrites and secondary amines, fungi can also promote the synthesis of nitrosamines (10). It was suggested that the acidity and enzymic activity in the moldy food may provide favorable conditions for the synthesis of *N*-nitroso compounds (10).

Fermented and Moldy Food

Correlation between EC Mortality Rate and the Consumption of Pickled Vegetables and Other Moldy Food. Traditionally, pickled vegetables have been a popular food in some high-EC-incidence areas in China. They were prepared each autumn by placing chopped and blanched leaves of Chinese cabbage, turnip, soybean, sweet potato, sesame, and other vegetables in a large ceramic container. The vegetables were pressed, covered with water, and allowed to ferment for several months. The products, usually covered with white mold, were said to be quite "tasty" due to the special flavor and sourness acquired during fermentation. The vegetables and juice were eaten either as is or cooked in gruel. During the summer, some of the juice was also consumed as a drink. In some families, the pickled vegetables were eaten daily for as long as 9 to 12 months a year as an important part of the diet. In 1973, the correlation between the consumption of pickled vegetables and EC mortality was studied in 30 communes in the triprovincial area of Henan, Hebei, and Sanxi and the northwestern region of Sichuan Province (28). Using the commune as a unit, a positive correlation between EC mortality rate and the frequency of pickle consumption was found. That is, in communes where more people ate pickled vegetables or ate pickled veg-

etables for a greater portion of the year, the EC mortality rates were higher. However, such a correlation was not established for the people in the 8 communes in Guangdong Province, for, in general, the consumption of pickled vegetables was low in that area (28).

The consumption of other fermented or moldy food is also common in high-EC-incidence areas (28). In the high-incidence areas in northeastern Sichuan Province, the people consume a fermented food, *Laozao* (made from rice, corn, millet, and sweet potato), over a period of 3 to 4 months or longer per year. In Nanao Island of Guangdong Province, people eat fish pastes made by fermenting small fish and shrimp for 1 to 2 years. In certain localities in the triprovincial area in North China, people eat food several days after being cooked. Mold contaminations are evident, and the food is usually eaten without reheating. The consumption of fungal-infested corn, dried sweet potatoes, and dried turnips is also common. The use of fermented and moldy foods is much lower in low-EC-incidence areas in comparable geographical locations (28).

Mutagens, Carcinogens, and Fungi in Pickled Vegetables. The mutagenicity of pickle samples from Linxian was tested by scientists in the National Cancer Research Institute in Tokyo. The samples were positive in 2 strains of *Salmonella typhimurium* (TA 100 and TA 98) (38, 51). Extracts from pickled vegetables and concentrated pickle juice, when fed to rats, can induce cancer (10, 26). The carcinogens in pickled vegetables have not been identified. It was observed that the pickled vegetables were heavily infested by fungi. Among 24 samples analyzed in one study, 20 contained *G. candidum*, some samples contained *Mucor* spp. and yeasts, and a few samples contained *A. flavus*, *A. niger*, *Aspergillus fumigatus*, *Aspergillus nidulans*, and *Fusarium* spp. (26, 75). As will be discussed later, some of these fungi are believed to play important roles in carcinogenesis.

The problem of pickled vegetables has received great attention both inside and outside China (18, 38, 51). The pickle samples contain secondary amines, nitrite, dimethylthiotetra-nitrosodiiron, and some yet unidentified mutagens and carcinogens. Nevertheless, the available evidence has not defined the role of this type of food as a causative factor of EC.

Experimental Carcinogenesis with Pickled Vegetables, Moldy Cornmeal, and Fungi. The extracts and concentrated liquid of pickled vegetables from Linxian were fed to Wistar rats (body weight, 60 to 80 g). Among 29 rats fed for 330 to 730 days, one developed adenocarcinoma of the glandular stomach, one had angioendothelioma of the thoracic wall, 4 had fibrosarcoma of the liver, and many had epithelial dysplasia lesions in the esophagus and the forestomach. No tumors were noted in the 10 control rats (23, 26).

In a series of studies in Henan Province, cornmeal was inoculated with fungi to simulate the conditions of mold contamination. After incubation at 26° for 6 to 8 days, the moldy cornmeal was mixed with uncontaminated cornmeal and fed to Wistar rats. *Fusarium poae* (Peck) Wr. -infested cornmeal was found to induce papillomas of the stomach, carcinoma of the forestomach, and other cancers, whereas *A. flavus* Link-infested cornmeal did not induce any tumor (43). Cornmeal infested by *F. moniliforme* or *Fusarium semitectum* Berk. was found to induce tumors on several different tissues. Carcinoma of the esophagus was not observed, but epithelial hyperplasia was induced by *F. moniliforme*-infested samples (42). In Hebei

Province, moldy foods and *F. moniliforme*-infested cornmeal have been shown to induce "precancerous" changes and papillomas of the esophagus and stomach of rats and mice (66). In a preliminary study on the synergism between moldy food and nitrosamine, methylbenzyl nitrosamine was given at a dosage of 0.75 mg/kg/day to 30 rats maintained on fungi-infested cornmeal. After 176 days, about 65% of the rats developed EC as compared to 15% of the control group fed with unmoldy cornmeal (62).

Moldy corn bread has been reported previously (38, 62) to produce some esophageal carcinoma (3 of 16 Wistar rats). This interesting result remains to be confirmed with a larger number of animals.

In order to investigate the carcinogenicity of fungi, *G. candidum* Link, a fungus found in most pickled vegetables in Linxian, was cultured in Sabouraud's medium. After the cultured medium was fed to rats and mice for 20 months, epithelial dysplasia and precancerous lesions of the forestomach were found in a large percentage of rats and mice. Nevertheless, only a few cases of epithelial dysplasia and precancerous lesions of the esophagus were found. The fungal culture was more effective in inducing the precancerous lesions of the forestomach in rats maintained on a vitamin A-deficient diet than in those on normal diets (76). When fed to mice, the fungi promoted the action of methylphenylnitrosamine in inducing cancer or precancerous lesions of the forestomach (76).

The above results showed that moldy foods and pickles can induce epithelial hyperplasia and dysplasia of the esophagus and tumors of the stomach and other organs. Their ability to induce carcinoma of the esophagus, however, has not been established. Most of these studies were hindered by insufficient number of animals and inadequate animal care facilities. Additional studies with larger number of animals for longer durations under well-defined conditions are needed to establish the relationship between moldy food and EC.

Nutritional Factors and Eating Habits

Dietary Pattern. It is the impression of several investigators that the incidence of EC and the precancerous dysplasia state is higher in families with nutritionally inadequate diets than in those with better diets in the same area. Data from systematic dietary and nutritional surveys are not available. This section is based on personal observations and communications.

The diet in Linxian, and probably in other high-EC-incidence areas, is extremely simple, consisting mainly of corn, wheat, millet, rice, sweet potato, and some seasonal vegetables. The diet is extremely low in animal products and fat. Consumption of vegetables and fruits is low. In a survey a few years ago based on the food available to 130 inhabitants of Linxian,⁶ it was found that 80% of the calories was from grains, 12% was from tubers, 7% was from beans and other plant products, and less than 1% was from animal products. Of the total caloric intake, 81% was from carbohydrates, 11% was from proteins, and 8% was from fats. Only 0.5% of the protein and 9% of the fat were from animal sources. Due to the limited food variety, amount of cooking oil, and cooking facilities, food preparation is very simple. Often, a pot of millet gruel containing some

vegetables is simmered for hours on a coal stove. This is usually the sole food for a meal.

Adequacy of Nutrients. The above survey also showed that the supply of calories and protein reached about 90% of the Recommended Dietary Standards established by the Chinese Government.⁶ Deficiencies in calcium and riboflavin, which meet only 76 and 66% of the standards, respectively, were indicated. Symptoms of riboflavin deficiency, e.g., cheilosis, have been observed among the population in Linxian in the winter. Riboflavin deficiency may be an important factor in carcinogenesis of the esophagus, because it can produce epithelial changes in humans and various experimental animals. It has been shown to increase the mitotic rate of skin buccal and esophageal mucosa of baboons (67). Flavocoenzymes are essential parts of the mixed-function oxidase system, an enzyme system responsible for the detoxification as well as the activation of carcinogens. Riboflavin deficiency is known to affect the rate of carcinogen metabolism (74).

Vitamin A deficiency has been shown to enhance carcinogenesis (3, 16, 54, 55), and vitamin C has been suggested to have anticarcinogenic activity (9). Although the calculated amounts of carotene and vitamin C in the foods appear to be sufficient on a yearly basis, losses during drying, storage, and cooking can be significant. Deficiencies in vitamins A and C are possible for certain portions of the population during winter when fresh vegetables and fruits are scarce. It was found that, in the spring of 1975, the urinary ascorbate of 55 inhabitants in Linxian averaged 10.7 mg/day, one-ninth of the value in Xinyangxian, a low-risk area (11i). Vitamin C may be involved in the metabolism of nitrates. In a study of 27 woman volunteers, it was observed that after this vitamin was taken for 6 days (300 mg, 3 times a day), the urinary nitrites were reduced from 5 to 2 mg/24 hr (14). As discussed previously, deficiencies in trace elements may also exist.

Sorghum and Persimmons. On the basis of the belief that tannins are carcinogenic, Morton (53) suggested that the high-tannin-containing kaoliang (a dark sorghum) might be a causative factor for the high incidence of EC in North China. This appears unlikely since the consumption of kaoliang was not excessive in high-incidence areas as compared to many low-incidence areas. Although the carcinogenicity of tannins has not been clearly established (37, 53, 68), tannin-containing substances should be considered in studying the etiology of EC. For example, the consumption of persimmons is quite common in Linxian. Some persimmons are consumed as fresh fruits, but most of them are dried together with the bran of millet and ground. The mixture is ingested as a gruel or hot cereal after mixing with hot water. The food is known to be coarse and to contain a high level of tannins. The leaves of persimmons are used as a medicine (11j). This group of substances should receive more attention since the extracts of both the unripe fruits and leaves of persimmons have been shown to be carcinogenic in rats (36, 37).

Eating of Hot Food. In one survey in 1965, it was found that 77% of the inhabitants in Linxian habitually ate food with temperatures of 60–70° (75). Some even ingested food at 80–88°. In experiments simulating these conditions, hot water was force fed to mice. Twelve hr after feeding water at 80°, severe coagulative necrosis of the epithelium was observed on the esophagus along with acute interstitial inflammation. In 1 to 3

⁶ S-f. Zheng, unpublished results.

days, ulceration and epithelial regeneration was observed. These symptoms disappeared after 1 week, but hyperplasia was seen and mild dysplasia could be observed in some animals. With water at 75°, the damage was less, but hyperplasia was seen in some of the animals. Damage, however, was not observed with water at 60–70°.

Other Factors

Genetic Factors. In 1971, the pedigrees of 7 high-risk families were studied (11k). A large number of cases can be explained on a hereditary basis, while others cannot. The family link of EC was also studied in Shanxi Province. Several families had a very high incidence of EC; in 2 of these families, 2 persons had EC at 15 years of age. In a cytogenetic study, short-term cultures of phytohemagglutinin-stimulated lymphocytes from 103 members of high-incidence families and 30 controls from families with no EC incidence in 5 generations were made (70). The result showed that cells with aneuploidy and various types of structural aberrations were more frequent in high-incidence families.

Polycyclic Hydrocarbons. During winter, most families in Linxian used to cook on coal stoves located in the bedroom. The stove also served as a room heater. Chimneys were not available in some homes, and the rooms were poorly ventilated. The presence of CO and SO₂ was apparent. In 1975 and 1976, the contents of benzo(a)pyrene in some rooms in Yaocun Commune of Linxian were determined to evaluate the contamination by polycyclic aromatic hydrocarbons (27). The air contained an average of 1.84 to 7.49 µg of benzo(a)pyrene per 100 sq m, much higher than the value of 0.69 µg for air outdoors. Generally, rooms with chimneys had lower benzo(a)pyrene contents than those without (27). It has been demonstrated that compounds inhaled from the respiratory tracts can reach the esophagus (34). Most polycyclic aromatic hydrocarbons are carcinogens and inducers of the mixed-function oxidase system and, probably, are also promoters in carcinogenesis (17, 35). When used together with nitrosamines, benzo(a)pyrene has been shown to have a synergistic effect in pulmonary carcinogenesis in rats (2). The role of polycyclic hydrocarbons in carcinogenesis of the esophagus requires further investigation.

Smoking and Drinking. The use of tobacco and alcoholic beverages has been implicated in many studies as contributing factors of cancer of the esophagus, especially when the 2 factors are combined (15, 67, 71, 72). In Linxian, smoking of locally grown tobacco is common, but a correlation between smoking and EC was not observed (28). With regard to drinking, a distillate of kaoliang (sorghum) has been previously suggested as a possible etiological factor of EC in North China (reviewed in Ref. 67). However, drinking does not appear to be a problem in Linxian; the population consumes little or no alcohol (28).

Tea and Medicinal Herbs. Tea and herbs have been suspected as causative factors of EC in some areas outside of China (52, 53, 60). In the high-EC-incidence area in North China, tea is not produced locally; thus, tea drinking is less common than in many other low-incidence areas in China. Therefore, tea is unlikely to be a contributing factor. On the other hand, the use of locally produced medicinal herbs is common. It is known that the extracts, especially the tannin-containing extracts, of many plants are carcinogenic in exper-

imental animals (36, 37, 59). The carcinogenicity of medicinal herbs is thus an important subject for investigation.

Oral Health. It has been reported that dental caries is more serious in EC patients than in normal subjects. The oral hygiene of the population in Linxian is generally poor. Many people lose most of their teeth before 50 years of age. Professional dental care is limited, and dentures are unavailable. In a survey conducted in 1975 to 1976, in Linxian, 1084 adults and 1400 school children were examined; dental caries were present in 80.7 and 68.9% of the subjects, respectively, much higher than the average rate of 50 to 60% in China. The average number of caries was 5.47 for adults and 2.25 for school children. Furthermore, 77.3% of caries in adults was deep caries and residual caries roots. Poor dental hygiene and low fluoride content of the water have been suggested as contributing factors (25). Poor oral hygiene may contribute to carcinogenesis of the esophagus through the following actions: (a) food, especially those that are coarse in texture, swallowed without sufficient chewing can irritate or damage the epithelium of the esophagus; (b) oral microorganisms may produce carcinogens or precursor of carcinogens; (c) the oral cavity can be a source of microorganisms for the infection of the esophagus. In a study in 1975, the incidence of oral aphthae among the inhabitants in Linxian (84 of 249) was found to be much higher than in Xinyangxian (3 of 142), a low-EC-incidence area. In Linxian, this oral disease was found to be more common and serious among patients with EC or epithelial dysplasia and hyperplasia of the esophagus (11).

Precancerous Lesions and Pathogenesis

Pathology. The pathology of EC has been studied in a great number of cases. In one study, 858 resected cancerous human esophageal specimens were examined (11m). The cancer was located at the middle third of the esophagus in 58.3% of the cases, at the lower third in 38.9% of cases, and at the upper third in only 2.8% of cases. Among the 524 samples examined histologically, 90.6% were squamous cell carcinoma, with the remaining cases mainly adenocarcinoma and adenoacanthoma. The pathology of early esophageal squamous cell carcinoma has also been reported in detail (63). An electron microscopic investigation of the cancer cells was made; no virus-like particles could be detected (12).

In Linxian, a high-EC-incidence area, a large number of cancers of the stomach were also found, almost all of them located in the cardia. It is possible that the same carcinogenic factor(s) caused tumors at both sites. A pathological study of 9 cases of double primary carcinomas of the esophagus and stomach was recently published (41).

Mass Screening. One of the most outstanding works on EC in China is the mass screening using the technique of *Lawang*, meaning "to pull a (fishing) net." An inflatable balloon covered with a nylon mesh net is swallowed by the patients to the desired depth in the esophagus or cardia. The balloon is inflated with air and pulled up while the size of the balloon is regulated with a syringe connected to the balloon through tubing (11n, 10, 38). In the process, mucous membrane cells and cancer cells, if they exist, are collected on the net. Cyto-smears are then made for cytological studies. Professor Shen Qiong of Henan Medical College, working in Linxian and Zhangzhou of Henan Province, has made important contributions in adapting and perfecting this technique as well as in

vigorously pursuing the early detection and early treatment of EC.

About 25,000 persons have been examined in mass surveys in Yaocun Commune of Linxian (10). The quality, thoroughness, and high degree of accuracy of the cytological preparations are considered outstanding (38). A large number of cases of epithelial dysplasia and early carcinoma of the esophagus were detected. For example, in a survey in 1974 covering 14,002 persons over 30 years of age in Yaocun Commune, 75% of the cancer cases detected were early lesions (11o). Many of these early esophageal lesions were not seen by esophagoscopy or radiographic examination. For patients with epithelial dysplasia, the cytology was repeated in follow-up work. This allows the relationship between dysplasia and cancer to be illustrated. Mass screening for EC has also been carried out in several other areas in China (11o).

Relationship between Epithelial Dysplasia and Carcinoma of the Esophagus. Mass cytological surveys in different geographical areas disclosed that the incidence of esophageal dysplasia coincided with that of EC (11o, 19). The average age of patients with severe dysplasia was about 7 or 8 years younger than that of the cancer patients. The relationship between dysplasia and carcinoma is believed to be as follows (10):

Normal \rightleftharpoons mild dysplasia \rightleftharpoons severe dysplasia \rightarrow

early cancer \rightarrow advanced cancer

In a study conducted during 1961 to 1969 on 105 patients with mild dysplasia, 15.2% progressed to severe dysplasia, 40% remained unchanged, and 44.8% returned to normal in 4 years. Of 79 patients with severe dysplasia, 26.6% progressed to cancer, 32.9% remained the same or alternated between mild and severe dysplasia, and 40.5% regressed into normal or mild dysplasia (19). Similar results were also observed in other studies (46). In a retrospective study in Yaocun Commune of Linxian in 1975, the rate of progression from severe dysplasia to carcinoma was studied (11o). Among 327 cases followed for 1 to 2 years, 7.9% progressed to cancer. In 142 cases with a 2- to 5-year follow-up period, 20.5% progressed to cancer. The progression rate increased to 34% (15 of 44 cases) and 53% (9 of 17) in 5 to 9 and 9 to 12 years of follow-up, respectively.

Fungal Invasion and Carcinoma of the Esophagus. In high-incidence areas of EC, fungal invasion of the esophagus is common. The presence of fungus, as determined by cytosmear, correlated with the degree of dysplasia. For example, fungus was found in the esophagi of 31% (64 of 207) of normal and mild dysplasia subjects, 72% (180 of 248) of those with severe dysplasia, and 90% (90 of 100) of those with carcinoma of the esophagus (10). Fungal invasion of the esophagus was also studied in biopsies and resected specimens (73). Among 185 samples, the incidence of fungal invasion was: hyperplastic epithelium of noncancerous patients, 30%; hyperplastic epithelium of early EC, 50%; cancerous tissue of early EC, 15%; and apparently normal epithelium, 3.1%.

Electron microscopy showed that the fungi invaded between the esophageal epithelial cells as well as inside the cytoplasm of the cells. The epithelial cells adjacent to the invading fungi often showed various degrees of change, ranging from simple hyperplasia to mild and severe dysplasia and to early malignant

change. The area of infection is normally in the middle third of the esophagus, similar in location to that of the carcinoma. The average age of patients with the infection is about 7 years younger than that for the EC patients (11p).

Candida species is the commonest invader, and a pure culture of *Candida albicans* has been isolated from the hyperplastic epithelium and carcinoma *in situ* of the esophagus. *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis*, *Torulopsis glabrata*, and *Torulopsis tomata* have also been isolated from oral and esophageal samples (61). The role of fungal infection in the malignant change of the esophagus is under active investigation.

Treatment of Severe Epithelial Dysplasia. In a nonrandomized trial started in 1975 and completed recently, patients with severe dysplasia were treated with the following drugs for 8 months: Group A, the herbal mixture Antitumor B,⁷ 72 patients; Group B, Antitumor B plus 5-fluorouracil, 162 patients; Group C, tilorone, 43 patients (8). After 15 months, the regression rates were 75.0, 48.1, and 48.8%, respectively. In 125 cases of an untreated group (patients refused treatment) with similar dysplasia, the natural regression rate was 29.8%, significantly lower than the treated groups. The incidences of malignancy were 1.4, 2.5, and 2.3%, respectively, in Groups A, B, and C, significantly lower than the 7.4% of the untreated group. The effect of therapy in certain patients with second-degree dysplasia or suspected cancer, however, was insignificant (8). Retinoic acid was also given to some patients, but this compound is said to cause headache.⁸ Attempts are being made to synthesize derivatives of retinoic acid to reduce or eliminate this side effect. This type of interventional therapy is of considerable interest. Randomized and controlled trials in the future should yield more definitive results.

Carcinogenesis in Domestic and Laboratory Animals

Pharyngeal and Esophageal Cancers in Domestic Fowls

Pharyngeal and esophageal carcinomas in chickens were observed in Linxian in the early 1970's (44). Later, the prevalence rates of these diseases in domestic fowls were surveyed (18, 29). Among 18,774 chickens in Linxian, 33 cases of histologically proven gullet cancers were found, whereas only 2 cases each were found in 11,399 chickens in Fanxian and in 9,420 chickens in Hunyuanxian. Thus, the incidence rates are 175.78, 17.55, and 21.23 per 100,000, correlating well with human EC mortality rates of 131.79, 23.67, and 1.32 per 100,000 for Linxian, Fanxian, and Hunyuanxian, respectively.

Stations were established to collect cancerous chickens in the 3 counties. Among the 152 cases of poultry pharyngeal and esophageal cancers collected, age distribution showed that 29.6% of the chickens were 2 to 4 years old, 50.0% were 5 to 6 years old, 16.4% were 7 to 9 years old, and only a few were under 2 years or above 9 years old. Only 2 of the involved were with roosters, probably because they were rarely kept for the long periods necessary for cancer to develop. Over 50% of the diseased chickens belonged to families with EC patients or their neighbors. The main site of the poultry cancer was at the

⁷ Antitumor B is made from 6 medicinal herbs: *Sophora subprostrata* Chun et T. Chen, *Polygonum bistorta* L., *Pastrinia villosa* "Thumb" Juss., *Prunella vulgaris* L., *Dioscorea bulbifera* L., and *Dictamnus dasycarpus* Turcz.

⁸ H-Y. Cai, personal communication.

level of the pharynx (58.5%); 27.0% were at the pharyngeal and esophageal openings, and 14.5% of the cases were at the upper end of the esophagus. The size of the tumors varied from 1 to 3 cm in diameter, the largest being 5.3 cm in diameter. There were 145 cases (96.6%) of squamous cell carcinoma and 7 cases of adenocarcinoma and adenoacanthoma. Most of the tumors showed a medium degree of cell differentiation. Twenty-three cases had multiple primary tumors, and 19 of these contained primary lesions in both the pharynx and the esophagus (29).

Incidence of Gullet Cancer in Chickens Raised by Immigrants from Henan. In 1975, the prevalence of pharyngeal and esophageal carcinoma among chickens was studied in Zhongxiang (Chung-hsiang) County of Hubei Province (30). The incidence rates of chickens in 2 communes of Henan immigrants⁹ were compared with those in 2 communes of native Hubei people. Among 5,484 chickens examined in the immigrant communes, 12 cases of pharyngeal and pharyngo-esophageal cancers were observed, whereas none was observed among 2,371 chickens from the native communes. The immigrants themselves have an EC incidence of 82.81/100,000 which is much higher than that of the native population (21.53/100,000). It is not known whether the human cancer was initiated before or after the immigration. The high cancer rate of their chickens, however, is most probably a result of the eating and living habits that these immigrants brought along. Soil and water appear not to be contributing factors in this case. This interesting observation deserves further investigation.

The above studies illustrated the close parallelism between human and chicken in the prevalence and pathology of EC. The chickens usually shared the same food sources and natural environment as their owners and therefore can be a useful model for studying the EC problem. For example, a decrease of cancer rate may be detected in chickens before such a trend can be observed in the human population. It may also be a good model for experimental carcinogenesis of the esophagus.

Esophageal Carcinoma in the Goat

In 1973, a case of squamous cell carcinoma of the esophagus was observed in a male goat, about 7.5 years old, in Linxian (13). This is the only case reported for goats in China, although up to 657 esophagi (mainly from goats 2 to 3 years old) have been examined.

Studies on Precancerous Changes and Carcinogenesis

Rodent Models. Precancerous lesions and cancers of the esophagus and forestomach of rats and mice were induced by *N*-nitrososarcosine ethyl ester or its precursors (7). When 0.5 g of *N*-nitrososarcosine ethyl ester (or 2 g of sarcosine ethyl ester plus 0.3 g of sodium nitrite) per kg body weight was given to mice twice weekly p.o., precancerous lesions developed in the epithelium of the forestomach of all mice after 10 to 11 feedings. About 50% of the cases progressed to carcinomas in 77 days without additional carcinogen feeding. The results were highly reproducible. When the carcinogens were given at the same dosage and frequency to male Wistar rats, all of the

⁹ They were from Xichuan County of Henan Province. This county is a medium-risk area for EC.

9 animals developed precancerous lesions of the esophagus, and one had early cancer after 23 to 31 days. With 32 feedings, the incidence of EC was about 80% (21 of 30 rats) in 107 to 112 days and 90% (9 of 10 rats) in 153 days. Histological examination revealed squamous cell carcinomas in both rats and mice. The carcinogenic process was divided into 4 stages: simple hyperplasia; dysplasia; early cancer; and advanced cancer. The development of mouse forestomach cancer was shown to have many features similar to that of human EC (7). Since *N*-nitrososarcosine ethyl ester can induce the precancerous lesions and carcinomas in a fairly short period with good reproducibility without showing any toxicity, these models are excellent for experimental drug therapy and etiological research.

Intervention of the Precancerous Changes. Several agents were tested in the animal models for their ability to inhibit precancerous changes. Tilorone, a weak interferon stimulator which has been reported to inhibit the growth of certain cancers (1), was found to inhibit carcinogenesis of the esophagus. Tilorone solution (0.02%) was given *ad libitum* 6 days weekly either before treating rats with *N*-nitrososarcosine ethyl ester or after the precancerous lesions were developed. A significant inhibition was observed in both cases, although the inhibition was more pronounced when tilorone was used before the carcinogen (6). In another study, retinoic acid was used at 200 mg/kg twice weekly or 10 mg/kg 5 times weekly p.o. Both dosages were able to inhibit the progression of precancerous lesions to carcinoma and to cause regression of the dysplasia in certain instances (5). A similar inhibitory action was also observed with an herbal medicine made from persimmon leaves, the herbal mixture Antitumor B, or Antitumor B plus 5-fluorouracil (8, 11j).

Cancer and Precancerous Changes Induced by Nitrosamine in Chickens. Sarcosine ethyl ester and sodium nitrite were fed to 4-month-old chickens. All the chickens died during a 30- to 300-day period with different stages of cancer and precancerous lesions. The number of lesions increased, and the changes were more marked in chickens which died late. Among 67 fowls, a total of 12 cases of dysplasia lesions in the pharynx and esophagus were observed along with one case of early adenocarcinoma and 3 cases of adenomatoid lesions of the glandular stomach (11q). Additional studies with this animal model may be fruitful because of the apparent parallelism between the cancer incidence in human and chicken in North China.

Other Laboratory Investigations

Epithelial Cell Line from Human EC. An epithelial cell line (Eca 109) from human squamous carcinoma of the esophagus was established in 1973 from an explant of resected esophagus from a 37-year-old female patient in Linxian. The biological characteristics, proliferation kinetics, chromosomal number, and enzyme pattern have been studied. It consists mainly of polygonal pleomorphic cells, is hypotriploid, and has a marker chromosome. When injected s.c. into X-irradiated newborn rats, it produced carcinoma. It has now been propagated for more than 250 passages and still maintains the original appearance of its primary culture (20). The fine structure of Eca 109 cells was compared with that of cultured normal esophageal epithelial cells with electron microscopy (56). Clonal anal-

ysis was carried out, and spheroid culture was successfully cultivated on filter paper (10). In 1975, a second EC cell line (EC 56) was established in Linxian and has been passaged over 50 times. The specimen was taken from a 35-year-old male patient. The cells differ from that of the Eca 109 in several biological and morphological characteristics (11r).

Cell line Eca 109 was used to study the mechanism of action of *Maytenus* extracts and vincristine, the effects of 6 herbal drugs, and the effects of the other antimetabolic drugs (10, 11s, 21). It was also used to study the synergistic killing effect of hyperthermia and camptothecin (10).

Transformation of Human Esophageal Fibroblasts *In Vitro*. Neoplastic transformation of primary fibroblast culture derived from the normal esophageal tissue of a male esophageal cancer patient was induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. The cells showed the biological and morphological properties characteristic of malignant cells and produced fibrosarcoma after heterotransplantation into immunosuppressed newborn mice (69).

Immunological Studies. Lymphocyte-mediated cytotoxicity was studied *in vitro* using human EC cell line Eca 109 as target. Cytotoxicity was assessed by both visual counting and [³H]thymidine incorporation. The positive rates were 45% in EC patients, 18 to 23% in other cancer patients, and 4% in normal subjects (58). Serum carcinoembryonic antigen was determined by radioimmunoassay, but the positive rate was only 40% in EC (10). In other studies, tumor antigen was extracted with 3 M KCl from fresh resected specimens of EC. When autologous extracts were used in skin test for delayed-type hypersensitivity *in vivo*, a 50% positive rate was observed (10, 11t). The result of this skin test can be correlated with the lymphocyte-mediated cytotoxicity assayed *in vitro* (58).

Prevention and Treatment

The 5 Preventive Measures

Prevention is always being emphasized in China. Although the cause of EC is not established, several preventive measures have been undertaken. These measures are expected to improve the health of the population, even if they do not directly reduce the incidence of EC.

The Use of Molybdenum Fertilizer. In order to reduce the amounts of nitrates and nitrites in grains and vegetables, ammonium molybdate has been used as a trace-element fertilizer in Linxian since 1974. This supplement significantly increased the yield and the molybdenum content of the crops and decreased the nitrate and nitrite contents. It also elevated the ascorbic acid content of vegetables (22, 24).

Prevention of Mold Contamination. Previously, grains usually became moldy as a result of inadequate drying and improper storage. Cement roads have been built recently in many villages to serve as drying grounds. Concrete storage jars are also becoming widely available. Mass education advising people to stop making and eating "pickled vegetables" and to avoid other moldy foods has been conducted with appreciable results.

Removal of Nitrosamines and Their Precursors. In addition to the above 2 measures, extensive efforts have been made to improve the quality of the water. Many wells, water purification stations, and water supply systems have been constructed.

Elimination of Undesirable Eating Habits. Besides "pickled

vegetables," the people were also advised not to eat food while too hot. They were also advised to refine foodstuffs that are coarse in texture and to chew thoroughly.

Treatment of Precancerous Lesions. As a result of thorough cytological screening, a large number of cases of epithelial dysplasia were detected. The cases were followed up and the patients were encouraged to receive treatment. Although several drugs appear to be efficacious, more effective treatments are being sought.

The "3 Early's" in Dealing with EC

Early detection, early diagnosis, and early treatment have been emphasized in several high-EC-incidence areas in China. Many means were used to publicize these and the "7 symptoms"¹⁰ of EC. Such mass education has led to the discovery and treatment of many early cancers, although reluctance of patients to seek treatment is not uncommon.

Treatment

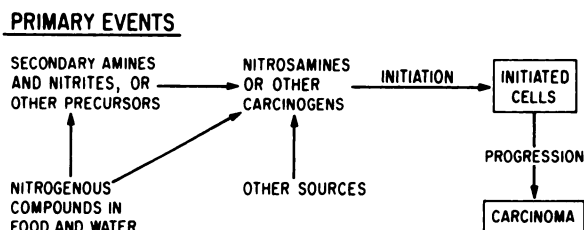
Surgery, radiation therapy, and chemotherapy were used, sometimes in combination, for the treatment of EC (10, 31, 38). Sometimes the survival rate was said to be higher⁵ than that in the United States, due possibly to the large number of early cases treated in China, as well as to a difference in statistical treatment. The radiation therapy and chemotherapy were much less sophisticated in comparison to American techniques. Of special interest is the use of herbal medicines, sometimes in combination with chemotherapy or radiation therapy for the treatment of cancer (11u, 11v). This approach was reported to have some beneficial effects which remain to be investigated more thoroughly.

Concluding Remarks

Assessment of Research. The strength of the research on EC in China lies in the epidemiological and mass screening for early detection work. The social structure, low mobility of the population, and "mass-line approach" enable such studies to be carried out on a massive scale. The quantity and quality of the work are remarkable despite a lack of sophisticated data-analyzing systems. Laboratory investigations were limited by the availability of facilities, reagents, and animals. Some of the analytical methods were less sensitive or less specific than those available to the scientists in the developed nations. In most studies, the number of animals and animal care facilities were inadequate. Even with these limitations, the Chinese researchers have put forth great efforts and contributed significantly to our understanding of the EC problem. The stage is set for more definitive investigations on the etiology and other aspects of this disease.

Primary Events and Contributing Factors in the Carcinogenesis of the Esophagus. Although a great deal of information on EC has been obtained, the causative factors of this disease remain to be established. The following (Chart 2) is the author's speculation on the primary causative factor(s) and contributing factors to the EC in the high-incidence areas in North China. Nitrosamines are the primary suspects in causing the cancer, although mycotoxins and other carcinogens are

¹⁰ The "7 symptoms" are: feeling of obstruction when swallowing food, sharp pain behind the breast bone, feeling of something stuck in the esophagus, stomachache, dry throat, belching when taking food, and soreness of the back.

**CONTRIBUTING FACTORS**

1. LOW MOLYBDENUM CONTENT IN THE SOIL
2. MICROBIAL CONTAMINATION IN FOOD AND WATER
3. NUTRITIONAL DEFICIENCIES
4. POLYCYCLIC HYDROCARBONS FROM THE AIR
5. POOR ORAL HYGIENE AND UNDESIRABLE EATING HABITS
6. FUNGAL INFECTION OF THE ESOPHAGUS

Chart 2. Primary events and contributing factors in EC.

also suspected. Nitrosamines can be synthesized either *in vitro* or *in vivo* from secondary amines and nitrites. Both precursors can be derived from nitrogenous compounds in food and water through the actions of fungi or other microorganisms. Low molybdenum content in the soil may be an indirect contributing factor because it increases the amount of nitrates (nitrites) in crops and decreases the vitamin C content in vegetables. Nutritional deficiencies appear to be a common feature among high-EC-risk populations worldwide and among alcoholics. Thus, the role of nutritional deficiencies in carcinogenesis deserves more attention. Polycyclic hydrocarbons may play a role as cocarcinogens or promoters. Poor oral hygiene and undesirable eating habits may facilitate carcinogenesis by continuously injuring the epithelium of the esophagus. Although fungal infection is not a prerequisite for EC, the fungi may contribute to carcinogenesis by producing carcinogens or promoters at the infection sites or by inducing hyperplasia. Defects in the DNA repair and immune defense mechanisms may also increase susceptibility to cancer. The roles of these factors in EC remain to be elucidated.

Future Developments. Chinese scientists have come close to identifying the carcinogen(s) and several contributing factors of human EC. Cancer research inside and outside China has provided knowledge about possible preventive measures. The implementation of the "5 preventive measures" and the gradual rise of living standards tend to eliminate these cancer-causing factors. From the viewpoint of cancer research, it is important to identify the carcinogen(s) and contributing factors more definitively before they disappear. It appears to be important to investigate the following aspects of the EC problem in the high-incidence areas in China: (a) to screen for mutagens-carcinogens in food samples as well as in human urine and fecal samples by short-term bacterial or cell cultural systems; (b) to identify possible carcinogens in food samples chemically; (c) to test the carcinogenicity of these compounds in animal models; and (d) to analyze the nutritional status of the people and the effects of nutrition on various aspects of carcinogenesis. International collaborative research in some of these areas may prove to be very fruitful.

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¹¹ In some of the references, the names of the research groups rather than individual names were shown as the authors in the original publications. The abbreviations used are: CAMS, the Chinese Academy of Medical Sciences; CICAMS, Cancer Institute of CAMS; LRTPTC, Linxian Research Team for the Prevention and Treatment of Esophageal Cancer (it belongs to CAMS); and TPTRGHP, Tumor Prevention, Treatment, and Research Group of Henan Province. Many research reports were collected in Ref. 11; the individual papers are identified by a letter. Some of the journals do not have volume numbers but use issue numbers and the year of publication; the issue number or month is shown in parentheses in this review. Some journals (in Chinese) do not have standard English names; their names in Pinyin phonetics are listed as follows: Anticancer Communications (Commun.), Kang Ai Tongxun; Medical References (Med. Ref.), Yiyao Cankao Ziliao; and Research on Cancer Prevention and Treatment (Res. Cancer Prev. Treat.), Zhongliu Fang Zhi Yanjiu.

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