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THE GASTRIC CANCER PROBLEM*

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The importance of gastric carcinoma as the cause of death in the United States can be appreciated when we consider that during World War II, according to the former Surgeon General Thomas Parran, as many people died from cancer of the digestive tract as were lost in the armed forces of the United States as the result of enemy action. It is estimated that of the people living in the United States today, between 4,000,000 and 5,000,000 will die of cancer of the stomach. Gastric carcinoma causes more deaths than any other cancer. Because of the difficulties in early diagnosis, only 2 to 6 per cent of all patients that have gastric carcinoma are alive at the end of five years. Walters and co-workers at the Mayo Clinic found that about 25 per cent are suitable for curative surgery, and of these about 25 per cent are alive and well at the end of five years, and 20 per cent are alive at the end of ten years.

It is a disease of later life, the average age of patients being 55 years. There is a preponderance in the male of nearly two to one. The death rate from cancer in certain countries is higher than in other countries. It is much higher in Holland than in England. It is higher in the Northern States of the United States than it is in the Southern States, according to Collins, Gover, and Dorn. Kirschner stated that 50 per cent of cancer deaths among men in Germany were due to cancer of the stomach. It has been found that cancer of the stomach is higher in the Italians who came over from Italy to work in the mills in Connecticut than it is in the general population of that State. However, in the second and third generation Italians, the death rate from cancer of the stomach is about the same as in the rest of the population.

Genetics seems to have an influence upon the incidence of gastric carcinoma. The genetic influence is probably organ specific. There are exceptional families known for their high incidence of cancer of the stomach. The family of Napoleon is perhaps the most famous; as Napoleon, his father, his grandfather, all three of his sisters, and one of his four brothers are said to have died from gastric carcinoma.

Most forms of cancer found in human beings are also known to occur in animals. Cancer of the esophagus and of the stomach, however, are outstanding exceptions and are among the rarest types of tumors in animals. Welles et al. described 8 cancers of the forestomach, which corresponds to the mouth, pharynx, and esophagus, and 3 adenocarcinomas of the pars glandularis, which corresponds to the stomach, in 142,000 mice dying of natural causes, many of old age. This ex-
tremely low incidence of carcinoma of the stomach in animals is remarkable considering that if they had been human beings the incidence of carcinoma of the stomach would have been about 30,000 instead of 11.

McCarrison, while a medical officer in the Indian Army Medical Service, spent about nine years among three remote tribes of northern India. During that time he performed nearly 4,000 operations, many being for hernia, goiter, cataract, etc., but he did not see a single case of cancer, appendicitis, or colitis during that whole time. He was so impressed by the absence of many other diseases which are so prevalent in other parts of India that he made a careful study for possible reasons. He concluded that it was because of their diet, inasmuch as they lived on natural foods direct from the soil, thus retaining their protective elements. He later set up a laboratory in southern India, where he put animals—including pigeons, guinea pigs, rabbits, and monkeys—on diets which were common in various parts of India as well as on a diet made up of foods commonly used in England. His control animals numbering a total of 1,198 were put on the diet, mainly lacto-vegetarian, of these healthy tribes of northern India. During a period of two years they were watched, and at the end of that time they were autopsied and carefully examined, and he found no evidence of any disease whatsoever except a few tapeworm cysts. On the other hand, a group of 2,443 animals which were put on improper diets common among the people of other parts of India and in England showed all kinds of diseases, including two cases of carcinoma of the stomach. Thus if the 142,000 animals autopsied by Welles et al. had been on the improper diets that McCarrison gave his animals, and their response had been the same, the incidence of cancer of the stomach would have been 3,300 instead of 11. On the other hand, if in addition to the diet given these animals he had been able to subject them to irritants that humans commonly use, such as tobacco, alcohol, condiments, hot beverages, and other types of irritants, undoubtedly the incidence of carcinoma would have been much higher.

Although nutritional deficiencies have an important bearing on the cause of carcinoma of the stomach, clinical surveys indicate that these irritants are significant exciting factors. Lintott compared a large group in Holland with a similar group in England. The incidence of gastric cancer in Holland was about twice that of England. The diet of the Hollanders contained large amounts of bread, cheese, vegetables, and a smaller amount of meat. However, in Holland the food was taken at a higher temperature; and the consumption of spices, alcoholic beverages, and tobacco was higher.

Hurst has stated that approximately 75 per cent of gastric carcinomas develop on a pre-existing gastritis. Among the causes of chronic gastritis he gives the following: alcohol, especially strong spirits on an empty stomach; strong tea and coffee; tobacco; condiments; mechanical and thermal injuries; infections due to oral sepsis; and certain drugs, particularly bromides, digitalis, mercury, and salicylates.

Ivy and Peacock are of the opinion that the use of excessively hot foods is probably a factor in the development of gastritis and gastric carcinoma. The oral mucous membrane will tolerate food 15 per cent hotter than will the skin; this explains why tea cups have handles. A patient whom I saw recently with carcinoma of the stomach would tend to bear this out. This man, aged 40, an oil-well driller, states that for several years he drank up to 20 cups of hot coffee a day. Widmark has demonstrated a substance from roasted coffee which produces cancer in the skin of mice.

Vitamin A deficiency is known to have an
adverse effect on the integrity of the mucous membrane of the digestive tract. Passey, Lees, and Knox have demonstrated that papillomatosis of the preventriculus of mice can be brought about by feeding them a diet deficient in vitamin A. Studies of the metabolism of cancer patients which have been carried out at the Memorial Hospital in New York reveal several abnormalities, particularly that of vitamin A deficiency and hypoproteinemia. However, Peacock and Kirby have shown that large doses of vitamin A do not protect against the development of gastric papillomatosis when carcinogenic hydrocarbons are fed to animals.

Schindler is also of the opinion that atrophic gastritis and pernicious anemia are frequent precursors of gastric cancer. Kaplan and Rigler have stated that the incidence of cancer of the stomach in patients dying with pernicious anemia is about 12.3 per cent. In a series of 259 apparently well pernicious anemia patients, they found 18 cases of gastric carcinoma, and 17 cases of benign tumor in the stomach. Bourne, of England, recently reported a study of 15 cases of asymptomatic pernicious anemia patients observed by both X-ray and gastroscopic examination, and in 15 patients he found three cases of cancer of the stomach. He points out that increased sedimentation rate is of value in suggesting the onset of cancer in pernicious anemia patients.

Gastric polyps are a frequent occurrence in atrophic gastritis and pernicious anemia. Kaplan and Rigler are of the opinion that the demonstration of a gastric polyp in association with pernicious anemia has almost the same significance as the demonstration of carcinoma per se. Wangensteen found a high incidence of gastric polyps in patients who were achlorhydric to histamine. True histamine fast achlorhydria is a common condition. It is not present at birth but tends to appear in early adult life. Barrett states that 20 to 25 per cent of the general population of gastric cancer age have achlorhydria. Approximately 65 to 75 per cent of gastric cancer patients have achlorhydria. It is in the group that has free hydrochloric acid that there is the greatest danger of not making adequate study. Our most promising field in the early detection of cancer of the stomach lies in the frequent examination (at least 3 times a year) of patients with achlorhydria and pernicious anemia. This should include X-rays as well as gastroscopic examinations where X-ray findings are negative or are suspicious. All patients with pernicious anemia should be watched carefully for the presence of gastric polyps. Large polyps probably should be removed; whereas small polyps should be watched frequently with the gastroscope.

There is considerable difference of opinion as to the relationship of gastric ulcer to gastric cancer. Probably the most important feature of this problem is the danger of confusing benign with malignant ulcers. It has been found that approximately 10 per cent of ulcers which are believed to be benign under average diagnostic measures are malignant when removed. Sampson and Sosman believe that cancerous ulcers outnumber benign ulcers three to one.

Ulcers about the cardia and the subcardia as well as those of the anterior and posterior walls are also more often malignant than benign, but ulcer of the greater curvature is almost always malignant. The fact that the patient who has a gastric ulcer is put on a medical regime and is relieved of his distress and may even show some improvement in the X-ray film may not be an indication that the lesion is not malignant. It is variously estimated that from between 10 to 20 per cent of patients with gastric ulcer will develop carcinoma of the stomach. Ogilvie and Schindler on the other hand believe that gastric ulcer rarely ever becomes malignant, and that one
of the most important services that the gastroscopist can perform is to differentiate between benign ulcer and malignant ulcer. Yarnis has reported three cases with benign ulcer with an independent carcinoma in the same stomach, and states that peptic ulcers in the body of the stomach may heal in the presence of a malignant growth causing pyloric obstruction. Wangensteen suggests that since gastric resection for ulcers can be performed by the experienced surgeon at risks well below 5 per cent, there seems little justification for the physician to assume so conservative an attitude toward gastric ulcers as a patient's future may be compromised thereby.

Since there is no characteristic symptom complex of cancer of the stomach, it is not surprising that notable members of the medical profession have died of the very disease which they spent their lives combating. These include such illustrious surgeons as W. J. Mayo, Mikulicz, Martin Kirschner, and others. Ogilvie reports that during the past five years two famous surgeons suddenly discovered that they had carcinoma of the stomach by feeling a mass bump against the operating table, that one celebrated radiologist swallowed a cup of barium to try out a newly installed apparatus, and much to his horror, when the film was developed it showed a large cancer of the stomach.

Among the early symptoms of carcinoma of the stomach may be mentioned the following: fatigue, dyspepsia, loss of appetite, loss of weight, distaste for certain foods, particularly meat, and epigastric distress. Anyone developing digestive disturbances after the age of 40 should be thoroughly investigated. About one fourth of patients with carcinoma of the stomach, however, give a long dyspeptic history. About 65 to 75 per cent of patients with gastric cancer will have no free hydrochloric acid. On the other hand, we may see patients with gastric carcinoma with relatively high gastric acidity. This is particularly true in cases where there is a malignant gastric ulcer.

Marshall and Aronoff, in reporting 464 cases with tumor of the stomach who were operated on at Lahey Clinic, stated that 98 per cent of the tumors were malignant and only 2 per cent were benign. The benign lesions included fibro-adenomas, myomas, lipomas, hemangiomas, and neurofibromas.

Benign tumors have a tendency to hemorrhage, and pedunculated polyps which arise most frequently in the pyloric antrum may prolapse through and produce symptoms of obstruction. Most malignant gastric tumors are carcinomas, but there are several types of sarcomas that are seen, such as lymphosarcomas, leiomyosarcomas, and Hodgkins disease. There are no characteristic symptoms of sarcoma of the stomach. Epigastric distress, loss of appetite, loss of weight, and massive hemorrhage are the more common ones.

Syphilis of the stomach is usually confused with gastric cancer. On X-ray examination there is a filling defect in the stomach which cannot be distinguished from carcinoma. Gastroscopically, the findings are very much the same in the two conditions. A patient under my care recently demonstrated this difficulty very graphically. X-ray examination revealed a large filling defect in the stomach which was diagnosed as cancer. He was referred to an expert gastroscopist, who stated that the gastroscopic picture was that of an extensive infiltrating carcinoma, and advised a total gastrectomy. At surgery, in addition to the lesion of the stomach, large nodes were found near the cardia and at the pylorus. A total gastrectomy was performed and a large jejunal pouch was made just below the anastomosis of the jejunum to the esophagus. This was done in order to provide him with as large a "bread basket" as possible, as he was a laborer and in his 40's. Unfortunately the patient's serology
The report was not received until after surgery. The pathological findings were compatible with that of syphilis of the stomach. The patient got along very nicely postoperatively and has been completely relieved of all digestive symptoms and has gained 12 pounds in weight within the past four months in spite of doing hard manual labor.

Marshall and Aronoff state that because syphilis of the stomach is rarely seen, even in the presence of a positive Wassermann where X-rays shows a definite defect, laparotomy should be performed early, as waiting for antiluetic treatment may convert an operable lesion into an inoperable one. Biopsies of suspicious stomach lesions should be done more frequently than are being done at the present time.

Carcinoma not infrequently develops upon tuberculous lesions of the stomach. White, in a series of 300 cases of tuberculosis of the stomach, found that 10 per cent had gastric carcinoma. It is also known that lupus is frequently followed by epidermoid carcinoma. Ivy has discussed the possible relationship of bile as being a factor in the production of gastric cancer. The reason for this is that methylcholanthrene, a highly potent carcinogen, has a very close chemical relationship to the normal constituents of the bile. Another reason for this suspicion is that practically all cancers of the duodenum are located in the ampulla of vater, being the area of the duodenum which comes most intimately in contact with the bile. A third fact that adds to the suspicion of bile is that subcutaneous injections of desoxycolic acid into rats has produced subcutaneous sarcomas. Ivy also suggested that other possible actions of the bile may be due to the action of the bile salts upon fat-soluble substances and would influence the action of the carcinogenic hydrocarbons in the stomach.

Patients having gastric residue sometimes present a problem in diagnosis. A Swiss physician, Seneque, recommends the administration of 40 grams of syrup of ipecac (occasionally in addition the patient may be given 0.1-1.2 gm. powdered ipecac) one-half hour before studies. This, in his hands, emptied the stomach and gave good visualization of the stomach. He was then able to diagnose carcinoma, which was not visible otherwise, the lesion being located in the pyloric region. He also recommended the use of ipecac to improve diagnosis of lesions of the lesser curvature, and particularly of ulcers of the posterior aspect of the stomach, which are difficult to show by ordinary roentgenographic methods. The ipecac assists in emptying the stomach and stimulates peristaltic action, which allows visualization of some lesions which cannot be seen in the atonic stomach.

Mass surveys by fluoroscopic methods have proved to be impractical. St. John, Swenson, and Harvey studied 2,413 well people over 50 years of age with a brief fluoroscopic survey of the stomach. In this group two gastric cancers and one lymphosarcoma were found, an incidence of 1.24 per thousand patients. These patients were visitors to the hospital and were unselected other than for their age.

Routine physical examination alone is not of much value in detecting carcinoma of the stomach. A careful history is essential, and patients with suspicious histories should receive a complete work-up, including blood counts, gastric analysis, stool tests for occult blood, and sedimentation rate. If barium meal is negative, a gastroscopic examination should be performed.

Wangensteen states that 2 to 4 cc. of blood is sufficient to give a positive guiac test in the stool, and that it takes approximately 70 cc. of blood to produce a stool in which the presence of blood may be detected grossly. A plan that we have been using of late is to give patients who come in for examination Hematest
Reagent Tablets,* with proper instructions to the patient to run an occult blood test on his stool. Those having occult blood in their stool would then bring a specimen of stool to the laboratory for examination. These patients are given a more careful examination of the entire gastro-intestinal tract.

The value of early diagnosis of cancer of the stomach is well illustrated in the report of Rene Gutmann. He reports 19 cases of early carcinoma of the stomach consisting of two types: one is carcinoma in situ, or malignant degeneration of the epithelial cells in situ without invasion of underlying tissue; the second type is a small cancer confined to an area of approximately 1 cm. in diameter, showing classical histological picture of invasion, with only slight extension to the surface. These patients were about equally divided among the two different types. Of these 19 cases 18 were followed from 6 to 11 years after operation, and only one of these died with recurrence. This enviable record of 5-year survival of around 94 per cent indicates that if early diagnosis could be made, the 5-year survival at present might be a great deal higher than the 5 per cent of all cases of carcinoma of the stomach that we now see.

The 15 asymptomatic pernicious anemia patients studied by Bourne, in which he found 3 early carcinomas, had been under treatment for 10 years. Two of these were apparently carcinoma in situ. One case showed on X-ray examination rigidity of the prepyloric region somewhat suggestive of carcinoma, in which gastroscopy showed that the lower one third of the stomach was fixed and pale, with no peristalsis. At surgery no palpable evidence of neoplasm was found, and the abdomen was closed without biopsy and without resection, but the patient died of carcinoma of the stomach two years later. In the second case X-ray showed the pyloric antrum to be narrowed, with normal peristaltic waves, and distensible. Gastroscopic examination revealed a small reddish nodule at the angulus. Gastric resection was carried out and an early carcinoma was demonstrated.

Bourne believes that the general contraction of the pyloric area, when seen in pernicious anemia patients, may be the first indication of carcinomatous change, especially when associated with abnormal antral mucosa, and that these conditions "should be viewed with as much suspicion as hyperchlorhydric cases with prepyloric ulcers." He suggests that the common prepyloric carcinoma in pernicious anemia patients does not arise in localized polyposis, but that it is associated with rather diffuse mucosal changes detectable by the gastroscope at an early stage and demonstrated radiologically as narrowing of the pyloric antrum.

It has been shown that 25 per cent of cases of deaths from carcinoma of the stomach that are found at autopsy have died of lesions which were operable, as the node extension was not beyond those in the immediate area of the stomach. An extensive lesion of this type was illustrated in a recent personal experience with a patient who had a large palpable tumor with practically complete obstruction, which proved to be a limitis plastica involving nearly the entire stomach. At surgery there was no extension found beyond the immediate nodes of the stomach; a successful total gastrectomy was performed. A rather extensive case on whom I performed a total gastrectomy seven years ago is still alive and well.

In recent years there seems to be a trend toward more total gastrectomies. We believe that this operation will improve the five-year cures in the infiltrative types of carcinoma. Schindler has stressed that the infiltrative types of carcinoma give the poorest prognosis. With the combined abdominothoracic ap-

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*Nemtest Reagent Tablets—manufactured by the Ames Company, Elkhart, Indiana.
proach, with intratracheal anesthesia, the technical difficulties of total gastrectomy are not too great for one experienced in gastric surgery. The operative mortality in my small series of 8 cases has been 12½ per cent.

It should be stressed again that surgical attack upon the stomach for carcinoma should be much more radical than the type of resections that are done for peptic ulcer. An operation for gastric carcinoma is not complete unless all the gastrohepatic and the greater omenta are removed, the resection going well beyond the limits of the disease, including practically the whole lesser curvature.

The discussion of methods of early diagnosis of the stomach would not be complete without mention of the cytological studies of gastric contents for carcinoma cells. This, up to the present time, is only in the experimental stage, but may develop into something of value.

SUMMARY AND CONCLUSIONS

The fact that only 5 per cent of patients with carcinoma of the stomach are alive and well at the end of five years is responsible for the dictum that there are two types of physicians practicing medicine: one who is always looking for a case of early carcinoma of the stomach and never finds it, and the other who never looks for an early case of carcinoma of the stomach and never finds it. This pessimistic outlook should make the members of the medical profession conscious of the problem which confronts us, and should stir us to determined action by every known means at our disposal to reduce this appalling mortality rate. Not only is it necessary to keep this to the forefront in the minds of the physicians, but an educational program is necessary in behalf of the layman. Much has been accomplished of late in this latter field by the American Cancer Society.

All patients with pernicious anemia and unexplained anemia and those having anacidity to histamine stimulation require repeated and thorough examinations, including X-ray and gastroscopic studies on suspicious cases.

The establishment of gastric cancer detection centers for research and clinical investigation of men over the age of 40 and women past the age of 50 would contribute to the solution of this problem.

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