PRIMARY LYMPHOSARCOMA OF THE STOMACH

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PRIMARY lymphosarcoma of the stomach is not a common surgical disease. They comprise from 40 to 50 per cent of all gastric sarcomata, which, in themselves, form but 1 to 2 per cent of all gastric neoplasms. However, with the increase of surgical procedures upon the stomach, it was felt of value to consider these lesions from a diagnostic and prognostic point of view; especially as it is improbable that any one surgeon will deal with any large number of cases, whereby he may judge the value of a particular type of therapy.

No attempt will be made to clarify the perplexing problem of neoplastic and neoplastic-like lesions of the lymphoid system. Until a clearer conception of the histogenesis of these lesions is available, disagreement in both terminology and classification is inevitable. An effort has been made here to include only those cases of lymphosarcoma that arise primarily from the lymphoid tissue of the stomach and are not a part of like changes taking place simultaneously in similar tissue in other portions of the body. Cases with insufficient data and those that were not clear-cut histologically have been omitted from the statistics. However, for the sake of completeness, a number of these closely related cases* have been included in the bibliography.

Five proven cases were found in the files of Presbyterian Hospital. These will be reported in detail, as they seem significant in calling attention to variations in the natural history of the disease—particularly in viewing the outcome in relation to the treatment given.

In 1871, Cruveilhier reported the first case of gastric lymphosarcoma (quoted from Forni). By 1914, Forni, in collecting 200 cases of gastric sarcoma, found 33 lymphosarcomata. He, for the first time, emphasized the necessity of a histopathologic classification of these sarcomata, to supplant the purely morphologic, endogastric and exogastric, division. D'Aunoy and Zoeller, in 1929, reviewed the literature and brought Forni's series up to date. Since then, except for case reports and small series from individual clinics, there has been no extensive review of the literature. The data presented here will be based on 152 cases of primary lymphosarcoma collected from the literature up to 1937, including five cases reported for the first† time from this hospital.

Etiology.—The average age of the patients in this series was 44.3 years, which closely approximates the figures quoted by most authors. The youngest

Submitted for publication July 8, 1938.

* References for these cases are marked with an asterisk in the bibliography.

† Case 5 was presented, in 1933, by Dr. David Bull before a meeting of the New York Surgical Society.

case was three years and eight months old. He recovered after subtotal resection. The oldest patient was 80 years of age, on whom the diagnosis was made at postmortem. It will be seen that the average age of these patients is about 10 years younger than of those with carcinoma. Furthermore, there is a considerably greater proportion in the first four decades of life than would be found in a similar carcinoma series, 20 of 114 cases being less than 40 years of age.

The sex is known in 124 cases. There are 78 males and 46 females, a ratio of 1.6 to 1—a less marked male preponderance than the 3 to 1 usually quoted for carcinoma.

As with most neoplasms, there has been considerable speculation regarding the etiology of these tumors. Perhaps the most prominent "exciting cause" has been attributed to trauma. This causative factor was made much of by many of the early authors. However, although there are striking examples of coincidental injuries preceding discovery of the lesion, critical examination of the data is far from conclusive.

Peptic ulcer also has been incriminated as a precursor of these tumors. No such relationship has been borne out on histologic examination, even though the gross appearance at operation is very suggestive of gastric ulcer.

Although it has often been suggested that benign lesions of the stomach may degenerate into malignant ones—polyps to carcinoma or myoma to sarcoma —there is no evidence that lymphosarcoma arises from such growths.

Some pathologists feel that tuberculous lesions of the stomach may be the irritative and initiating factor—particularly in the presence of aberrant, undifferentiated cells in the submucosa.

Pathology.—Primary lymphosarcoma of the stomach can arise from any lymphatic tissue in the organ. It is probable, however, that the lesion begins most often in a lymph follicle in the submucosa. From this point of origin, it penetrates along the tissue spaces and infiltrates the various layers. The muscle layers particularly are involved, each band of muscle being separated by large masses of tumor cells. The submucosa is enormously thickened, and this explains the giant rugae that are sometimes seen in a roentgenogram. The mucosa, not being the site of the original growth, does not show the early characteristic ulceration of carcinoma. However, later ulceration does take place, and "characteristic" ulcer niches and craters may develop. These tend to be more shallow than in carcinoma and frequently are multiple. Involvement of the serosa is usually a late manifestation but often assumes great proportions. Due perhaps to compromise of the blood supply by diffuse infiltration of all the layers, necrosis is frequent, and for this reason perforation is not uncommon.

Grossly, the lesions may be divided into four types (Pack and McNeer, 1935): (I) A single bulky polypoid growth well demarcated from the normal stomach; (II) solitary or multiple ulcers with surrounding infiltration; (III) multiple nodular tumors in the submucosa; (IV) diffuse thickening of the wall. This last type strongly resembles the fibrocarcinoma designated as

"linitis plastica"—except that the stomach is not contracted and large mucosal folds are frequently present. Unfortunately, the largest number are of Types II and IV. As the well demarcated growths are comparatively infrequent, lymphosarcoma does not share the advantages that some other of the sarcomas have over carcinoma from a surgical standpoint. The large pedunculated growths of the exogastric type found in other types of sarcoma are not found with lymphosarcoma.

Gross diagnosis is not always possible. The lesion is most frequently confused with carcinoma. Some cases have been treated operatively on the assumption that a peptic ulcer was the basis of the pathology. Gastric syphilis may also be confusing, but the frequent presence of large, isolated, succulent perigastric nodes may serve to differentiate this condition.

The curvatures are usually considered as being the commonest site of origin. Actual involvement of the orifices is unusual, although the lesions frequently extend to involve both the anterior and the posterior walls. Even though the prepyloric region is often involved, pyloric stenosis is an unusual finding. The location of the lesion is known in 74 of the cases collected. Fifty-five of the cases involved one or both of the curvatures in the lower half of the stomach. Only six cases had pyloric stenosis. Three patients had lesions high in the cardia, one of whom complained of dysphagia. Ten cases were of the diffuse infiltration "linitis plastica" type.

These tumors may simulate at least two of the cell types found in lymphoid tissue—the small lymphocytes and the reticulum cells, which lend their names to the two types of lymphosarcoma encountered. Whether or not the parent cells of the follicles can give rise to a neoplasm has not been definitely established. Undoubtedly, these three cell types bear a close histogenetic relation to one another. Just what this relationship is, is not clear, as is demonstrated by the apparent change in cell type in some cases of giant follicular hyperplasia as they are followed throughout their course. However, in primary lymphosarcoma of the stomach a division into two types, lymphocytic cell and reticulum cell, seems adequate, and each type has its characteristic histology. In the lymphocytic type the cells resemble atypical lymphocytes in size and in the relation of nucleus to cytoplasm, and have deep staining hyperchromatic nuclei. At times there may be some variation in size, and cells nearly as large as mononuclear cells with a somewhat different nuclear arrangement are noted. Thus, the impression may be given of there being two cell types present. However, the small round cell resembling a lymphocyte is the predominant and distinctive one. Mitoses are frequent and often atypical. Multinucleated and "giant" cells are occasionally noted. Polymorphonuclear cells may be found scattered through the tumor tissue, but surrounding fibrosis and inflammatory reaction is usually not present, even though areas of liquefaction and necrosis are frequently found in the tumor.

The cells have not the definite connective tissue stroma that is the framework of a carcinoma, and even with special stains, only a fine, fibrous reticulum is demonstrated as the supporting structure. It is this character of the stroma

that accounts for absence of "shrinking" of the stomach and narrowing of the lumen with subsequent stenosis.

All of the layers of the stomach wall may be entirely replaced by the tumor. Large areas may show no intact mucosa and only tiny remnants of glands will be found lying among masses of tumor cells. The muscularis mucosae is usually intact and is involved only in the most advanced cases.

In the reticulum cell type, infiltration of the layers may be present in a similar manner, but the predominant cells are cuboidal to polyhedral in shape, the nuclei hyperchromatic, and a large, well-defined cytoplasm is present. These cells may vary in size and shape in various parts of the tumor and are frequently bizarre in appearance. In some cases, a slightly more prominent fibrous framework is present. Usually the histology is just as distinctive as in the lymphocytic cell type. However, to differentiate some of these lesions from highly undifferentiated anaplastic carcinomata is sometimes very difficult, and the correct diagnosis can be inferred only from the subsequent course of the patient.

The perigastric and adjacent retroperitoneal nodes are the most frequent sites of extension. They are smooth and large and are relatively soft in contrast to the hard, more discrete metastatic nodes of carcinoma. Often they are matted together so that with involved omentum and areolar tissue, they make a mass larger than the original tumor itself. On section, the nodes are gray to pink and their structure appears completely lost. Metastases to liver, spleen and pancreas are found, but large nodules are infrequent. In Case 1, reported herewith, at autopsy, metastases were noted in perigastric, peripancreatic, aortic, iliac, mesenteric and cervical nodes, omentum, pancreas, both ovaries, both lungs, pleura, diaphragm and peritoneum.

Since sarcomata, in general, are considered to have exclusively blood stream metastases, considerable discussion has taken place concerning the mode of extension of these tumors. Certainly this type of metastasis does occur in lymphosarcoma. However, the primary lymph node metastases must be considered as occurring by direct extension or metastasis through the lymphatics to the adjacent nodes. Tumor cells actually infiltrating the lymphatics of the stomach have been demonstrated in several cases.

Clinical and Laboratory Data.—Careful evaluation of the clinical and laboratory findings reveals no single pathognomonic sign in the individual case. However, when taken as a group there are some suggestive points of differentiation. Pain of the ulcer type is a constant and often an outstanding symptom. "Dyspepsia" and anorexia are prominent findings, but a long history of anorexia with advanced emaciation is unusual. Some weight loss is the rule. Vomiting, if present, is usually not of the obstructive type, a finding which is easily explainable by the infrequent occurrence of pyloric stenosis. Hematemesis is not common, being noteworthy in but 12 cases in the present series. Straus (1925) believes it to be diagnostically significant in the presence of a nonobstructing tumor in a young patient. Melena is a frequent finding and occult blood was always found when a test was made for it. Perforation

of these lesions is considerably more frequent than with carcinoma. A palpable mass is present in almost two-thirds of the cases and is frequently quite large, in striking contrast to the absence of advanced emaciation in the patient.

There is no general agreement concerning the presence or absence of free hydrochloric acid. Douglas (1920) states that in the presence of a gastric lesion, youth and free hydrochloric acid are the most important factors suggesting a diagnosis of lymphosarcoma. In 17 of the 33 cases, in which gastric analyses are reported, the free hydrochloric acid was normal or elevated. This is a higher proportion than would be expected in a similar carcinoma series.

Roentgenologic Examination.—The case of Balfour and McCann is the only* recorded case in which the diagnosis was made roentgenologically, preoperatively. There is a unanimity of opinion among most radiologists that there is no typical picture upon which to establish a positive diagnosis of lymphosarcoma. The lesion is most frequently mistaken for a carcinoma, and even in retrospect, the roentgenologic findings are often "typical" of carcinoma. It is also, at times, indistinguishable from peptic ulcer, particularly when a single "calloused" ulcer defect is noted in the prepyloric area on the lesser curvature.

If the history and clinical findings are taken into consideration, there are some suggestive points: two or more defects in separate portions of the stomach should arouse suspicion, when they do not appear to be consistent with polyposis. In the presence of a large palpable tumor, instead of narrowing of the pylorus as with carcinoma, there may even be widening of the lumen. Rarely, these lesions when arising in the cardia may show roentgenologic evidence of extragastric penetration through the diaphragm. This is not found with carcinoma. Exaggeration of the mucosal folds to form giant rugae is seen, but this is not in itself diagnostic, however, when they are present and a filling defect is noted in a stomach with pliable walls, one has what is probably the most "typical" picture of lymphosarcoma.

Gastroscopy.—Four cases have been observed through the gastroscope. None of these, however, was correctly diagnosed preoperatively. Schindler (1937) feels that the picture is sufficiently characteristic to enable him to make the diagnosis in the future.

Treatment.—Radical, subtotal gastrectomy followed by intensive deep radiotherapy has usually been considered the treatment of choice. Operation is contraindicated only in those patients who are obviously in the last stages of the disease. Even then some effort should be made to establish a histologic diagnosis. This point is emphasized because of the marked regression following radiation, sometimes seen, in patients who appear to have a far advanced gastric neoplasm. Zanetti's case (1935) appeared to be in excellent health and showed no roentgenologic evidence of disease, two years after presenting himself with an apparently hopelessly advanced lesion. Undoubtedly, a number of patients with lymphosarcoma have died with the diagnosis of carcinoma. Had the correct histologic diagnosis been established, it is reasonable to assume

* Case of Escudera, quoted by Gomez y Gomez (1931) and referred to by Bastiony (1935) was not available for study.

that a few of these might have received at least palliation. In very sick patients and where tissue examination is impossible a therapeutic trial with radiation seems justifiable.

The Pólya type of resection, with whatever modifications the surgeon is best acquainted, is well suited to the disease unless the situation or extent of the lesion requires complete gastrectomy. Since radiation stands as an effective subsequent means of treatment, resection should be performed if technically feasible, even if it appears questionable that all the local extension of the disease can be completely removed. Palliative procedures, such as gastroenterostomy, are rarely indicated, since stenosis is quite unusual and because radiation is of more value.

In this series of 152 cases, celiotomy was performed in 118 patients. Seventy-six of these had subtotal gastrectomy performed, with 12 postoperative deaths—an operative mortality of 15.8 per cent. This 50 per cent resectability is much greater than carcinoma and the operative mortality somewhat less.

It is exceedingly important to administer the roentgenotherapy carefully. Due to the marked intolerance to radiation over the epigastrium, only relatively small amounts can be given under the most favorable circumstances. The exact site of the lesion, with the patient in the position he is to assume during treatment, should be determined by barium meal and the corresponding area delineated on the abdominal wall. This is essential in order to deliver the maximum radiation directly to the lesion. Nausea, anorexia and "burning" distress may be so marked as to preclude further therapy if it be poorly directed or if too large daily doses are delivered.

Scaled, fractional doses over a period of 25 to 35 days are considered the optimum plan of therapy. As Pack and McNeer (1935) recommend, the radiation is best delivered to the outlined lesion through three portals, left anterior, left posterior and left lateral. Between 50 and 100r. is given at each sitting, depending upon the tolerance of the individual patient. A total tumor dosage between 2,500-4,000r. is desirable. If marked improvement results, but the disease remains, demonstrable clinically or by gastro-intestinal series, a second and third series may be administered at intervals of from six to eight weeks or more. When the tumor seems to be susceptible and gross metastatic lesions are noted, these should also be radiated.

Radiation of hollow viscuses containing large ulcerating tumor masses always entails the real danger of gross hemorrhage. For this reason, Holmes (Cabot Case, 1934) endorses resection whenever possible before radiation. However, Pack and McNeer (1935), while acknowledging the danger, have not had this complication in treating a number of patients with irremovable lesions. The possibility of producing adrenal insufficiency with radiation in this area has been also noted, but it has been shown that this probably does not occur unless the gland is already the site of neoplastic infiltration.

Undoubtedly, radiation has secured remarkable results with regression of all signs of the growth for long periods—if not actual "cures." However, the

degree of radiosensitivity of the growth, apparently, is not predictable from the study of the pathologic material. Thus, a far advanced growth may react favorably for a number of years to what is generally considered inadequate treatment, while an apparently favorable one will rapidly come to fatal termination with excellent therapy. This suggests that these lesions have a life history independent of the type of therapy administered and what appears to be "curative" treatment may be only coincidental in the "natural" course of that particular neoplasm.

Results.—Including two cases from this hospital, 13 of the 152 cases were living and well 5 to 22 years after the diagnosis had been established. A brief synopsis of the essential data relevant to the 11 cases reviewed is appended.

No. 1.—Cheever, D. (1932): Female, age 52, had a segmental resection of middle third of stomach. Pathologic Report: Lymphocytic cell lymphosarcoma. Two roentgen ray treatments were given postoperatively. Living and well five years later.

No. 2.—Pack, G., McNeer, G. (1935), Case 5: Female, age 46, complained of pain and dysphagia. Bulky tumor involving pars media and cardia found at operation. Biopsy: Reticulum cell lymphosarcoma. With radium pack, 48,000 mg. hours was given at a distance of 15 cm., anteriorly and posteriorly to cross-fire the stomach. Living and well six years later.

No. 3.—Pack, G., McNeer, G. (1935), Case 7: Male, age 53, was operated upon by Dr. S. Harvey; had a segmental resection of the prepyloric area. No roentgen ray treatment. Pathologic Report: Lymphocytic cell lymphosarcoma. Living and well 7½ years later.

No. 4.—Collins, E., Carmody, M. (1937): Male, age 9, had a partial gastrectomy and posterior gastro-enterostomy. No roentgen ray treatment. Pathologic Report: Lymphocytic cell lymphosarcoma. Living and well 22 years later.

No. 5.—Falta, W. (1926): Male, age 55, had a subtotal gastrectomy and gastro-enterostomy. Line of resection, distally, went through what was considered a "peptic ulcer." Pathologic Report: Lymphosarcoma. Immediate intensive radium treatment. Five other treatments in next 24 months. Two "prophylactic" exposures to radium later. Living and well 6¾ years postoperatively.

No. 6.—Clar, K. (1935): Male, age 22, had a Bilroth II-Hoffmeister resection of the stomach. No roentgen ray treatment. Pathologic Report: Lymphocytic cell lymphosarcoma. Adjacent excised nodes showed only hyperplasia. Living and well seven years later.

No. 7.—Gunsett, A., Oberling, C. (1928): Male, age 48, had a prepyloric tumor penetrating through to pancreas with many metastatic nodes on lesser curvature. Biopsy and anterior gastro-enterostomy. Pathologic Report: "Pure" lymphosarcoma. Received 17 radiotherapy treatments in three weeks for a total of 26 hours. A total of 12,700 (French) r. given anteriorly, posteriorly and from both sides at a distance of 40 cm. through 1 Mm. of copper at 2.5 m.a. Living and well at five years. G. I. series negative for recurrence.

No. 8.—Weeden (1929), Gibson (1927): Male, age 34, had pain in epigastrium six months coming on one hour after eating. Weight loss 20 lbs. Operative Pathology: A mass size of palm of hand in posterior surface of stomach with enlarged nodes. Operation.—Distal one-third of stomach resected (Gibson pylorectomy). Pathologic Report: Lymphosarcoma. In excellent health nine years later.

No. 9.—Leriche, R., Irman, E., (1929): Male, age 43, had epigastric distress one year previously, at which time a G. I. series was negative. Recurrence of pain with weight loss and appearance of large mass in right epigastrium. Operative Pathology: A large tumor of the antrum with extension on lesser curvature. Operation.—Pólya resection with anterior gastro-enterostomy. Pathologic Report: Lymphosarcoma of stomach. Well for six years, when epigastric distress recurred. Roentgen ray suggested gastrojejunal ulcer. Operation.—Gastrotomy. No trace of original disease or ulcer. Discharged in good health six years and six months after operation for original disease.

No. 10.—Kaiser (1934): Female, age 51, had pain in left epigastrium. Weight loss 6 Kg. Hard mass beneath left costal margin. G. I. series showed tumor arising from greater curvature in upper third of stomach. Operation.—Biopsy only, as mass was too large to remove. Pathologic Report: Lymphocytic cell lymphosarcoma. Muscle is infiltrated but serosa is not involved. Patient received three roentgen ray treatments over a period of three months to a field 18x18 cm. The radiation was delivered by a 200 K.V. machine at 2.5 m.a. with 1.3 Mm. Cu. and 1.0 Mm. Al. filter. Between 70 and 77 per cent of the skin erythema dose was delivered to the tumor. G. I. series, in 1928 and again in 1929, were negative for persistence of disease. Patient is living and well eight years after biopsy.

No. 11.—Ruppert (1912), (Shopf): Female, age 57, had a complete gastrectomy for a diffuse infiltrating lesion. Pathologic Report: Typical infiltrating, primary endogastric lymphosarcoma. Living and well 14½ years later; with negative G. I. series. Small intestine was shown to have pouched out considerably and served as a temporary food reservoir.

RÉSUMÉ OF FIVE CASE HISTORIES FROM THE PRESBYTERIAN HOSPITAL, N. Y.

Case 1.—No. 222365: F. F., White, female, age 48, married, was admitted to the hospital April 16, 1934, complaining of swelling and distention of abdomen for three weeks. For years had been troubled with "indigestion" and gas, especially following fatty foods. For the last three weeks patient had noted abdominal swelling with feeling of pressure in epigastrium relieved by belching. She had had anorexia for last four days. Her bowel habit was regular and stools normal. She had lost a small amount of weight. Orthopnea had been noted for the past two days.

Physical Examination.—Revealed a poorly developed, chronically ill woman. Almond-sized hard node palpable in right supraclavicular fossa. No general node involvement. Lung signs were compatible with a right hydrothorax. The abdomen was greatly distended and tense. There was shifting dulness. Pitting edema in both legs. Hemoglobin

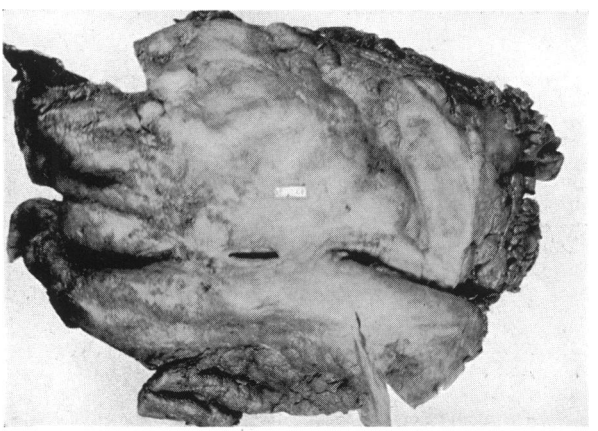

FIG. 1.—Case 1: The stomach specimen showing the smooth nonulcerated mucosa and the diffuse infiltration (linitis plastica) of practically the entire stomach.

80 per cent, R. B. C. 4,250,000, W. B. C. 7,850, polys 82, lymph. 9, monos. 7, eosinophils 1, basophils 1, urine negative, Wassermann negative.

Roentgenologic examination of chest showed right hydrothorax and some evidence of congestion on the left but no absolute evidence of metastases. A G. I. series demonstrated an extensive growth involving the entire lesser curvature—a "saddle growth" extending around posteriorly and anteriorly. Surgically she was felt to be a far advanced case of malignant disease with the stomach as primary focus, and the outlook hopeless. Temporary relief was obtained by paracentesis and thoracentesis. The fluid obtained contained cells about the size of large lymphocytes with dark ground glass cytoplasm and a round dark nucleus filling about half the cell. Some cells were in mitosis. She died suddenly just before discharge to a home for incurables. *Clinical Diagnosis:* Carcinoma of the stomach with metastases to peritoneum; pleural cavities.

Autopsy.—No. 11538: Dr. A. Longacre. *Pathologic Examination; Gross:* "The stomach wall is markedly thickened and firm throughout, except for a small area near the cardia. On the lesser curvature there are several large nodular masses (lymph nodes) covered with peritoneum which appear continuous in places with the gastric wall. On section they consist of white, granular tissue with areas of necrosis. On opening the stomach the mucosal surface is smooth, except for some areas where distinct ridges are present (Fig. 1). No ulceration is seen. On section the markedly thickened mucosa is seen infiltrated with grayish tissue which in places extends through the entire thickness of stomach. Gross evidence of metastases are seen in regional lymph nodes, pancreas, omentum and diaphragm and small foci in pleura, ovaries and cervical nodes."

Microscopic.—The mucosa, submucosa, muscularis and serosa are densely infiltrated with tumor cells. The cells are predominantly of two types—a round cell the size of a small lymphocyte with dense hyperchromatic nuclei surrounded by narrow zone of basophilic cytoplasm (Fig. 2). The other is about the size of a mononuclear with homogeneous, acidophilic cytoplasm. An oval nucleus is situated at a pole or along one side of the cell. Mitoses are frequent. A rare giant cell is seen. There is practically no stroma (Fig. 3). There are many capillaries. The mucosa shows some autolysis and replacement of some of the glandular elements with tumor. Muscularis mucosa is intact. Submucosa is markedly increased in width. The muscle fibers are separated by masses of tumor cells. The serosa is thickened by tumor infiltration.

Note by Dr. A. M. Pappenheimer: "A very characteristic lymphosarcoma of the stomach, which infiltrates the entire viscus as well as the regional lymph nodes, pancreas, omentum and diaphragm. There are small metastatic foci in the pleura and ovaries. The tumor cells are for the most part not highly atypical. Many of them closely resemble small lymphocytes, but there is an admixture of larger elements."

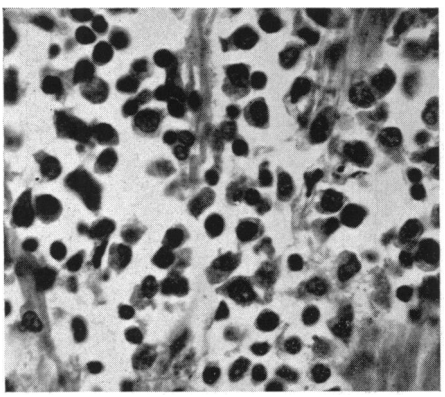

FIG. 2.—Case 1: Photomicrograph of a section of stomach. The predominant cells resemble small lymphocytes with hyperchromatic nuclei. There is an admixture of larger elements with eccentrically placed nuclei (×700).

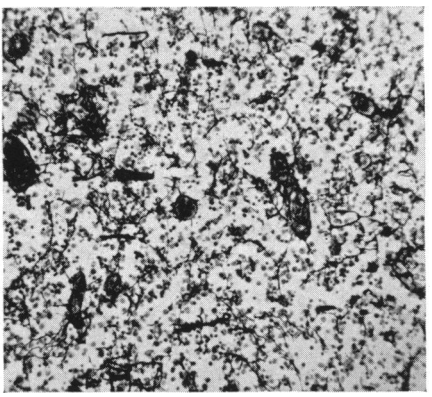

FIG. 3.—Case 1: Same section as Fig. 2, with reticulum stain clearly demonstrating the sparsity of stroma (×150).

This is an example of Type IV in Pack's and McNeer's classification, showing diffuse thickening of the wall, much like a "linitis plastica" lesion. Microscopically it is of the lymphocyte type of lymphosarcoma. Undoubtedly little could be done therapeutically for this particular patient, but it serves to demonstrate how easily a lymphosarcoma of the stomach may go on to fatal termination with a histologically unproven diagnosis of "typical carcinoma with metastases."

Case 2.—No. 230783: T. M., Negro, male, age 40, married, was admitted to the hospital June 18, 1935, complaining of abdominal pain for two months. He had always enjoyed general good health. "Blood tests" were said to be negative, but he had received some intramuscular injections. He had had crampy pain in the epigastrium for two months, usually coming on 15 minutes p. c. and relieved temporarily by food. He was told he had an ulcer one month before (no roentgen ray examination was done). Prescribed diet and powders had failed to relieve pain. Had vomited for first time four days before admission. Tarry stools were noted several times in the last six days.

Physical Examination.—Patient did not appear acutely ill. No superficial lymphadenopathy. The abdomen was not distended or tender. A lemon-sized mass was

palpable in the epigastrium just to the left of the midline. There was no hepatosplenomegaly. Hb. 82 per cent, R. B. C. 3,970,000, W. B. C. 6,760, P. 81, L. 18, M. I. Urine negative. An Ewald test meal showed free HCl 38, total acid 55. Stool had a 4+ guaiac. Wassermann negative.

Roentgenologic examination of the stomach showed 100 per cent six-hour retention, and nothing could be forced through pylorus. The antrum was fixed, tender and inflexible and showed no peristalsis. Impression: An extensive carcinoma of the antrum, invading and involving pylorus (gastric lues was considered a possibility).

Operation.—June 25, 1935: Under spinal anesthesia patient was explored by Dr. J. F. Roberts through a transverse incision. A rounded elastic tumor was found involving the pylorus and extending up on lesser curvature. Posteriorly it was bound down to the pancreas. There appeared to be infiltration by tumor of the gastrohepatic omentum. Several small perigastric nodes were palpable. A resection seemed inadvisable, and a posterior isoperistaltic gastrojejunostomy was performed. He had a smooth postoperative course, except for some evidence of atelectasis on second day. Examination by Dr. V. F. Frantz of the specimen removed from gastrohepatic omentum showed it to be simply a peritoneal band with some fibroblastic proliferation. The question was raised whether the changes might be due to syphilis. Patient was discharged July 14, 1935 on an ulcer diet and was to receive antiluetic treatment.

Subsequent Course.—He was relieved of pain during the following month, but despite antiluetic treatment, the lesion in stomach progressed to involve the duodenal bulb. Roentgen ray diagnosis, August 1, 1935, was carcinoma of antrum, probably not lymphoblastoma. He was readmitted for attempt to resect, in view of the negative biopsy.

Second Operation.—August 8, 1935: Under spinal anesthesia, Dr. J. F. Roberts demonstrated a stony-hard tumor involving the lower half of the stomach and upper portion of duodenum. It was adherent to the adjacent structures and to the old incision. The lesion extended to within 4 cm. of the old posterior gastro-enterostomy. Lymph nodes seemed to be free of disease. The first part of the duodenum and the stomach were resected up to the old posterior gastro-enterostomy. The patient had an unusually smooth postoperative course and was discharged September 4, 1935. Readmitted October 12, 1935, because of evidence of wound infection. This was relieved by instituting adequate drainage. Roentgenotherapy was begun September 3, 1935. G. I. series, February 10, 1936, was negative for recurrence. Readmitted April 30, 1936, complaining of pain in lumbar region and right flank. The abdomen was distended, and a sizable mass was palpable in midabdomen. Some abnormality of the right kidney was shown by retrograde pyelogram but surgery was not advised. Patient continued downhill after discharge April 18, 1936, and died June 1, 1936.

Roentgenotherapy.—September 3, 1935 to December 18, 1935: Received 2,300r. through an anterior portal over the stomach to area 10x10 cm., in divided doses of 100-150r. The factors were 190 K. V., 50 cm. T. S. D., 8 m. a., filter 0.5 Mm. Cu. + 1 Mm. Al. 600r. was given through each of two portals over palpable recurrences, between April 8, 1936 and May 5, 1936. The factors were 190 K. V., 50 cm. T. S. D., 8 m. a., filter 1.86 Mm. Cu + 1 Mm. Al.

Pathologic Examination.—Dr. F. M. Smith. *Gross:* The peritoneal surface is smooth and contains no suggestive tumor nodules. A portion of pancreas is adherent to the posterior wall near pylorus. On opening the stomach, it is seen to be almost entirely filled by a large, smooth spongy tumor completely denuded of mucous membrane (Fig. 4). The line of resection is within 0.5 cm. of the proximal line of resection. The tumor is elevated above the normal mucous membrane and in the antrum completely encircles the lumen. It has grown in such a manner as to form a crater-like depression at one point, where there is ulceration. Subadjacent to this there is a large area of necrosis in the tumor. In some areas the tumor has attained a thickness of 2 cm. and has infiltrated all of the layers except the serosa. *Microscopic* section shows a small round cell tumor which has replaced nearly all elements of stomach wall (Fig. 5). Occasional fragments

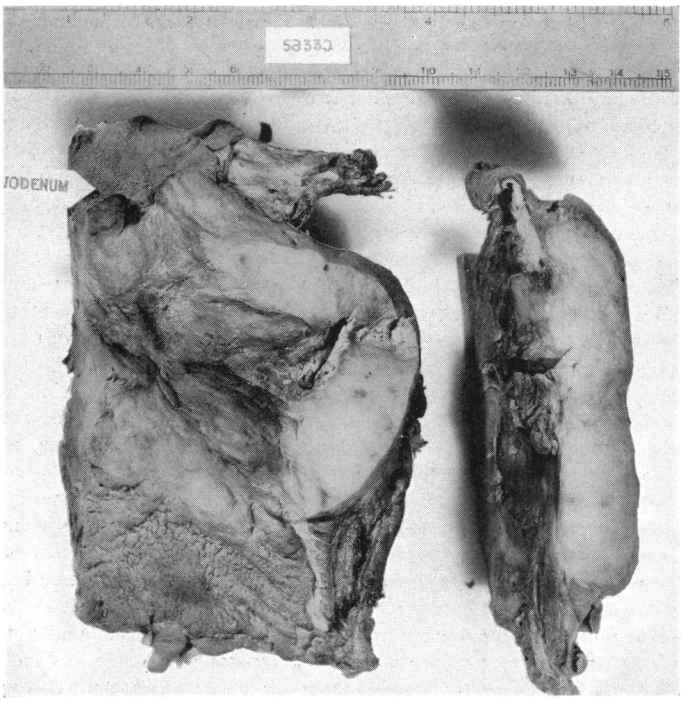

FIG. 4.—Case 2: Stomach specimen. There is marked thickening of the antrum where the tumor completely encircles the stomach. Ulceration and necrosis is clearly seen in the crater-like center of the tumor. Attached duodenum appears uninvolved. The cross-section, on the right, shows the enormous thickening of the wall.

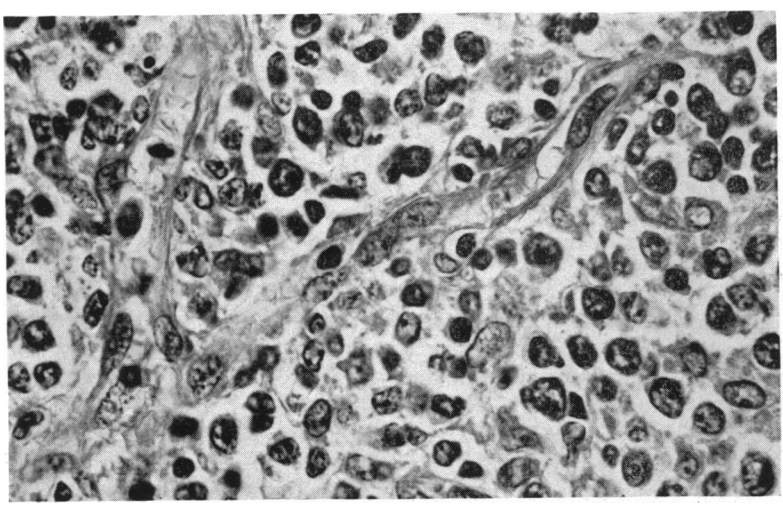

FIG. 5.—Case 2: Photomicrograph of a section of the stomach clearly demonstrates the morphology of the normal tumor cells lying in a scant supporting frame work. (×1100)

of mucous membrane and nests of acid glands are seen, and nearly all of the muscle is replaced. The serosa is involved, but the lymph nodes are not. The tumor invades up to the line of resection. The individual cells are the size of small lymphocytes with a small amount of clear cytoplasm and hyperchromatic nuclei, often eccentrically placed. There is little supporting stroma and practically no fibrosis nor inflammatory reaction. There are some areas of liquefaction necrosis.

This is a lymphocytic cell type of lymphosarcoma of the bulky polypoid variety. The difficulty of making a correct diagnosis of the disease, even upon direct examination, is well brought out. The roentgenologist's note concerning the flexibility of the walls is perhaps the only suggestive finding, even in retrospect. Microscopically this appeared to be a radiosensitive tumor, yet the amount of roentgenotherapy given presumably did little but relieve pain, and death ensued within 10 months after resection.

Case 3.—No. 222561: I. K., female, age 36, married, was admitted to the hospital September 13, 1933, complaining of loss of weight, weakness and vomiting for one year. First admission, September 18, 1929, was for partial thyroidectomy for adenoma of thyroid. March 10, 1932, at second admission, had a full term spontaneous delivery at which time added diagnosis of fibromyoma of uterus was made. First G. I. symptoms were in 1930, with vomiting p. c. without pain. A G. I. series, December 22, 1930, was suggestive of an anomalous first part of duodenum possibly associated with gallbladder disease. January 2, 1931, gallbladder dye series was negative. Patient continued to have distress intermittently despite a dietary regimen but went through a second pregnancy in 1931-2. She developed more distress and anorexia during February, 1933. A second G. I. series was done March 5, 1933. Peristalsis was present only on the greater curvature and was irregular. The prepyloric region appeared narrowed. This was first considered an early sclerotic type of carcinoma, but a review of films did not substantiate this point and the patient was placed on a diet. She continued to have vomiting, anorexia and began to lose weight. A gastric analysis showed free HCl 16, total acid 29. Another G. I. series demonstrated the picture of advanced carcinoma of stomach involving the posterior wall and greater curvature, in the pars media; "a surprising amount of mobility is present in considering the size of the associated mass." Patient was readmitted September 13, 1933. Hb. 62, R. B. C. 3,970,000; W. B. C. 13,300, P. 81, L. 16, M. 3, Stool guaiac 4+. No free HCl found in gastric expression.

Operation.—September 18, 1933, through a left paramedian incision under spinal anesthesia a Pólya type of partial gastrectomy with posterior gastro-enterostomy and entero-enterostomy was performed by Dr. F. Meleney. Her postoperative course was uncomplicated. She was discharged to a convalescent home on the twenty-fourth postoperative day.

Subsequent Course.—Readmitted October 31, 1933, complaining of abdominal cramps for two days and back pain. She appeared quite weak and emaciated. A questionable mass was palpated in the left upper quadrant. A G. I. series showed no definite evidence of recurrence. The severe cramps were relieved by roentgenotherapy and patient discharged November 23, 1933. Presented herself March 7, 1934, two months pregnant. A therapeutic abortion was performed March 17, 1934. She did well until May 2, 1934, when cramps returned and she began to have difficulty in swallowing. A routine G. I. series was equivocal, but a thick meal showed narrowing and distortion of the esophagus at the cardia, which was considered to be a recurrence in the wall of the esophagus. Partial relief followed roentgenotherapy until September 1, 1934, when vomiting and difficulty in swallowing precluded all eating. A definite mass noted in epigastrium, and a G. I. series showed multiple defects in stomach. She could tolerate no further roentgenotherapy and was referred for terminal care. She died October 26, 1934, 13 months after operation.

Roentgenotherapy.—November 15, 1935 to January 19, 1934: Received 1,800r. in divided doses of 100-120r. through anterior portal to area 15x15 cm. over mass. The factors were 180 K. V., 50 cm. T. S. D., 4 m. a., filter 0.53 Mm. Cu. and oil. Subsequently (February 2, 1934 to February 23, 1934) a similar field over suspected mass below

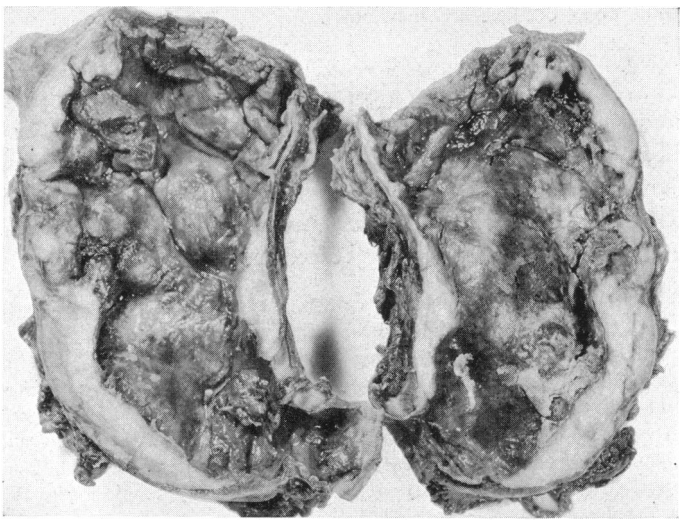

FIG. 6.—Case 3: Operative specimen with stomach bisected and pylorus below, shows involvement of practically the entire greater curvature and a portion of the lesser curvature. The extent of the thickening of the wall is clearly seen.

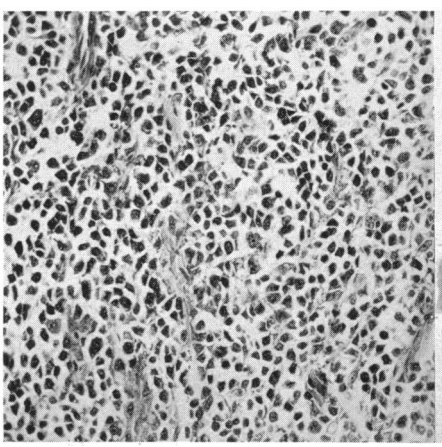

FIG. 7.—Case 3: Photomicrograph showing that the polygonal tumor cells are seen to vary somewhat in size but resemble the reticulum cell of the lymphoid system. No tendency to acini formation is observed. (×500)

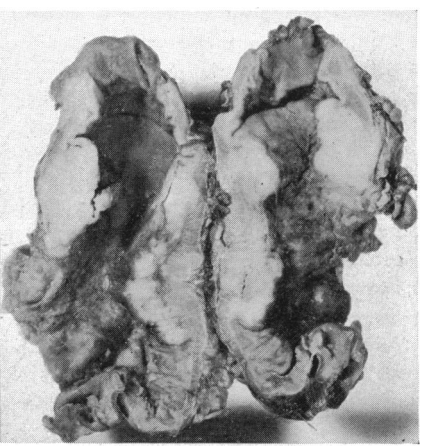

FIG. 8.—Case 4: Gross specimen of the stomach as removed at operation. Specimen bisected with pylorus at the top. The massive, bulky tumor is seen to be fairly well demarcated from normal mucosa as the cardia is reached.

and to left of original area received 600r. The factors were 190 K. V., 50 cm. T. S. D., 8 m. a., filter 0.55 Cu. + 1 Mm. Al. In May, 1934, 625r. were given anteriorly to area corresponding to esophageal and cardiac involvement. An incomplete series was given just before patient's death in September, 1934. In all, 4,800r. were given in six series over a period of seven months.

Pathologic Examination.—Dr. A. P. Stout. *Gross:* There is a large soft nodular tumor with a superficially ulcerated surface which extends from the pyloric ring for a distance of 10 cm. along the lesser and 17 cm. along the greater curvature, completely encircling the stomach (Fig. 6). The thickness varies from 5 to 20 Mm. and in most areas the muscle coat although invaded has not been completely penetrated. The tumor appears to end abruptly just as the pyloric area is reached, and resection is ample as a part of duodenum is excised distally. *Microscopically,* there is disease one millimeter from proximal line of resection. The tumor cells are polygonal and vary greatly in size and shape (Fig. 7). The nuclei are hyperchromatic and the cytoplasm is well defined and amphophylic. There are many mitoses. The cells are arranged in foliate pattern in a delicate reticulum with no tendency to form acini. The lymph nodes removed contain sinuses dilated with lymphocytes and polygonal cells similar to the tumor cells in stomach.

This is a lymphosarcoma of the reticulum cell type. Unfortunately, there was some question on first examination whether or not it was an anaplastic carcinoma, and for this reason there was a delay in administrating roentgenotherapy.

Case 4.—No. 81486: J. M. K., male, age 64, married, was admitted to the hospital April 17, 1929. Always had general good health in past, except for "hunger pain" for 20 years. In 1925, had pain low in abdomen, not related to eating but relieved by soda and food. In 1927, began to lose weight and vomited occasionally. A diagnosis of ulcer was suggested, without roentgenologic examination. Patient gained 20 lbs. after nine weeks of diet and bed rest. Patient had hematemesis and tarry stools in September, 1927 and he was in bed six weeks. He remained asymptomatic until December, 1928, when the pain recurred. Had a remission again until April, 1929, when the pain recurred. Patient had had a hematemesis the day before admission. On admission he complained only of "gas" and epigastric pain. Physical examination was equivocal except for some pallor and abdominal distention. There were no signs of shock. He was placed on bleeding ulcer regimen with nothing p. o., and given hypodermoclyses and rectal instillations. Hb. 43 per cent, R. B. C. 3,460,000, W. B. C. 13,050, P. 74, L. 24, M. 2. Urine was essentially negative. He showed no evidence of further gross hemorrhage and was placed on a modified Sippy regimen, April 19, 1929. He improved slowly, having pain only at night. Stools on five consecutive days were negative to guaiac. Gastric analysis showed a free HCl 14, total acidity 54. On May 15, 1929, a G. I. series demonstrated a broad incisura on the greater curvature of the stomach with narrowing of lumen to about one centimeter. The lesser curvature in this region was somewhat irregular. Peristalsis was present above and below this region but did not pass through it. Stomach walls were quite flexible. There was a 25 per cent gastric retention at six hours. "Findings are those of gastric ulcer." He received four transfusions 600-800 cc., which brought his Hb. up to 100 per cent. However, he continued to show some gastric retention and, June 4, 1929, a second G. I. series showed the marked constriction persisted and a small projection was noted on the lesser curvature side at this point. There was a six-hour retention of 50 per cent. He was discharged with diagnosis of gastric ulcer.

Subsequent Course.—He was readmitted, November 12, 1929, as he had episodes of severe pain during summer months. Stool examinations were persistently positive for blood. He also had had one small hematemesis. A recent G. I. examination showed a large, greater curvature crater which suggested carcinoma. Hb. 88 per cent, R. B. C. 4,770,000. He had had no weight loss. Because of the persistence of bleeding and the roentgenologic findings, operation was decided upon.

Operation.—November 13, 1929: Under spinal anesthesia and drop ether, the abdomen was explored through a T-shaped incision, by Dr. A. O. Whipple. A large ulceration was found on greater curvature with infiltration on lesser curvature and posterior wall extending well to the cardia. Although it appeared almost impossible to get above

the lesion, which was considered to be a carcinoma, it was decided to resect in view of absence of metastases in liver and adjacent lymph nodes. A Bilroth II with gastro-jejunostomy and entero-enterostomy was performed. A drain was placed down to duodenal stump because of insecure inversion. A 700 cc. transfusion was given post-operatively. Smooth course postoperatively, except for development of gastric fistula on the eighth day. This was exceedingly bothersome often draining 1,500 cc. in 24 hours; it, however, healed slowly and the patient was discharged in generally good condition on the thirty-eighth postoperative day. He subsequently developed a large ventral hernia.

Pathologic Examination.—Dr. A. P. Stout. *Gross:* The stomach is rather bulky and rounded. Peritoneal surface is smooth. On opening the organ just above the pylorus, the wall becomes suddenly thickened to 16 Mm. (Fig. 8). This thickening encompasses the entire circumference and extends along the lesser curvature for 2 cm. and the greater curvature for 5.5 cm.

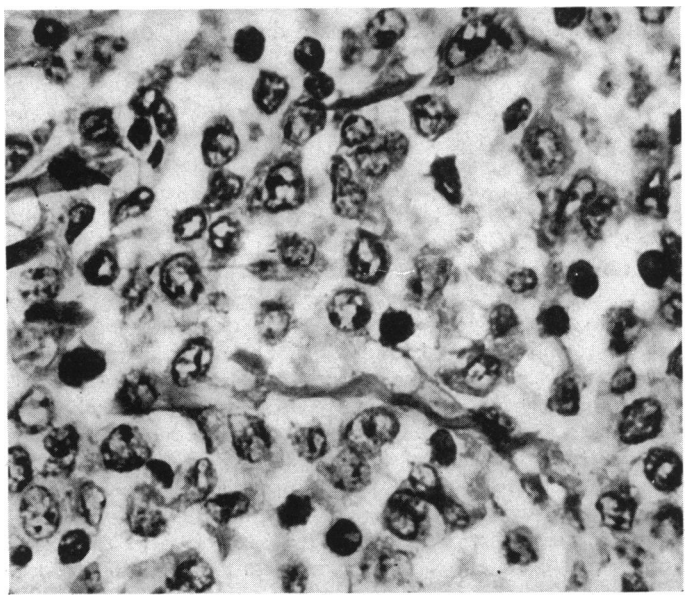

FIG. 9.—Case 4: Photomicrograph of a section through the tumor, showing the tumor cells, cuboidal in shape, and having large hyperchromatic nuclei. There is very little supporting frame work. (×1100)

Microscopic.—A section through tumor mass shows that it is composed of solid masses of small cuboidal cells separated by fibrous tissue strands (Fig. 9). An unusual power of infiltration is noted without corresponding destruction. The individual cells are hyperchromatic with large nuclei and small cell body. Mitoses are frequent. The mucous membrane retains semblance of its architecture but tumor tissue widely separates the glands. There is no attempt at gland formation by the tumor cells. Tumor cells are noted in lymphatic spaces. Proximal line of resection goes through tumor bearing tissue. Only a very fine supporting framework is noted with special stains. *Pathologic Diagnosis:* Anaplastic carcinoma (?) of stomach.

At no time did this patient receive any roentgenotherapy. He had been regularly followed and repeatedly examined by his personal physician, and when last seen, October 26, 1937, at the age of 73, he was in excellent health and showed no evidence of recurrence—eight years after operation.

This lesion exemplifies the massive bulky type of growth fairly well demarcated from the normal stomach. In retrospect nothing in the symptoms or roentgenologic findings particularly suggested the correct diagnosis.

On reviewing this case in 1934, it was felt that the pathology was that of a reticulum cell lymphosarcoma as was originally suggested by the sarcomatous appearance of the gross specimen. As the patient had remained in excellent health for five years, no roentgenotherapy was suggested.

Case 5.—No. 268878: F. M., male, age 19, was first seen, February 4, 1931, following an attack of syncope associated with body tremors but no actual convulsion. A subsequent neurologic examination was negative, except for hypertension (170/90). Patient showed definite antisocial tendencies and "a type of personality that is always on the defensive." He stated that the convulsive-like seizure was always preceded by right lower quadrant pain. He was seen December 28, 1931 in clinic, complaining of epigastric distress p. c. for two months; partially relieved by food. He had lost 10-20 lbs. He had had a previous operation for right undescended testicle, November, 1928, and an appendicectomy, November, 1929.

Physical Examination showed pallor of face and mucous membrane (blood donor). Carious teeth. Blood pressure 120/70. Abdomen was negative. Hb. 63 per cent, R. B. C. 3,900,000, W. B. C. 6,200, P. 57, L. 35, M. 3, E. 5. Chest film negative. Scout film of abdomen was negative. Wassermann negative. January 5, 1932, three hours after a G. I. series, patient showed typical signs of perforation of a hollow viscus. *Preoperative Diagnosis.*—Perforated gastric ulcer.

Operation.—Dr. D. Bull: A perforation was found on the anterior surface of the stomach in the prepyloric area, with induration extending 10 cm. proximally and 4 cm. distally. Ridged, indurated, enlarged rugae were palpated along the posterior wall through the perforation. A number of enlarged nodes suggestive of neoplastic involvement were palpable. A biopsy of the stomach wall and a lymph node were taken and a simple closure of the perforation was performed, with a free omental graft. He had a very smooth postoperative course. A review of the G. I. series showed a constant incisura at the great curvature near the antrum; with mucosal folds so exaggerated as to give an almost polypoid appearance.

Pathologic Examination.—Dr. A. P. Stout. *Microscopic.*—The stomach biopsy shows an extensive inflammatory reaction. There are many tumor cells varying considerably in size and shape. An occasional mitosis is seen. There is no tendency to glandular arrangement. The cells do not form mucin. Many of the cells have the characteristics of lymphoblasts (Fig. 10).

The lymph node shows practically complete replacement with tumor cells similar to those in stomach wall. Mitoses are more frequent than in stomach specimen. The connective tissue stroma is meager, but there is slightly more than usually found in lymphosarcoma (Fig. 11).

It was felt from the stomach specimen that this was a highly malignant tumor—either anaplastic carcinoma or a reticulum cell lymphosarcoma. The lymph node, however, was so characteristic of reticulum cell lymphosarcoma that there was no doubt as to the diagnosis and plans for roentgenotherapy were made. After five treatments the patient decided to go away for a rest. He returned, February 17, 1932, and was given a course of 10 treatments.

April 16, 1932, six hours following one of the patient's unconscious spells, he was seen in the Admitting Clinic with typical signs of perforation. An immediate operation by Dr. Bull demonstrated a perforation similar in location to the first one. Because of the dense adhesions and the patient's poor condition, no biopsy or exploration was done. Closure of perforation was easily accomplished by plication, and the abdomen closed

without drainage. Again, he had an exceptionally smooth postoperative course, and was discharged May 1, 1932.

The patient was very refractory to treatment and refused any further roentgenotherapy.

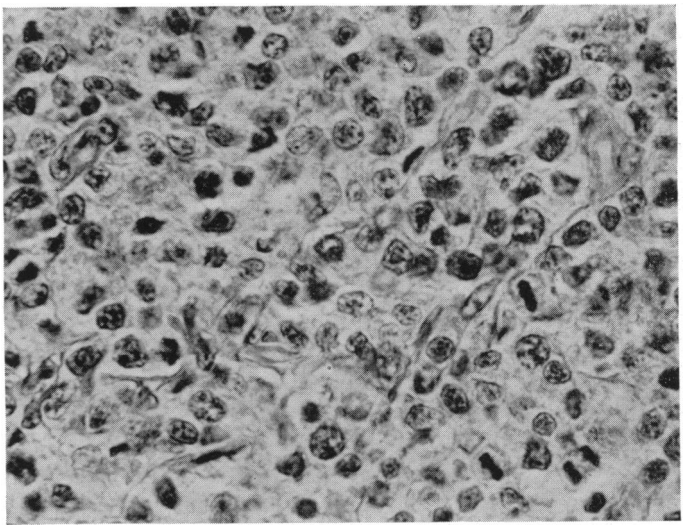

FIG. 10.—Case 5: Photomicrograph of a section of the stomach wall at site of perforation. Note absence of inflammatory reaction. Tumor cells, resembling those of the lymphoblast series, are seen to vary considerably in size and shape. Mitoses are frequent. There is no tendency to glandular arrangement. (×1100)

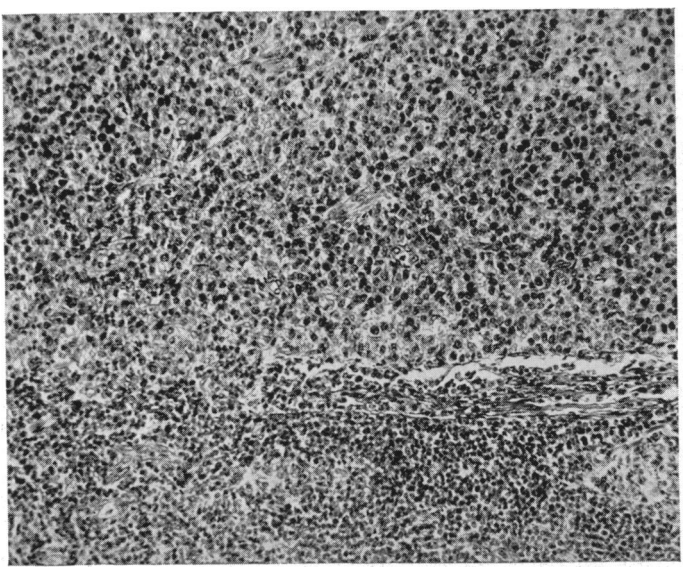

FIG. 11.—Case 5: Photomicrograph of a section of the lymph node, demonstrating the dense infiltration of the tumor cells above, in contrast to the normal lymphoid tissue below. (×250)

A G. I. series was done, March 29, 1933, and showed a constant incisura along greater curvature near the antrum. This was attributed to postoperative scarring. G. I. Series done April 9, 1934, showed no change in the findings. He continued to do fairly well, notwithstanding complete disregard of diet, smoked excessively, and drank freely.

June 12, 1934, he was again admitted for abdominal pain. Abdominal cramps had appeared previously, associated with nausea and vomiting. Bowel movements had been only clear fluid for the previous 48 hours. Three-position roentgenograms of the abdomen confirmed the clinical impression of ileus. He was completely relieved by rectal treatments and parenteral fluids.

The patient continued to do well on a dietary regimen until September 1, 1935, when he again developed abdominal cramps, which were relieved by rectal treatments. A G. I. series, February 20, 1937, gave the impression that there was some thickening of the antral wall, because of decreased activity and some interruption of peristalsis in this region.

He was last seen, September 3, 1937, by a social worker, who found the patient in good health. He had married, in spite of advice to the contrary and has two children. He continues to be refractive to all suggestions as to therapy except when the acute episodes described above occurred.

Roentgenotherapy was completely inadequate, due to patient's lack of cooperation. Through two portals (ant. and post.) over the stomach a total of but 1,380r. was delivered in divided doses, over a period of six months; the patient completing but one full series. The factors were 200 K. V., 50 cm. T. S. D., 8 m. a., filter 1.8 Mm. Cu. + 1.0 Mm. Al. Operatively, nothing was done to alter the course of the disease by way of radical removal. It is perhaps conceivable to believe that this tumor is so radiosensitive that it is kept at least in abeyance by the small amounts of radiation obtained during repeated gastro-intestinal examinations during the years following his first, and only course of planned radiation.

This is a remarkable case of a male, age 25, living and apparently well five years and 10 months after having been shown to have a reticulum cell lymphosarcoma of the stomach of the Type II, described by Pack and McNeer.

In retrospect, this patient shows a number of the findings that have been considered suggestive of lymphosarcoma—his youth; his ulcer-like symptomatology and operative findings; the tendency to perforate; and the original roentgenologic findings of mucous folds exaggerated to an almost polypoidal degree.

Discussion.—Two patients are alive seven, and five years and ten months, respectively; one, with incomplete removal of the lesion and no roentgenotherapy, and the other, with only biopsy and inadequate radiation. This is in distinct contrast to Cases 2 and 3, that had radical excision of the lesion and a greater amount of radiation, only to die from the disease within 10 and 13 months, respectively. A consideration of the other 12 cases of "five-year cure," reveals that a number of these had also received rather unorthodox treatment. Thus, from the analysis of end-results, it is difficult to be dogmatic as to a method of choice in treatment of these lesions as a whole.

It would seem that in the few instances, when the lesion is completely removable, radical surgery offers the best means of cure.

The case for cure by radiation is certainly not as clear-cut from the data assembled. Undoubtedly, remarkable regression of far-advanced lesions often occurs. This is particularly true in more recent years, with improvement in technic. There are at least six cases in the recent literature that have been symptom-free up to two and one-half years, following only roentgenotherapy, and one case (Kaiser, 1934) has gone eight years. However, when apparent cures occur, as in Cases 4 and 5, it becomes difficult to evaluate the absolute

curative results of roentgenotherapy when compared to what might be termed control cases.

It would seem that frequently these lesions have a natural history, individual to the particular case and to a degree independent of the method of treatment. At least, until further knowledge is obtained concerning this neoplasm, not only should every attempt be made to treat these lesions, no matter how far advanced, but also histologically exact diagnosis should be obtained more frequently, before pronouncing a gastric neoplasm beyond therapeutic aid.

SUMMARY.—(1) One hundred forty-seven cases of primary lymphosarcoma of the stomach have been collected from the literature, and five new cases are added.

(2) They have been analyzed as to age, sex, symptomatology, clinical and laboratory data.

(3) Of the 118 patients operated upon, 76 had subtotal gastrectomy, a 50 per cent resectability of the total number of cases (152), with a 15.8 per cent operative mortality.

(4) Thirteen patients are living and well, 5 to 22 years after discovery of the lesion.

CONCLUSIONS

(1) Diagnosis is very difficult; only a single case having been correctly diagnosed preoperatively. There are no pathognomonic clinical findings, and, as yet, no typical roentgenographic appearance. Gastroscopy may, in the future, be a valuable diagnostic aid.

(2) A treatment of choice is difficult to evaluate, due to the number of "cures" that have received what is considered inadequate surgical or roentgenotherapy.

(3) Complete surgical removal is of course ideal, but in only a few cases did this appear possible. Radiation alone, particularly with newer technic, has accomplished clinically complete remission of the disease up to eight years, even in far-advanced cases.

(4) The course of some of the cases, suggests that there may be definite individual variation in their life history that at times is completely unrelated to the type and extent of therapeutic intervention.

(5) Attention is called to the desirability of establishing a histologic diagnosis of a gastric neoplasm before it is regarded as beyond aid.

The author wishes to express his appreciation to Doctors Whipple, Meleney, Bull and Roberts, for the privilege of having access to the cases operated upon; and to Doctor Pappenheimer, of the Department of Medical Pathology, for permission to use the autopsy material presented in Case 1. The author is particularly indebted to Dr. A. P. Stout, for his kind suggestions and criticisms.

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