

Primary lymphoid neoplasms of the stomach

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EDITORIAL SYNOPSIS Primary lymphoid neoplasms of the stomach may closely simulate carcinomata but carry an appreciably better prognosis after surgical treatment. This paper reports a clinical and pathological study of local gastric lymphoid tumours and also studies in patients with gastric involvement with generalized reticulosis.

Although the malignant reticuloses are generally widely distributed throughout the body and are probably multifocal in origin, similar neoplasms apparently originating at one site have been described in various organs, *e.g.*, the intestine (Ullman and Abeshouse, 1932; Marcuse and Stout, 1950; Irvine and Johnstone, 1955), lung (Rose, 1957; Sternberg, Sidransky, and Ochsner, 1959), thyroid (Kellett and Sutherland, 1949; Brewer and Orr, 1953; Walt, Woolner, and Black, 1957), and bones (Jaffe, 1958). Primary lymphoid neoplasms of stomach are comparatively rare and though they have been extensively reported in the American literature (Taylor, 1939; Snoddy, 1952; Allen, Donaldson, Sniffen, and Goodall, 1954; Thorbjarnarson, Beal, and Pearce, 1956) only a few small series (Skrimshire, 1955; Azzopardi and Menzies, 1960) or individual cases have been described in Britain.

From results reported in the literature some of these gastric neoplasms seem to have a better prognosis than carcinoma, although their behaviour is apparently unpredictable from histological examination. The following investigations were carried out in order to compare the histological, clinical, and follow-up findings in a series of cases collected in the United Birmingham Hospitals and the Regional Histological Collection of the Department of Pathology, University of Birmingham.

MATERIALS AND METHODS

All cases described as reticulosarcoma, lymphosarcoma, reticulosis of any type, sarcoma, or anaplastic carcinoma of stomach in the surgical histology files of the United Birmingham Hospitals from 1950 to 1960 and in the Regional Histological Collection from 1953 to 1960 were examined histologically. Initial studies were made independently and without reference to other data. Stained sections and paraffin blocks were available and

all undifferentiated tumours were stained with Ehrlich's haematoxylin and eosin, and by Gomori's method for reticulin, by the periodic acid-Schiff technique, and Southgate's mucicarmine. Alcian blue and Van Gieson stains were also occasionally employed. Altogether 240 tumours of stomach were examined.

For purposes of comparison with this surgical series, all cases of malignant reticulosis, excluding leukaemia, extracted from the post-mortem records of the Queen Elizabeth Hospital, Birmingham, from 1950 to 1959 were examined. In addition two instances of primary gastric lymphoid neoplasm which had been encountered at necropsy were found in the Regional Histological Collection.

DIAGNOSTIC CRITERIA

A definitive diagnosis of lymphoid neoplasm is as difficult in the stomach as elsewhere (*cf.* thyroid, Brewer and Orr, 1953), as differentiation from anaplastic carcinoma can never be absolute. Using the criteria described by the various authors mentioned above and from observations on the material itself, it was possible to select a group of neoplasms which differed from anaplastic carcinoma in general pattern and cytology. This was not a homogeneous group and it could be subdivided into two main types, lymphosarcoma and reticulosarcoma. The lymphosarcomata consisted of closely packed groups of cells with little recognizable cytoplasm and dense nuclei, identical in appearance to small lymphocytes (Figs. 1 and 2). In some of these tumours the cell pattern was uniform, but in others larger cells with more cytoplasm and larger open nuclei were also found. In two cases there was a recognizable follicular pattern but this was focal and was not a major feature (Fig. 3). The type designated reticulosarcoma had larger cells with more cytoplasm and rounded or slightly twisted nuclei with prominent nucleoli (Fig. 4). Occasionally multinucleated cells were seen and in some tumours

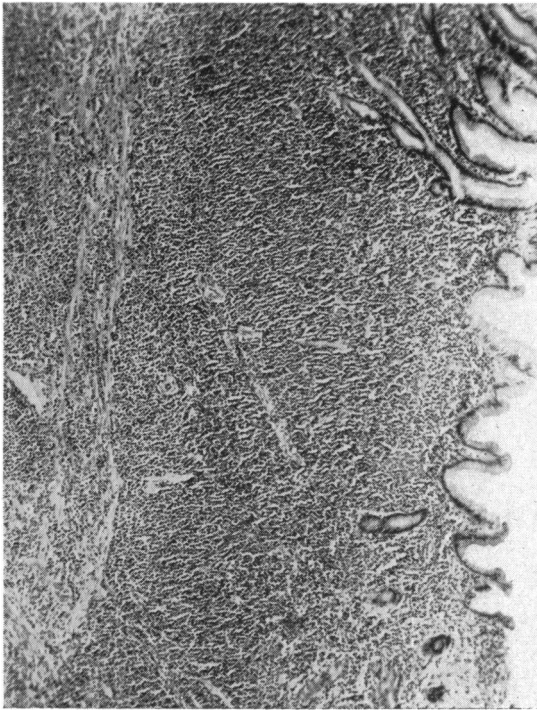


FIG. 1

FIG. 1. *Lymphosarcoma involving the mucosa and submucosa. The muscularis mucosae is preserved. Haematoxylin and eosin $\times 75$.*

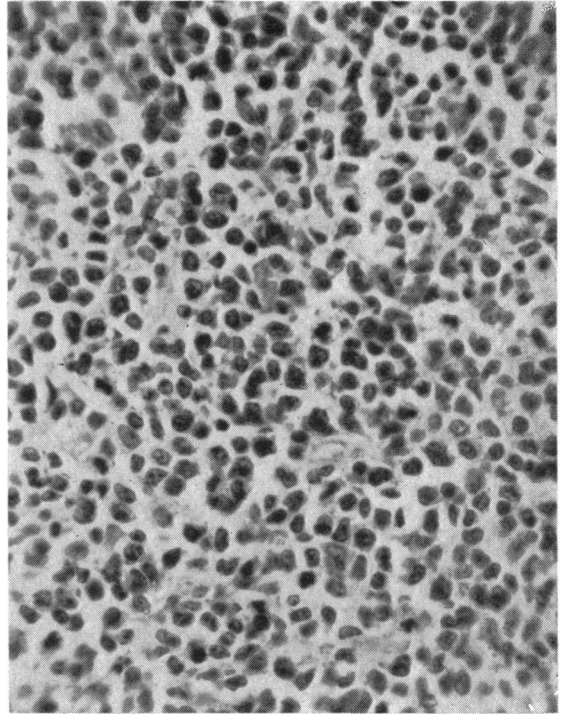


FIG. 2

FIG. 2. *High-power view of lymphosarcoma. Haematoxylin and eosin $\times 450$.*



FIG. 3. *Area of lymphosarcoma showing a follicular pattern. Haematoxylin and eosin $\times 75$.*

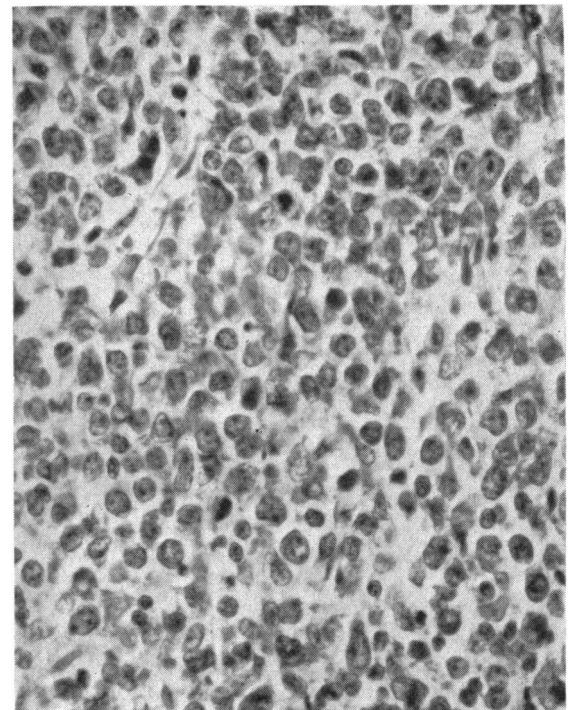


FIG. 4. *High-power view of reticulosarcoma. Haematoxylin and eosin $\times 450$.*

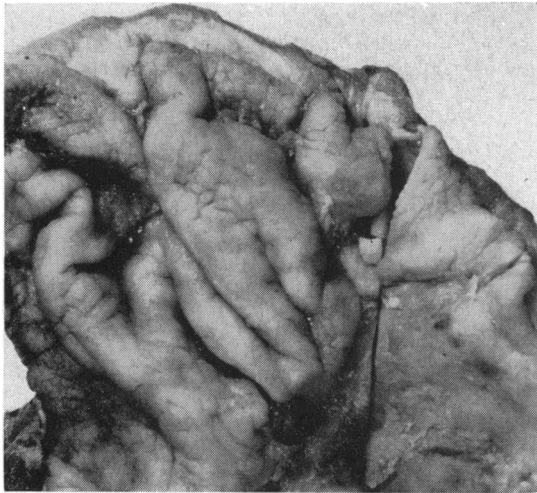


FIG. 5. Margin of ulcerated reticulosarcoma showing giant rugae. Fixed specimen $\times 1.5$.

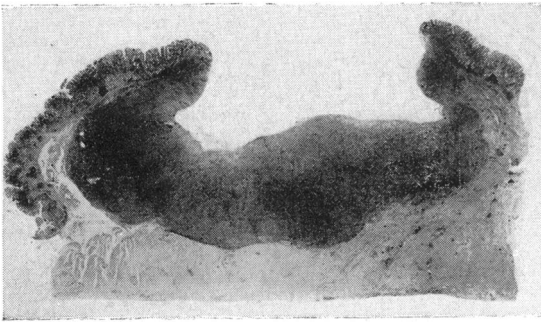


FIG. 6. Section of ulcerated lymphosarcoma with raised edges. To the left the tumour is invading the muscularis as a solid mass and to the right is infiltrating between muscle fibres. Van Gieson $\times 3.5$.

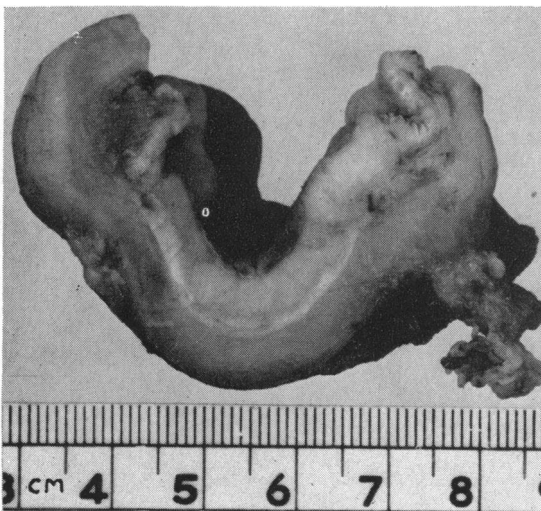


FIG. 7. Section of superficial diffusely infiltrating reticulosarcoma with ulceration in the centre.

the cell pattern was more pleomorphic. Eosinophils and plasma cells were sometimes seen in both groups. Stains for mucin were negative in all cases.

RESULTS

SURGICAL SERIES Twenty-four cases were diagnosed as lymphoid neoplasms, nine lymphosarcoma and 15 reticulosarcoma. Hodgkin's disease and giant follicular lymphoma were not encountered but a follicular pattern was noted in some areas in two cases.

The relevant clinical, pathological, and follow-up data are shown in Table I. There were 16 males and eight females. The age range was 29-71 years, with the peak incidence in the seventh decade (nine cases) and this did not differ to any great extent from carcinoma of stomach.

Macroscopic appearances Macroscopic descriptions were available in 20 of the 24 cases. None had been diagnosed as lymphoid neoplasm on naked-eye examination alone and the tumours presented in four main types: 1 Lesions indistinguishable from chronic peptic ulcers; 2 polypoid tumours, either single or multiple; 3 large single or multiple ulcers with raised rolled edges (Figs. 5 and 6); 4 diffusely infiltrating tumours, sometimes associated with giant rugae (Figs. 5 and 7).

Appearances corresponding to each of these types have also been seen in carcinoma of the stomach. In many cases the tumours were superficial, but in others the muscle was penetrated deeply. In two cases perforation was the initial indication for surgery. The lower end of the oesophagus was invaded in two cases.

Histological appearances Apart from the cytological appearances initially used in selection and the absence of mucin staining, there were several histological features of interest. The lamina propria and submucosa were usually very heavily involved and in some cases the muscle coat was not deeply penetrated. The muscularis mucosae was often preserved even when the neoplastic process continued from the lamina propria to the submucosa (Fig. 1). Fibrosis in relation to the neoplasm was uncommon but in a few cases there was fairly dense fibrosis in relation to ulcerated areas. The tumours invaded the muscle coat either on a broad front or by infiltration between individual muscle fibres (Fig. 6) but on occasions infiltration was mainly along the fibrous septae (Fig. 8). This mode of spread, in our opinion, did not differ substantially from that of carcinoma.

Giant rugae associated with some of these cases did not always show infiltration by neoplastic cells. In some the appearances were due to oedema and

TABLE I

DETAILS OF 24 CASES OF PRIMARY GASTRIC LYMPHOID NEOPLASMS

Case No.	Sex	Age	Main Clinical Features	Treatment	Macroscopic Appearances	Histology	Lymph Node Involvement	Course	Survival Years
1	F	58	Epigastric pain for 3 months	Total gastrectomy, splenectomy, partial pancreatectomy	Ulcerating tumour 8 cm. in diameter. Spleen and pancreas not invaded	Reticulo-sarcoma	—	Remained well and died nine years later from cardiovascular disease. <i>Necropsy</i> : No recurrence or metastases	D.9
2	F	70	Iron-deficiency anaemia 3 years, diverticulitis, laparotomy	Partial gastrectomy	Massive polypoid tumour on greater curvature, not ulcerated	Reticulo-sarcoma	—	Deteriorated and died with metastases in liver. No necropsy	D.1
3	M	52	First admission 1952 Ulcer history for 8 years Partial gastrectomy Second admission 1958, lymphosarcoma in peritoneum and intestine	1 Partial gastrectomy 2 Resection of segment of large intestine	Ulcer 2 × 1 cm. on lesser curvature, 10 cm. from pylorus	Lympho-sarcoma	—	Remained well after partial gastrectomy for 5 years Developed abdominal pain Since resection of bowel has remained well	A.9
4	M	59	Long history of epigastric discomfort Treated medically 1948 and 1952 for chronic peptic ulcer	Partial gastrectomy, deep x-ray therapy	—	Lympho-sarcoma	—	Two months after partial gastrectomy developed mass in hypochondrium. Tonsillar mass developed after 1 year and mediastinal and inguinal node enlargement after 1½ years No necropsy	D.2
5	F	38	Anorexia and nausea for 6 weeks	Total gastrectomy	Large ulcerating tumour of cardiac end of stomach invading lower end of oesophagus	Reticulo-sarcoma	+	Died after 7 months with local recurrence No necropsy	D. 7/12
6	F	61	Vomiting after meals and continuous epigastric pain for several months	Partial gastrectomy	Large ulcerated neoplasm of pyloric end of stomach	Reticulo-sarcoma	+	Metastases developed in liver. No necropsy	D.1 5/12
7	F	68	Diarrhoea for several weeks	Total gastrectomy	Diffuse neoplasm Stomach wall 1.5 cm. thick	Reticulo-sarcoma	+	Died 3 days post-operatively No necropsy	D.O.
8	M	60	Dyspnoea and pain in chest 9 months. Mass in hypochondrium	Partial gastrectomy	Large ulcer 12 cm. diameter astride lesser curvature	Lympho-sarcoma	—	Developed metastases in lungs and spine. No necropsy	D.1
9	M	44	Abdominal pain for 5 weeks	Total gastrectomy	Large sessile tumour in fundus	Reticulo-sarcoma	+	Died 4 weeks post-operatively	D.O.
10	M	62	Three months epigastric discomfort	Partial gastrectomy	Deep ulcerated tumour	Reticulo-sarcoma	—	Remains well	A.5 6/12
11	M	69	Epigastric pain for 1 month	Partial gastrectomy	Ulcerated tumour	Lympho-sarcoma	—	Remains well	A.5
12	M	29	Abdominal pain for 1½ years	Total gastrectomy, pancreatectomy, splenectomy	Large superficial ulcer 6 cm. in diameter on greater curvature near fundus	Lympho-sarcoma	—	Died 4 weeks after operation <i>Necropsy</i> No metastases	D.O.
13	M	63	Admitted as an emergency following perforation	Partial gastrectomy, deep x-ray therapy	Large ulcer 7 × 8 cm. on lesser curvature	Reticulo-sarcoma	—	Developed ulcerated mass in tonsil which responded to deep x-ray therapy Remains well	A.5
14	M	45	Epigastric pain for 2 months	Partial gastrectomy, deep x-ray therapy	—	Lympho-sarcoma	—	Died 3 weeks post-operatively No necropsy	D.O.
15	M	69	Admitted as an emergency with a perforation	Partial gastrectomy	Large necrotic ulcerated tumour with a perforation in the centre	Lympho-sarcoma	—	Died the following day No necropsy	D.O.
16	M	57	Indigestion 16 years, treated medically for duodenal ulcer 4 years previously	Partial gastrectomy	Diffuse thickened nodular mucosa	Lympho-sarcoma	—	Remains well	A.4
17	F	70	Loss of weight and epigastric pain for 2 months	Partial gastrectomy	Multiple ulcers on lesser curvature	Reticulo-sarcoma	—	Alive but with a local recurrence of neoplasm	A.3
18	F	63	Loss of weight 1 year, anorexia 4 months	Partial gastrectomy	—	Reticulo-sarcoma	—	Remains well	A.3
19	F	49	Vomiting after food for 2 weeks	Partial gastrectomy	Large, diffuse, ulcerated tumour	Reticulo-sarcoma	—	Died. No necropsy	D.29/12
20	M	47	Epigastric pain 8 months	Partial gastrectomy	—	Lympho-sarcoma	—	Remains well	A.3
21	M	71	Loss of weight and epigastric pain for 4 months	Oesophago-gastrectomy	3 cm. polypoid ulcerated tumour at cardia	Reticulo-sarcoma	—	Remains well	A.1 9/12
22	M	51	Vomiting and abdominal pain for 6 months	Partial gastrectomy, deep x-ray therapy	Irregular ulcer 6 cm. in diameter near pylorus	Reticulo-sarcoma	+	Remains well	A.1 8/12
23	M	47	Abdominal pain and loss of weight for 6 months	Partial gastrectomy, deep x-ray therapy	Large ulcerated tumour with raised edges	Reticulo-sarcoma	+	Remains well	A.1 6/12
24	M	62	Epigastric pain and loss of weight for 7 months	Partial gastrectomy	Flat indurated ulcer 7 × 6 cm. on lesser curvature	Reticulo-sarcoma	+	Died. No necropsy	D.1

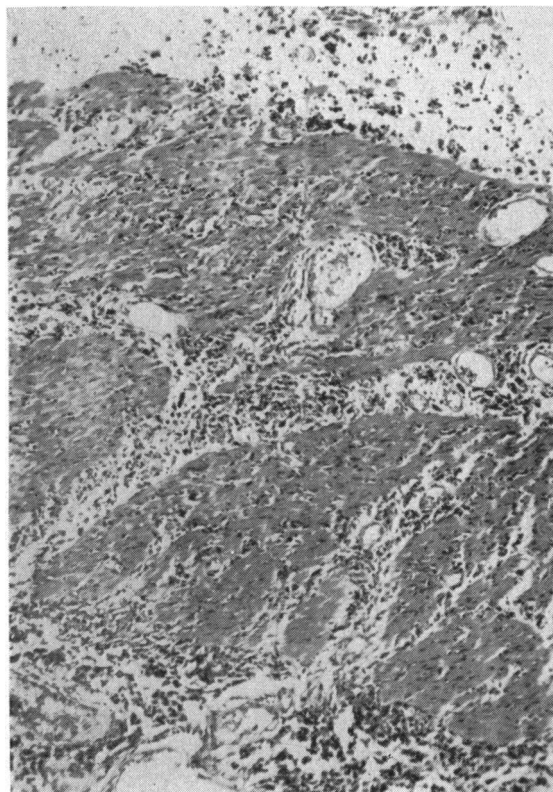


FIG. 8. Reticulosarcoma infiltrating along fibrous septae and between muscle fibres. Haematoxylin and eosin $\times 100$.

similar appearances were sometimes found in the submucosa in the absence of giant rugae. The reticulin pattern was very variable, not only from case to case but also in different parts of the same specimen. In general the pattern in carcinoma was much heavier but this was often associated with fibrosis.

Lymph node involvement Of 20 cases in which sections of lymph nodes were available, seven showed involvement. Usually the whole lymph node was replaced but in a few cases localized deposits were found.

Follow-up data Five patients died in the immediate post-operative period, leaving 19 in whom follow-up studies could be carried out for a minimum period of 18 months. A post-mortem examination was carried out on one of the five patients dying after operation and no involvement of other organs was found (case 12).

The survival rates are shown in Table II, in which a comparison is made with all histologically proven cases of carcinoma of stomach subjected to partial or total gastrectomy and with a group of poorly differentiated gastric carcinomata.

TABLE II
SURVIVAL RATES FOR GASTRIC LYMPHOID NEOPLASMS
AND CARCINOMA OF STOMACH

	Total ¹	% Survival (years)				
		1	2	3	4	5
Gastric lymphoid neoplasms	19	95	73	64	55	50
Gastric carcinoma all types ²	419	64	40	30	23	20
Gastric carcinoma poorly differentiated ²	72	60	36	26	17	11

¹Excluding post-operative deaths.

²Regional Histological Collection 1951-55. All cases treated by surgical resection and examined histologically.

In the first year survivals there is a highly significant difference ($P < 0.001$) between the lymphoid group of tumours and the anaplastic carcinoma group but thereafter the numbers become too small to give significance to individual years of survival. There is, however, a clear trend where the proportionate survival rate increases in favour of the lymphoid group. This lends support to the view that gastric lymphoid neoplasms form a group distinct from anaplastic carcinoma.

POST-MORTEM SERIES The results are shown in Table III. Of a total of 54 cases of systematized reticulosis (including four cases in which the main lesions were in the gastrointestinal tract), gastric involvement was found in 11 cases (30% of reticulosarcoma and 31% of lymphosarcoma cases). In one of these 11 cases the major post-mortem finding was the presence of multiple lesions in the gastrointestinal tract. The relevant pathological and clinical findings of these 11 cases are included in Table IV.

TABLE III
NECROPSY SERIES QUEEN ELIZABETH HOSPITAL, 1950-1959,
FOR ALL CASES OF RETICULOSIS EXCLUDING LEUKAEMIA

	Total	Reticulo-sarcoma	Lympho-sarcoma	Hodgkin's Disease
All cases	54	23	13	18
Generalized	50	20	13	17
Gastrointestinal	4	3	0	1
Gastric lesions	11	7	4	0
Generalized cases	10	6	4	0
Gastrointestinal cases	1	1	0	0

The gross appearances of these lesions did not differ substantially from those of the surgical series, except that multiple deposits were much more common and the tumours were mainly superficially situated within the gastric mucosa. The cytological appearances of the lesions in the surgical and post-mortem series were indistinguishable.

TABLE IV

DETAILS OF 11 CASES OF WIDESPREAD RETICULOSIS WITH GASTRIC INVOLVEMENT AT NECROPSY						
Case No.	Sex	Age	Main Clinical Features	Main Necropsy Findings	Nature of Gastric Involvement	Diagnosis
25	M	53	Six months' loss in weight, lymphadenopathy, hepatomegaly	Generalized lymphadenopathy, tumour in stomach, small intestine, spleen, heart, kidney, adrenal, and thyroid	Three mucosal nodules, one showing erosion	Reticulosarcoma
26	F	78	Eight months' swelling angle of jaw and neck due to large lymph nodes, tumour mass in nasopharynx	Tumour in stomach, nasopharynx, lung, liver and kidneys, cervical lymphadenopathy	One mucosal lesion upper part lesser curve, raised margin ulcerated base measuring 6 × 4 cm.	Reticulosarcoma
27	M	59	Four years' loss in weight, steatorrhoea, macrocytic anaemia	Tumour in stomach jejunum and ileum, mesenteric nodes involved	One mucosal lesion in fundus measuring 2 × 1 cm., raised edges ulcerated base	Reticulosarcoma
28	F	53	Four months' swelling axillary lymph nodes, abdominal mass palpable	Generalized lymph node involvement, tumour in stomach, spleen, kidney, lung, liver, and heart	Several subserous nodules measuring 0.3 cm. diameter	Reticulosarcoma
29	M	78	Seven months' swelling axillary lymph nodes with increasing weakness, hepatomegaly	Generalized lymph node involvement, tumour in tonsil, stomach, oesophagus, and spleen	Multiple discrete mucosal nodules along lesser curve, some ulcerated	Lymphosarcoma
30	F	69	Six months' general lymph node enlargement and abdominal pain, hepatosplenomegaly	Generalized lymph node involvement	Single small mucosal deposit	Reticulosarcoma
31	M	67	Eighteen months' cervical and mediastinal lymphadenopathy with dyspnoea and dysphagia	Enlarged paratracheal cervical and mediastinal lymph nodes	Multiple mucosal nodules measuring up to 5 cm. in diameter	Lymphosarcoma
32	M	61	Twenty-seven years' attacks of diarrhoea. Five years previously found to have steatorrhoea. Four months' generalized lymph node enlargement	Generalized enlargement of lymph nodes, tumour in stomach, small intestine, lung, kidney, pancreas, adrenal, and liver	Multiple mucosal nodules majority ulcerated measuring up to 5 cm. diameter, mainly in fundus and body	Reticulosarcoma
33	F	30	Two weeks' pyrexia with cough and dyspnoea. Chest radiograph revealed 'mottled' pattern of all lobes	Tumour deposits in stomach, oesophagus, pleura, lungs, pericardium, liver, kidney and thyroid. Generalized lymph node involvement	Two ulcerated mucosal nodules one 2.5 cm. diameter in mid lesser curve, the other 1.0 cm. diameter on anterior wall	Reticulosarcoma
34	M	54	Three months' cervical and mediastinal lymph node enlargement with superior vena caval obstruction and pleural effusion	Large mediastinal mass of tumour, lesions in stomach, kidney, and thyroid	Five ulcerated mucosal nodules measuring up to 1.5 cm. diameter on mid-posterior wall	Lymphosarcoma
35	M	49	Eight months' generalized lymph node enlargement and pleural effusion	Tumour in lymph nodes stomach, spleen, liver, and pancreas	Multiple raised ulcerated nodules in mucosa up to 2 cm. diameter on posterior wall	Lymphosarcoma

TABLE V

DETAILS OF TWO CASES OF LOCALIZED GASTRIC LYMPHOID NEOPLASMS FROM THE REGIONAL HISTOLOGICAL COLLECTION

Case No.	Sex	Age	Main Clinical Features	Main Necropsy Findings	Diagnosis
36	M	54	Nausea and pain in epigastrium for nine months. Died with haematemesis	Diffusely infiltrating tumour of stomach invading spleen, tail of pancreas, and kidney	Lymphosarcoma
37	M	37	Six weeks' diarrhoea and loss of weight	Large solitary ulcer of stomach penetrating pancreas, peritonitis	Reticulosarcoma

The two cases of primary lymphoid neoplasms of stomach coming to necropsy are shown in Table V. Widespread metastases were not found and the tumours were confined to the stomach area.

DISCUSSION

The results of this investigation confirm those of other series, namely, that the survival rate is higher

in this group of tumours than in carcinoma of the stomach. The five-year survival is similar to that in other series; for example, Allen *et al.* (1954) had 50% survival rate at five years. No difference has been found between the histological appearances of the tumours in those patients who survive for long periods and those who die soon after a diagnosis has been made. Similarly no cytological differences have been noted in the deposits in the

stomach in systemic reticuloses and those where the lesions appear to be primary, although in the former the lesions tend to be more superficial in position and there is comparatively little deep invasion. In addition, the histological appearances were no guide to the prognosis: thus of the two patients surviving longest, case 1 (nine years) had a reticulosarcoma and case 3 (nine years) a lymphosarcoma.

PATHOLOGICAL FEATURES The gross features of these neoplasms were not very helpful in the diagnosis, as similar appearances could be found in carcinoma. This has also been noted in gastroscopic (Palmer, 1950) and radiological examinations (Redd, 1959) where differentiation is not possible in most cases.

On a histological basis the lymphosarcoma is very readily recognized and confusion with carcinoma is unlikely to occur. However, the reticulosarcomata more closely resemble anaplastic carcinoma and it may be quite impossible on occasion to differentiate the two groups. Various histological rather than cytological criteria have been described by different authors. The most important differentiation lies in the completely structureless nature of the reticulosarcomata and the absence of mucus secretion. Other differences are the absence of any transitions between the epithelium and the tumour, the superficial nature of some of these tumours, with heavy involvement of the mucosa and submucosa and frequent preservation of the muscularis mucosae (Fig. 1), and the frequent absence of fibrosis except in relation to some ulcerated zones and the method of invasion. The method of invasion was not found to be helpful in individual cases and the reticulin pattern was too variable to be of any assistance.

When all these factors are considered, one is still left with the problem that the basic histological method of differentiating reticulosarcoma is by excluding recognizable carcinoma and other forms of sarcoma. This is an unsatisfactory position, but the same conditions are found in other sites. Willis (1948) has emphasized the difficulties inherent in classification of undifferentiated tumours. With the small cell lymphosarcomata the position is quite different, as these tumours are cytologically readily distinguishable from carcinoma. Even in this group, however, their subsequent behaviour is unpredictable.

generalized reticuloses presented clinically as a primary gastric neoplasm. However, the subsequent behaviour of apparently primary tumours suggests that in some cases at least a generalized form develops. Thus cases 4 and 13 subsequently developed lesions in the tonsils. Cruickshank (1957) has reported three cases with involvement of the tonsils and gastrointestinal system, in which the lesions were apparently localized to these areas. However, in our series case 4 later developed a generalized lymphadenopathy, so that the association of tumour in these two sites would appear to be coincidental.

Apart from five post-operative deaths, eight other patients have died between seven months and nine years after operation. A post-mortem examination was carried out in only one of these patients (case 1) nine years after the removal of the neoplasm, and no evidence of metastases was found. The other seven patients died with clinical evidence of metastases or local recurrence in the abdomen. Of the 11 patients still alive, case 3 had a recurrence in the abdomen after six years but is still alive nine years after operation, case 17 has a local recurrence, and all others have no evidence of recurrence. It appears that in some cases the neoplastic process becomes generalized, but in others the lesion seems to remain localized to the stomach.

The assumption has been made that these are truly neoplastic lesions but the considerations of Brewer and Orr (1953) in the thyroid apply equally to the stomach. The behaviour of some of these lesions, which on a histological basis would be considered highly malignant, makes it very difficult to exclude the possibility that some may be reactive rather than neoplastic. This, however, remains a speculation and at the moment there is no means of deciding which lesions will metastasize and which will apparently be cured.

We wish to acknowledge the help and cooperation of Dr. S. C. Dyke, Curator of the Regional Histological Collection, and the pathologists on the Birmingham Regional Hospital Board. We also wish to thank Dr. J. A. H. Waterhouse and Miss D. J. Powell, of the Department of Medical Statistics, University of Birmingham, and Miss J. M. Levi, of the Follow-up Department.

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RELATION OF PRIMARY LYMPHOID NEOPLASMS TO GENERALIZED RETICULOSES None of the surgical cases was considered to have a generalized reticulosis at the time of operation and conversely none of the

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