Detailed studies suggest that the relapse in these cases could be largely attributed to the fact that on release from close supervision as in-patients both these persons failed to persevere with the chemotherapy and with the more general measures required for the complete arrest of their pulmonary lesions. Further periods of hospital treatment have been provided, using other chemotherapy, but to date the sputa have remained persistently positive. We can therefore still maintain the conclusion stated above, that ethionamide is a valuable antituberculous drug.

REFERENCES

- Brouet, G., Marche, J., Rist, N., Chevallier, J., and LeMeur, G. (1959). *Amer. Rev. Tuberc.*, **79**, 6.
 Somner, A. R., Ross, J. D., MacLeod, H. M., Stewart, S. M., Horne, N. W., and Crofton, J. W. (1959). *Brit. med. J.*, **1**, 486.
 Vêran, P., Moigneteau, C., Trichereau, R., and Rist, N. (1959). *Rev. Tuberc.*, **23**, 454.

PRIMARY LYMPHOSARCOMA OF THE SMALL INTESTINE

AN UNUSUAL CASE, WITH LONG SURVIVAL

BY

J. S. CORNES, M.B., B.Sc., D.C.P.

Senior Registrar, Westminster Hospital; Research Assistant,
 St. Mark's Hospital, London

Malignant lymphomas form roughly 25% of all the malignant tumours found in the small intestine. Many of these tumours are secondary deposits in a generalized lymphomatosis, but in about a third of the cases the lesions are apparently primary in the bowel. Most patients with primary lesions are dead within two years from the time of diagnosis or treatment, and only a small percentage are alive and well 10 years later (Dawson, Cornes, and Morson, 1960). Why some cases have a short course and others live for such long periods of time has never been fully explained. So far as can be determined all the well-documented cases of primary intestinal malignant lymphomas surviving 10 years or more from the time of diagnosis were treated by surgery, and this was often combined with a post-operative course of deep x-ray therapy.

Several writers have shown that the type of tumour, its situation in the intestinal tract, and the type of treatment given significantly affect the patient's chance of survival (Marcuse and Stout, 1950; Skrimshire, 1955; Azzopardi and Menzies, 1960). Similar attempts to show that age and sex, the number of tumours found, and involvement of the regional lymph nodes have a significant effect upon prognosis have produced conflicting results. The difficulty attending any assessment of the behaviour of these tumours is illustrated by an unusual case treated at Westminster Hospital. This patient had multiple tumours in the small intestine, and lived for more than 16 years after their incomplete surgical removal.

Case Report

A man aged 50, first seen in January, 1943, under the care of Mr. G. T. Mullally and later of Mr. E. Stanley Lee, gave a two and a half years' history of intermittent attacks of colicky abdominal pain associated with abdominal distension and vomiting. The attacks had recently increased in severity, rendering him a complete invalid. No abnormality was found on clinical examination or by sigmoidoscopy.

Occult blood was found in the stools. The haemoglobin was 9.4 g./100 ml. and the white blood cell count was 7,300/c.mm., with a normal differential. At laparotomy in December, 1942, several small tumours thought to be inflammatory masses were found in the proximal ileum, and the adjacent mesenteric lymph nodes were slightly enlarged. Biopsies taken from a mesenteric lymph node and one of the bowel lesions showed a lymphosarcoma of the proximal ileum.

A second laparotomy was therefore performed two months later, and three small tumours were found in the ileum, only one of which was causing obstruction. Two pieces of ileum, each approximately 22 cm. long and each containing a small tumour, were resected, and a mesenteric lymph node was taken for histology. One tumour, not causing intestinal obstruction, was left behind. The specimens showed lymphocytic lymphosarcomas invading and destroying the muscle coats, with infiltration of the surrounding mesenteric fat. The tumour cells were small and rounded, with a narrow rim of basophilic cytoplasm, and central, round, darkly staining nuclei. The muscle coats appeared to be eaten away by the tumour masses, and there was a conspicuous absence of any surrounding fibrous reaction. The mesenteric lymph node was replaced by lymphosarcoma.

The patient made a quick recovery from this operation, and, although no post-operative radiotherapy was given, he remained in fairly good health for the next 10 years, apart from occasional attacks of colicky abdominal pain and vomiting. In August, 1953, these attacks became more frequent and more severe, and he was readmitted for further observation and investigation. A soft irregular mass was palpable in the abdomen. The liver and spleen were not palpable, and there was no palpable superficial lymphadenopathy. A plain x-ray film of the abdomen showed an incomplete obstruction of the small bowel. A chest x-ray film appeared normal, and there was no obvious enlargement of the mediastinal lymph nodes. The haemoglobin was 16.6 g./100 ml., and the white blood cell count was 4,600/c.mm., with a normal differential.

A third laparotomy was performed in September, 1953, when the lesion previously left behind in the proximal ileum was found, together with a similar lesion in the jejunum, and two large masses in the mesojejunum. These mesenteric masses felt firm and rubbery, and had surface diameters of 5 cm. and 8 cm. respectively. A piece of ileum and a piece of jejunum, each approximately 14 cm. long and each containing a bowel tumour, were removed, but the mesenteric gland masses were left behind. The specimens showed lymphocytic lymphosarcomas of the jejunum and ileum, with invasion and destruction of the muscle coats and involvement of the regional lymph nodes. The histological appearances were identical with those of the tumours removed ten years previously. A post-operative course of deep x-ray therapy was given over a period of 36 days using 220 kV. and opposing anterior and posterior 20-cm. circular abdominal fields. The total skin dose was 2,640 r, and the total centre dose 1,890 r. The patient was discharged fit and well in November, 1953.

In August, 1957, he developed a cough with haemoptysis and in May, 1958, a chest x-ray film showed an opacity in the left upper lobe, and bronchoscopy showed a tumour of the left-upper-lobe bronchus. Because the tumour was beyond the reach of the biopsy forceps a biopsy was not possible, and since there was no clinical evidence to suggest a recurrence of his lymphosarcoma a diagnosis of bronchial carcinoma was made. Radiotherapy was given, and after some temporary clinical improvement his condition deteriorated and he died in March, 1959, 18 years from the onset of his first illness and 16 years after the first operation for intestinal lymphosarcoma. At necropsy (Dr. H. G. Close) a large necrotic carcinoma of the left-upper-lobe bronchus was found, and metastases were present in the right adrenal and the left temporal lobe. No lymphosarcoma was found. Sections from the tumour and its

metastases (Dr. J. C. Burne) showed an anaplastic carcinoma. Islands of squamous-cell carcinoma could be seen throughout the tumour masses, with oat or spindle cells predominating.

Discussion

The interesting and unusual features of this case are the patient's long survival after incomplete surgical removal of multiple lymphosarcomas in the small intestine; the ability of a lymphosarcoma to remain localized in the small intestine and mesenteric lymph nodes for such a long period of time without spreading to other parts of the body; the response to radiotherapy; the patient's death several years later from an unrelated bronchial carcinoma; and the failure to demonstrate any remaining lymphosarcoma at necropsy.

Stout (1953) refers to a case of gastric lymphosarcoma which was incompletely removed. The patient received no further treatment and died almost 19 years later without evidence of recurrence or metastasis. I have been unable to find any comparable intestinal case. Coley (1928), McSwain and Beal (1944), and Allen *et al.* (1954) describe cases surviving 6 to 10 years after the incomplete surgical removal of intestinal lymphomas, but in every case post-operative radiotherapy was given. The present case appears to be unique in remaining localized in the small intestine and mesentery for a period of 10 years without radiotherapy having been given, and in the opportunity to confirm the nature of the tumours histologically.

The patient's death from an apparently unrelated bronchial carcinoma is of considerable interest. The two types of tumour found in this patient were quite dissimilar, and each type had its own clear-cut and readily recognizable histology. There was no possibility of one tumour being an anaplastic variant of the other. A relationship between malignant lymphomas of the intestinal tract and carcinoma is suggested from a survey of these tumours in the pathology laboratories of Westminster, St. Mark's, and the Gordon Hospitals, London. In a consecutive series of 40 cases of malignant lymphoma affecting the small and large intestines there were five carcinomas. The malignant lymphomas and the carcinomas were confirmed histologically in every case. The principal data from these five cases are summarized in the Table, and a detailed description of three of them has been given elsewhere (Cornes, 1960).

Weitzel (1958) found a slightly raised incidence of carcinoma in patients with lymphoma and/or leukaemia compared with patients suffering from multiple primary carcinoma. Moertel and Hagedorn (1957) could find no evidence to show that malignant lymphomas predisposed to the development of carcinoma. It may be that lymphomas in certain sites, such as the small or large intestine, are more likely to be followed by carcinoma than similar lymphomas elsewhere. Clinically it is important to recognize that carcinoma can develop

in these cases, and one should not be too ready to assume that a second tumour is necessarily a recurrence or a metastasis from the original primary lymphoma.

In any general survey of malignant lymphomas there are always 2-3% of cases which have a long survival irrespective of the extent of lymph-node involvement or of the treatment given (Stout, 1942). Some malignant lymphomas such as giant follicular lymphoma and Hodgkin's paraganuloma usually remain localized for many years before spreading to other parts of the body. Lymphoblastic lymphosarcoma, Hodgkin's disease, Hodgkin's sarcoma, and reticulum-cell sarcoma usually spread fairly rapidly. Lymphocytic lymphosarcomas have a variable behaviour: in most of these cases the patients are dead within a few years, whilst a small number, similar to the present case, can remain localized for several years before spreading to other parts of the body (Gall and Mallory, 1942). With the development of new staining techniques, tissue-culture studies, and the increasing use of chemotherapeutic agents in the treatment of malignant disease, it may become possible to separate different types of lymphosarcoma on the basis of histochemistry, cultural behaviour, or therapeutic response. But at present it is not possible to predict on the basis of histology alone which of two clinically similar intestinal lymphocytic lymphosarcomas is likely to spread rapidly and which will remain localized for a long period of time. In either case the best method of treatment would appear to be a wide surgical removal of the intestinal lesion with or without post-operative radiotherapy, and radical surgery should be attempted wherever possible.

Summary

An unusual case of multiple lymphocytic lymphosarcomas of the small intestine and adjacent mesenteric lymph nodes is described. Despite incomplete surgical removal and no radiotherapy being given, the tumour remained localized in the jejunum, ileum, and mesenteric nodes for the next 10 years. Further surgery was attempted and post-operative radiotherapy was given. The patient died six years later from an unrelated carcinoma of the left-upper-lobe bronchus.

Cases of long survival after incomplete surgical removal of malignant lymphomas of the gastro-intestinal tract are discussed.

Intestinal lymphomas may be associated with carcinoma. In a consecutive series of 40 cases there were five carcinomas.

It is usually possible to predict the behaviour of malignant lymphomas from a study of their histology. Lymphocytic lymphosarcomas, however, have a variable behaviour: while most cases show an early and fairly rapid spread, a small number remain localized for several years before spreading to other parts of the body.

Five Cases of Malignant Lymphoma of the Intestinal Tract Associated with Carcinoma

Age and Sex	Malignant Lymphoma			Carcinoma		Interval Before Development of Carcinoma
	Cell Type	Site	Treatment	Cell Type	Site	
57 M	Lymphocytic lymphosarcoma	Rectum	Resection, radiotherapy	Mucus-secreting adenocarcinoma	Rectum	Synchronous
52 M	" "	Terminal ileum	" "	" "	Sigmoid colon	1 year
52 M	Reticulum-cell sarcoma	Ascending colon	" "	Five mucus-secreting adenocarcinomas	Sigmoid colon, rectum	20 months
66 M	Lymphoblastic lymphosarcoma	Duodenum	Laparotomy, biopsy	Mucus-secreting adenocarcinoma	Prostate	Synchronous
48 M	Multiple lymphocytic lymphosarcoma	Jejunum, ileum	Incomplete resection, radiotherapy	Anaplastic carcinoma	Bronchus	15 years

I am grateful to Mr. E. Stanley Lee for permission to use the patient's case notes, to Dr. M. O. J. Gibson for details of the patient's final illness, and to Dr. H. G. Close for his necropsy report. I thank Dr. Alan Morgan and Dr. J. C. Burne for histological material, and Dr. Joseph Humble and Dr. C. E. Dukes for their helpful advice and criticism. The work was supported by a generous grant from the British Empire Cancer Campaign.

REFERENCES

- Allen, A. W., Donaldson, G., Sniffen, R. C., and Goodale, F., jun. (1954). *Ann. Surg.*, **140**, 428.
 Azzopardi, J. G., and Menzies, T. (1960). *Brit. J. Surg.*, **47**, 358.
 Coley, W. B. (1928). *Ann. Surg.*, **88**, 641.
 Cornes, J. S. (1960). *J. clin. Path.*, **13**, 483.
 Dawson, I. M. P., Cornes, J. S., and Morson, B. C. (1960). *Proc. roy. Soc. Med.*, **53**, 655.
 Gall, E. A., and Mallory, T. B. (1942). *Amer. J. Path.*, **18**, 381.
 McSwain, B., and Beal, J. M. (1944). *Ann. Surg.*, **119**, 108.
 Marcuse, P. M., and Stout, A. P. (1950). *Cancer*, **3**, 459.
 Moertel, C. G., and Hagedorn, A. B. (1957). *Blood*, **12**, 788.
 Skrimshire, J. F. P. (1955). *Quart. J. Med.*, **24**, 203.
 Stout, A. P. (1942). *J. Amer. med. Ass.*, **118**, 968.
 — (1953). *Tumors of the Stomach*, Sect. VI, fasc. 21, p. 79.
 Armed Forces Institute of Pathology, Washington, D.C.
 Weitzel, R. A. (1958). *Cancer*, **11**, 546.

Medical Memoranda

Megaloblastic Erythropoiesis Associated with Sick-cell Anaemia

The association of megaloblastic erythropoiesis with sickle-cell anaemia in adults has been described by Jonsson *et al.* (1959) and Oliner and Heller (1959), but its occurrence in infants has not previously been reported. This association in the absence of nutritional deficiencies in one case of sickle-cell anaemia and one case of sickle-cell haemoglobin-C disease occurring in Nigerian infants is described.

CASE 1

A 3-year-old Ibo boy was first seen on November 27, 1958, with a short history of cough and recurrent bouts of fever. He had been born in a maternity home in Lagos in March, 1955; delivery was normal, weight 7 lb. (3.175 g.). He was breast-fed for the first year, and during this time was often seen by a doctor for coughs and colds. During the next two years he thrived and was taking a reasonable mixed diet, including tinned milk daily, meat twice a week, fish three or four times a week, and occasional eggs. On examination he was well nourished but ill, weighing 32 lb. (14.5 kg.); his head was large (circumference 19 in.; 48 cm.) and showed marked bossing (see Fig.). The mucosae were pale, the heart was enlarged, the liver and spleen were both easily palpable, and there was evidence of consolidation at the base of the right lung.

Investigations.—Hb, 4.6 g./100 ml.; P.C.V., 14%; M.C.H.C., 32.8%. Target cells were present and the red cells showed macrocytosis, microcytosis, anisocytosis, and poikilocytosis. W.B.C., 24,250/c.mm. (polymorphs 70%, lymphocytes 27%, eosinophils 1%, monocytes 2%). Sickling of the red cells was observed in saline. Haemoglobin electrophoresis showed only haemoglobin S. Alkali denaturation of the same specimen revealed 3.5% foetal haemoglobin. Tibial-marrow aspiration showed a hypercellular marrow with a mixed normoblastic and intermediate megaloblastic erythropoiesis with reversal of the myeloid/erythroid ratio and evidence of iron deficiency. No malarial parasites were found in peripheral blood films or marrow smears. The urine contained an excess of urobilinogen. X-ray examination revealed a right basal patchy consolidation and generalized cardiac enlargement, and bossing of the skull. The Heaf test was negative, and microscopy of the stool revealed no abnormality.

Crystalline penicillin, 200,000 units six-hourly, was given, and the basal pneumonia gradually resolved. Folic acid, 5 mg. b.d., and iron supplements were begun on December 1; the haemoglobin rose steadily to 10.4 g./100 ml. in the next six weeks, when he was discharged from hospital. For the next four weeks the haemoglobin level was maintained at about 10 g./100 ml., folic acid, 5 mg. b.d., still being given.

In February, 1959, the haemoglobin began to fall and the child developed icteric sclerae, multiple joint pains, splenic pain, and a right basal pneumonia. On readmission investigations showed: Hb, 7.4 g./100 ml.; W.B.C., 19,300/c.mm. (polymorphs 74%, lymphocytes 24%, monocytes 1%, basophils 1%). The film appearances of the red blood cells were unaltered, target cells were seen, and sickling of red cells in saline was observed. No malarial parasites were found in the peripheral blood. His haemoglobin dropped at the rate of 1.7 g./100 ml. a day, and when it reached 4 g./100 ml. he was transfused with 1 pint (570 ml.) of fresh blood. After the transfusion the haemoglobin rose to 10.7 g./100 ml., and his pneumonia resolved on penicillin and postural drainage.

Case 1, showing enlarged head and bossing.

During this admission he was given pyrimethamine, 12.5 mg. a week, as a malarial prophylactic, folic acid, 5 mg. b.d., and vitamin B₁₂, 100 µg. on alternate days by injection. The haemoglobin level rose to 11.1 g./100 ml. after two weeks, but the marrow remained megaloblastic, though features of iron deficiency were no longer present. He was discharged from hospital on folic acid, 10 mg. b.d., iron supplements, and pyrimethamine, 12.5 mg. weekly. During the next four months he was well, with no crises, and the haemoglobin stayed at about 11.5 g./100 ml.

In July a further marrow examination revealed megaloblastic features, and pyrimethamine was stopped in case it was maintaining megaloblastic erythropoiesis by its folic-acid antagonist action. Four weeks later megaloblasts, though less prominent, were still present in the marrow. However, as he was asymptomatic and the haemoglobin was 11.6 g./100 ml., he was discharged from hospital on folic acid, 5 mg. b.d., and had remained well up to the time of writing.

Family History.—The child is the only living offspring, a younger sibling having died at 1 year. Investigation of the parents gave the following results. Father: Hb, 14 g./100 ml.; sickle-cell test positive in reducing buffer at two hours; haemoglobin electrophoresis A and S; no foetal haemoglobin on alkali denaturation. Mother: Hb, 13.5 g./100 ml.; sickle-cell test positive in reducing buffer at two hours; haemoglobin electrophoresis A and S; no foetal haemoglobin on alkali denaturation. Genotyping therefore supported the diagnosis of homozygous sickle-cell anaemia.

CASE 2

A male Ibo child was born in a maternity hospital in Lagos in February, 1957. Delivery was normal, and his birth weight was 7 lb. 8 oz. (3.400 g.). He thrived on the breast with vitamin supplements (his father was a trained nurse) until the age of 1, when he developed joint pains,