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The Zollinger-Ellison syndrome due to an infiltrating tumour of the stomach

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SUMMARY This is the first case report of the Zollinger-Ellison syndrome due to an infiltrating tumour of the stomach. Plasma gastrin levels were high and gastrin was demonstrated in argyrophil tumour cells by an immunofluorescent technique. Evidence is presented that the tumour arose from the G cells.

In 1955 Zollinger and Ellison described the syndrome of recurrent peptic ulceration, gastric hypersecretion, and an associated pancreatic tumour arising from the non-beta cells of the islets of the pancreas. Since then over 800 further cases have been described and it is now clearly established that the aggressive peptic ulceration is due to excessive production of gastrin by the tumour. The tumour itself may lie outside the pancreas, and in the series reported by Howe (1965) 10% occurred in the duodenal wall, 2% as a discrete adenoma of the pyloric region of the stomach, and in 9% no primary tumour could be discovered even at necropsy in the presence of widespread metastases.

This paper describes a patient with the Zollinger-Ellison syndrome due to an infiltrating gastrinoma of the stomach.

Case Report

A man aged 65 presented in April 1969 with a 14-year history of epigastric pain which occurred in cycles and wakened him at night. A diagnosis of chronic duodenal ulcer was made and this was confirmed by barium meal. In November 1969 laparotomy revealed a grossly scarred duodenum with an active ulcer, but no abnormality of the stomach was detectable at that time. Truncal vagotomy was performed with posterior gastro-jejunostomy and the patient made an uneventful recovery.

He remained well for 14 months, but then epigastric pain recurred with heartburn and bilious vomiting. A barium meal showed coarse mucosal folds but no evidence of recurrent ulceration; these folds were clearly seen on gastroscopy but no ulcer was observed. The basal acid output of the stomach (BAO) was 17·9 m-equiv/hr and the maximal histamine response (MHR) using 0·04 mg histamine acid phosphate per kg by intravenous infusion was 23·8 m-equiv/hr giving a ratio BAO: MHR of 75%. Results of plasma gastrin assays (resting) were: radioimmunoassay (Temperley and Stagg, 1971) > 1 ng/ml (normal 80-100 pg/ml), bioassay (Smith, Lawrence, Colin-Jones, and Schild, 1970) 100 ng/ml (normal unrecordable).

A diagnosis of the Zollinger-Ellison syndrome was made and in May 1971 a further laparotomy was performed. The pancreas was mobilized and carefully palpated but no evidence of tumour could be found in it. The only abnormality detected in the stomach was slight diffuse thickening. Total gastrectomy was performed, with retrocolic oesophagojejunal Roux-en-Y anastomosis and recovery was uneventful. Plasma gastrin estimation performed one month and again four months after total gastrectomy showed a level too low to record. The patient has remained well to date (August 1972).

Pathology

The specimen consisted of the whole stomach measuring 29 cm along the greater curve, 10 cm along the lesser with a portion of small intestine attached by an anastomosis near the pylorus. The mucosa of almost all of the stomach except a small area near the pylorus showed a pattern of thickened, exaggerated rugae with craggy, nodular surfaces (Fig. 1). On

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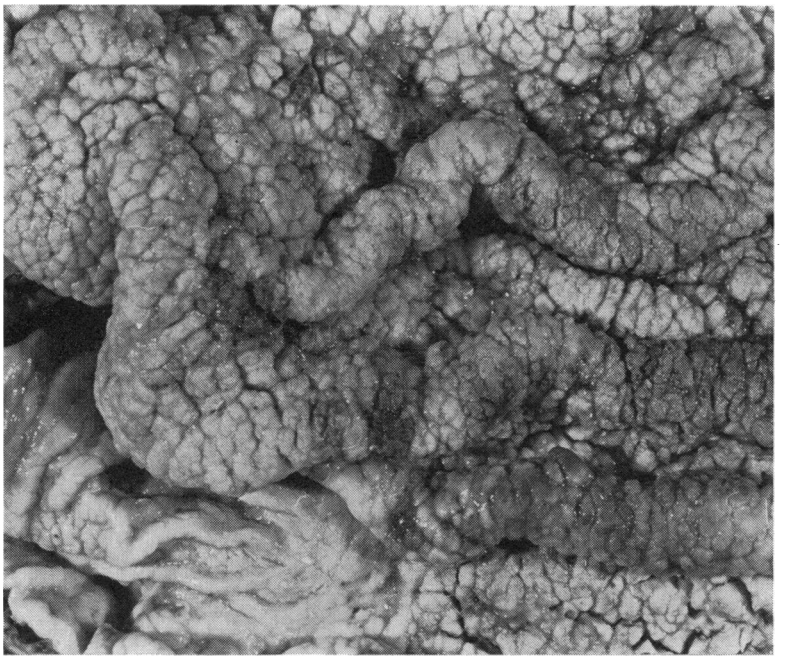

Fig. 1. *Mucosa of the stomach showing an exaggerated pattern of thickened, craggy rugae. A few rugae of normal size may be seen at the bottom left.*

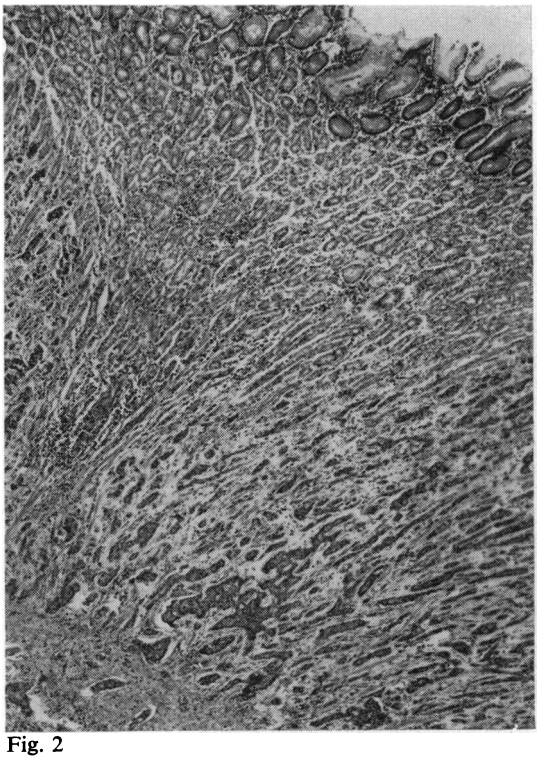

Fig. 2

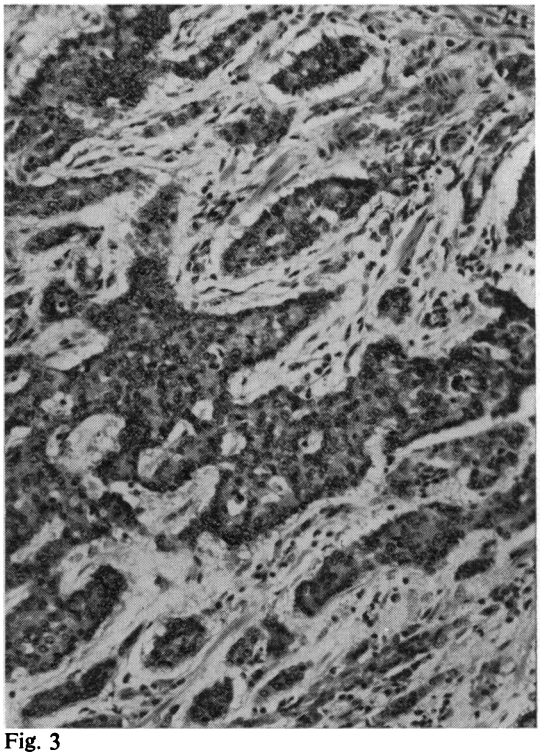

Fig. 3

Fig. 2 *The gastric pits and gastric glands of an uninvaded portion of the mucosa are seen on the left. Tumour occupies the mucosa on the right and infiltrates the muscular mucosae at the bottom left* ($\times$ *38*).

Fig. 3 *Detail from Fig. 2* ($\times$ *160*).

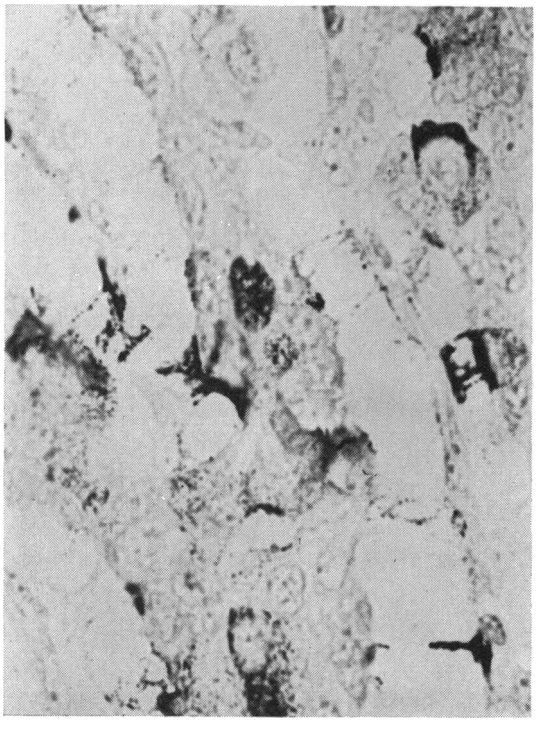

Fig. 4 *Argyrophil granules in tumour cells* (× *1 120*).

cutting through the wall of the stomach the mucosa was seen to be thickened and to consist of homogenous pale tissue. Microscopically, the thickening of the rugae was seen to be caused by neoplastic tissue consisting for the most part of strands and solid clumps of small compactly arranged cells (Figs. 2 and 3) but there was a tendency for them to be arranged in tubules in a few scattered places. Nuclei were round or oval and were uniform in staining and of fairly uniform size; occasional mitotic figures were present but they were not numerous. Staining of the tumour cells for argentaffin granules by the Masson-Fontana method and by the diazo-reaction proved negative but argyrophil granules were demonstrated in the cytoplasm of the tumour cells by Hellweg's modification of the Bodian method (Fig. 4). The tumour infiltrated the muscularis mucosae, submucosa, and main muscle and extended into connective tissue just outside the stomach on the lesser curve. Only one lymph node could be found in the specimen; it was not invaded.

Immunofluorescent Studies

Formalin-fixed portions of tumour and of uninvaded antral mucosa were treated by the indirect Coons technique (Coons, Leduc, and Connolly, 1955) using rabbit antihuman-gastrin I serum for the first layer and fluorescein-labelled goat-anti-rabbit IgG glo-

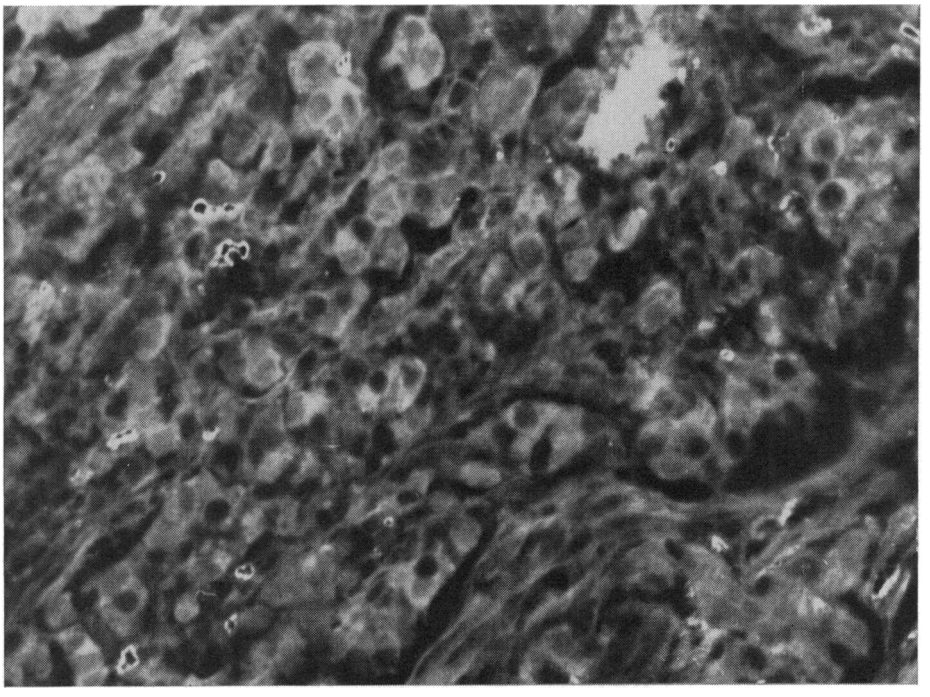

Fig. 5 *Fluorescence of tumour cells treated with antihuman-gastrin* (× *400*).

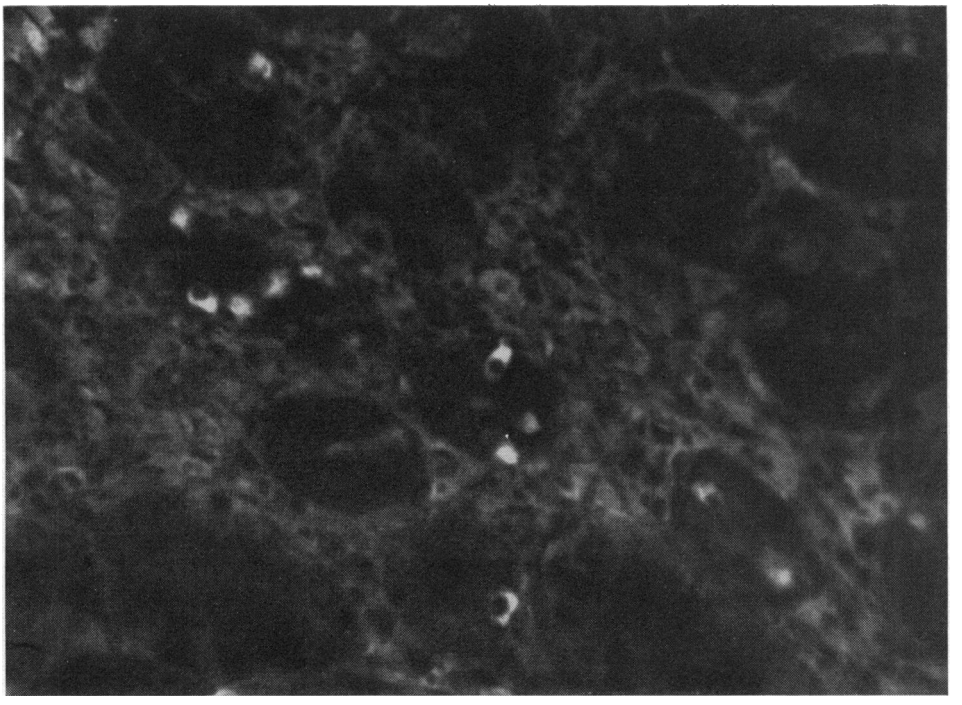

Fig. 6 *Fluorescence of G cells treated with antihuman-gastrin in an uninvaded portion of stomach (× 400).*

bulin (Hyland) for the second layer. The following controls were used: (1) antihuman gastrin serum with added excess of synthetic gastrin I followed by fluorescein-labelled antiglobulins; (2) normal rabbit serum followed by the second layer; (3) fluorescein-labelled goat-anti-rabbit globulin alone; (4) observation of untreated sections by fluorescence microscopy. After immunofluorescence staining, some sections were restained by the lead-haematoxylin technique (Solcia, Capella, and Vassallo, 1969) for endocrine granules.

Tumour cells showed a green-yellow cytoplasmic fluorescence with unstained nuclei (Fig 5). Normal gastrin-producing cells (G cells) of the uninvaded part of the stomach can be seen in Figure 6. The lead-haematoxylin method showed secretory granules stained a violet bluish colour in the cytoplasm of the tumour cells.

From the cytochemical, histological, and immunofluorescent results it is concluded that the tumour in the wall of the stomach consisted of endocrine tissue which was producing gastrin.

Discussion

Edkins (1906) first suggested that a hormone, 'gastrin', was released from the stomach that caused acid secretion. Gregory and Tracy (1964) subsequently extracted gastrin from hog antral mucosa having previously extracted a 'gastrin-like' substance from a pancreatic tumour in a case of the Zollinger-Ellison syndrome (Gregory, Tracy, French, and Sircus, 1960).

Solcia *et al* (1967) described argyrophil non-enterochromaffin, endocrine-like cells in the gastric antro-pyloric mucosa which they named G cells. Light and electron microscopy provided a sharp distinction of these argyrophil cells from the 5-hydroxytryptamine storing enterochromaffin cells. They observed that the G cells were provided with all the morphological features of protein-secreting cells and appeared to be involved in the secretion of a protein or of a peptide hormone. They proposed the hypothesis that gastrin might be secreted by the G cells and pointed out that the staining and fine structure of the antro-pyloric G cells appeared similar to those found in the gastrin-secreting cells which compose the Zollinger-Ellison tumours of the pancreas as well as in the D cells of the normal pancreatic islets. The following year McGuigan (1968), using an immunofluorescent technique, showed that some cells of the mucosa of the stomach contained gastrin. Bussolati and Pearse (1970), using both immunofluorescent and silver techniques, showed that the cells described by the previous workers were the same.

The tumour we have described consisted of argyrophil but non-argentaffin (non-enterochroma-

ffin) cells which contained gastrin as demonstrated by immunofluorescence, and was associated with high levels of plasma gastrin. It is therefore suggested that it arose from the G cells. Friesen, Bolinger, Pearse, and McGuigan (1970) have reported a decrease in the plasma gastrin levels after total gastrectomy in patients with metastasis from primary gastrin-secreting tumours of the pancreas (but no tumour in the stomach). It is theoretically possible therefore that the high gastrin levels may have been due wholly or in part to a tumour in the pancreas, still undetected; against this is the rapid fall in plasma gastrin level postoperatively compared with the slow decline in the cases reported by Friesen *et al* where tumour tissue was still present.

The tumour infiltrated the tissue of the stomach in the manner of a malignant growth but 15 months later metastasis is not evident. In view of the possibility that metastasis may occur eventually it is intended to repeat plasma gastrin estimations from time to time as an attempt to detect recurrence or metastasis. We are not aware of any previous report of an infiltrative, probably malignant, tumour of the stomach which has been demonstrated to secrete gastrin.

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