II Studies in pernicious anaemia and the Zollinger-Ellison syndrome

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SUMMARY Serum gastrin was measured by radioimmunoassay in four patients with pernicious anaemia and four patients with the Zollinger-Ellison syndrome before and after the intravenous injection of 1 mg glucagon. Serum gastrin fell significantly in the patients with pernicious anaemia whilst in the patients with the Zollinger-Ellison syndrome there was a significant rise. Concomitant measurement of gastric acid output in one subject with the Zollinger-Ellison syndrome also showed a rise in acid output with glucagon.

The reason for the paradoxical rise in gastrin in response to glucagon in the Zollinger-Ellison syndrome is unknown, but the response may provide a further diagnostic aid to this condition.

Part I of this study has shown that glucagon lowers serum gastrin in normal subjects (Hansky, Soveny, and Korman, 1973). It has also been shown that secretin lowers the serum gastrin in patients with pernicious anaemia (Hansky, Korman, Soveny, and St. John, 1971) and sporadic case reports indicate that a paradoxical rise is observed in patients with the Zollinger-Ellison syndrome (Isenberg, Walsh, and Grossman, 1971; Korman, Scott, Hansky, and Wilson, 1972).

To determine whether glucagon injection lowers the hypergastrinaemia of pernicious anaemia and further raises the gastrin level in Zollinger-Ellison syndrome as does secretin, studies were performed in patients with the two diseases.

Material and Methods

Four patients with documented pernicious anaemia and hypergastrinaemia and four patients with proven Zollinger-Ellison syndrome were the basis of this study. The four patients with pernicious anaemia were four females aged between 52 and 78 years; the patients with the Zollinger-Ellison syndrome were two females aged 61 and 82 and two males aged 37 and 62. The males were both studied following total gastrectomy; one female subsequently died from tumour metastasis without active treatment and one female had an intact stomach so that both acid secretory and gastrin data were available after glucagon injection.

After an overnight fast, a 19 gauge court needle was inserted into a forearm vein and kept patent with a solution of 1000 units of heparin in 0·9% sodium chloride. Blood was withdrawn for gastrin estimation 15 minutes and just before the intravenous injection of 1 mg glucagon (Eli Lilly and Co., Indianapolis, USA) and then at five, 10, 15, 20 30, 45, and 60 minutes after injection. Serum gastrin was estimated in a dilution of 1/10 and 1/50 in duplicate by radioimmunoassay (Hansky and Cain, 1969; Hansky, Soveny, and Korman, 1971).

In the patient with the intact stomach and the Zollinger-Ellison syndrome, a nasogastric tube was positioned in the stomach under fluoroscopic control and after a basal hour's aspiration of gastric contents, four 15-minute gastric aspirates were collected after glucagon. Acidity was estimated by electrometric titration to pH 7·0 and acid output calculated from the product of acidity and volume and expressed as milliequivalents per period.

The injection of glucagon produced transient nausea in the patients with pernicious anaemia but this effect was not noted in the Zollinger-Ellison syndrome patients.

Results

PERNICIOUS ANAEMIA

Figure 1 shows the gastrin response to glucagon in all four patients with pernicious anaemia. Results are presented individually because of the wide range of basal levels in the four patients studied. In each there was a marked fall in serum gastrin, the nadir occurring from 15 to 20 minutes after the glucagon, with a fairly rapid return towards basal levels. In no patient did the serum gastrin fall within the range found in a normal control population (0 to 120 pg/ml).

ZOLLINGER-ELLISON SYNDROME

Figure 2 shows the results in three patients with the Zollinger-Ellison syndrome. There was a significant rise in serum gastrin in each patient, the zenith

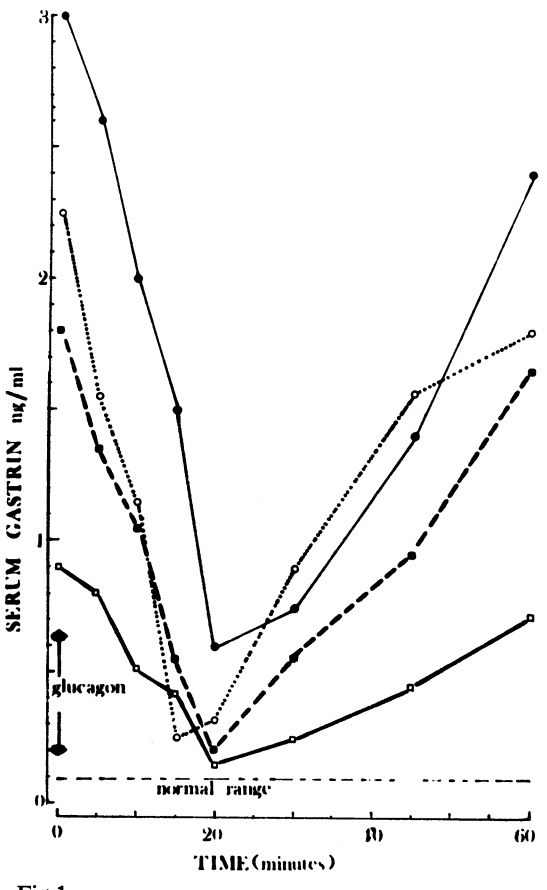

Fig 1

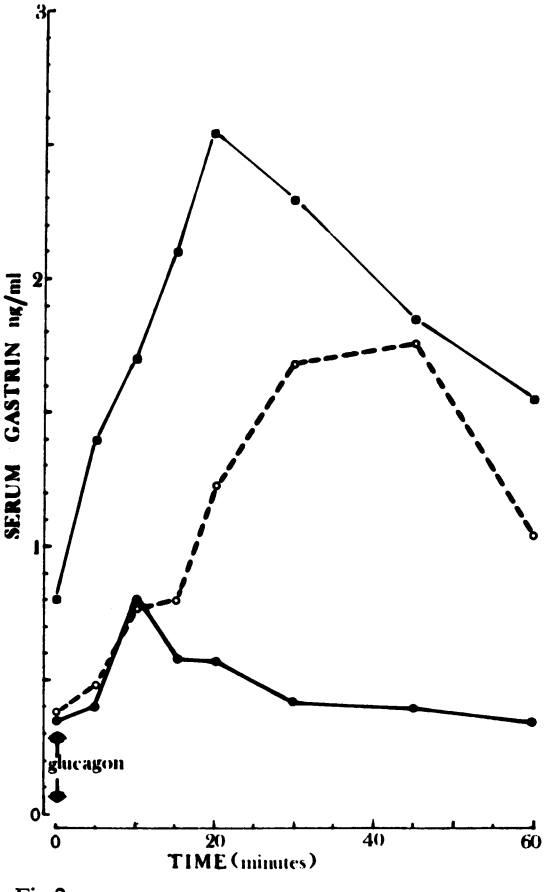

Fig 2

Fig 1 *Serum gastrin after the intravenous injection of 1 mg glucagon in four patients with pernicious anaemia.*

Fig 2 *Serum gastrin after the intravenous injection of 1 mg glucagon in three patients with the Zollinger-Ellison syndrome.*

occurring from 10 to 45 minutes after glucagon and then falling towards basal levels. The fourth patient is not shown on the graph because his gastrin level rose from a basal level of 3·2 ng/ml to a peak of 9·8 ng/ml and was outside the limits of this graph. Figure 3 shows the effect of glucagon on the serum gastrin and gastric acid output in the patient with Zollinger-Ellison syndrome and an intact stomach. There was a rise in both gastrin and acid, the rises occurring almost simultaneously.

Discussion

These studies show that the serum gastrin in response to glucagon injection mirrors that achieved with secretin. Thus gastrin released from the antrum is inhibited (normals and pernicious anaemia) and that released from an islet cell tumour or extraantral source (Zollinger-Ellison syndrome) is stimulated by glucagon. The reason for this paradoxical rise in gastrin in the Zollinger-Ellison syndrome is not apparent. The structural similarity between secretin and glucagon suggests that the mechanism for this paradoxical stimulation of gastrin secretion (and gastric acid secretion) in the Zollinger-Ellison syndrome is identical for both hormones.

Isenberg, Walsh, Passaro, Moore, and Grossman (1972) recently reported a patient with suspected Zollinger-Ellison syndrome whose serum calcium, serum gastrin, and gastric acid secretion increased

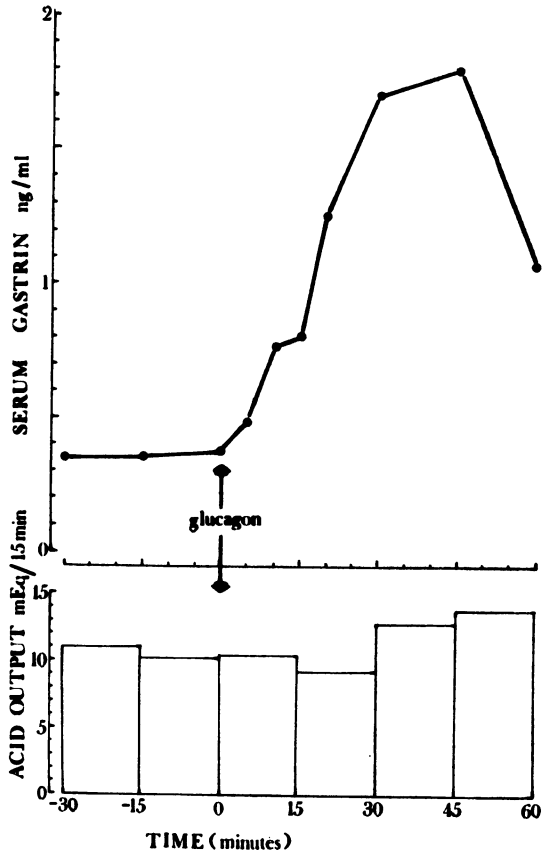

Fig 3 *Serum gastrin and gastric acid response in a patient with the Zollinger-Ellison syndrome to the intravenous injection of 1 mg glucagon.*

following secretin infusion. They postulated that secretin released calcium which further stimulated gastrin release. Trudeau and McGuigan (1969) also showed that calcium infusion raised serum gastrin levels in the Zollinger-Ellison syndrome and so this may be the mode of action of secretin. The present study has not measured calcium levels after glucagon so that further consideration is purely speculative. However, it has recently been shown that glucagon stimulates parathormone release (cited by Isenberg *et al*, 1972) and so this mechanism of stimulation of gastrin release in the Zollinger-Ellison syndrome remains a possibility.

The elevation of serum gastrin after glucagon injection in the Zollinger-Ellison syndrome does, however, add another diagnostic clue to its presence. On the basis of this and previous communications, we would recommend a basal serum gastrin and measurement of gastrin release after secretin and glucagon in the diagnosis of the Zollinger-Ellison syndrome.

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