Islet tumours of the pancreas with intractable diarrhoea

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SYNOPSIS This paper reports the association between severe, prolonged, watery diarrhoea and islet cell tumours of the pancreas. There appear to be significant differences between patients with these symptoms and those with the classical Zollinger-Ellison syndrome.

The association of non-insulin-secreting islet cell tumours of the pancreas with intractable peptic ulceration has been well documented by Zollinger and Ellison (1955) and by Ellison (1956). In their first communication (1955) they reported two such patients, both of whom presented with chronic ulceration of the jejunum. In each patient various surgical procedures, normally judged sufficient to control peptic ulceration, failed to prevent early recurrence. Necropsy in the first revealed a pancreatic islet cell tumour, whereas in the second, at a fifth abdominal exploration for recurrent gastrointestinal ulceration, routine inspection of the abdominal viscera disclosed two nodules in the pancreas; histological examination showed them to be composed of cells other than the B type. In neither patient was there evidence of hyperinsulinism, though in one a glucose tolerance test showed a slight defect.

Since 1955 many more examples of the Zollinger-Ellison syndrome have been reported (Summerskill, 1959; Pender, 1959; Rawson, England, Gillam, French, and Stammers, 1960). Indeed, by 1959 Zollinger and Elliott had collected a total series of 75 patients. The main features of this syndrome are intractable peptic ulceration of the stomach, duodenum, or jejunum, rapid recurrence of ulceration after apparently adequate surgery, a high level of gastric secretion, hypertrophic gastritis, and a non-insulin-secreting islet cell tumour of the pancreas, more commonly malignant than benign. More recently steatorrhoea has been noted (Summerskill, 1959; Maynard and Point, 1958; Rawson et al., 1960).

The first patient described by Zollinger and Ellison also complained of intractable diarrhoea which had begun eight years before the diagnosis of peptic ulceration; the absence of pathogens in the stools, together with the failure of oral antibiotics to control the diarrhoea, lead to an erroneous diagnosis of spastic colitis. Unfortunately this case report does not comment on the further course of the diarrhoea throughout the remaining two years of life which followed the diagnosis of jejunal ulceration; in fact little attention seems to have been paid to this diarrhoea at any point, although it was the patient’s main disability. Forty and Barrett (1952) had previously described a patient with multiple islet cell tumours of the pancreas in whom persistent diarrhoea developed one year before peptic ulceration. Priest and Alexander (1957) reported a patient who, four years before coming under their care, had had a tumour of the body and tail of the pancreas removed. She remained well after this until jaundice developed for which cholecystectomy was performed. In the following year she developed watery diarrhoea; at necropsy several months later an islet cell tumour of the pancreas was found. In this patient there was no history or evidence of peptic ulceration until she was treated by cortisone, after which she developed melaena. Verner and Morrison (1958) described two more patients in whom severe intractable diarrhoea had developed; in each an islet cell tumour of the pancreas was found at necropsy, but in neither was there evidence of associated gastrointestinal ulceration.

In this article a further example of intractable diarrhoea (the daily stool volume being accurately known) associated with a non-insulin-secreting pancreatic tumour is recorded, and the literature is reviewed. We suggest either that peptic ulceration is not necessarily part of the Zollinger-Ellison syndrome, which in any case must be enlarged to include diarrhoea and steatorrhoea, or that the association of intractable diarrhoea, hypokalaemia, hyponatraemia, and islet cell tumours of the pancreas (excluding those arising in the insulin-secreting B cells), constitutes a syndrome entirely distinct from that described by Zollinger and Ellison.
CASE REPORT

On 13 March 1958 a married Jewess, aged 55, was referred with a history of loss of weight, thirst, and frequency of 28 days' duration, and of pruritus vulvae for 10 days. Examination revealed only glycosuria, marked anxiety, and loss of weight. A glucose tolerance test on 18 March confirmed the diagnosis of diabetes mellitus, the blood sugar values being 130 mg. % fasting, and 260, 340, 330, and 260 mg. % respectively. Sugar was present in all urines except the fasting specimen; ketone bodies were absent. Early admission was arranged, but the patient defaulted.

Her previous history was of good general health. In 1940 a right simple mastectomy had been carried out for recurrent abscesses (she was childless). In August 1957 she was very thoroughly investigated by Professor L. N. Pyrah for what appeared to be a left pyelitis with frequency, brief haematuria, and some dysuria. Culture of the urine, cystoscopy, and intravenous pyelography were all negative in September: she was given symptomatic treatment, including a course of oxytetracyclin, and her symptoms disappeared. These three examinations were repeated in December 1957, again with negative findings. During the last four months of 1957 she had had recurrent attacks of diarrhoea, with intervals of complete freedom. The motions varied from three to five a day, and were said to be loose and creamy. The diarrhoea seemed to have begun when she was receiving oxytetracycin, and she received independent treatment for spastic colon.

She was seen again by M.T. on 16 September 1958, this time urgently at her home for gross diarrhoea and loss of weight. It transpired that after she had refused admission for stabilization of her diabetes, diarrhoea returned sharply, and she had seen another consultant who admitted her to hospital. Radiological investigation by barium meal and enema was negative, and the diabetes was said to have been controlled by a Lawrence diet of 12 black and nine red lines. She continued, however, to lose weight, and the diarrhoea soon returned. In June 1958, she sought the advice of a consultant in London, and was in hospital for seven weeks, returning home at the end of August. A barium meal and enema were repeated with negative findings, the diabetes was stabilized by diet and 20 units of Lente insulin daily, and she gained 2 stones in weight. The replacement of Lente insulin by Tolbutamide was followed rapidly by a return of diarrhoea, and she was mildly diarrhoeic at the time of discharge. The alkaline phosphatase was noted to be 67 units. Immediately after her return to Leeds at the end of August, diarrhoea became much worse, and when she was seen at home on 16 September, she was dehydrated, grossly emaciated, and unable to control the almost continuous passage of watery stools into her bed. Her blood pressure was 120/80 mm. Hg, the abdomen flatusent and distended, but examination was otherwise unrewarding. She was admitted to the General Infirmary at Leeds on 17 September.

SUBSEQUENT CLINICAL PROGRESS This may be summed up as a continuous metabolic battle, characterized by slow but relentless clinical deterioration, persistent hypokalaemia and hypotension, ending by death on 16 December in electrolytic chaos, and high-lighted throughout the passage of fantastically large, featureless, watery fluid stools, the daily totals regularly exceeding 4 and 5 litres, and on three occasions 8 litres, the highest being 6,900 ml. Permission for necropsy was refused.

Clinically the main features were steady decline and loss of weight, frequent vomiting, and inerexable dehydration. She was always afebrile, and her pulse rate ran between 72 and 96. No abnormality was ever found in the abdomen, though it was at times 'doughy'. All other systems were always normal. Repeated blood counts showed only haemoconcentration in the early stages, typical findings being, R.B.C.s 5-4 million and Hb 109 %, and in the later, secondary anaemia of the order of Hb 66 % and R.B.C.s 3-3 million. Two barium meals and two barium enemas had been reported normal elsewhere; Professor A. S. Johnstone carried out a barium enema examination in September, and barium meals on the 24 September, 22 October, and 11 November 1958. He found no evidence of peptic ulceration in stomach, duodenum, or jejunum, no sign of fistula formation, and no disease of the colon. The colon was observed to function 'like a large conduit', and some flocculation of the barium was seen in the terminal ileum. Three sigmoidoscopies were negative. Stool examination and culture were repeatedly quite unhelpful, though once Staphylococcus aureus was grown: treatment with erythromycin was rapidly and permanently effective in as much as the stools became negative for staphylococci on culture, but the general course of the illness was not affected. The total plasma proteins and albumin/globulin ratios were normal on five occasions.

The serum electrolytes and plasma CO₂-combining power were estimated on 38 occasions; values for serum sodium ranged from 113 to 139 mEq./l, for serum potassium 2-2 to 3-8 mEq./l, for serum chloride 78 to 100 mEq./l, and for CO₂-combining power 15-5 to 24 mEq./l. Serum calcium and phosphorus were estimated weekly, values for the former ranging from 9-5 to 13-0 and for the latter 0-8 to 2-1 mEq./l respectively. Red cell potassium on 25 November 1958 and 4 December was 86 and 96 mEq./l. The alkaline phosphatase values at approximately weekly intervals were 45, 47, 52, 20, 7, 21, and 18 units.

Certain other investigations were carried out.
1. Faecal fat excretion On 6 October 1958, output, 7% containing 6% split, 1% neutral, fat; on 14 October, intake 150 g. over 72 hours and output 25 g. a day.
2. Hydroxyindole acetic acid excretion On 30 October and 23 November, nil.
3. 17-Ketosteroid excretion 4-8 mg. in 24 hours.
4. Urinary calcium excretion on normal ward diet 310 mg. (volume = 830 ml).
5. Urinary potassium excretion On 27 November, 39 mEq./l.; on 1 December, 7-9 mEq./l.
6. Urinary chloride excretion On 27 November, 58 mEq./l.; on 1 December, 21-4 mEq./l.
7. Tests for arsenic, antimony, mercury, copper, lead, zinc, and thallium poisoning were negative.
8. An E.C.G. on 20 November showed changes...
FIG. 1. Tumour cells forming papillary processes, islets, and strands in a partly hyaline stroma. The tumour cells are deeply stained with regular nuclei; the staining reaction of the intracellular granules suggests that the cells are of alpha type (haematoxylin and eosin × 300).

consistent with hypokalaemia, which had disappeared on 29 November.

9 On 18 October carmine appeared in the stools six hours after a capsule had been given orally.

TREATMENT The diabetes was always easily controlled by a 12 black and eight red line diet, and some 20 units of Lente insulin daily. It was noted that whenever metabolic control improved the number of daily motions fell, though the total volume remained unchanged.

The persistent loss of fluid, sodium, and potassium was corrected by daily oral or parenteral replacement, regularly reaching a maximum of 5 litres and as much as 6 g. of KCl or KHCO₃. Despite this it was only with difficulty that hypokalaemia and dehydration could be avoided. Symptomatic treatment of the diarrhoea with a gluten-free diet, salazopyrine, and antispasmodics such as Probanthine, was completely ineffective. Prednisolone, 10 mg., t.d.s., and later cortisone, 50 mg., b.d. increasing to 50 mg., six hourly, produced no appreciable diminution in the volume of faeces. In the course of her steroid therapy, she had a small haematemesis on the 5th and 11th November, the cause being uncertain. No transfusion was needed.

On 5 December her condition had improved sufficiently to allow Mr. A. J. C. Latchmore to carry out a long-awaited laparotomy. The only abnormality was a large and obviously malignant growth involving the body and tail of the pancreas; the growth was extremely soft and vascular, and inoperable. There was no evidence of peptic ulceration. A biopsy was taken, and Dr. T. W. Sutherland reported as follows:—

'The biopsy material was stained by haematoxylin-eosin, phosphotungsic acid haematoxylin, Masson’s tri-chrome stain, and Gomori’s chrome-alum haematoxylin. Microscopically columnar and polyhedral epithelial cells form slender strands intermingled with densely hyaline stroma. In some parts the appearances suggest an adenopapillary pattern. Gomori’s stain reveals red granules in most of the cells. The findings indicate that this is an adenocarcinoma (Fig. 1) of low-grade malignancy arising in the alpha or delta cells of the Islets of Langerhans'.

DISCUSSION

Verner and Morrison (1958) noticed particularly the refractory watery diarrhoea in their two patients,
and were able to collect from the literature seven further patients. In five of these the diarrhoea pre-
ceded the symptoms of peptic ulcer by many years, a point noted originally by Zollinger and Ellison
(1955), later by Donaldson, vom Eigen, and Dwight (1957), Maynard and Point (1958), Summerskill
(1959), and Rawson et al. (1960). The association of steatorrhoea with the Zollinger-Ellison syndrome
has been recorded by Maynard and Point (1958), Summerskill (1959), and Rawson et al. (1960). The
most acceptable explanation is incomplete neutraliza-
tion of the large amount of HCl by pancreatic bicarbonate in the small bowel, the low pH im-
pairing emulsification and lipolysis.

We suggest that non-insulin-secreting islet cell
tumours of the pancreas may be responsible for
more than one clinical syndrome. It is clear that
profuse intractable watery diarrhoea, hypokalaemia,
and hyponatraemia are associated with such pan-
creatic islet cell tumours, that peptic ulceration may
either never develop or that many years may elapse
before it finally appears. Table I summarizes 11
case histories, 10 previously recorded and the present
one. There seems no doubt that clinicians generally
are not fully aware of the association of intractable
diarrhoea and islet cell tumours of the pancreas:
few examples so far have been recorded.

Only four of the 10 patients in Table I developed
peptic ulceration, and in each it had been preceded
by a long period of diarrhoea; in one it was terminal.
This is very different from the Zollinger-Ellison
syndrome, as generally defined, in which peptic
ulceration and gastric hypersecretion appear early
and are the dominant features. The absence of
peptic ulceration in seven, and its late appearance in
four, of the patients in Table I, certainly suggest that
excessive acid secretion was not the prime
cause in these 11 patients. It is true that in only a few
of the cases reports the degree of gastric hypersecretion
have been measured (Zollinger and Ellison, 1955;
Donaldson et al., 1957; Maynard and Point, 1958;
Summerskill, 1959; Rawson et al., 1960). A further
difficulty is the absence of precise analysis of the
faecal discharge; we have been able to discover no
report of the electrolytic composition of the faeces,
and only in one patient (Rawson et al., 1960) has
the faecal volume been measured. On the other
hand removal of the tumour in one patient (Brown,
Neville, and Hazard, 1950) relieved the diarrhoea.
Improvement occurred in Pender's (1959) patient
after removal of a pancreatic islet cell tumour, but
the most successful result is that described by
Rawson et al. (1960) in whose patient removal of
the tumour produced complete relief of symptoms
and reduced the excessive secretion of acid by the
stomach.

The mechanism of the severe faecal loss, which in
our patient varied from 1,750 to 6,900 ml daily,
must clearly be caused in one of two ways; failure of
the absorptive mechanism of the gastrointestinal
tract, or increased output of fluid and electrolytes
by the gastrointestinal tract. Since a terminal
ileostomy normally discharges less than 1 litre of
fluid daily which is isotonic with plasma (Smiddy,
Smith, Gregory, and Goligher, 1960), it appears
most likely that the mechanism involved is over-
secretion and hurry. This hypothesis is substantiated
by two further facts: first, in five of the 11 patients
fat balance studies were made; one had steatorrhoea,
but in four normal or near-normal values of faecal
fat excretion were found, thus suggesting that the
absorptive capacity of the small bowel was essentially
normal; secondly, though cortisone normally lowers
the fluid output of the small bowel as a result of
increased absorption of water and sodium (Smiddy
et al., 1960), in our patient 200 mg. of cortisone
daily produced no diminution in the faecal loss. The
possibility also arose that this patient was suffering
from hypercatabolic hypoproteinaemia, in which
condition diarrhoea has occasionally been reported
(Schwartz and Jarnum, 1959), but oedema was never
observed and the serum protein levels remained
within normal limits throughout.

It is unfortunate that the histological studies of all
the tumours so far reported are of little help, because
the methods used failed to identify the various islet
cell types (Gomori, 1941). Even in the patient
described by Rawson et al. (1960) the results were
equivocal despite the most modern techniques. The
most that can be said from all the reports, including
our own, is that the islet cell tumours are not of the
insulin-secreting B cell type. Our patient appears to
be alone in having proven diabetes in addition.

Solitary tumours were present in nine, and multiple
adenomata in two, patients (Table I); five were
benign, four malignant, and in two patients the
nature of the tissue is not stated. Lymph node
metastases were present in one. The proportion of
malignant tumours in these 11 patients is much
lower than Ellison's (1956) series of 24, of which 19
were malignant. The rate of growth varies con-
siderably; the tumours may remain small, and in
three patients were not found at laparotomy. Where
excision has been successful, the clinical results
appear so far to be good (Brown et al., 1950;
Rawson et al., 1960).

The clinical picture of the 11 patients set out in
Table I differs significantly from that described by
Zollinger and Ellison in four main respects; profuse
intractable watery diarrhoea is present for several
years; hypokalaemia develops concurrently, and is
the commonest mode of death (six of 11 patients);
<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age</th>
<th>Presenting Symptoms</th>
<th>Duration of History</th>
<th>Previous Operation</th>
<th>Hypokalaemia</th>
<th>Peptic Ulceration</th>
<th>Fat Absorption</th>
<th>Laparotomy</th>
<th>Cause of Death</th>
<th>Necropsy</th>
<th>Cell Type</th>
<th>Nature of Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zollinger and Ellison (1955)</td>
<td>F</td>
<td>36</td>
<td>Diarrhoea, loss of weight</td>
<td>8 yr.</td>
<td>No</td>
<td>Suspected on clinical history given</td>
<td>Developed after 5 yr.</td>
<td>Not investigated</td>
<td>Jejunal ulcer</td>
<td>Duodeno-oesophago-cutaneous fistula</td>
<td>Islet cell tumour (small)</td>
<td>Unknown</td>
<td>Benign</td>
</tr>
<tr>
<td>Moldawer et al. (1954)</td>
<td>F</td>
<td>57</td>
<td>Diarrhoea, loss of weight</td>
<td>4 yr.</td>
<td>No</td>
<td>Renal tubular changes found at necropsy suggested long-standing hypokalaemia</td>
<td>Absent</td>
<td>Normal</td>
<td>Not done</td>
<td>Hypokalaemia</td>
<td>Islet cell tumour (large)</td>
<td>Unknown</td>
<td>Benign</td>
</tr>
<tr>
<td>Priest and Alexander (1957)</td>
<td>F</td>
<td>56</td>
<td>Diarrhoea, loss of weight</td>
<td>6 mth.</td>
<td>Excision of neoplasm</td>
<td>Proved</td>
<td>Absent but gastric ulcer developed during steroid therapy</td>
<td>Normal</td>
<td>Negative</td>
<td>Hypokalaemia</td>
<td>Islet cell tumours (small)</td>
<td>Unknown</td>
<td>Not staged probably malignant</td>
</tr>
<tr>
<td>Donaldson et al. (1957)</td>
<td>M</td>
<td>35</td>
<td>Diarrhoea, tetany, hyperchloroaemic alkalosis</td>
<td>2 yr.</td>
<td>No</td>
<td>Proved</td>
<td>Perforated jejunal ulcer</td>
<td>Normal</td>
<td>Perforated jejunal ulcer with peritonitis</td>
<td>Hypokalaemia + peritonitis</td>
<td>4 peptic ulcers, 2 islet cell tumours</td>
<td>Unknown</td>
<td>Malignant</td>
</tr>
<tr>
<td>Forty and Barrett (1952)</td>
<td>F</td>
<td>55</td>
<td>Diarrhoea, loss of weight, recurrent epigastric pain</td>
<td>3 yr.</td>
<td>No</td>
<td>Not investigated</td>
<td>Associated ulcer 3rd part of duodenum</td>
<td>Not investigated</td>
<td>Perforation of recurrent ulcer post-operatively</td>
<td>Hypokalaemia</td>
<td>2 islet cell tumours, ulceration of jejunal opposite gastrojejunal stoma</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Brown et al. (1950)</td>
<td>F</td>
<td>74</td>
<td>Diarrhoea, loss of weight</td>
<td>4 mth.</td>
<td>No</td>
<td>Not investigated</td>
<td>Absent</td>
<td>Not investigated</td>
<td>Tumour of pancreas</td>
<td>Survived; after resection of pancreas, diarrhoea subsided</td>
<td>Islet cell tumour (large)</td>
<td>a - cell</td>
<td>Benign</td>
</tr>
<tr>
<td>Verner and Morrison (1958)</td>
<td>M</td>
<td>67</td>
<td>Diarrhoea, loss of weight</td>
<td>10 mth.</td>
<td>No</td>
<td>Proved</td>
<td>Absent</td>
<td>Normal</td>
<td>Not done</td>
<td>Hypokalaemia</td>
<td>Medium islet cell tumour, chromophobe adenoma of pituitary</td>
<td>Unknown</td>
<td>Benign</td>
</tr>
<tr>
<td>Verner and Morrison (1958)</td>
<td>M</td>
<td>19</td>
<td>Diarrhoea, loss of weight</td>
<td>3 yr.</td>
<td>Exploration of para-thyroids</td>
<td>Proved</td>
<td>Absent</td>
<td>Normal</td>
<td>Not done</td>
<td>Hypokalaemia</td>
<td>Islet cell tumour (? size)</td>
<td>Not b cell</td>
<td>Benign</td>
</tr>
<tr>
<td>Gordon and Olivetti (1947)</td>
<td>M</td>
<td>26</td>
<td>Diarrhoea, loss of weight, acute onset of upper abdominal pain</td>
<td>1 yr.</td>
<td>No</td>
<td>Not proven, complained of progressive weakness</td>
<td>Perforated oesophageal ulcer after 1 yr. associated with 3 chronic duodenal ulcers</td>
<td>Not investigated</td>
<td>Jejunostomy only</td>
<td>Perforated oesophageal ulcer</td>
<td>Multiple pancreatic tumour and adrenal cortical adenomata</td>
<td>Unknown</td>
<td>Malignant</td>
</tr>
<tr>
<td>Smiddy and Telling (1961)</td>
<td>F</td>
<td>47</td>
<td>Diarrhoea, loss of weight</td>
<td>13 mth.</td>
<td>No</td>
<td>Proved</td>
<td>No ulcer at operation, haematemesis during steroid therapy</td>
<td>Slight</td>
<td>Tumour of pancreas</td>
<td>Hypokalaemia</td>
<td>Not done</td>
<td>d - cells</td>
<td>Malignant</td>
</tr>
<tr>
<td>Maynard and Point (1958)</td>
<td>M</td>
<td>53</td>
<td>Diarrhoea, loss of weight, abdominal pain</td>
<td>4 yr.</td>
<td>None for relevant condition, appendicectomy, cholecystectomy</td>
<td>Not proved, 'non-tropical sprue' diagnosed</td>
<td>Absent</td>
<td>Gross, diagnosed as 'non-tropical sprue'</td>
<td>Large tumour of pancreas, no ulceration found at 2 laparotomies</td>
<td>Malignant cachexia and vomiting</td>
<td>Multiple terminal jejunal ulcers (one had perforated)</td>
<td>Carcinoma of islets of Langerhans</td>
<td>Malignant</td>
</tr>
</tbody>
</table>
Islet tumours of the pancreas with intractable diarrhoea

In this paper we have stressed the association between severe watery diarrhoea and islet cell tumours of the pancreas. The clinical picture of this syndrome appears to differ sharply from that of the classical Zollinger and Ellison syndrome in that the clinical course of the disease is prolonged, is dominated by diarrhoea with an attendant severe hypokalaemia, and there is no or very late peptic ulceration. In addition, in the majority of patients there is no steatorrhoea and a lower incidence of malignancy. Comparison, therefore, of these two syndromes suggests that there may be two different types of non-insulin-secreting islet cell tumours but this hypothesis cannot be substantiated in the absence of clear histological methods of differentiating between islet cell types.

We are indebted to Dr. F. M. Parsons, Assistant Director of the M.R.C. Unit, for his help in the control of the electrolyte disturbances, and to the nursing staff for their unfailing care and skill.

REFERENCES


