MULTIPLE ENDOCRINE ADENOMA SYNDROME*

BY

W. T. COOKE, D. I. FOWLER, R. GADDIE, E. V. COX, M. J. MEYNELL, and D. BREWER

From the General Hospital, Birmingham

The case history of a 40-year-old woman with a fatal haemorrhage from a duodenal ulcer, jejunitis, renal lithiasis, hypertrophy of the adrenal glands, multiple adenomas of the pancreas, and three adenomas of both the parathyroid and pituitary glands is reported. Though there was histological evidence, in the bones, of hyperparathyroidism, the serum levels of calcium, phosphorus, and phosphatase and the urinary excretion of calcium were normal.

The significance of low calcium and high phosphorus excretion in the urine as an indication of parathyroid disorder is discussed.

“Multiple endocrine adenoma syndrome” is suggested as the appropriate designation for the clinical disorders in which adenomas of one or more endocrine glands are associated with disorders of the alimentary tract when patients present with recurrent peptic ulceration, pancreatic dysfunction, or watery diarrhoea.

During the past 20 years there have been an increasing number of reports of the occurrence of adenomas of one or more of the endocrine glands and disturbances of the alimentary tract. Reviews of the reported patients have been made, amongst others, by Moldawer, Nardi, and Raker (1954), Ellison (1956), and Donaldson, Vom Eigen, and Dwight (1957). In general, the clinical manifestations present in three ways, gastric hypersecretion and recurrent peptic ulceration often in unusual sites, pancreatitis and pancreatic lithiasis, and persistent watery diarrhoea. The group presenting with peptic ulceration has perhaps gained most prominence as the Zollinger-Ellison syndrome of a non-insulin secreting adenoma of the pancreas and recurrent peptic ulceration. The anatomical findings, however, in all three clinical groups overlap to a considerable extent and the presence of adenomas in many endocrine glands is common. Few patients have been diagnosed accurately during life even with surgical exploration of the abdomen.

The following case report emphasizes the diagnostic difficulties and afforded an opportunity to review our methods of diagnosis with particular reference to the presence of a parathyroid adenoma.

CASE REPORT

Mrs. J., aged 38, was first seen on July 27, 1956, on account of loss of weight and a recent attack of renal colic. Though she had had an episode of severe epigastric pain 10 years previously, she had been well until two years previously when she had begun to pass two loose stools daily. About the same time, she had had her first attack of renal colic; in all she had four such episodes of renal colic during the next two years. Six months previously, after her second pregnancy, her stools had become more frequent—five or six times a day—pale and often watery. During these two years, she had lost 22 lb. in weight. Physical examination showed no significant features beyond mild finger clubbing. Her blood pressure was 120/80 mm. Hg. Investigations showed marked proteinuria and a heavy urinary infection with B. proteus. An intravenous pyelogram was normal but there were a number of calcified opacities anterior and in the region of the tail of the pancreas. A glucose tolerance test showed a fasting blood sugar level of 75 mg./100 ml. rising to 215 mg. at 30 min. and returning to fasting levels in two hours. A diagnosis of chronic pyelonephritis and chronic pancreatitis with probable pancreatic lithiasis was made. The urinary infection responded to antibiotic therapy and the diarrhoea was controlled with pancreatin.

The patient was seen regularly. She continued, however, to lose weight and suffered two severe attacks of epigastric pain radiating through between the shoulder blades. She vomited on a number of occasions and epigastric discomfort became more persistent, necessitating admission to hospital for further investigation.

FIRST HOSPITAL ADMISSION.—The patient was first admitted on July 12, 1957. The physical findings were unchanged. Investigations revealed a normal blood count: R.B.C.s 5.3 x 10^6, haemoglobin 15.9 g. %, W.B.C.s 11,500 with P.C.V. 48 % and M.C.V. 89 c.u.,
M.C.H.C. 33%. The blood urea level was 29 mg./100 ml.; sodium 142, potassium 4.0, chloride 110, and CO₂ 26.5 mEq/litre; albumin 3.4 g./100 ml., globulin 2.1 g./100 ml., calcium 10.6 mg./100 ml., phosphorus 2.8 mg./100 ml., and alkaline phosphatase 12 units. Serum amylase was 144 units. Faecal fat excretion over 19 days averaged 19 g. per day, varying from 9.4 to 30.6 g. X-ray examination of the stomach and small intestine revealed an excess of resting juice and coarse, widened folds in the duodenum and jejunum. An intravenous pyelogram showed a staghorn calculus in the left kidney. X-ray examination of the skull and pituitary fossa was normal. Questionable demineralization of the thoracic and lumbar spine was reported. Radiology of the hands was normal.

Four determinations of the serum calcium varied between 10.1 and 10.6 mg./100 ml. and that of phosphorus between 2.3 and 3.6 mg. per 100 ml. A tentative diagnosis of hyperparathyroidism, chronic pancreatitis, chronic jejunitis, and renal lithiasis was made. Balance studies after a preliminary period of one week on a diet containing 125 mg. calcium and 603 mg. phosphorus per day revealed over six days a daily urinary excretion of 75 mg. calcium and 660 mg. phosphorus per day. Faecal fat excretion during this period was 19 g. per day. In view of the low urinary calcium excretion and levels of serum calcium and phosphorus which were not obviously abnormal, the diagnosis of hyperparathyroidism was considered to be ill founded. She was discharged, taking antacids, pancreatic, and probanthine, to be reviewed frequently as an out-patient. She remained well for four months but the epigastric pain returned, radiating through to the back, relieved occasionally by food or alkalies; it was much worse at night. Admission was arranged in order to carry out an exploratory laparotomy to exclude a pancreatic adenoma.

Second Hospital Admission.—This was on February 28, 1958. Physical examination revealed no new features except increased clubbing of the fingers and toes. The blood count was 4,190 x 10⁶ red cells, 12.3 g.% Hb, and 15,600 leucocytes (11,500 polymorphonuclears). The day after admission she vomited 200 ml. blood and despite blood transfusions continued to show signs of intestinal haemorrhage. Laparotomy was carried out on March 3, 1958. The body and tail of the pancreas were macroscopically normal. In the second part of the duodenum was a large ulcer on the posterior wall and several “glands” behind the head of the pancreas. The wall of the duodenum and jejunum was thickened with induration and inflammation of the upper jejunum. It proved impossible to ligate the bleeding point directly, and the pylorus, therefore, was divided and occluded with a gastrojejunostomy below the level of the affected bowel. The operation was temporarily successful in controlling the haemorrhage, but 36 hours later she collapsed and, despite transfusion with 13 pints of blood, she continued to have haematemesis and melaena. She died on March 6.

Post-mortem examination showed no abnormality in the heart or lungs. There was a large transverse ulcer, 5 cm. x 2 cm., about 4 cm. proximal to the ampulla of
FIG. 3.—Bone showing two areas of osteoclastic absorption and early fibrosis. Haematoxylin and eosin × 150.

FIG. 4.—Tumour behind the head of the pancreas. An islet tumour with surrounding remnant of lymph node. Haematoxylin and eosin × 100.

FIG. 5.—Two small islet adenomas. Haematoxylin and eosin × 100.

FIG. 6.—Pancreatic duct showing marked hyperplasia with many newly formed small ducts. Haematoxylin and eosin × 100.
Vater with blood clot firmly adherent to the base (Fig. 1). The mucosa of the stomach, despite great distension with blood, showed thickening and mammillation. In the ileum, there were several areas of slight narrowing with some fibrous thickening of the peritoneum; the mucosa was normal. The pancreas appeared normal in size and appearance but there was a tumour, 2 x 3 cm., behind and lateral to the duodenum adjacent to the head of the pancreas. The liver showed mild fatty change. The left kidney contained a large staghorn calculus. The thyroid gland was normal. Three parathyroid tumours, 2 x 1, 1.5 x 0.3, and 2.5 x 1 x 0.5 cm., in size (Fig. 2) were identified. The suprarenals showed moderate diffuse hyperplasia (21g). The pituitary was macroscopically normal. The skeleton was not obviously softened.

HISTOLOGY.—All bones examined showed small areas of osteoclastic reabsorption and fibrosis (Fig. 3) with a few areas of striking intratrabecular reabsorption. Three parathyroids consisted of clear cells with small areas of oxyphil cells and were adenomata with normal glands attached to each. The pituitary (examined completely by serial sections) contained three microscopic chromophobe adenomata with varying amounts of hyaline stroma. The ulcer of the duodenum was eroding the muscle coats and penetrating the pancreas. The small intestine showed mild non-specific chronic inflammation. The adrenals showed a thickened hyperplastic cortex containing a large amount of sudanophil birefringent fat. The tumour adjacent to the head of the pancreas was a large islet tumour apparently involving a lymph node (Fig. 4). Of the 14 blocks cut through the pancreas only three were normal. Numerous small islet tumours of varying sizes were present in the remainder (Fig. 5) with differing degrees of fibrous atrophy, ductal proliferation (Fig. 6), and dilatation.

COMMENT

The finding of an abnormal gastric mucosa recalls the observation of Kenney, Dockerty, and Waugh (1954) that 10-15% of patients with giant rugae have endocrine adenomas. The finding of multiple adenomas in the pancreas was disquieting since it had been examined specifically with this possibility in mind both at laparotomy and at necropsy and pronounced macroscopically normal by two experienced workers.

The extrapancreatic tumour was thought to be a lymph gland at operation and was so confirmed at necropsy though it was completely replaced by tumour tissue. A somewhat similar difficulty was noted by Zubrod (1958).

Renal lithiasis, pancreatic dysfunction, and jejunitis caused us to suspect the presence of a parathyroid adenoma, but the significance of the gastric hypersecretion shown radiologically and jejunitis did not lead the diagnosis of pancreatic adenoma to be seriously considered until the investigations for hyperparathyroidism were apparently indecisive. The presence, therefore, of three large parathyroid adenomas with little evidence of bone disorder or upset blood chemistry was surprising. In particular the low urinary excretion of calcium was unexpected, though Gross (1958) has recorded a similar low calcium output in a patient with a parathyroid adenoma and pancreatic lithiasis.

Reviewing the calcium and phosphorus balances carried out at this hospital on a calcium intake of 125 mg./day and phosphorus of 620 mg./day showed that the increased phosphorus urinary excretion above 550 mg. may have diagnostic significance. Amongst the patients studied were four patients with pancreatic lithiasis, three of whom had marked steatorrhoea. Two of these had had a parathyroid adenoma removed; one had completely normal excretions, but in the other phosphorus excretion was 550 mg./24 h. The third had no steatorrhoea but normal calcium and phosphorus urinary excretions. The fourth, a man aged 45, had had pancreatic lithiasis since the age of 30, renal lithiasis for five years, diabetes for three, radiological evidence of jejunitis and normal calcium, phosphorus, and phosphatase values in the blood. The urinary calcium and phosphorus excretions were essentially similar to those found in the patient reported above (Ca 69 mg./24 hr., P 740 mg./24 hr.). Exploration of the parathyroids revealed an adenoma.

Accurate balance studies are time consuming and difficult. In our experience, the results of calcium infusion tests and the determination of the creatinine-phosphorus excretion ratios have not been helpful. Preliminary observations suggest that measurement of the diffusible calcium in the serum may be of value. In a further patient, a man aged 54, with pancreatic adenoma, severe diarrhoea and gastric hypersecretion and with normal calcium and phosphorus values in the serum, the diffusible calcium was significantly raised at 6.9 mg./100 ml. of ultrafiltrate, a finding of diagnostic significance for hyperparathyroidism according to Lloyd and Rose (1958).

DISCUSSION

This case throws little light on the aetiology of the peptic ulceration and adenoma formation but it does underline the likelihood that more than one endocrine gland is involved when a patient presents with recurrent peptic ulceration, pancreatic dysfunction, or watery diarrhoea. The multiple endocrine adenoma syndrome would, therefore, seem to be an apt diagnostic label for all this group. As to the aetiology of the syndrome, it seems unlikely that it is dependent upon a primary pituitary
upset since at present there is no proven pancreatic or parathyroid tropic hormone of the pituitary. Wermer (1954, 1958) postulates that some factor, presumably chemical, which is responsible for the orderly development of the pituitary, parathyroids, and pancreas at an early stage of embryonic life, is absent. A tendency to familial incidence in some of the reported examples is in favour of such speculation. It is evident that much remains to be learnt about these conditions but it is to be hoped they may provide some new clue as to the causation of some common disorders of the alimentary tract.

REFERENCES