MULTIPLE ENDOCRINE ADENOMATA WITH PITUITARY FAILURE AFTER HAEMATEMESIS

BY

J. P. DUFFY, M.D., M.R.C.P., M.R.C.P.I.

*Registrar, Cardiac Department, London Chest Hospital;
Formerly Medical Registrar, Chase Farm Hospital, Enfield*

In the curious polyglandular syndrome adenomata occur in several endocrine glands. A case may present with hyperinsulinism, hyperparathyroidism, or evidence of over- or under-activity of the pituitary. Sometimes a pituitary tumour presents as acromegaly, but more often there is a slowly developing insufficiency of the gland. When the adenoma outstrips its own delicate blood-supply spontaneous necrosis may precipitate pituitary failure, so-called pituitary apoplexy (Jefferson and Rosenthal, 1959; Pieper and Ryan, 1961). Severe peptic ulceration is also a constant feature; when in the case described below this was complicated by massive haemorrhage overt hypopituitarism was precipitated, analogous to that which follows post-partum haemorrhage (Sheehan, 1937; Sheehan and Murdock, 1938).

Case Report

An unmarried woman schoolteacher aged 68 developed severe left loin pain in 1956. Excretion and retrograde pyelography showed one large and two small calculi in the upper pole of the left kidney. These were removed by partial nephrectomy. The wound was slow to heal, and a persistent normochromic anaemia developed which was not permanently influenced by iron pills or transfusion. The plasma calcium was 10.8 mg./100 ml. and the haemoglobin 8 to 9 g./100 ml. The house-surgeon commented that her pallor was disproportionate to the anaemia. She was then alert, vivacious, and energetic. She insisted on resuming teaching, at which she is said to have excelled. The haemoglobin never rose above 11 g./100 ml.

In 1958 she had slight bilateral ankle oedema. The blood urea was 86 mg./100 ml.; haemoglobin 10.4 g./100 ml.; white cell count 6,500/c.mm. (differential count normal). E.S.R. (Westergren) was 45 mm. in the first hour. Excretion pyelography was normal apart from evidence of resection of the upper pole of the left kidney.

In 1959 she complained of dyspepsia, but a barium-meal examination revealed nothing abnormal.

In March, 1960, she was admitted to hospital with crushing substernal pain. Signs of acute pericarditis with effusion and a right pleural effusion were found. The pleural fluid proved to be a straw-coloured sterile exudate. The initial blood urea was 177 mg./100 ml., settling to 100 mg./100 ml. later. Haemoglobin ranged from 7.5 to 11 g./100 ml. Absolute indices and blood-film appearances were those of a microcytic slightly hypochromic anaemia. Plasma electrolytes were normal. L.E. cells were not found in the peripheral blood. With nursing care and haematinics she slowly improved. The heart shadow returned to normal size, the pleural effusion cleared, and the E.C.G. reverted to normal. She was now the life and soul of the ward. When presented at a clinical meeting as a diagnostic dilemma she greatly amused the doctors with a witty, forthright history. Despite the anaemia and chronic uraemia she resumed work.

Ulcer-type dyspepsia became a prominent complaint, and in July, 1960, she was readmitted to hospital in a very weak condition with severe indigestion. Her haemoglobin was 7 g./100 ml. While being transfused she collapsed with a massive haematemesis and melaena. The blood-pressure became unrecordable. After urgent resuscitation, emergency laparotomy was done and a chronic duodenal ulcer with a

bleeding gastro-duodenal artery in its base was found. Partial gastrectomy was performed. Despite injections of mephentermine sulphate, hypotension persisted for 48 hours post-operatively. Blood transfusions were given at intervals for the anaemia. Recovery was very slow and she was still very weak when she was discharged from hospital on September 24, 1960.

Her friends now noticed a complete change in her disposition. There was progressive mental slowing, forgetfulness, and loss of energy. The flash of her mind had gone and she slept for long periods without disturbing the bedclothes. Her skin became dry and scaly and the hairdresser commented on her dry falling hair. Her hearing was impaired and her dentures became loose. During 1961 her general practitioner was called to see her on three occasions when she passed into coma and appeared to be dying. Each time she slowly recovered. Once when a short course of betamethasone was given for an urticarial reaction a transient dramatic improvement ensued. Finally, in January, 1962, when persistent drowsiness and listlessness developed, she was again admitted to hospital.

She presented a classical picture of panhypopituitarism. There was general wasting and absence of body hair. The skin was pale, fine, and translucent. The scalp hair was dry and brittle, with frontal balding. The eyebrows were thin, the eyeballs sunken and lustreless. Rectal temperature was 93° F. (33.3° C.), pulse rate 76/minute, and blood-pressure 110/70. Despite moderate bilateral ankle oedema there was no evidence of cardiac failure. There was marked somnolence progressing to semicoma. The visual fields were later assessed by confrontation and they appeared to be normal. The optic fundi were normal and no abnormal neurological signs were detected.

Investigations.—These were limited by her poor condition. Twelve-hour fasting blood sugar, 50 mg./100 ml.; blood urea, 113 mg./100 ml.; plasma sodium, 139 mEq./l.; plasma potassium, 4 mEq./l.; plasma chlorides, 105 mEq./l.; plasma calcium, 5.7 mEq./l. (11.4 mg./100 ml.); plasma inorganic phosphate, 2.7 mEq./l. (4.6 mg./100 ml.); plasma alkali reserve, 14.4 mEq./l.; plasma cholesterol, 144 mg./100 ml.; haemoglobin, 7.5 g./100 ml., with evidence of normocytic normochromic anaemia; serum protein-bound iodine, 4.9 µg./100 ml.; 24-hour urinary volume, 405 ml.; urine creatinine, 0.34 g./24 hours; total 17-OH-corticosteroid excretion, 1.7 mg./24 hours (normal 6–16 mg./24 hours); neutral 17-ketosteroid excretion, 1.1 mg./24 hours (normal 2.5–8 mg./24 hours). E.C.G. was normal. The skull x-ray examination showed an enlarged sella turcica, erosion of the dorsum sellae, with an intrasellar ring of calcium and flecks of calcification in the suprasellar region. No radiological evidence of hyperparathyroidism was found in the skull, chest, spine, or hands.

The association of renal calculi, chronic peptic ulceration, and a pituitary adenoma indicated that this was a case of the polyglandular syndrome.

Substitution therapy was quickly begun with tablets of cortisone and L-thyroxine. She also received vitamins and anabolic agents. Marked improvement followed and she was soon sitting up, conversing sensibly. She celebrated her 75th birthday with some zest, but the same evening she became confused and later comatose. A blood-sugar estimation was 76 mg./100 ml. and the rectal temperature was 97° F. (36.1° C.). She slowly improved over the next 24 hours after intravenous infusions of 5% dextrose and hydrocortisone. Further attacks of coma supervened despite normal blood sugar, blood electrolytes, and body temperature. There was now no real response to intravenous dextrose and hydrocortisone. She aspirated vomitus and died on February 23.

Necropsy

A large pituitary adenoma measuring 2.5 cm. in its longest axis was found. It had eroded the posterior clinoid processes, projecting backwards and downwards compressing the mid-brain and pons. The tumour completely replaced

the anterior pituitary. It was soft, weighed 4 g., and presented cystic necrotic areas. There was a left parathyroid adenoma the size of a marble, and it weighed 2.35 g. The thyroid was atrophic and weighed 16.2 g. The pancreas was hard and nodular, with a swelling the size of a golf ball in the head of the gland. There was atrophy of the ovaries and adrenals, the combined weight of the latter being 6.2 g. The upper part of the left kidney had been removed. The renal capsules were adherent and the interlobular vessels were prominent. Nephrocalcinosis could be seen as white streaking in the medulla of both kidneys, but there was no further stone-formation. The gall-bladder was thickened, and contracted down on a single pigment stone. The gastric mucosa was hypertrophic and a shallow healing ulcer was present proximal to the gastro-jejunal anastomosis. Much gastric content was present in the air-passages and there was basal pulmonary oedema. The pericardial sac was obliterated; the heart was normal in size, but it showed severe brown atrophy.

Histology.—The pituitary tumour was a chromophobe adenoma and that of the parathyroid a chief-cell adenoma. The pancreas showed a remarkable picture of proliferation of all islet-cell tissue with many large adenomata. Examination of excised ribs revealed evidence of hyperparathyroidism. Areas of tubular calcinosis with alternating zones of glomerular obliteration and hypertrophy were seen in the kidneys. The overall picture was one of chronic pyelonephritis and calcium deposition.

Discussion

The pituitary gland, placed as it is in a rigid bony cave, with a delicate double portal blood system, is in considerable jeopardy when the intrasellar volume is increased by neoplasm or hyperplasia. Severe circulatory shock can then lead to necrosis. In the poly-endocrine syndrome, with a pituitary adenoma and pernicious peptic ulceration, the situation is ripe for catastrophe as severe gastro-intestinal haemorrhage may occur especially in the elderly arteriosclerotic patient. When an emergency operation is performed it is easy to ascribe subsequent asthenia and refractory anaemia to a post-gastrectomy state. Sheehan and Summers (1949) emphasize the long duration required for the evolution of true Simmonds's disease. In the syndrome elucidated by Sheehan (1937) in post-partum patients, however, acute ischaemic necrosis of the gland leads to the development of hypopituitarism within months. In pituitary apoplexy acute failure of function is superimposed on the slow, insidious picture. A dramatic acceleration of the process occurred in this case after the gastro-intestinal haemorrhage, although it is clear, in retrospect, that pituitary function was mildly impaired for some years previously.

Peptic ulcer may be associated with a variety of endocrine disorders. Increased incidence is found in stress situations such as burns, in adrenal hyperfunction, after corticosteroid administration, and in hyperparathyroidism. In the last-mentioned condition calcinosis, hyperaemia, and vascular thrombosis may be seen in the gastric mucosa, but gastric hypersecretion is not a constant feature of this disease and a causal relationship cannot be proved (Wilder *et al.*, 1961; Adesola *et al.*, 1961). In Zollinger and Ellison's (1955) syndrome large volumes of gastric juice containing a high concentration of hydrochloric acid cause intractable ulcers, diarrhoea, electrolyte imbalance, particularly hypokalaemia, and steatorrhoea due to inactivation of digestive enzymes. Alpha-cell adenomata of the islets of Langerhans are found, and recently it has been shown that these produce a substance similar in action to gastrin (Gregory *et al.*,

1960). Peptic ulcer is a constant feature of the poly-endocrine syndrome. Hyperparathyroidism and hyperinsulinism have been offered as explanations of this high incidence. Welbourn and Ward (1961) show that organic hyperinsulin states are rarely associated with peptic ulcers.

Gastric hypersecretion and Menetrier's disease, or giant rugal hypertrophy, have been described with multiple endocrine tumours (C.P.C. at the National Institute of Health, 1958). Indeed, it seems likely that the Zollinger–Ellison syndrome is but a facet of the variable polyglandular disturbance (Zollinger and Craig, 1960). Wermer (1954, 1958) describes remarkable family histories of the syndrome and claims that the ulcer is an associated factor. There is little doubt now, however, that the secretion of a gastrin-like substance by non-beta islet tumours of the pancreas is a direct cause of the ulcer in most cases. The finding of much free gastric hydrochloric acid in the presence of hypopituitarism, where achlorhydria is common (Sheehan and Summers, 1949) should lead to the suspicion of other endocrine adenomata. Our patient's father died of peritonitis at the age of 32 after perforation of a peptic ulcer, and her brother, who was killed in the second world war, suffered from a duodenal ulcer.

Dangerous coma readily occurs in hypopituitarism. Infections, trauma, or vomiting may precipitate a dangerous crisis. Hypothermia, hypotension, sodium depletion, and hypoglycaemia appear to play a part. All these factors were absent in the terminal stupor in the present case. At necropsy there was clear evidence of mid-brain compression from the pituitary adenoma. The remarkable resemblance of the coma to normal sleep leads us to speculate whether interference with the ascending reticular formation (Magoun, 1958) may not have been responsible.

Summary

A case of multiple endocrine adenomata is described. Overt panhypopituitarism developed after a massive gastro-intestinal haemorrhage.

Analogies with Sheehan's syndrome and pituitary apoplexy are drawn.

The endocrine background of peptic ulcer and the mechanisms of pituitary coma are briefly discussed.

I am grateful to Dr. C. Allan Birch for invaluable advice in the preparation of this paper and to Dr. J. T. Prendiville for the necropsy details.

REFERENCES

- Adesola, A. D., Ward, J. T., McGeown, M. G., and Welbourn, R. B. (1961). *Brit. J. Surg.*, **49**, 112.
- C.P.C. National Institute of Health (1958). *Ann. intern. Med.*, **49**, 1389.
- Gregory, R. A., Tracy, H. J., French, J. M., and Sircus, W. (1960). *Lancet*, **1**, 1045.
- Jefferson, M., and Rosenthal, F. D. (1959). *Ibid.*, **1**, 342.
- Magoun, H. W. (1958). *The Waking Brain*. Thomas, Springfield, Illinois.
- Pieper, W. J., and Ryan, R. J. (1961). *Ann. intern. Med.*, **55**, 478.
- Sheehan, H. L. (1937). *J. Path. Bact.*, **45**, 189.
- and Murdock, R. (1938). *J. Obstet. Gynaec. Brit. Emp.*, **45**, 456.
- and Summers, V. K. (1949). *Quart. J. Med.*, **18**, 319.
- Wermer, P. (1954). *Amer. J. Med.*, **16**, 363.
- (1958). C.P.C. at National Institute of Health, *Ann. intern. Med.*, **49**, 1389.
- Welbourn, R. B., and Ward, J. T. (1961). *Lancet*, **2**, 986.
- Wilder, W. T., Frame, B., and Haubrich, W. S. (1961). *Ann. intern. Med.*, **55**, 885.
- Zollinger, R. M., and Craig, T. V. (1960). *Amer. J. Med.*, **29**, 761.
- and Ellison, E. H. (1955). *Ann. Surg.*, **142**, 709.