Abstract. A 40 year old woman presented with a 10 year history of watery diarrhoea and an acute quadriplegia. On clinical examination there was severe muscle weakness and a nodule was palpable in the thyroid gland. Biochemical testing revealed a hypokalaemia at 1.6 mmol/l. Plasma levels of VIP were raised at 202 pmol/l. CT scanning demonstrated a mass in the area of the left adrenal gland, and isotope scanning of the thyroid gland showed a ‘cold’ nodule. The plasma catecholamines and calcitonin were elevated. The patient also presented with psychiatric symptoms, and the relevance of these to her condition has been discussed. At operation a left adrenal tumour was removed. Post-operatively the patient’s symptoms disappeared and the plasma hormone levels returned to normal values. Histological examination of the tumour revealed a well differentiated phaeochromocytoma which contained VIP and calcitonin. The thyroid nodule was excised and showed histological features of autoimmune thyroid disease. It is suggested that in all cases of the WDHA syndrome where the tumour is in an extra-pancreatic site patients should be screened for phaeochromocytoma.

In 1958 two cases of severe watery diarrhoea in association with non-insulin secreting adenoma of the pancreas were described (Verner & Morrison 1958). This has subsequently been called the Verner-Morrison Syndrome, WDHA syndrome (watery diarrhoea, hypokalaemia and achlorhydria), and ‘pancreatic cholera’. The commonest cause of this syndrome is a Vasoactive Intestinal Polypeptide (VIP) secreting pancreatic adenoma (Long et al. 1981). The next most frequent cause is due to VIP production by ganglioneuroblastomas, particularly in children. Rarely, the syndrome can be due to other tumours including bronchogenic carcinoma, medullary thyroid carcinoma and phaeochromocytoma (Said & Faloona 1975). Failure to appreciate that tumours can secrete both VIP and catecholamines may lead to serious complications at the time of operation (Loehry et al. 1975). We present a patient with a phaeochromocytoma producing VIP, adrenaline, noradrenaline and calcitonin. Pre-operative assessment and localisation of the tumour allowed safe removal with resolution of symptoms.

Case Report

A 40 year old woman presented with a one day history of profound muscle weakness. She gave a 10 year history of watery brown diarrhoea with 7–10 bowel movements a day. Previous investigation for diarrhoea had incidentally revealed biochemical hypothyroidism in association with a goitre. This had been treated with thyroxine until 2 months before the present admission when the patient had stopped her medication. There was no family history of endocrine disease. She was known to have a cyclothymic personality, with a past history of puerperal depression 14 years before. On examination a flaccid quadri-paralysis was found. The blood pressure was 130/80. A nodular goitre was found with a distinct 1 cm nodule in the isthmus. Investigation...
revealed a sodium of 140 mmol/l, potassium of 1.6 mmol/l, urea of 5.9 mmol/l, chloride of 108 mmol/l and bicarbonate of 13 mmol/l. Fasting blood glucose was 7.1 mmol/l. A provisional diagnosis was made of profound muscle weakness due to hypokalaemia associated with some potassium losing bowel pathology. Her paralysis rapidly disappeared following treatment with intravenous potassium. She continued to produce 1.5–2 l of watery diarrhoea daily, with a faecal potassium excretion of greater than 30 m eqv/day (normal 2–5 m eqv/day). Total body potassium, measured by counting endogenous potassium 40 isotope, was 93% of the predicted value for age and sex (Boddy et al. 1972).

Examination of plasma hormone levels revealed raised concentrations of VIP, adrenaline, noradrenaline, calcitonin and prolactin (Table 1). The 24 h excretion of normetadrenaline was raised at 75.0 nmol/l confirming the presence of a phaeochromocytoma. Normal levels of pancreatic polypeptide, gastrin, glucagon, substance P, growth hormone, neurotensin, and ACTH were found. Abdominal CT scanning showed a solid 8 cm mass, in the region of the left adrenal gland. Metaiodobenzylguanadine (MIBG) scanning revealed an uptake of 1.5% in this area with no other regions of uptake. CT scanning of the pituitary fossa was normal.

Thyroid function tests showed a normal T₃ and T₄ with a raised TSH at 21.9 U/l indicating biochemical hypothyroidism, and the patient was recommenced on thyroxine therapy. A positive titre of anti-microsomal antibodies at a dilution of 1/102 400 was detected with no anti-thyroglobulin antibodies. An ultrasound scan confirmed the presence of a solid nodule and an ¹²³I scan showed that this was 'cold', raising the possibility of medullary carcinoma of the thyroid gland and the multiple endocrine neoplasia syndrome. The plasma calcitonin level did not rise further on stimulation with pentagastrin, 0.5 µg/kg body weight, and the level of carcinoembryonic antigen was normal. To determine the source of the various hormones venous catheterization was performed (Fig. 1). None of the hormones could be particularly localized to a single source, and similar values were found in all sites.

During this time the patient developed an acute manic psychosis. She was assessed by a psychiatrist who suggested treatment with pimozide, a phenothiazine. Over the next few weeks she improved steadily and pimozide was discontinued, prior to surgical removal of the tumour.

The patient was treated with phenoxybenzamine 10 mg twice daily, and at laparotomy an 8 cm vascular tumour was removed from the left adrenal bed. The pancreas was normal on examination. During surgery there were no complications of arrhythmia, hypertension, or hypotension. Peak noradrenaline levels of 300 nmol/l and adrenaline of 775 nmol/l were found during mobilization of the tumour. Post-operatively the patient was normotensive with no recurrence of diarrhoea. Plasma levels of VIP, catecholamines, calcitonin and prolactin and the 24 h urinary excretion of normetadrenaline were normal one month after surgery (Table 1). Two months following abdominal surgery the thyroid nodule was removed and histological examination showed features of auto-immune thyroid disease. The patient remains well on thyroxine therapy.

### Results

Microscopy showed the features of a phaeochromocytoma with large numbers of mature ganglion cells containing melanin. The tumour was chromaffin positive. Immunoperoxide staining revealed that many cells were positive for VIP. Scattered cells stained positively for calcitonin, somatostatin and neuropeptide Y. Electron microscopy confirmed the presence of neuroendocrine granules.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pre-operative concentration</th>
<th>Post-operative concentration</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIP</td>
<td>202 pmol/l</td>
<td>&lt; 30 pmol/l</td>
<td>&lt; 30 pmol/l</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>11.5 nmol/l</td>
<td>0.9 nmol/l</td>
<td>&lt; 5 nmol/l</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>6.0 nmol/l</td>
<td>&lt; 0.1 nmol/l</td>
<td>&lt; 1 nmol/l</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>66 ng/l</td>
<td>&lt; 30 ng/l</td>
<td>10–45 ng/l</td>
</tr>
<tr>
<td>Prolactin</td>
<td>470 U/l</td>
<td>110 U/l</td>
<td>&lt; 360 U/l</td>
</tr>
</tbody>
</table>
Percutaneous venous sampling showing levels of vasoactive intestinal polypeptide (VIP), noradrenaline (Na), adrenaline (Ad) and calcitonin (C) at the sites indicated.

**Discussion**

Vasoactive intestinal polypeptide is a 28 amino acid peptide with powerful vasodilator and smooth muscle relaxant activity (Fahrenkrug & Emson 1982). It modulates intestinal secretion, and has been shown to be the hormone responsible for the Verner-Morrison syndrome. The classical picture of watery diarrhoea in association with hypokalaemia and a low serum bicarbonate is highly suggestive of the diagnosis (Long et al. 1981; Verner & Morrison 1974), and confirmed by the presence of a raised plasma VIP level. Of cases 75% are due to pancreatic tumours, with the commonest extra-pancreatic tumour a non-catecholamine secreting adrenal ganglioneuroblastoma (Long et al. 1981), and a normal plasma pancreatic polypeptide level suggests a non-pancreatic tumour. Abdominal ultrasound or computed tomography is commonly performed to further localize the site of the tumour. In cases where no tumour is detected, venous sampling via the systemic venous system has been attempted, but this can be misleading, and percutaneous portal sampling may aid localization to the pancreas (Kingham et al. 1978). In the present case venous catheterization was unhelpful in determining the source of the elevated hormones, which all returned to normal levels after removal of the tumour.

Phaeochromocytomas are tumours arising from the chromaffin cells, secreting adrenaline and noradrenaline. Hypertension is a common clinical feature of these tumours which can be permanent or paroxysmal. In a small number of patients hypertension is absent (Lips et al. 1984). The world literature contains nine other documented cases of Vipoma syndrome due to phaeochromo-
cytomas which co-secrete VIP (Loehry et al. 1975; Said 1976; Trump et al. 1977; Cooperman et al. 1978; Pais 1978; Matta et al. 1978; Bernard et al. 1980; Viale et al. 1985; Sackel et al. 1985). Hypertension as a presenting feature has only been noted in one case (Loehry et al. 1975). The absence of hypertension is presumably due to the vasodilator effects of the VIP counteracting the hypertensive effects of the catecholamines. Hypertension may subsequently develop during surgery and failure to appreciate that these tumours may secrete both VIP and catecholamines has led to the development of potentially life threatening arrhythmias and hypertension (Loehry et al. 1975; Trump et al. 1977; Matta et al. 1978; Bernard et al. 1980). In a further case, ultrasonic localization sited a tumour in the tail of the pancreas, and it was only at operation that the adrenal nature of the tumour was discovered (Cooperman et al. 1978). We suggest that all patients with this syndrome due to extra-pancreatic tumours and tumours in the tail of the pancreas are screened for the secretion of catecholamines.

The finding of a 'cold' thyroid nodule in this patient with a phaeochromocytoma and increased plasma calcitonin raised the clinical possibility of a type II Multiple Endocrine Neoplasia Syndrome with medullary carcinoma of the thyroid gland (Lips et al. 1984). Against this diagnosis was the absence of a family history and the fact that calcitonin did not rise following stimulation with pentagastrin. There are no documented cases of the WDHA syndrome in association with a phaeochromocytoma and the MEN type II syndrome. Cases of the syndrome due to pancreatic adenoma as part of the MEN type I syndrome have been reported, including one of the cases in the original description (Verner & Morrison 1958). In a review of 65 cases of Vipoma, five had abnormalities in other endocrine organs (Burckhardt 1976), and in a series of 50 patients two patients with a family history of pancreatic tumour and one case of MEN type I were found (Long et al. 1981).

The manic psychosis which occurred in our patient is not a recognized feature of phaeochromocytoma, although anxiety is a common finding (Lips et al. 1984). This feature is not mentioned in any of the other case reports and may have been coincidental. It is possible that her cyclothymic personality erupted into a manic state as a result of the metabolic and endocrine perturbations to which she was exposed. Alternatively, the tumour may have been producing a peptide, as yet uncharacterized, which affected her mental state. This seems unlikely as her psychosis improved prior to removal of the tumour.

Histological examination of the tumour shows that it is unique in staining for VIP, calcitonin, somatostatin and neuropeptide Y. It is not unusual for phaeochromocytomas to secrete other hormones, and the secretion of calcitonin, somatostatin, neurotensin, substance P, ACTH, betamsh, beta-endorphin, lipotrophin and preproenkephalin are described (Lips et al. 1984). This is consistent with the concept that these tumours arise from totipotential neuroectodermal cells which migrate to somatic areas. These cells have the potential to produce many peptide hormones and have in common a number of ultrastructural and histochemical characteristics, including amine precursor uptake and decarboxylation (APUD). Neoplastic growth of the APUD cells may produce several polypeptides or amines which may include any of the polypeptides normally produced by APUD cells (for review, see Lips et al. 1984). Prolactin has not been documented as being secreted from phaeochromocytomas, but VIP promotes secretion of prolactin from the anterior pituitary (Fahrenkrug & Emson 1982), and this is a possible explanation for the raised level found in our patient.

Acknowledgments

Thanks to Dr Gordon Inglis for measurement of catecholamines, to Professor Bloom, Royal Postgraduate Medical School, Hammersmith, and Professor Buchanan, Belfast for measurement of peptide hormones, Dr Graham Beastall for measurement of calcitonin, to Dr Fred Adams for performance of venous catheterization and to Bill East for the measurement of total body potassium. Finally thanks to our colleagues in MRC Blood Pressure Unit, Western Infirmary for advice and discussion with particular thanks to Dr Chris Isles, Dr Peter Semple and Professor Stephen Ball.

References


Received July 1st, 1986.
Accepted September 26th, 1986.

Dr B. M. Fisher,
Ward 7C
Gartnavel General Hospital,
Glasgow, Scotland.