Multiple endocrine neoplasia type I

E. BEUKES, D. M. DENT, J. C. DE VILLIERS, J. L. MILLER

Summary
During the 13-year period 1970 - 1983 only 7 cases of multiple endocrine neoplasia type I (MEN I) were seen at Groote Schuur Hospital, suggesting that the associated gene is rare in this area. Only 1 of these patients was black. Endocrine associations were as follows: hyperparathyroidism — 6 cases, pituitary hypersecretion — 6 cases (3 each involving growth hormone and prolactin), and pancreatic hypersecretion — 3 cases (2 of gastrinoma and 1 of insulinoma). The presenting features were predictably diverse and depended on the component which manifested first. There was little difficulty in reaching a diagnosis on routine investigation. All patients with hyperparathyroidism underwent a subtotal gland parathyroidectomy as the first treatment procedure, normal calcium being achieved in 5 cases, but persistent hypercalcaemia in the 6th suggested a supernumerary gland. A pituitary adenoma was removed in 4 cases, but persistent prolactinaemia necessitated bromocriptine therapy in 3. Successful distal pancreatectomy was undertaken in a patient with insulinoma and a patient with gastrinoma, and a further patient with gastrinoma awaits surgery. The overall prognosis in cases of MEN I appears to depend on the most aggressive component, often the pancreatic lesion; our patients have run a surprisingly benign course with only 1 late death, from hypertensive heart disease.

Patient data
Of the 7 patients with MEN I, 3 were female and 4 male. Their ages ranged from 20 to 60 years, most patients being in their 4th or 5th decade. The endocrine associations are shown in Table I. Six patients had hyperparathyroidism, 6 had pituitary hypersecretion and 3 had pancreatic islet cell tumours. The most common combination was hyperparathyroidism and a pituitary tumour. Only 1 patient in this series had a combination of lesions at all three sites.

Clinical presentation
The presenting features were predictably diverse. Two patients presented with symptoms and signs attributable to a pituitary lesion — headache, acromegaly or amenorrhoea. The patients with gastrinoma presented with haematemesis from recurrent peptic ulceration, having undergone previous peptic ulcer surgery at peripheral hospitals. The patient with insulinoma had typical symptoms of hypoglycaemia. Only 2 of the 6 patients with hyperparathyroidism were symptomatic, both having had urolithiasis; the remaining 4 had biochemical evidence of hyperparathyroidism without any clinical features and were diagnosed on routine screening.

Investigations
The three patients with prolactinoma had raised random prolactin levels of 58, 169 and 50.6 µg/l (normal < 20 µg/l, in the absence of any drugs known to elevate prolactin levels or of primary hypothyroidism). Patients 2, 5 and 6 had clinical features of acromegaly; serum growth hormone estimations were performed on many occasions, the highest levels recorded being 51.47 and 14.6 µg/l (normal < 5 µg/l). All patients with pituitary lesions had clearly demonstrable abnormalities of the pituitary fossa on plain skull radiographs. Computed tomography (CT) showed a large tumour with suprasellar extension in case 6 and an intrasellar tumour in case 4. Case 7 had a partially empty sella on air encephalography. Abnormal pituitary dynamics, as shown by insulin-induced hypoglycaemia, did not contribute much additional information.

The relevant investigations performed for hyperparathyroidism are shown in Table II. Hypercalcaemia in the presence of a concurrent endocrine abnormality of the pituitary gland or pancreas was judged to be persuasive evidence of hyperparathyroidism. The nephrogenous cyclic adenosine monophosphate level (used as an index of biological activity of parathyroid hormone) was elevated in each of the 4 cases in which it was measured, and that of immunoreactive parathyroid hormone was elevated in 1 of the 2 cases in which it was measured. Discriminant analysis (a computer-based analysis of serum calcium, phosphate, chloride and bicarbonate levels, calcium excretion rate and tubular reabsorption of phosphate) was suggestive of hyperparathyroidism in both instances in which it was computed. Attempts to localize the glands in each case with ultrasound were disappointing.

The 2 patients with gastrinoma had elevated fasting serum gastrin levels (464 and 500 pg/ml — normal 25 - 115 pg/ml) and both had a positive response to the secretin test (an inappropriate rise in the serum gastrin level after intravenous
### TABLE I. ENDOCRINE ASSOCIATIONS AND CLINICAL PRESENTATION IN CASES OF MEN I

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Parathyroid Hyperplasia</th>
<th>Pancreas</th>
<th>Insulinoma</th>
<th>Pituitary</th>
<th>Clinical Presentation</th>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Amenorrhoea, galactorrhoea</td>
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<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Urolithiasis</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Recurrent duodenal ulcer</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Hypoglycaemia</td>
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<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Urolithiasis</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Headache</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Recurrent duodenal ulcer</td>
</tr>
</tbody>
</table>

### TABLE II. INVESTIGATIONS FOR PRIMARY HYPERPARATHYROIDISM

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum calcium (albumin corrected)</th>
<th>Serum phosphate (0.80 - 1.40 mmol/l)</th>
<th>Alkaline phosphatase (30 - 85 U/l)</th>
<th>Nephrogenous cAMP (0.29 - 2.81 mmol/l/100 ml GRF)</th>
<th>Discriminant analysis*</th>
<th>PTH (0 - 0.88 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.11</td>
<td>0.70</td>
<td>111</td>
<td>3.27</td>
<td>-13</td>
<td>5.00</td>
</tr>
<tr>
<td>2</td>
<td>2.68</td>
<td>0.93</td>
<td>175</td>
<td>8.6</td>
<td>-13</td>
<td>0.48</td>
</tr>
<tr>
<td>3</td>
<td>3.04</td>
<td>0.50</td>
<td>124</td>
<td>6.53</td>
<td>-23.3</td>
<td>0.48</td>
</tr>
<tr>
<td>4</td>
<td>2.67</td>
<td>0.95</td>
<td>186</td>
<td>4.5</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>0.97</td>
<td>186</td>
<td>6.53</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>6</td>
<td>2.8</td>
<td>0.65</td>
<td>81</td>
<td>4.5</td>
<td></td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Primary hyperparathyroidism < -11; non-parathyroid hypercalcaemia > -11.

Angiography was carried out in 2 of the 3 patients with pancreatic lesions (cases 3 and 4), and proved accurate in both. CT was not available at the time the first 2 cases were investigated, but demonstrated the lesions in case 4. In case 7 both CT and ultrasound failed to show a pancreatic lesion.

### Operative findings and clinical outcome

(Table III)

The parathyroid lesion most commonly found was 4-gland hyperplasia (5 cases); 1 patient had what was initially thought to be a massive adenoma plus 3-gland hyperplasia, although later review showed this to be asymmetrical hyperplasia. No autotransplantation or cryopreservation was undertaken in this

### TABLE III. OPERATIVE MANAGEMENT AND CLINICAL OUTCOME

<table>
<thead>
<tr>
<th>Case</th>
<th>Parathyroid</th>
<th>Pituitary</th>
<th>Pancreas</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/4-gland parathyroidectomy</td>
<td>Transsphenoidal hypophysectomy</td>
<td>Distal pancreatectomy</td>
<td>Normocalcaemic (3 yrs); persistent prolactinaemia; bromocriptine therapy Normal (3 yrs)</td>
</tr>
<tr>
<td>2</td>
<td>Ipsilat. 1/2-gland parathyroidectomy, contral. thyroid lobectomy</td>
<td>Transsphenoidal hypophysectomy</td>
<td>Distal pancreatectomy</td>
<td>Normocalcaemic (4 yrs) Normal insulin level; persistent prolactinaemia; bromocriptine therapy Normocalcaemic (1 yr); died from hypertensive heart disease</td>
</tr>
<tr>
<td>3</td>
<td>3/4-gland parathyroidectomy</td>
<td>—</td>
<td>Distal pancreatectomy</td>
<td>— Awaiting further surgery Hypocalcaemic; persistent prolactinaemia; bromocriptine therapy Normocalcaemic</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>—</td>
<td>Distal pancreatectomy</td>
<td>— Awaiting further surgery Normocalcaemic</td>
</tr>
<tr>
<td>5</td>
<td>3/4-gland parathyroidectomy</td>
<td>Failed transsphenoidal hypophysectomy</td>
<td>Distal pancreatectomy</td>
<td>— Awaiting further surgery Hypocalcaemic; persistent prolactinaemia; bromocriptine therapy Normocalcaemic</td>
</tr>
<tr>
<td>6</td>
<td>3/4-gland parathyroidectomy</td>
<td>Transsphenoidal hypophysectomy</td>
<td>—</td>
<td>— Awaiting further surgery Hypocalcaemic; persistent prolactinaemia; bromocriptine therapy Normocalcaemic</td>
</tr>
<tr>
<td>7</td>
<td>3/4-gland parathyroidectomy</td>
<td>—</td>
<td>—</td>
<td>— Awaiting further surgery Normocalcaemic</td>
</tr>
</tbody>
</table>

Administration of secretin.)

Acid studies in case 3 gave basal and maximal readings within the normal range, a finding reported to be compatible with gastrinoma. Case 7, however, had the more typical markedly raised basal plus maximal acid output levels. The single case of insulinoma was diagnosed by the demonstration of an inappropriately elevated fasting serum insulin level (13.5 μIU/ml) in the presence of a low fasting serum glucose level (1.5 mmo/l).

Angiography was carried out in 2 of the 3 patients with pancreatic lesions (cases 3 and 4), and proved accurate in both. CT was not available at the time the first 2 cases were investigated, but demonstrated the lesions in case 4. In case 7 both CT and ultrasound failed to show a pancreatic lesion.

Operative findings and clinical outcome

(Table III)

The parathyroid lesion most commonly found was 4-gland hyperplasia (5 cases); 1 patient had what was initially thought to be a massive adenoma plus 3-gland hyperplasia, although later review showed this to be asymmetrical hyperplasia. No autotransplantation or cryopreservation was undertaken in this
series. Only 1 of the 2 patients with gastrinoma has undergone surgery to date; distal pancreatectomy was performed, the histological findings confirming the presence of a gastrinoma. Patient 7 awaits surgery for gastrinoma. The patient with insulinoma had two macroscopic lesions in the tail of the pancreas and partial pancreatectomy was performed. Histological examination revealed no less than five separate insulinomas in the specimen. Pituitary adenomas were removed in 4 patients but the operation had to be abandoned in case 6 because of excessive dural bleeding.

Five of the 6 patients submitted to parathyroidectomy remain normocalcaemic 6 months to 4 years later; case 6 remains persistently hypercalcaemic despite a 3/2-gland parathyroidectomy, thus suggesting a possible occult fifth gland or hyperfunction of the remaining half gland. Successful distal pancreatectomy was performed in cases 3 (gastrinoma) and 5 (insulinoma). Patient 7 awaits surgery.

The results of pituitary surgery in this series were disappointing; the operation had to be abandoned in 1 instance through technical difficulty, while in 3 cases persistent hyperprolactinaemia necessitated bromocriptine therapy. There has, however, been no progression of any of the pituitary lesions. Patient 7 is being managed on bromocriptine pending further investigation of his gastrinoma.

There has been 1 death in this series (case 5), from hypertensive heart disease a year after surgery.

Discussion

The introduction of the APUD cell concept by Pearse in 1969 and the description of the term ‘apudoma’ by Szip et al. in the same year opened up a new field of endocrinological thought, which has subsequently fascinated clinicians and produced extensive publication. The majority of patients with apudomas present with an isolated organ lesion, e.g. insulinoma or gastrinoma; however, in a small percentage several organs will be affected synchronously or metachronously - so-called multiple endocrine neoplasia or adenopathy (MEN or MEA). In 1954 Wermer described a family in which several members had tumours of the pituitary, pancreas and parathyroids, and this combination of apudomas subsequently became known as the MEN type I syndrome (Wermer’s syndrome). The involvement of the parathyroids in MEN is something of an enigma, in that they are not apudomas in the true sense of the term but possibly arise from related neuroectodermal cells. Subsequently the association of medullary carcinoma of the thyroid and phaeochromocytoma was described, and the term MEN II or Sipple’s syndrome was introduced. The parathyroids are also involved in up to 20% of these cases.

MEN I is in our experience a rare disease. Over a 13-year period only 7 cases were seen at Groote Schuur Hospital (a referral hospital for the Cape area consisting of 13,000 beds with 50,000 admissions per year). In these 13 years during which the 6 patients with pituitary adenomas as part of the MEN syndrome were encountered, 324 pituitary adenomas were treated in our pituitary clinic. This is a somewhat greater number than that found by Hollenhorst and Young (4 cases amongst 1,000 with pituitary adenomas), but both figures are based on hospital admissions and do not represent the true incidence. The rarity of the disease may be explained by an infrequency of the gene in this country. Only 1 of our patients was black, 1 was white and the remainder were of mixed ancestry (coloured). Our setting makes screening of asymptomatic families difficult, and this may also contribute to the infrequency of this syndrome at our hospital.

The parathyroids were involved in over 80% of our cases, and this is in keeping with the incidence reported in the literature. In the isolated case of primary hyperparathyroidism a single adenoma would be the likely lesion; in the MEN I setting, however, 4-gland hyperplasia is almost invariably encountered. All our cases explored to date have had this finding, including 1 patient who had 3-gland hyperplasia plus a massive asymmetrical fourth hyperplastic gland. Our management of the parathyroid abnormality in the context of MEN I is thus to perform a near-total parathyroidectomy — usually removing 3 1/2 glands — irrespective of the lesion encountered. This attitude is drawn from the experience of others who have shown that while glandular involvement is usually synchronous, metachronous lesions may occur with consequent recurrent hyperparathyroidism. Autotransplantation or cryopreservation was not undertaken in this series. Over 80% of our cases were normocalcaemic after surgery, which compares well with the reports of 45-89% in the literature. One patient remains hypercalcaemic, despite a 3/2-gland parathyroidectomy, and he will be submitted to further surgery.

No less than 86% of our cases had involvement of the pituitary gland, which contrasts with the reported incidence of 65%. Because of the small size of the tumours the transsphenoidal approach was used in all patients who underwent pituitary surgery. The procedure had to be abandoned in one instance because of excessive bleeding from the dura of the sellar floor. This is a known but fortunately rare complication of this approach, and has only been encountered on one other occasion in our experience with 190 operations by this route. The response to surgery was somewhat disappointing, in that only in 1 patient did levels of the relevant pituitary hormone (human growth hormone) revert to normal; even in this patient the thyrotrophin-releasing hormone stimulation test result was abnormal, although the growth hormone levels never exceeded 5 µg/l. Dural infiltration of the tumour could be demonstrated in all patients except case 5. This is known to be a cause of surgical failure since such tumours are beyond the reach of surgical extirpation even when an operating microscope is used. This has been our experience with prolactinomas and growth hormone-secreting tumours, and this feature has been commented on by others. The high incidence of dural infiltration in these patients may be of significance in relation to the basic stimulus which gives rise to these tumours. Those patients with prolactinomas who did not respond to surgery were all managed with bromocriptine and there is no evidence of tumour extension to date. There have been no other untoward complications of surgery.

Two of our patients had gastrinomas and 1 an insulinoma, a total of 43% — in keeping with the incidence reported for MEN I. Both patients with gastrinomas presented with recurrent peptic ulceration after gastric surgery. Parathyroid hyperplasia was present in both cases. Serum gastrin levels were elevated in all and the secretin test confirmed the diagnosis in all cases. Gastric acid values were within the normal range in 1 case; in this regard up to 50% of proven cases have been reported to have normal gastric acid levels — particularly those who have already undergone parathyroid resection. The relationship between hypercalcaemia (as caused by hyperparathyroidism) and elevated serum gastrin levels is a complex one, for hypercalcaemia promotes the secretion of gastrin, which in turn stimulates the secretion of gastric acid. Parathyroidectomy in MEN I patients has been reported to reduce acid secretion, and may even cure duodenal ulceration. Also, cases have been described where parathyroid glands were apparently secreting gastrin. One could thus advance the argument that only histological proof would be acceptable to make a definite diagnosis of gastrinoma in the presence of parathyroid hyperplasia or proven MEN I.

The introduction of cimetidine, an H₂-receptor antagonist, widened the scope for the management of patients with gastrinoma. In many cases it was possible to control the effects of
the tumour without having to resort to surgery; previously
total gastrectomy was necessary if a resectable pancreatic
tumour could not be demonstrated. Where pre-operative inves-
tigations show a pancreatic lesion, surgery may be confined to
resection of the tumour alone, as in case 3.17 The reason for
always dealing with the hyperparathyroidism first in these
cases has been stated.

The single death in this series (case 5) was unrelated to the
underlying MEN I. The favourable outlook in treated cases of
MEN I was thus confirmed.

MEN has a strong hereditary base and it is estimated that
up to 50% of the offspring of a MEN sufferer will have MEN,
often in a latent form.18 Sexes are affected equally, as in our
series. The pattern of inheritance is thought to be autosomal
dominant. We have found that effective screening of the
immediate relatives of our patients poses a great problem,
since the majority are members of migrant population groups,
many being referred from distant rural areas; we have not
only experienced great difficulty in arranging regular follow-up of
these patients at our endocrine clinic, but have also found it
impossible to persuade the family members to attend for
screening procedures. The fact that the majority of those
affected are probably still asymptomatic or are receiving treat-
ment elsewhere serves to complicate matters.

It is evident that a thorough screening for all the MEN
components is necessary in the patient who presents with one
of them. The matter is complicated by the fact that presenta-
tion of an additional apudoma can occur at any stage up to the
age of 50 years,19 so screening and follow-up should be
lifelong. This also applies, under ideal circumstances, to the
immediate family members of a MEN sufferer.

Support from the South African Medical Research Council is
gratefully acknowledged.

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Taalonderzoek en Commentaar/News and Comment

Endoskopie teenoor bariummaal

Radiofysiase onderzoek is baie jare lank as die belangrikste
diagnose van letseis van die boonste gastrointestinale traktu-
(get) gebruik. Veral sedert die 60-er jare, toe die dubbelkon-
trasbariummaal bekend geword het. Endoskopie is die afgelope
tyd al meer dikwels gebruik weens die duidelike groter diagno-
siese akkuraatheid daarvan. Die waarde van baie van die
proefnemings wat onderzoek ondernem om die diagnostiese akkuraat-
heid van die twee tegnieke te vergelyk is egter weens foutiewe
ontwerp beveelstrukte. 'n Nuwe toets is nou uitgevoer waarin
hierdie voute hopelik uitgesakel is (Dooley et al., Ann Intern Med 1984; 101:
538). Honderd pasiente het aan 'n ondersoek deelgeneem, van wie 53% een of ander letsel in die boonste
get gehad het. Die meeste van die algemeen gevorderde letseis was
karsinoom en varices, gastrische ulkus en gastritis wat die
die algemeenste letsel van die duodenum. Endoskopie was as aansienlijk
akkurat (92%) as die dubbelkontrasbariummaal (54%) en was
ook meer specifiek (100% teenoor 91%). Hierdie resultate dui
skynbaar op endoskopie as die primêre ondersoekemetoode vir
die boonste GIT. Daar is egter struikelblokke, waarvan die
eerste koste is. In die VSA is endoskopie 2-3 maal duurder as
radiografie. Daar is ook 'n aansienlik hoër morbidity- en
mortaliteitstansyfer wanneer endoskopie gebruik word. Meer
beduidend is dat daar nog nie verbeterde pasienteuresultate met
endoskopie aangetoon kon word nie. Totdat dit bereik is en 'n
ekostevoordeelontleding duidelik aangetoon het dat endoskopie
doeltreffender is, sal die bariummaal waarskynlik sy voorkeur-
posisie behou.

Removing cactus spines

There are a number of mishaps which can always provoke
roars of laughter among connoisseurs of slapstick humour.
These include slipping on banana skins, falling into open
manhole covers and sitting on a cactus. However, the reality is
that a cactus, or more commonly falling against one, usually involves
the highly uncomfortable procedure of pulling the minute
spines out one by one with the aid of a magnifying glass and a
pair of eyebrow tweezers. However, new hope for cactus spine
sufferers has been provided by a bright idea contained in a
letter to JAMA (1984; 252: 3368). A thick layer of white
woodworking glue is applied to the affected area and covered
with a piece of linen. When the glue has dried, the linen and
glue film are peeled off, taking all the embedded cactus spines
with them.