Abstract: Introduction Somatostatin-secreting neuroendocrine tumours may present with diabetes, cholelithiasis and steatorrhoea. In addition, hypoglycaemia has been associated with somatostatinomas. However, the mechanism of hypoglycaemia in patients with somatostatinomas has not been well characterized. Methods We describe two patients with recurrent neuroglycopenic episodes caused by somatostatin-secreting neuroendocrine tumours in the liver, detected by abdominal CTs and whole-body octreotide scintigraphy scans and confirmed by biopsy. Results Pancreatic islet hyperplasia and co-secretion of insulin (in addition to somatostatin) from tumour cells, respectively, have been characterized as completely distinct mechanisms of hypoglycaemia at both the functional and morphological levels in these two patients. Conclusions Hypoglycaemia may be caused by different mechanisms in patients with somatostatinomas.

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Somatostatinomas are rare neuroendocrine tumours usually located in the pancreas or in the periampullary region of the duodenum, rarely in the jejunum, the ovaries or elsewhere. Patients with somatostatinomas most often present with nonspecific symptoms such as abdominal pain or weight loss. A more specific clinical manifestation is the somatostatinoma syndrome characterized by diabetes, cholelithiasis and steatorrhoea. Moreover, hypoglycaemia has been associated with somatostatinomas. However, the mechanism of hypoglycaemia in patients with somatostatinomas has not been well characterized.

Methods: We describe two patients with recurrent neuroglycopenic episodes caused by somatostatin-secreting neuroendocrine tumours in the liver, detected by abdominal CTs and whole-body octreotide scintigraphy scans and confirmed by biopsy.

Results: Pancreatic islet hyperplasia and co-secretion of insulin (in addition to somatostatin) from tumour cells, respectively, have been characterized as completely distinct mechanisms of hypoglycaemia at both the functional and morphological levels in these two patients.

Conclusions: Hypoglycaemia may be caused by different mechanisms in patients with somatostatinomas.

Keywords
hyperinsulinaemia, hypoglycaemia, neuroendocrine tumour, somatostatinoma
however, did not provoke hypoglycaemia. A tumour-produced incretin could not be identified (we checked for GLP-1, CCK, pro CCK and GIP), but somatostatin levels were markedly increased in the basal state (5 nmol/L, normal <0.1) and decreased during the glucose challenge. Selective arterial calcium stimulation with hepatic venous sampling (ASVS) was performed, and insulin concentrations were measured as previously described. ASVS demonstrated increased insulin secretion in response to calcium injection into all arteries supplying the pancreas but not in response to calcium injection into the proper hepatic artery supplying the tumour (Figure 1). Biopsy of the liver tumour was performed, and histological examination revealed a neuroendocrine tumour. A diagnosis of a somatostatin-secreting neuroendocrine tumour with postprandial hypoglycaemia, mild diabetes mellitus and cholecystolithiasis was made.

Because the patient declined resection of the right hepatic lobe, transarterial tumour embolization was performed. Postprandial hypoglycaemia improved following the procedure. However, within three years, the neuroendocrine tumour progressed and the patient died at the age of 79 years. Post-mortem analysis revealed a malignant somatostatinoma with disseminated tumour infiltrates forming nodules up to 10 mm in the pancreas and prominent liver metastasis. The primary localization of the somatostatinoma in the pancreas was not detected until autopsy. In addition to the somatostatinoma, histological examination of the pancreas revealed islet hyperplasia throughout the pancreas. Most strikingly, the number
of islets of Langerhans was increased, and their size and shape were very variable with individual hypertrophic islets. Islet hyperplasia as cause of hypoglycaemia in this patient was well characterized at the functional (ASVS test) and morphological level.

Patient 2, a 56-year-old woman, presented with recurrent hypoglycaemic episodes. Neuroglycopenic symptoms developed in an erratic manner but preferentially while fasting. In a local hospital, an HbA1c of 4.0%, random low blood glucose readings and a liver tumour by an abdominal CT scan were found. She was sent to us for further investigations and treatment. During a supervised fast, plasma glucose concentration dropped to 1.1 mmol/L after 21 hours. Insulin concentration at the time of hypoglycaemia (458 pmol/L) confirmed hyperinsulinaemic hypoglycaemia. The abdominal CT scan showed a large liver tumour (10 cm in diameter) in the left hepatic lobe. An octreotide scan of the liver tumour was positive (Figure 2). A biopsy of the liver tumour was performed, and histological examination revealed a neuroendocrine tumour positive for synaptophysin and chromogranin A. The differential diagnosis included islet carcinoma of the pancreas metastatic to liver that could not be detected. However, the ASVS test demonstrated a normal insulin secretion response to calcium injection into all arteries supplying the pancreas but a markedly increased (more than 10-fold) insulin secretion following calcium injection into the left hepatic artery. Moreover, calcium stimulated the secretion of somatostatin by the liver tumour (more than 13-fold) but not from the pancreas (Figure 1). Resection of the liver tumour was performed. Immunohistochemically, tumour cells stained markedly positive for somatostatin (95%) and insulin (5%); interestingly, staining for the two hormones was restricted to distinct cell populations and not uniform throughout the tumour (Figure 3).

Following resection of the liver tumour, insulin fell rapidly whereas plasma glucose levels increased, initially overshooting to an increased level and soon returning into a normal range. The patient remained free of hypoglycaemia and diabetes for the rest of her life. However, manifestations of tumour disease recurred after 3 years, and repeated imaging then revealed progressive hepatic but no pancreatic tumour masses. The patient died 6 years after surgery (at the age of 62 years). Her family members declined a post-mortem analysis. Evidence for somatostatin secretion by liver tumours is very rare, and usually, somatostatin-positive neuroendocrine tumours are derived from the pancreas and the duodenum. Co-secretion of insulin (in addition to somatostatin) by the hepatic somatostatinoma was well characterized as mechanism of hypoglycaemia in this patient.

In conclusion, pancreatic islet cell hyperplasia and co-secretion of insulin (in addition to somatostatin) from tumour cells, respectively, have been characterized as completely distinct mechanisms of hypoglycaemia at the functional and morphological level in these two patients with malignant somatostatinomas.

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CONFLICT OF INTEREST
The authors declare no conflict of interest in relation to this work.

AUTHORS’ CONTRIBUTIONS
PW, VP, MB and CS were directly involved in the management of the patients and contributed to the final manuscript. TP performed the ASVS tests, and AP performed the pathological examinations.

ETHICS STATEMENT
Both patients gave informed consent to publish their data.

DATA AVAILABILITY
Data sharing is not applicable to this article as no new data are shown. Data to support the findings are available from the corresponding author (PW), upon reasonable request.

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