C.D. Johnson and C.W. Imrie

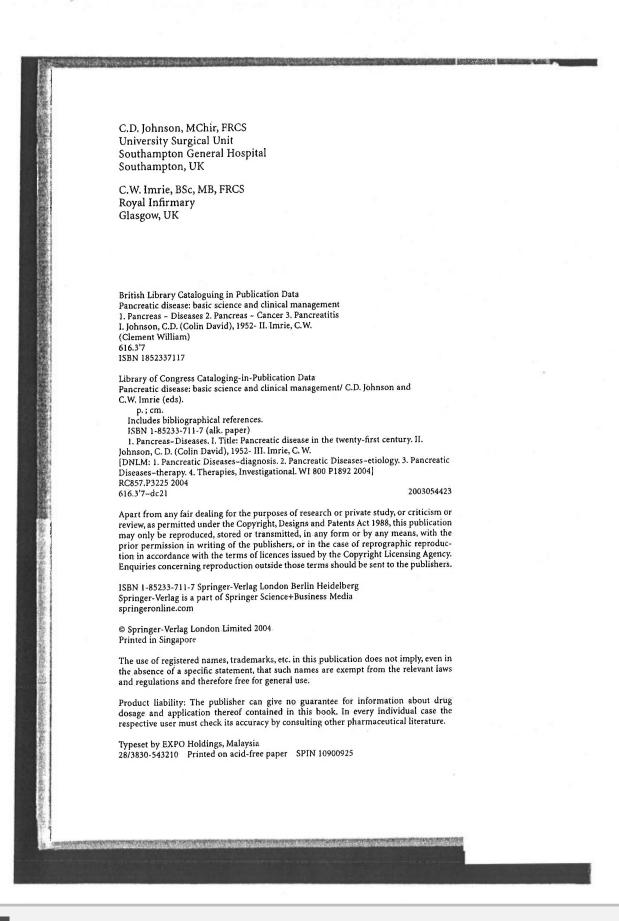
Pancreatic Disease

Basic Science and Clinical Management

With 82 Figures

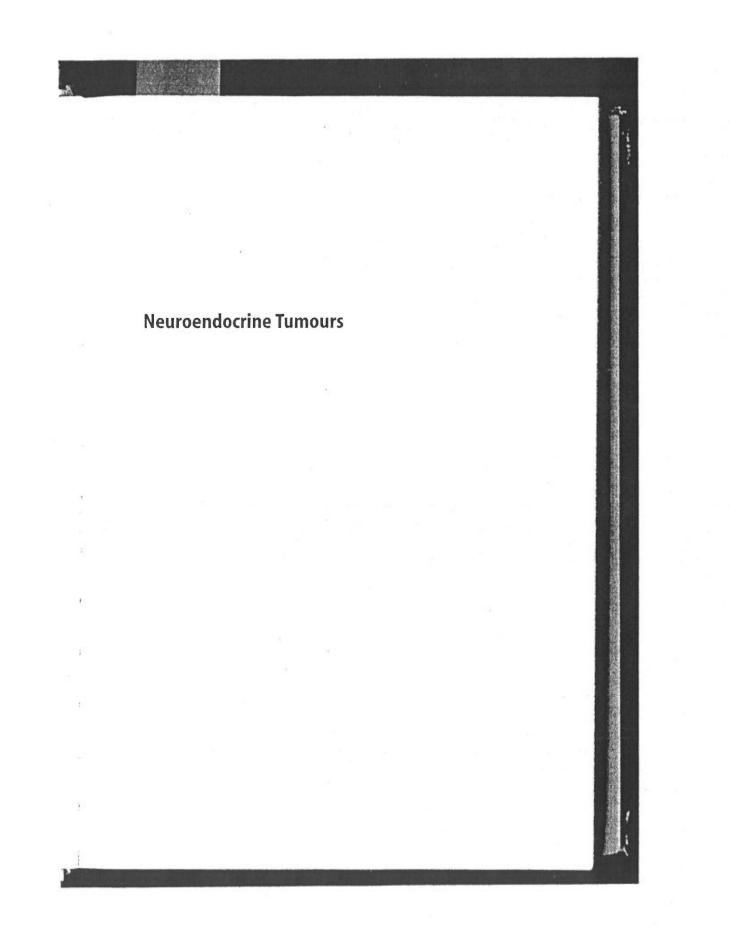


DOCKET A L A R M Find authenticated court documents without watermarks at <u>docketalarm.com</u>.



Find authenticated court documents without watermarks at docketalarm.com.

DOCKE



DOCKET ALARM Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

4 GI Hormone Producing Tumours: Syndromes and Treatment Options

Mary McStay and Martyn E. Caplin

Neuroendocrine tumours of the pancreas (also called pancreatic endocrine tumours or islet cell tumours) may be *functioning* or *non-functioning*. Functioning tumours are those associated with a clinical syndrome that is caused by hormone release, and are named according to the hormone that they secrete (Table 4.1). Non-functioning neuroendocrine tumours of the pancreas include those that have all the histological characteristics of a neuroendocrine pancreatic tumour (NPT), but no associated clinical syndrome related to hormone hypersecretion. NPTs are rare tumours, with an incidence of less than 1/100 000 population/year. Non-functioning tumours form the biggest group (30–40%), followed by gastrinomas and insulinomas, which have approximately the same incidence. With the exception of insulinomas, the majority of NPTs are malignant.

Eight of the NPTs are well established and are included in most classifications. These are gastrinomas, insulinomas, VIPomas, glucagonomas, somatostatinomas, growth-hormone releasing factor secreting tumours (GRFomas), ACTH secreting tumours of the pancreas (ACTHomas), and 'non-functioning' tumours, which may in fact be pancreatic polypeptide-secreting tumours (PPomas). Other rarer NPTs have recently been considered as causing syndromes, including NPTs causing hypercalcaemia (producing parathyroid hormone and parathyroid hormone-related protein), NPTs secreting calcitonin and NPTs causing the carcinoid syndrome.

Pathophysiology and Pathology of Neuroendocrine Tumours

The histological diagnosis of neuroendocrine tumours relies first on the identification of general markers of neuroendocrine differentiation, and then cell-specific characterisation. Neuroendocrine differentiation is evaluated by immuno-histochemistry using antibodies against secretory granule proteins (chromogranin A, synaptophysin) and cytosolic proteins (neuron-specific enolase, protein gene product 9.5). The cell-specific characterization of neuroendocrine tumours requires hormone immunohistochemistry. According to the World Health Organisation (WHO) classification, neuroendocrine tumours of the gastroenteropancreatic tract are classified as well-differentiated and poorly differentiated depending on their histological and functional features.

31

Table 4.1. The different types of pancreatic neuroendocrine tumours and their associated hyperfunctional syndromes

Tumour	Cell type	Predominant hormone	Major clinical symptoms	Tumour location	Percent malignant
Gastrinomas	G	Gastrin	Recurrent peptic ulcer	Pancreas 50% Duodenum 50%	90
Insulinoma	В	Insulin	Hypoglycaemia (fasting or nocturnal)	Pancreas	10
VIPoma	?	Vasoactive intestinal polypeptide (VIP)	Watery diarrhoea, hypokalaemia, achlorhydria	Pancreas 90%	60
Glucagonoma	A	Glucagon	Diabetes mellitus, necrolytic migratory erythema	Pancreas	90
Somatostatinoma	D	Somatostatin	Diabetes mellitus	Pancreas 55% Duodenum 45%	80
GRFoma	?	Growth-hormone releasing- hormone	Acromegaly	Pancreas 30% Lung 50% Jejunum 15%	60
ACTHoma	7	ACTH	Cushing's syndrome	Pancreas 90%	95
PPoma	PP/F	Pancreatic polypeptide (PP)	Hepatomegaly, abdominal pain	Pancreas 100%	80

32

Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

DOCKET A L A R M



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.