Abstract
Carney triad is a rare multitumoral syndrome of unknown etiology that was first described in 1977. The neoplasms affect the stomach, lungs, paraganglionic system, adrenal cortex, and esophagus. Approximately 150 cases have been identified. The disorder occurs in young women primarily and is not familial. Multifocal tumors develop in the organs affected. No patient has had tumors in all 5 organs. One patient had tumor in 4 organs; most patients have them in 2. Thus, the syndrome is usually only partially expressed. The gastric tumors are malignant and metastasize to the liver, peritoneum, and lymph nodes. The lung, adrenal, and esophageal tumors are benign. The paraganglionic tumors are usually benign. Long-term follow-up shows that the syndrome is a chronic, persistent, and generally indolent condition whose outcome is largely dependent on the behavior of the metastases of the gastric sarcoma. Among the 79 affected patients described in 1999 (average follow-up 8 years, 64 were alive, 19 were apparently free of tumors, 45 had residual or metastatic disease, and 15 were dead (10 died of causes related to the syndrome)).

The multitumoral syndrome referred to as Carney triad (CTr) was described in 1977 under the rubric ‘The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma’ [1]. The article was based on findings in 7 patients; 4 were patients at Mayo Clinic, Rochester, Minn., USA, and 3 were patients whose cases were reported in the literature. In 1981, Grace et al. [2] presented the first subsequent case of the disorder and referred to it as ‘Carney’s triad.’

Definition

CTr is a syndrome of neoplasms that affect the stomach, lungs, paraganglionic system, adrenal cortex, and esophagus. Multiple tumors develop in affected organs. The disorder affects young women primarily. It is not familial. The gastric lesions are ma-
lignant; the lung, adrenal, and esophageal tumors are benign; and the paragangliomas are usually benign.

**Background**

Patients with 2 different tumors, each occurring singly, are not uncommon. Patients with 3 different tumors, each occurring singly, are infrequent. Patients with 3 uncommon or rare tumors each occurring multifocally would be extraordinary indeed, especially if all the patients were young women. On the basis of those extraordinary circumstances, the syndrome described in this chapter was initially suspected.

In 1977, Carney et al. [1] reported the cases of 7 young women, with combinations of intramural stromal gastric tumors, pulmonary cartilaginous tumors, and extra-adrenal paragangliomas. The 3 neoplasms were unusual or rare – one, pulmonary chondroma, was unfamiliar or unknown even to pathologists.

Since 1977, over 140 cases of the condition with different combinations of the 3 neoplasms have been described or have come to my attention; all but 2 are single case reports [3, 4].

**Historical**

Recognition of the syndrome stemmed from my interest in the multiple endocrine neoplasia (MEN) syndromes, disorders that feature multifocal tumors in 2 or more endocrine organs, affect young patients of both sexes, and are familial with transmission by autosomal dominant inheritance. One of the syndromes, MEN2B, includes a nonendocrine tumor component (ganglioneuromatosis).

In August 1975, I was presented a case for pathologic diagnosis: a young woman (case 1) had 2 types of endocrine tumors (paraganglioma and adrenocortical adenoma) and a nonendocrine tumor (gastric leiomyosarcoma). The findings caught my attention because of their general resemblance to the tumor pattern of MEN2B: 1 of the endocrine tumors, the paraganglioma, was multicentric and the other, the adrenal adenoma, was single. The patient also had nonendocrine gastric tumors.

These findings immediately came to mind 3 months later when I encountered a somewhat similar patient. This patient (case 2), a 25-year-old woman, had an endocrine tumor (carotid body paraganglioma) excised at age 11 and, as an adult, had surgery for multiple nonendocrine gastric tumors (leiomyosarcomas) followed by excision several months later of 5 calcified lung lesions (clinically thought to be metastases from the gastric sarcoma). The patient had bilateral congenital abnormalities of her external and middle ears.
Cases 1 and 2 were similar in that each had endocrine and nonendocrine tumors. I wondered whether the resemblance might not coincidental and considered the possibility that they had a disorder similar to the MEN2B. Neither patient had a similarly affected relative; thus there was no support for a familial disorder, but the combination of tumors was intriguing.

At a chance meeting in August 1976 with S. G. Sheps MD, the Mayo Clinic clinician most experienced with paraganglioma, I mentioned the 2 cases and inquired whether he had encountered similar ones. He sent me a list of 8 Mayo Clinic patients who had paraganglioma and other tumors. The list included 2 with paragangliomas and gastric sarcomas (cases 3 and 4).

Summaries of the findings in the 4 Mayo Clinic patients are presented in table 1.

### Cases 1–4

**Case 1**
A 15-year-old adolescent girl (fig. 1) was found to have hypertension at a school physical examination. At age 16, she had upper gastrointestinal tract bleeding and was treated for anemia. Two years later, abdominal discomfort led to discovery of an epigastric mass. Persistent hypertension prompted measurement of the urinary content of metanephrines, which was elevated. Laparotomy was performed and 3 para-aortic paragangliomas, a small adrenal cortical adenoma, and 10 gastric leiomyosarcomas with an omental metastasis were found and resected. Postoperatively, the patient was still hypertensive and the urinary content of catecholamines and metanephrines remained elevated. Chest imaging findings were normal. No family member had paraganglionic, adrenocortical, or gastric tumors. No family member was similarly affected. The patient was referred to Dr. Sheps at Mayo Clinic.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
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<th>Gastric epithelioid leiomyosarcoma</th>
<th>Pulmonary chondroma</th>
<th>Paraganglioma</th>
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- = Absent; + = present.

a Patients 1–4 were patients at Mayo Clinic. Patients 5–7 were patients whose cases were reported in the literature.
b Number of tumors is shown in parentheses.
c Pulmonary chondroma developed subsequent to report.
Case 2
A 25-year-old woman (fig. 2) was born with bilateral anomalies of the external and middle ears that resulted in left-sided deafness and partial deafness in the right ear. An asymptomatic mass was excised from the left carotid bifurcation at age 12; microscopically, it was a paraganglioma (carotid body tumor). At age 24 years, she had massive hematemesis and was comatose on arrival at the hospital. Emergency partial gastrectomy was performed. The resected stomach contained 5 antral leiomyosarcomas, 1 of which was ulcerated and the source of the gastric hemorrhage. Preoperative evaluation had been impractical because of the patient’s serious condition but postoperative evaluation revealed 4 left lung masses, which were clinically thought most likely to be metastases from the gastric tumors. The patient was also hypertensive, and urinary content of catecholamines and metanephrines was elevated. The lung lesions were resected (as was a tumor attached to the para-aortic sympathetic chain found incidentally at surgery). The pulmonary tumors were solid with a cartilaginous appearance and were interpreted microscopically as pulmonary hamartomas. The sympathetic chain lesion proved to be a paraganglioma. Postoperatively, the blood pressure and urinary content of pressor amines were normal. No family member had similar tumors.

Case 3
Routine chest imaging revealed a 5-cm tumor in the left lung of a 17-year-old adolescent girl. Because of its rapid growth, it was removed. Histologic examination showed a pulmonary hamartoma. Hematemesis and melena at age 24 led to discovery and resection of 2 gastric tumors. Microscopically, they were leiomyosarcomas. Three years later, melena recurred and gastrectomy was completed for 3 new leiomyosarcomas with lymph node metastasis. At age 32, the patient had tachycardia, nocturnal sweating, and occasional paroxysmal headaches. Four years later, she complained of dyspnea; a mediastinal mass was found that proved to be an aortopulmonary paraganglioma that was only partly resectable. A calcified left lung tumor that had been present for 8 years was not resected. Postoperatively, plasma and urinary catecholamines and their metabolites were elevated. Despite intensive radiotherapy to the paraganglioma, progressive superior vena caval and respiratory obstruction developed and led to the patient’s death at age 39 years. No family member was similarly affected.

Case 4
Lymphedema praecox was diagnosed in a 12-year-old girl. During adolescence, Raynaud phenomenon affected her hands. At age 24, investigation of a 4-year history of anemia led to the diagnosis of 12 gastric ‘fibrosarcomas’, for which total gastrectomy was performed. At that time she was hypertensive. Laparotomy at age 24 revealed multiple hepatic metastases. Resection of a left lower lobe calcified mass at 33 years of age disclosed 2 cartilaginous neoplasms. Paroxysmal hypertension, headaches and sweating led to finding an elevated urinary content of the pressor amines and their metabolites. Nephrotomography showed a mass anterior to the upper pole of the left kidney, consistent with a paraganglioma. The patient declined further surgery. She died at age 41, reportedly of metastatic leiomyosarcoma. No family member was similarly affected.

Cases 5–7
The similarity of the findings among cases 1–4 suggested the likely existence of an unrecognized multitumoral syndrome that was not familial. A search of the international medical literature identified 3 pertinent articles. Summaries of the 3 reports follow, and the findings are included in table 1.
Case 5
At age 12, an Italian girl had episodes of hematemesis and melena [5]. An epigastric mass was palpated. Gastric radiographs showed masses in the antrum and body. Subtotal gastrectomy was performed for multiple tumors, interpreted pathologically as leiomyomas. Seven months later, a calcified right lower lobe hamartochondroma was excised. The family history was not mentioned.

Case 6
A 14-year-old American adolescent girl complained of fatigue, pallor and dizzy spells. She was treated for anemia [6]. A firm, nontender upper abdominal mass was palpated at age 16. Gastric radiographs showed a multilobular gastric neoplasm in the lesser curvature and protruding into the gastric lumen. There was a partially calcified 3 × 2 cm lesion in the apex of the left lung. Laparotomy revealed a multilobulated 15 × 8 cm mass in the lesser curvature. A 90% gastrectomy was performed. Pathologically, the tumors were interpreted as leiomyoblastomas. The pulmonary lesion was excised and diagnosed as a chondromatous hamartoma. Hypertension and spells of weakness, tremulousness, and palpitations were present at age 26. Examination revealed a right-sided 12th cranial nerve palsy and a 2-cm mass at the right carotid bifurcation. Carotid angiography showed a glomus jugulare tumor with intracranial extension, a mass behind the internal carotid artery, and a carotid body tumor. Urinary excretion of catecholamine metabolites was increased. The cervical lesions were interpreted as functioning paragangliomas and irradiated. No family member was similarly affected.

Case 7
Iron deficiency anemia in a 20-year-old Swiss woman led to discovery of a lesser curvature gastric tumor [7]. Partial gastrectomy was performed and revealed an ulcerated lesion that was 7 cm in diameter and a second tumor that was 1.5 cm in diameter. The neoplasms were interpreted microscopically as leiomyomas. A chest radiograph 10 months later revealed 2 right-sided masses and 1 left-sided mass that were thought to be probable metastatic leiomyosarcoma.

The Next Case Reported in 1981
Although the 1977 findings were very suggestive if not convincing of a new disorder they needed to be corroborated. Four years passed before the first supporting report appeared. The article reported a case of a young woman who had an aorticopulmonary paraganglioma and gastric leiomyoblastoma [2]. Since then, almost 150 addi-

Fig. 1. Case 1. a Several tumors with excrescences were evident on the gastric serosa. b Polygonal epithelium-like cells with granular eosinophilic cytoplasm and mildly irregular nuclei. c Two paraganglionic tumors formed a dumbbell-shaped mass. d Left upper lobe calcified nodule consistent with pulmonary chondroma. e Extra-adrenal paraganglioma attached to the right adrenal gland. f Right adrenal cortical adenomas. The extratumoral cortex was 0.9 mm thick (normal thickness 1 mm) and was histologically normal. g There was a left adrenal pheochromocytoma and an extra-adrenal paraganglioma attached to the adrenal capsule. h The left adrenal gland contained a pheochromocytoma. The cortex showed normal zonation.
tional patients with 3 of the three tumors or 2 of the three have been described or brought to my attention.

**Nomenclature of the Gastric and Pulmonary Tumors**

**Gastric Tumors**

Several titles were given to the gastric tumors in the earliest case reports. Virtually all suggested a smooth muscle origin. In 1998, this interpretation was proven to be incorrect; the tumors were shown to arise from the interstitial cells of Cajal, the pacemaker cells of the gut [8].

Before 1960, most intestinal intramural mesenchymal spindle cell tumors were thought to arise in smooth muscle and, consequently, were interpreted as leiomyomas or leiomyosarcomas. Some had a round cell component with clear cells and eccentric nuclei. To distinguish these tumors from pure spindle cell lesions, the terms benign leiomyoblastoma and malignant leiomyoblastoma were introduced. Later, because the round cells simulated epithelial cells, the terms epithelioid leiomyoma and epithelioid leiomyosarcoma were advanced. This terminology [9] was favored at the time of our 1977 article [12].

In 1987, an article by Saul et al. [10] described findings in sporadic (nonsyndromic) intramural alimentary tract spindle cell tumors distributed from the esophagus to the colon. The authors introduced the umbrella term gastrointestinal stromal tumors for these tumors. Subsequently, the abbreviated term GIST was used to refer to the round and spindle cell gastric tumors in CTr. However, because the CTr lesions are different clinically, pathologically, behaviorally, and etiologically from sporadic alimentary tract gastrointestinal stromal tumors of the stomach (table 2), the GIST designation is not appropriate for them. Gastric stromal sarcoma is a more accurate terminology.

**Fig. 2.** Case 2. a The cells in the carotid body tumor had clear cytoplasm and were arranged in clusters (zellballen) supported by vascular stroma. b Two submucosal tumors (sectioned), one with ulceration (arrow). c Congenital deformity of the left external ear. d Imaging revealed multiple calcified lesions in the left lung. e Pulmonary chondroma showed benign-appearing cartilage and bone surrounded by a thin pseudocapsule. f Multiple calcified pulmonary lesions were seen in chest X-ray. g Enlargement of the left adrenal gland was evident on abdominal CT examination. h Left adrenal gland featured two juxtaposed neoplasms, one (left) dull yellow with brown and black zones, the other yellow. The slices of the extra-tumoral cortex showed a very thin yellow cortical rim around the medulla. i Two populations of cells, one with clear cytoplasm, the second with granular eosinophilic (pink) cytoplasm were seen in the right tumor in h. j The extratumoral cortex seen in g was 0.2 mm thick (normal ~1 mm) and made up of small cells with eosinophilic cytoplasm. A zona reticularis was not seen. There were also two cortical clear-cell nodules. The pink mass outside the adrenal capsule was hypertrophied smooth muscle of tributary of central vein.