The Origin of Sporadic Gastrinomas Within the Gastrinoma Triangle

A Theory

Edward Passaro, Jr, MD; Thomas J. Howard, MD; Mark P. Sawicki, MD; Philip C. Watt, MD; Bruce E. Stabile, MD

Sporadic gastrinomas are found predominantly within the gastrinoma triangle (85%), frequently within lymph nodes in the triangle (40%) and often multiple (40%). In addition, they are homologous with pancreatic polypeptidomas and express pancreatic polypeptide. We hypothesized that, if gastrinomas were of ventral pancreatic bud origin, several (7) predictions could be made. The data from the investigation of these predictions have supported the theory. We postulate that sporadic gastrinomas in the triangle arise from stem cells from the ventral pancreatic bud that become dispersed and incorporated into lymph tissue and the duodenal wall during the ventral bud’s embryonic dorsal rotation within the area of the triangle.

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Current theories about the origin of pancreatic islet cells suggest that they arise from pancreatic stem cells found at the tips of developing pancreatic ductules. While no theory has been put forward as to the origin of pancreatic endocrine tumors, the elaboration of hormones analogous to their islet endocrine cell counterparts has suggested that they may arise from the corresponding pancreatic stem cells.1 Gastrinomas, commonly considered to be pancreatic endocrine tumors, are different from other tumors inasmuch as no precursor or gastrin-containing cell of the human islet has been found. Although some investigators have found gastrin in human fetal islet tissue transiently, the current consensus is that gastrin cells are not found in human pancreatic islet tissue. No theory for the origin of gastrinomas has been advanced.

We have noted that sporadic gastrinomas lie predominantly in the anatomical area referred to as the gastrinoma triangle.2 The gastrinoma triangle is defined as the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially, both dorsally and ventrally (Figure 1). In considering this unique distribution, the suggestion was made (T.J.H.) that the area of the triangle corresponds to an area of pancreatic development, where the ventral pancreatic bud rotates 180° around the primitive foregut to fuse with the dorsal pancreatic bud. Furthermore, this area is noted for many pancreatic developmental anomalies such as annular pancreas, ectopic pancreas, and pancreas divisum. A decade ago, we hypothesized that, if sporadic gastrinomas were to arise from stem cells of ventral pancreatic bud origin, many predictions could be made. Herein, we list the 7 predictions that were made and the subsequent data that suggest that sporadic gastrinomas found in the gastrinoma triangle arise from stem cells originating from the ventral pancreatic bud dispersed during its embryonic rotation.

See Invited Commentary at end of article

1. The distribution of pancreatic endocrine tumors occurs in 2 distinct clusters that correspond topographically to the anatomic areas derived from the ventral and dorsal pancreatic buds.

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In man, the embryonic ventral pancreatic bud gives rise to the pancreatic polypeptide (PP) cell exclusively, which is considered to be a marker for tissue of ventral pancreatic bud origin. The dorsal pancreatic bud gives rise to the insulin- and glucagon-producing cells predominantly. Thus, pancreatic endocrine tumors, if derived from their corresponding pancreatic islet cells, would be expected to show a dominant distribution within the pancreas, which is consistent with either ventral or dorsal pancreatic bud origin, depending on the particular tumor cell type. Anatomically, the area within the gastrinoma triangle coincides with ventral pancreatic bud derivation, whereas localization within the pancreas outside of the gastrinoma triangle coincides with dorsal pancreatic bud derivation. A review of 577 reported pancreatic endocrine tumors with data on their intraabdominal location confirmed this assumption. These data show 2 distinct distributions or clusters of tumors: one of them consists of gastrinoma, pancreatic polypeptideoma (PPoma) and somatostatinoma, of which 71% to 80% are localized within the gastrinoma triangle (ventral pancreatic bud derivation); the other consists of glucagonoma and insulinoma, of which 74% to 77% are localized outside the gastrinoma triangle (dorsal pancreatic bud derivation).

2. Given the known distribution of pancreatic islet endocrine cells in various portions of the pancreas and assuming that they all have an equal risk for tumor formation, a prediction can be made of the expected number of each type of endocrine tumor that will occur for each region of the pancreas. This expected distribution for pancreatic endocrine tumors can then be compared with their reported distribution.

Working “backward,” the predicted distribution for each of the known pancreatic endocrine tumors correlates very well with their observed frequency (Table 1). Inasmuch as the cell of origin of sporadic gastrinomas is unknown, a prediction cannot be made for them. Nevertheless, their predominant anatomical pattern of distribution (peripancreatic, duodenal, and pancreatic head) suggests that they arise from a ventral pancreatic bud source. Also, gastrinomas are common relative to other pancreatic endocrine tumors, suggesting that either their cell of origin is abundant or transformation of a putative stem cell to a gastrinoma is favored over transformation to other endocrine cell types.

Gastrinomas have great homology to PPomas. They have the same relative distribution, the same localization (adjacent to but not in the pancreas), the same incidence of being found in lymph nodes, and the same rate of being cured by excision. These attributes are shared by all the tumors considered to be of ventral pancreatic bud origin and are markedly different from insulinomas and glucagonomas that have none of these characteristics and are considered to be of dorsal pancreatic bud origin.

In particular, the multiplicity of gastrinomas, their high incidence of extrapancreatic location (40%), and their frequent location in lymph nodes (40%) suggest that the putative stem cell of their genesis is of ventral pancreatic bud origin and that these ventral pancreatic bud cells migrate during the posterior rotation of the ventral pancreatic bud to become incorporated in embryonic lymph tissue, later coalescing to form lymph nodes (Figure 2). These lymph node tumors in sporadic gastrinoma are in-

![Figure 1. The retroperitoneal structures showing the pancreas, duodenum, extrahepatic biliary system, superior mesenteric artery (SMA), and superior mesenteric vein (SMV). The anatomic areas to the right and left of the SMA are shown separated by a solid vertical line drawn through the neck of the pancreas. The gastrinoma triangle is depicted (dashed lines) to the right of the SMA. (Reproduced, with permission from Howard et al.)](image-url)

<table>
<thead>
<tr>
<th>Endocrine Tumors</th>
<th>Peripancreatic</th>
<th>Duodenum</th>
<th>Pancreas</th>
<th>Within Gastrinoma Triangle</th>
<th>Outside Gastrinoma Triangle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinomas</td>
<td>48</td>
<td>32</td>
<td>51 (NA)</td>
<td>20 (NA)</td>
<td>23 (NA)</td>
</tr>
<tr>
<td>Pancreatic polypeptideoma</td>
<td>3</td>
<td>1</td>
<td>11 (18)</td>
<td>3 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>0</td>
<td>5</td>
<td>15 (7)</td>
<td>1 (11)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>0</td>
<td>0</td>
<td>20 (21)</td>
<td>32 (41)</td>
<td>34 (24)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>0</td>
<td>2</td>
<td>71 (64)</td>
<td>115 (129)</td>
<td>92 (87)</td>
</tr>
</tbody>
</table>

*Adapted from Howard et al.†
†Predicted distributions were calculated from the endocrine cell volume density measurements for pancreatic islets, as reported by Rahier et al.‡
‡P<.05 by x² test.
troubling because of the following characteristics: histopa-thologically, they contain benign features; clinically, they behave in a benign fashion; and, in several instances of single lymph nodal gastrinomas (without the corresponding “mother” tumor), they have been resected for long-term cures.6,7 Similarly, PPomas would be expected to arise in the same way. The relative greater numbers of gastrinomas compared with PPomas suggest that either gastrinoma stem cells are more prevalent or gastrinoma formation is favored from a common stem cell progenitor during tumor development.

4. If stem cells of ventral pancreatic bud origin are found in lymph nodes in the gastrinoma triangle as a result of embryonic migration, then ectopic pancreatic tissue in lymph nodes would also be expected to be found in the gastrinoma triangle.

The expectation is that formed pancreatic elements, ie, ectopic pancreatic acinar and islet tissue, and the theoretically more common isolated stem cells of ventral pancreatic bud origin, would be found in lymph nodes in the area of ventral pancreatic bud migration, the gastrinoma triangle. When first postulated, we never expected to find such an instance. In fact, 4 examples of ectopic pancreatic tissue in lymph nodes are recorded.8 Of these, 3 are noted to be in the gastrinoma triangle and the only 1 that was studied contained islets with PP staining cells (see below). This suggests that the postulated mechanism of ventral pancreatic bud elements migrating during the rotation of the ventral pancreatic bud and being incorporated into lymphoid elements is possible. The recent finding of chromogranin A staining putative endocrine cells in the lymph nodes of patients undergoing a Whipple procedure for adenocarcinoma of the head of the pancreas (gastrinoma triangle) is also consistent with this hypothesis.9 Unfortunately, staining for PP in this series was not reported.

5. Sporadic gastrinomas found in the gastrinoma triangle should contain PP immunoreactivity to a higher degree than sporadic gastrinomas found on the left side of the abdomen, outside the gastrinoma triangle.

Pancreatic polypeptide is secreted by pancreatic endocrine cells derived almost exclusively from the ventral pancreatic bud. Because of this singular embryonic derivation, expression of PP has been proposed as a marker for ventral pancreatic bud derivation.1 Expression of PP has been found in up to 57% of pancreatic endocrine tumors. We found PP immunoreactivity in 7 (50%) of 14 sporadic gastrinomas that were evaluated.10 Of sporadic gastrinomas found within the gastrinoma triangle, however, 7 (78%) of 9 contained PP immunoreactivity whereas no PP expression was found in the 5 sporadic gastrinomas removed from the left side of the abdomen (outside the gastrinoma triangle). This finding of a high incidence of PP immunoreactivity in gastrinomas found within the gastrinoma triangle and no PP immunoreactivity in gastrinomas found outside the gastrinoma triangle is consistent with our hypothesis of ventral pancreatic bud origin.

6. Ectopic extrapancreatic gastrinomas would be found predominantly on the right side of the abdomen (ventral pancreatic bud origin).

Most such gastrinomas are found in the ovary. On review, 11 of 13 extrapancreatic gastrinomas were found on the right side of the abdomen.11 Ovarian tissue is considered to be pluripotential and, in fact, has been associated with many endocrine tumors such as thyroid or adrenal gland tumors. These other tumor types have never been shown to have a predilection for either the right or left side of the abdomen. This preponderance of ovarian gastrinoma on the right side defies this balance and suggests a common origin with those tumors found in the gastrinoma triangle.

7. Gastrinomas found outside the gastrinoma triangle, which presumably have a different origin than those derived from the ventral pancreatic bud, may have different clinical characteristics or biological behavior.

Our recent investigation of this prediction among 60 sporadic gastrinomas from 2 large series11,12 shows that tumors thought to be of ventral pancreatic bud origin are predominantly benign, commonly found within lymph nodes, often extrapancreatic in location, and only rarely metastasizing to the liver, whereas tumors found in the body and tail of the pancreas (dorsal bud) are rarely within lymph nodes, and are never found in extrapancreatic locations. Metastases to the liver are frequent with sporadic gastrinomas found outside the gastrinoma triangle (nonventral pancreatic bud origin), as is death from the tumor; both supporting the notion that these gastrinomas behave differently from those found within the gastrinoma triangle (Table 2).

The finding that sporadic gastrinomas from different anatomical regions have markedly different biological behavior implies that their cellular phenotypes are distinctly different. Either each tumor (ventral bud and nonventral pancreatic bud) originates from an identical stem cell and subsequent differentiation results in a benign (ventral) or malignant (nonventral) phenotype, or—alternatively—the tumors arise from 2 phenotypically distinct stem cells: one, derived from the ventral pancreatic bud, results in a benign tumor while the other from the nonventral bud results in a malignant tumor.
consistent with the hypothesis, with an exception for so-

surprised with the frequency with which the data were

may arise from a fetal stem cell.

ally, pheochromocytomas, which are often multiple and

the head and neck region, where no primary tumor is ever

for up to 27 years.13 It seems possible that “metastatic”

alternative pancreatic bud origin (outside the gastrinoma triangle) and those of dorsal pancreatic bud origin (outside the gastrinoma triangle) suggests markedly different molecular mechanisms for the development of these tumors.

We consider the predilection for gastrinoma tumor formation in the ventral pancreatic bud over other tumor types (PPoma or somatostatinoma) to be an important observation. Gastrinomas may preferentially occur because the putative stem cell would be an embryonic stem cell capable of producing gastrin, which is known to have important trophic effects on the gastrointestinal tract during prenatal development. In the rat, for example, gastrin is present in the embryonic pancreatic islet during their early stages of development, but it disappears from the islet just prior to birth.

An important aspect of this theory is that a fetal cell present in the adult is being implicated in tumor (gastrinoma) formation. This requires that such fetal cells persist in adults. We believe that this may be more common than is recognized. Recently, for example, it was detected that fetal cells can persist in the mother’s blood for up to 27 years.11 It seems possible that “metastatic” squamous cell cancers contained within lymph nodes in the head and neck region, where no primary tumor is ever detected could arise by a similar mechanism. Additionally, pheochromocytomas, which are often multiple and can be found in ectopic sites (organ of Zuckerkandl), have many of the same characteristics as gastrinomas and also may arise from a fetal stem cell.

In the course of these investigations, we have been surprised with the frequency with which the data were consistent with the hypothesis, with an exception for so-

mamatostatinomas. As yet, we have no plausible explana-

ation for this discrepancy, but the number of tumors studied at this time may be inadequate to resolve the question.

Gastrinomas are not found in “normal gastrin-bear-
tissues,” ie, the gastric antrum and duodenum. Gastrinomas found in the duodenum are suberosal or intramural, or submucosal in location. If these tumors were from a gastrin-producing cell originating within the duodenal mucosa, the expectation would be that the result tumor is found intraluminally, as are all other gastro-

testinal tumors of mucosal origin. These observations suggest that gastrinomas found in the duodenum are not of duodenal but of ventral pancreatic bud origin, whose cells became incorporated into the duodenal wall during embryonic development.

Table 2. Clinical Characteristics of 60 Patients With Sporadic Gastrinoma*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Right of SMA:</th>
<th>Left of SMA:</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Total No. of patients</td>
<td>47 (78)</td>
<td>12 (22)</td>
<td>. . .</td>
</tr>
<tr>
<td>Extrapancreatic tumors</td>
<td>16 (34)</td>
<td>0</td>
<td>.001†</td>
</tr>
<tr>
<td>Tumor in lymph nodes</td>
<td>27 (57)</td>
<td>1 (8)</td>
<td>.005†</td>
</tr>
<tr>
<td>Multiple tumors</td>
<td>10 (21)</td>
<td>4 (31)</td>
<td>.5†</td>
</tr>
<tr>
<td>Hepatic metastases</td>
<td>9 (19)</td>
<td>9 (69)</td>
<td>.002†</td>
</tr>
<tr>
<td>Cures*</td>
<td>19 (40)</td>
<td>1 (7)</td>
<td>.004†</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>94±15</td>
<td>111±25</td>
<td>.4§</td>
</tr>
</tbody>
</table>

* Analyzed according to whether the tumor was found to the right, ie, within the gastrinoma triangle (GT), or left, ie, outside GT, of the superior mesenteric artery (SMA). Adapted from Howard et al.35
†P value calculated using the Fisher exact test.
‡Cure defined as eugastrinemia, a negative secretin stimulation test result, and no tumor recurrence on follow-up evaluation.
§P value calculated using the unpaired t test.

The known clinical data of sporadic gastrinomas, ie, their clustering within the gastrinoma triangle, high incidence of multiplicity and extrapancreatic location, occurrence within lymph nodes in the gastrinoma triangle, homology with PPomas, and their staining for PP, lead us to hypo-
thesize that these gastrinomas are of ventral pancreatic bud stem cell origin. We postulate that, during development, stem cells from the ventral pancreatic bud became dis-
persed and incorporated into developing lymphoid tissue and the duodenal wall during the ventral pancreatic bud’s embryonic dorsal rotation. Such a putative stem cell should be found within lymph nodes in the gastrinoma triangle and duodenal wall and stain for endocrine markers such as chromogranin A and (strongly) for PP.

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tor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl
The original report by Stabile et al that the gastrinoma triangle harbored most sporadic gastrinomas was a seminal clinical observation. Its importance to the study of gastrointestinal endocrine tumors is no less than that of William Beaumont to gastric physiology. From the observation that most sporadic (nonhereditary, i.e., multiple endocrine neoplasia type I) gastrinomas occurred in the gastrinoma triangle, these investigators have continued to examine this phenomenon. They have removed the mystery from the “ectopic” gastrinomas. The mystery sprung from the false concept that all gastrinomas should arise in the pancreas; the original patients had pancreatic neoplasms. No gastrin-containing cells can be identified in the adult human pancreas. The authors’ work has been hampered by the relative rarity of these tumors and the inability to conduct a prospective randomized trial. However, their prescient observation and persistent examination have led them to their current description. Passaro et al provide a strong argument for 2 types of sporadic gastrinomas: those that occur (most) in the gastrinoma triangle that apparently arise from a stem cell from the ventral pancreatic bud, the cells of which produce pancreatic polypeptide—an marker of ventral bud origin—and those that arise outside. Tumors that arise in the gastrinoma triangle or, possibly, from the ventral bud have different, less aggressive, biologic behavior from those sporadic gastrinomas that arise outside the triangle. The authors propose that the role of these cells during early fetal development (none can be found in the adult) may possibly be related to the known trophic effects of gastrin, which we and others have described, and that they are vital for the development of the gut; this may explain the less aggressive tumors.

The article by Passaro et al should be studied and restudied by clinicians and clinical investigators for the importance of the message that critical clinical observation coupled with knowledge of biology can explain not only relatively rare phenomena, but also that the same principles can be applied to more common occurrence. I salute these investigators for their contribution to our knowledge and for the lessons they have taught us.

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IN OTHER AMA JOURNALS

JAMA
Managing the Interface Between Medical Schools, Hospitals, and Clinical Research
John I. Gallin, MD; Helen L. Smits, MD

Objective.—To review how academic health centers are coping with the changing environment of health care delivery with special emphasis on the impact of the changing health care system on clinical research.

Design.—In response to Health and Human Services Secretary Donna Shalala’s 1995 mandated review of the National Institutes of Health (NIH) Warren Grant Magnuson Clinical Center, an NIH review team visited 30 health facilities and government-owned organizations throughout the country. The review team determined what strategies are used by academic health centers to survive and thrive in the changing health care marketplace. The findings have implications for the NIH Clinical Center as well as academic health centers.

Conclusions.—Management strategies in successful academic health centers include streamlined governance structures whereby small groups of highly empowered group leaders allow institutions to move quickly and decisively; an active strategic planning process; close integration of hospital and medical school management; heavy investment in information systems; and new structures for patient care delivery. Successful centers are initiating discussions with third-party payers and are implementing new initiatives, such as establishing their own managed care organizations, purchasing physician practices, or owning hospitals. Other approaches include establishing revenue-generating centers for clinical research and new relations with industry. Attention to the infrastructure required to support the training and conduct of clinical research is essential for the future vitality of medical schools. JAMA. 1997;277:631-634

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