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COMMON ORIGIN FOR ALL NEUROENDOCRINE TUMORS

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Believing we have reasonably well established the carcinoid-islet cell concept, we feel obligated to explore what we believe to be significant overlap between carcinoid-islet cell tumors and the other neuroendocrine tumors. The other neuroendocrine tumors, which are thought to originate embryologically from the neural crest and to be of ectodermal origin, include tumors of any of the glands that secrete peptide hormones (anterior pituitary, thyroid, parathyroid, carotid body, thymus, adrenal medulla). The ovaries, testes and adrenal cortex originate from the nephrogenic ridge, are thought to be of mesodermal origin, and not secrete peptide hormones (26).

It is striking that carcinoid-islet cell tumors may secrete gastrin, insulin, serotonin, or histamine in any combinations. It is even more striking that what were formerly called carcinoid tumors have been associated with the production of glucagon, ACTH, MSH, catecholamines, kallikrein, and bradykinin (20, 24). What were formerly called islet cell tumors have been implicated in the production of glucagon ADH, catecholamines, ACTH, MSH, and secretin (5, 11, 24—27, 30). If we lump the carcinoid-islet cell tumors together we may say that these tumors are potentially capable of secreting almost any of the peptide hormones. Furthermore, chemodectomas have also been found that secreted catecholamines (22, 24), and there is evidence to suggest that 5HIAA and VMA are formed chemically from a common decarboxylase (12).

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Medullary thyroid carcinomas have been known to secrete ACTH and produce Cushing's syndrome. On bioassay of 2 of these tumors, in patients with Cushing's syndrome, DONAHOWER et coll. found elevated ACTH levels in the tumor cells. One of these patients also had pheochromocytomas in both adrenal medullas (3).

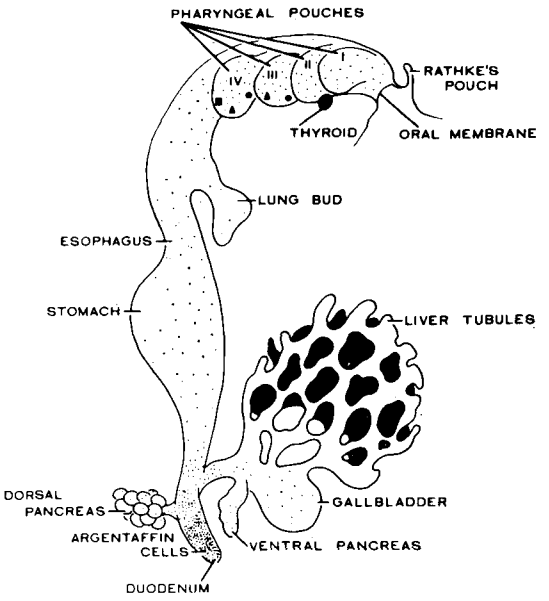
Werner's syndrome (multiple endocrine adenomatoses, MEA) is a well established entity. According to other authors, it occurs in as many as 25 per cent or more of patients with the Zollinger-Ellison syndrome (19, 29, 31). Eighteen per cent of the patients with carcinoid-islet cell tumors that we presented in an earlier paper (7) had other neuroendocrine tumors and thus the MEA syndrome. There is also a familial form of this syndrome.

The most common variant of the MEA syndrome includes adenomas of the anterior pituitary, parathyroid and pancreatic islets. 'Carcinoids' have also been associated with this syndrome relatively frequently (6, 10, 23, 24).

So, grouping carcinoid and islet cell tumors together, we may say that the most common variant of the MEA syndrome is: tumors of the anterior pituitary gland, of the parathyroid gland, and carcinoid-islet cell tumors. All of these tumors can be related to neural ectoderm and all are capable of producing peptide hormones. The second most common variant of the MEA syndrome is: tumors of the thyroid, adrenal medulla and adrenal cortex. One of us (R. W.) has suggested that the association of the adrenal cortex to the tumors of the thyroid and adrenal medulla is probably not a true part of the MEA syndrome but is an incidental or secondary phenomenon (24). The medullary thyroid carcinoma-pheochromocytoma-neurofibromatosis syndrome is clearly of neural ectodermal origin and is also considered to be a variant of the MEA syndrome (24).

Chemodectomas have been found in association with thyroid carcinomas in several patients, and it was postulated that this association is possibly a neural ectodermal dysplasia related to the medullary thyroid carcinoma-pheochromocytoma-neurofibromatosis syndrome (1). Medullary thyroid carcinomas have also been associated with functioning parathyroid adenomas (4, 8, 13, 15, 16, 17, 18, 21, 24). The association of thyroid and parathyroid adenomas links the two main variants of the MEA syndrome previously mentioned and thus suggests that the entire MEA syndrome may be a dysplasia of neural ectoderm. The familial variant of this syndrome supports this hypothesis.

The following tumors have been associated with the production of serotonin: carcinoid-islet cell tumors; acinar and ductal carcinomas of the pancreas; oat cell, squamous cell and adenocarcinomas of the lung; medullary carcinomas of the thyroid gland and neuroblastomas. Some of these tumors have also produced insulin, ACTH, and catecholamines (24—27). They seemed however to be linked by their production of a common hormone, serotonin. Therefore, since



Diagrammatic representation of the distribution of argentaffin cells in the nervous system, gastrointestinal tract and their derivatives. The dots represent sites where argentaffin cells have been found and reported. ● Parathyroid. ▲ Thymus. ■ Ultimobranchial body.

serotonin production is associated with argentaffin cells, and since all these tumors secreted serotonin, it would seem logical to assume that they contained argentaffin cells or precursors to argentaffin cells, even though the tumors are not the same histologically. All of these tumors can either be related to neutral ectoderm or arise where neuroectodermal cells are found.

All of these facts point to a functional overlap among the neuroendocrine tumors that is more than casual and clearly shows that neuroendocrine tumors of different histologic types may secrete a common hormone (e.g. anterior pituitary tumors and medullary thyroid carcinomas may secrete ACTH) and neuroendocrine tumors of the same histologic type may secrete different hormones (carcinoid islet cell tumors may secrete insulin, gastrin, serotonin, kallikrein, catecholamines, etc.). It has been suggested previously by one of us (R. W.) that all the neuroendocrine tumors arise from a single stem cell, the argentaffin cell (26), which originates in the neural crest embryologically. These cells may be found normally in the central nervous system, stomach, gallbladder, pancreas and small bowel (Figure).

The histologic type of tumor that develops from this common stem cell has not been explained, and we have no good explanation; many factors are probably responsible. That there is such a significant overlap in function among the neuroendocrine tumors and that there is a multiplicity of tumors in some patients

presents a confusing perspective regarding them. It therefore would seem inappropriate to continue to regard these complex tumors as separate, unrelated entities. We believe that some system for grouping them together more closely is needed so that they may be better understood in the future. This may be accomplished with a new nomenclature system as follows: Key: Neuroendocrine tumor (s), location (s) ____, histologic type (s), secreting ____.

For instance, some of the tumors from the literature and that we have dealt with in our own experience would be:

Case 1: Neuroendocrine tumors, I parathyroid gland and II duodenum, I parathyroid adenoma histologic types, secreting I parathormone, and II carcinoid-islet cell histologic type, II secreting gastrin and insulin.

Case 2: Neuroendocrine tumor, pancreas, carcinoid-islet cell histologic type, secreting gastrin and insulin.

Case 3: Neuroendocrine tumor, duodenum, carcinoid-islet cell histologic type secreting gastrin.

Case 4: Neuroendocrine tumor, pancreas, gastrointestinal tract, lungs, carcinoid-islet cell type secreting gastrin and 5HIAA.

Case 8: Neuroendocrine tumor, pancreas, carcinoid-islet cell histologic type, non-secreting.

Other examples would be: Neuroendocrine tumor, bladder, chemodectoma histologic type, secreting catecholamines (22, 24). Another, neuroendocrine tumors, I thyroid and II adrenal medulla, I medullary thyroid carcinoma and II pheochromocytoma histologic type, I secreting ACTH (3).

This nomenclature system would seem to both simplify our thinking about these complex tumors and to stimulate us to consider that a neuroendocrine tumor may either be multifunctional or be associated with other neuroendocrine tumors. Therefore, patients with a neuroendocrine tumor should be considered for a complete neuroendocrine analysis.

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SUMMARY

The neuroendocrine tumors, which originate embryologically from the neural crest, secrete peptide hormones and consist of carcinoid-islet cell tumors, anterior pituitary tumors, thyroid tumors, parathyroid tumors, chemodectomas, pheochromocytomas and others, have been found to possess significant functional overlaps and to be related more closely than was previously thought. We have devised a new nomenclature system for this group of

tumors aimed at providing a clearer understanding of them and their relationships to each other.

ZUSAMMENFASSUNG

Die neuroendokrinen Tumoren, die embryologisch von der Neuralleiste herstammen, sezernieren Peptidhormone und bestehen aus Karzinoid-Inselzell-Tumoren, Tumoren des Hypophysenvorderlappens, der Thyreoidea und Parathyreoidea, Chemodektomen, Pheochromozytomen und anderen Tumoren; diese zeigen signifikante funktionelle Überschneidungen und sind enger miteinander verwandt als zuvor angenommen. Die Autoren haben ein neues Nomenklatursystem für diese Gruppe von Tumoren konstruiert, das ein besseres Verständnis dieser Tumoren und deren Verwandtschaft zueinander vermitteln soll.

RÉSUMÉ

Les tumeurs neuro-endocrines qui proviennent embryologiquement de la crête neurale, sécrètent des hormones peptidiques et consistent en tumeurs de cellules carcinoïdes, en tumeurs hypophysaires antérieures, en tumeurs thyroïdiennes, tumeurs parathyroïdiennes, chémodectomes, phéochromocytomes et autres; les auteurs ont constaté que leurs fonctions se chevauchent de façon importante et qu'elles sont apparentées plus étroitement qu'on ne le pensait auparavant. Les auteurs ont créé un nouveau système de nomenclature pour ce groupe de tumeurs de façon à permettre une compréhension meilleure de ces tumeurs et de leurs relations mutuelles.

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