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# Current Status of the Apudomas

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THE APUD CELLS were described by Pearse in 1968[13] and the term "apudoma" was applied to a tumor arising from apud cells by Szijj and her colleagues the following year.[19] The apud cells have common cytochemical characteristics, clearly related to the synthesis of polypeptides and amines, and are distributed widely in the body. The apudomas are a family of endocrine tumors which arise from them and which have interesting and important relationships. The cytochemical, ultrastructural and immunological features of normal and neoplastic cells are very similar.

## The Apud Concept

The apud cells derive their name from the initial letters of their first three, and most important, properties, namely (1) a high content of *A*mine, (2) the capacity for amine *P*recursor *U*ptake, and (3) the presence of amino-acid *D*ecarboxylase for the conversion of the aminoacid precursors to amines.

The ultrastructural characteristics of the apud cells, as seen on electronmicroscopy, are similar to those of other polypeptide-secreting cells. Most of them are 100 to 200 $\mu$m in diameter and many contain dense storage granules of their polypeptide products. Many of those in the gut have long apical processes, which reach the glandular lumen, ending in tufts of microvilli, which may be sensory (Fig. 1).

The polypeptide products of apud cells can be displayed specifically by immunological techniques. One involves immunofluorescence (Fig. 2), and another labeling with peroxidase (Fig. 3).

The apud cells may be considered in 3 groups (Tables 1, 2 and 3), namely: 1) central, 2) general and 3) alimentary.

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Knowledge about their secretory products is advancing very rapidly and many, perhaps most, of them are now known. Some secrete polypeptides only, some amines only and some both. Many of these humoral agents are hormones (e.g. ACTH, gastrin and epinephrine), while others have not achieved this status, although some may well do so in time (e.g. gastric inhibitory polypeptide—GIP and somatostatin).[8] One at least (vasoactive intestinal polypeptide—VIP) has no known physiological function, but plays a major role in disease.

Some polypeptide-secreting cells are *not* apud in character. The parathyroid cells, while not apud, are closely related in ways which will be described later. Those cells of the anterior pituitary, which secrete glycoproteins (TSH, FSH and LH), and the endocrine cells of the kidney and placenta are probably unrelated.

At an early stage in the investigation of the apud cells it was noticed that in certain ways they were structurally and chemically similar to nerve cells. In particular, the neuroectodermal cells of the neural crest display apud characteristics from an early stage. This observation prompted Pearse in 1966 to suggest that the neural crest cells must be considered as possible ancestors of all the polypeptide-secreting cells of the apud series. The cells of the adrenal medulla and sympathetic nervous system and the melanocytes of the skin have long been known to arise from the neural crest. It is now established that the apud cells of the carotid body and thyroid come from the same source. Evidence is accumulating that those of the alimentary tract and other

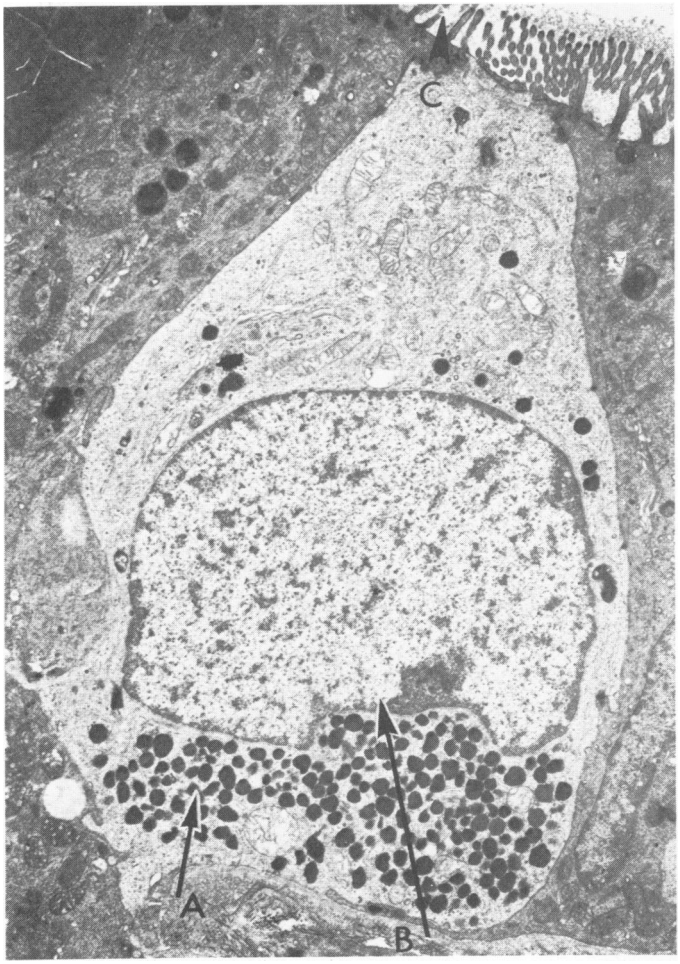


FIG. 1. Electronmicrograph of an apud cell with numerous electron dense secretory granules localized towards vascular pole and microvilli in lumen of gland (×8,400). A-Storage Granules; B-Nucleus; C-Microvilli in Lumen.

sites may well do so too. Recent work suggests that the hypothalamus and both lobes of the pituitary are a single, rather than composite, entity of neuroectodermal origin and that the parathyroids, which have long been regarded as of endodermal origin, may arise from neuroectoderm also.[15]

## The Apudomas

There is little etymological justification for the word "apudoma," but it is useful because it emphasizes the common characteristics of neoplastic lesions of the apud cells. They may be described in both pathological and biological terms. Pathologically apudomas are endocrine neoplastic lesions which take the form of adenoma, adenomatous hyperplasia or carcinoma. For convenience, apud cell hyperplasia (although not neoplastic) may be classed with the apudomas because it resembles them functionally (Fig. 3). All possess the apud cytochemical and ultrastructural characteristics, most of them with great clarity. Biologically the apudomas are neoplastic lesions, derived from apud cells and thus neuroectodermal in quality, which secrete normal or modified polypeptide hormones or prohormones of the apud cell series and/or one or more of the apud amine hormones.

At least half the apud cells which have been recognized are known to give rise to apudomas (Tables 2 and 3) and new ones are being discovered frequently. Some tumors, which are well known, but not recognized as such, may turn out to be apudomas. Neoplastic cells tend to be less differentiated in structure and function than their parent cells and the secretory capacity of apudomas is very versatile. Many (e.g. insulinomas and pheochromocytomas) are orthoendocrine and secrete the normal hormones of their presumptive cells of origin, but many are *para*endocrine and secrete, either instead or in addition, hormones or humoral agents which are characteristic of other apud cells. This versatility suggests that they are capable of mobilizing all the primitive secretory capacity of the neural ectoderm and, in particular, of the neural crest. Some paraendocrine apudomas, like tumors of other types, secrete substances, such as prostaglandins, histamine, erthyropoietin and other humoral agents, which are characteristic products of other, non-apud, cells. This property, which is poorly

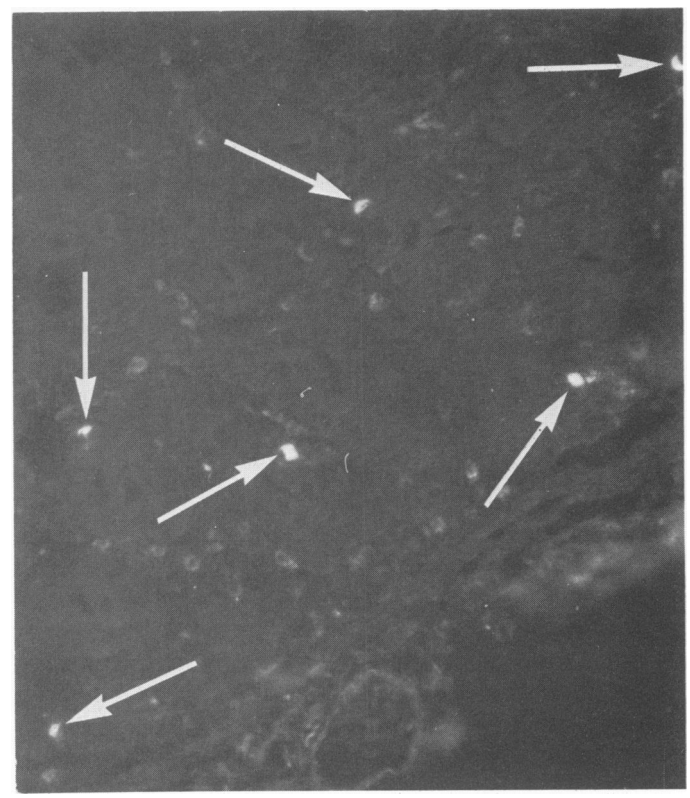

FIG. 2. Human jejunum stained with an indirect (sandwich) immunofluorescent method using procine anti-GIP antibody. Six GIP cells can be seen localized mainly in basal portion of gland (marked with arrows) (×165).

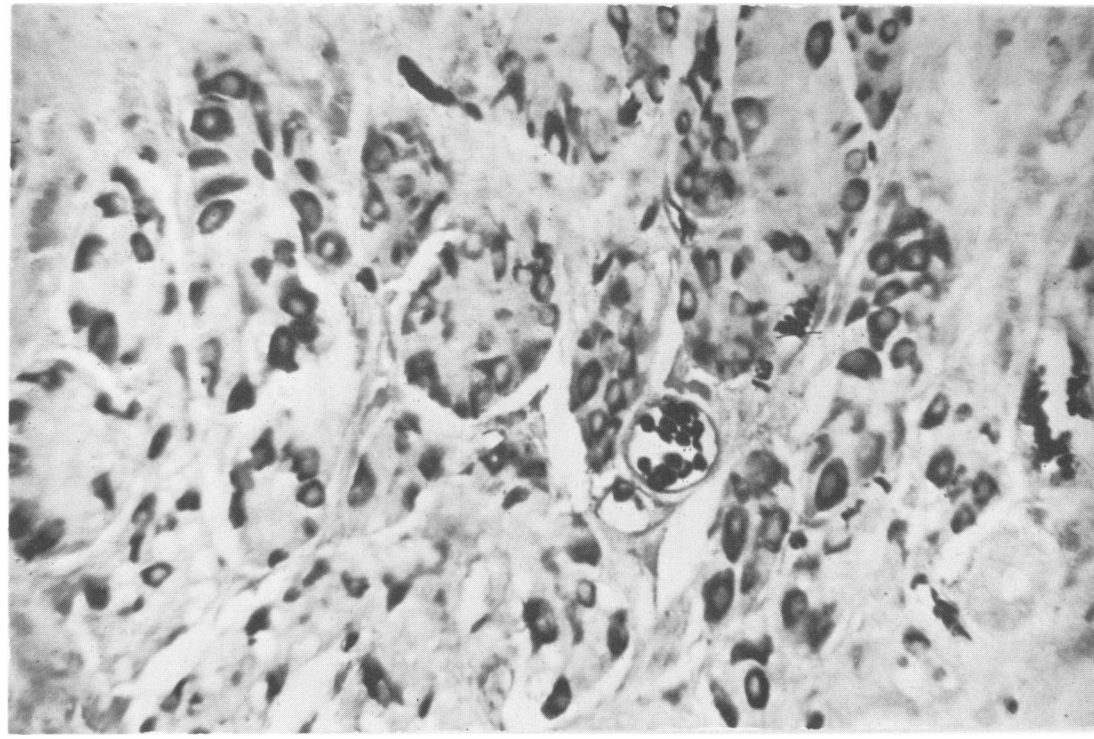

FIG. 3. Human antrum stained with an immunoperoxidase method using antibodies to human gastrin I. G cells appear numerous (moderate hyperplasia) and heavily stained (×390).

understood, is unlikely to derive specifically from their presumptive neural origin, but rather to reflect a function of neoplastic tissue in general.

The apudomas constitute a large part of surgical endocrinology. The brief account which follows is not comprehensive, but concentrates on recent advances in their understanding in relation to the apud concept and in other more specific details.

### *Identification of Apudomas*

Apudomas may be studied in various ways. The concentrations of polypeptides and amines may be measured in the peripheral blood, and in the venous blood draining the tumor, by radioimmunoassay and by other methods. The tumors may be examined by conventional light microscopy, cytochemical methods, electronmicroscopy and immunocytochemistry, and extracts from the tumors may be analyzed for their products. Specific immunocytochemistry (Fig. 4) will usually provide a positive result only if there is ultrastructural evidence of the presence of at least a few storage granules in each cell. The full secretory properties of an apudoma will be elucidated only if every suspected tumor is tested, not only for its presumptive hormone, but also for as many others as possible. Hormones which are clinically "silent"

TABLE 1. *Centrally Located Apud Cells, Their Products and Their Associated Apudomas and Clinical Syndromes*

| Organs | Cells | Products | | Apudomas | Orthoendocrine Syndromes |
|---|---|---|---|---|---|
| | | Polypeptides | Amines | | |
| Hypothalamus | Neurones | Releasing & inhibiting hormones | Dopamine, Norepinephrine & 5-HT | ? | ? |
| Posterior pituitary | Neurones | ADH | — | ? | ? |
| | | Oxytocin | — | ? | ? |
| Anterior pituitary | c | ACTH | ? Tryptamine | Hyperplasia | Cushing's |
| | m | MSH | ? Tryptamine | Adenoma | Pigmentation |
| | s | GH | — | Carcinoma | Acromegaly or giantism |
| | l | Prolactin | — | | Forbes-Albright |
| Pineal body | P | Melatonin | 5-HT | Pinealoma | Hypogonadism |

*Abbreviations*: ACTH = (Adreno)corticotrophin; ADH = Antidiuretic hormone; GH = Growth hormone; 5-HT = 5-hydroxytryptamine; MSH = Melanocyte-stimulating hormone.

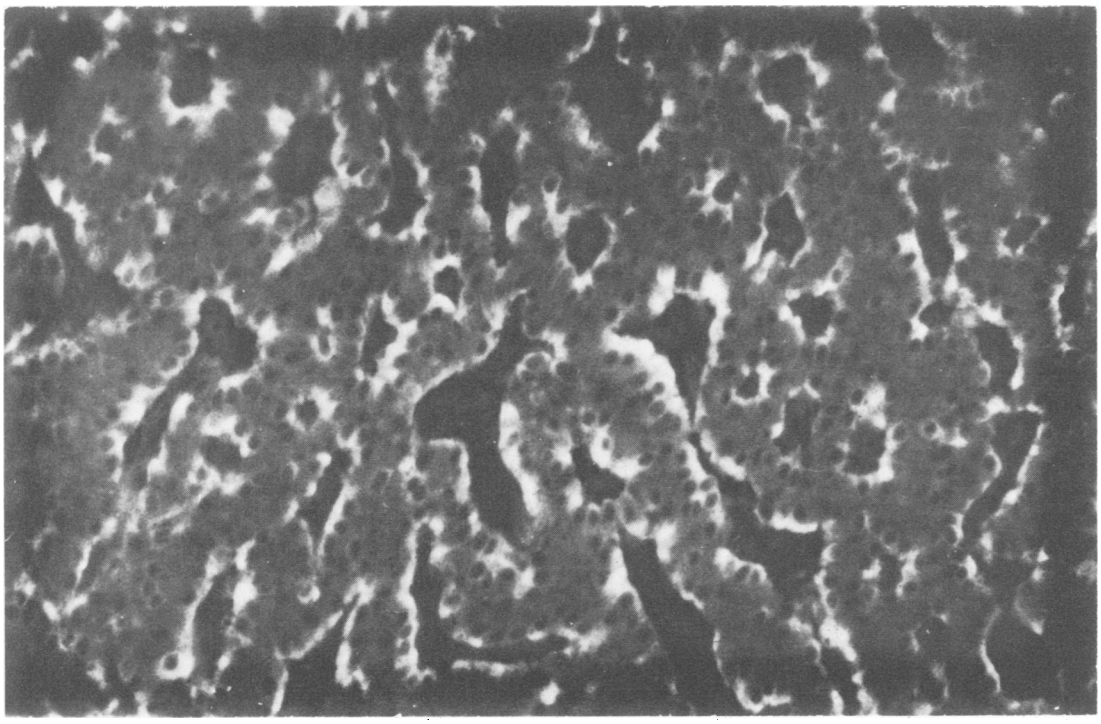

FIG. 4. Human pancreatic insulinoma stained with an indirect immunofluorescent method using antibodies to insulin. Tumor cells appear brightly stained (×320).

may predominate, as in calcitoninomas (medullary carcinomas of the thyroid) and some paraendocrine tumors.

Apudomas may be named conveniently after their endocrine products. For single hormone tumors the terms "insulinoma" and "gastrinoma" are well established, but others such as "corticotrophinoma," "calcitoninoma" "glucagonoma" and "vipoma" may also be applied. To avoid unnecessary hybrids in multihormone-producing apudomas, the combined pathological/histological description could well be "apudoma secreting ACTH/MSH" and so on.

TABLE 2. *Generally Distributed Apud Cells, Their Products and Their Associated Apudomas and Clinical Syndromes*

| Organs | Cells | Products: Polypeptides | Products: Amines | Apudomas | Ortho-endocrine Syndromes | Principal Paraendocrine Syndromes (& Hormones) |
|---|---|---|---|---|---|---|
| Thyroid | C | Calcitonin | ? 5-HT | Medullary carcinoma | Hypercalcitoninemia | Cushing's (ACTH) |
| Adrenal medulla | E | ? | Epinephrine | Pheochromocytoma | Hypertension, etc. | Cushing's (ACTH) |
| | NE | ? | Norepinephrine | Ganglioneuroblastoma | | WDHA (VIP) |
| Carotid body | Type 1 (Glomus) | ? | Catecholamines & 5-HT | Chemodectoma | Hypertension, etc. | ? |
| Lungs | P (Feyrter) | ? VLP | ? | ? Oat cell carcinoma | ? | Cushing's, etc. (ACTH, MSH, 5-HT) Schwartz-Bartter (ADH) |
| | EC | ? | ? 5-HT<br>? 5-HTP | Carcinoid | Atypical carcinoid | Cushing's (ACTH, 5-HT) |
| Urinary tract | U | ? Urogastrone | ? | ? | ? | ? |
| | EC | ? | ? 5-HT | ? | ? | ? |
| Skin | Melanocyte | ? | ? | Melanoma | ? | Cushing's (ACTH) |

*Abbreviations*: 5-HTP = 5-hydroxytryptophan; VIP = Vasoactive intestinal polypeptide; VLP = Vasoactive lung peptide; Others as in Table 1.

TABLE 3. *Apud Cells of the Alimentary Tract, Their Products and Their Associated Apudomas and Clinical Syndromes*

| Organs | Cells | Products: Polypeptides | Products: Amines | Apudomas | Orthoendocrine Syndromes | Principal Paraendocrine Syndromes (& Hormones) |
|---|---|---|---|---|---|---|
| Salivary glands | ? | ? Urogastrone | — | ? | ? | ? |
| Stomach | G | Gastrin | — | Hyperplasia, carcinoma | Zollinger-Ellison | ? |
| | D | Somatostatin | — | ? | ? | ? |
| | EC | ? Substance P | 5-HT, ? 5-HTP | Carcinoid | Atypical carcinoid | ? |
| Pancreas: islets | B ($\beta$) | Insulin | — | Hyperplasia | Hypoglycemia | Zollinger-Ellison (gastrin) |
| | A ($\alpha$) | Glucagon | — | Adenoma | Diabetes, dermatitis, etc. | Cushing's (ACTH) |
| | D ($\delta_1\alpha_1$) | Somatostatin | — | Carcinoma | ? | WDHA (VIP)<br>? Malignant carcinoid (5-HT) |
| inter-acinar cells | $D_1$ | Pancreatic polypeptide | — | ? Ditto | ? | ? |
| | EC | ? | 5-HT, ? 5-HTP | Carcinoid | Malignant carcinoid | ? |
| Duodenum & small intestine | S | Secretin | — | ? | ? | ? |
| | EC | Motilin, ? Substance P | 5-HT | Carcinoid | Malignant carcinoid | Cushing's (ACTH) |
| | I | CCK | — | ? | ? | ? |
| | K | GIP | — | ? | ? | ? |
| | ? | Gastrin | ? | Adenoma or carcinoma | Zollinger-Ellison | ? |
| | D | Somatostatin | — | ? | ? | ? |
| | ? H | VIP | — | ? | ? | ? |
| Large intestine | ? H | VIP | — | ? | ? | ? |
| | EG | Enteroglucagon | — | ? | ? | ? |

*Abbreviations*: CCK = Cholecystokinin-pancreozymin; GIP = Gastric inhibitory polypeptide; Others as in Tables 1 and 2.

*Classification of apudomas*

It is convenient to divide the apudomas into the following groups: 1) Orthoendocrine—(A) Tumors secreting normal polypeptides of their cells of origin. (B) Tumors secreting normal amines of their cells of origin. 2) Paraendocrine—(A) Tumors of endocrine glands secreting hormones or humoral agents characteristic of other glands or cells. (B) Tumors of organs or tissues, not usually regarded as endocrine in nature, secreting hormones or humoral agents. 3) Multiple endocrine adenopathy, in which more than one endocrine gland in the same individual is the site of neoplasia, often an apudoma, which may be orthoendocrine or paraendocrine. Most known apudomas in group 1 and the more common ones in group 2 are listed in the tables.

## Orthoendocrine Apudomas Secreting Polypeptides

*The Alimentary Tract*

In the alimentary tract (Table 3)[4] the great majority of orthoendocrine apudomas develop in the pancreatic islets of Langerhans. Indeed, in the stomach and intestines no orthoendocrine polypeptide-producing tumors, other than those secreting gastrin, have yet been recognized. Those in the pancreas are often multiple. They are usually benign adenomas, less commonly malignant carcinomas, rarely adenomatous hyperplasia and, very rarely, simple hyperplasia. Carcinomas, even after metastasizing, tend to run a prolonged course and, provided the major symptoms can be controlled, patients may survive in reasonable health for many years. The islet cells, as will be described later, are also a major site of paraendocrine apudomas. Pancreatic polypeptide is secreted by many islet cell tumors, both orthoendocrine and paraendocrine, but its significance is unknown.[16] Selective angiography has greatly facilitated the preoperative localization of islet cell tumors of all types.

*Insulinoma (Episodic Hypoglycemia).* Insulin-secreting islet cell tumors of the pancreas or insulinomas, causing hypoglycemia, have been known for many years and arise from the B ($\beta$) cells. An insulinoma may be the only endocrine lesion present or may represent part of a syndrome of multiple endocrine adenopathy. Immunofluorescence may reveal the presence of insulin (Fig. 4) and/or proinsulin in the tumor and analysis of venous blood draining the tumor shows a higher concentration of insulin than in the peripheral blood. There

is no evidence that other hypoglycemia-producing tumors, such as hepatomas and mesotheliomas, are apudomas or that they secrete insulin.

Diagnosis has been improved greatly by the measurement of immunoreactive insulin, at the same time as glucose, in the blood. Several tests are available, which depend on the principle that normally there is a direct relationship between the blood concentrations of glucose and of insulin and that hypoglycemia from most other causes is associated with hypoinsulinemia. In nearly all patients with organic hyperinsulinism this relationship is lost, and high or normal (instead of low) levels of insulin accompany hypoglycemia.

Treatment is directed towards removal of the tumor or tumors, and it must be remembered that in at least 10% of patients there are two or more. If a tumor cannot be found or, usually because of malignancy, cannot be removed completely, the hypoglycemic symptoms can usually be controlled with diazoxide. Non-resectable carcinomas can often be treated effectively for a time with streptozotocin by infusion, either intravenously or into the hepatic artery. Both drugs are toxic and may not be tolerated.

*Pancreatic Glucagonoma*. These apudomas arise from the A ($\alpha$) cells of the islets, which secrete glucagon. Although there are several reports in the literature of islet cell tumors containing hyperglycemic material, these could not be investigated fully until the development of a radioimmunoassay for pancreatic glucagon. The first proved case, with diabetes and high concentrations of pancreatic glucagon in the plasma and in an extract of the tumor, was described by McGavran in 1966. The patient had a rash, and this clue to the diagnosis allowed eight cases to be recognized recently in the South of England.[11]

The characteristic lesion is a necrolytic migratory erythema, and any patient presenting with this lesion, who is also a diabetic, should be suspected of having a glucagonoma. Other features include loss of weight, anemia, angular stomatitis and painful glossitis. Estimation of pancreatic glucagon in the blood and selective angiography should then confirm the diagnosis and reveal the site of the tumor(s). Several patients have been cured, at least temporarily, by removal of a tumor.

*Gastrinoma*. Orthoendocrine gastrinomas of the stomach and small intestine are described later, together with the paraendocrine gastrinomas of the pancreas, causing the Zollinger-Ellison syndrome.

### *The Anterior Pituitary*

Tumors or hyperplasia of the anterior pituitary cause general features, by secreting hormones in excess, and local effects, by exerting pressure on the adjacent normal tissues in the pituitary and in the hypothalamus. The lesions are nearly always benign and occasionally form part of the syndrome of multiple endocrine adenopathy.

Apudomas secreting corticotrophin (ACTH), which arise from the c cells (corticotrophs), are the most common cause of Cushing's syndrome. An almost constant companion of ACTH is the melanocyte stimulating hormone (MSH) which, when present in great excess, causes pigmentation. Although the c and m cells are listed separately (Table 1), it is uncertain whether or not they are distinct. Patients with large tumors, and especially those tumors which continue to grow after bilateral adrenalectomy, often develop severe Addisonian pigmentation.

Apudomas secreting growth hormone arise from the s cells (somatotrophs) and cause acromegaly in adults and giantism in adolescents.

Tumors secreting prolactin arise from the l cells (lactotrophs) and cause the Forbes-Albright syndrome of galactorrhoea and amenorrhoea. Although they have not been studied in detail, they are probably apudomas also.

It has long been believed that so-called "chromophobe adenomas" do not secrete hormones, but cause pressure effects only. It now appears that the great majority of those in women and a few of those in men actually secrete prolactin, which may be clinically silent,[6] and that they are probably apudomas also.

Until recently, only two methods were used widely for the removal or destruction of pituitary tumors, namely surgical hypophysectomy by the transfrontal route and external radiotherapy, which were often used in the same patient. The disadvantages of these procedures were that the former carried an appreciable operative mortality, except in a few centers, and that the latter was not very effective. In recent years three other methods have been developed and tested thoroughly, namely external irradiation with a proton beam, transethmosphenoidal hypophysectomy and internal irradiation with radioactive isotopes. In the few centers where they are available, all are yielding excellent results, but controlled trials to compare them with each other or with older methods have not been undertaken.

### Calcitoninoma
### (Medullary Carcinoma of the Thyroid)

This apudoma, which accounts for 6 to 8% of thyroid malignancies, arises from the C cells of the thyroid and secretes large quantities of calcitonin. This hormonal excess does not in itself produce any clinical features, presumably because it stimulates a secondary hypersecretion of parathormone whose effects are antagonistic. The high blood levels of calcitonin, which can be further provoked by a calcium infusion or other stimuli, are

diagnostic of the tumor, and serial measurements of calcitonin after treatment may help to monitor the progress of the disease.

About 20% of patients suffer from diarrhea, which may be caused by a prostaglandin secreted by the tumor and which may respond to treatment with nutmeg.[1]

Surgical removal of the affected lobe or lobes of the thyroid and of all involved lymph nodes is the only effective form of therapy, and three-quarters of the patients so treated survive 5 years.

These lesions may form part of a familial syndrome of multiple endocrine adenopathy and may then be diagnosed at a preclinical stage.

### Orthoendocrine Apudomas Secreting Amines

These apudomas arise mainly from apud cells in the gastrointestinal tract and the sympathetic nervous system including the adrenal medulla.

#### *Carcinoid Tumors*

These apudomas are thought to arise from the enterochromaffin (EC) cells of the gut. Most are benign and are found in the appendix after appendectomy or incidentally in other parts of the bowel after resection. Malignant carcinoids are most common in the terminal ileum, where they are often multiple. At least one-third of patients with carcinoids of the small bowel have a second, unrelated, malignant tumor, often in another part of the alimentary tract. Occasionally the tumor forms part of a syndrome of multiple endocrine adenopathy. Although malignant carcinoids metastasize to the liver and elsewhere, they tend to grow extremely slowly and many patients survive in reasonable health for several (and sometimes many) years.

Most carcinoids of the midgut and its derivatives are argentaffin and secrete 5-hydroxytryptamine (5-HT) together with the enzyme kallikrein, which is responsible for the formation of bradykinin in the blood. Large malignant tumors secrete these substances in great amounts but, since they are normally inactivated in the liver (where they are carried by the portal circulation), no harm results. When large hepatic metastases develop and secrete them also, they enter the systemic circulation directly and cause the malignant carcinoid syndrome. A few carcinoids have been described in sites, such as the ovary, which drain into the systemic circulation directly and cause the syndrome in the absence of metastases.[9] Motilin (a humoral agent which stimulates gastric motility) and possibly substance P (perhaps a local hormone which stimulates smooth muscle and dilates blood vessels) have been identified as products of the small intestinal EC cells, but have not yet been found in tumors.

The syndrome is diagnosed on clinical grounds and on investigation in the laboratory. The most common symptoms are flushing, diarrhea and asthma, and the most sinister complication is tricuspid or pulmonary stenosis. The most helpful investigation is measurement of the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of 5-HT.

Initial treatment is removal of as much of the primary tumor and the hepatic metastases as possible. Cytotoxic agents may be administered systemically or by local infusion into hepatic vessels. Cyclophosphamide, 5-fluorouracil and streptozotocin, given systemically, have caused regression of the syndrome in some patients. Infusion of 5-fluorouracil into the portal vein, after ligation of the common hepatic artery, decreases the size of the liver secondaries and causes regression of the syndrome, at least temporarily, in a few. The excretion of 5-HIAA falls after resection of the tumor and often after successful treatment with cytotoxic agents. Periodic measurement gives valuable and early information about recurrence.

Drug therapy is not uniformly effective, but may be helpful in the relief of symptoms. Methysergide, a 5-HT antagonist, helps to relieve diarrhea and bronchospasm and p-chlorophenylalanine may relieve diarrhea and improve appetite and wellbeing. $\alpha$-Methyldopa is probably the best drug for the relief of flushing.

Carcinoid tumors of the foregut and its derivatives (stomach and bronchi) tend to secrete 5-hydroxtryptophan (5-HTP, the precursor of 5-HT) and histamine, and to cause the very severe "atypical carcinoid syndrome."

Carcinoid tumors at all sites, as will be described later, also form paraendocrine tumors.[14]

#### *Adrenal Medulla and related structures*

Sympathogonia, the most primitive cells of the neural crest, are the putative origin of the highly malignant neuroblastomas, while the differentiated ganglion cells, pheochromocytes and paraganglion cells give rise to ganglioneuromas, pheochromocytomas and paragangliomas respectively. Most of these tumors are benign.

All the cells of origin are apud cells and all the tumors are probably apudomas, although only the pheochromocytomas have been studied extensively from this point of view. Nearly all pheochromocytomas, 75% of ganglioneuromas and neuroblastomas (and intermediate types of tumor), and an unknown proportion of paragangliomas are orthoendocrine and secrete excessive quantities of the catecholamines, epinephrine and/or normetanephrine. A few of these tumors are paraendocrine and secrete polypeptides also.

*Pheochromocytomas*[12] arise from pheochromocytes in the adrenal medulla (80%) or elsewhere in sympathetic

nervous ganglia from the neck to the pelvis. About 99% are found within the abdomen. Tumors are multiple in some 20% of adult patients and in a higher proportion of children. Most, but not all, in the adrenal medulla secrete mainly epinephrine and most elsewhere secrete mainly norepinephrine.

The symptoms are well known, the most important being arterial hypertension and sweating, which are often paroxysmal. Others, however, are many and various. Diagnosis involves measurement of the urinary excretion of vanilmandelic acid (VMA), the main metabolite of the catecholamines, which is higher than normal in 95% of patients. The urinary metanephrines and catecholamines themselves are raised in a higher proportion still. Localization of the tumors is achieved, after $\alpha$-blockade by selective arteriography and, when this fails, by selective venous sampling and measurement of catecholamines in the blood.

Pheochromocytomas must be removed surgically. Treatment has been transformed in recent years by the use of sympathetic $\alpha$-blockade before operation (and before invasive radiodiagnostic procedures) and the infusion of plasma after removal of the tumor or tumors. The rationale of these measures is that catecholamines cause constriction, not only of the arterioles (causing arterial hypertension), but also of the great veins (causing reduction of the blood volume). Failure to recognize this in the past led to severe hypotension as soon as the tumor(s) had been removed, necessitating the infusion of noradrenaline. Although therapy based on the assumption that patients are hypovolemic is highly effective, actual measurements of blood volume in those with pheochromocytomas frequently reveal normal blood volumes, perhaps because the methods used are too crude or because not all patients are hypovolemic.

Since pheochromocytomas are often multiple and in extra-adrenal sites, they are best approached through a long midline or paramedian incision, so that both adrenals, the whole paraaortic region and the pelvis can be explored. An exception to this rule may be made if a tumor greater than about 5 cm in diameter is seen on one side, when a lateral incision, through the bed of the 11th rib on the left or the 10th rib on the right, gives easier and safer access. On the right side the proximity of the tumor to the inferior vena cava makes this particularly desirable. In these circumstances the peritoneal cavity should be opened and explored after removal of the tumor. If a second tumor is found, it may be removed through a second appropriate incision, perferably at the same operation.

Despite preliminary $\alpha$-blockade, squeezing a pheochromocytoma causes a brisk rise in arterial blood pressure, which may be controlled with phentolamine or phenoxybenzamine intravenously. The use of $\beta$-blockers is reserved for cardiac irregularities. They are rarely needed preoperatively, but are useful during the operation.

After operation urinary measurements of catecholamines and/or their metabolites should be repeated to ensure removal of all tumorous tissue. These should be delayed for about two weeks (or longer if the postoperative course is complicated) because the metabolic response to major operative stress increases urinary excretion for 10 days or so.

Removal of pheochromocytomas cures all the symptoms, especially those of an episodic nature, but some degree of sustained hypertension usually persists.

*Neuroblastoma and Ganglioneuroma.* These tumors (the former highly malignant and the latter benign) and many intermediate forms are apudomas. About three-quarters of them secrete catecholamines in sufficient quantity to increase the urinary excretion above normal, but they rarely cause general metabolic features. At operation, however, the blood pressure may rise alarmingly and they are best managed in the same way as pheochromocytomas. Some patients have severe diarrhea, which is cured by removal of the tumor. This may be due to the paraendocrine secretion of vasoactive intestinal polypeptide (VIP).

## Paraendocrine Apudomas

Paraendocrine syndromes (PES) are clinical states, usually associated with hypersecretion of hormones by particular glands, but occurring in different circumstances. There are two main groups of syndromes which involve apudomas.

*Paraendocrine Syndromes Type 1.* In PES 1, tumors of endocrine glands secrete hormones or humoral agents which are foreign to their presumptive cells of origin, but characteristic of others (e.g. tumors of glands other than the anterior pituitary secrete ACTH and cause Cushing's syndrome).

The main tumors, hormones, humoral agents and syndromes are listed in Tables 2 and 3. The most common tumors are those of the islets of Langerhans, which are usually malignant when causing paraendocrine syndromes, and carcinoid tumors, especially of the bronchus. The most common paraendocrine syndrome is Cushing's (ectopic ACTH) syndrome. These tumors may secrete their normal (orthoendocrine) hormones in addition to abnormal ones, up to a total of about eight. The resulting clinical syndromes depend on the hormones or humoral agents released into the circulation, one or more of which may be "silent." For example, an islet cell tumor may secrete ACTH, MSH and gastrin in large quantities, producing Cushing's syn-

drome and pigmentation, but no gastric hypersecretion or peptic ulceration.

According to the hypothesis that apudomas arise from cells of neural crest origin, paraendocrine secretion is the result of dedifferentiation, whereby the apud cell apparatus mobilizes the primitive potential of its embryological anlage and assumes the secretory properties of any members of the series. Parathyroid cells are not apud cells and parathyroid lesions are not apudomas. However, as pointed out earlier, the parathyroids may arise from neuroectoderm and share some fundamental properties of the derivatives of the neural crest. Other paraendocrine tumors in the thymus, ovary and adrenal cortex, secrete ACTH, parathormone (PTH), gonadotrophins and erythropoietin. These properties cannot yet be explained.

*Paraendocrine Syndromes Type 2.* In PES 2, tumors or other lesions of organs or tissues, which are not usually regarded as endocrine in nature, secrete hormones or humoral agents characteristic of endocrine tissues. The most common of these is an oat cell carcinoma of the bronchus, secreting ACTH or ADH or, more rarely, other hormones. It is an apudoma, but its cell of origin is not known. Both the P and the EC cells have been proposed. Melanomas arise from melanocytes, which have no known secretion, but are apudomas and rarely secrete ACTH. Other paraendocrine apudomas, whose cells of origin are not known, have been described in the gut and in the kidney.

Paraendocrine tumors of other types, arising in the bronchi or in other organs, and not known to be apudomas, may sometimes secrete hormones, some of which are normal products of apud cells and some normally derived from cells of other types. There is no simple explanation for the secretion of polypeptide hormones by any of these tumors. One suggestion is that the tumor cells are hybrids of two types of cell, one of them an apudoma, and that they assume the properties of both.[24]

## *Paraendocrine Syndromes (PES)*

Some of the PES are of particular importance to the surgeon and are amenable to surgical treatment. Others may be terminal manifestations of tumors which are far advanced.

*Cushing's (ectopic ACTH) Syndrome.* Cushing's syndrome is the most common form of paraendocrine syndrome of both types. The most common causative lesions are oat cell carcinoma of the bronchus, carcinoid tumors (especially of the bronchus), epithelial carcinoma of the thymus, islet cell tumor of the pancreas, pheochromocytoma and ovarian carcinoma. Most of these secrete ACTH and MSH, which overstimulate the adrenal cortices, rendering them hyperplastic, and cause pigmentation. Very rare tumors have been described, which secrete corticotrophin-releasing hormone (CRH), the hypothalamic hormone which stimulates the secretion and release of ACTH by the anterior pituitary.

The syndrome is usually very acute in onset, and metabolic disorders, such as hypokalemic alkalosis and diabetes, usually precede the ordinary clinical features. The syndrome is more common in men than in women (unlike the ordinary form), muscle wasting and weakness are usually severe, and pigmentation is common. The plasma ACTH and plasma and urinary cortisol levels are usually elevated much more than in the common form of the syndrome.

These features should lead to the suspicion of an ectopic site of ACTH secretion and to a search for the underlying tumor. Bronchial carcinoma is usually far advanced, and effective therapy is impossible. Carcinoid tumors, however, may be benign, and their removal cures the syndrome. Adrenalectomy is rarely justified, except in the case of a slow-growing tumor which cannot be eradicated.

*Gastrinoma (Zollinger-Ellison Syndrome)*[22] Zollinger and Ellison's original description in 1955 referred to two patients who exhibited a triad of: 1) fulminant peptic ulceration, which recurred despite gastric operations; 2) gross gastric hypersecretion; and 3) non-$\beta$ islet cell tumor of the pancreas. Within the next few years many more patients were reported and it was established that many of them had multiple endocrine adenopathy; that the tumors secreted gastrin (or sometimes big gastrin) and were therefore gastrinomas; that more than half of them were malignant; that they were not always in the pancreas; that gastric hypersecretion was not necessarily gross; and that the only reliable form of treatment was total gastrectomy. Since radioimmunoassay for gastrin became available the preoperative diagnosis of the gastrinomas has been relatively easy in most cases, although in a few the level in the blood may not be high until stimulated by calcium or secretin. Patients with pernicious anemia may have similarly high levels of gastrin in the blood, owing to the failure of acidification of the gastric antrum, but they are readily distinguished by the hematological findings and the presence of achlorhydria.

Pancreatic gastrinomas are apudomas. Since the pancreas does not normally secrete gastrin, they are paraendocrine tumors, but their cell of origin is disputed. The important point is that they are apudomas secreting gastrin, which could theoretically arise from any cell of the apud series.

Several reported series include patients with the syndrome in whom no tumor was found, and the cause of the hypergastrinemia and gastric acid hypersecretion

was not clear. It is possible that some of these had hyperplasia of the apud G cells of the gastric antrum, a form of lesion closely related to the apudomas, which may cause the same syndrome as a pancreatic gastrinoma and which was first described by Cowley and his colleagues in 1973.[7,17]

It is now clear that five different types of apudoma and possibly a sixth type of lesion may produce gastrin in excess and cause variants of the Zollinger-Ellison syndrome. The five apudomas are: **Paraendocrine:** *Pancreas* Islet cell tumor (adenoma or carcinoma); Islet cell hyperplasia. **Orthoendocrine:** *Stomach* G cell hyperplasia (fig. 3); G cell carcinoma; *Elsewhere* Carcinoma or adenoma in duodenum. The sixth lesion is parathyroid adenoma or hyperplasia, which will be discussed later.

In patients with hypergastrinemia causing gastric hypersecretion, with duodenal or jejunal ulceration, the preoperative investigations should include selective angiography of the pancreas for localization of a tumor and immunofluorescent staining of antral biopsies for the diagnosis of G cell hyperplasia. The latter responds to antrectomy (which has usually been combined with vagotomy), and total gastrectomy is not necessary. Gastrinomas in the duodenum probably arise in apud cells in the mucosa and those in the splenic hilum in ectopic islet cell tissue. A single example of a G cell carcinoma of the pyloric antrum has been described.[18]

Some patients, who are unsuitable or not ready for total gastrectomy, may be treated with $H_2$ receptor blocking agent metiamide, which reduces the secretion of gastrin and of gastric acid and cures the ulceration.[21] Unfortunately it is toxic and must be used only as a last resort. Other effective anti-secretory agents (some of them hormones) are, however, likely to become available soon.

*The WDHA Syndrome (Pancreatic Cholera, Vipoma).*[3,23] In 1958 Verner and Morrison observed that two patients with non-$\beta$ islet cell tumors of the pancreas, presenting with watery diarrhea, did not develop peptic ulcers and had low gastric acid secretion. The syndrome has since been named the WDHA syndrome after the initial letters of its three principle characteristics, namely *W*atery *D*iarrhea, *H*ypokalemia and hypo- or *A*chlorhydria. It is rare, being about one-tenth as common as the Zollinger-Ellison syndrome, and is sometimes part of the syndrome of multiple endocrine adenopathy, type I.

A non-$\beta$ islet cell tumor of the pancreas is usually present and about half the tumors are malignant. Several cases have been described with bronchial (probably oat cell) carcinoma or with retroperitoneal neuroblastoma. The tumors release vasoactive intestinal polypeptide (VIP), a polypeptide humoral agent normally secreted by the small and large intestines. In large doses it causes vasodilatation, increases the blood flow to the gut, induces watery diarrhea, reduces gastric secretion and has a strong cardiac inotropic action. These features are responsible for the clinical syndrome. In spite of achlorhydria, the gastric mucosa appears normal, and biopsy shows no loss of parietal cells. In some patients the secretion of acid may rise during episodes of remission from diarrhea.

Patients usually present with explosive watery diarrhea, which does not respond to simple measures. All have a low plasma potassium ranging from 1 to 3 mEq per litre (1–3 mmol/l) when first seen, and they often have associated hypercalcemia, the cause of which is unexplained, but which has been cured by the removal of the tumor. Facial flushing has been observed occasionally.

The diagnosis is usually made by elimination of other possible causes of watery diarrhea associated with hypokalemia. Gastric secretion should be measured, preferably the one hour basal output and the peak acid output in response to pentagastrin (6 $\mu$g/kg). Achlorhydria or hypochlorhydria would suggest the WDHA syndrome. This may be confirmed by the finding of high levels of VIP in the blood, if a radioimmunoassay is available. An attempt should then be made to identify a pancreatic or other tumor.

Treatment is directed towards finding and removing the tumor or tumors, and successful results have been reported. Steroids sometimes provide temporary amelioration of symptoms. Deposits in the liver may be treated effectively by intraarterial infusion of streptozotocin.[10]

### Multiple Endocrine Adenopathy (MEA)

The term multiple endocrine adenopathy describes a group of syndromes, often familial, in which two or more endocrine glands undergo hyperplasia or tumor formation in the same individual, either at the same time or consecutively. The glands usually exhibit hyperfunction and secrete their normal major hormones (orthoendocrine syndromes). They may, however, secrete abnormal hormones instead or as well (paraendocrine syndromes). There are two main varieties of MEA.

*Multiple Endocrine Adenopathy Type I (MEA I).* In this group the parathyroid glands are most frequently involved (90%), and chief cell hyperplasia is the most common lesion, giving rise usually to hyperparathyroidism, which is often mild. The pancreatic islet cells are also involved often (80%), causing the Zollinger-Ellison syndrome, hyperinsulinism, or the WDHA syndrome, in that order of frequency. The anterior pituitary is involved next (65%), causing space-occupying features of a pituitary tumor, acromegaly or, very rarely,

Cushing's syndrome. Hyperplasia of the adrenal cortex, when present, is probably secondary to an ACTH-secreting tumor of the pituitary. Carcinoid tumors are not uncommon.

Many of these lesions are apudomas, and the syndrome may result from a widespread dysplasia of apud cells. However, the parathyroid lesions cannot be readily explained in this way, since the parathyroid cells are not APUD in type and do not arise from the neural crest. They may, however (as mentioned already) arise from related neuroectoderm. Another possibility is that the hyperparathyroidism is secondary to hypersecretion of other hormones, for several of the intestinal hormones stimulate the secretion of calcitonin, and this, in turn promotes the secretion of PTH.

Duodenal ulceration is a common feature of the syndrome, and in patients with islet cell gastrinomas its occurrence is easily explained. However, in those without such a lesion the pathogenesis is obscure. It may be related to the hyperparathyroidism, for hypercalcemia promotes the secretion of gastrin and this, in turn, stimulates the secretion of gastric acid. Parathyroidectomy (in patients with or without MEA I) often reduces the secretion of gastrin and of acid, and sometimes cures duodenal ulceration. A few patients have been described in whom the parathyroids were apparently secreting gastrin.[5,20] Others apparently harbor relatively occult pancreatic gastrinomas, which may reveal themselves again some years later. If it is possible to do so, operation for duodenal ulcer should be postponed until all the endocrine lesions have been treated. It may then be unnecessary, unless the patient has a pancreatic gastrinoma, in which case total gastrectomy will probably be required.

*Multiple Endocrine Adenopathy, Type II (MEA II) (Sipple's Syndrome).* In this syndrome a medullary carcinoma of the thyroid is associated with a pheochromocytoma, hyperparathyroidism and other lesions, including subcutaneous and submucous fibromas and hyperplasia of melanoctyes. The thyroid tumor produces large quantities of calcitonin which could give rise to secondary hyperparathyroidism. The whole syndrome may be regarded as an apud cell dysplasia.

The pheochromocytoma is the lesion which requires the most urgent treatment, because investigation or treatment of other lesions may precipitate a fatal hypertensive crisis.[2] For this reason the possibility of MEA II should be considered in all patients with medullary carcinoma of the thyroid or hyperparathyroidism, and they should be screened for the presence of a pheochromocytoma.

Measurement of calcitonin in the blood may reveal the presence of medullary carcinoma or a precancerous lesion, at a preclinical stage, in members of affected families, even in childhood.[25] Thyroidectomy, however, should not be undertaken lightly because the disease may run a long and relatively benign course.

## Conclusion

The realization that many apparently unrelated endocrine tumors can be classed together into a family, known as apudomas, provides a convenient unifying concept which increases their understanding and may in the course of time lead to more effective methods of treatment.

Many apudomas, such as carotid body tumors, await investigation of their secretory potential and others, particularly in the gut, probably await discovery. For instance, no tumors have yet been found to synthesize secretin, motilin, somatostatin or urogastrone, and it is to be hoped that awareness of these possibilities will lead to appropriate investigation of patients.

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