Thyroid carcinoma and Cushing's syndrome

A report of two cases with a review of the common features of the 'non-endocrine' tumours associated with Cushing's syndrome

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SYNOPSIS Two cases of thyroid carcinoma and Cushing's syndrome are reported. Nine other previously published cases of this association are reviewed: in one the thyroid tumour was described as medullary, in two as papillary, and in the other six as anaplastic, undifferentiated, atypical, or solid carcinoma. Both of our own cases were medullary carcinomas of the thyroid, and on reviewing the histology of five of the other cases all proved to be medullary carcinoma with identifiable amyloid in the stroma. A consideration of the temporal relationships of the development of the carcinoma and of Cushing's syndrome suggested that in the two cases with papillary carcinoma these conditions could have been unrelated, but that in eight of the nine cases with medullary carcinoma there was evidence that thyroid carcinoma was present at the time of diagnosis of Cushing's syndrome.

The other main groups of the so-called 'non-endocrine' tumours associated with Cushing's syndrome are briefly reviewed, and evidence that a surprising number of these cases are related to carcinoid tumours is put forward. Medullary carcinoma of the thyroid is also probably related to this group of tumours. It is suggested that the great majority of the tumours associated with Cushing's syndrome are derived from cells of foregut origin which are endocrine in nature. In neoplasms derived from these cells the polypeptide hormone may well be imperfectly formed, and possess an amino-acid sequence in common with ACTH or other biologically active polypeptides.

The association of 'non-endocrine' tumours with Cushing's syndrome is a subject that has expanded considerably since 1928 when Hurst Brown described a case of diabetes and hirsutism in a woman with an oat-cell carcinoma of the lung. For some years after Thorne's review (1952) it seemed as if this association was confined to tumours of the thymus, lung, and pancreas, but over the last 10 years or so tumours of widely diverse origins have been reported with Cushing's syndrome. The work of Meador, Liddle, Island, Nicholson, Lucas, Nuckton, and Luetscher (1962) has suggested that the mechanism of this association is the production of an ACTH-like substance by the tumour, but although this is a logical explanation it still leaves unanswered the problem as to why such a multiplicity of tumours should be able to produce a substance with an ACTH-like activity.

We would like to report two cases of thyroid carcinoma and Cushing's syndrome. While there

are some complex aspects to this relationship it does provide a clue to the understanding of the association of 'non-endocrine' tumours with Cushing's syndrome. Taken together with a review of other published cases of thyroid and non-thyroidal carcinomas with Cushing's syndrome, we can put forward a possible explanation for the production of ACTH by such widely differing tumours.

CASE REPORTS

CASE 1 This woman of 46 was admitted complaining of marked weakness and clumsiness. She had been known to be hypertensive for three years and diabetic for two years. On admission she had a round, florid face, slight buffalo hump, an enlarged abdomen with rather thin legs, abdominal striae, and subcutaneous ecchymoses. Investigations showed a BMR of + 33%, and generalized osteoporosis. The blood chemical findings on admission were essentially normal. The 24-hour 17-ketosteroid excretion was 9.1 and 13.4 mg/24 hr and 17-hydroxy-steroids 31.2 mg/24 hours. After ACTH the 17-keto-

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steroid excretion rose to 41.8 mg/24 hours and that of 17-hydroxysteroids to 109 mg/24 hours. The blood pressure was 220/140 mm Hg and the heart rate 120. These levels persisted despite treatment. Subsequently the non-protein nitrogen level was 54 mg%, sodium 121 m-equiv/l, chlorides 91 m-equiv/l, and potassium 4.5 m-equiv/litre. The clinical diagnosis of Cushing's syndrome was made. The patient suddenly collapsed and died while laparotomy was being carried out.

At necropsy metastatic tumour was found in the cervical and tracheobronchial lymph nodes, lungs, pleura, pericardium, liver, adrenals, ovaries, and small intestine, with a small primary carcinoma in the thyroid. Both adrenals were enlarged and contained phaeochromocytomas, one 20 cm diameter, weighing 1,080 g, and the other 17.5 g. Both adrenal cortices were thickened, nodular, and hyperplastic. A single oxyphil parathyroid adenoma was also found and the pituitary gland showed hyalinization of the basophils. A postmortem specimen of urine was found to contain 1,173 mg of catecholamines. Histological studies confirmed the diagnosis of phaeochromocytoma. The thyroid tumour (Fig. 1), as well as the metastases, were all of the medullary carcinoma type, with amyloid in the stroma as well as numerous calcospherites. The amyloid was identified histochemically.

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CASE 2 This 49-year-old woman died in December 1947. In June 1946 she had an operation for a tumour of the thyroid, followed by x-ray therapy. Her general condition remained poor and about a year after the operation she began to have diarrhoea. She became weak, complained of a bad taste in her mouth, and was admitted to hospital. She was found to be diabetic but died the following day.

At necropsy the body was noted to be slightly pigmented and mildly hirsute. The left lobe of the thyroid was absent and the right was replaced by white tumour tissue with local invasion. Microscopical examination showed that the carcinoma was composed of islands of small regular cells with a tendency for peripheral palisading. No follicles or papillae were seen; a few small areas of necrosis were present. Staining with Thioflavine T and methyl violet revealed the presence of small amyloid deposits in the stroma of the tumour and it was concluded that this was a medullary carcinoma (Fig. 2).

FIG. 1. Thyroid tumour from case 1. Solid islands of cuboidal cells with extensive amyloid deposition. (Haematoxylin and eosin $\times 150$.)

FIG. 2. Thyroid tumour from case 2. Islands of spindle-shaped cells with small deposits of amyloid. (Haematoxylin and eosin $\times 140$.)

FIG. 3. Pituitary from case 2. Trinucleate Croke cell showing the typical hyaline cytoplasm. (Acid fuchsin-aniline blue, $\times 1,000$.)

The pituitary contained a microscopic chromophobe adenoma and showed very prominent hyalinization of the basophils (Fig. 3).

DISCUSSION

The first of our two cases is fully documented both from the clinical and pathological points of view. The second case is poorly documented, but there can be no doubt of the diagnosis of Cushing's

syndrome because of the finding of numerous Croke cells in a patient with pigmentation, hirsutes, and diabetes who died before cortisone or ACTH were used as therapeutic agents. This case was discovered during a survey of 67 cases of medullary carcinoma of the thyroid collected from several London hospitals (Williams, Brown, and Doniach, 1966). We have found nine other case reports of thyroid carcinoma and Cushing's syndrome in the literature (Table I). The mean age of these 11 cases (nine female and two male) was 40. While these points are not remarkable, the descriptions given of the tumour histology do not represent a cross-section of all types of thyroid carcinoma. Only two of the 11 tumours were papillary in type, none was follicular. Four occurred in young adults, and were described as 'undifferentiated', 'anaplastic' and 'atypical'. Anaplastic carcinoma of the thyroid is extremely rare in this age group, and, as both our own cases were of medullary carcinoma, it seemed possible that several of the other cases might also be examples of this type of thyroid tumour. We are extremely grateful to the physicians and pathologists concerned who allowed us to review the histology of the thyroid tumours from five of these cases. A description of the histological appearance of each tumour follows.

CASE 3 This thyroid section contained a partially encapsulated tumour nodule, with adjacent vascular invasion. The tumour was composed of solid islands of cells with abundant granular cytoplasm and regular nuclei; no follicles or papillae were seen. The stroma showed massive deposition of hyaline eosinophilic material. No special stains were available, but the hyaline areas gave the birefringence and colour change of amyloid.

CASE 4 Sections from three areas showed a uniformly solid tumour without papillary or follicular formation. Large areas were composed of closely packed spindle cells (Fig. 4); in others the cells had abundant foamy

TABLE I

THYROID CARCINOMA AND CUSHING'S SYNDROME

Case No.		Age	Sex	Histological Type	Reviewed Histology	Adrenal Findings
1	Present report	46	F	Medullary	—	Bilateral pheochromocytoma, cortical hyperplasia
2	Present report	49	F	Medullary	—	Hyperplastic, no tumour
3	Dyson (1959)	19	F	Undifferentiated	Medullary	Nodular medullary hyperplasia, cortical hyperplasia
4	Höckfelt <i>et al.</i> (1959)	31	F	Anaplastic	Medullary	Hyperplastic, no adenomata
5	Riggs and Sprague (1961)	62	F	Papillary	—	Hyperplastic
6	Roberts (1962)	17	F	'Atypical'	Medullary	—
7	Jensen <i>et al.</i> (Case II) (1965)	50	M	Carcinoma solidum	Medullary	Hyperplastic, no metastases
8	Jensen <i>et al.</i> (Case III) (1965)	63	M	Carcinoma anaplasticum	Medullary	Normal size, no metastases
9	Mirouze <i>et al.</i> (1965)	41	F	Papillary	—	Lt normal, Rt hyperplastic
10	O'Riordan <i>et al.</i> (1966)	33	F	Medullary	—	Cortical hyperplasia
11	Anderson and Glenn (1966)	24	F	Anaplastic	See footnote ¹	Bilateral hyperplasia

¹Illustration, age at onset, and clinical course all suggest medullary carcinoma rather than anaplastic carcinoma.

FIG. 4. Thyroid tumour from case 4. Solid groups of spindle-shaped cells with a fibrous stroma. Abundant stromal amyloid was present in other areas.

FIG. 5. Thyroid tumour from case 6. Extensive amyloid deposition (top right and bottom right) in this solid thyroid tumour. (Haematoxylin and eosin $\times 150$.)

cytoplasm. In one region there was extensive stromal amyloid, confirmed with methyl violet and thioflavine T techniques. Other smaller areas of amyloid and scattered foci of calcification were also seen.

CASE 6 This tumour showed abundant amyloid, positive with methyl violet and thioflavine T. The cellular portion was solid, with some spindle cell areas (Fig. 5). Mitoses were few. Lymphatic permeation was a prominent feature.

CASE 7 Several sections of tumour showed a uniform pattern of solid cell nests of regular cells, with abundant granular eosinophilic cytoplasm and uniform nuclei with finely granular chromatin. Mitoses were few. Scattered small areas of amyloid were present; these had a typical appearance in haematoxylin-and-eosin-stained sections and were positive with thioflavine T.

CASE 8 This again showed a uniform pattern and was composed of islands and broad trabeculae of spindle cells with oat-shaped nuclei and little cytoplasm. Few mitoses were present. No amyloid was seen in the sections

stained with haematoxylin and eosin but all sections showed several small strands of thioflavine-T-positive material in the stroma.

From the review of the histological findings in these five tumours, it can be seen that all were solid but not anaplastic carcinomas with stromal amyloid. These are, therefore, examples of medullary carcinoma of the thyroid, a tumour which is relatively uncommon, forming about 10% of all thyroid carcinomas (Williams, Brown, and Doniach, 1966). We have not been able to study sections of the tumour from case 11 but the illustrations show that the primary tumour was composed of solid islands of cells separated by a dense stroma. The first thyroid swelling was noted in this patient at the age of 15 and total thyroidectomy was carried out at 24. The patient survived over 20 years before presenting with Cushing's syndrome and widespread metastases. These features provide strong evidence that the tumour was a medullary carcinoma

and not an anaplastic carcinoma of the thyroid. In the following discussion this tumour will be included with the other medullary carcinomas on these grounds, even though complete proof is not available.

The finding that nine out of 11 of the thyroid carcinomas with Cushing's syndrome are medullary in type suggests that this is a special relationship, a suggestion which is supported by an analysis of the temporal relationship of the two diseases in these 11 cases. In neither of the two cases with papillary carcinoma of the thyroid and Cushing's syndrome is there any reason to question the histological diagnosis. In both, the Cushing's syndrome preceded the diagnosis of thyroid carcinoma: by one and three-quarter years in one and by six years in the other patient. Of the nine cases of medullary carcinoma and Cushing's syndrome, six were known to have thyroid carcinoma for several years (one, 20) before the Cushing's syndrome was diagnosed. Secondary tumour was known to be present in all but one of these six patients when the diagnosis of Cushing's syndrome was made. In the three other cases both diagnoses were made within a short time; the patients died within three weeks of adrenalectomy, and in all widespread secondary thyroid carcinoma was found. Because of these points we consider that the nine cases of medullary carcinoma of the thyroid with Cushing's syndrome form a homogeneous group, and that the clinical course in these patients is compatible with the production of an ACTH-like substance by the thyroid tumour.

In contrast the two cases of papillary carcinoma of the thyroid with Cushing's syndrome may represent merely a chance association; in neither case do we have evidence that thyroid tumour was present at the time of diagnosis of Cushing's syndrome, in one the hypokalaemic alkalosis so often found in Cushing's syndrome associated with carcinoma was not present, in the other no investigations are quoted.

Two of the nine cases of medullary carcinoma had bilateral tumours of the adrenal medulla; this is an uncommon but recognized association of tumours; the phaeochromocytomas are commonly bilateral and the condition may be familial (Williams, 1965). Cushing's syndrome and phaeochromocytoma have occurred together in several patients (Bourgoignie, Dupont, and Noiret, 1964); in one case an ACTH-like substance was isolated from the phaeochromocytoma (Liddle, Island, Ney, Nicholson, and Shimizu, 1963). In our own case, and in that of Dyson (1959), the phaeochromocytomas were probably congenital, and the onset of Cushing's syndrome was related to the development of metastatic thyroid carcinoma.

In six of the other seven cases of medullary carcinoma and Cushing's syndrome reviewed here the adrenals were examined and found to be free of tumour; we think it unlikely that the phaeochromocytomas in these two cases were in any way related to the Cushing's syndrome. Before considering the significance of this association of medullary carcinoma of the thyroid and Cushing's syndrome it is relevant to review briefly the major types of 'non-endocrine' tumour which have been associated with Cushing's syndrome.

In the lung the type of tumour found has been an oat-cell carcinoma in the great majority of cases. Squamous and adenocarcinoma of the lung have been found so infrequently as to suggest a mistaken histological diagnosis or a fortuitous association. However, there have been a number of reports of Cushing's syndrome in patients with bronchial carcinoids or similar tumours (Table II). It seems likely on morphological grounds that oat-cell carcinoma and bronchial carcinoids are related tumours, and this suggestion is supported by the occasional ability of oat-cell carcinomas to produce the carcinoid syndrome, with evidence of 5-hydroxytryptamine (5HT) production by the tumour (Williams and Azzopardi, 1960; Gowenlock, Platt, Campbell, and Wormsley (1964). One example of a patient with a carcinoma of the lung and features of both the carcinoid syndrome and Cushing's syndrome has been recorded (Harrison, Montgomery, Ramsey, Robertson, and Welbourn, 1957).

Thymic tumours in patients with Cushing's syndrome were first described by Leyton, Turnbull, and Bratton in 1931. Both of their cases were of the uncommon pure epithelial thymic tumour with solid cords and islands of cells separated by a connective tissue stroma. Berthelot, Benhamou, and Fauvert (1961) reviewed 15 cases of thymic tumour with Cushing's syndrome; where the histological type was adequately described it was clearly the same as that in the original report.

Tumours of the stomach have only rarely been recorded with Cushing's syndrome; they are mentioned because in one case (Davis and Kennedy, 1962) the gastric lesion was described as a carcinoid.

Pancreatic tumours have occurred with Cushing's syndrome on a number of occasions. Several of these tumours were described as islet cell tumours, and in a number of others it is possible that the true diagnosis may have been an islet cell tumour. Hallwright, North, and Reid (1964) interpreted a pancreatic tumour associated with Cushing's syndrome as a carcinoid, and Sayle, Lang, Green, Bosworth, and Gregory (1965) described a case with a pancreatic islet cell tumour, Cushing's syndrome, and a very high urinary 5-hydroxyindole acetic acid

TABLE II

'CARCINOIDS'¹ AND CUSHING'S SYNDROME

Author	Age	Sex	Site of Tumour	Histology	Urinary 5-HIAA	Clinical Carcinoid Syndrome	Comment
Harrison <i>et al.</i> (1957)	55	F	Lung	Anaplastic carcinoma	Raised	Yes	
Cohen <i>et al.</i> (1960)	33	M	Lung	Adenoma	—	No	
Cohen <i>et al.</i>	25	F	Lung	Adenoma	—	No	
Christy (1961)	57	F	Lung	Malignant carcinoid	—	No	
Escovitz and Reingold (1961)	35	M	Lung	Malignant carcinoid	37 mg/24 hr	Yes (flush only)	Also four small intestinal carcinoids
Sobota and Reed (1964)	21	F	Lung	Carcinoid	—	No	Multiple carcinoid adenomas
Riggs and Sprague (1961)	32	F	Lung	Carcinoid	—	—	
Prunty <i>et al.</i> (1963)	63	M	Lung	Carcinoid	—	—	
Meador <i>et al.</i> (1962)	53	M	Lung	Oat-cell carcinoma	50 mg/24 hr	No	
O'Riordan <i>et al.</i> (1966)	26	F	Lung	Carcinoid	—	No	
Petersen, Gorry, and Rupp (1967)	27	M	Lung	Carcinoid	—	No	
Morse, Kerenyi, and Nelson (1967)	35	F	Lung	Carcinoid	—	No	
{ Bagshawe (1960)	57	M	?Lung or thymus	Undifferentiated carcinoma	Raised	No	
{ Engel and Kahana (1963)		M	Stomach	Carcinoid	100 mg/24 hr	Yes (constant flush)	
Davis and Kennedy (1962)		F	Pancreas	Islet cell carcinoma	Very high	Yes (diarrhoea and flush)	
Sayle <i>et al.</i> (1965)	62	F	Pancreas	Carcinoid	Normal	No	
Hallwright, North and Reid (1964)	32	F	Pancreas	Carcinoid	Normal	No	
Smith (1965)	24	F	Appendix	Carcinoid	15 mg/24 hr	No	Pancreatic primary not excluded
Brown and Lane (1965)	74	F	Ovary	Carcinoid	95 mg/24 hr	Yes	

¹Cases are included either on histological or biochemical grounds

(5-HIAA) excretion. In the absence of a positive argentaffin reaction, carcinoids of the pancreas and islet cell tumours are difficult to separate on morphological criteria. These are clearly related tumours, and it seems likely that the great majority of pancreatic tumours associated with Cushing's syndrome are either islet cell tumours or carcinoids.

While examples of Cushing's syndrome in patients with tumour of sites other than those briefly reviewed have been described, for example, ovary, breast, and colon, they form only a small minority of the whole group. A number of these cases with primary tumours which did not fit in to the general pattern have been critically reviewed by Engel and Kahana (1963) and several cases rejected.

The main group of 'non-endocrine' tumours associated with Cushing's syndrome are undoubtedly of bronchial, thymic or mediastinal, and pancreatic origin. With this group we will also discuss the less common thyroid and gastric neoplasms associated with Cushing's syndrome. The members of this group are interrelated in a number of ways. Firstly, they are all epithelial tumours derived from structures of foregut origin. Also, in nearly all instances the tumours are not the common differentiated type of carcinoma of the organ concerned—squamous and adenocarcinoma of the lung, lymphoepithelioma of the thymus, papillary or

follicular carcinoma of the thyroid, adenocarcinoma of the pancreas—these are conspicuous by their absence in any list of the histological types of tumour associated with Cushing's syndrome. In contrast carcinoids are surprisingly common, and it may be that the majority of these tumours are of a related type.

The evidence for this for tumours of the lung, pancreas, and stomach has been quoted. The thymic tumour associated with Cushing's syndrome show some histological similarities to carcinoids but their cell of origin is not clear. Medullary carcinoma of the thyroid does not show papillary or follicular differentiation, and it has been suggested by Williams (1966) that these tumours arise from para-follicular cells. It has been shown in sheep that thyroid para-follicular cells contain 5HT (Falck, Larson, Mecklenburg, Rosengren, and Svenaeus, 1964) and recently Moertel, Beahrs, Woolner, and Tyce (1965) have described the occurrence of the carcinoid syndrome in a patient with a solid carcinoma of the thyroid gland. Medullary carcinoma cells are frequently argyrophil (Williams, Brown, and Doniach, 1966) as are bronchial and intestinal carcinoid cells. On these grounds it seems likely that medullary carcinoma of the thyroid may also be considered as related to the carcinoid group of tumours.

Recent evidence has shown that the major symptoms of the carcinoid syndrome are probably due largely to the production of a bradykinin-like substance (Oates, Melmon, Sjoerdsma, Gillespie, and Mason, 1964). Both bronchial and intestinal carcinoid tumours have been shown to contain kallikrein, an enzyme which is secreted by the cell and acts on a globulin substrate to produce bradykinin or other similar short-chain polypeptides. Foregut carcinoids differ in a number of ways from the typical midgut carcinoids (Williams and Sandler, 1963), and the clinical differences in the syndrome produced by these two groups of tumours may well be due to the production of other polypeptide hormones in addition to bradykinin. We would therefore like to suggest that the common features which unite the great majority of the so called 'non-endocrine' tumours associated with Cushing's syndrome is that they arise from cells of foregut origin which are endocrine in nature, producing a variety of hormones, often including 5HT. We would suggest that the polypeptide hormone which these tumours produce may either be identical with that produced by the cell of origin or may be imperfectly formed and possess an amino acid sequence in common with ACTH or other biologically active polypeptides.

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