MEDULLARY THYROID CARCINOMA:
ECTOTIC PRODUCTION OF PEPTIDES WITH ACTH-LIKE,
CORTICOTROPHIN RELEASING FACTOR-LIKE AND
PROLACTIN PRODUCTION-STIMULATING ACTIVITIES

By
Jan C. Birkenhāger¹), G. Virginia Upton²),
H. Jaqueline Seldenrath, Dorothy T. Krieger,
and Armen H. Tashjian Jr.

ABSTRACT
A 45-year-old women had medullary thyroid carcinoma associated with
Cushing's syndrome and galactorrhea. Elevated plasma immunoreactive
ACTH and cortisol were partially suppressed by intravenous dexamethasone, appreciably raised by lysine vasopressin, and urinary excretion
of 17-oxogenic steroids slightly elevated by metyrapone.

¹) Address reprint requests to Dr. Birkenhāger at the University Hospital "Dijkzigt",
Rotterdam-3002, The Netherlands.

²) Present address: Wyeth International, Ltd., Philadelphia, PA 19101, USA.
Supported in part by grants from the Veterans Administration Research Funds,
Connecticut Division of the American Cancer Society, the National Institute of Neuro-
logical Diseases and Blindness (NB 02899) and the National Institute of Arthritis,
Metabolism and Digestive Diseases (AM 10206 and AM 11011).
A large arterio-venous increase in plasma corticotrophin releasing factor-like activity across the thyroid gland was observed and tumour tissue contained corticotrophin releasing factor-like activity. Biologically active ACTH was not detected in tumour extracts before incubation with trypsin, but after trypsinization a value of 3.2 mU per gram was obtained. Arterial plasma contained biologically active ACTH (1.5 mU/100 ml) prior to trypsinization. Venous effluent from the thyroid gland contained biologically active (9.6 mU/100 ml) and immunoreactive ACTH (970 pg/ml) before trypsinization. Tumour extracts also contained prolactin production-stimulating activity. These findings can explain the Cushing's syndrome and the galactorrhea both of which disappeared completely after thyroidectomy.

Medullary carcinoma of the thyroid gland is known to synthesize and secrete calcitonin. In addition, the tumour is often associated with phaeochromocytomas and hyperparathyroidism and less commonly with the ectopic ACTH-syndrome (Williams 1970). We have studied a patient with medullary thyroid carcinoma, galactorrhea and Cushing's syndrome who showed the laboratory characteristics of the pituitary-dependent type of Cushing's syndrome rather than of the classical type of the ectopic ACTH syndrome. Results of our studies serve to explain the patho-physiology in the following way. The Cushing's syndrome appeared to be due to the ectopic production by the tumour of corticotrophin releasing factor-like material which stimulated the secretion of ACTH from the patient's pituitary gland. The tumour also contained a prolactin production-stimulating factor which could explain the galactorrhea through stimulation of pituitary prolactin synthesis and secretion.

CASE REPORT

A 45-year-old woman was seen in January 1972. During the previous year she noted that her face had become round and red, her skin had darkened, her body hair had increased, her scalp hair had thinned, and she had increased perspiration. Three months before admission, bilateral breast enlargement and galactorrhea occurred.

On physical examination she had a "moon face", moderate proptosis of both eyes with swelling of the lids and chemosis, blood pressure of 160/100 mmHg, truncal obesity, increased skin pigmentation, slight galactorrhea and increased hair growth. Striae were not observed. A firm 3 cm nodule was palpable in the left lobe of the thyroid gland. Laboratory investigation: urinalysis and complete blood count were normal; erythrocyte sedimentation rate was 14 mm, plasma creatinine 1.0 mg/100 ml, Na 147, K 3.2, Cl 106 and HCO₃ 29.3 mEq/l; Ca 10.0 and P 2.5 mg/100 ml; alkaline phosphatase 50 IU/l (normal upper limit 45); total protein 69.9 g/l, serum protein electrophoresis was normal. Oral glucose tolerance test resulted in a diabetic curve. ECG showed an old anterior myocardial infarction. Radiological examination of the chest was normal. The sella turcica had a normal size. The dorsum sellae and the vertebral column exhibited osteoporosis.
METHODS

Plasma immunoreactive calcitonin and parathyroid hormone were measured by the methods of Hackeng et al. (1970) and Lequin et al. (1970), respectively. Plasma luteinizing hormone (LH) was estimated by Calbiochem. Systemic plasma immunoreactive ACTH was measured by the method of Landon & Greenwood (1968). Thyroid arterial and venous blood samples were collected at surgery from the left side of the gland, the plasma was extracted, and the peptides isolated and partially purified by the method of Upton et al. (1973). Thyroid tumour tissue (from the left thyroid lobe and lymph nodes) was extracted and fractionated for peptide isolation as previously outlined (Upton & Amatruda 1971). Partially purified plasma ACTH from the thyroid artery and thyroid vein, and partially purified tumour ACTH were measured biologically both before and after incubation with trypsin (for 10 seconds) by the method of Sayers et al. (1971), as modified by Sayers & Beall (1972), and radioimmunologically by the method of Landon & Greenwood (1968). Corticotrophin releasing factor (CRF)-like activity was measured in partially purified tumour and plasma extracts using the method of Arimura et al. (1967), as modified by Upton & Amatruda (1971). CRF-like activity in the tumour fractions was also measured by Dr. George Hedge (Arizona) using the intrapituitary injection of Hedge et al. (1966), as modified by Brown & Hedge (1972).

Tumour extracts were assayed for immunoreactive growth hormone and prolactin (PRL) by Dr. Robert Ryan, Mayo Clinic, Minn. Tumour fractions with CRF-like activity were assayed for immunoreactive calcitonin content using the method of Tashjian (1973). Prolactin production-stimulating activity was determined by measuring the effects of graded doses (equivalent to 0.01 to 25 mg tissue per ml) of tumour extracts on the production of prolactin by the GH3 strain of rat pituitary cells in culture (Tashjian et al. 1970). Calcium and glucagon provocative tests for calcitonin secretion were performed according to Melvin et al. (1970). Plasma cortisol was measured by a modification of the competitive protein binding assay of Murphy (1967) as described by de Jong & van der Molen (1972). Cortisol secretion rate was determined by the method of Thijssen et al. (1967). Urinary 17-OH corticosteroids (17-OHCS) and 17-oxogenic steroids (17-OGS) were estimated according to Silber & Porter (1954) and Appleby et al. (1955), respectively. Procedures used for the overnight dexamethasone screening test, oral dexamethasone suppression test, intravenous dexamethasone suppression test, metyrapone and lysine vasopressin (LVP) tests were those described by Nugent et al. (1965), Liddle (1960), Croughs et al. (1973), Liddle et al. (1959) and Gwinup (1965), respectively.

RESULTS

1. Pre-operative endocrine studies

Thyroid scan showed a "cold" nodule in the left lobe. Plasma immunoreactive calcitonin was 32 ng/ml (normal range 105 to 395 pg/ml). Infusion of calcium (15 mg/kg for 4 h) as calcium gluconolactobionate (Sandoz) produced an appreciable increase in plasma calcitonin, whereas glucagon infusion did not (Fig. 1). Two weeks after total thyroidectomy, the basal plasma calcitonin level was 10.4 ng/ml with a lesser rise during the infusion of calcium
Plasma calcitonin concentrations before and at the end of calcium and glucagon infusions before and two weeks after thyroidectomy. Calcitonin values above the dotted horizontal line are not detected in normal subjects.

(Fig. 1). Basal serum immunoreactive parathyroid hormone varied from 445 to 825 pg bovine hormone equivalents/ml with an average of 610 (normal range from <25 to 410) (calcium levels normal). Urinary excretion of methoxyhydroxymandelic acid was 44 μmoles/24 h (normal up to 40), and that of 5-hydroxyindoleacetic acid was 18.1 μmoles/24 h (normal up to 45). Urinary gonadotrophin excretion was 140 MUU/24 h (normal for pre-menopausal women 10–40 MUU/24 h). Plasma immunoreactive LH was greater than 200 ng/ml (normal for pre-menopausal women up to 50 ng/ml); however, the patient had had a hysterectomy in 1970.

2. Steroid hormone studies and plasma ACTH

Cortisol secretion rate was 65 mg/24 h (normal upper limit 30 mg/24 h).

Plasma cortisol diurnal rhythm was investigated pre-operatively on 2 occasions and was found to be absent (I and II in Table 1). Plasma cortisol during a dexamethasone screening test (1 mg orally 11 p.m. the previous night) was
Table 1.
Pituitary-adrenocortical functions tests: Plasma values.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Post-operative</th>
<th>Post-operative</th>
<th>Post-operative</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-4 weeks</td>
<td>5 months</td>
<td>16 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortisol (µg/100 ml)</td>
<td>ACTH (pg/ml)</td>
<td>Cortisol (µg/100 ml)</td>
<td>ACTH (pg/ml)</td>
</tr>
<tr>
<td>I</td>
<td>15.5</td>
<td>14.4</td>
<td>14.4</td>
<td>7.7</td>
<td>8.8</td>
</tr>
<tr>
<td>II</td>
<td>17.5</td>
<td>14.5</td>
<td>10.1</td>
<td>4.8</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>17.8</td>
<td>15.5</td>
<td>6.4</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Dexamethasone iv</td>
<td>0</td>
<td>13.1</td>
<td>320</td>
<td>14.6</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>7.8</td>
<td>320</td>
<td>9.0</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>8.2</td>
<td>200</td>
<td>7.7</td>
<td>26</td>
</tr>
<tr>
<td>Lysine-vasopressin</td>
<td>0</td>
<td>20.4</td>
<td>255</td>
<td>9.8</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>37.4</td>
<td>455</td>
<td>10.8</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>40 min</td>
<td>34.8</td>
<td>–</td>
<td>11.4</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>26.8</td>
<td>415</td>
<td>9.6</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>36.8</td>
<td>425</td>
<td>7.4</td>
<td>48</td>
</tr>
<tr>
<td>Metyrapone</td>
<td>0</td>
<td>220</td>
<td>12</td>
<td>24 h</td>
<td>280</td>
</tr>
</tbody>
</table>

1) Cortisol diurnal rhythm.
2) Immunoreactive.
Urinary 17-oxogenic steroids and 17-hydroxycorticosteroids during metyrapone and dexamethasone administration pre-operatively and during metyrapone administration after thyroidectomy.

12.2 μg/100 ml (normal up to 5 μg/100 ml; Cushing's syndrome, greater than 10 μg/100 ml). Dexamethasone 8 mg daily, orally, reduced the urinary excretion of 17-OHCS and 17-OGS (Fig. 2) (the latter from 50 to 24 mg/g of creatinine), whereas dexamethasone administered intravenously (5 mg in 5 h) had a definite suppressive effect on plasma cortisol (Table 1).

Lysine vasopressin (10 pressor units im) produced an increase of 17 μg/100 ml in plasma cortisol (Table 1). In patients with pituitary dependent Cushing's syndrome increases of 12-46 μg/100 ml have been reported after this dose of LVP im (James et al. 1968; Croughs 1970) and of 17-73 μg/100 ml with 5 PU infused in 1 h (Bethge et al. 1969). No change in 24-h urinary corticoid excretion was observed on the day of the vasopressin test (LVP, Fig. 2), and corticoid excretion on the following day was not measured.

During a metyrapone test the excretion of 17-OHCS and 17-OGS showed a late rise of greater than 100 % (Fig. 2).

Basal plasma immunoreactive ACTH was 220–320 pg/ml (normal < 60 pg/ml) and decreased from 320 to 200 pg/ml with intravenous dexamethasone (Table 1).

During the vasopressin test, an increase from 255 pg/ml to 445 pg/ml at 20 min was observed (Table 1). In the metyrapone test, only a small increase in plasma ACTH was seen.

Post-operatively, the symptoms and signs of cortisol-excess, and the galactorrhoea abated rapidly accompanied by a return to normal of the steroid

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data (Table 1 and Fig. 2). Cortisol secretion rate was 16 and 22 mg/24 h 3 weeks and 5 months post-operatively, respectively. Diurnal rhythm of plasma cortisol also returned post-operatively, but the response of plasma cortisol, in contrast to that of plasma ACTH, to lysine vasopressin was absent 5 months post-operatively (Table 1). Sixteen months post-operatively, when the plasma cortisol response to vasopressin was still sluggish, the intravenous administration of ACTH (500 µg synacthen given over 5 h) produced a normal rise of plasma cortisol from 14.7 to 38.5 µg/100 ml.

3. Histopathological findings

The left lobe of the thyroid gland contained a firm nodule of about 3 cm in diameter. Thyroid arterial and venous plasma (on the left side) and portions of tumour tissue were frozen for extraction and assay. Microscopically, the tumour mass contained sheets and nests of elongated cells with round or oval nuclei and a considerable amount of amorphous extracellular eosinophilic material which stained positively for amyloid with Congo Red. Only a small number of mitoses was found. The histological features of the tumour were

![Figure 3](image-url)

**Fig. 3.**
Thyroid tumour-neuroendocrine interactions. PRL-SA is prolactin production-stimulating activity. One unit (U) is defined as that amount required to double the rate of prolactin production/24 h by pituitary cells in culture. All values for ACTH were determined by bioassay; the tumour content was measured after trypsin treatment.
### Table 2.
Assays for prolactin production-stimulating activity.

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Test materials</th>
<th>Dose (^1)</th>
<th>Hormone production (^2)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolactin ((\mu g/mg\text{ protein/24,h}))</td>
<td>Growth hormone ((\mu g/mg\text{ protein/24,h}))</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Control</td>
<td>—</td>
<td>8.3 ± 0.20</td>
<td>2.2 ± 0.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour Extract A</td>
<td>25</td>
<td>14 ± 1.5</td>
<td>2.1 ± 0.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour extract B</td>
<td>10</td>
<td>12 ± 1.2</td>
<td>2.5 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Control</td>
<td>—</td>
<td>22 ± 2.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TRH</td>
<td>10</td>
<td>58 ± 2.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour Extract A</td>
<td>25</td>
<td>60 ± 2.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>41 ± 1.8</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>0.25</td>
<td>29 ± 1.0</td>
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<td></td>
<td></td>
<td>0.025</td>
<td>21 ± 1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour extract C</td>
<td>10</td>
<td>58 ± 2.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>52 ± 2.5</td>
<td>—</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>33 ± 1.8</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>0.010</td>
<td>23 ± 1.5</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Control</td>
<td>—</td>
<td>19 ± 1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TRH</td>
<td>10</td>
<td>60 ± 2.4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human calcitonin</td>
<td>1.0</td>
<td>19 ± 1.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Control</td>
<td>—</td>
<td>38 ± 2.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medullary carcinoma A(^3)</td>
<td>400</td>
<td>35 ± 2.5</td>
<td>—</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>40</td>
<td>37 ± 2.0</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>4</td>
<td>39 ± 1.4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medullary carcinoma B(^3)</td>
<td>130</td>
<td>39 ± 3.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>38 ± 2.0</td>
<td>—</td>
<td></td>
</tr>
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<td></td>
<td>1.3</td>
<td>38 ± 2.0</td>
<td>—</td>
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</tr>
</tbody>
</table>

\(^1\) The concentrations of tumour extracts A, B and C from the present case are given in \(\mu g\) of dried tumour fraction/ml of pituitary cell culture medium. Extracts A, B and C are similar, but not identical, fractions prepared as described by Upton & Amatruda (1971) for CRF-like activity. The concentration of TRH is given in ng/ml culture medium and that of synthetic human calcitonin in \(\mu g/ml\). The concentration of the two control medullary thyroid carcinoma extracts are given in \(\mu g\) of extract protein/ml culture medium.

\(^2\) The values given are mean values of duplicate culture dishes ± the range. The durations of incubation of the test materials with the CH\(_3\) pituitary cells were 3, 4, 4 and 3 days, respectively, in experiment numbers I, II, III and IV.

\(^3\) Extracts of two medullary thyroid carcinomas from patients without galactorrhoea.
those typical of medullary thyroid carcinoma. In the right thyroid lobe were multiple very small nodules (diameter up to 3 mm) composed of moderately well differentiated tumour cells that had the typical "ground glass" nuclei of thyroid papillary carcinoma. Amyloid-like material was not present on the right side. On the left, 5 enlarged lymph nodes containing medullary thyroid carcinoma tissue were extirpated. Four parathyroid glands were positively identified by biopsy and appeared to be of about normal size.

4. Assays of tumour-hormone activities

Fig. 3 shows the hormonally active substances found in the medullary thyroid carcinoma and in arterial and venous blood across the thyroid gland. Arterial plasma contained 1.5 mU of ACTH/100 ml prior to trypsinization as determined by bioassay; after trypsinization there was a 17% drop in ACTH-like activity. Thyroid venous plasma contained 9.6 mU of ACTH/100 ml before trypsinization and after trypsinization there was a 40% decrease in ACTH-like activity. Immunoreactive ACTH in arterial plasma was < 135 pg/ml and in thyroid venous plasma 970 pg/ml.

The tumour contained 3.2 mU of ACTH-like activity/g after trypsinization as determined by bioassay. No activity was detected before trypsinization. Arterial plasma contained 10.2 mU of CRF-like activity/100 ml, while the concentration in the thyroid venous effluent was 290 mU/100 ml. The tumour contained 5.3 mU of CRF-like activity/g.

Prolactin production-stimulating activity was measured in several different tumour extracts (Table 2). About 25 μg dry weight of extract A and about 10 μg of extract C were equivalent to 10 ng of TRH in prolactin production-stimulating activity (Table 2, expt. II). Synthetic human CT at 1.0 μg/ml (and also at 0.10 and 0.01 μg/ml, data not shown) did not stimulate prolactin production (Table 2, expt. III). Likewise, extracts of two medullary thyroid carcinomas from patients without galactorrhoea did not stimulate prolactin production by GH3 cells (Table 2, expt. IV).

The tumour contained more than 40 MRC U of calcitonin/g. Only fractions with CRF-like activity were assayed for calcitonin content, and therefore an estimate of total calcitonin content was not possible. The tumour extracts were tested for growth hormone and prolactin content and none was found.

DISCUSSION

More than two hundred cases of the ectopic ACTH syndrome have been reported (Landon et al. 1967). In most of these cases tumour ACTH-like biological activity or immunoreactive ACTH have been measured (Meador et al. 1962; Nichols et al. 1962; Liddle et al. 1963; Marks et al. 1963; Pfohl & Doe

Although the ectopic ACTH syndrome is usually characterized by absence of dexamethasone suppression, absence of response to metyrapone, and absence of response to lysine vasopressin (Meador et al. 1962; Liddle et al. 1963; Landon et al. 1967), exceptions have been reported. Dexamethasone suppression has been observed (Pfohl & Doe 1963; Miura et al. 1967; Strott et al. 1968; Jones et al. 1969; Burke & Beardwell 1972) as well as responses to metyrapone (Christy 1961; Meador et al. 1962; Pfohl & Doe 1963; Miura et al. 1967; Strott et al. 1968; Jones et al. 1969) and lysine vasopressin (Landon et al. 1967; Strott et al. 1968).

In the differential diagnosis of Cushing’s syndrome, the pituitary-dependent type of the syndrome is characterized by suppression of plasma cortisol by a high oral or intravenous dose of dexamethasone as well as by elevation of plasma cortisol in response to lysine vasopressin (Liddle 1960; Webb-Peploe et al. 1967; Bethge et al. 1969; Croughs et al. 1973).

By these criteria, the patient presented appeared to have the pituitary-dependent type of the syndrome (Table 1). However, a unique finding in the present case was the demonstration of an arterio-venous gradient for the ectopic production of a peptide with CRF-like activity. Although small foci of papillary thyroid carcinoma were found in the right thyroid lobe in this case, it should be emphasized that the tumour tissue extraction and the thyroid venous sampling were performed solely on the left side where only medullary thyroid carcinoma was found by careful histologic examination.

The finding that the Cushing’s syndrome in this case was associated with the ectopic secretion of large amounts of CRF-like activity as well as a considerable amount of ACTH may help to explain the responses to dexamethasone and lysine vasopressin. Both dexamethasone and vasopressin may well have acted directly on the anterior pituitary gland whose responsiveness was maintained by the tumour CRF-like activity (Clayton et al. 1963; Gonzalez-Luque et al. 1970; Yates et al. 1971). By analogy, the suppression of ACTH secretion by high dosage dexamethasone, that is usually seen in pituitary-dependent Cushing’s syndrome, may be the result of direct action of the steroid on the pituitary gland rather than on the hypothalamus. The late response to metyrapone, however, differs from the response seen in pituitary dependent Cushing’s syndrome and suggests that the hypothalamic-pituitary axis has not been fully suppressed. One might argue that this late response to metyrapone has influenced the results of the LVP test, but this does not invalidate the quick rise in plasma cortisol seen 20 min after the administration of LVP.

Because tumour extracts with CRF-like activity also contained high concentrations of calcitonin, it was necessary to examine the possible effect of calcitonin in the CRF assay. Synthetic salmon calcitonin (up to 800 ng) and
synthetic human calcitonin (up to 25 μg) were tested in the in vivo CRF assay and were found to be inactive.

The chemical nature of ACTH in plasma and tumour tissue in this case was unusual. Yalow & Berson (1971) have described the presence of "big ACTH" in plasma and in tumour extracts. Such "big ACTH" is biologically inactive, but it can be converted to biologically active "little ACTH" following controlled trypsinization (Gewirtz et al. 1974). Although the full significance of "little" and "big" ACTH, in general, has yet to be demonstrated, it is noteworthy that the ACTH found in the venous effluent of the tumour was readily detectable without trypsinization, whereas tumour ACTH was not detectable unless first treated with trypsin. Thus, the tumour not only secreted biologically active and immunoreactive ACTH but also appeared to convert "big" to "little" ACTH.

Drugs, hypothyroidism, and a pituitary tumour appear to have been ruled out as causes of the galactorrhea in the case presented. Turkington (1971) described ectopic prolactin secretion in patients with hypernephroma and with undifferentiated bronchogenic carcinoma. In the present case, we found that the thyroid tumour did not contain prolactin but did contain material that stimulated the production of prolactin by functional pituitary cells in culture (Table 2). Unfortunately, plasma prolactin concentrations were not measured pre-operatively. We postulate that the galactorrhea in this case was due to stimulation of prolactin synthesis and its subsequent excessive release from the pituitary gland induced by the prolactin production-stimulating material extracted from the medullary thyroid carcinoma. Two control medullary thyroid carcinomas did not contain prolactin production-stimulating material, and human calcitonin did not stimulate prolactin production. Whether the material present in the thyroid tumour is related in any way to the prolactin production-stimulating material extracted from calf liver and kidney (Tashjian et al. 1970) is uncertain. However, the finding that the tumour material did not affect growth hormone production suggests that it is a different type of prolactin production-stimulating material (Tashjian et al. 1970). Both the Cushing’s syndrome and the galactorrhea were related to the presence of the major tumour mass because the signs and symptoms of both ACTH-excess and PRL-excess disappeared completely after total thyroidectomy and removal of a number of metastases.

ACKNOWLEDGMENTS

The authors wish to thank Vera Dunne, Tony Liotta, Janet McDonough and Anoush Knaian for expert assistance, Drs. W. H. L. Hackeng, F. H. de Jong and R. J. M. Croughs for assays of calcitonin, cortisol and ACTH, respectively, Dr. S. W. J. Lam-
berts for assistance in the clinical studies, and Dr. R. O. van der Heul for the histopathological data. Miss Henny Noort is thanked for secretarial assistance.

These findings were presented in part at the 56th annual meeting of The Endocrine Society, Atlanta, Georgia, June 1974.

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