SECRETION OF VARIOUS ENDOCRINE SUBSTANCES BY ACTH-SECRETING TUMORS—GASTRIN, MELANOTROPIN, NOREPINEPHRINE, SEROTONIN, PARATHORMONE, VASOPRESSIN, GLUCAGON

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Six cases of ACTH-secreting* tumors—which are shown to secrete additional hormonal substances—are reported. The high incidence of this phenomenon among our 15 observed cases with ACTH-secreting tumor suggests that polyhumoral secretion in ACTH-secreting tumors is more common than previous reports would indicate. Although several of our cases are unique in that the particular combination of endocrine substances produced has not been previously reported, the tumor types (islet-cell carcinoma, carcinoid, pheochromocytoma, oat-cell carcinoma) are in general those which may be endocrine active in a variety of ways. Ectopic corticotrophin production arises principally in tumors of endocrine tissue, neuroendocrine tissue, endocrine dependent tissue and in oat-cell carcinoma of the thorax. The possibility that oat-cell carcinoma of the lung and mediastinum may be a more malignant variety of carcinoid tumor is not proven but should not yet be discounted.

THE ABILITY OF SOME MALIGNANT NEOPLASMS to produce endocrine active substances not known to be elaborated by the tissue of origin has been well delineated in recent years. A variety of neoplasms is accompanied by adrenal cortical hyperplasia and clinical hypercorticism.[24, 25, 39] Some undifferentiated carcinomas of the lung are associated with inappropriate antidiuresis and this antidiuretic activity has been assayed in plasma and tumor from afflicted patients.[6, 52] Similarly insulin-like activity,[5, 44] glucagon activity,[28] parathormone-like activity,[15] erythropoietin-like activity[9] and thyrotropin-like activity[48] have been assayed from certain neoplasms. Other remote clinical effects of tumors may be due to amine, peptide and protein hormones elaborated by the neoplasm.[17, 26]

Isolated case reports have appeared over the years which indicate that on occasion an endocrine active tumor may secrete multiple humoral substances with diverse effects. This phenomenon has not been observed or reported very frequently and then mostly in single case reports. The occurrence of six cases of ACTH-secreting tumors which appear to be elaborating additional endocrine substances in our own experience indicates that these polyhumoral tumors are more common than previously suspected.

CASE REPORTS

Case 1. M.J., a 48-year-old woman, had had duodenal ulcer diagnosed in 1956. This was

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* ACTH—Adrenocorticotrophic hormone; MSH—Melanocyte stimulating hormone; 17-KS—17-ketosteroids; 17-OHCS—17-hydroxycorticosteroids; ADH—Antidiuretic hormone, vasopressin; 5-HIAA—5-hydroxyindoleactic acid; VMA—3-methoxy-4 hydroxymandelic acid.

controlled with medical therapy until January 1960 when she was operated on for intractable vomiting. An islet-cell tumor of the tail of the pancreas and multiple liver metastases were found and a gastroenterostomy was done. In July 1960 she began to develop signs and symptoms of Cushing's syndrome; she entered hospital with overt Cushing's syndrome and hypokalemic alkalosis in January 1961. Because of grand mal siezure, dilantin was given. Shortly thereafter a remission of her Cushing's syndrome occurred; this deferred anticipated adrenalectomy.

Several months later cutaneous pigmentation increased and Cushing's syndrome recurred. (Steroid studies are shown in Fig. 1.) At that time gastrointestinal roentgenogram series showed minimal duodenal deformity. Bilateral total adrenalectomy and partial pancreatectomy were done in May 1961. The adrenals were quite hyperplastic. Following this —on maintenance steroid therapy—she was relieved of Cushing's syndrome. In August 1961 gastrointestinal roentgenogram series showed obstruction at the gastroenterostomy; at operation a jejunal ulcer was found and resected and a gastric antrectomy and gastroduodenostomy were done. She promptly developed duodenal ulceration which persisted to death.

During early 1962 she had intermittent hypercalcemia, hypophosphatemia, hypercalcuria and decreased tubular reabsorption of phosphorus, which suggested hyperparathyroidism (Fig. 2). In the early part of 1962 there was also hyponatremia (Na 125 mEq/liter), decreased plasma osmolality (270 mOsm/liter) with a higher urinary osmolality (325 mOsm/liter) in the presence of naturiesis (urine sodium 223 mEq/24 hours). This pattern—consistent with the inappropriate secretion of ADH—was found on several occasions. Gastric aspirate in early 1962 was 1800–2050 ml/24 hours, with a total acid output of 1.3 to 3 mEq/hour. During the latter part of 1962 she became progressively more ill with hepatomegaly and in progressive distress because of the duodenal ulcer. She died in December 1962.

At autopsy two huge duodenal ulcers (one of which was eroding into the liver) were found. The liver was largely replaced by metastatic carcinoma. Hepatic hilar nodes showed metastases. Metastases were also present in thoracic vertebrae. There was tumor thrombus in the inferior vena cava. The thyroid, parathyroids, brain and kidneys were normal. There was no persistent adrenal cortical tissue. There was no persistent carcinoma in the pancreatic stump.

The fluorescent-antibody technique was used to study the primary tumor and the metastases in this patient. These studies indicated that both the primary and metastatic tumor tissue stained specifically with fluorescent labeled antibodies to ACTH.[20] Electron microscopy of the tumor showed granules consistent with alpha cell islet tumor (Fig. 3). Multiple endocrine assays were done on the plasma and tumor of this patient; the results are listed here:

Plasma, ACTH, May 1961	1–1.2 mU/100 ml (Nelson)
Plasma, ACTH, Dec. 1962	13 mU/100 ml (Liddle)
Pancreatic tumor, ACTH, May 1961	6.0 mU/Gm (Liddle)

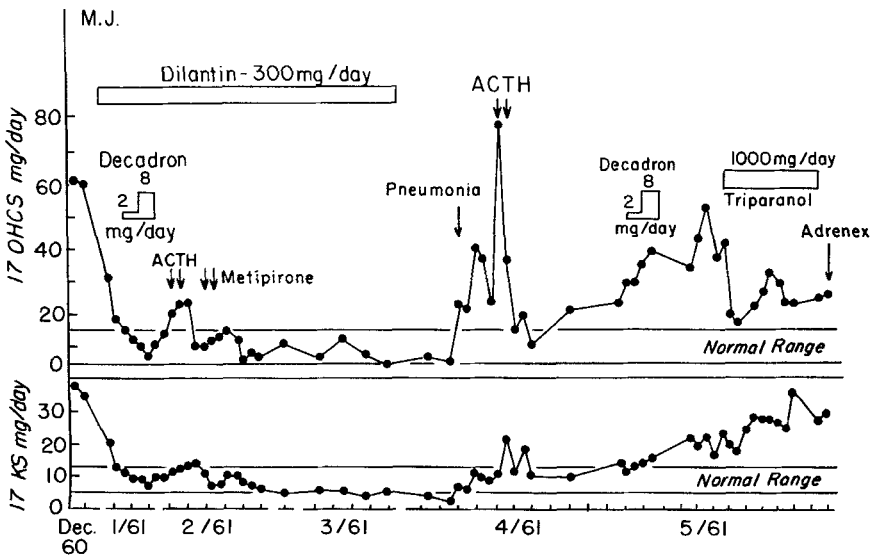

FIG. 1. Urinary steroid values, case 1. A clinical remission of Cushing's syndrome occurred in February and March at the same time that the urinary steroids fell to within the normal range. It is not known whether this was spontaneous or due to the administration of dilantin.

Liver metastasis, ACTH, May 1961	48 mU/Gm (Liddle)
Plasma, MSH, Dec. 1962	630 mU/100 ml (Shimizu)
Tumor, MSH, Dec. 1962	1344 mU/Gm (Shimizu)
Pancreatic tumor, gastrin, May 1961	Positive bioassay (Endahl)
Liver metastasis, gastrin, Dec. 1962	Positive bioassay (Endahl) 20μg gastrin per gram of lyophilized tumor (McGuigan-radioimmunoassay)
Liver metastasis, insulin, Dec. 1962	No insulin activity
Pancreatic tumor, glucagon, May 1961	64.7 mμg/Gm (Unger)
Uninvolved pancreas, glucagon, May 1961	54 mμg/Gm (Unger)
Pituitary, ACTH, Dec. 1962	41 mU/mg (Liddle)

Comment: Previous cases of Cushing's syndrome have been associated with islet-cell carcinoma of the pancreas. In most of these Cushing's syndrome was the only endocrine effect noted. Balls et al.[2] reported a case that was associated with hyperinsulinism. Law et al. reported a case similar to ours that had the Ellison-Zollinger syndrome in addition to Cushing's syndrome and assays in their case showed ACTH, MSH and gastrin arising in the tumor.[23]

The present case is unique in the number and variety of hormonal substances produced by an islet-cell tumor. Assays of the tumor were positive for ACTH, MSH, gastrin and glucagon and the clinical laboratory studies suggested that parathormone-like and vasopressin-like substances were also being elaborated. Inappropriate antidiuresis has not previously been reported in a case with islet carcinoma but it has been reported in a case with adenocarcinoma of the pancreas.[47]

The peripheral effects of the hormones in our case were somewhat intermittent—Cushing's syndrome, ulcer disease, hyperparathy-

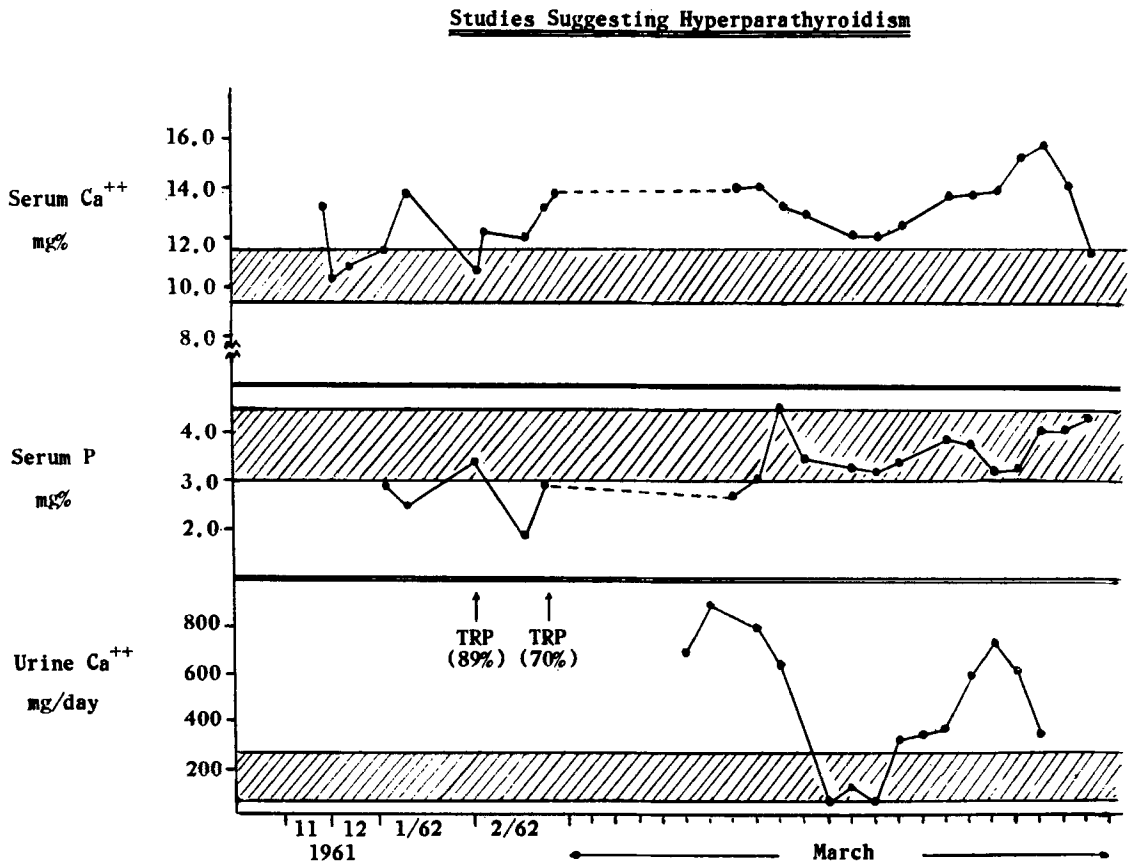

FIG. 2. Calcium and phosphorus studies, case 1. Both before and after this period there was no apparent disturbance in calcium metabolism.

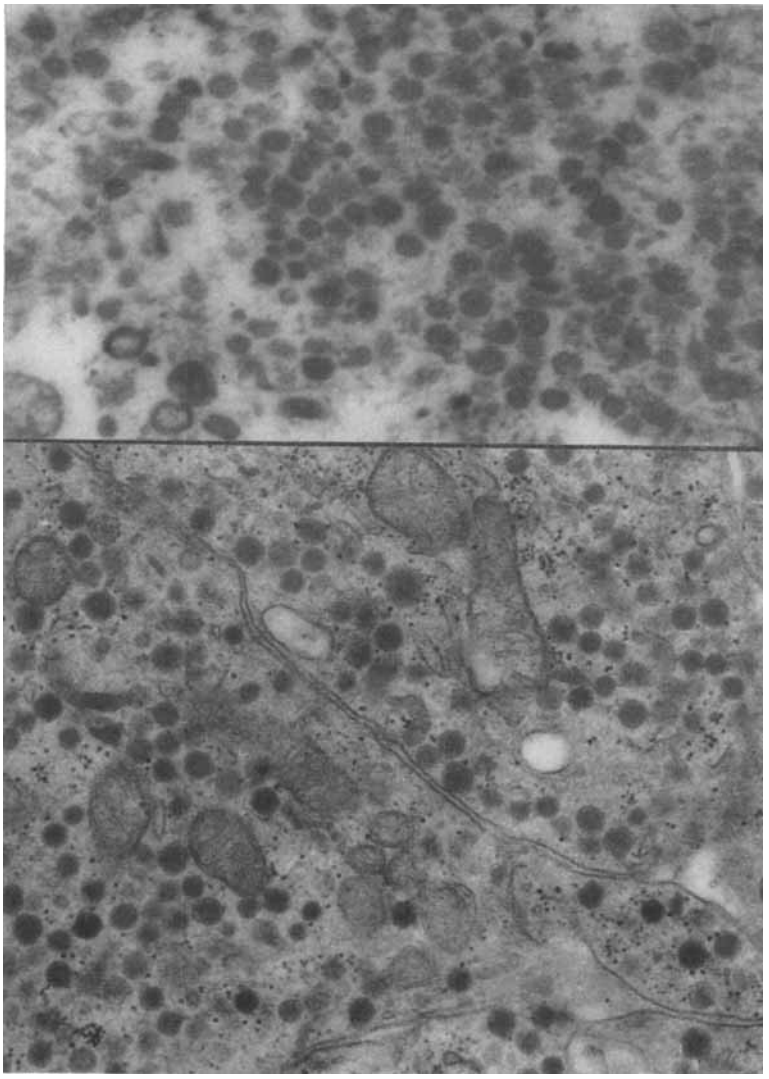

FIG. 3A. (upper) Electron microscopic study of islet-cell tumor, case 1, showing round to ovoid granules with no definite limiting membrane. These are alpha granules. B (lower) For comparison electron microscopy of an islet-cell tumor associated with the Ellison-Zollinger syndrome also showing alpha granules. This patient had no sign of hypercorticism. (Courtesy Dr. Felice Caramia, Institute of General Pathology, University of Rome, Italy.)

roidism and inappropriate antidiuresis fluctuated a great deal. The pigmentation, however, was progressive and marked. During her prolonged survival (18 months) after palliative adrenalectomy had relieved her Cushing's syndrome the effects of the other hormones—particularly gastrin—continued to cause serious clinical problems.

Most of the islet tumors associated with gastrin production are, as our case, alpha cell tumors,[4, 18, 57] as was the reported case of glucagon secreting islet-cell tumor.[28] It is not known whether alpha granules are characteristic of corticotrophin secretion in an islet-cell tumor since there have been no previous electron-microscopic studies. No effects of glucagon secretion were clinically apparent in our case. The amount of glucagon in the tumor was small compared to that assayed in a reported case of islet-cell cancer associated with hyperglycemia.[28]

Case 2. M.M., a 26-year-old Caucasian woman, was admitted on October 5, 1962. She had had an uncomplicated pregnancy and normal delivery of her second child on August 15, 1962. Shortly thereafter she exhibited psychotic behavior and was admitted to a psychiatric institution. Blood pressure was found to be 250/160. She had generalized acne and a suggestion of truncal obesity. Mentally she had fluctuating levels of communication and detachment.

On admission at our hospital the blood pressure was 180/135. She had diffuse acne and pyodermia and marked facial hirsutism. The extremities were thin and some ecchymoses were present. The abdomen was rotund.

Hemoglobin was 16.8 mg/100 ml, fasting blood sugar 184 mg/100 ml, plasma sodium 134 mEq/liter, potassium 2.7, chloride 84 and carbon dioxide 35.9. The urinary 17-KS excretion varied between 54 and 261 mg/24 hours and the 17-OHCS excretion between 64 and 402 mg/24 hours. Roentgenographic studies showed a 3 × 4 cm mass in the right adrenal area.

At operation on October 30, 1962 a 4-cm spherical tumor of the right adrenal was removed. Cut section revealed this to be a medullary tumor surrounded by hyperplastic adrenal cortex. In spite of large doses of hydrocortisone her blood pressure had to be maintained by the administration of norepinephrine for 2 days following operation. Following operation she developed lung abscesses, cystitis and pyodermia but eventually recovered. In January 1963 (without steroid replacement therapy) baseline 17-OHCS excretion was 6.9 mg/24 hours and 17-KS 6.4 mg/24 hours. Urinary 17-OHCS rose to 23.4 mg/24 hours with ACTH stimulation.

Assay of the patients's plasma for ACTH showed 0.88 mU/100 ml and assay of the tumor tissue showed 28 mU/Gm ACTH. Electron microscopy showed granules consistent with norepinephrine granules (Fig. 4A).[8, 56]

Comment: Several cases of pheochromocytoma in association with Cushing's syndrome have been reported[34, 55] and in these cases relief of Cushing's syndrome was also achieved on removal of the tumor. Assay of the tumor for ACTH in this case and relief of hypercorticism by removal of the adrenal medullary tumor with its surrounding cortex confirm that pheochromocytoma can be an inciting lesion in Cushing's syndrome.

Instances of Cushing's syndrome associated with other types of retroperitoneal tumor of nerve tissue origin have been reported (sympathicoblastoma and ganglioma).[21, 24] The few pheochromocytomas among the increasing spectrum of corticotrophin-secreting tumors are remarkable in that they are benign while most of the tumors of other sites are malignant.

Case 3. M.B., a 52-year-old Caucasian man, was admitted on February 3, 1965. He was well until December 1964 when he developed pneumonia. In January 1965 he complained of headache, felt giddy and lost consciousness. He was said to have had a convulsion. At his local hospital the blood pressure was registered as 280/120. Skull films and carotid angiogram were normal. Regitine test was normal and urinary VMA and 5-HIAA assays were normal. Progressive weakness developed and he was transferred to Barnes Hospital.

Blood pressure on admission was 160/80. Except for some puffiness of the face the physical examination was not remarkable. Serum sodium was 127 mEq/liter, potassium 3.7, carbon dioxide 29.6, chloride 78 on admission. Serum sodium later ranged from 121–125 mEq/liter. Urine osmolality was 466–540 mOs/kg and plasma osmolality 279 mOs/kg, with urinary sodium 192 mEq/24 hours. Chest film was normal.

No specific treatment was given. He was discharged on February 26 and readmitted on April 10, 1965. In the interval he had complained of increasing weakness and a change in his appearance. On examination his blood pressure was 210/120. His face was puffy and ruddy. Compared to his previous examination in February, his extremities seemed smaller. His appearance was that of Cushing's syndrome. Plasma electrolytes showed hypokalemic alkalosis. Urinary 17-OHCS excretion was 76.5 mg/24 hours and 17-KS 42.2 mg/24 hours. Chest film now showed a paratracheal infiltrate.

A scalene node biopsy showed undifferentiated carcinoma ("oat cell"). Betatron therapy was given to the mediastinum. Roentgenographic evidence of the chest infiltrate regressed but his Cushing's syndrome progressed and urinary 17-OHCS levels remained high. He was discharged on May 2, 1965 and died at home on May 19, 1965.

The autopsy findings were: pulmonary embolus and infarction; metastatic carcinoma of the liver, adrenals, diaphragm, brain and retroperitoneal and mediastinal lymph nodes. The primary site was uncertain. The adrenals were markedly hypertrophied. There were mulitple ulcers in the small intestine. A carcinoma of the prostate of different cell type was found.

Comment: It is well known that undifferentiated tumor in the chest can be associated with secretion of excess amounts of ADH. ADH has been assayed from the plasma and tumors of such cases.[6, 52]

The evidence for inappropriate ADH secretion in our patient is presumptive and is based on hyperosmolality of the urine and hypoosmolality of plasma and hyponatremia in the presence of naturesis. Later, when Cushing's syndrome developed, the hypokalemic alkalosis characteristic of that syndrome was evident and the laboratory evidence of ADH secretion was effaced. Schwartz et al.[42] noted that adrenal steroids caused partial reversal of the water and electrolyte abnormalities in a patient with the inappropriate ADH syndrome associated with oat-cell cancer of the lung. It is possible that the combined association of ADH and ACTH secretion from oat-cell carcinomas of the lung is more frequent

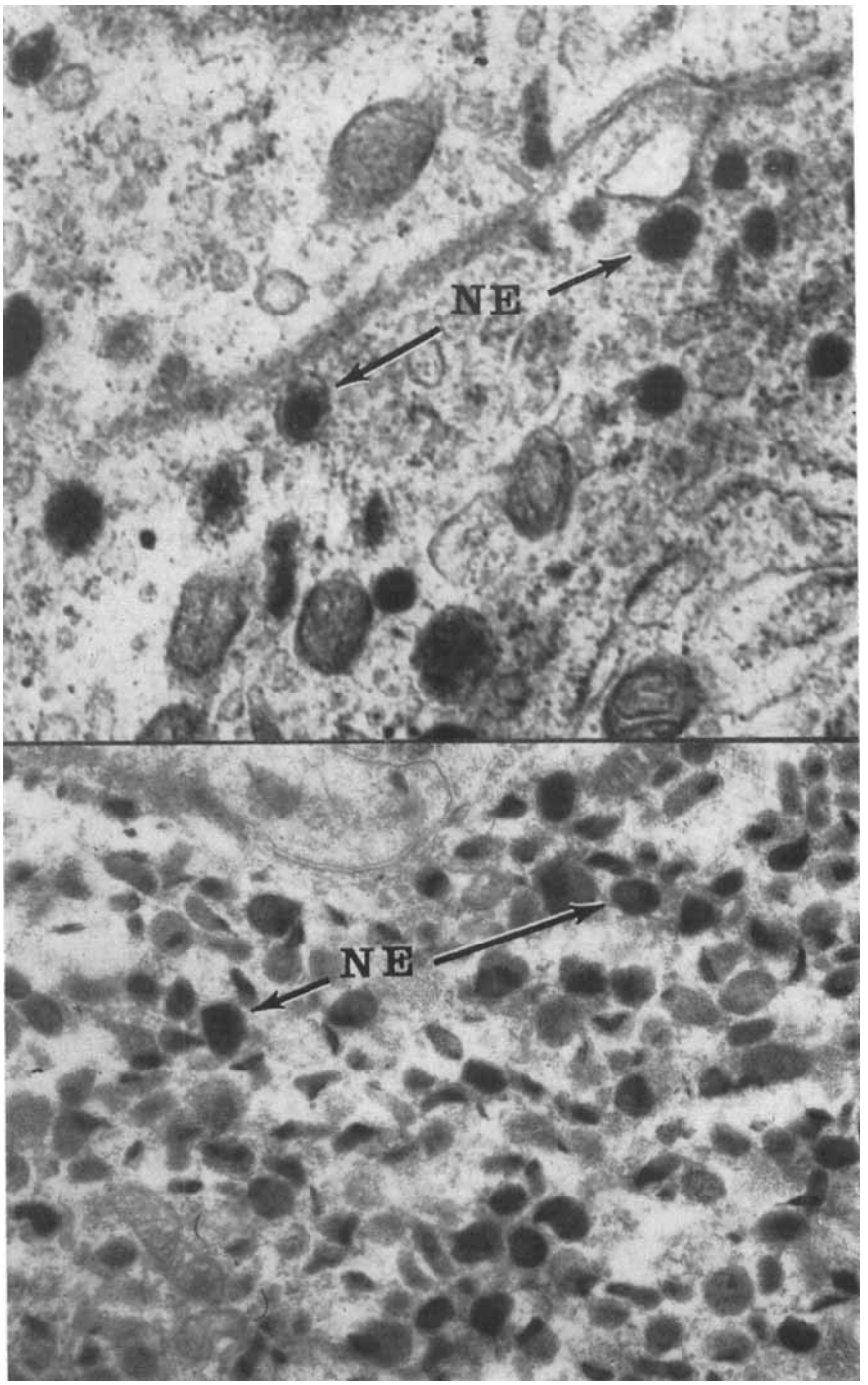

FIG. 4. A (upper), Electron microscopy of an ACTH-secreting pheochromocytoma, showing typical norepinephrine granules (NE), case 2. B (lower), For comparison electron microscopy of a pheochromocytoma from another patient. This was an ordinary functioning pheochromocytoma of the adrenal medulla. Slightly lower magnification than A.

than the literature would suggest but the marked electrolyte effects of severe hypercorticism may mask the effects of vasopressin.

Case 4. J. H. was 45 years old when admitted to Barnes Hospital in April 1963. He had had a duodenal ulcer diagnosed in 1943; it had been symptomatic off and on since that time. He had known of high blood pressure for 5 years. Four years before admission here he had an episode of confusion and melena. His hemoglobin then was found to be 5 mg/100 ml. Blood transfusions were given. Roentgenograms showed "ulcer" but operation was not recommended.

He returned to good health until 6 months

before admission when ulcer symptoms recurred and roentgenograms were said to show active ulcer. Two weeks before admission he developed sore throat and fever and became confused. He was found to have a severe alkalosis and was transferred here. He had had no dyspnea, edema, cyanosis, flushes, diarrhea or steatorrhea.

On admission he was confused, disoriented and sometimes obtunded to the extent that he could not be aroused. Blood pressure was 185/100. A soft systolic murmur was head at the apex. The remainder of physical examination was not helpful. Flushing was not noted but there was a constant rubrous appearance of neck and anterior chest.

Electrolyte studies showed a severe hypokalemic alkalosis (sodium 138, potassium 2.2, carbon dioxide 54.3 mEq/liter). On April 22 a fall in hemoglobin was noted and on the following day a further fall. An April 23, 2000 ml of coffee-ground material was aspirated from the stomach and 2000 ml of whole blood was given. Thereafter no further bleeding occurred. With intensive electrolyte therapy the losses in urine and gastric aspirate were replaced and the blood electrolyte levels became more normal. Gastric aspirate was persistently alkaline.

Operation was done on April 29, 1963. There was induration in the region of the pylorus and gastrotomy revealed a large channel ulcer. A 2-cm nodule was felt in the terminal ileum and several hard nodes measuring 1 to 2 cm were felt in the mesentery. A right colectomy and ileal resection (40 cm) were done with end-to-end ileocolostomy. A subtotal gastrectomy and Billroth I anastomosis were also done. The liver was free of metastatic nodules.

Preoperative blood pressures were 170–210/90–120; postoperatively the pressures were 100–130/60–80. He was discharged on May 9, 1963. On June 27, 1963 urinary 17-KS excretion was 14.6 mg/24 hours and 17-OHCS 7.8 mg/24 hours. In September 1963 he was normotensive, felt well, was working regularly and gastrointestinal roentgenographic series showed no recurrent ulcer. In March 1965 he was readmitted because of abdominal pain and roentgenograms then showed duodenal ulcer. Plasma electrolytes were normal, and urinary histamine, 5-HIAA, 17-KS and 17-OHCS were normal. Repeat gastrointestinal roentgenographic series in June 1965 showed healing of the duodenal ulcer. In April 1967 he wrote that he felt well.

Histologically this was a typical ileal carcinoid 6 cm from the ileoceal valve. There was lymphatic permeation about the tumor and four of 18 lymph nodes examined showed metastatic carcinoid. A separate carcinoid

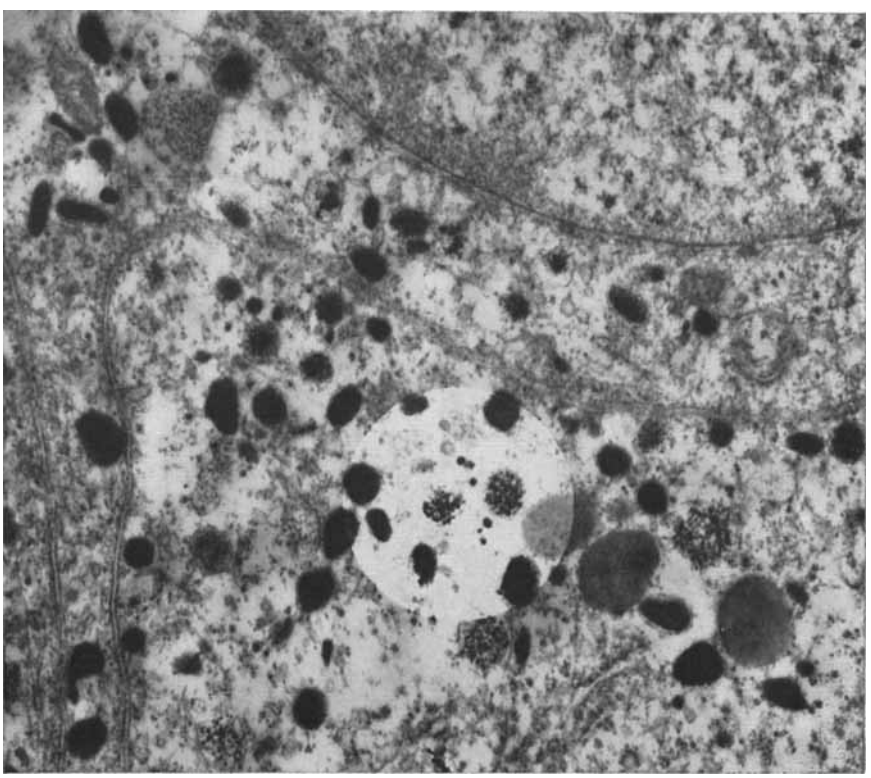

FIG. 4. C, Electron microscopy of normal human adrenal medulla. The circled area shows the variability in fine structure of the granules which are dense, round, ovoid or irregular. Some granules have a distinct punctate central region. They are membrane limited. These granules are identical to those in A and B and this type has been shown to contain norepinephrine.[8, 56]

tumor was found in the ileum 27 cm proximal to the larger carcinoid. The pyloric ulcer was benign. Electron microscopy showed no differences between his carcinoid tumor and other carcinoids which have been studied (Fig. 5).[3, 27] Staining for ACTH by the fluorescent antibody technique gave positive results.[20] Although he did not have the carcinoid syndrome, assay of the tumor for 5-hydroxytryptamine showed 2.4 mg/Gm of tissue (Sjoerdsma). Assay for gastrin showed no response (Endahl). Bioassay for ACTH was inconclusive due to insufficient tissue (Liddle).

Comment: The common symptoms and findings associated with malignant carcinoid[45] were not observed in the present case, but the tumor was shown to contain large amounts of serotonin.

The evidences of hypercorticism in this patient are not well documented. He had hypertension, a marked hypokalemic alkalosis and moderately elevated urinary steroids on one occasion (possibly partial collection). The adrenal glands were not exposed at operation. However, there was marked fluorescence of the tumor and of its metastases with the fluorescent anti-ACTH antibody.[20] One previous case of Cushing's syndrome due to malignant appendiceal carcinoid has been reported[38] but this is the first one reported associated with intestinal carcinoid.

Feyrter noted peptic ulcer in 16 (17%) of 94 cases with carcinoid tumor coming to autopsy.[13] The carcinoid tumor was located in the ileum in 14 of these 16 cases. The ulcer was located in the stomach in 11 cases and in the duodenum in five.

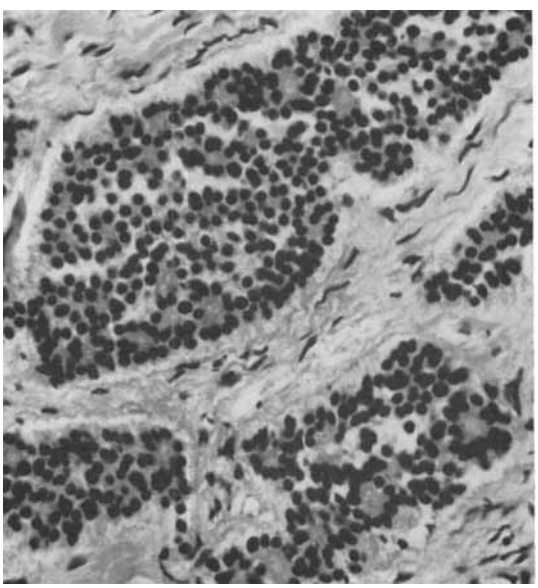

FIG. 5A, Light microscopy of ACTH-secreting carcinoid, case 4, showing typical pattern of carcinoid.

The failure to extract gastrin-like activity from this tumor is not surprising since extracts of other carcinoids have also failed to elicit acid secretion from a denervated fundic pouch. Corticotrophin itself has been shown to increase gastric secretion in dogs[35] and may be implicated in the hypersecretion in this case.

Case 5. N. S., 56-year-old man, entered Jewish Hospital, St. Louis, on October 20, 1964 because of melena. Stools were guaiac positive and radiographs showed postbulbar duodenal ulcer. He continued to bleed for several days and transfusions were given. The hematocrit then became stable and he was discharged.

He was readmitted September 8, 1965 because of prostatism. There had been no ulcer symptoms in the intervening time. The prostate was enlarged and smooth but no prostatic nodules were felt. Intravenous pyelography was normal. Cystoscopy revealed urethral prostatic obstruction. A chest film showed a left hilar mass. Serum electrolytes were normal.

A scalene node biopsy and excision of a nodule of the chest wall were done. These showed metastatic carcinoid. Exploratory left thoracotomy revealed tumor mass in the left upper lobe, in the pulmonary hilum and metastatic involvement of nodes in the hilum. Biopsy of hilar lymph nodes and lung showed malignant carcinoid. Cobalt^{60} therapy to the chest was begun and he was discharged on October 2.

He was readmitted November 5, 1965. In the interval he had developed progressive lower extremity edema and progressive pigmentation. Cobalt^{60} therapy had been given for a total of 24 days. He was extremely weak and was noted to be less alert than previously. There had been no history of flushes. Examination showed blood pressure 140/80. There was tanning of the skin—particularly of exposed surfaces. The prostate was enlarged as before. There was marked edema of the legs and ankles. Laboratory investigation confirmed the presence of hypercorticism (urinary 17-OHCS 43–51 mg/24 hours, urinary 17-KS 31–32 mg/24 hours, plasma cortisol 47 μg/100 ml). Urinary 5-HIAA varied between 29.2 and 36 mg/24 hours (normal 2–9).

On November 18 bilateral total adrenalectomy was done. The adrenal cortices were slightly hyperplastic and there was a metastatic tumor nodule in each adrenal. Postoperatively hypokalemia persisted until replacement steroid medication was reduced to

maintenance levels. He returned to his office work and has continued to work for over a year since operation. He has not exhibited the carcinoid syndrome.

Comment: The ordinary case of bronchial carcinoid is not endocrine active at a clinically discernible level. Individual tumors may, however, be associated with the carcinoid syndrome and 5-hydroxytryptamine, kinen peptides[32, 37] and epinephrine and norepinephrine[14] have been isolated from some tumors. Previous instances of ACTH-secretion in bronchial carcinoid have been reported.[12, 39, 46] Malignant bronchial carcinoid is frequently an indolent tumor and palliative adrenalectomy—as done in this case—may be worthwhile when Cushing's syndrome is present.

Case 6. F. A. W., a 54-year-old man, was admitted to Barnes Hospital October 21, 1966. In September 1966 he had complained of abdominal distension, nocturia, polydipsia and ankle edema. He was seen by his physician and found to have a blood sugar of 420 mg/100 ml. Previously his health had been good.

On examination the blood pressure was 150/90. He was obese and his face and anterior chest were flushed. The skin of the face and arms was dark. There was a grade III aortic low-pitched systolic murmur radiating to the right supraclavicular area and out to the apex. Hepatomegaly was noted but no hepatic nodules were felt. Pitting angle edema was present.

Laboratory examination showed hemoglobin 15.1 mg/100 ml, white count 11,650 with normal differential. Hypokalemic alkalosis (potassium 1.7 mEq/liter, carbon dioxide 45 mEq/liter) was present. Urine 17-OHCS was 151 mg/24 hours, urine 17-KS 68.2 mg/24 hours and plasma cortisol 95 μg/100 ml.

Chest film showed a right lower lobe mass and hilar adenopathy. Liver scan revealed multiple cold nodules in the liver. In an attempt to palliate his hypercorticism, total adrenalectomy was done November 2, 1966. There were multiple metastatic nodules 1 to 4 cm in diameter in the liver. The adrenals were large and hyperplastic, weighing 18 and 22 Gm each when dissected from fat. There

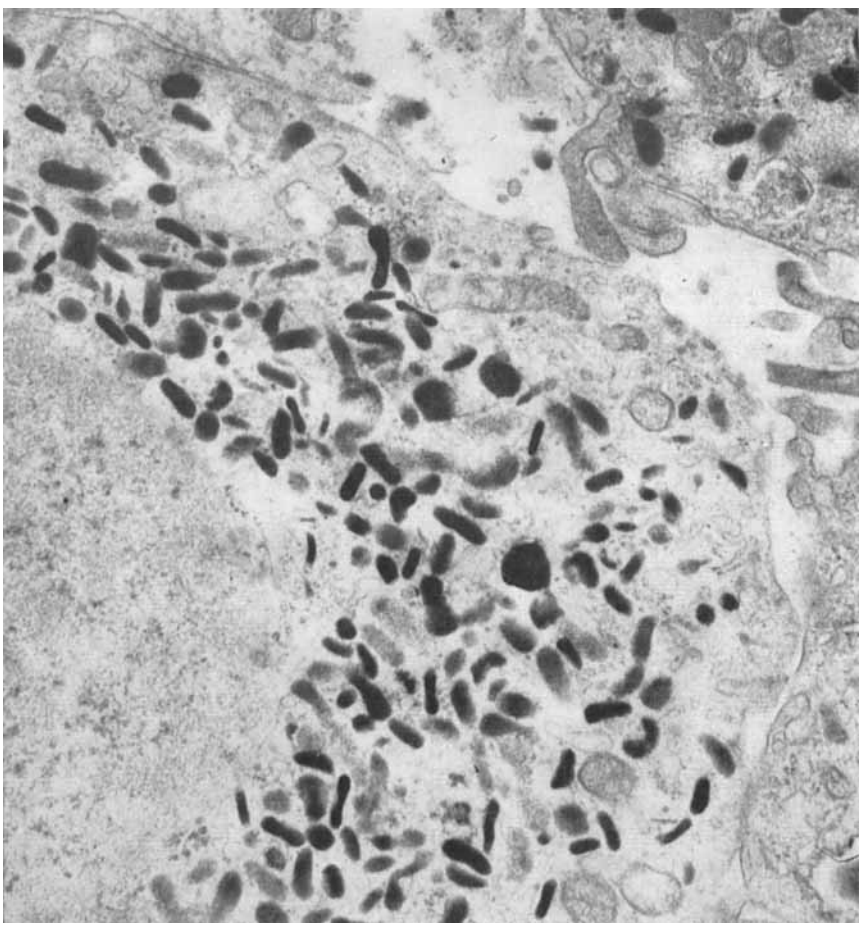

FIG. 5. B, Electron microscopy of carcinoid, case 4. These dark serotonin granules are variable in shape and density. Many are biconcave. No membrane encloses the granules.

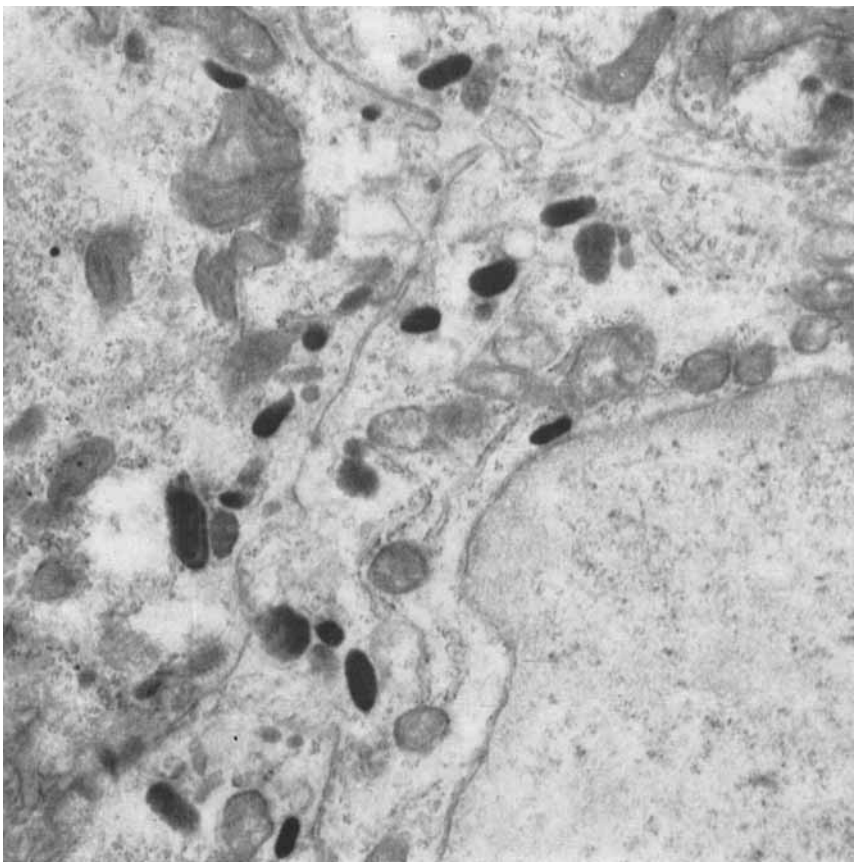

FIG. 5. C, For comparison electron microscopy of another carcinoid of the ileum. The carcinoid syndrome was present but not hypercorticism. The dark granules are the same type of granules as in 5B. This type of granule has been shown histo-chemically to contain serotonin.[3, 27]

were small metastases in the adrenals. Liver biopsy showed metastatic oat-cell carcinoma.

By November 9 cortisone dosage had been reduced to 50 mg twice daily orally. Urine 5-HIAA level was 32 mg/24 hours. On November 10, pedal edema reappeared. Hyponatremia (130–135 mEq/liter) developed. Urine osmolality was 512–674 mOsm/liter and plasma osmolality 275 mOsm/liter. On November 13 a fall in blood pressure to 102/50 and a tachycardia were noted. Shortly thereafter he passed a stool of dark blood. The hemoglobin was 8 mg/100 ml. Multiple transfusions were given but the bleeding increased in severity. He was never thereafter in sufficiently good condition to tolerate laparotomy. He died November 19, 1966.

The findings at autopsy were: absence of adrenals; oat-cell carcinoma of the right lower lobe of the lung with metastases in visceral pleura, peribronchial and mediastinal lymph nodes and liver; a 4 cm posterior perforated duodenal ulcer eroding a large artery and multiple smaller ulcers in the small bowel.

Comment: Postoperatively the laboratory studies were consistent with vasopressin secretion but assays of the tumor and its metastases for vasopressin were negative (Utiger). The ulcer was not noted at operation but in any case progressed after operation. Its pathogenesis is uncertain but may be related to hypercorticism. Except for flush of the face and anterior chest no other aspects of the carcinoid syndrome were apparent and the urinary 5-HIAA elevation was modest. Administration of corticoids may alleviate some of the symptoms of the carcinoid syndrome,[32] and hence spontaneous hypercorticism in a serotonin-secreting tumor may mask some of the effects of serotonin.

DISCUSSION

In Table 1 the endocrine aspects of these cases are summarized. We have observed 15 instances of hypercorticism which were associated with neoplasms that were not of pituitary or adrenal cortical origin. In addition to the six reported here we have seen three other cases with oat-cell carcinoma in the chest, one case with uncertain origin (possibly seminoma of testis; possibly oat-cell of lung), one with metastatic oat-cell tumor in liver with inapparent primary, one each with carcinoma of parotid and of prostate, and two

TABLE 1. ACTH-Secreting Tumors with Evidence of Other Endocrine Activity

Case	Tumor	Evidence of ACTH secretion	Other endocrine aspects
1. M.J.	Islet carcinoma of pancreas	Cushing's syndrome Urinary 17-OHCS 62 mg/24 hr Urinary 17-KS 42 mg/24 hr Hypokalemic alkalosis Adrenal cortical hyperplasia Plasma ACTH 13 mU/100 ml Tumor ACTH 6 mU/Gm Metastatic tumor ACTH 48 mU/Gm	MSH: Heavy pigmentation Tumor melanotrophic activity 1344 mU/Gm Gastrin: Ellison-Zollinger syndrome. Assay using fundic pouch of dog positive for gastrin. Radioimmunoassay, gastrin 20μg/Gm lyophilized tumor Glucagon: Positive assay, 64.7 mμg/Gm Insulin: Negative assay Parathormone: (Presumptive) Serum calcium 11–16 mg/100 ml Serum phosphorus 2–4 mg/100 ml TRP 70%, 89% Hypercalcuria ADH: (Presumptive) Hyponatremia (125–128 mEq/l) Urine osmolality > plasma osmolality (325 vs. 270 mOsm/l)
2. M.M.	Pheochromocytoma of right adrenal medulla	Cushing's syndrome Urinary 17-OHCS 64–402 mg/24 hr Urinary 17-KS 54–261 mg/24 hr Adrenal cortical hyperplasia Hypokalemic alkalosis Plasma ACTH 0.88 mU/100 ml Tumor ACTH 28 mU/Gm Removal of tumor relieved Cushing's syndrome	Norepinephrine: On excision of tumor, blood pressure fell, sustained with norepinephrine. On electron microscopy granules consistent with norepinephrine were demonstrated in tumor. Bioassay (rabbit aorta strip) positive for norepinephrine
3. M.B.	Oat-cell carcinoma of mediastinum	Cushing's syndrome Urinary 17-OHCS 76.5 mg/24 hr Urinary 17-KS 42.2 mg/24 hr Hypokalemic alkalosis Adrenal cortical hyperplasia	ADH: (Presumptive) Hyponatremia (127 mEq/l) Urine osmolality > plasma osmolality (540 vs. 270 mOsm/l) Naturesis-urine Na 192 mEq/24 hr
4. J.H.	Malignant carcinoma of ileum	Urinary 17-OHCS 17.3 mg/24 hr Urinary 17-KS 25.3 mg/24 hr Hypokalemic alkalosis Tumor positive for ACTH with fluorescent antibody technique Removal of tumor relieved hypercorticism	Serotonin: Electron microscopy similar to usual carcinoid, including granules. Tumor contained serotonin 2.4 mg/Gm
5. N.S.	Malignant bronchial carcinoid	Hypokalemic alkalosis Urinary 17-OHCS 43.5, 51.0 mg/24 hr Urinary 17-KS 31.9, 31.5 mg/24 hr Adrenal cortical hyperplasia	MSH: (Presumptive) Pigmentation Serotonin: Urinary 5-HIAA 29.2–36 mg/24 hr (normal 2–9 mg/24 hr)
6. F.A.W.	Oat-cell carcinoma of lung	Cushing's syndrome Hypokalemic alkalosis Urinary 17-OHCS 153 mg/24 hr Urinary 17-KS 68.2 mg/24 hr Adrenal cortical hyperplasia	MSH: (Presumptive) Pigmentation Serotonin: Urinary 5-HIAA 32 mg/24 hr ADH: Assay of tumor and metastasis negative for vasopressin

with the complete syndrome which have had adrenalectomy but have not as yet had any clinical evidence of tumor. We have no evidence that humoral substances other than ACTH and MSH were elaborated in these nine cases.

The increasing frenquency with which these cases are being seen and reported suggests that they have not been recognized in the past. Four of our six cases reported here in detail and nine of the fifteen in all had the physical appearance of Cushing's syndrome. All had documented hypercorticism and all had hypokalemic alkalosis at some time during their course. In 37 cases of ACTH-secreting tumor Liddle et al.[24] noted other endocrine activity in three cases: Islet-cell carcinoma with ACTH, MSH and gastrin; oat-cell carcinoma

with ACTH and ADH; and oat-cell carcinoma with ACTH and parathormone.

Duodenal or intestinal ulcers were known to be present in five of the six cases reported here and they presented serious clinical problems in four patients.

The types of tumor which our cases exhibited are in general those which are known to secrete a wide variety of endocrine substances either as a single phenomenon or in combination. Generally in reported cases endocrine activity has been assayed in those cases in which clinical effect has been observed.

Islet-cell carcinomas of the pancreas in particular are ubiquitous fabricators of hormones: Insulin, glucagon,[28] gastrin, ACTH, MSH,[43] serotonin[53] and now possibly parathormone and ADH have been reported. Watery diarrhea and hypokalemia in the absence of ulcer may occur in nongastrin secreting islet-cell tumors, indicating the presence of an as yet unidentified hormone.[30]

Oat-cell carcinoma in the chest is known to secrete ADH, parathormone, serotonin,[16, 29] ACTH and MSH.[43] Oat-cell carcinoma is also frequently associated with neuromuscular disorders, bone marrow suppression[11] and peptic ulcer. Unger et al. found small amounts of insulin and glucagon in such a tumor.[51]

The gastrointestinal carcinoids may secrete serotonin and related compounds and in our case ACTH. The bronchial carcinoids when endocrine active may secrete 5-HT, 5-HTP, kinen peptides,[32, 37] ACTH and epinephrine and norepinephrine.[14] The pheochromocytomas of course secrete the usual catecholamines and very rarely ACTH.

Aside from the oat-cell tumor in the chest—which is the most common site of ectopic ACTH production—the occurrence of this phenomenon in tumors of endocrine, endocrine-related and neuroendocrine structures is striking. Corticotrophin production has been reported in pheochromocytoma, islet-cell carcinoma, intestinal carcinoid, bronchial carcinoid, thyroid cancer,[1] ovarian cancer,[36] sympathicoblastoma,[21] prostatic cancer,[54] mammary cancer,[39] testicular cancer, ganglioma,[24] acidophil adenoma of pituitary[10] and chromophobe adenoma of pituitary. Origin in all of the classical endocrine glands except parathyroid has now been reported. In the cases of hyperparathyroidism associated with Cushing's syndrome which Raker et al. reported, surgical relief of the hyperparathyroidism did not influence the severity of the hypercorticism.[40]

Some of the ACTH secreting tumors of endocrine glands do not have the typical histologic appearance of tumors of these sites but nevertheless give collateral evidence that they truly originate from the purported tissue rather than from some widely dispersed tissue incorporated in the structure (such as argentaffin or chromaffin tissue). A metastasis from an ACTH-secreting thyroid tumor took up large amounts of radio-iodine.[1] In our case with carcinoma of the prostate—which was later associated with hypercorticism—the tumor initially had regressed after orchiectomy. Our cases of islet carcinoma, pheochromocytoma, intestinal carcinoid and bronchial carcinoid were apparently secreting some of the customary hormones from these sites in addition to ACTH and had the typical microscopic appearance of tumors of their type.

The variety of neoplasms causing Cushing's syndrome may not be so extensive as the literature indicates. Some of the cases with exotic "primary" tumor sites died later with extensive mediastinal and lung tumor. Possibly some of these were cases in whom the first clinical evidence of disease was a metastasis from an oat-cell tumor in the chest mistakenly called primary.

These oat-cell tumors of lung and mediastinum are proving to be endocrine-active tumors to a high degree. Their ability to secrete neuroendocrine substances (vasopressin, serotonin) at least suggests the possibility that the tissue of origin of the oat-cell thoracic tumor is derived from the neural crest. The "hints of histological similarity"[7] between bronchial adenoma and pulmonary oat-cell carcinoma are accompanied by hints of similar endocrine activity. The "thymomas" associated with hypercorticism are thymomas only by location in the interior mediastinum. Histologically they differ from the usual group of thymic tumors. The suggestion[7] that bronchial carcinoid, oat-cell carcinoma of the lung and the anterior mediastinal malignant tumors associated with hypercorticism are varieties of the same tumor or at least arise from the same type of tissue is gaining support from recent endocrine studies. Recent demonstration of carcinoid-like granules in oat-cell carcinoma lends further support to this hypothesis.[49]

It is not known how general the phenomenon of corticotrophin production by neoplasms is. Minor degrees of ectopic ACTH production should simply result in decrease in pitui-

tary secretion of ACTH via the adrenal cortical hypophyseal homeostatic mechanism. Clinical hypercorticism would not occur until secretion by the tumor exceeds normal pituitary production. Generally in cases with ectopic ACTH secretion in which the pituitaries have been studied, ACTH content in the pituitaries is low.[24, 25, 31]

Increased numbers of Crooke's cells, which are pathognomonic of hypercorticism, were found in 16 of 20 patients with oat-cell cancer—none of whom had clinical hypercorticism.[22] Certainly the usual oat-cell carcinoma or islet-cell carcinoma (as well as the usual chromophobe adenoma of the pituitary) does not secrete sufficient amounts of ACTH to cause noticeable clinical effects. This observation does not negate the possibility that many or most tumors of these types actually do secrete minute amounts of ACTH (and other hormones) and that clinical emergence occurs in the tumors with greater secretory activity, particularly as they increase in mass. Our case 1 was known to have had the tumor for a year prior to the development of hypercorticism, and in this is similar to many reported cases. As in most other hormonally active tumors, a clinical threshold may not be reached until the tumor has been present for some time.

None of the patients reported here were known to have multiple endocrine adenomas, such as those reported by Underdahl et al.[50] and Schmid et al.[41]

When a direct surgical attack on the endocrine active tumor is possible, this should be done, as in our cases 2 and 4 in which relief of hypercorticism followed excision of a pheochromocytoma and of an intestinal carcinoid. In some instances palliative adrenalectomy may be attempted (cases 1, 5 and 6) and will relieve the hypercorticism but the effects of other peptide and amine hormones, when present, may continue to cause difficulty in addition to the problems of progressive neoplastic disease.

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