Hormone Production in Non-Endocrine Tumors

Naguib A. Samaan, M.D.

Among the topics of great interest in the study of cancer is the inappropriate production of hormones by neoplasms of apparently non-endocrine origin. Ectopic endocrine tumor activity causes metabolic and systemic effects that resemble oversecretion of a hormone of some specific endocrine tissue, although the respective endocrine gland usually shows depressed function in such conditions. These tumors may secrete substances that are the same as the natural hormone, or they may elaborate active principles that are chemically different from the true hormone but capable of imitating it biologically.1

To include a tumor within the "ectopic" hormone or paraendocrine syndrome requires the demonstration of one or more inappropriate hormones produced by a neoplasm that arises from cells not considered a normal source of that hormone. This is accomplished either by: (1) finding high tumor content of the hormone compared with control normal tissue; (2) examining arteriovenous differences in hormone levels across the tumor bed; or (3) observing that the hormone excess and its metabolic effects disappear following surgical removal or adequate therapy of the tumor.2

Accurate clinical knowledge of this syndrome is important in differential diagnosis and treatment. Failure to realize that cancer may produce clinical symptoms similar to those of the endocrine organs may lead to incorrect diagnosis. Proper management of the metabolic complication may be of more immediate importance than the treatment of the underlying tumor. In addition, ectopic hormone production by the tumor may aid in the detection and screening of neoplasia and the monitoring of therapy. For example, an awareness that the inappropriate production of one or more polypeptide hormones represents an important aberration of differentiated function will increase our understanding of those mechanisms underlying the control of heritable differentiated characteristics in cells.

PATHOPHYSIOLOGY OF INAPPROPRIATE HORMONE PRODUCTION

Perhaps the most interesting of the proposed hypotheses of ectopic hormone production by non-endocrine tumors is Gellhorn’s so-called "deletion defect."3 This theory is based on the con-
cept that all body cells must contain the
general transformation necessary for the
synthesis of body proteins, including
polypeptide hormones. The fact that
only specific cells in an endocrine organ
produce a hormone is presumably
caused by the suppression or deletion of
genetic potential in all other body cells.
Any factor that modifies or reduces this
deletion should extend the biosynthesis
of individual hormones to tissues and
organs that are normally non-producers.
The suppression of the deletion phenom-
emon by the neoplastic process, in the
course of its chaotic protein metabolism,
may reasonably explain the ectopic pro-
duction of one or more polypeptide hor-
mones. Unfortunately, this theory leaves
many questions unanswered.
Azzopardi and Williams suggested
that tumors involved in the ectopic hor-
mone syndromes are linked by a single
progenitor cell type, normally associ-
ated with peptide production, which
must be multipotential and migratory in
nature.4 The amine precursor uptake and
decarboxylation (APUD) cell system
was proposed by Pearse, who theorized
that it originates from the neural crest.5
Andrews has argued that the neural crest
origin does not apply to the gastrointes-
tinal APUD cells;6 at least two distinct
origins of APUD cells have been postu-
lated.
The neuroectoderm gives rise to
pheochromocytes and thyroid "C" cells, but the endoderm is a more likely
source of the enterochromaffin and arg-
egentaffin/argyrophil cells of the gas-
trointestinal tract and pancreas.7,8 This
separation of APUD cells into two
groups with endodermal or neuroecto-
dermal origin accords with the separa-
tion of familial multiple endocrine ade-
nomatosis (MEA) into two types.9 The
first type of MEA is associated with en-
odermal derivations, including tumors
of the carcinoid syndrome arising from
enterochromaffin or argyrophil cells of
the gastrointestinal tract and those of the
Zollinger-Ellison syndrome, which
originate in pancreatic islets.10 Carci-
noid tumors also occur in the lung and
can be linked histochemically with oat
cell carcinoma4,11 and the mediastinal
tumors thought to develop from argyro-
phil cells in the thymus.12 The second
type of multiple endocrine adenomatosis
includes pheochromocytoma, medul-
lar carcinoma of the thyroid and parathy-
roid adenoma.13 Evidence shows that
this group is of neuroectodermal ori-
gin.14
Levine and Metz reviewed the litera-
ture and postulated another classifica-
tion of ectopic hormone-producing
tumors, but did not provide definitive
conclusions.15 In an attempt to rati-
alize the change in function, Weichert
developed a unified theory of hormone
production by tumor cells, and con-
ccluded that the syndrome of multiple en-
docrine adenomatosis may simply be a
dysplasia of the neural ectoderm.16
None of the above hypotheses gives
a complete explanation of the patho-
physiology of inappropriate hormone
production by non-endocrine tumors.
Well-documented study of ectopic hor-
mone production by a wide variety of
tumors, using rigorous scientific cri-
iteria, including immunocytochemical
experiments for histologic diagnosis,
may enable the critical examination of
developed proposed classification schemes.17
From the clinical standpoint, it is im-
portant to be aware of the existence of
multiple hormone-producing neoplasms
and their possible cell origin. The dis-
covery of one functioning tumor may
lead to the detection of a co-existing
tumor, perhaps in a subclinical stage.
Polyhormonal Potential
Some neoplasms are capable of produc-
ing several hormones simultaneously. It
is also common that an endocrine tumor
secretes the appropriate hormone as well
as another ectopic hormone, for in-
stance, medullary carcinoma of the
thyroid producing calcitonin and ACTH. Rarely, a tumor may produce the hormone appropriate to its site of origin, plus several other ectopic hormones.

At present, there is good evidence that tumors may give rise to several ectopic hormones, including adrenocorticotropic hormone (ACTH), melanotropics-stimulating hormone (MSH), parathyroid hormone (PTH), calcitonin, luteinizing hormone (LH), antidiuretic hormone (ADH), insulin-like activity (IL.A), gastrin, erythropoietin, a thyroid-stimulating hormone (TSH), and human placental lactogen (HPL).

CLINICOPATHOLOGICAL ENTITIES

Ectopic ACTH

Cushing’s syndrome, resulting from ectopic ACTH hormone production, was first described by Brown in 1928. His patient had diabetes, hirsutism, hypertension, adrenal hyperplasia and oat cell carcinoma of the lung, but no comment was made on the possible connection between the neoplasm and the other disorders. The nature of this relationship was clarified by Christy who reported elevated adrenal weight-maintaining activity in the plasma of two patients. According to Holub and Katz, one of these patients had ACTH-like material in the lung tumor at autopsy. Since 1963, Liddle and colleagues have studied more than 100 patients with Cushing’s syndrome and have concluded that the hypersecretion is a result of ectopic production of ACTH by tumor tissue. They also found that the ectopic ACTH was indistinguishable from pituitary ACTH when subjected to a variety of physicochemical manipulations.

Recently, the presence of “big” and “little” ACTH has been described in both plasma and tumor tissue of patients with ectopic ACTH-producing tumors. “Big” ACTH, considered the precursor of “little” ACTH, is generally the major fraction in bronchogenic tumor extracts and a minor fraction in pituitary extracts. It has also been reported that 30 percent of patients with chronic obstructive lung disease had elevated values of ACTH; this may be diagnostically useful as a method of screening patients with suspected lung cancer, or with a precancerous lesion, and as an objective test of cancer therapy. However, such findings must still be substantiated.

Although some patients with the ectopic ACTH syndrome exhibit the typical clinical features of Cushing’s syndrome, some do not. Despite high levels of cortisol, patients with ectopic ACTH production usually do not have centripetal obesity and cutaneous striae. Most do not develop osteoporosis, because of the brief duration of their cancers. However, hypertension and impairment of glucose tolerance are common. In two patients referred to us as having diabetes mellitus, associated edema of the legs led to the suspicion of Kimmelstiel-Wilson syndrome. However, the patients did not show the albuminuria or fundus changes classically seen in Kimmelstiel-Wilson syndrome, and thorough examination revealed a bronchogenic carcinoma that was producing ACTH and causing metabolic alterations. (Figs. 1 and 2.)

Hypokalemia, weakness and edema are more common in patients with ectopic ACTH production than in those with other types of Cushing’s syndrome. The edema is often misdiagnosed as a result of heart failure, lymphatic or venous obstruction, and the patients are given a diuretic; associated hypokalemia may be inaccurately attributed to the diuretic agent. An ACTH-producing tumor should therefore be regarded as one of the important causes of hypokalemic alkalosis.

Ectopic ACTH may be produced by a variety of tumors, but the most com-
mon are oat cell carcinoma of the lung, carcinoma of the pancreas (including islet cell and carcinoid), thymoma, benign bronchial adenoma (including carcinoid) and cancer of the thyroid, especially medullary carcinoma.

Ectopic MSH
The first clue that MSH might be secreted by a non-endocrine tumor was provided in 1956 by Engel and his associates who observed a patient with Cushing’s syndrome that recurred after subtotal adrenalectomy. Recurrence of hypercorticalism was accompanied by the development of hyperpigmentation. In the course of their investigations, a mediastinal carcinoma was removed; this was followed by adrenal insufficiency and disappearance of the hyperpigmentation. Using a combination of bioassays and radioimmunoassays, Abe et al. found immunoreactive α-MSH, while most of the biological MSH activity of tumor extracts could be attributed to β-MSH.

Ectopic Parathyroid Hormone
Another metabolic derangement observed in cancer patients is potentially lethal hypercalcemia. Most patients with hypercalcemia and cancer have roentgenographic evidence of skeletal metastasis. The findings of hypercalce-
Fig. 2. Bilateral edema of the lower limbs which was previously investigated for lymphatic and venous obstruction. This patient was referred with a diagnosis of possible Kimmelstiel-Wilson syndrome. The edema was secondary to an ACTH-producing bronchogenic carcinoma.

mia, hypophosphatemia and hypercalcemia in a patient with negative skeletal surveys may be the result of parathyroid hormone production by cancer (ectopic hyperparathyroidism) or coexistent primary hyperparathyroidism.

The importance of a careful history in the differential diagnosis of pseudohyperparathyroidism and primary hyperparathyroidism has been stressed by Lafferty. A history of renal stones or radiographic evidence of subperiosteal bone resorption is diagnostic of primary hyperparathyroidism, as is the finding of a high gradient of immunoreactive PTH (iPTH) in the neck vein. Riggs and associates showed that, by using a different antiserum, it may be possible to differentiate primary hyperparathyroidism from pseudohyperparathyroidism. They reported less increase in PTH serum levels in patients with the ectopic syndrome than in those with primary hyperparathyroidism for an equivalent increase in serum calcium. This may be explained by their later studies, which showed that the quantity of a circulating inactive fragment of the PTH molecule (the portion adjacent to the COOH terminal) is greater in the primary than the ectopic syndrome. In contrast, the concentration of an active fragment
of the hormone (NH₂ terminal residue of PTH) was similarly increased in both ectopic and primary hyperparathyroidism. Thus, both syndromes are capable of producing hypercalcemia. Using a highly sensitive radioimmunoassay system to determine the inactive PTH form, it was found that in cancer patients the increases of inactive serum PTH were lower for a given serum calcium value than in patients with primary hyperparathyroidism. Riggs and co-workers concluded that, with an overlap of about eight percent, their assay system can effectively differentiate ectopic from primary hyperparathyroidism.

In the past, it has been stressed that the presence of bone metastases excludes the diagnosis of pseudohyperparathyroidism. We believe this is not always valid since in some instances treatment of localized metastatic disease may result in the disappearance of hypercalcemia. A good example is the case of a 64-year-old man who was diagnosed to have a squamous carcinoma of the lung, which was removed; a few weeks later, hypercalcemia was detected by a chemical survey test. Clinical examination showed a small metastatic lesion in the fourth rib. The hypercalcemia was managed by hydration and
diuretics. The metastatic lesion was irradiated. After radiotherapy, the hypercalcemia disappeared (Fig. 3), and the patient remained normocalcemic for four months without further treatment until he developed widespread metastases and hypercalcemia, and died. Conversely, a patient may have hypercalcemia in the presence of cancer, with localized metastases to bone. The removal of the primary tumor may result in normocalcemia, or even tetany. In a patient with hypernephroma and localized metastases to the pelvis, removal of the tumor resulted in tetany.

A history of extraparathyroidal tumor in a patient with hypercalcemia does not exclude the possibility of coexisting primary hyperparathyroidism. Our studies have revealed that primary hyperparathyroidism may be associated with other tumors in the body more commonly than previously realized. During the past two years at M.D. Anderson Hospital, we noted 78 patients with hypercalcemia who had high levels of parathyroid hormone in the serum, which was obtained by venous catheterization of the neck. At operation, primary hyperparathyroidism was confirmed. Twenty-five of these patients had tumors in other parts of the body. (Fig. 4.)

Our investigations also showed that the finding of a high level of PTH in the superior vena cava may not be diagnostic of primary hyperparathyroidism, but could be the result of ectopic PTH from metastases in the mediastinal region or cancer of the lung.

Ectopic parathyroid hormone may be produced by a variety of tumors, most commonly squamous carcinoma of the lung, hypernephroma, hepatoma and carcinoma of the pancreas and colon.

**Ectopic Calcitonin**

Calcitonin is normally secreted by the C-cells of the thyroid gland, which are of neuroectodermal origin. It is found in excess in the C-cell type tumor, medullary carcinoma of the thyroid.

With the development of a radioimmunoassay of calcitonin in biological fluids, it was found that cancers secreting calcitonin are more common than suspected, because of the frequency of tumors of neural crest origin. High serum calcitonin was detected in patients with oat cell carcinoma of the bronchus, intestinal and bronchial carcinoids and pheochromocytoma. This hormone may, indeed, prove to be the most constant of all the biologically active substances identified in the APUD series.

Recently, we reported three patients with carcinoid tumors associated with hyperparathyroidism. All showed a high circulating immunoreactive calcitonin level, without differential increase in the neck venous catheterization specimens, indicating that the high concentration of circulating immunoreactive calcitonin may be caused by the carcinoid tumor. Such data suggest that the hyperparathyroidism in these patients was primary, and that the association with carcinoid tumor represents another form of multiple endocrine tumor formation.

**Ectopic Gonadotropin**

Since gonadotropins are normally produced by both pituitary and trophoblastic tissues, ectopic gonadotropins must, by definition, be secreted by non-pituitary/non-trophoblastic tumors. Certain neoplasms may present with gynecomastia in the adult or precocious puberty in the child, and may show an increased level of gonadotropic hormone (HCG). These presentations may precede clinical detection of the tumor. With the development of βHCG radioimmunoassay, ectopic HCG secretion can be differentiated immunologically from luteinizing hormone produced by the pituitary gland. High serum levels of βHCG have been described in a variety of tumors, such as the lung, breast, liver and ovaries.
Fig. 4. This patient had carcinoma of the breast and later developed hypercalcemia, which was the result of primary hyperparathyroidism confirmed at surgery.

Ectopic Antidiuretic Hormone (ADH)
The syndrome of inappropriate secretion of antidiuretic hormone was fully described by Bartter and Schwartz who showed that the tumor cell produces an aberrant peptide closely resembling and probably identical to vasopressin.

The features of this syndrome include: hypotonicity of the plasma with hyponatremia; urinary solute concentrations higher than plasma solute concentrations; excretion of sodium in the urine despite hyponatremia; depression of plasma renin despite hyponatremia; and normal renal function. Under appropriate circumstances, however, each of these characteristics may be absent in a given patient with moderate water deprivation and may be unmasked by water loading. Hypopituitarism, myxedema and Addison's disease may mimic all of the features of this syndrome. The most difficult differential diagnosis concerns the patient who has cirrhosis or cardiac failure with low urinary sodium. Whereas water loading in such patients produces or aggravates hyponatremia, it does not appreciably increase urinary sodium; hyperabsorption of salt and water in the proximal tubule is extensive.

Ectopic Insulin-like Activity
Hypoglycemia can be produced by a va-
riety of extrapancreatic tumors, most commonly those of mesenchymal origin (fibrosarcoma, mesothelioma, neurofibroma, spindle cell carcinoma, rhabdomyosarcoma and leiomyosarcoma), hepatoma and adrenal carcinoma.

The mechanism of hypoglycemia associated with extrapancreatic tumors has not been conclusively demonstrated. Many theories have been proposed, but none seems to apply to all cases. Serious consideration has been given to the possibility that, because of the large size of those tumors associated with hypoglycemia, glucose consumption may be so great that it is removed from the circulation faster than it can be delivered from the liver, thereby producing clinical hypoglycemia. However, our studies and those of others do not substantiate this theory.47

It has also been postulated that these tumors produce leucine and tryptophane, which stimulate insulin secretion; however, most, if not all, patients have low immunoreactive insulin both at fasting and during the glucose tolerance test.48 Furthermore, we did not find an abnormal increase in plasma leucine or tryptophane in patients with hypoglycemia secondary to extrapancreatic tumors.47

The most popular theory is the production of an insulin-like substance by the tumor. Several investigators have shown that non-suppressible insulin-like activity or "atypical" insulin-like activity, which is biologically active but immunologically non-reactive, was elevated in some patients. Recently, strong evidence has been presented that "atypical" insulin-like activity or non-suppressible insulin-like activity (ILA), described by us in 1962,49,50 may be the same as the sulphation factor described by Salmon et al.51 or the somatomedin described by Megyesi and co-workers.52 Using a radioimmunoassay, the latter group showed that somatomedin is increased in some, but not all, patients, with hypoglycemia secondary to extrapancreatic tumors.52 Study is needed to define the mechanism of hypoglycemia in extrapancreatic tumors.

**Ectopic Gastrin**

In 1955, Zollinger and Ellison reported that certain patients with severe gastrin hypersecretion and intractable peptic ulceration had non-insulin-secreting adenomas of the islets of Langerhans.53 These authors suggested that the pancreatic adenomas produced a gastrin secretogogue, a hypothesis that was substantiated when Gregory and Tracy isolated two heptadecapeptides of identical amino acid sequence (gastrin I and II).54 In 1967, Gregory and associates isolated, from two pancreatic tumors, a gastrin-like material that had the same amino acid composition as human gastric gastrin.55 Using a sensitive radioimmunoassay for gastrin, McGuigan and Trudeau found high levels of gastrin both in the peripheral serum and in tumor tissue extract from patients with the Zollinger-Ellison syndrome.56

Recent evidence shows that gastrin is normally produced by a certain type of islet cell (D-cell), and that this cell is the prototype of the gastrin-secreting neoplasm found in patients with the Zollinger-Ellison syndrome.57 Such observations lead one to suspect that the ectopic gastrin syndrome may not be "ectopic" at all.

**Ectopic Erythropoietin**

It is generally agreed that the hormone, erythropoietin, is produced whenever there is a deficit between tissue-oxygen demand and adequate tissue-oxygen transport by red cells. Erythropoietin is elaborated mainly by as yet unidentified cells in the kidney, in response to anemia, hypoxemia or impaired circulation; the hormone acts on erythropoietic-responsive cells of the bone marrow to produce an increased number of red blood cells.
In anemic states, increased levels of erythropoietin are found in the plasma and urine, generally in proportion to the severity of the anemia. Erythropoietin levels are characteristically not increased in the absence of anemia or hypoxia, but there are patients who have inappropriate production of erythropoietin without a normal physiological stimulus.

Since Carpenter's description of a patient with a cerebellar hemangioblastoma and erythrocytosis,58 many documented cases have been published. The association of erythrocytosis has been reported with certain benign or malignant tumors. More than half of these are solid or cystic tumors affecting the kidney. Other sites include the liver, central nervous system, uterus, adrenal, ovary, lung and thymus. Ectopic erythropoietin has the physical properties of normal erythropoietin.

Patients with ectopic erythropoietin production by tumors may have abnormal elevation of the red cell count, hematocrit, hemoglobin and red cell mass. This syndrome can be differentiated from polycythemia vera by the absence of pancytosis or splenomegaly, and from secondary "polycythemia" by the absence of decreased arterial oxygen saturation. Erythrocytosis in these patients can be corrected by removal of the erythropoietin-producing tumor.

**Ectopic Thyrotropin**

Several patients with hyperthyroidism in association with trophoblastic tumors have been reported.60 However, the material extracted was biologically, but not immunologically, similar to human pituitary TSH. In view of the finding of TSH-like material in normal placentas, one wonders whether the TSH-like substances contained in trophoblastic neoplasms should be considered ectopic.

**Human Placental Lactogen (HPL)**

HPL is normally found in the sera of pregnant women or in patients with trophoblastic disease, but not in normal subjects.60 Recently, it was noted that HPL may be present in the sera of patients with cancer, and it was suggested that this substance may be particularly useful for treatment and monitoring, since the assay normally gives "negative" results in patients not harboring tumors.61

**METABOLIC CHANGES AND CANCER**

Various metabolic changes may be associated with cancer, such as the anemias, coagulation disorders, neuropathies, osteoarthropathies, fever and generalized wasting. All of these disorders might conceivably be caused by humoral substances produced by the neoplastic cells or by the endocrine glands as a result of abnormal stimuli triggered by the cancer.

The occurrence of diabetic-type glucose tolerance curves in many patients with cancer has been well documented. Marks and Bishop demonstrated a decreased fractional rate of total glucose disappearance in cancer patients, as well as decreased insulin responsiveness.62 According to Glicksman and Rawson, diabetic-type glucose tolerance curves were present in 35 of 100 patients with breast cancer, compared to 10 percent of patients with benign lesions.63 In our study of 23 patients with metastatic mammary carcinoma, 12 had diabetic-type glucose tolerance curves; in these patients, insulin secretion following a glucose load was delayed and the levels were lower than in non-cancer patients, suggesting decreased pancreatic insulin reserve.64,65 Nine of the 23 patients had paradoxical hypersecretion of growth hormone in response to a glucose load, probably due to abnormal regulation of growth hormone. This abnormality in growth hormone secretion disappeared following hypophysectomy, which indicates that the high growth hormone
found in these patients is pituitary in origin and not ectopic from the tumor.

We recently studied patients with various types of cancer, both before and after hyperalimentation. Abnormal diabetic glucose tolerance, hyperinsulinemia and paradoxical rise in levels of growth hormone were seen in the majority. After hyperalimentation, these abnormal responses to glucose load improved in patients who gained weight and showed general clinical improvement. The effect of cancer on nutrition and of nutrition on cancer patients is a subject of great importance for future research.

References

1. Omenn, G.S.: Ectopic polypeptide hormone production by tumors. Ann. Int. Med. 72:136-138, 1970.
2. Omenn, G.S., and Wilkins, E.W., Jr.: Hormone syndromes associated with bronchogenic carcinoma. Clues to histologic type. J. Thorac. Cardiovasc. Surg. 59:877-881, 1970.
3. Gei1thorn, A.: Recent studies on pathophysiologic mechanisms in human neoplastic disease. J. Chronic Dis. 8:158-170, 1958.
4. Azzopardi, J.G., and Williams, E.D.: Pathology of "nonendocrine" tumors associated with Cushiing's syndrome. Cancer 22:274-286, 1968.
5. Pears, A.E.G.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic, and pathologic implications of the concept. J. Histochem. Cytochem. 17:303-313, 1969.
6. Andrews, A.: A study of the developmental relationship between enterochromaffin cells and the neural crest. J. Embryol. Exp. Morph. 11:307-327, 1963.
7. Lambert, A.E.; Orci, L., and Renold, A.E.: Some factors controlling differentiation and/or modulation of rat pancreatic islet cells. Advances Metab. Dis. 1: Suppl. 35-43, 1970.
8. Brown, R.E.; Schweitzhal, M.R., and Still, W.J.S.: Ultrastructural observations on the embryogenesis of islet cells in the rat pancreas in vitro. Proc. Soc. Exp. Biol. Med. 136:441-445, 1971.
9. Kaplan, E.L. et al.: Adrenal medullary calcitonin-like factor: A key to multiple endocrine neoplasia, type 2? Surgery 68:146-149, 1970.
10. Wernim, P.: Endocrine adenomatosis and peptic ulcer in a large kindred. Inherited multiple tumors and mosaic pleiotropism in man. Am. J. Med. 35:205-212, 1963.
11. Bensch, K.G.; Gordon, G.B., and Miller, L.R.: Studies on the bronchial counterpart of the Kulitschitz (argentaffin) cell and innervation of bronchial glands. J. Ultrastr. Res. 12:668-686, 1965.
12. Rosai, J., and Higa, E.: Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of eight cases. Cancer 29:1061-1074, 1972.
13. Steiner, A.L.; Goodman, A.D., and Powers, S.R.: Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, type 2. Medicine 47:371-409, 1968.
14. Pearse, A.E.G., and Polak, J.M.: Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. Gut 12:783-788, 1971.
15. Levine, R.J., and Metz, S.A.: A classification of ectopic hormone-producing tumors. Ann. N.Y. Acad. Sci. 230:533-546, 1974.
16. Weichert, R.F., 3rd: The neural ectodermal origin of the peptide-secreting endocrine glands. A unifying concept for the etiology of multiple endocrine adenomatosis and the inappropriate secretion of peptide hormones by nonendocrine tumors. Am. J. Med. 49:232-241, 1970.
17. Rosen, S.W., and Weintraub, B.D.: Ectopic hormones from tumors. (Comments to the editor). Ann. Int. Med. 83:117-118, 1975.
18. Melvin, K.E. et al.: Cushing's syndrome caused by ACTH- and calcitonin-secreting medullary carcinoma of the thyroid. Metabolism 19:831-838, 1970.
19. Croughs, R.J.M. et al.: ACTH and calcitonin-secreting medullary carcinoma of the thyroid. Clin. Endocrinol. 1:157-171, 1972.
20. O'Neal, L.W. et al.: Secretion of various endocrine substances by ACTH-secreting tumors—gastrin, melanotropin, norepinephrine, serotonin, parathormone, vasopressin, glucagon. Cancer 21:1219-1232, 1968.
21. Brown, W.H.: Case of pluriglandular syndrome: "diabetes of bearded women." Lancet II:1022-1023, 1928.
22. Christy, N.P.: Adrenocorticotrophic activity in the plasma of patients with Cushing's syndrome associated with pulmonary neoplasms. Lancet 1:85-86, 1961.
23. Holub, D.A., and Katz, F.H.: A possible etiologic link between Cushing's syndrome and visceral malignancy. Clin. Res. 9:194, 1961.
24. Liddle, G.W. et al.: The ectopic ACTH syndrome. Cancer Res. 25:1057-1061, 1965.
25. Liddle, G.W. et al.: Clinical and laboratory studies of ectopic humoral syndromes. Recent Progr. Hormone Res. 25:283-314, 1969.
26. Yalow, R.S., and Berson, S.A.: Characteristics of "big ACTH" in human plasma and pituitary extracts. J. Clin. Endocrinol. Metab. 36:415-423,
