Case Presentation

A 69-year-old man was admitted to the Massachusetts General Hospital in December 1983, following referral from another hospital, for evaluation of hypoproteinemia, peripheral edema, and weakness. He was known to have type II diabetes when he underwent a gastroenterostomy and, later, a vagotomy, two-thirds gastrectomy, and gastroenterostomy in 1972 for peptic ulcer disease. His blood glucose levels had been well controlled with an oral hypoglycemic agent until September 1983, when he was admitted to another hospital for investigation and treatment of uncontrolled hyperglycemia (blood glucose level, 543 mg/dl), severe muscle wasting, an increased alkaline phosphatase level (336 IU/L), a normal plasma aldosterone level, a cortisol level of 28 μg/dl, a low thyroid-binding globulin level, but normal free thyroxine and thyroid-stimulating hormone levels. Results of a small bowel biopsy were normal, and computed tomographic abdominal and liver/spleen scans were reportedly normal.

Over the course of a long hospitalization in September and again in November 1983, he was noted to have new-onset hypertension (blood pressure, 170–200/95–105 mm Hg), hypokalemia (K⁺, 2–3 mEq/L), severe muscle wasting, an increased alkaline phosphatase level (336 IU/L), a normal plasma aldosterone level, a cortisol level of 28 μg/dl, a low thyroid-binding globulin level, but normal free thyroxine and thyroid-stimulating hormone levels. Results of a small bowel biopsy were normal, and computed tomographic abdominal and liver/spleen scans were reportedly normal.

The patient was unable to give a detailed history, but on questioning thought his skin had become darker recently and was particularly concerned about muscle weakness, mild insomnia, fatigue, and a 40-pound weight loss over the preceding 6 months. There was no family history to suggest multiple endocrine neoplasias. An aunt and his mother had had diabetes mellitus, and a daughter had undergone a thyroid operation. The patient did not drink alcohol and had not smoked for the past 20 years. There was no history of cough, hemoptysis, melena, abdominal pain, hematuria, visual disturbances, headaches, or chest pain. Medications on admission were KC1, 40 mEq, and NPH insulin, 16 units administered subcutaneously, every day.

Physical examination of the patient revealed mild cachexia, severe proximal myopathy, profuse petechiae and ecchymoses, deeply pigmented areolae and pigment deposition in his abdominal scars, mild proptosis, normal-sized thyroid gland and testes, basilar rales, mild pitting edema of the lower extremities, and a distal lower extremity sensory neuropathy. The visual fields were full to confrontation, and no abdominal masses or organ enlargement was detected. The pulse was 100/min and irregularly irregular. The blood pressure was 170/100 mm Hg, and auscultation of the precordium revealed only physiological heart sounds. There was no gynecomastia or truncal obesity.

Initial investigations disclosed the following values: hematocrit, 35%; hemoglobin, 11.8 g/dl; white blood cell count, 4.7 × 10³/mm³; mean corpuscular volume, 81 μm³; platelet count, 128,000/mm³; prothrombin time, 10.6/10.8 sec; partial thromboplastin time, 27
sec; erythrocyte sedimentation rate, 15 mm/hr; Na+, 143 mEq/L; K+, 2.0 mEq/L; Cl-, 97 mEq/L; CO2, 35 mEq/L; blood urea nitrogen, 17 mg/dl; blood glucose, 71 mg/dl (fasting); Ca++, 7.2 mg/dl; PO4, 3.5 mg/dl; Mg++, 3.5 mEq/L; creatinine, 0.7 mg/dl; total proteins, 5.1 g/dl (albumin, 2.6 g/dl; globulin, 2.5 g/dl); aldolase, 8.8 U/L; 17-ketosteroids, 58 mg/24 hr; 17-
hydroxysteroids, 55 mg/24 hr (urine volume, 700 ml/24 hr); cortisol, 90 at 0735 and 81.2 pig/dl at 1445; T3, 1.1 μg/dl; T3 resin uptake, 40%; thyroid-stimulating hormone, <0.5 μU/ml; urinary Na+, 6 mEq/L; urinary K+, 105 mEq/L. A gastrointestinal series was normal. Computerized body tomography of the mediastinum revealed multiple low-density lesions within the liver and bilateral adrenal masses; low lung volumes and bibasilar subsegmental atelectasis without evidence for a lung lesion; a small anterior pericardial effusion, a normal mediastinum, and calcification of the tail of the pancreas.

After admission the patient’s blood pressure fluctuated widely, ranging from 148/90 to 200/120 mm Hg. The plasma cortisol level remained above 50 μg/dl despite the administration of 1, 2, and then 8 mg of dexamethasone. The urinary free cortisol level was 3162 and 1407 μg/24 hr on the seventh and eighth days after admission, and adrenocorticotropic hormone (ACTH) levels were 500, 375, and 325 pg/ml on the third, fifth, and sixth days, respectively, after admission. A regimen of metyrapone, 500 mg t.i.d., and dexamethasone was started, using metyrapone, 500 mg t.i.d., combined with replacement doses of dexamethasone. The metyrapone produced marked inhibition of the 11β-hydroxylases, a decreased plasma cortisol level (from 51 to 18 μg/dl) and a concurrent elevation of 11-deoxycorticisol levels. As would have been predicted, the patient continued to deteriorate, became febrile, and most likely died of gram-negative septic shock.

Despite therapy, the patient’s condition continued to deteriorate, and he became confused and disoriented approximately 12 to 14 days after admission. However, his blood pressure remained moderately high, ranging from 130/90 to 150/110 mm Hg. On the seventeenth day after admission, the patient became hypotensive (blood pressure, 80/50 mm Hg), febrile (38.4 °C), and obtundated. A urine specimen showed abundant bacteria and many white blood cells. Antibiotic therapy was begun, but the patient remained hypotensive, became apneic, and died that day. Permission for an autopsy was denied.

Case Discussion

The clinical presentation of this 69-year-old man is the most frequent for ectopic Cushing’s syndrome. He had a 6-month history of muscle weakness, fatigue, weight loss, and perhaps, increased pigmentation of the skin. Three months before his death, his diabetes mellitus type II, which had been reasonably well controlled with orally administered hypoglycemics, became markedly worse and he was started on a regimen of insulin. During his September and November 1983 hospitalizations new onset of moderate hypertension, rather severe hypokalemia, hypoproteinemia, and elevated alkaline phosphatase were noted. Although the diagnostic impression during these two hospitalizations is unknown, the attending physicians were motivated to obtain what seems to be random plasma aldosterone and cortisol measurements. Aldosterone level was reported to be normal, and cortisol level was found to be 28 μg/dl, which is elevated; however, random samples are seldom diagnostic.

The patient was transferred to Massachusetts General Hospital (probably because the suspected diagnosis was ectopic Cushing’s syndrome caused by an unlocated tumor) where the patient received a thorough examination. He was found to have marked increases in the urinary excretion of 17-ketosteroids and 17-hydroxysteroids and extremely high morning cortisol levels with no significant decrease in the afternoon. A low and high dose dexamethasone suppression test revealed no significant changes in plasma cortisol level. His plasma ACTH level was clearly elevated on several occasions. Diagnostic imaging revealed multiple low density lesions within the liver and bilateral adrenal masses and calcifications in the tail of the pancreas.

The diagnosis of a neoplasm with ectopic production of ACTH was evident, and therapy of the hypercortisolism was started, using metyrapone, 500 mg t.i.d., combined with replacement doses of dexamethasone. The metyrapone produced marked inhibition of the 11β-hydroxylases, a decreased plasma cortisol level (from 51 to 18 μg/dl) and a concurrent elevation of 11-deoxycortisol levels. As would have been predicted, the patient continued to deteriorate, become febrile, and most likely died of gram-negative septic shock.

The clinical manifestations of ectopic ACTH production depend on the biological nature of the tumor. Slowly growing malignant or benign tumors tend to give clinical manifestations of Cushing’s syndrome, while rapidly growing or aggressive tumors present with manifestations similar to those shown by this patient: marked weakness, hypertension, hypokalemic alkalosis, and rapid deterioration. The type of tumor this patient had is not immediately apparent. Although no evidence for a tumor was found during his first admission, metastatic lesions in the liver, as well as bilateral adrenal masses, were found on the final evaluation. The adrenal glands in ectopic ACTH syndrome usually weigh 14 to 16 g, although they may weigh more than 20 g. Normal adrenal gland weights in instances of sudden death without prior illness are between 2.8 and 5.5 g. If death is preceded by prolonged illness, adrenal gland weights vary between 2.7 and 9.4 g.2

The source of the primary tumor is unclear from the history. The following list summarizes the types and incidence of tumors that can produce ACTH1,3:

Carcinoma of the lung (50%)
1. Oat cell (38%)
2. Large cell (4%)
3. Adenocarcinoma (6%)
4. Squamous (2%)
Carcinoid (16%)
1. Bronchus (8%)
2. Thymus (2%)
3. Gastrointestinal (6%)
Thymus (10%)
Pancreas (islet cell) (6%)
Medullary carcinoma of thyroid (6%)
Pheochromocytoma (2%)
Other (10%)

The tumors can be divided into two general groups: amine precursor uptake and decarboxylation (APUD) tumors, which constitute over 80% of the list, and other miscellaneous tumors of non-APUD origin, which include a wide variety of cancers such as squamous cell carcinoma, adenocarcinomas, and hepatomas. In children, ectopic ACTH production is less frequent and originates from tumors common to this age group including paragangliomas, neuroblastomas, ganglioneuroblastomas, pheochromocytomas, and thymic and islet cell tumors.4

Extraadrenal or pituitary tumors can produce hypercortisolism by secreting excessive quantities of ACTH or corticotropin-releasing hormone (or both).5,6 which in turn stimulates the pituitary secretion of ACTH, which then acts on the adrenal gland. A case of medullary carcinoma of the thyroid has been described that produced a bombesin-like peptide that was assumed to be responsible for an ectopic ACTH-like syndrome.7 The production of ACTH by tumors is more common than is the presence of hypercortisolism.8 Immuno-reactive ACTH is found in most carcinomas of the lung; however, few of these have manifestations of Cushing’s syndrome.9 Most of these tumors have high molecular weight ACTH of little biological activity.

The ACTH molecule is known to be a cleavage product, along with β-lipotropin, from a common precursor molecule, pro-opiomelanocortin.10 In the pituitary, pro-opiomelanocortin is cleaved into a 16K fragment, ACTH, β-lipotropin, and other fragments of unknown function. The β-lipotropin is split further into γ-lipotropin (1–58) and β-endorphin (61–91), and these latter two fragments can also be found in tumor tissue.11 A portion of the 16K fragment, γ-melanocyte-stimulating hormone, may play a physiological role in adrenal growth12 and potentiation of the adrenal action of ACTH.13,14 In addition, ACTH can be converted to α-melanocyte-stimulating hormone and corticotropin-like intermediate-lobe peptide in the intermediate lobe of the pituitary,15 and these substances have been demonstrated in some tumors.16 The secretion of ACTH, β-lipotropin, and the N-terminal proopiocortin (pro-γ-melanocyte-stimulating hormone) is equimolecular.16 The plasma concentration of high molecular weight ACTH immunoreactivity produced by most ectopic ACTH tumors tends to be greater than that of the smaller biologically active ACTH as compared to pituitary Cushing’s disease; however, this is not always the case.9,17

The diagnosis of hypercortisolism secondary to ectopic production of ACTH is usually straightforward when a tumor is evident but can be more difficult in benign or slowly growing malignant tumors. The diagnosis is established by a finding of an elevated secretory rate of cortisol, as reflected by elevated excretion of 17-hydroxysteroids and 17-ketosteroids, urinary free cortisol, and plasma cortisol. In addition, plasma ACTH levels are usually greater than those seen in patients with Cushing’s disease18 and cortisol is not suppressed by high doses of dexamethasone. The response to corticotropin-releasing hormone stimulation is also blunted in ectopic ACTH production.19 Rarely, patients with Cushing’s disease also have elevated plasma ACTH concentrations and the concomitant elevated levels of urinary 17-hydroxysteroids and serum cortisol that are not suppressed by high doses of dexamethasone.20 In these patients, the absence of a tumor after a thorough search or the removal of a tumor without the relief of the syndrome21 raises suspicion. The diagnosis can be established by selective catheterization and sampling of the petrosal vein effluent and measurement of ACTH.21

Cushing’s Syndrome and Hypertension

Moderate to severe hypertension was recognized by Harvey Cushing22 as early as 1912 and reported in 1932. In 1924, Oppenheimer and Fishberg22 reported a few cases of adrenal tumors and hypertension that, in retrospect, must have been Cushing’s syndrome. The incidence of hypertension in Cushing’s syndrome is very high and depends in part on the cause, as can be seen in the following list:16,23

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s disease</td>
<td>88</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>83</td>
</tr>
<tr>
<td>Adrenal adenomas</td>
<td>100</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>55</td>
</tr>
<tr>
<td>Ectopic ACTH</td>
<td>17</td>
</tr>
<tr>
<td>Iatrogenic Steroids</td>
<td>27</td>
</tr>
</tbody>
</table>

Although the blood pressure tends to be greater in patients with adrenal carcinomas,24 elevated blood pressure is seldom the cause for the initial consultation.25 The death rate attributable to cardiovascular complications of Cushing’s syndrome before effective antihypertensive drugs were available was 40%.26 The mechanism by which hypertension is produced in Cushing’s syndrome is not well understood but clearly involves the hypersecretion of glucocorticoids, mineralocorticoids, and perhaps, “hypertensinogenic” steroids.27 Over the years, the effects of mineralocorticoids and glucocorticoids on blood pressure have been studied extensively, primarily in experimental animals in which there are species-dependent differences in the effect of steroids, particularly glucocorticoid, on blood pressure regulation. For example, synthetic glucocorticoids elevate blood pressure in the rat28 but have no effect in sheep29 or dog.30 Synthetic mineralocorticoids also seem to have minimal or no effect on blood pressure elevation in humans.31,32 nor is the incidence of hypertension in patients receiving ACTH as high as that in patients with endogenous Cushing’s syndrome.33 Therapeutic use of ACTH is usually intermittent, however, which might explain this difference in the incidence of hypertension.
Mechanisms of Hypertension in Cushing's Syndrome

The following list summarizes the various mechanisms postulated for the blood pressure elevation seen in Cushing's syndrome:

- Mineralocorticoid overproduction
- Mineralocorticoid effects of cortisol overproduction
- Overactivity of the renin-angiotensin system
- Increased vascular reactivity induced by glucocorticoids
- Presence of hypertensinogenic steroids

Mineralocorticoid Overproduction

Plasma potassium concentrations are normal in over 90% of patients with Cushing's disease or Cushing's syndrome due to an adrenal adenoma but tend to be low in patients with adrenal carcinomas and in ectopic ACTH production. Although urinary or plasma aldosterone levels have been found to be normal in most patients with Cushing's syndrome, they can be low or high. Levels of the ACTH-dependent mineralocorticoid deoxycorticosterone are increased in a significant number of patients with Cushing's syndrome. The excretion of urinary "free" deoxycorticosterone is elevated in a significant number of patients with Cushing's disease and tends to be highest in patients with adrenal carcinomas. The excretion of free deoxycorticosterone correlates with and tends to parallel that of free cortisol. The degree of abnormal production of deoxycorticosterone and corticosterone correlates with the hypokalemic alkalosis and is greater in patients with adrenal carcinomas and in ectopic ACTH-producing tumors. The mechanism by which mineralocorticoids induce hypertension is incompletely understood, but it involves increases in total body sodium levels and peripheral resistance.

Mineralocorticoid Effects of Cortisol Overproduction

Several studies have shown a good correlation between hypokalemic alkalosis and cortisol production. Although cortisol is predominantly a glucocorticoid, it has marked mineralocorticoid activity at higher concentrations. Hypokalemic alkalosis occurs in a minority of patients with Cushing's syndrome and at a lower frequency than that of hypertension. In a few patients with Cushing's syndrome, especially those with adrenal adenomas, cortisol is the only steroid that is markedly elevated; this supports the argument that cortisol alone is the predominant cause of the hypertension that occurs with Cushing's syndrome. Cortisol administration to rats elevates the blood pressure by a mechanism that is not dependent on sodium intake. Corticosterone, which is somewhat similar to cortisol in its glucocorticoid and mineralocorticoid activity, produces increased plasma volume, extracellular fluid volume, and blood pressure.

In contrast to the effects produced by excess mineralocorticoid administration, short-term administration of corticosterone produces a negative sodium and water balance due to the shift of sodium from the intracellular to the extracellular space. This effect is also seen in humans after administration of ACTH or cortisone.

Overactivity of the Renin-Angiotensin System

The renin-angiotensin system has been studied extensively in patients with Cushing's syndrome; these findings are summarized in Table 1. In Cushing's syndrome, plasma renin activity tends to be normal (and occasionally elevated) or low and responds normally to stimulation with furosemide. Synthetic glucocorticoid administration to rats elevates their blood pressure and plasma renin activity. Short-term administration of ACTH elevates plasma renin activity in humans but decreases plasma renin activity in sheep.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plasma renin Activity</th>
<th>Plasma renin Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's syndrome</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Excess synthetic glucocorticoids</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Excess ACTH</td>
<td>Acute</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone.

The increase in plasma renin substrate levels is more uniform in clinical and experimental ACTH or glucocorticoid excess and is due to the stimulation of synthesis in the liver. Plasma renin substrate level is about twice normal in Cushing's syndrome or synthetic glucocorticoid excess. For kinetic reasons this elevation in substrate increases the velocity of the renin reaction by 20 to 30%.

Administration of saralasin, an angiotensin II antagonist, was reported to cause marked decreases in blood pressure in some patients with Cushing's syndrome and in experimental glucocorticoid hypertension. However, several subsequent reports have shown that saralasin either does not reduce the blood pressure or has a mild pressor effect in patients with Cushing's syndrome and normal or low plasma renin activity. Converting enzyme inhibition with captopril also has been shown to reduce the blood pressure in experimental glucocorticoid hypertension. However, captopril was not effective in reducing the blood pressure in a group of patients with Cushing's syndrome. Thus, the renin-angiotensin system, which is usually normal in patients with Cushing's syndrome, may play a role in the hypertension of a minority of patients, particularly the few with high plasma renin activity.

Increased Vascular Reactivity Induced by Glucocorticoids

The lack of adrenal steroids diminishes cardiovascular reactivity to pressor substances. Patients with Cushing's syndrome, both spontaneous and iatrogenic, have an increased digital vascular responsiveness to catecholamines. Glucocorticoids can induce this increased responsiveness in vitro and they also have an important role in the control of phenylethanolamine N-methyltransferase activity in the adrenal me-
dulla. This enzyme catalyzes the conversion of norepinephrine to epinephrine. The concentration of cortisol in the normal adrenal medulla is very high; however, children with ACTH deficiency have low levels of plasma epinephrine. Thus, it is possible that increased epinephrine synthesis occurs in Cushing's syndrome and plays a major role in hypertension.

While enhanced vascular responsiveness is observed in regional vascular beds and in vitro, systemic pressor alterations have not been uniformly demonstrated. In addition, ACTH-induced hypertension in sheep does not change or reduce plasma levels of epinephrine and norepinephrine.

Presence of Hypertensinogenic Steroids

The concept of hypertensinogenic steroids was proposed by Scoggins et al. to explain ACTH-induced hypertension in sheep. Chronic administration of ACTH produces an adrenal-dependent rise in blood pressure in sheep, rats, and humans. In sheep, the rise in blood pressure occurs within 24 hours and is associated with an increase in cardiac output and heart rate. Blood pressure remains elevated throughout the administration of ACTH. The induced hypertension has features of both glucocorticoid and mineralocorticoid excess, but administration of either class of steroid alone or together does not reproduce the temporal pattern or amplitude of the rise in blood pressure.

In sheep, infusion of a mixture of cortisol (5 mg/hr), corticosterone (0.5 ng/hr), 11-deoxycorticosterone (1 mg/hr), deoxycorticosterone (25 mg/hr), and aldosterone (3 mg/hr) produced blood concentrations similar to those obtained after ACTH administration but failed to increase the blood pressure. Subsequent studies demonstrated the adrenal production of 17α-hydroxyprogestosterone and 17α, 20α-dihydroxyprogestosterone. Although 17α-hydroxyprogestosterone and 17α, 20α-dihydroxyprogestosterone possess no measurable hypertensive or corticoid effects by themselves, their administration in combination with the steroid mixture described above reproduced the metabolic and blood pressure effects induced by ACTH. These steroids have been labeled "hypertensinogenic" steroids. In humans, ACTH administration elevates blood pressure and causes definite increases in 17α-hydroxyprogestosterone and 17α, 20α-dihydroxyprogestosterone. The hypertension is increased by salt loading during ACTH infusions.

The structural requirements for hypertensinogenicity have been studied extensively in sheep. Cortisol, dexamethasone, or aldosterone infusions produce minimal elevations of blood pressure, while infusion of the synthetic glucocorticoid (0.2 mg/day) 9α-fluorocortisol mimics the temporal pattern and amplitude of the ACTH-induced blood pressure elevation with minimal, if any, metabolic effects. These studies indicate that the actions of glucocorticoids or mineralocorticoids by themselves cannot explain ACTH-induced hypertension in sheep. Conversely, ACTH does not raise blood pressure in the dog, but it does potentiate the chronic hypertensinogenic effects of angiotensin II or norepinephrine infusions. Neither cortisol nor aldosterone infusions can reproduce this potentiation. The relevance of these studies in the pathogenesis of hypertension in Cushing's syndrome is unknown because of the marked interspecies variations. Similar studies need to be conducted in humans.

Although these postulated mechanisms offer intriguing explanations, the exact cause of hypertension in Cushing's syndrome is unclear. The pathogenesis may vary depending on the various etiologies, the degree of the quantitative and qualitative abnormality of steroid secretion that occurs in tumors with altered steroidogenesis, or the altered secretory activity of ACTH and other components of the pro-opiomelanocortin molecule that can occur in pituitary or ectopic ACTH-producing tumors. Clarification of the pathogenesis of hypertension in Cushing's syndrome may depend on the study of the hypertension in cases segregated according to their etiology.

Therapy

Therapy of Cushing's syndrome in ectopic ACTH-producing tumors depends on the nature of the tumors. Benign or surgically approachable tumors are treated by resection, which results in improvement or cure of the hypertension. Unfortunately, most tumors causing ectopic ACTH production are not resectable.

The presence of nonsuppressible hypercortisolism is associated with a very poor prognosis, although therapy of the hypercortisolism may improve some of the clinical manifestations and the quality of life. Several agents have been used to decrease adrenal production of steroids including mitotane, which destroys the zona fasciculata and reticularis. The disadvantage in using mitotane is that the drug takes 3 to 6 months to work and is not helpful in most cases of ectopic ACTH syndrome, where a faster decrease in adrenal production is needed.

Aminogluthimide is an inhibitor of the cytochrome P-450 side chain cleavage enzyme as well as other enzymes. It affects zona glomerulosa function to a greater extent than that of zona fasciculata but is effective in about 42% of the cases of Cushing's syndrome. Metyrapone is an inhibitor of the cytochrome P-450 11β-hydroxylase and side chain cleavage enzymes. The effect on the latter enzyme is of lesser importance. Aminogluthimide and metyrapone are used in combination with a glucocorticoid to prevent iatrogenic hypoadrenalism.

Another drug that has been used to treat Cushing's syndrome is triostane, an inhibitor of 3β-ol-dehydrogenase. The initial results were enthusiastic, but more recently triostane has been found to be relatively ineffective in Cushing's syndrome. Ketoconazole, an imidazole derivative with antifungal properties, has been shown to block adrenocorticosteroid synthesis and blunt ACTH-induced cortisol release. It has been used in a small group of patients with ectopic ACTH syndrome and found to be very helpful. If the efficacy of ketoconazole is confirmed in a larger number of patients, it will become the treatment of choice for medical (palliative) therapy of Cushing's syndrome because of its easy availability and profile of side effects.
References

13. Pederson RC, Brownie AC. Adrenocortical response to corticotropin is potentiated by part of the amino-terminal region of pro-corticotropin/endorphin. Proc Natl Acad Sci USA 1980;77:2239-2243
29. Lohmeier TE, Kastner PR. Chronic effects of ACTH and cortisol excess on arterial pressure in normotensive and hypertensive dogs. Hypertension 1982;4:652-661
47. Rudman D, Moffitt SD, Fernhoff PM, Blackston RD, Faraj BA. Epinephrine deficiency in hypocorticotropin hypopituitary
264 HYPERTENSION VOL 8, No 3, MARCH 1986


(Hypertension 8: 258–264, 1986)
Cushing's syndrome and hypertension.
C E Gomez-Sanchez

Hypertension. 1986;8:258-264
doi: 10.1161/01.HYP.8.3.258

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/8/3/258.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/