

## **ADRENAL CORTICAL HORMONES**

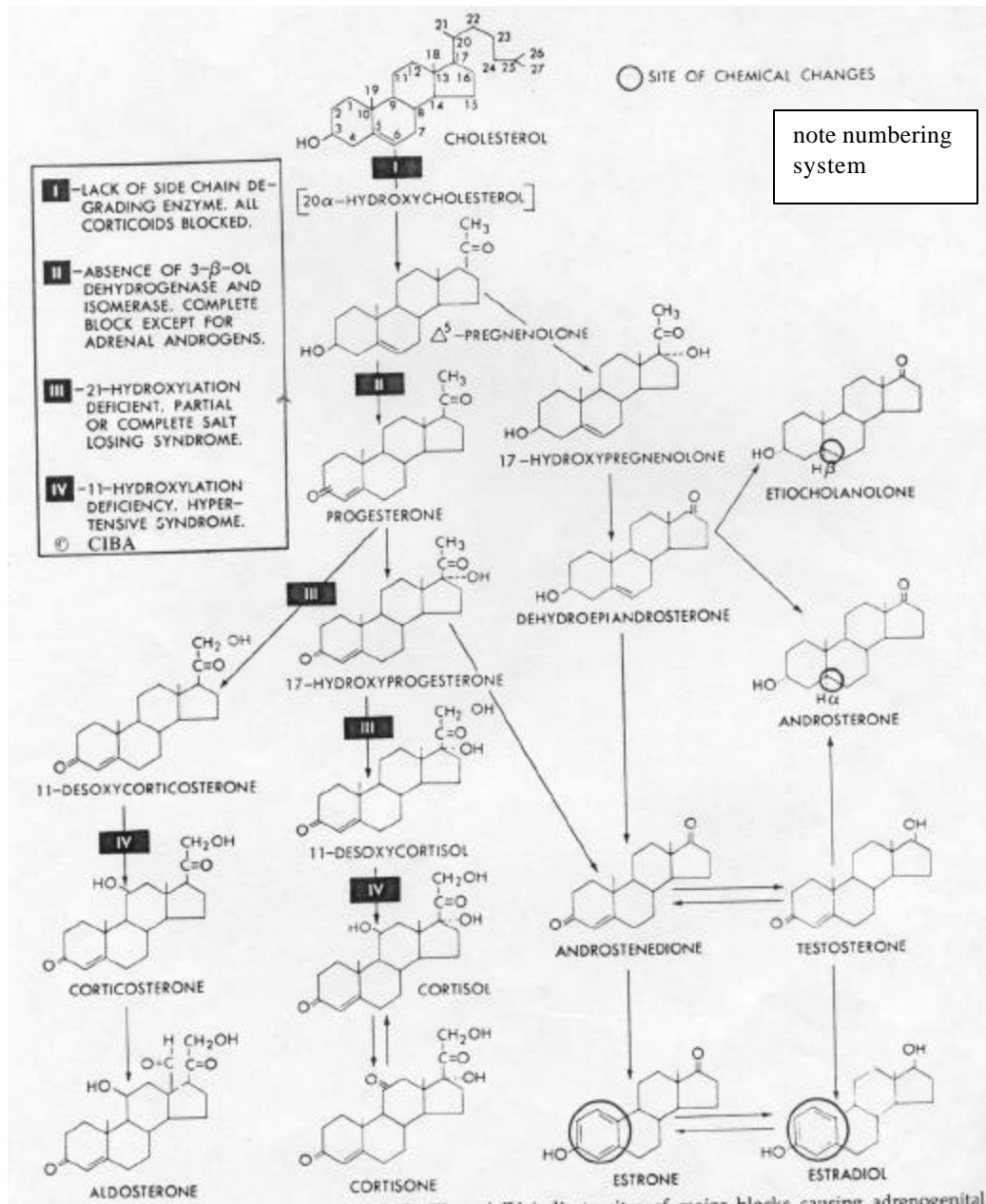
### **OBJECTIVES**

1. Draw the structures of common steroid hormones, identify the carbon atoms by number.
2. Give examples of glucocorticoid, mineralocorticoid, sex hormone, steroid hormone.
3. Describe the feedback mechanism between the adrenal cortex and anterior pituitary gland and the diurnal rhythm of plasma levels of cortisol and ACTH.
4. Describe the regulatory relationship between aldosterone, sodium balance and blood volume.
5. List the primary effects of cortisol, aldosterone and adrenal androgens.
6. Describe the patterns of lab results expected in Cushing's syndrome (1<sup>o</sup>, 2<sup>o</sup>, and ectopic), Addison's disease, and adrenogenital syndrome.

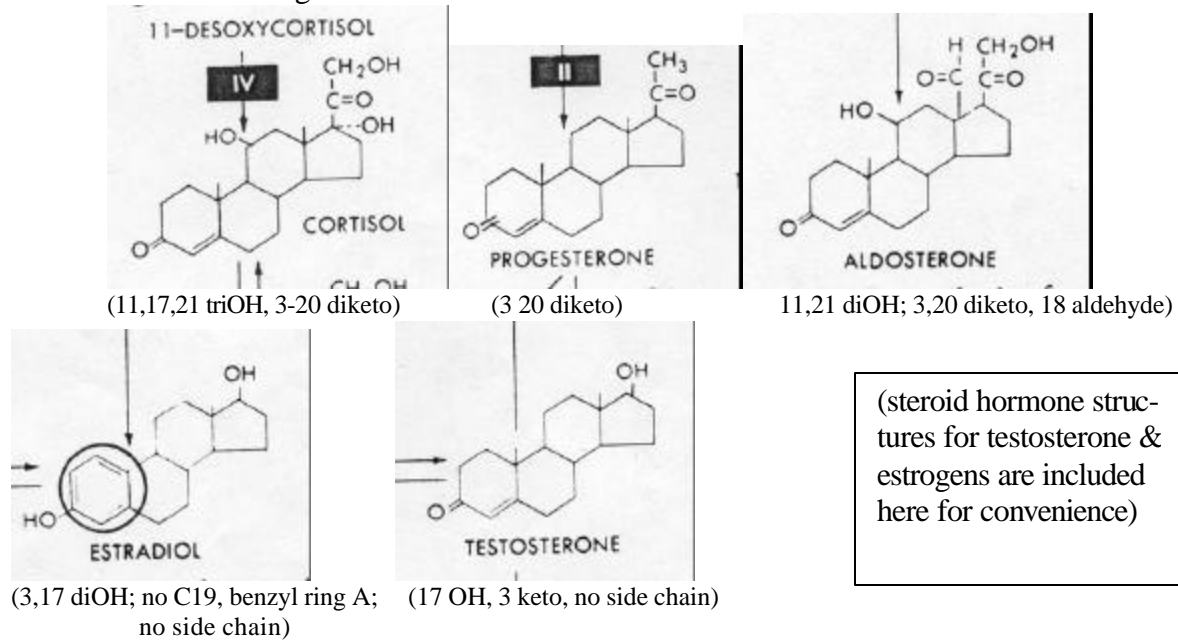
# I. Structure of Steroid Hormones

All are derived from cholesterol by a series of enzymatic reactions

- desmolase enzymes cut off side chains
- hydroxylase enzymes add hydroxyl groups
- dehydrogenase enzymes turn hydroxyls into keto groups
- isomerases move double bond from C4=5 to C5=6



Need to be able to recognize and draw these 5 steroid hormones:

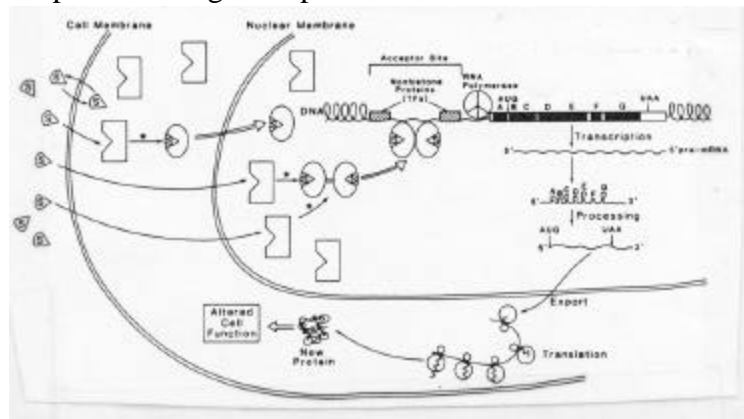


Sites of important substitutions:

C3 C5 C11 C17 C18 C19 C20 C21

## II. Functions of Steroid Hormones

Steroid hormones are fat soluble,  $\therefore$  they dissolve through plasma membrane of target cell  $\rightarrow$  dock with cytoplasmic receptor  $\rightarrow$  alter gene expression



3 separate layers of cells in adrenal cortex synthesize 3 classes of steroid hormones:

- zona glomerulosa is outside layer
  - contains 18-hydroxylase,  $\therefore$  synthesizes aldosterone
- zone fasciculata is middle layer
  - synthesizes mainly cortisol
- zona reticularis is inner layer
  - synthesizes mainly androgens

Cortisol is also called glucocorticoid because it → ↑ gluconeogenesis → ↑ blood glucose

other functions of cortisol:      suppresses immune response  
   stimulates erythropoiesis  
   affects distribution & metabolism of fat and protein  
when in large amounts, cortisol has a little aldosterone activity

cortisol is not required for life

Aldosterone is also called mineralocorticoid because it causes  $\text{Na}^+$  retention

also affects blood volume (and blood pressure), and  $\text{K}^+$  &  $\text{H}^+$  excretion

aldosterone is required for life

Adrenal androgens (mostly androstenedione)

have partial androgenic effect: strong bones and muscles

in excess → male phenotype in woman (deep voice, hair distribution, genital changes)  
excess in utero → male phenotype regardless of chromosomes  
deficiency in utero → female phenotype regardless of chromosomes

[testosterone from testis → male secondary sexual characteristics]

[There are no adrenal estrogens; estradiol from ovary → female secondary sexual characteristics;  
adipose tissue can convert adrenal androgens to estrogens]

### III. Regulation

Adrenal androgens have no independent regulatory system

Aldosterone regulation (see notes from Electrolyte Balance and Renal Function)

↓ blood flow to kidney → renin excretion → converts plasma angiotensinogen to angiotensin I → pulmonary ACE converts it to angiotensin II → stimulates adrenal cortex (zona glomerulosa cells) to secrete aldosterone → enhances  $\text{Na}^+$  reabsorption by DCT) → ↑ blood volume → ↑ blood flow to kidney

Cortisol level has negative feedback regulation by hypothalamus and anterior pituitary hormones

Plasma cortisol is ~10% free, active hormone and ~90% bound to cortisol-binding globulin (CBG)

free cortisol can be filtered by kidney

∴ sometimes measure urinary cortisol to monitor daily cortisol production

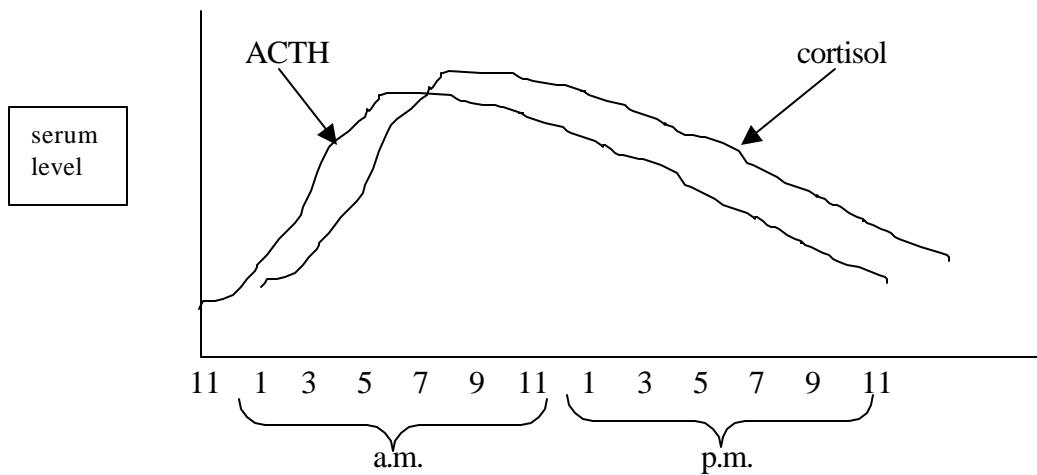
↓ free plasma cortisol stimulates hypothalamus to secrete corticotropin releasing hormone (CRH)

→ CRH stimulates anterior pituitary to secrete corticotropin (= ACTH = adreno-cortico-trophic hormone)

→ ACTH stimulates adrenal cortex (zona fasciculata) to secrete cortisol

→ ↑ plasma cortisol level

ACTH has diurnal rhythm, therefore cortisol level also has diurnal rhythm



morning cortisol level (~8:00 a.m.) should be > 3x the evening level (~11:00 p.m.)

if diurnal pattern is not present (i.e., level is approximately constant) then suspect hyperadrenal corticism (Cushing's syndrome)

peak and valley are correlated with normal periods of activity

ex: 3<sup>rd</sup> shift worker who sleeps during the day will be shifted to maximum value ~ 12:00 midnight, and minimum value ~ 2:00 p.m.

#### IV. Abnormalities in Adrenal Cortical Hormones

Hyper- and hypoaldosteronism: see notes on Electrolyte Balance and Renal Disease

Hypercortisolism → Cushing's syndrome

symptoms: fat face ("moon facies")  
 enlarged fat pad between shoulder blades ("buffalo hump")  
 fat body and skinny arms & legs ("centripetal fat distribution")  
 ↑ serum glucose level ("steroid diabetes")

1° disease of zona fasciculata cells ex: adenoma → excess cortisol without regard for feedback hormone concentrations; 1° hypercortisol is only ~ 10% of cases

↑ FBS  
 ↑ plasma cortisol at both 8 a.m. and 11 p.m.  
 no diurnal variation 11 p.m. value is > 1/3 of 8 a.m. value; and sometimes the  
 11 p.m. ≅ 8 a.m. value  
 ↓↓ ACTH at 8 a.m.

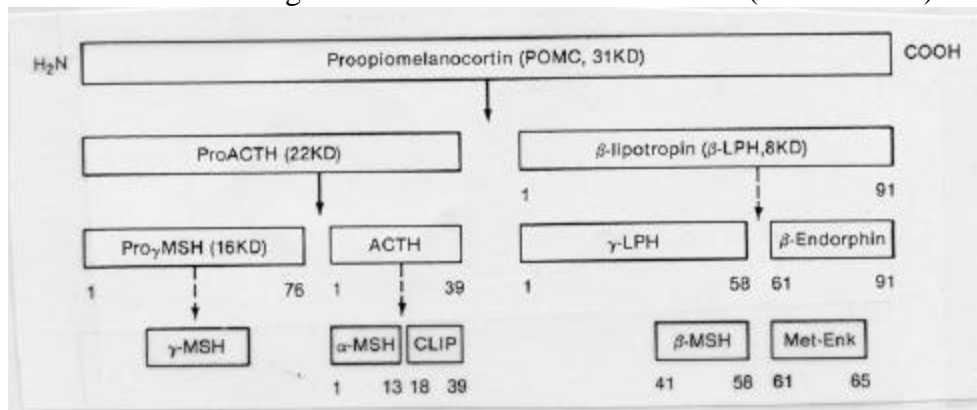
2° hypercortisol is almost always 1° hyper- ACTH ex: adenoma → excess ACTH  
 without regard for feedback hormone concentrations

↑ FBS  
 ↑ plasma cortisol at both 8 a.m. and 11 p.m.  
 no diurnal variation (as above)  
 ↑↑ ACTH at 8 a.m.

When ACTH is synthesized, other hormones are synthesized as by-products including MSH = melanocyte stimulating hormone

∴ people with 2° hypercortisolism have an all-over tan  
 2° hypercortisol due to 1° hyper-pituitarism = Cushing's disease

Cushing's disease is the most common cause (~ 2/3 of cases) of hypercortisol





## WEAKNESS, WEIGHT LOSS, AND HYPOTENSION

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A 40-year-old single woman complained of increasing lassitude and fatigue over the past six months. For the past three months she had experienced recurrent upper respiratory tract infections and a poor appetite accompanied by abdominal cramps, diarrhea, and a weight loss of 25 lb (11 kg). The patient had given up aerobic exercise class because of joint pains, increasing muscle weakness, and dizzy spells following even mild exercise. She admitted to decline of libido and sexual performance but attributed the decline to her chronic illness. She denied recreational use of drugs and taking any medications. She noted amenorrhea for the past three months. Her history was negative for diabetes, tuberculosis, and malignancy.

Physical examination disclosed a well-developed woman, 64 inches (1.6 m) tall, weighing 102 lb (46 kg), and in no acute distress. Her supine blood pressure was 120/65 mm Hg and her heart rate was 86 BPM. After one minute of quiet standing, her blood pressure fell to 90/58 mm Hg, the heart rate increased to 120 BPM, and she complained of dizziness. Her skin had a soft texture; no abnormal pigmentations were noted, but patches of vitiligo were observed on the right leg. Neck examination revealed a diffusely enlarged thyroid without discrete masses; there were no cervical adenopathies. The heart displayed no abnormalities, and lungs were clear to auscultation and percussion. The abdomen was flat and diffusely tender with no rebound, no organomegaly, and no masses; hyperactive bowel sounds were heard. Extremities showed no edema; peripheral pulses were weak but bilaterally synchronous. External genitalia and distribution of pubic hair were those of a normal adult female. No central nervous system (CNS) abnormalities were observed.

Initial laboratory findings were as follows:

Analyte	Value, conventional units	Reference range, conventional units	Value, SI units	Reference range, SI units
Hemoglobin (B)	9.4 g/dL	11.7-15.5	5.83 mmol/L	7.26-9.62
Leukocyte count (B)	$7.6 \times 10^3/\mu\text{L}$	4.8-10.8	$7.6 \times 10^9/\text{L}$	4.8-10.8
Sodium (S)	126 mmol/L	136-145	Same	
Potassium (S)	5.8 mmol/L	3.5-5.1	Same	
Chloride (S)	98 mmol/L	98-107	Same	
CO <sub>2</sub> , total (S)	20 mmol/L	23-29	Same	
Creatinine (S)	1.8 mg/dL	0.7-1.2	159 $\mu\text{mol/L}$	62-106
Calcium (S)	11.3 mg/dL	8.4-10.2	2.83 mmol/L	2.10-2.54
Phosphorus (S)	2.6 mg/dL	2.7-4.5	0.84 mmol/L	0.87-1.45
Urea nitrogen (S)	52 mg/dL	7-18	18.6 mmol urea/L	2.5-6.4
Urea nitrogen/creatinine ratio	29:1	12:1-20:1	117:1 (urea:creatinine mole ratio)	48.5:1-80.8:1
Urinalysis (U)	Within normal limits			

Chest X-ray examination showed a normal cardiac shadow. The electrocardiogram (ECG) was essentially normal except for peaked T waves.

Since the patient's presentation was suggestive of adrenal insufficiency, possibly Addison's disease, she was hospitalized, and hydration with isotonic saline was started. Blood specimens for ACTH, cortisol, aldosterone, FSH, and TSH were obtained. Results were as follows:

Analyte	Value, conventional units	Reference range, conventional units	Value, SI units	Reference range, SI units
ACTH (P)	100 pg/mL	10-50	22 pmol/L	2-11
Aldosterone (P)	7 ng/dL	7-24	194 pmol/L	194-666
Cortisol (S)	10 µg/dL	12-26	276 nmol/L	331-717
FSH (S)	40 mU/mL	≤18	40 U/L	≤18
TSH (S)	9.8 µU/mL	0.4-5.5	9.8 mU/L	0.4-5.5

Dexamethasone and fludrocortisone were initiated to forestall adrenal collapse during testing. On each of two successive days after baseline urine collections, 40 U of ACTH in 500 mL dextrose/saline were administered intravenously over an 8-h period. The results of the ACTH challenge test were

	17-OHCS, mg/d (µmol/d)	17-KS, mg/d (µmol/d)	Aldosterone, µg/d (nmol/d)
Day 1, baseline	2.2 (6.1)	3.8 (13.2)	2.3 (6.4)
Day 2, baseline	2.1 (5.8)	4.0 (13.9)	2.4 (6.7)
Day 3, ACTH	2.0 (5.5)	5.0 (17.3)	2.6 (7.2)
Day 4, ACTH	1.9 (5.2)	4.0 (13.9)	2.5 (6.9)
Day 5, post-ACTH	0.8 (2.2)	3.6 (12.5)	1.8 (5.0)

The results of the ACTH stimulation test clearly documented adrenal failure. Further, they pinpointed the problem as primary adrenal failure. Values after stimulation should rise at least to twice baseline and to absolute levels of >12 mg for urinary 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) and of >15 µg for urinary aldosterone. Patients with primary adrenal failure show no increase in urinary metabolites with sustained ACTH stimulation. In secondary adrenal failure, a "stepladder" increase in the levels of urinary steroids is obtained with sustained ACTH stimulation. In addition, the elevated serum levels of pituitary hormones (ACTH, FSH, and TSH) provided additional evidence ruling out hypopituitarism as a cause of adrenal failure.

Additional tests and results included the following:

Tuberculosis serology	Negative
Histoplasmosis serology	Negative
Angiotensin-converting enzyme	Within reference range
Thyroid microsomal antibodies titer	1:50,000 (Normal, ≤ 1:100)

## INTERMITTENT RIGHT FLANK PAIN

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Fred Gorstein, Reviewer

A 59-year-old, previously healthy, white male office manager presented to his local physician complaining of intermittent right-sided flank pain. He described a 10-day history of awaking at night with sharp stabbing pain in his right side, a pain that often radiated from his abdomen to his flank. The pain would last from seconds to minutes and was relieved by sitting upright or by lying in a fetal position. There was no history of fever, chills, nausea, vomiting, diarrhea, melena, bloody stools, dysuria, or hematuria. He did mention a 15-lb (6.8-kg) weight loss over the last six months that he attributed to dieting.

Physical examination revealed a tall, well-developed, pleasant white male in no apparent distress. Vital signs were within normal limits. The lungs were clear to auscultation, and cardiac examination revealed a regular rate and rhythm without murmurs, gallops, or rubs. The abdominal examination was significant for an easily palpable, nontender, right-sided mass. There was no peripheral adenopathy. The extremities were negative for cyanosis, clubbing, and edema. Rectal examination was negative for palpable masses; stool was negative for occult blood.

The patient agreed to an immediate hospital admission to determine the nature of his right abdominal mass.

Chest X-ray examination was negative for effusions, infiltrates, and masses. A plain abdominal X-ray film confirmed the presence of a large, partially cystic, right abdominal mass. The lesion was thought to be arising from liver, adrenal gland, or superior pole of the kidney.

Laboratory data were as follows:

Analyte	Value, conventional units	Reference range, conventional units	Value, SI units	Reference range, SI units
Leukocyte count (B)	$8.8 \times 10^3/\mu\text{L}$	4.8-10.8	$8.8 \times 10^9/\text{L}$	4.8-10.8
Hemoglobin (B)	15.5 g/dL	14-18	9.62 mmol/L	8.69-11.17
Platelet count (B)	$357 \times 10^3/\mu\text{L}$	130-400	$357 \times 10^9/\text{L}$	130-400
Prothrombin time (B)	12 s	10-13	Same	
Urinalysis (U)	Within normal limits			
Sodium (S)	138 mmol/L	135-145	Same	
Potassium (S)	4.5 mmol/L	4.1-5.3	Same	
Chloride (S)	100 mmol/L	98-108	Same	
CO <sub>2</sub> , total (S)	27 mmol/L	20-28	Same	
Urea nitrogen (S)	13 mg/dL	5-18	4.6 mmol urea/L	1.8-6.4
Creatinine (S)	1.1 mg/dL	0.4-1.4	97 $\mu\text{mol/L}$	35-124
Glucose (S)	86 mg/dL	60-110	4.8 mmol/L	3.3-6.1
Protein, total (S)	6.8 g/dL	6.2-8.0	68 g/L	62-80
Albumin (S)	3.8 g/dL	3.8-5.0	38 g/L	38-50
Cholesterol (S)	164 mg/dL	167-240	4.24 mmol/L	4.32-6.21
Calcium, total (S)	8.9 mg/dL	8.4-10.2	2.22 mmol/L	2.10-2.54
Bilirubin, total (S)	0.5 mg/dL	0.1-1.2	9 $\mu\text{mol/L}$	2-21

Analyte	Value, conventional units	Reference range, conventional units	Value, SI units	Reference range, SI units
ALP (S)	85 U/L	20-90	1.42 $\mu\text{kat/L}$	0.33-1.50
LDH (S)	935 U/L	100-190	15.59 $\mu\text{kat/L}$	1.67-3.17
AST (S)	37 U/L	8-38	0.62 $\mu\text{kat/L}$	0.13-0.63
Cortisol, 0800 h (S)	12 $\mu\text{g/dL}$	5-23	331 nmol/L	138-635
Cortisol, 1600 h (S)	7 $\mu\text{g/dL}$	3-13	193 nmol/L	83-359



## Differential Diagnosis

At this point, renal cell carcinoma, adrenal cortical neoplasm, pheochromocytoma, and a hepatic tumor were considered possible causes. Laboratory data gave no indication of hematopoietic dysfunction, renal impairment, or electrolyte imbalance. Studies that supported normal liver function included the prothrombin time, total protein, albumin, total bilirubin, ALP, and AST. The markedly elevated LDH was thought to reflect probable tumor necrosis from the abdominal mass. Based on physical examination, absence of an endocrinopathy, and normal serum chemistry studies reflecting no evidence of hepatic injury, renal impairment, or electrolyte imbalance, the favored diagnoses included renal cell carcinoma, oncocyoma, and a nonfunctioning adrenal neoplasm.

An intravenous pyelogram (IVP) highlighted an inferiorly displaced right kidney with a normal filling time. Abdominal computed tomography (CT) favored a right adrenal mass with extension to the right hemidiaphragm, liver, kidney, and inferior vena cava (IVC). Laboratory results for a 24-h urine specimen were as follows:

Analyte	Value, conventional units	Reference range, conventional units	Value, SI units	Reference range, SI units
Total volume	2.0 L/d	0.6-1.6	Same	
Creatinine	1888 mg/d	995-1990	16.7 mmol/d	8.8-17.6
17-Ketosteroids	37 mg/d	8-20	128 $\mu$ mol/d	28-69
11-Ketoandrosterone	0.9 mg/d	0.21-1.01	3.0 $\mu$ mol/d	0.7-3.3
Catecholamines, total	83 $\mu$ g/d	0-100	491 nmol/d	0-591
Metanephrines, total	0.4 mg/d	0-1.6	2.2 $\mu$ mol/d	0.0-8.7
Vanillylmandelic acid	7.7 mg/d	1.5-7.5	39 $\mu$ mol/d	8-38

Elevation of urinary 17-ketosteroids was suggestive of an adrenal cortical neoplasm. Secreting adrenal cortical tumors are generally accompanied by some of the greatest increases in 17-ketosteroids (may be up to 70 mg/d). Moderate elevations, as seen in this patient, can also be observed in silent tumors. If such elevations occur in adult males, clinical presentations related to 17-ketosteroid excess may not be apparent. Urinary catecholamines, metanephrines, and vanillylmandelic acid levels reflected normal adrenal medullary function.

An arteriogram revealed a moderately vascular neoplasm deriving its vascular supply from the right middle adrenal artery. A venogram confirmed extrinsic compression of the IVC by the mass but no gross intraluminal involvement. A preoperative bone scan was negative.

Based on IVP, abdominal CT, and arteriography, this was an adrenal neoplasm; 24-h urine studies were more suggestive of an adrenal cortical neoplasm with mild 17-ketosteroid excess than of a medullary process. The final preoperative differential diagnosis included a clinically silent adrenal cortical carcinoma and a nonfunctioning pheochromocytoma.

The patient underwent successful surgical resection of a well-encapsulated 1700-g adrenal cortical carcinoma. There was no gross invasion of the kidney, hemidiaphragm, liver, or IVC. Grossly, the tumor was composed of soft tan-pink parenchyma with central cystic degeneration and scattered necrosis and hemorrhages. On microscopical examination, poorly organized alveolar nests and diffuse sheets of polygonal cells demonstrated eosinophilic cytoplasm and moderate nuclear pleomorphism. There was no invasion of the capsule or vasculature.

The patient recovered rapidly, declined adjuvant therapy, and was followed closely in the outpatient clinic.

This case demonstrates the diagnostic dilemma of dealing with a clinically silent or nonfunctioning adrenal cortical carcinoma. Fortunately, these account for 50% or less of all cases. The majority of patients with adrenal cortical carcinoma present with Cushing's syndrome secondary to uncontrolled cortisol production nonsuppressible by high-dose dexamethasone administration. Plasma cortisol and free urinary cortisol levels are markedly elevated. Clinical virilism is associated with marked elevation of urinary 17-ketosteroids. Feminization secondary to estrogen excess is rare and is associated with a dismal prognosis.