Cushings Disease

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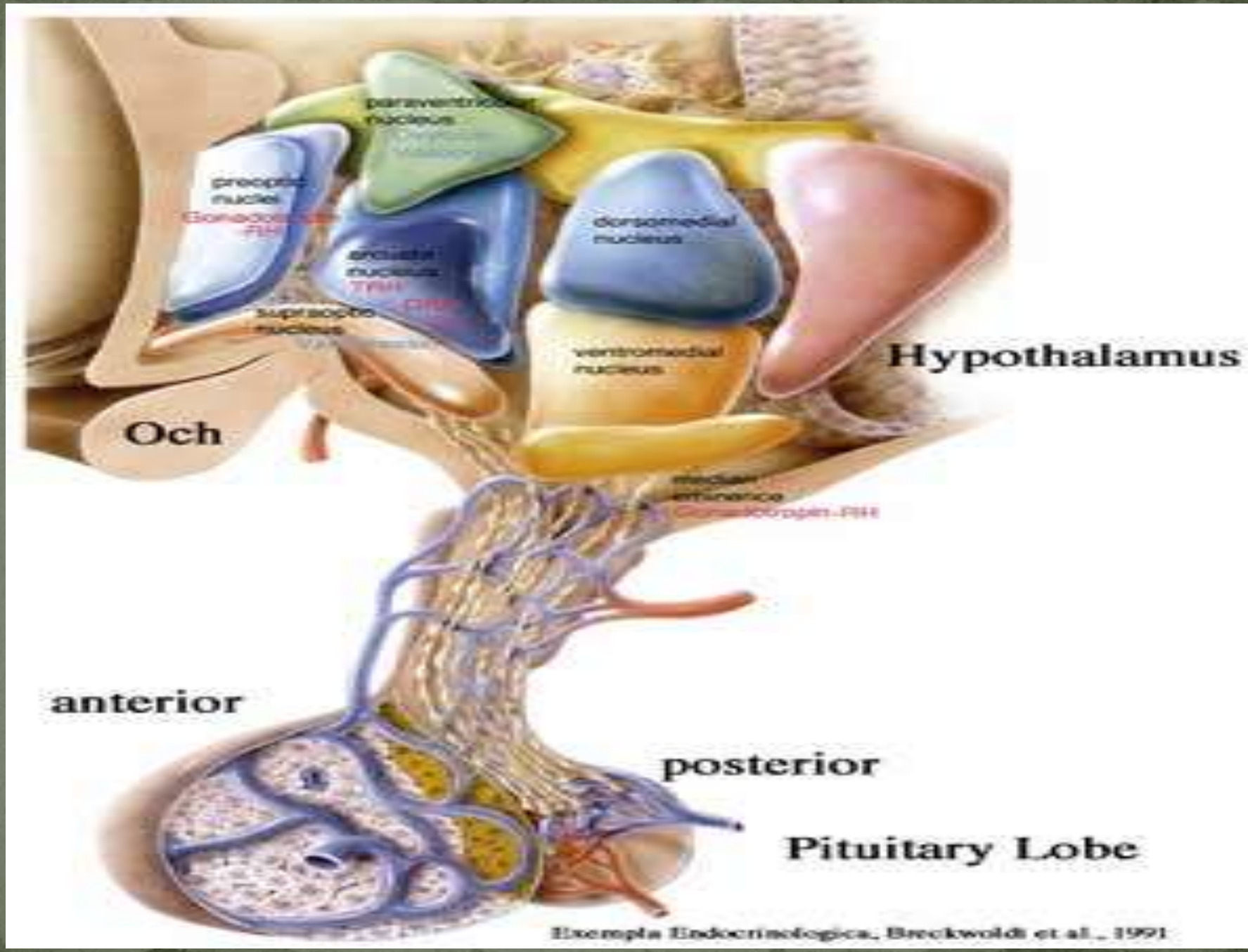
Learning objectives

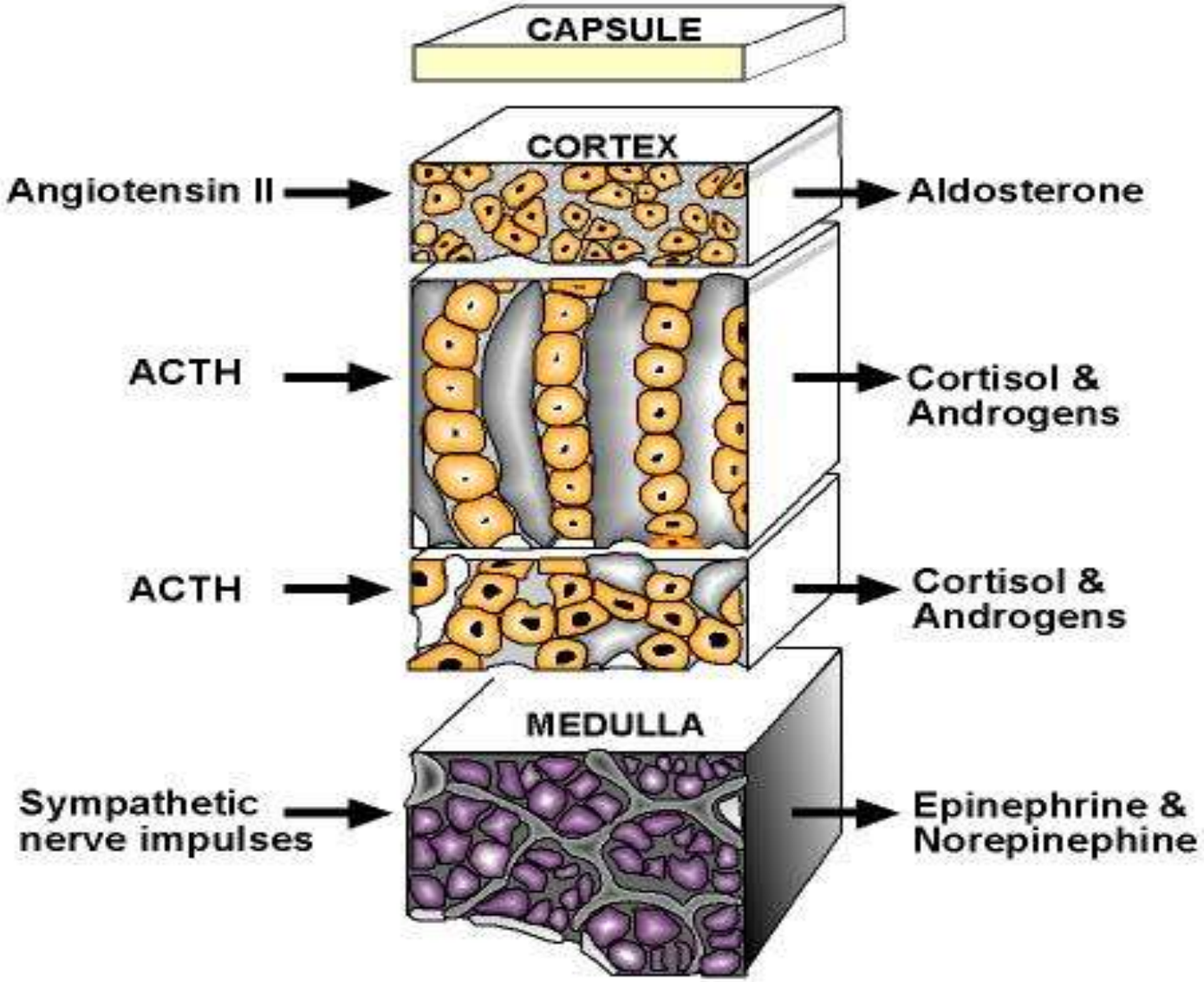
- • The anatomy and function of the adrenal and other endocrine glands
- • The diagnosis and management of endocrine disorders
- • The role of surgery in the management of endocrine disorders

HARVEY CUSHING (1932)

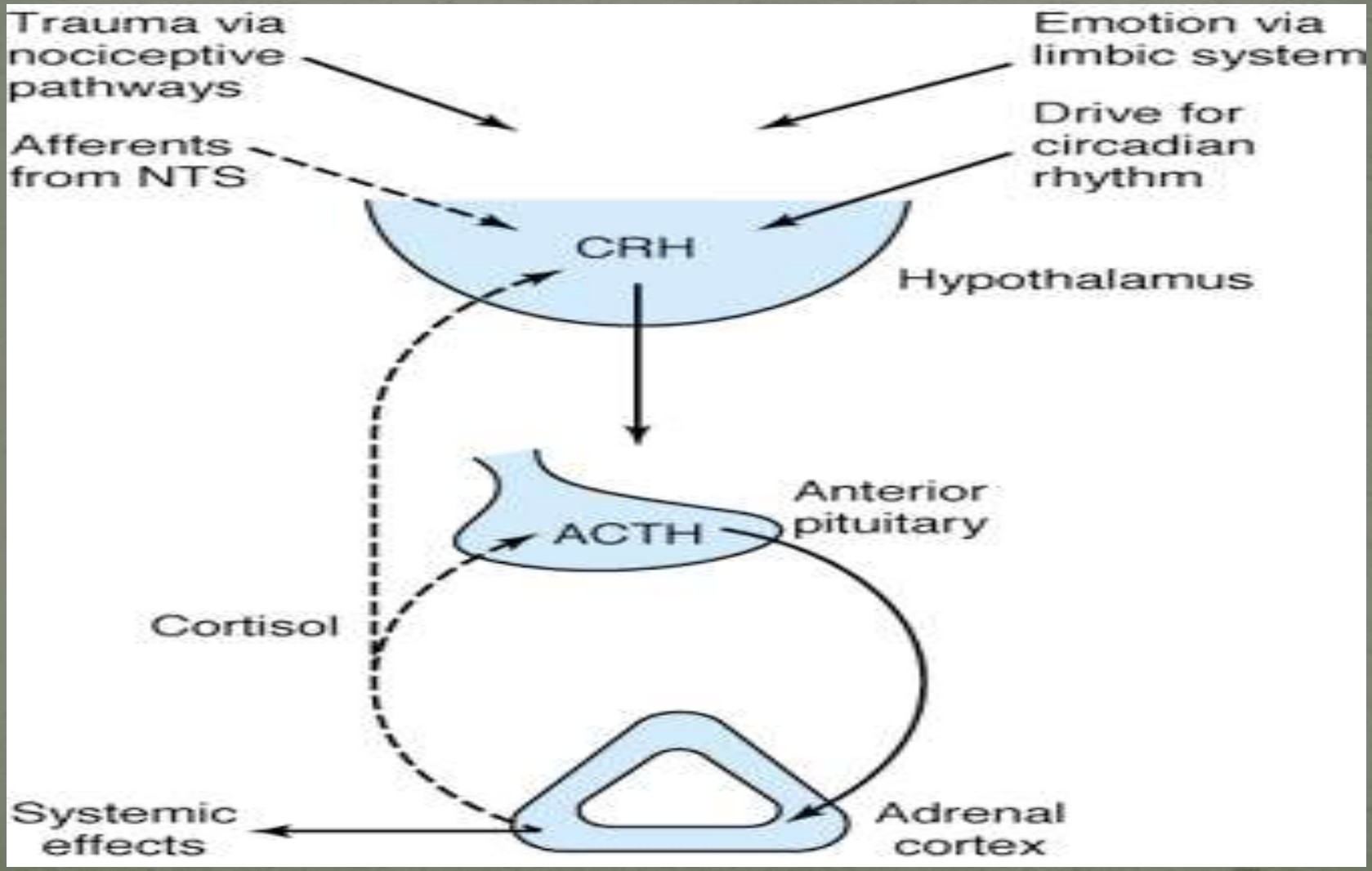
"Which has been found at autopsy in 6 out of 8 to be associated with pituitary adenoma, in 5 cases definitely composed of basophil elements."

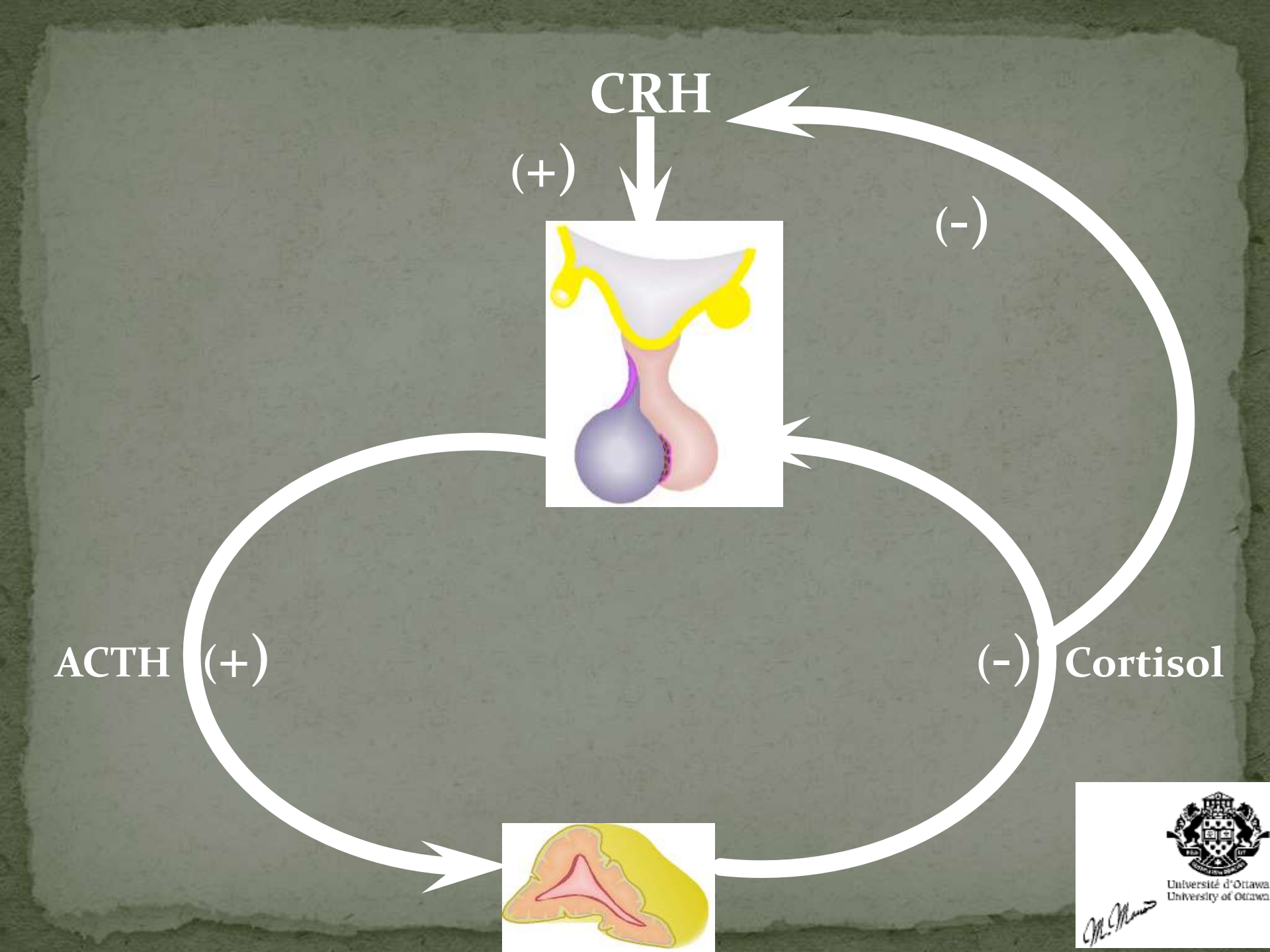

paraventricular nucleus
dorsomedial nucleus
ventromedial nucleus
Hypothalamus
Och
anterior
posterior
Pituitary Lobe
Exempla Endocrinologica, Breckwoldt et al., 1991

ADRENAL GLAND

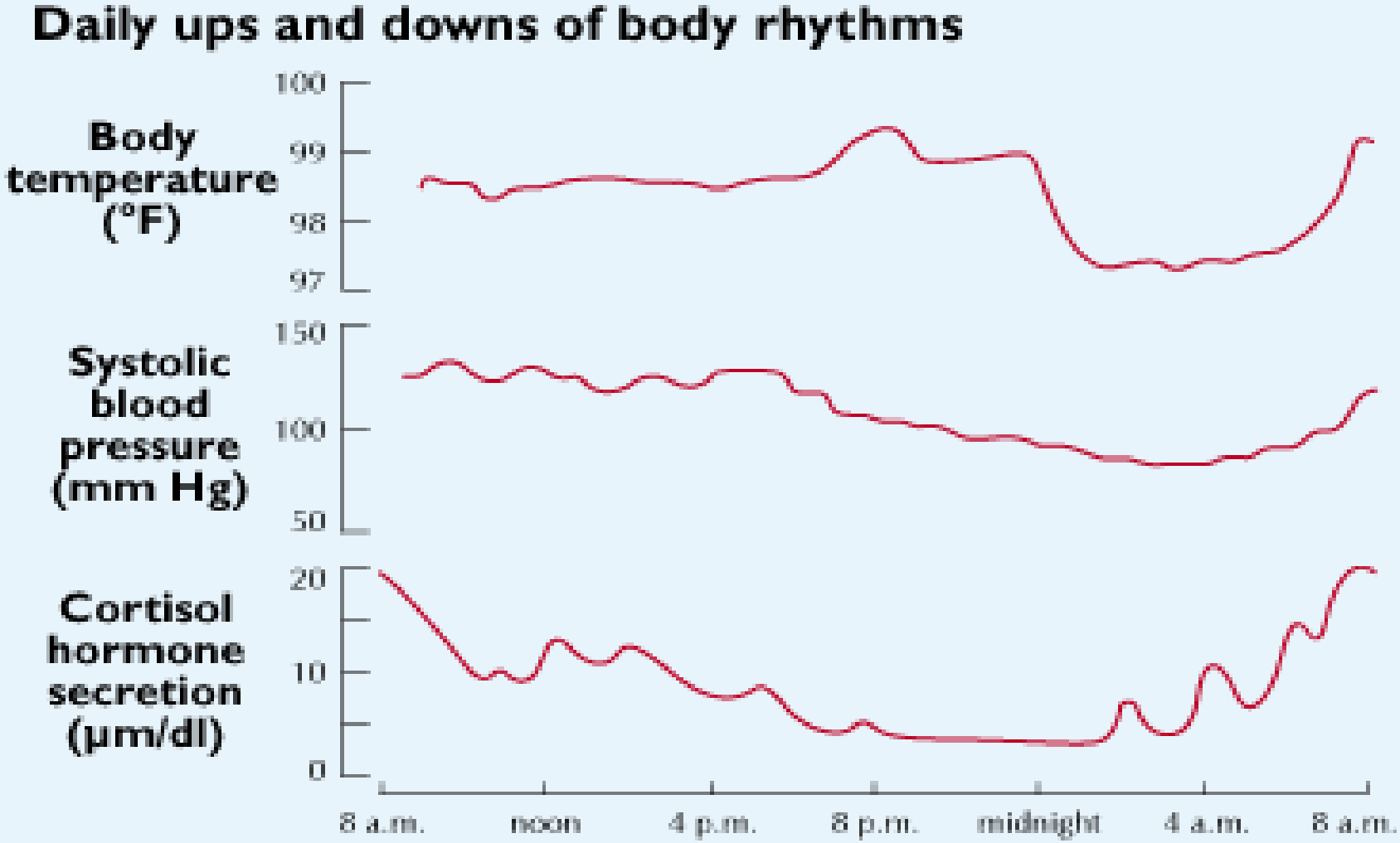


Hypothalmus-Pituitary-Adrenal Axis





Cortisol Circadian Rhythm



- Cushing described patients with a peculiar fat deposition, amenorrhea, impotence (in men), hirsutism, purple striae, hypertension, diabetes, and other features that constitute the syndrome
- He also recognized that several of these patients had basophilic tumors of the pituitary gland and concluded that these tumors produced hormones, which caused adrenocortical hyperplasia, thus resulting in the manifestations of the syndrome

Cushing's Syndrome

red cheeks

moon face

Osteoporosis; compressed (codfish) vertebrae

bruisability ecchymoses

Excessive Cortisol

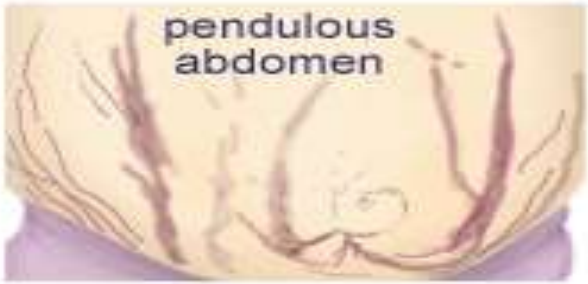
high blood pressure

pendulous abdomen

fat pads (buffalo hump)

thin skin

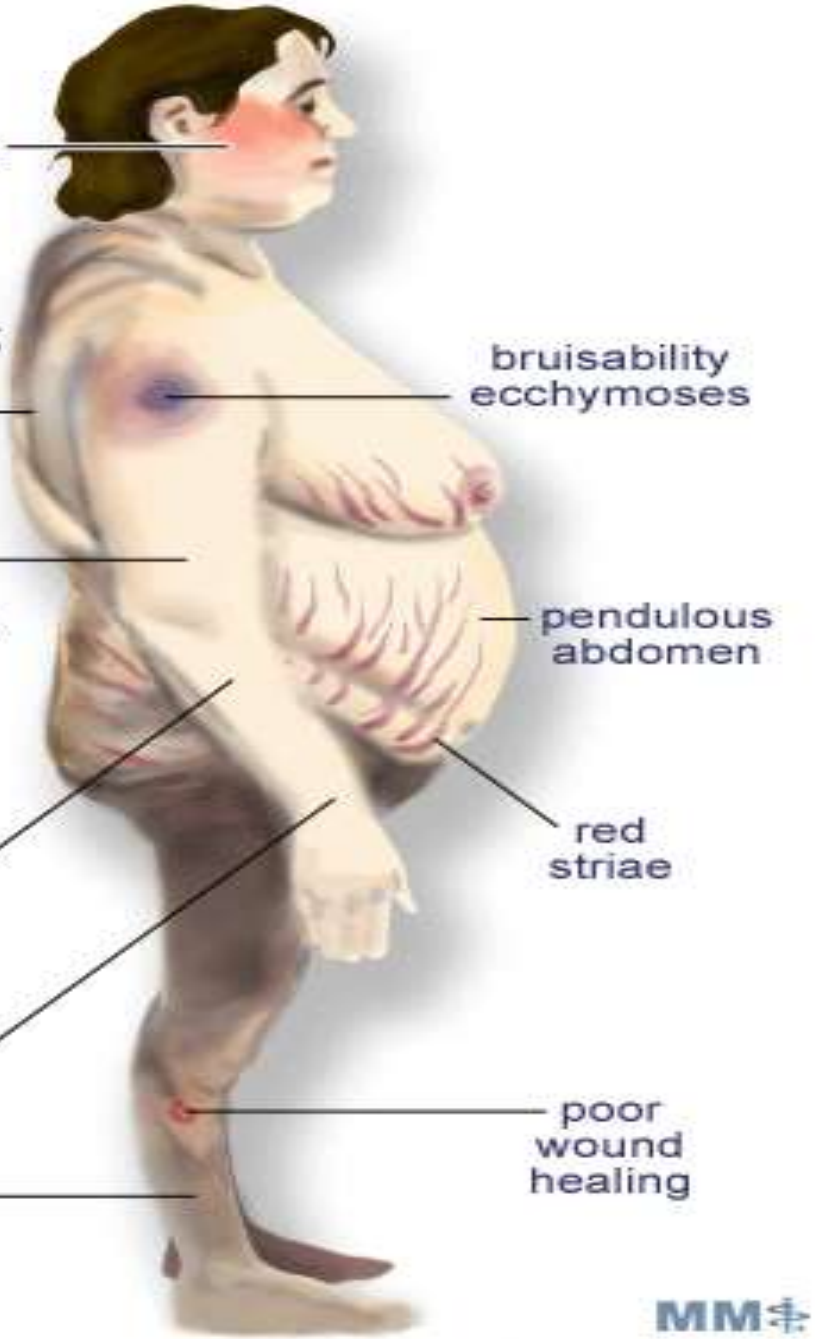
red striae



pendulous abdomen

thin arms and legs

poor wound healing



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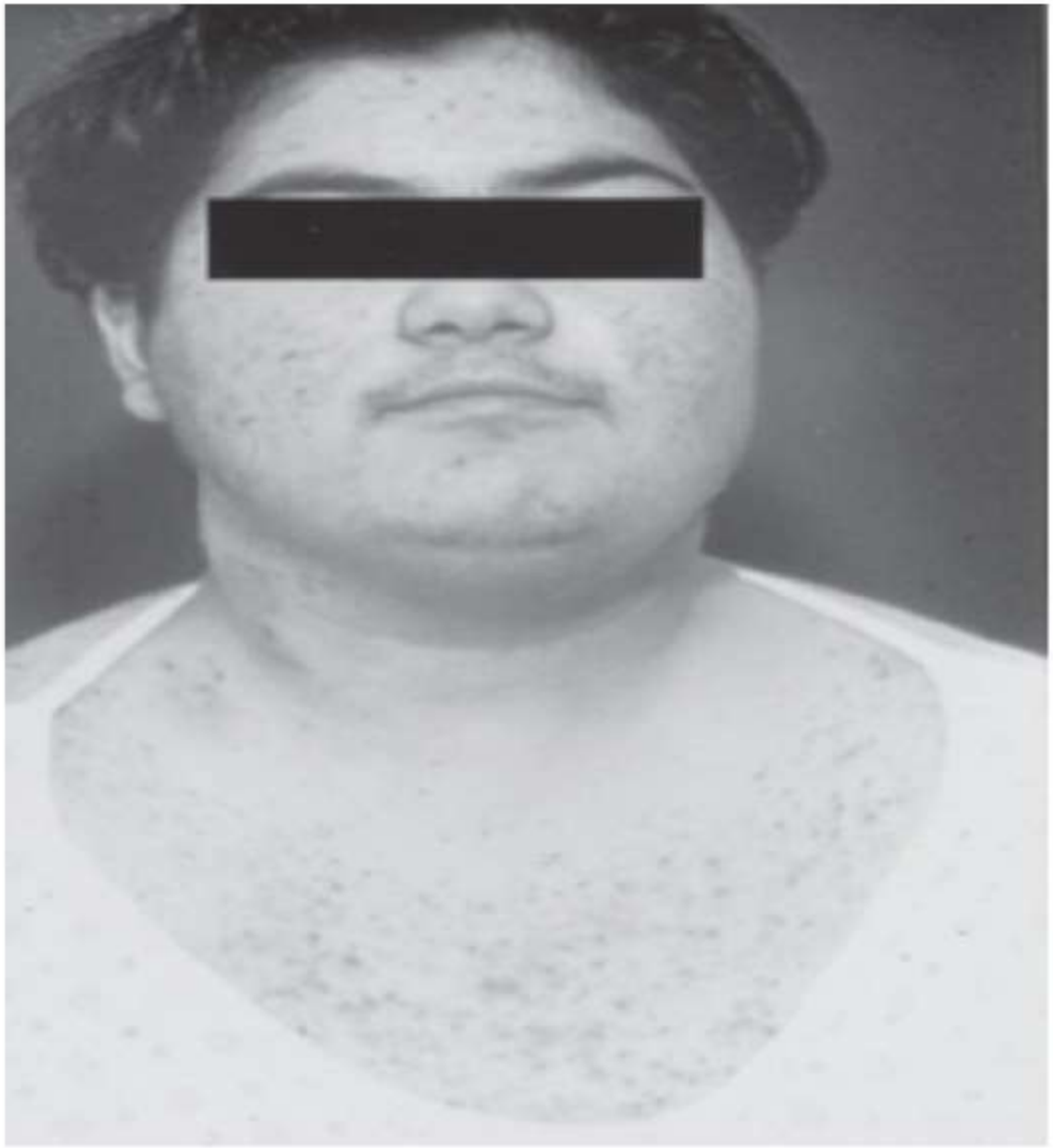


Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

- the term ***Cushing's syndrome*** refers to a complex of symptoms and signs resulting from hypersecretion of cortisol regardless of etiology.
- In contrast, ***Cushing's disease*** refers to a pituitary tumor, usually an adenoma, which leads to bilateral adrenal hyperplasia and hypercortisolism.
- Cushing's syndrome (endogenous) is a rare disease, affecting 10 in 1 million individuals. It is more common in adults but may occur in children. Women are more commonly affected (male:female ratio 1:8).

- Cushing's syndrome may be classified as ACTH-dependent or ACTH-independent
- ACTH dependant
  - Pituatry adenoma or cushing disease 70%
  - Ectopic ACTH production 10%
  - Ectopic CRH production
- ATCH Independent
  - Adrenal adenoma (10-15%)
  - Adrenal carcinoma (5-10%)
  - Adrenal hyperplasia

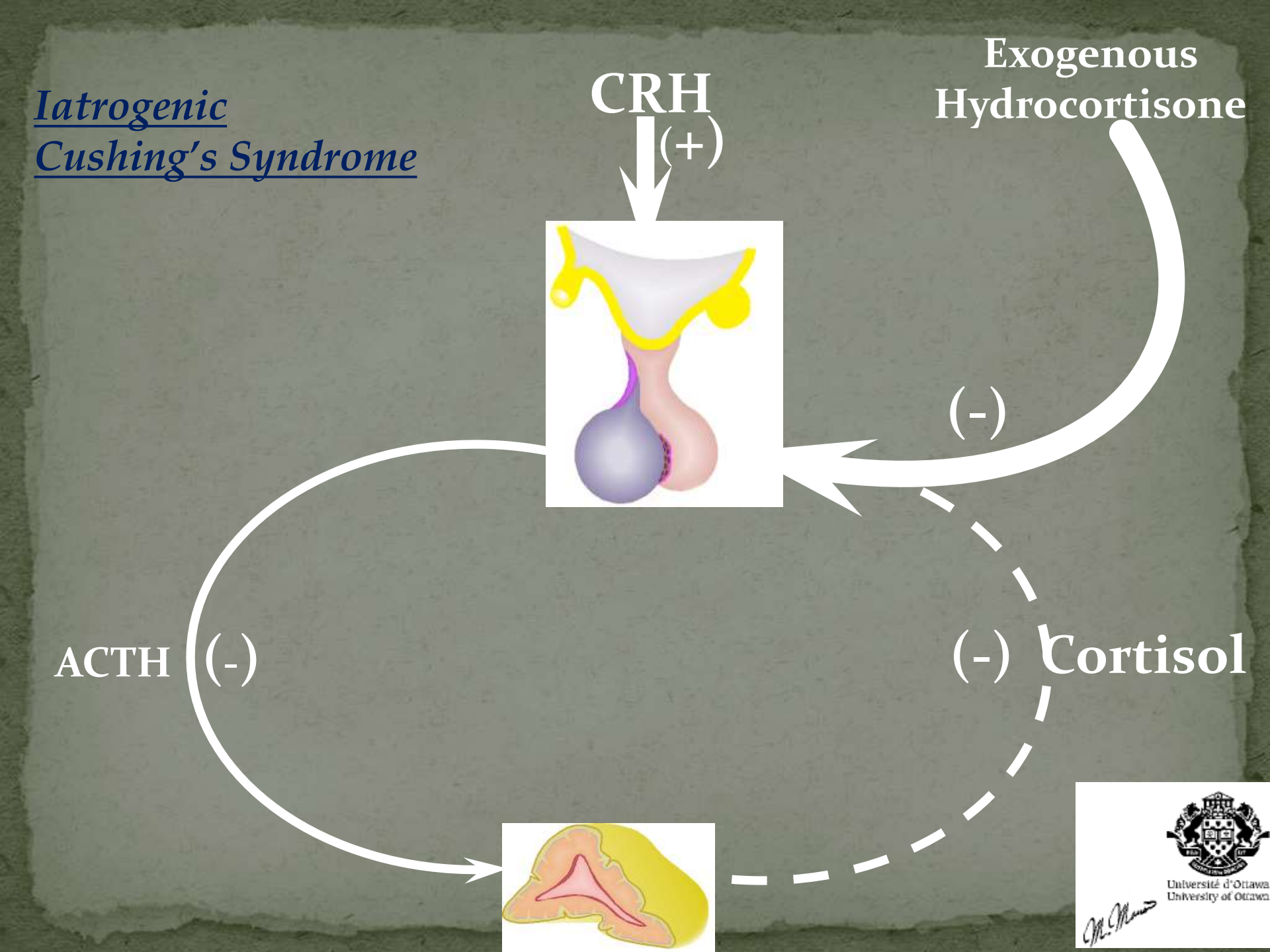
Causes of Cushing's syndrome

- The most common cause of hypercortisolism is ingestion of prescribed medication, usually for Non-Endocrine disease.
  - Oral
  - Injected
  - Topical (intra-articular, epidural, nasal, & dermal)
  - Inhaled glucocorticoids

Cizza J Clin Endocrinol Metab. 1996

Raff H. The Endocrinologist. 1998

Iatrogenic Cushing's Syndrome



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ACTH-dependent Cushing's disease

CRH (+)

Autonomous ACTH secreting tumour

ACTH (+)

(-) Cortisol

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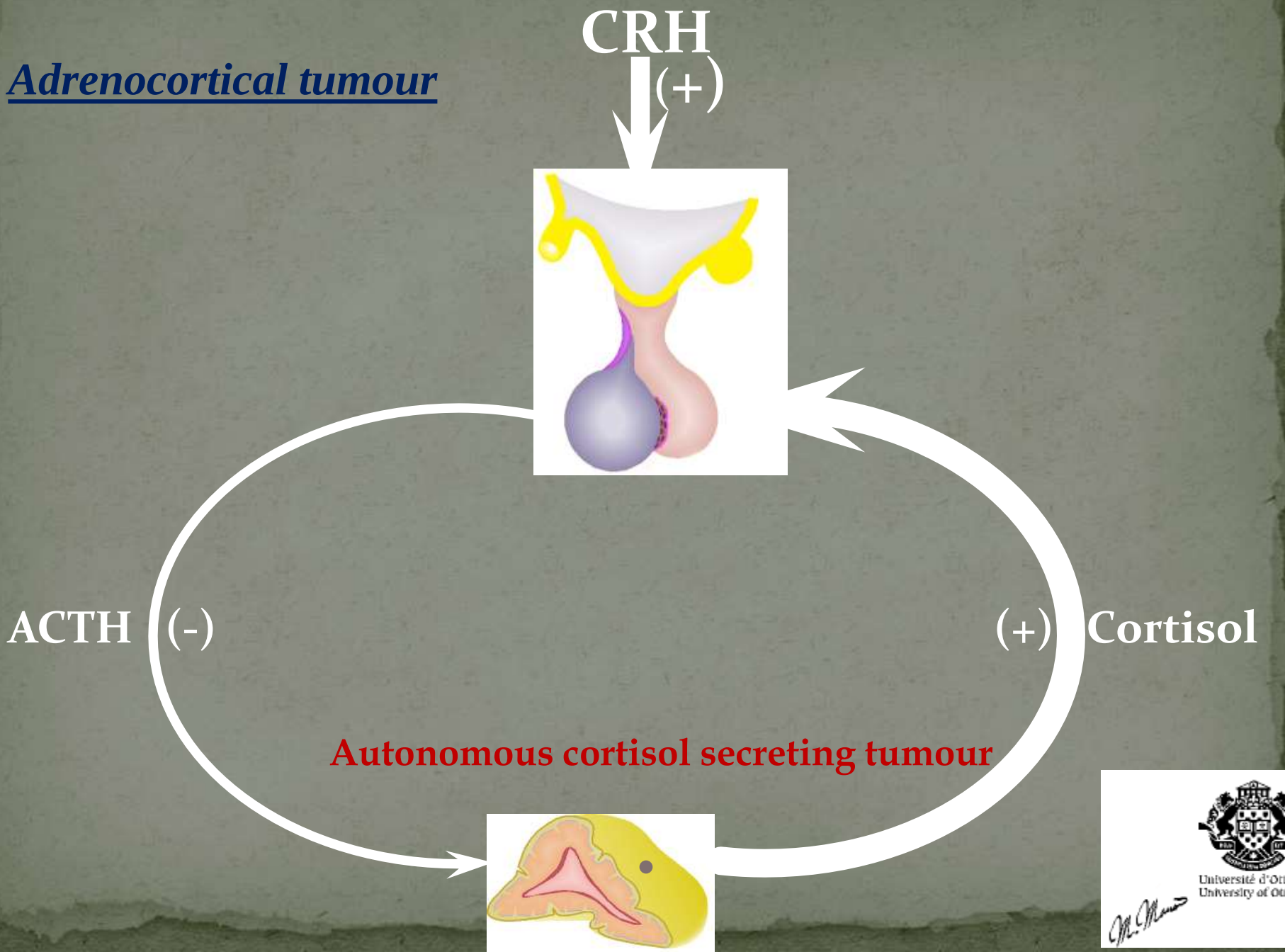
Adrenocortical tumour



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Ectopic ACTH syndrome

CRH (+)

(+) Cortisol

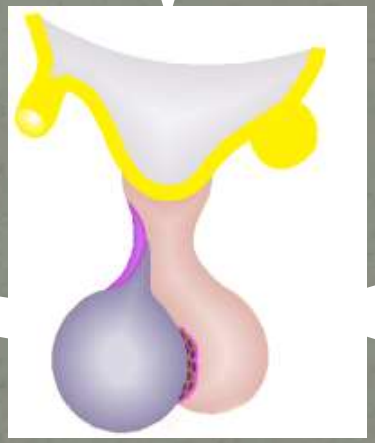
Ectopic ACTH secreting tumour

ACTH (+)

Ectopic CRH producing tumour

CRH (+)

Ectopic CRH secreting tumour



ACTH (+)

(+) Cortisol

Clinical features

- General
  - Weight gain, Obesity ,fat deposition
- Integumentary
  - Hirsuitism ,plethora,acne,striea, eccymosis
- Cardiovascular
- Musculoskeletal
- Neuropsychiatry
- Metabolic
- Renal
- Gonadal

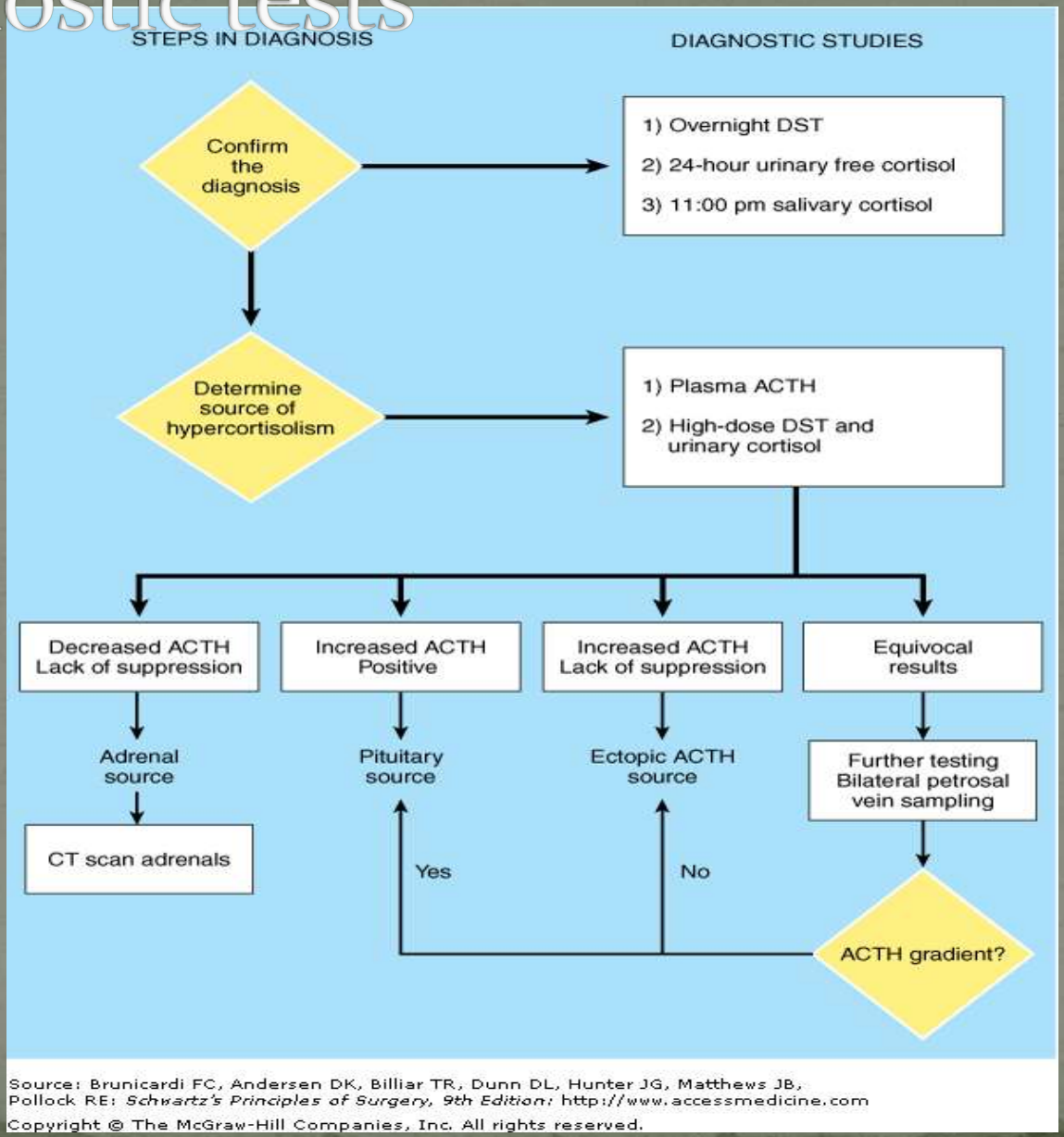
Striae in Cushing's disease

Axillary and lower abdominal striae in a 21-year-old man with Cushing's disease. Abdominal obesity is also present.
Courtesy of David N Orth, MD.

- Mnemonic
- The word "cushingoid" is a useful way to consider the complications and symptoms of Cushing's.
- **C**ataracts
- **U**lcers
- **S**kin: striae, thinning, bruising
- **H**ypertension/ Hirsutism/ Hyperglycemia
- **I**nfections
- **N**ecrosis, avascular necrosis of the femoral head
- **G**lycosuria
- **O**steoporosis, obesity
- **I**mmunosuppression
- **D**iabetes

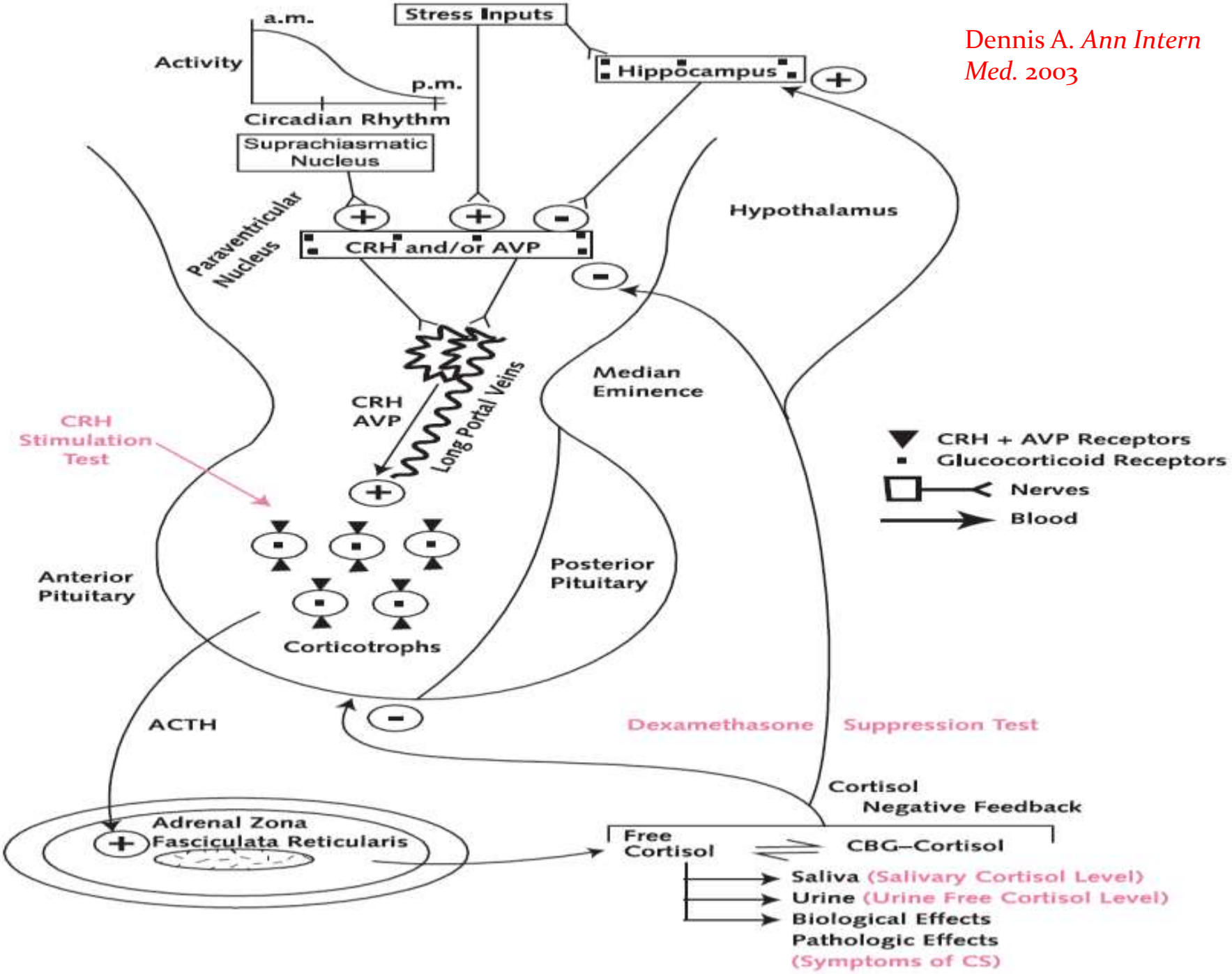
- Diagnosis

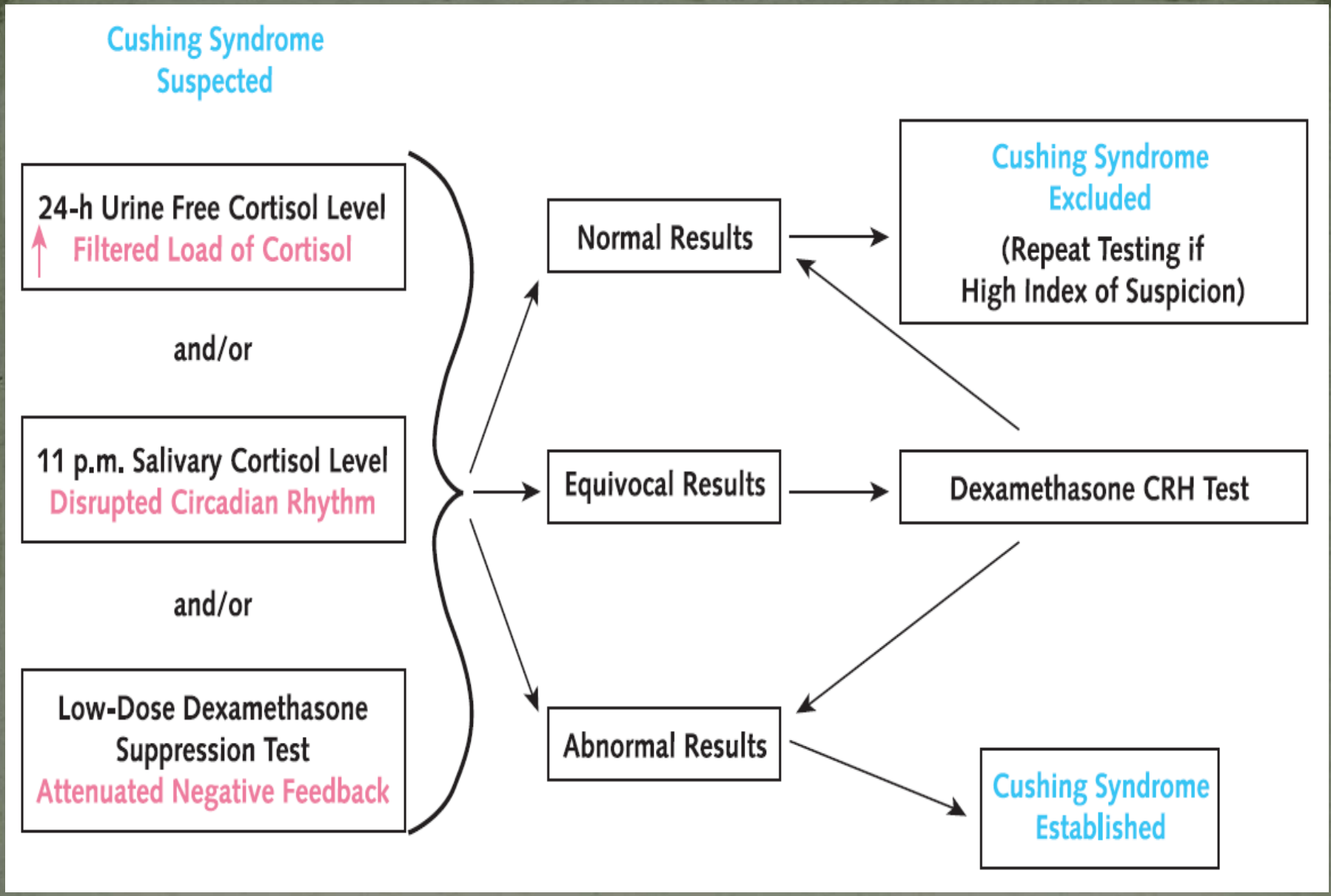
Diagnostic tests



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Dennis A. *Ann Intern Med.* 2003




Cushing Syndrome Suspected
24-h Urine Free Cortisol Level
Filtered Load of Cortisol
and/or
11 p.m. Salivary Cortisol Level
Disrupted Circadian Rhythm
and/or
Low-Dose Dexamethasone Suppression Test
Attenuated Negative Feedback
Normal Results
Equivocal Results
Abnormal Results
Cushing Syndrome Excluded
(Repeat Testing if High Index of Suspicion)
Dexamethasone CRH Test
Cushing Syndrome Established

Salivary cortisol levels

- Many studies have demonstrated great promise In the use of this test as a screening test for CS
  - More than 140 patients found an Increased bedtime salivary cortisol levels yield both a
    - Sensitivity of 93%
    - Specificity of 100%

Papanicolaou J Clin Endocrinol Metab. 2002

Low-Dose Dexamethasone Suppression Test

- 1mg of dexamethasone at 2300 hours and measurement of plasma cortisol at 0800 or 0900 hours the next morning.
  - High diagnostic accuracy with a sensitivity of 98% using a post-dexamethasone *serum cortisol value of less than 50nmol/l (1.8µg/l)*
- Consensus opinion in the United Kingdom: value of less than 50nmol/l (1.8µg/l) effectively Excludes the Cushing syndrome

Wood Ann Clin Biochem1997

- False positive results can occur because:
  - Failure to take dexamethasone as prescribed.
  - Accelerated hepatic metabolism
    - Phenytoin, Carbamazepine, Barbiturates, Aminoglutethimide or Rifampicin), and ETOH.
  - Increased concentration of cortisol binding globulin (CBG)
    - Pregnancy or Estrogen treatment.

Dexamethasone-CRH Test

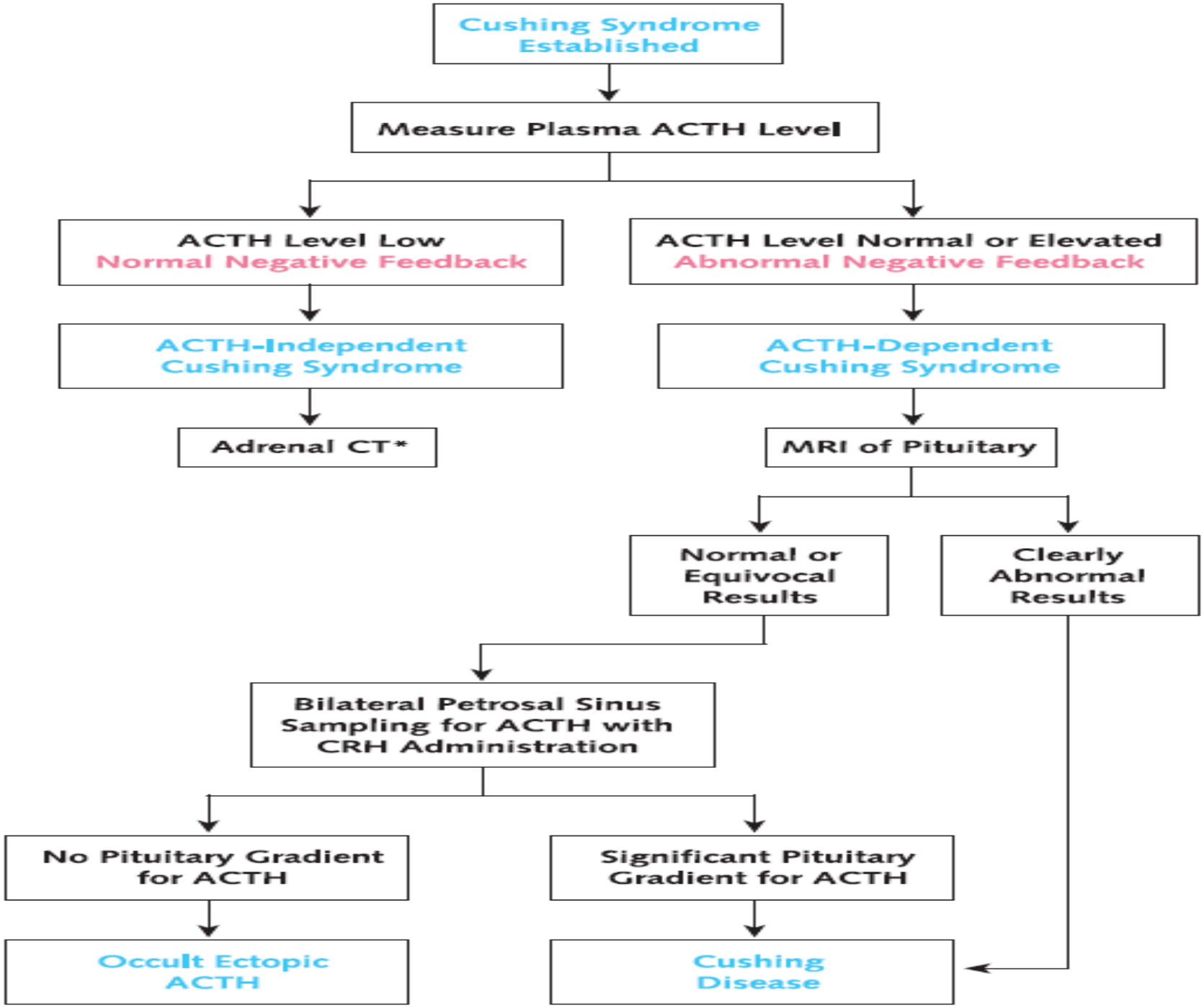
- Dexamethasone (0.5 mg Q 6 hours) is given X8, the first dose at noon and the last dose at 6:00 a.m.

- Corticotropin-releasing hormone CRH (1µg/kg) is then administered IV at 8:00 a.m., and plasma cortisol and ACTH levels are obtained at 15-minute intervals for 1 hour.

- Cortisol level greater than 39 nmol/L (1.4 g/dL) measured 15 minutes after the administration of CRH correctly identifies patients with the **Cushing syndrome**, and levels of 39 nmol/L or less (1.4 g/dL) are considered normal.

- ??Normal ACTH response.
  - Patients with the Cushing syndrome usually have a peak ACTH response exceeding 3.3 pmol/L (15 pg/mL) during the test.

- The dexamethasone-CRH test is usually reserved for patients with equivocal results on other diagnostic tests and a high index of suspicion for the Cushing syndrome.


Cushing Syndrome Established
Measure Plasma ACTH Level
ACTH Level Low
Normal Negative Feedback
ACTH Level Normal or Elevated
Abnormal Negative Feedback
ACTH-Independent Cushing Syndrome
ACTH-Dependent Cushing Syndrome
Adrenal CT*
MRI of Pituitary
Normal or Equivocal Results
Clearly Abnormal Results
Bilateral Petrosal Sinus Sampling for ACTH with CRH Administration
No Pituitary Gradient for ACTH
Significant Pituitary Gradient for ACTH
Occult Ectopic ACTH
Cushing Disease

- CT
- MRI

Treatment

- Laparoscopic adrenalectomy
- Open adrenalectomy more than 6 cm
- Bilateral adrenalectomy
- Transsphenoidal excision of pituratry adenoma
- Pituatry irradiation