NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Navigating the Complexity of the Endocrine System

by

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Preparation

Read the following article:

- Cleveland Clinic. (2025). Cortisol. [Webpage]. Cleveland Clinic. <https://my.clevelandclinic.org/health/articles/22187-cortisol>

Answer the questions below after studying Figure 1 to review the gross and microscopic anatomy and physiology of the adrenal gland.

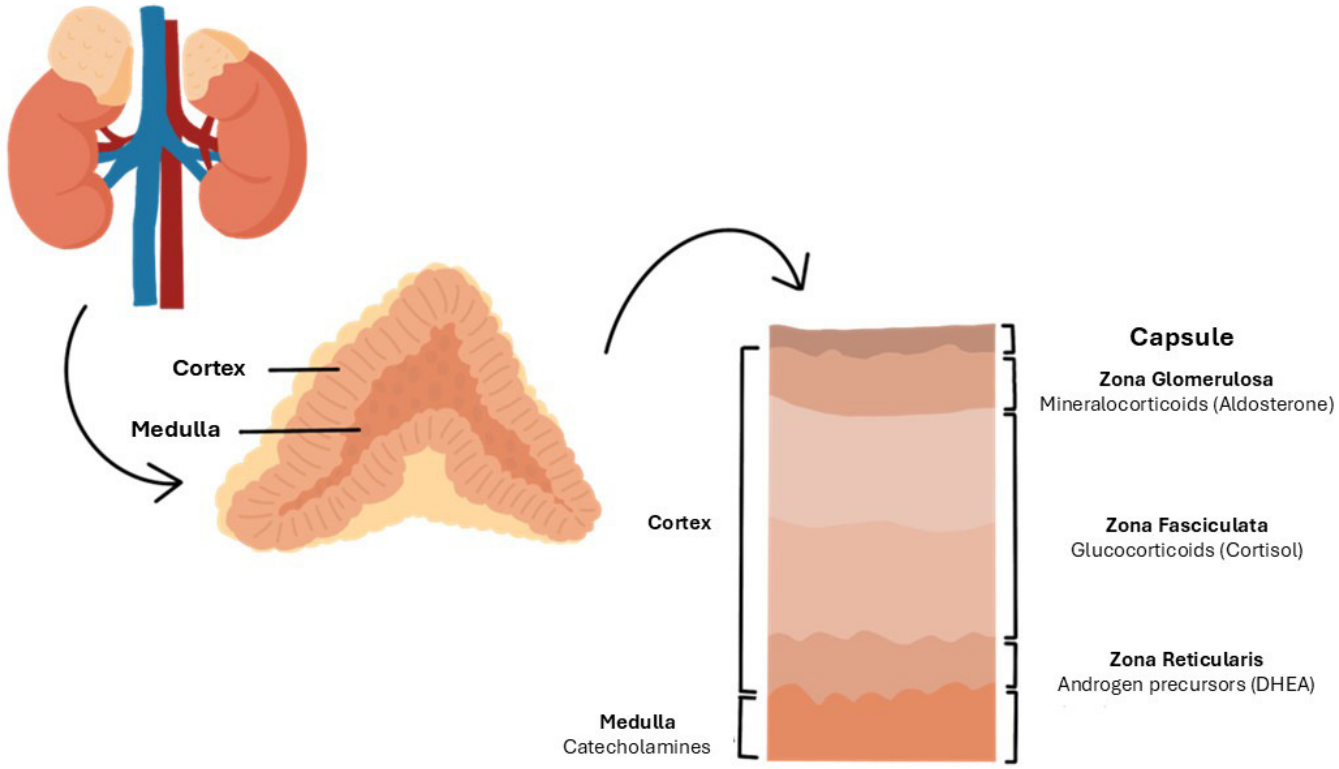

Figure 1. Zones of the cortex and medulla of the adrenal gland. The adrenal gland is divided into two major regions, the outer cortex and deep medulla. The cortex can be further divided into multiple zones, including the zona glomerulosa, the zona fasciculata, and the zona reticularis, each producing steroid hormones. The zona glomerulosa releases mineralocorticoids. The zona fasciculata releases glucocorticoids. The zona reticularis releases androgen precursors. *Credit:* Annalise Speer.

Questions

1. Choose the correct pair of terms to complete the following: *The superficial layer of the adrenal gland is called the _____ while the _____ refers to the deeper region.*

   a. cortex; medulla

   b. dorsal side; ventral side

   c. medulla; capsule

   d. zona reticularis; zona fasciculata

2. Match the hormone with the region of the adrenal gland from which it is released.

Hormone:	*Region of the adrenal gland:*
___ Androgen precursor	a. Medulla
___ Catecholamines	b. Zona glomerulosa
___ Glucocorticoids	c. Zona fasciculata
___ Mineralocorticoids	d. Zona reticularis

3. Match the hormone with its general function.

Hormone:	*General function:*
___ Aldosterone	a. Increases blood pressure, increasing blood Na^+ levels.
___ Cortisol	b. Considered a stress hormone; increases blood pressure, increases blood glucose, and decreases serotonin.
___ DHEA	c. Prepares the body for fight-or-flight, binding to adrenergic receptors throughout the body.
___ Epinephrine & norepinephrine	d. A steroid promoting the production of sex hormones.

Part I – Eva's Symptoms

A 28-year-old female, Eva, visited her primary care physician due to hirsutism (excessive facial hair growth), acne vulgaris (cystic acne), and head hair loss eight months after the birth of her third child. She also noticed that she had been gaining substantial weight despite following a healthy diet and having a healthy weight previously. During her appointment, it was discovered that she had hyperglycemia (high blood sugar). Her doctor diagnosed her with polycystic ovarian syndrome (PCOS), a chronic hormonal condition affecting the female reproductive system, and prescribed her birth control and medication in hopes of alleviating her symptoms. She continued these medications for a year and a half before her doctor advised her to stop taking them and instead follow a strict diet and exercise plan. Over the next ten years, she sought several medical opinions. Other medical professionals concurred, diagnosing her with PCOS and some also diagnosing her with Hashimoto's (an autoimmune disease leading to hypothyroidism).

Due to menorrhagia (excessive menstrual bleeding), a hysterectomy (removal of the uterus) was performed. Six months after her hysterectomy, Eva was still struggling with weight gain, fatigue, and anxiety. Eva's gynecologist referred her to an endocrinologist (a medical professional specializing in hormone-related medicine).

Questions

1. Figure 2 below demonstrates the hormone release pattern from the hypothalamus to each target organ. Using the word bank, fill in the blanks with the names of each endocrine organ and the associated hormones. One box will contain two hormones.

Word Bank:
- hypothalamus
- anterior pituitary gland
- thyroid-stimulating hormone (TSH)
- follicle stimulating hormone (FSH)/ luteinizing hormone (LH)
- prolactin
- growth hormone (GH)
- oxytocin
- antidiuretic hormone (ADH)
- posterior pituitary gland
- adrenal corticotropin-releasing hormone (ACTH)

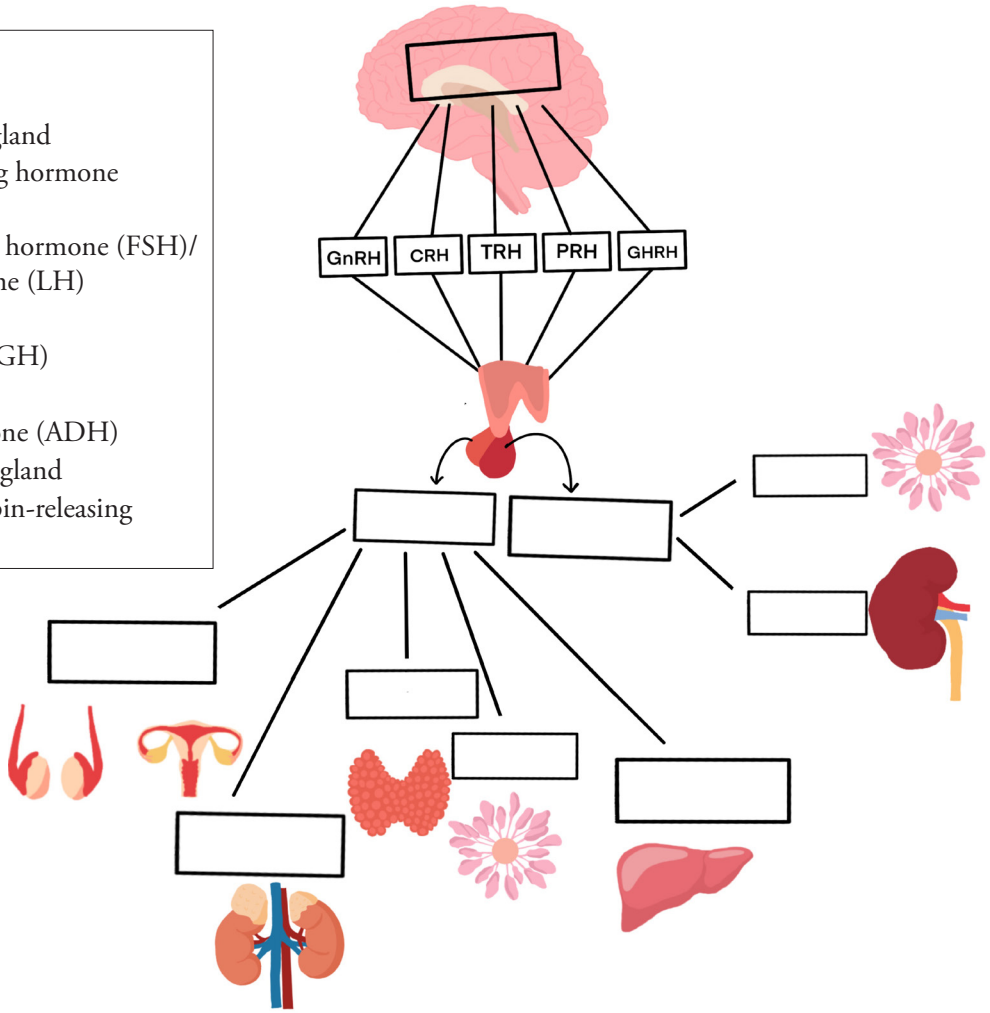

Figure 2. Hypothalamic-pituitary axis. The hypothalamus releases trophic hormones that act on the pituitary gland. The anterior and posterior pituitary glands release hormones that act on various organs. *Credit:* Annalise Speer.

2. Match the hormone with its function.

Hormone:	*Function:*
____ Adrenocorticotrophic hormone (ACTH)	a. Temperature and metabolism regulation.
____ Thyroid stimulating hormone (TSH)	b. Primary male sex hormone.
____ Prolactin	c. Stimulate thyroid gland to produce thyroid hormones (T3 and T4).
____ Growth hormone (GH)	d. Stimulates the liver to produce insulin-like growth factor, promotes skeletal and cartilage growth.
____ Triiodothyronine (T3) and thyroxine (T4)	e. Stimulates follicular growth and ovulation; trig gers the testes to produce testosterone.
____ Glucocorticoids	f. Triggers adrenal gland to produce cortisol.
____ Testosterone	g. Causes an increase in protein catabolism, blood glucose levels, and fat catabolism.
____ Mineralocorticoids	h. Primary female sex hormone.
____ Estrogen	i. Promotes development of mammary tissue and stimulates mammary glands.
____ Luteinizing hormone (LH)	j. Stimulates oogenesis and spermatogenesis.
____ Follicle stimulating hormone (FSH)	k. Stimulates the kidneys to reabsorb sodium.

Part II – Further Testing

The endocrinologist, Dr. Warner, noticed Eva's physical appearance, which included a moon face, buffalo hump, truncal obesity, fragile skin, and purple striae (Figure 2). She inquired further to gain more insight into Eva's possible condition.

Dr. Warner collected Eva's medical history:

- early morning arousal (i.e. she is waking around 3:30 a.m. and has difficulty falling back sleep)
- daytime fatigue
- caffeine dependance
- increased anxiety
- difficulty concentrating

Dr. Warner suspected a problem with Eva's hypothalamic-pituitary-adrenal axis. The physician ordered a full hormone panel, cortisol saliva test, and 24-hour urine cortisol test.

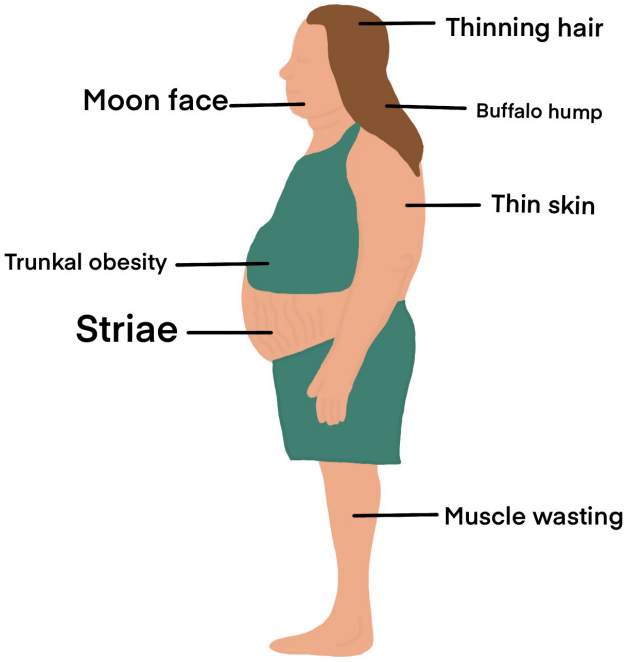

Figure 3. Overview of the classic symptoms associated with Eva's endocrine dysfunction. These symptoms include truncal obesity, hirsutism, striae, thin skin, moon face, and buffalo hump. *Credit:* Annalise Speer.

Questions

1. Cortisol is controlled by both a long and short negative feedback loop.
   a. Fill in the boxes and blanks of Figure 4 to describe the signaling pathway associated with cortisol production. Place organ names in the boxes and hormone names on the provided lines. Use the provided word bank.
   b. Add arrows indicating the long and short negative feedback loops.

Word Bank:
- corticotropin releasing hormone (CRH)
- hypothalamus
- adrenal gland
- cortisol
- adrenocorticotropic hormone (ACTH)
- anterior pituitary gland

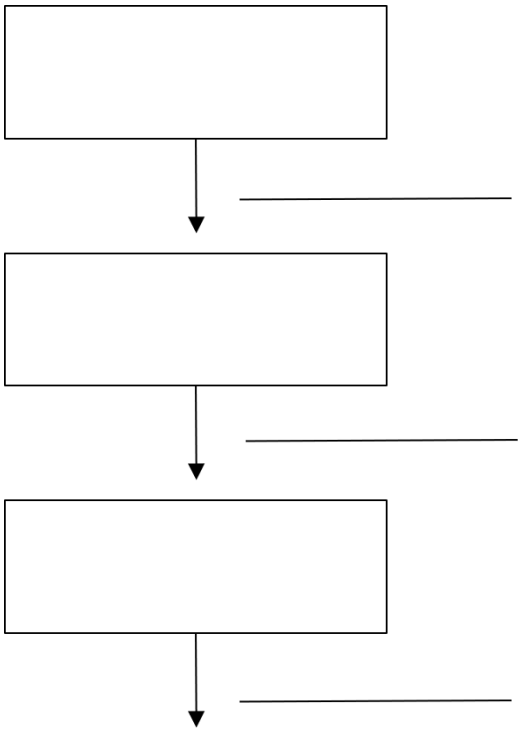

Figure 4. Long and short-feedback loops for cortisol regulation.

2. Cortisol is controlled by a circadian rhythm and negative feedback loop. Analyze Figure 5 and choose which response best describes cortisol's circadian rhythm.
   a. Cortisol levels remain consistent throughout the day.
   b. Cortisol levels peak in the morning before waking and gradually decline throughout the rest of the day, reaching their lowest levels at night.
   c. Cortisol levels are the lowest in the morning and highest at night.
   d. Cortisol levels peak during the middle of the day, decline for the remainder of the day, and peak again at night.

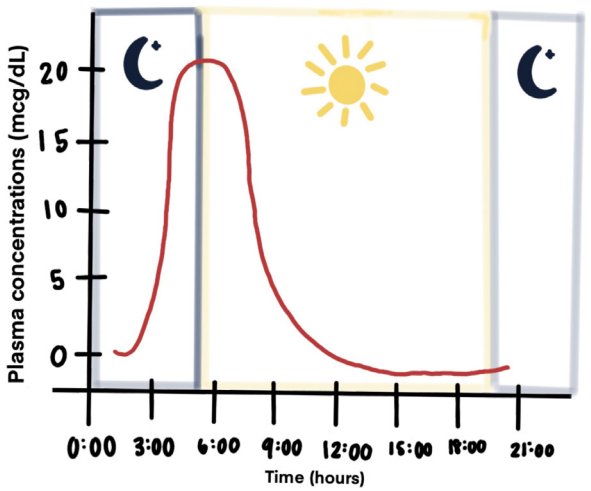

Figure 5. Cortisol graph reflecting normal secretion of cortisol over 24 hours. This graph is an adaptation of the graphs by ZRT Laboratory (n.d.) and Dixson (2023). *Credit:* Annalise Speer.

3. Examine Eva's hormone panel (Table 1). Highlight or circle any of Eva's values that are outside of the normal range.

Table 1. Eva's lab results from the full hormone panel compared against the normal range. Her lab values for estradiol, luteinizing hormone, DHEA sulfate, T4 (thyroxine), TSH, 17-hydroxyprogesterone, prolactin, FSH, testosterone, and ACTH were obtained from blood samples. Saliva cortisol was collected from saliva, and free cortisol was obtained from urine.

Component	*Eva's Value*	*Normal Range*
Estradiol	243 pg/mL	64–357pg/mL
Luteinizing hormone	1.6 mIU/mL	0.5–16.9 mlU/mL
*DHEA sulfate	329 mcg/dL	19–237 mcg/dL
T4 (thyroxine)	1.2 ng/dL	0.8–1.8 ng/dL
Thyroid-stimulating hormone	0.69 mIU/L	0.40–4.50 mIU/L
**17-Hydroxyprogesterone	32 ng/dL	23–102 ng/dL
Prolactin	13.8 ng/ML	3.0–30.0 ng/mL
Follicle-stimulating hormone	4.0 mIU/mL	1.5–9.1 mIU/mL
Testosterone	4.7 pg/mL	0.2–5.0 pg/mL
Adrenal corticotropic hormone	62 pg/mL	6–50 pg/mL
Saliva cortisol	0.19 mcg/dL	< or =.09 mcg/dL
Free cortisol (24hr test)	95.1 mcg/24h	4.0–50.0 mcg/24h

*Dehydroepiandrosterone sulfate (DHEA-s) is an androgen produced by the adrenal glands in both men and women. It plays a role in the production of testosterone and estrogen.

** 17-Hydroxyprogesterone is a substance produced by the adrenal glands and used to create cortisol.

4. Complete Table 2 below to compare different diseases associated with the HPA axis. Record whether the hormone levels are expected to be *high*, *low*, or *normal*. If you are unfamiliar with the diseases listed below, feel free to access the following articles:
   - Peppa, M., V. Pikounis, G. Papaxoinis, A. Macheras, T. Economopoulos, S.A. Raptis, & D. Hadjidakis. (2009). Adrenocortical carcinoma secreting cortisol, androgens and aldosterone: a case report. *Cases Journal* 2, 8951. <https://doi.org/10.4076/1757-1626-2-8951>.
   - Scaroni, C., N.M. Albiger, S. Palmieri, D. Iacuaniello, C. Graziadio, L. Damiani, M. Zilio, A. Stigliano, A. Colao, R. Pivonello, & the Altogether to Beat Cushing's Syndrome (ABC) study group. (2020). Approach to patients with pseudo-Cushing's states. *Endocrine Connections* 9(1): R1–R13. <https://doi.org/10.1530/EC-19-0435>
   - Thau L., J. Gandhi, & S. Sharma. (2023). Physiology, cortisol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK538239/>

   Table 2. Primary and secondary diseases associated with hyper- or hypo- cortisol secretions.

Hormone	*CRH Secreting Tumor*	*CRH Suppressing Tumor*	*Cushing's Disease (ACTH-secreting tumor)*	*ACTH Suppressing Tumor*	*Addison's Disease*	*Pseudo-Cushing's Disease (ectopic ACTH production)*
CRH						
ACTH						
Cortisol						

5. Which of the diseases listed in Table 2 best aligns with Eva's symptoms and hormones (Table 1)?

6. What additional information do you need to distinguish between the various possible diagnoses?

Part III – Determining the Root Cause

Dr. Warner continued her discussion with Eva. "Eva, I noticed that both your salvia and free cortisol level are elevated. You are experiencing hypercortisolism, indicating your cortisol, or stress hormone, is higher than normal."

She continued to explain to Eva that there are several possible causes of hypercortisolism, and that cortisol is regulated by communication between the hypothalamus, anterior pituitary and her adrenal glands. The physician suspected Eva had a secreting tumor in one of the organs of her stress regulation response, either the hypothalamus, anterior pituitary gland, or adrenal glands.

"To determine where the complication occurs, I want to run a dexamethasone, or DEXA, suppression test. Several factors can lead to elevated cortisol levels. Dexamethasone is a synthetic glucocorticoid (a steroid that raises blood glucose) that mimics cortisol, and this suppression test allows us to determine if the cause originates in one of the organs associated with the stress response. In normal conditions, glucocorticoids decrease the activity of the stress response system via negative feedback. In pathological conditions, the activity of the stress response system remains elevated despite an increased level of glucocorticoids. This test assesses whether the hypothalamic-pituitary-adrenal axis is properly suppressed by glucocorticoids." Dr. Warner continued explaining how the DEXA suppression test works and allowed Eva to ask questions.

Questions

1. To learn about the DEXA suppression test, watch the video listed below and then complete Table 3 using the following terms: *increase*, *decrease*, or *not suppressed*.
   - AJmonics. (2022). Dexamethasone suppression test: explained clearly! [Video]. Running time: 3:52 min. YouTube. <https://youtu.be/S0F42v2YOvM>

Table 3. Expected outcomes of dexamethasone suppression test.

	Impact of low dose (1mg) DEXA suppression test on:			*Impact of high dose (8mg) DEXA suppression test on:*		
	CRH	*ACTH*	*Cortisol*	*CRH*	*ACTH*	*Cortisol*
Healthy individual						
Hypercortisolism due to excess ACTH from the anterior pituitary						
Hypercortisolism due to an organ other than the anterior pituitary						

Dr. Warner ordered a high dose DEXA suppression test. Analyze Eva's laboratory results (Table 4) and then answer the questions below.

Table 4. Eva's lab results of the DEXA suppression test. Results reflect blood levels of adreno-corticotropic hormone and cortisol before and after the administration of dexamethasone.

	Day 1 (before 8 mg DEXA)		*Day 2 (after 8 mg DEXA)*	
Component	ACTH	Cortisol	ACTH	Cortisol
Eva's value	62 pg/mL	22.1 mcg/dL	<5 pg/mL	1.5 mcg/dL
Normal range	6–50 pg/mL	4.0–22.0 mcg/dL	6–50 pg/mL	4.0–22.0 mcg/dL

Questions

2. What changes can be observed within the time that the DEXA medication was administered?
   a. ACTH and cortisol levels remained the same after the administration of DEXA.
   b. ACTH and cortisol levels increased after the administration of DEXA.
   c. ACTH and cortisol levels decreased after the administration of DEXA.
   d. ACTH levels decreased and cortisol levels increased after the administration of DEXA.

3. What disease(s) are consistent with Eva's results after administering DEXA? Reference Tables 3 and 4. What additional information could help to confirm this prediction?

Part IV – Diagnosis and Treatment

Dr. Warner analyzed Eva's results and explained that they likely indicated that Eva had a secreting tumor of the anterior pituitary. To confirm the presence of a tumor, Dr. Warner referred Eva to a neurosurgeon to order and evaluate an MRI (magnetic resonance imaging).

Eva visited neurosurgeon Dr. Chow and underwent an MRI to produce a detailed image of her brain (Figure 6).

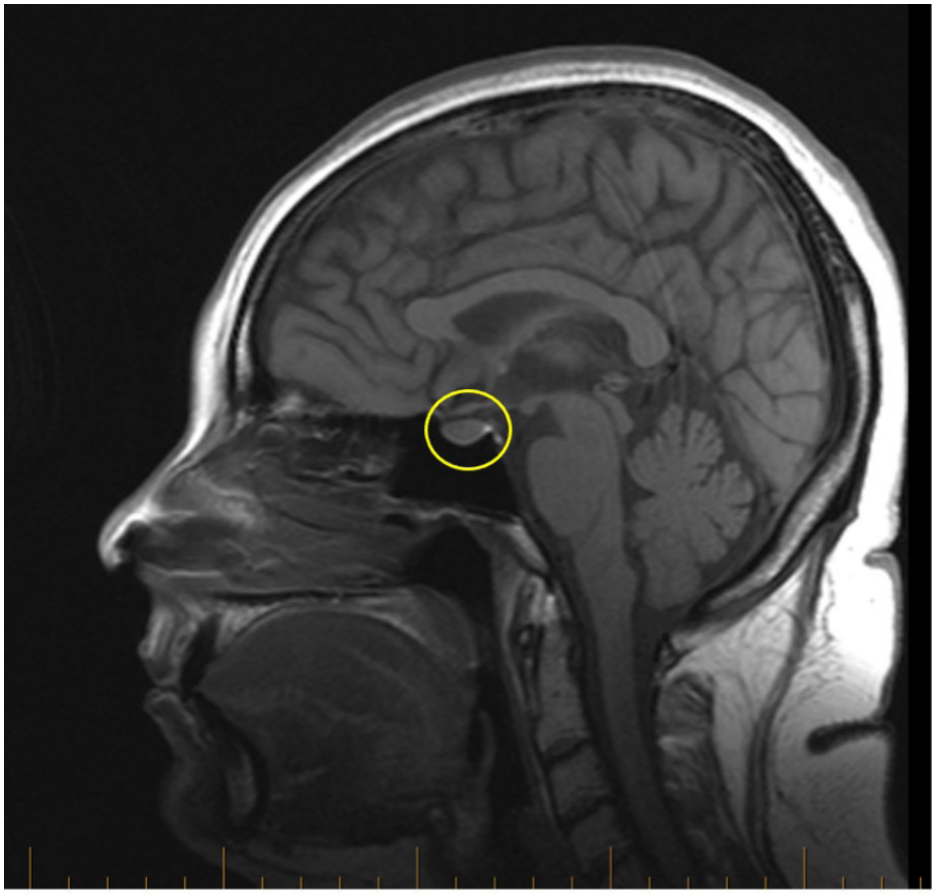

Figure 6. Magnetic resonance image (MRI) indicating a pituitary adenoma. The image shows a lesion of the right pituitary gland. Bright spot is the normal posterior pituitary. Image was obtained with the actual patient's consent.

Dr. Chow informed Eva and Dr. Warner that there was an ovoid, hypo-enhancing lesion measuring 1.1 × 1.0 × 0.6 cm on the right side of her pituitary gland. The presence of such a hypo-enhancing nodule was most consistent with a pituitary adenoma. Eva's MRI results and endocrine workup indicated that she had Cushing's disease (ACTH-dependent hypercortisolism). Dr. Chow explained that Cushing's disease is a condition that is typically diagnosed among adults between the ages of 20 and 50, and it is three times more likely to affect women than men. Due to its complex nature, Cushing's can be challenging to diagnose, and it is often overlooked in the early stages of its development.

Dr. Chow called Eva to his office to discuss her possible treatment options. He explained that her diagnosis of Cushing's disease could be treated with endoscopic endonasal transsphenoidal resection of the pituitary adenoma, so she decided to go through with that surgery.

Part V – Post Surgery

The surgery was a success and Eva underwent another MRI (Figure 7).

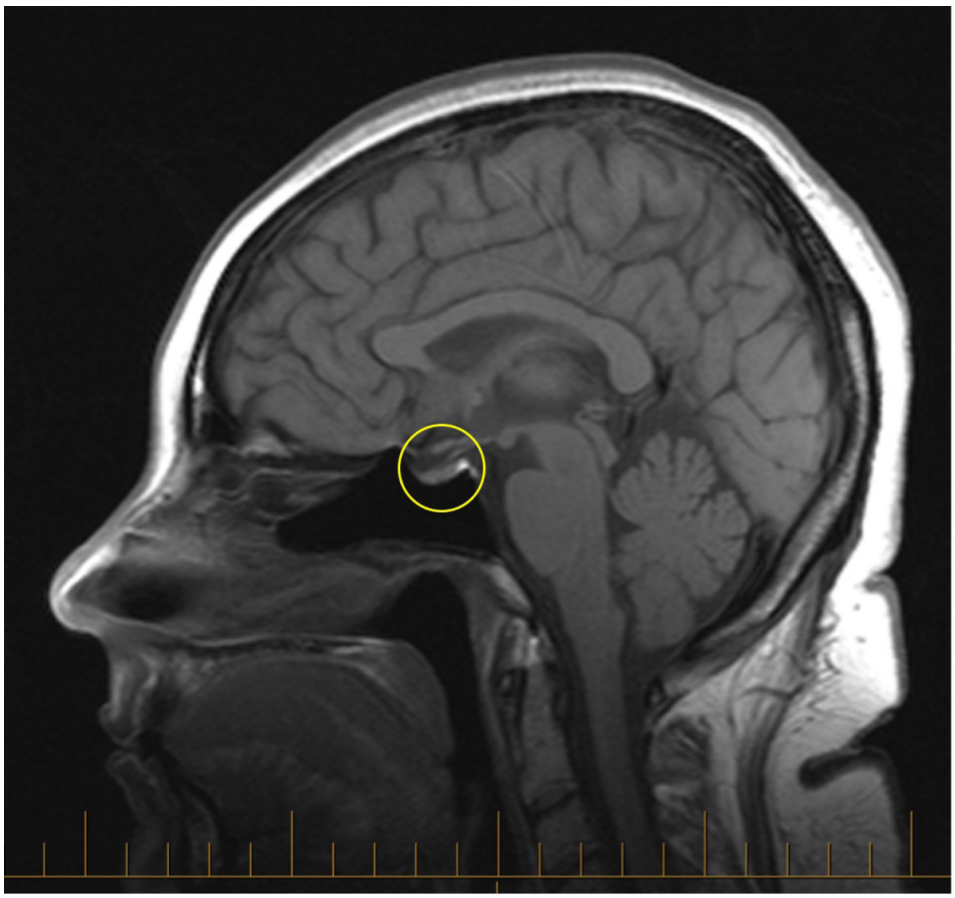

Figure 7. Magnetic resonance imaging following the removal of the pituitary adenoma. The image shows the right pituitary gland post-surgery. The rounded lesion previously observed on the right side of the pituitary gland is no longer visible, and the overall volume of the pituitary tissue appears normal. The bright spot is the normal posterior pituitary. This image was obtained with the actual patient's consent.

At Eva's post-operation appointment, Dr. Warner discussed with her that her cortisol levels were below the normal range. She informed Eva that recent research supports the use of steroid (cortisol) replacement therapy following the removal of an anterior pituitary tumor. To compensate for the lack of cortisol needed in her body, Dr.Warner prescribed oral hydrocortisone.

Eva wondered, "What will this steroid treatment entail? I've been on so many medications off and on for so long!"

Question

1. Hypothesize about possible reasons for Eva needing to take steroids after her tumor removal. What would happen if she didn't take steroids?

Conclusion

This case study is based on a true story. "Eva" has been on a journey of perseverance for over a decade, as she refused to give up on finding a diagnosis for her condition. She is grateful for the caring doctors she has met throughout her journey who have genuinely prioritized her health.

References

AJmonics. (2022). Dexamethasone suppression test: explained clearly! [Video]. Running time: 3:52 min. YouTube. <https://youtu.be/S0F42v2YOvM>

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Robertson-Dixon, I., M.J. Murphy, S.G. Crewther, & N. Riddell. (2023). The influence of light wavelength on human HPA axis rhythms: a systematic review. *Life* 13(10), 1968. <https://doi.org/10.3390/life13101968>

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ZRT Laboratory. (n.d.). Diurnal cortisol curves. [Webpage]. <https://www.zrtlab.com/landing-pages/diurnal-cortisol-curves/>