INTRODUCTION

Glucocorticoids are essential for survival. The term glucocorticoid refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, renal function, influence growth, development, bone metabolism, and central nervous system activity (**White 2003**).

There is evidence that inadequate exposure to glucocorticoid, such as with relative adrenal insufficiency, may be associated with hypotension, the development of bronchopulmonary dysplasia (**Watterberg et al 2000)** and death **(Scott and Cimino 2004)**. It is now known that normal development of the hypothalamic-pituitary-adrenal (HPA) axis is essential for regulation of intrauterine homeostasis, timely differentiation and maturation of vital organ systems, and may also influence the timing of parturition (**Ng 2000**).

One of the approaches to test the HPA axis is a measurement of its hormones and their subsequent targets together with the rapid ACTH stimulation test (**Vaedhara et al 2000, Jacobson 2005**).

Newborn infants may constitute a population uniquely vulnerable to relative adrenal insufficiency, as their HPA axis transitions from fetal to extrauterine function (**Fernandez et al 2008**).

There is scanty information regarding the normal reference values of cortisol and ACTH in Egyptian full term neonates.

AIM OF THE WORK

To establish reference ranges for serum cortisol and ACTH concentrations in full term, appropriate for gestational age, apparently healthy Egyptian neonates.

THE FETAL AND NEONATAL HYPOTHALAMIC–PITUITARY ADRENAL AXIS

For many years, the **pituitary gland** or **hypophysis** was called the "master" endocrine gland because it secretes several hormones that control other endocrine glands. The pituitary gland itself has a master the **hypothalamus.** This small region of the brain below the thalamus is the major link between the nervous and endocrine systems.Cells in the hypothalamus synthesize at least nine different hormones, and the pituitary gland secretes seven. Together, these hormones play important roles in the regulation of virtually all aspects of growth, development, metabolism, and homeostasis **(Tortora and Derrickson 2012**).

A general characteristic of fetal endocrine maturation across different species is the enhanced activity of the fetal hypothalamic–pituitary–adrenal (HPA) axis during late gestation. Precocious activation of this axis may occur when the fetus is exposed to an adverse intra-uterine environment, such as hypoxemia **(Challis et al., 2001).**

Steroid hormones produced by the Human Fetal Adrenal Cortex (HFA), along with progesterone produced by the placenta, play key roles in the maintenance of pregnancy, intrauterine homeostasis, fetal maturation, and the initiation of parturition. The fetal zone (FZ), a unique feature of fetal adrenals in primates, is a site of abundant production of the adrenal androgens DHEA/DHEAS, which serve as a source of C19 steroids for placental estrogen production (**Ishimoto and Jaffe 2011**).

DEVELOPMENT OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The pituitary gland, develops from two completely different parts: (1) an ectodermal outpocketing of the stomodeum (primitive oral cavity)immediately in front of oropharyngeal membrane, known as **Rathke`s pouch** and (2) a downward extension of the diencephalon, the **infundibulum (figure 1A) (Sadler 2012a)**.

When the embryo is approximately 3 weeks old, Rathke`s pouch appears as invagination of the oral cavity and subsequently grows dorsally toward the infundibulm. By the end of the second month, it loses its connection with the oral cavity and in then with close contact with the infundibulum **(Sadler 2012a)**.

During further development, cells in the anterior wall of the rathke`s pouch increase rapidly in number and form the **anterior lobe of the hpophysis**, or **adenohypophysis (figure 1B)**. A small extension of the lobe, the **pars tuberalis**, grows along the stalk of the infundibulum and eventually surrounds it **(figure 1C)**. The posterior wall of the rathke`s pouch develops into the **pars intermedia**, which in humans seems to have little significance **(Sadler 2012a)**.

The infundibulum gives rise to the stalk and the **pars nervosa**, or **posterior lobe of the hypophysis** (**neurohypophysis**) **(figure 1C)**.It is composed of neurological cells. In addition, it contains a number of nerve fibers from the hypothalamic area **(Sadler 2012a)**.

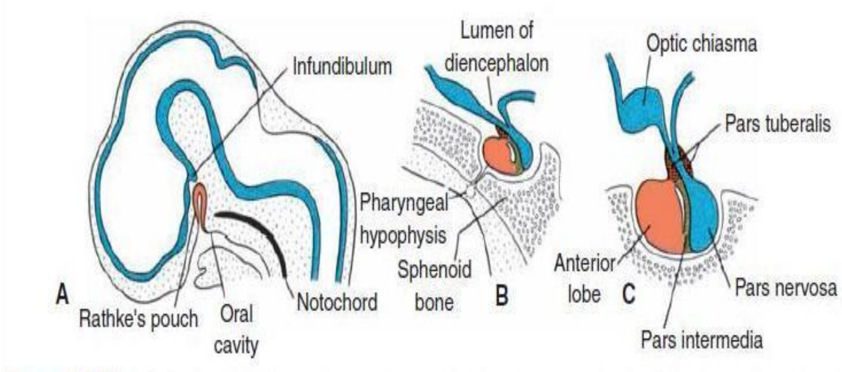


Figure (1A): Sagittal section through the cephalic part of 6-weeks emperyo showing rathke's pouch as adorsal outpocketing of the oral cavity and the infudibulum as thickening in the floor of the diencephalon.

Figure (1B, 1C): Sagittal section through the developing hypophysis in the 11th and 16th wk of development, respectively. Note formation of pars tuberalis encircling the stalk of the pars nervosa (Sadler 2012a).

<u>Suprarenal Gland:</u>

The suprarenal gland develops from two components:

(1) A mesodermal portion, which forms the **cortex,** and (2) an ectodermal portion, which forms the **medulla (Sadler 2012b).**

During the fifth week of development, mesothelial cells between the root of the mesentery and the developing gonad begin to proliferate and penetrate the underlying mesenchyme **(Figure 2)**. Here, they differentiate into large acidophilic organs, which form the **fetal cortex,** or **primitive cortex,** of the suprarenal gland **(Figure 3 A) (Sadler 2012b)**.

Shortly afterward, a second wave of cells from the mesothelium penetrates the mesenchyme and surrounds the original acidophilic cell mass.These cells, smaller than those of the first wave, later form the **definitive cortex** of the gland **(Figure 3 A, B) (Sadler 2012b)**.

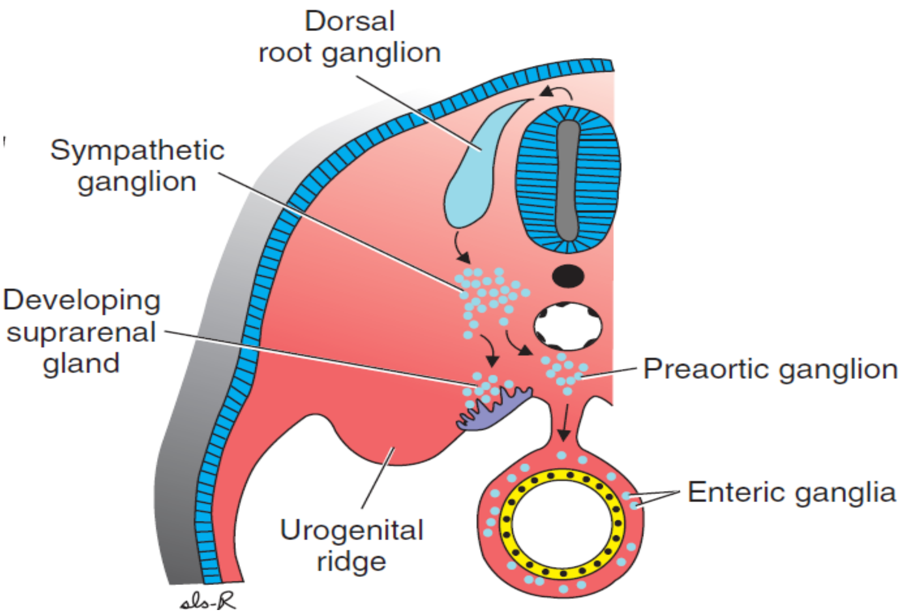


Figure (2): Formation of the sympathetic ganglia. A portion of the sympathetic neuroblasts migrates toward the proliferating mesothelium to form the medulla of the suprarenal gland **(Sadler 2012b)**.

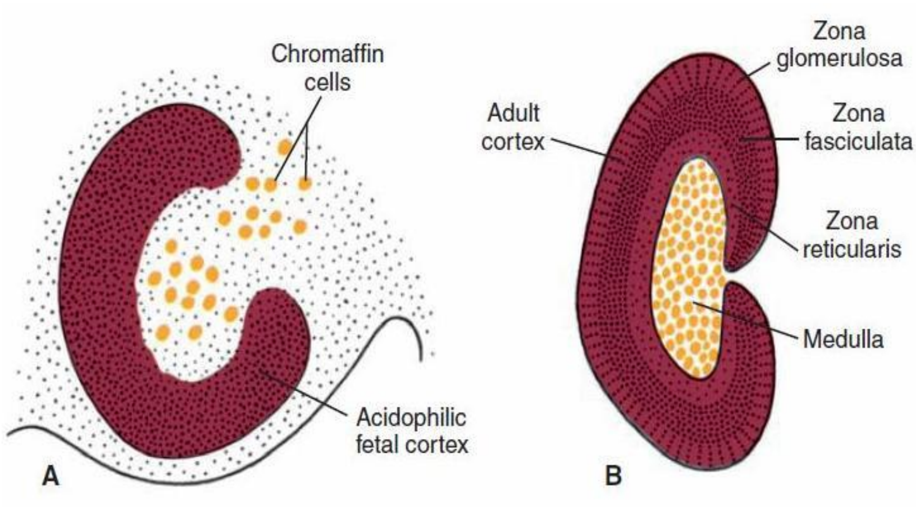
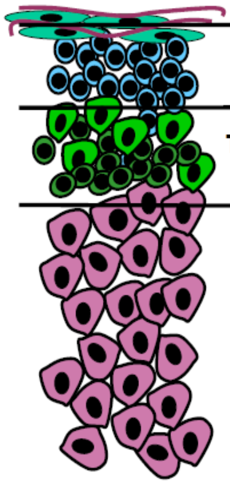


Figure (3A): Chromaffin (sympathetic) cells penetrating the fetal cortex of the suprarenal glands.

Figure (3B): later in the development, the definitive cortex surrounds the medulla almost completely **(Sadler 2012b).**

After the first trimester, the centrally located fetal zone accounts for most of the fetal adrenal mass and acts to provide steroid precursors that are used by the placenta to produce estrogens **(Figure 4) (Rainey et al 2004**).

The outer zone of the fetal adrenal is called the ‘‘definitive zone’’ or neocortex; this zone likely gives rise to the adult adrenal glomerulosa. A third zone called the ‘‘transitional zone’’ recently was identified using immunohistochemistry. It lies just between the neocortex and fetal zone and is believed to develop into the cortisol-producing zona fasciculata (**Suzuki et al 2000)**.



Fetal adrenal zones	Steroid products	Fetal functions
Definitive zone	Aldosterone	Initiated late in gestation to control mineral balance in the neonate
Transitional zone	Cortisol	Increases in late gestation to promote organ maturation and assist in timing of labor
Fetal zone	DHEA-S and Preg-S	Precursor for placental estrogen production. Late in gestation the increasing production of DHEA-S acts to influence the estrogen to progesterone ratio.

Figure (4): Human fetal adrenal functional zonation shown are the three putative fetal adrenal zones, which have been characterized based on immuno-histo-chemical analysis, with their primary steroid products and potential fetal functions (Rainey et al 2004).

DHEA-S: Dehydroepiandrosterone-sulfate.

Preg-S: Pregnenolonesulfate.

After birth, the fetal cortex regresses rapidly except for its outermost layer, which differentiates into the reticular zone. The adult structure of the cortex is not achieved until puberty **(Sadler 2012b)**.

BASIC ANATOMY & PHYSIOLOGY

Pituitary Gland and Its Relation to the Hypothalamus:

Pituitary Gland: Two Distinct Parts–The Anterior and Posterior Lobes. The ***pituitary gland*** **(Figure 5)**, also called the ***hypophysis,*** is a small gland about 1 centimeter in diameter and 0.5 to 1 gram in weight that lies in the ***sella turcica***, a bony cavity at the base of the brain, and is connected to the hypothalamus by the ***pituitary*** or ***(hypophysial*)** stalk. Physiologically, the pituitary gland is divisible into two distinct portions: the ***anterior pituitary***, also known as the ***adenohypophysis***, and the ***posterior pituitary***, also known as the ***neurohypophysis***. Between these is a small, relatively avascular zone called the ***pars intermedia***, which is almost absent in the human being but is much larger and much more functional in some lower animals **(Guyton and Hall 2006).**

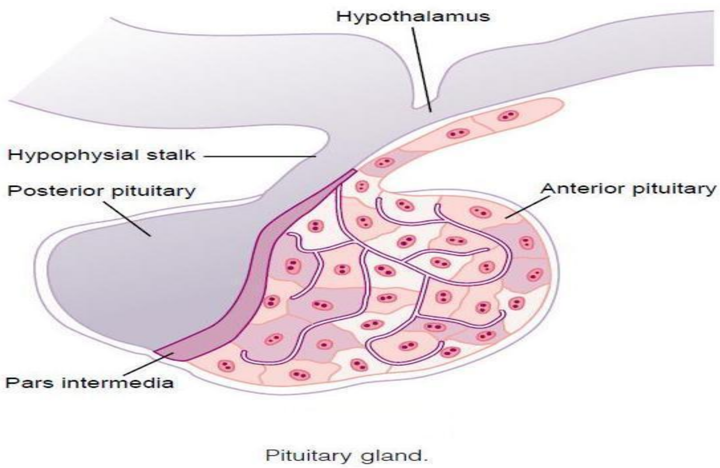


Figure (5): Relation between pituitary gland and hypothalamus **(Guyton and Hall, 2006).**

Six important peptide hormones plus several less important ones are secreted by the ***anterior*** pituitary, and two important peptide hormones are secreted by the ***posterior*** pituitary.The hormones of the anterior pituitary play major roles in the control of metabolic functions throughout the body, as shown in **(Figure 6) (Guyton and Hall, 2006)**.

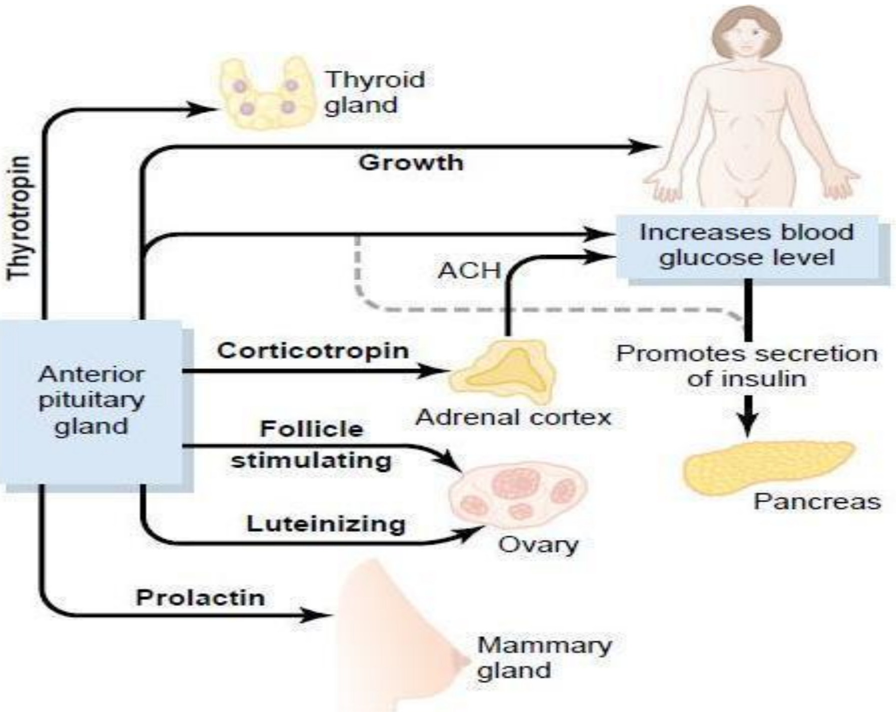


Figure (6): Metabolic functions of the anterior pituitary hormones. ACH, adrenal corticosteroid hormones ***(Guyton and Hall, 2006).***

Anterior Pituitary Gland Contains Several Different Cell Types That Synthesize and Secrete Hormones. Usually, there is one cell type for each major hormone formed in the anterior pituitary gland.

With special stains attached to high-affinity antibodies that bind with the distinctive hormones, at least five cell types can be differentiated **(figure 7) (table 1) (Guyton and Hall 2006)**.

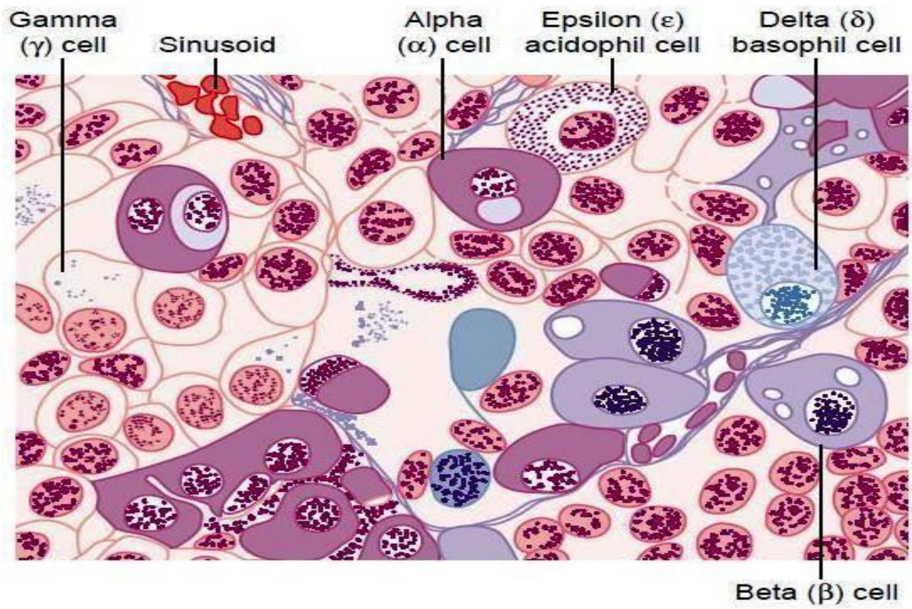


Figure (7): Cellular structure of the anterior pituitary gland **(Guyton and Hall 2006).**

Table (1): Cells and hormones of anterior pituitary and their physiological action **(Guyton and Hall 2006).**

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Actions
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

IGF, insulin-like growth factor

Adrenal glands:

The two ***adrenal glands***, each of which is a pyramidal structure approximately 4 g in weight, 2 cm wide, 5 cm long, and 1 cm thick lying immediately above the kidney on its posteromedial surface **(Stewart 2011)**, each gland is composed of two distinct parts, the ***adrenal medulla*** and the ***adrenal cortex*** **(Guyton and Hall 2006)**.

The adrenal medulla, the central 20 per cent of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones ***epinephrine*** and ***norepinephrine*** in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body **(Guyton and Hall 2006)**.

The Adrenal Cortex Has Three Distinct Layers, (figure 8) shows that the adrenal cortex is composed of three relatively distinct layers **(Guyton and Hall 2006)**.

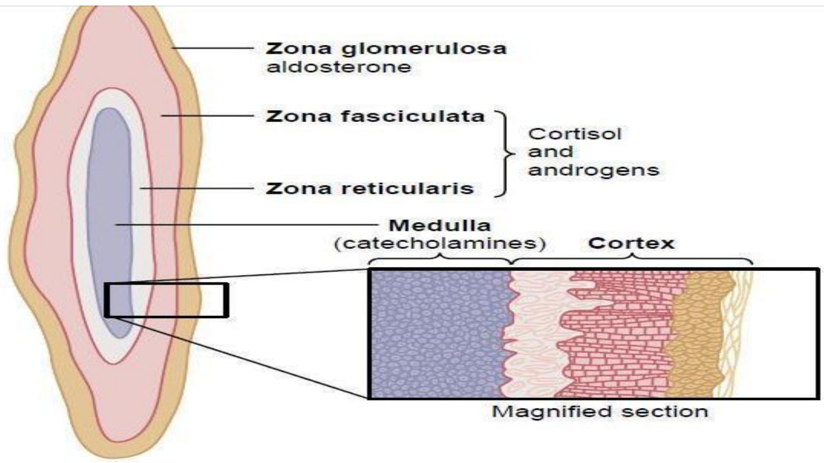


Figure (8): Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla **(Guyton and Hall 2006).**

1. Beneath the capsule, the zona glomerulosa constitutes approximately 15% of the cortex (depending upon sodium intake) **(figure 8)**. Cells are clustered in spherical nests and