Question 50
Which one of the following hormones shows the most consistent decline in blood levels (in both sexes) with ageing?

A. Cortisol
B. Adrenocorticotropic hormone (ACTH)
C. Thyrotropin
D. Dehydroepiandrosterone (DHEA)
E. Insulin

A. Cortisol

Cortisol is a corticosteroid hormone produced by the adrenal cortex that is involved in the response to stress; it increases blood pressure, blood sugar levels, may cause infertility in women, and suppresses the immune system. In pharmacology, cortisol is referred to as hydrocortisone, and is used to treat allergies and inflammation.

Diurnal variation
The amount of cortisol present in the serum undergoes diurnal variation, with the highest levels present in the early morning, and the lowest levels present around midnight, 3-5 hours after the onset of sleep. Information about the light/dark cycle is transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus. The pattern is not present at birth (estimates of when it starts vary from two weeks to 9 months.) Changed patterns of serum cortisol levels have been observed in connection with abnormal ACTH levels, clinical depression, psychological stress, and such physiological stressors as hypoglycemia, illness, fever, trauma, surgery, fear, pain, physical exertion or extremes of temperature.
There is also significant individual variation, although a given person tends to have consistent rhythms.

Effects
In normal release, cortisol (like other glucocorticoid agents) has widespread actions which help restore homeostasis after stress. (These normal endogenous functions are the basis for the physiological consequences of chronic stress - prolonged cortisol secretion.)
It acts as a physiological antagonist to insulin by promoting gluconeogenesis, breakdown of lipids (lipolysis), and proteins, and mobilization of extrahepatic amino acids and ketone bodies. This leads to increased blood glucose concentrations, resulting in increased glycogen formation in the liver. Prolonged cortisol secretion causes hyperglycemia.
It lowers the activity of the immune system in the blood. Cortisol prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to interleukin-1 (IL-1), and unable to produce the T-cell growth factor. It reflects leukocyte redistribution to lymph nodes, bone marrow, and skin. Acute administration of corticosterone (the endogenous Type I and Type II receptor agonist), or RU28362 (a specific Type II receptor agonist), to adrenalectomized animals induced changes in leukocyte distribution.
It lowers bone formation. Cortisol moves potassium into cells in exchange for an equal number of sodium ions. This can cause a major problem with the hyperkalemia of metabolic shock from surgery.
It helps to create memories when exposure is short-term; this is the proposed mechanism for storage of flash bulb memories. However, long-term exposure to cortisol results in damage to cells in the hippocampus. This damage results in impaired learning.
It increases blood pressure.
It inhibits the secretion of corticotropin-releasing hormone (CRH), resulting in feedback inhibition of ACTH secretion. Some researchers believe that this normal feedback system may break down when animals are exposed to chronic stress.
It increases the effectiveness of catecholamines.
In addition to the effects caused by cortisol binding to the glucocorticoid receptor, because of its molecular similarity to aldosterone, it also binds to the mineralocorticoid receptor. (It binds with less affinity to it than aldosterone does, but the concentration of blood cortisol is higher than that of blood aldosterone.)
Most serum cortisol, all but about 4%, is bound to proteins including corticosteroid binding globuin (CBG), and serum albumin. Only free cortisol is available to most receptors.

Disorders
- Cushings – increased cortisol
- Addisons – decreased cortisol
B. Adrenocorticotropic hormone (ACTH)

**Adrenocorticotropic hormone** (ACTH or corticotropin) is a polypeptide hormone produced and secreted by the pituitary gland. It is an important player in the hypothalamic-pituitary-adrenal axis. ACTH is synthesised from pro-opiomelanocortin (POMC) and secreted from corticotropes in the anterior lobe of the pituitary gland in response to the hormone corticotropin-releasing hormone (CRH) released by the hypothalamus. ACTH acts through the stimulation of cell surface ACTH receptors, which are primarily located on the adrenocortical cells. ACTH stimulates the cortex of the adrenal gland and boosts the synthesis of corticosteroids, mainly glucocorticoids but also mineralocorticoids and sex steroids (androgens).

ACTH is also related to the circadian rhythm in many organisms. The half-life of ACTH in human blood is about 10 minutes.

C. Thyrotropin

**Thyrotropin-stimulating hormone** (also known as TSH or thyrotropin) is a hormone synthesized and secreted by thyrotrpe cells in the anterior pituitary gland which regulates the endocrine function of the thyroid gland.

**Controlling the rate of release**

TSH stimulates the thyroid gland to secrete the hormones thyroxine (T4) and triiodothyronine (T3). TSH production is controlled by a Thyrotropin Releasing Hormone, (TRH), which is manufactured in the hypothalamus and transported to the Anterior Pituitary gland, where it increases TSH production and release. Somatostatin is also produced by the hypothalamus, and has an opposite effect on the pituitary production of TSH, decreasing or inhibiting its release.

The level of Thyroid hormones (T3 and T4) in the blood have an additional effect on the pituitary release of TSH. When the levels of T3 and T4 are low, the production of TSH is increased, and conversely, when levels of T3 and T4 are high, then TSH production is decreased. This effect creates a regulatory negative feedback loop.

**Subunits of TSH**

TSH is a glycoprotein and consists of two subunits, the alpha and the beta subunit.

The alpha subunit is identical to that of human chorionic gonadotropin (HCG), lutenising hormone (LH), follicle-stimulating hormone (FSH).

The β (beta) subunit is unique to TSH, and therefore determines its function.

**The TSH receptor**

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**Diagnostic use**

TSH levels are tested in the blood of patients suspected of suffering from excess (hyperthyroidism), or deficiency (hypothyroidism) of thyroid hormone. Generally, a normal range for TSH for adults is between 0.3 and 3.0 uIU/mL (equivalent to mIU/L), but the interpretation depends also on what the blood levels of thyroid hormones (T3 and T4) are. The National Health Service in the UK considers a "normal" range to be more like 0.1 to 5.0 uIU/mL.

TSH levels for children normally start out much higher. In 2002, the National Academy of Clinical Biochemistry (NACB) in the US recommended age-related reference limits starting from about 1.3-19 uIU/mL for normal term infants at birth, dropping to 0.6-10 uIU/mL at 10 weeks old, 0.4-7.0 uIU/mL at 14 months and gradually dropping to during childhood and puberty to adult levels, 0.4-4.0 uIU/mL The NACB also stated that it expected the normal (95%) range for adults to be reduced to 0.4-2.5 uIU/mL, because research had shown that adults with an initially measured TSH level of over 2.0 uIU/mL had "an increased odds ratio of developing hypothyroidism over the [following] 20 years, especially if thyroid antibodies were elevated".

D. Dehydroepiandrosterone (DHEA)

This is the correct answer – Levels of the adrenal sex steroid dehydroepiandrosterone (DHEA) and its sulfate ester fall progressively after 30 years of age, and after 60 years of age are less than half the levels in youth. Ref: Aging and Fountain of Youth Hormone Paul M Stewart M.D. NEJM 355; 16 pp 1724-1726 2006
DHEA is produced from cholesterol through two cytochrome P450 enzymes. Cholesterol is converted to pregnenolone by the enzyme P450 scc (side chain cleavage) and then another enzyme CYP17A1 converts pregnenolone to 17α-Hydroxypregnenolone and then to DHEA. In humans DHEA is the dominant steroid hormone and precursor of all sex steroids.

DHEA production is very high during fetal life by the fetal adrenal glands, declines after birth and remains low during childhood. Production begins around 6 years of age, increasing in quantity until peaking in early adulthood, around the age of 25, and declines afterwards to approximately 10% of peak levels by age 80. It is theorized by some that this decline may be due to reduced oxygen and glucose supply to the adrenal glands as a result of age-related atherosclerosis.

In a simple view DHEA can be understood as a prohormone for the sex steroids. Its DHEAS variation may be looked at as buffer and reservoir. Its production in the brain suggests that it also has a role as a neurosteroid. As most DHEA is produced by the zona reticularis of the adrenal, it is argued that there is a role in the immune and stress response. DHEA may have more biologic roles. As almost all DHEA is derived from the adrenal glands, blood measurements of DHEAS/DHEA are useful to detect excess adrenal activity as seen in adrenal cancer or hyperplasia, including certain forms of congenital adrenal hyperplasia. Women with polycystic ovary syndrome tend to have normal or mildly elevated levels of DHEAS.

E. Insulin

Insulin (from Latin insula, “island”, as it is produced in the Islets of Langerhans in the panceas) is a polypeptide hormone that regulates carbohydrate metabolism. Apart from being the primary agent in carbohydrate homeostasis, it has effects on fat metabolism and it changes the liver's activity in storing or releasing glucose and in processing blood lipids, and in other tissues such as fat and muscle. The amount of insulin in circulation has extremely widespread effects throughout the body.