Homework Assignment 13: Due at the beginning of class 3/18/02

In this homework assignment, your ultimate objectives in Questions 1-4 will be to:

- Find an antiderivative for a given function.
- Use the antiderivative to calculate the area under a curve.

In Question 5, you will compare the results of your calculations from Questions 1-4 to determine the effects of different substances, behaviors and medical conditions on the level of the hormone cortisol in the body.

If you are under a lot of pressure at the moment, skip to page 4 of this assignment. The last thing that we want is for this homework assignment to significantly raise your cortisol concentration.

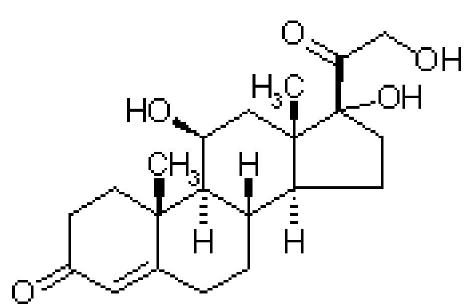

Figure 1: Molecular structure of cortisol.

Cortisol (see Figure 1[1]) is a glucocorticoid hormone that is naturally produced by the adrenal glands (see Figure 2[2]) in response to stress. Although undoubtedly real and regularly experienced by people in a complex, ever-changing world, the molecular and cellular events that cause us to feel "stressed" are only now being understood by researchers.

The biological term "stress" was introduced in the 1930's by Canadian endocrinologist Dr. Hans Seyle. Biological stress is usually conceptualized as a response to a disruption of the body's chemical and physical balance, *homeostasis*. The process by which the body adapts to regain its balance is called *allostasis*. The measures that the body has to take to return to its natural balance exert a toll called the *allostatic load*. Coping with the consequences of high levels of cortisol in the human body can be thought of as part of this allostatic load. The study of the response of a system as complex as a human body to disruptions of its natural balance is no easy task. Nevertheless, scientists believe that they are developing a reasonable understanding of the events that can trigger disruptions of homeostasis, and the tolls exerted by the allostatic load in some situations.

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[1] Image source: http://www.genome.ad.jp/kegg/catalog/cpd_steroid_hormone.html
[2] Image source: http://www.cnn.com/

The presence of cortisol in the body is almost always associated with some kind of biological stress (such as perception of a threat, consumption of a toxic substance or immediately after waking). The presence of cortisol in the body is so intimately associated with biological stress (in humans) that some physiologists define "stressful events" as those that result in an elevated level of cortisol in the body.

The production of cortisol by the body is not a simple one-step procedure - the biochemical reactions that take place in the human body in response to perceptions of physical or psychological threat are highly complex and only partially understood. The description of the biochemical pathway that is presented here should be regarded as a gross simplification[3] of the actual chemical and physiological changes that take place in the human body as a response to stressful stimuli.

When a normal human perceives a threat, a hormone called *corticotrophin-releasing hormone* (CRH) is released throughout the brain, and in very large quantities within a structure at the base of the brain called the *hypothalamus* (see Figure 3[4]). The CRH released by the hypothalamus travels to the nearby *pituitary gland* (see Figure 3) where it stimulates the release of *adrenocorticotrophin hormone* (ACTH).

Figure 2: Perceptions of threat trigger production of ACTH by the pituitary gland. ACTH triggers production of cortisol in the adrenal glands, which are located on top of the kidneys.

ACTH travels from the pituitary gland to the outer layers (cortex) of the adrenal glands (see Figure 4[5]) which are located on the kidneys. The presence of ACTH stimulates the kidneys to produce cortisol.

In a human being with a normally functioning endocrine system, the levels of cortisol are reduced to zero as soon as the threat is perceived to have passed. However, scientific studies have documented elevated levels of cortisol in humans who have taken certain substances (such as 3,4-methylenedioxymethamphetamine and alcohol) who engage in some types of competitive activity (such as long-distance running) and who are suffer from certain medical conditions (principally Cushing's Disease – see Question 3).

Although cortisol is a hormone that is naturally produced by the human body, prolonged exposure to high levels of cortisol have been linked to a number of mental and physical problems. These include:

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[3] This description is adapted from articles available from: http://wwwnlm.nih.gov/medlineplus/

[4] Image source: http://www.humboldt.edu/

[5] Image source: http://lancelot.bms.ac.edu/

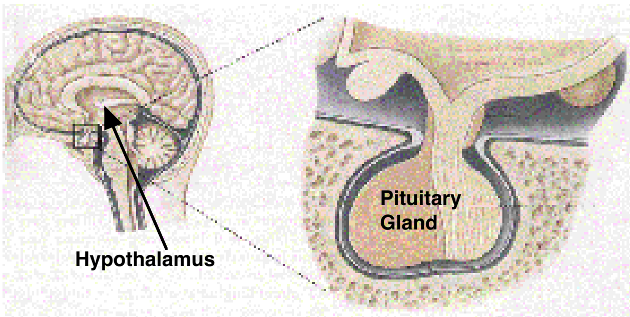

Figure 3: Location of hypothalamus and pituitary gland in human brain.

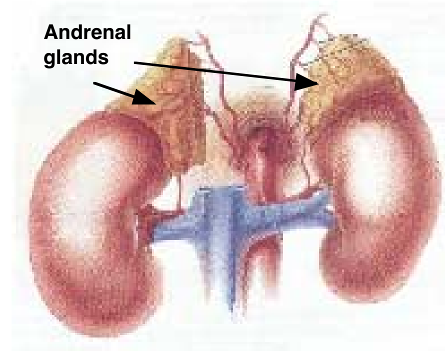

Figure 4: Location of the adrenal glands on top of the kidneys.

- Possible permanent damage to the hippocampal formation in the brain[6]. (A number of animal studies[7] have suggested that the hippocampal formation is important in regulating the production of cortisol. If the hippocampus is damaged, then the capacity of the body to regulate subsequent cortisol production may also be impaired.)
- Impairment of memory and learning ability[8].
- Mood alteration[9].
- Depression[10] and other psychiatric and neurological disorders[11].
- Psychosomatic disorders (such as chronic fatigue syndrome)[12].
- Immune system suppression[13].
- Obesity (in men)[14].

Clearly, any habit or activity that produces elevated levels of cortisol in the body for prolonged periods of time has some potential to create serious health (mental and physical), psychological and social problems for the person engaging in the behavior.

In this homework assignment, you will use antiderivatives and integrals to calculate the amount of cortisol produced by the body under various circumstances and evaluate the health risks involved with each of the situations described.

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[6] Source: L. R. Ember. (1998) "Surviving stress." *Chemical and Engineering News*, **76**(21): 1-13.

[7] For example, see: R. F. McGiven, P. Rittenhouse, F. Aird, L.D. Van der Kar and E. Redei. (1997) "Inhibition of stress-induced neuroendocrine and behavioral responses in the rat by prepo-thryrotropin releasing hormone 178-199." *Journal of Neuroscience*, **17**(12): 4886-4894.

[8] Source: J.W. Newcomer, G. Selke, A.K. Melson, T. Hershey, S. Craft, K. Richards and A.L. Alderson. (1999) "Decreased memory performance in healthy humans induced by stress-level cortisol treatment." *Archives of General Psychiatry*, **56**(6):527-533.

[9] Source: J. Smyth, M.C. Okenfels, L. Porter, C. Kirschbaum, D.H. Hellhammer and A.A. Stone. (1998) "Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion." *Psychoneuroendocrinology*, **23**(4): 353-370.

[10] Source: B.J. Carroll, G.C. Curtis and j. Mendels. (1976) "Neuroendocrine regulation in depression." *Archives of General Psychiatry*, **33**(11): 1039-1044.

[11] Source: F. Holsboer, A. Grasser, E. Friess and K. Wiedemann. (1994) "Steroid effects on central neurons and implications for psychiatric and neurological disorders." *Annals of the New York Academy of Sciences*, **746:** 345-359.

[12] Source: J.C. Pruenessner, D.H. Hellhammer and C. Kirschbaum. (1999) "Brunout, perceived stress, and cortisol responses to awakening." *Psychosomatic Medicine*, **61**: 197-204.

[13] Source: R. Glaser, B. Rabin, M. Chesney, S. Cohen and B. Natelson. (1999) "Stress-induced immunomodulation. Implications for infectious diseases." *Journal of the American Medical Association*, **281**(24): 2268-2270.

[14] Source: R. Rosmond, M.F. Dallman, P. Bjorntorp. (1998) "Stress-related cortisol secretion in men: Relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities." *Journal of Clinical Endocrinology and Metabolism*, **83**(6): 1853-1859.

IMPORTANT TERMS AND ABBREVIATIONS

The **concentration** of cortisol is the concentration of this hormone that was found in a blood sample collected from a test subject. The units are micrograms per deciliter, μg/dl (equivalent to micrograms per 100 ml).

The **total concentration** of cortisol is the area beneath the cortisol concentration curve. The units are microgram-hours per deciliter.

1. Figure 7[15] shows the cortisol produced in a person's body during the twenty-four hour period immediately after they had competed in a marathon.

Let T represent the number of hours since the end of the marathon and $m(T)$ the concentration of cortisol in micrograms per deciliter (μg/dl).

The graph shown in Figure 7 is quite well approximated by the function:

$$m(T) = \frac{460}{T+4}$$

- Find and antiderivative for $m(T)$.
- Use the antiderivative to find the total cortisol concentration (area under curve) for the twenty four hour period following the marathon.

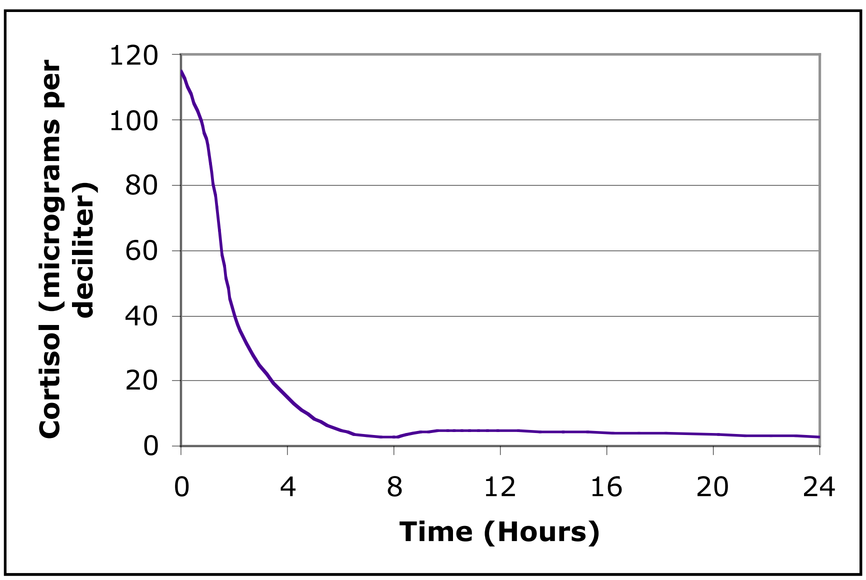

Figure 7: Cortisol levels for an athlete during the 24 hour period immediately after running a marathon.

[15] The source of the data presented in Figure 7 is: : http://www.ibl-hamburg.com/

Figure 5: Samples of MDMA tablets.

2. Figure 6[16] shows the cortisol produced in the body of a person who has taken a single 125 mg of the drug 3,4-Methylenedioxymethamphetamine (better known by its abbreviation of "MDMA" or its street name of "ecstasy" – see Figure 5[17]). When the drug is taken, the body begins to produce cortisol. This cortisol is produced in addition to any cortisol that the body produces naturally. The levels of cortisol peak approximately three hours after the drug is taken and return to normal approximately six hours after the drug is taken.

Let T represent the number of hours since the MDMA was administered to the subject and $m(T)$ the concentration of cortisol in micrograms per deciliter (μg/dl).

The graph shown in Figure 6 is quite well approximated by the function:

$$m(T) = 0.3693 \cdot T^4 - 4.0963 \cdot T^3 + 11.63338 \cdot T^2 - 1.4216 \cdot T - 0.0837$$

- Find and antiderivative for $m(T)$.
- Use the antiderivative to find the total cortisol concentration (area under curve) that a person would experience during the six hours immediately after ingesting one 125 mg dose of MDMA.

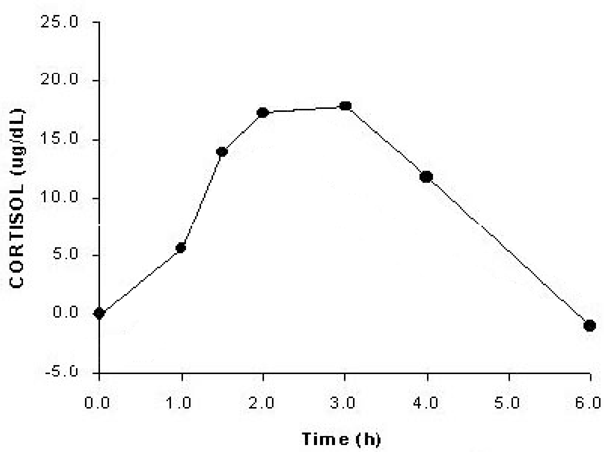

Figure 6: Cortisol concentrations from a subject who was given a 125 mg dose of MDMA.

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[16] This data is taken from: M. Parre, G. Hernandez-Lopez, R. Torre, P.H. Roset, M. Mas, J. Ortuno, E. Menoyo, H. Pizarro, J. Segura and J. Cami. (2000) "Pharmacokinetic and pharmacological effects of MDMA in humans." *Proceedings of the 6th Internet World Congress for Biomedical Sciences.* (February 14-24, Cindad Real, Spain).

[17] Image source: http://www.ecstasyaddiction.com/

Figure 8: Adult patient with Cushing's disease. Note the many bandages indicating that the patient's skin is easily damaged and takes a long time to heal.

3. Figure 8[18] shows a picture of a person suffering from Cushing's disease. Despite the fact that the person pictured appears to be a child, this is actually an adult patient. Cushing's disease is a relatively rare condition affecting perhaps 10 or 15 out of every million Americans. The symptoms of the disease include upper body obesity, an extremely rounded face, deposits of fat around the neck, an underdevelopment of lower body muscles, weakened bones, very fragile skin that bruises extremely easily and lengthened wound healing time. The condition results from an overproduction of cortisol by the adrenal glands. Figure 9[19] shows the cortisol produced by a person with Cushing's disease over a 24 hour period.

Let T represent the hour of the day and $m(T)$ the cortisol (in units of micrograms per deciliter, μg/dl).

The graph in Figure 9 is reasonably well approximated by the function:

$$m(T) = 48.2699 \cdot (0.9452690908)^T$$

- Find and antiderivative for $m(T)$.
- Use the antiderivative to find the total cortisol concentration (area under curve) for a person suffering from Cushing's disease over the course of 24 hours.

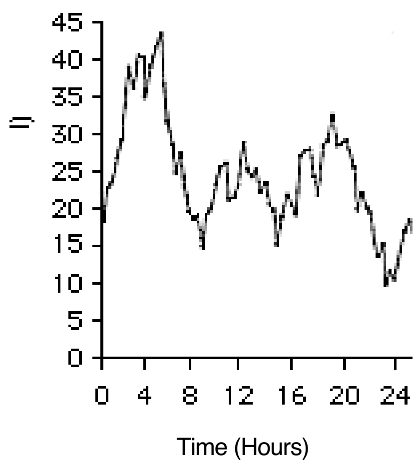

Figure 9: Cortisol production for a person with Cushing's disease over a 24 hour time period.

[18] Image source: http://mountzion.ucsfmedicalcenter.org/

[19] Image source: http://www.uptodate.com/patient_info/topicpages/pictures/episodic.gif

4. Figure 10[20] shows the cortisol graph for a healthy in a relatively stress-free environment. (During hours 18-24 the cortisol levels in the subject s were essentially zero.) In Figure 10, the dots represent data points collected from a group of 21 subjects, and the curve is the average of these readings.

Let T represent the hour of the day and $m(T)$ represent the cortisol in the patient (in units of micrograms per deciliter, μg/dl).

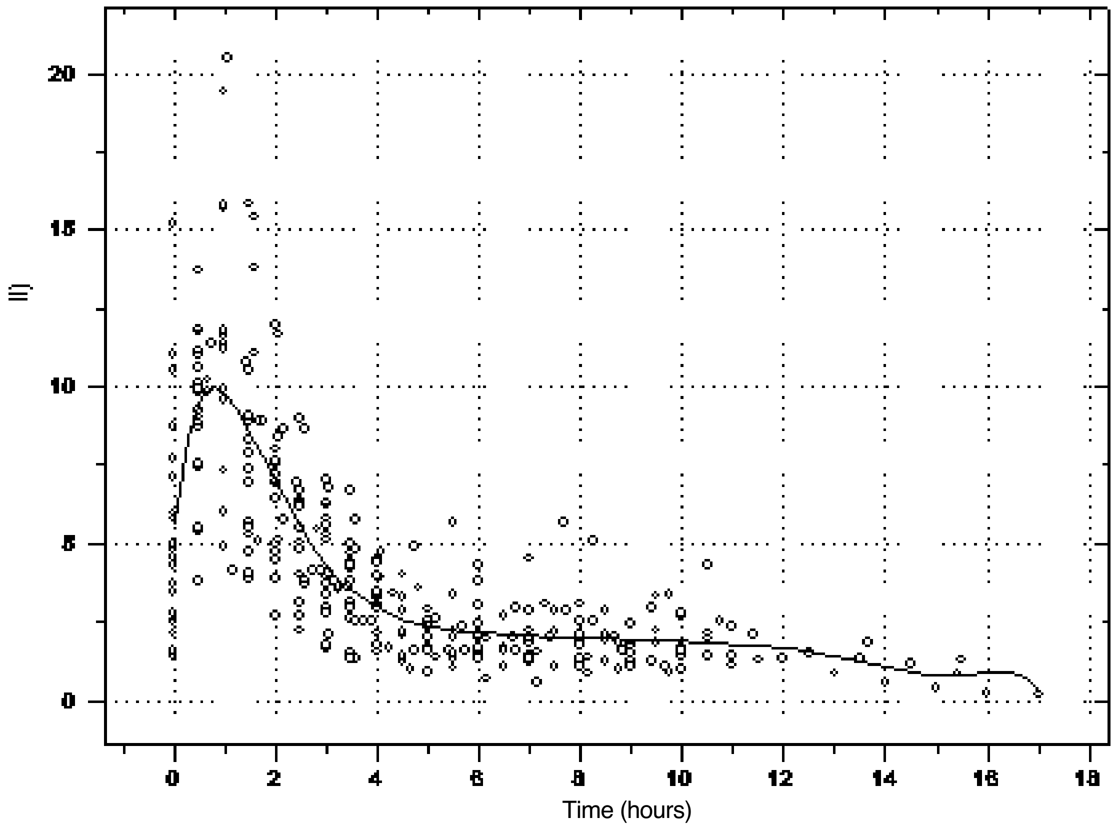

Figure 10: Cortisol production for a healthy adult in a reasonably stress-free environment.

The graph in Figure 10 is reasonably well represented by the function:

$$m(T) = -0.00071 \cdot T^4 + 0.02317 \cdot T^3 - 0.1939 \cdot T^2 - 0.3213 \cdot T + 7.7849$$

- Find and antiderivative for $m(T)$.
- Use the antiderivative to find the total cortisol concentration (area under curve) for a healthy adult during the eighteen hours of the day when they have non-zero levels of cortisol in their body.

[20] Source: http://www.ibl-hamburg.com/pics/cortis1.gif

5. Compare the total cortison concentrations (area under curve) that you obtained in Questions 1, 2 and 3 to the total cortisol concentration (area under curve) that you obtained in Question 4. Use your answers to explain why the observations offered below might have some scientific basis.

- According to DEA statistics[21], employees who test positive for drugs use consume almost twice the medical benefits of employees who do not test positive for drugs.
- According to a survey[22] of 2311 runners who competed in the Los Angeles marathon, one in seven got a cold within two weeks of competing. About one person in 35 gets a cold every two weeks in the population as a whole.
- A common symptom of Cushing's disease is lack of resistance to common diseases that rarely trouble the population at large.

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[21] Source: http://www.usdoj.gov/dea/concern/use.htm

[22] Source: D. Nieman. *The Exercise-Health Connection*. Champaign, IL: Human Kinetics Publishers, 1997.