General Instructions: READ THIS PAGE BEFORE YOU BEGIN THE EXAM.

1. Write your name and PID on all 6 pages. (5 points off for EACH unnamed page.)

2. For your own benefit, write your answers LEGIBLY in the space allotted. If we cannot read your handwriting, we cannot give you credit for your answer.

3. Do not write on the BACK of any page unless you get a TA’s permission FIRST.

4. About writing answers:
   • All questions can be answered briefly.
   • Answer the question that is asked specifically, precisely, and accurately.
   • For full credit, show your calculations when requested.
   • Problems that ask for an answer and for a reason, more credit will be given for a correct reason.
   • If you are asked for one reason, be sure you write down only the best one.

5. About grading:
   • We give credit for correct and relevant answers. We ignore true, but irrelevant statements.
   • We deduct points for statements that are both incorrect and irrelevant. (We don’t just ignore irrelevant answers because we need to let you know that you have some wrong ideas.)

6. Use a pen or pencil to write your answers, but do not use red ink or red pencil, and do not use white-out of any kind. If you want to have your exam regraded, you must use pen.

POTENTIALLY USEFUL EQUATIONS:

\[ \pi = \sigma RT(C_o-C_i) \]
\[ F = A\eta \frac{\Delta V}{\Delta X} \]
\[ R = \frac{8 \eta l}{\pi r^4} \]
\[ Q = \frac{(P_2-P_1)\pi r^4}{8 \eta l} \]
\[ V = IR \]
\[ P = QR \]
\[ J = -PS(C_{out}-C_{in}) \]
\[ R_{Total} = \Sigma R_i \]
\[ A = \pi r^2 \]
\[ J = k[(P_{cap}+\pi_{int})-(P_{int}+\pi_{cap})] \]
\[ R_{Total} = \Sigma \frac{1}{R_i} \]
\[ v = \frac{Q}{A} \]

TOTAL ___________

SCORE:

Page 2 ________
Page 3 ________
Page 4 ________
Page 5 ________
Page 6 ________

WAIVER: By signing this waiver I give permission that this exam can be left for me to pick up in the hall outside the elevators on the third floor of Pacific Hall. I realize that this procedure may expose my grade to public scrutiny and my exam to theft. If I do not sign this waiver, I understand I will be able to get my graded exam back only as described on the course Web site.

______________________________________________________________
Signature          Date
1. (18 points total) The concentration of Ca\(^{++}\) in our plasma is regulated primarily by two hormones: calcitonin, a peptide produced by C-cells in the thyroid gland, and parathyroid hormone (PTH), a peptide produced by the parathyroid glands. PTH increases plasma Ca\(^{++}\) levels by causing the release of Ca\(^{++}\) from bones, and calcitonin decreases plasma Ca\(^{++}\) levels by causing Ca\(^{++}\) to be deposited in bones. Low plasma Ca\(^{++}\) acts on parathyroid cells to cause the release of PTH, whereas high plasma Ca\(^{++}\) acts on C-cells to release calcitonin. The boxes below show the organs.

A. (6 points) Draw the missing arrows (and boxes, if needed) to show how plasma Ca\(^{++}\) is regulated, labeling the arrows appropriately and adding + or – signs to show the effects of the signals.

B. (4 points) How many feedback loops are in this system? Briefly explain whether each loop is positive or negative feedback.

There are two feedback loops. Both are negative feedback because each contains just one negative sign.

C. (4 points) Osteoporosis is a disease in which the amount of Ca\(^{++}\) in bones is diminished. Which of the two hormones, PTH or calcitonin, would be a good treatment for osteoporosis? Briefly explain.

Calcitonin causes Ca\(^{++}\) to be deposited in bone, so it would help to build up bone Ca\(^{++}\) (and would, therefore, strengthen the bone).

D. (4 points) If you receive an injection of PTH, would you expect to see an increase in plasma Ca\(^{++}\) levels within seconds, minutes, or hours? Briefly explain your answer.

Minutes, because it is a peptide hormone, so it is likely to bind to a surface receptor and activate second-messenger systems within the target cells. Such processes take minutes to produce an effect.

2. (6 points total) The uterus normally consists of multi-unit smooth muscles, but in the final stages of pregnancy, the uterine muscles become unitary.

A. (3 points) What is the major difference between multi-unit and unitary smooth muscle?

Unitary smooth muscle cells are strongly coupled, by gap junctions, to neighboring cells whereas multi-unit smooth muscle cells are not interconnected at all.

B. (3 points) Explain the functional significance of this switch-over from multi-unit to unitary smooth muscle in the uterus.

By being coupled, all the muscle fibers would contract at the same time, strengthening the contractions and help to push the baby out of the uterus, to be born.
3. (9 points total). A maverick drug company, Bioloonix, Inc., decided to develop a line of drugs that would increase the strength of skeletal muscles that they could sell to weight-lifters. They discovered three drugs that affected different molecules in these muscles. These drugs are listed below, along with their molecular effects. Tell whether each drug would increase the strength of muscle contractions, and briefly explain your answer.

A. (3 points) Bulkup (a total blocker of DHP activity)

This would block the release of Ca\(^{++}\) from the sarcoplasmic reticulum, so that it could not activate the actin-myosin interactions that cause contractions. Therefore, Bulkup would diminish (or even block) muscle contraction strength.

B. (3 points) Califtin (a partial blocker of the Ca\(^{++}\)-ATPase of the sarcolasmic reticulum)

This ATPase removes the Ca\(^{++}\) from the cytoplasm (myoplasm), which causes relaxation. By slowing the relaxation, the muscle fibers would stay active longer, so that the contractions would summate and the total contraction would be stronger. Califtin might appeal to the weight-lifters [although it might cause cramping if the dose was too high].

C. (3 points) Pressix (a partial activator of RyR, making it leaky at rest)

If the RyR was leaking Ca\(^{++}\) at rest, contractions would be stronger, because the strength of a contraction depends on the amount of Ca\(^{++}\) around the actin and myosin and the amount released during a contraction would add to the amount present before the contraction started. [Downside of Pressix: a lot of energy expended by the Ca\(^{++}\) ATPase, even at rest, so the muscles might get tired sooner.]

4. (10 points total) There is a class of heart diseases that are caused by genetic malformation of the voltage-gated K\(^{+}\) channels in the contractile muscle fibers. These channels open abnormally slowly.

A. (4 points) Using words or diagrams, indicate what effect would these mutations have on the action potentials in these cardiac fibers.

The action potentials would have a prolonged plateau phase, because these malformed voltage-gated K\(^{+}\) channels are responsible for turning off the depolarization in these muscle fibers and they would turn off more slowly.

B. (4 points) Using words or diagrams, indicate what effect would these mutations have on the ECG.

The time between the QRS complex and the T wave would be longer, because the QRS complex is caused by the depolarization of the ventricular muscle fibers and the T wave is caused by the re-polarization of these fibers. Because the plateau potential is longer, the T wave is delayed. [For your information: these clinical cases are called “The Long Q-T Syndrome.”]

C. (2 points) These diseases can cause ventricular fibrillation in “flight, fight, or fright” responses.

Propose a mechanism for how these mutations might lead to fibrillation during such responses.

The actual mechanism is not known, but the prolonged action potentials mean that they cannot keep up with the increased rate of action potential production in the SA node fibers (which are not affected by the mutations), so the ventricular muscle fibers must start firing out of synchrony with the SA node, and with other muscle fibers, to produce the fibrillation.
5. (10 points) Dexter, a friend of yours, moved to Denver (the “Mile-High City”). You saw Dexter six months later and he told you about his cardiovascular problems from living at the high altitude. His blood pressure has increased, and his hematocrit has increased so much that the viscosity of his blood has doubled. He has decided to take a drug that causes vasodilation, to lower his blood pressure. He remembered that viscosity and blood vessel diameter have opposite effects on blood pressure, so he has decided to take enough of this drug to double the diameters of his blood vessels. Use the appropriate equation to explain whether Dexter’s plan is a good one.

Dexter got the general relationship right, but he got the numbers all wrong. According to the equation:

\[ Q = \frac{(P_2 - P_1) \pi r^4}{8 \eta l} \]

if he doubles the diameters of his blood vessels, he would double the radius and the increase in blood flow would be increased by \(2^4\), or \(16\). Since the doubling of his blood viscosity (\(\eta\) in the equation) produced only a \(2\)X reduction of the flow, the 16-fold increase from vasodilation would result in a total increase in flow of \(8\). [In fact, the blood pressure control mechanism could not keep up with such a large increase in vasodilation, so his blood pressure would get dangerously low.] Not a good idea, Dexter!

6. (8 points) Each skeletal muscle generates maximal force when it starts its contraction at its rest length, but the maximal force generated by a cardiac muscle is at a longer length (about 1.4X of the rest length). Explain the functional significance of these two observations.

A. (4 points) Skeletal muscle (maximal force at rest length):

By being held near the peak of their length-tension curves at rest, skeletal muscles produce nearly maximal contractile force over most of their physiological range of motion. This is an efficient way to get maximal force from the muscle.

B. (4 points) Cardiac muscle (maximal force at 1.4X rest length):

By being on the upward slope of the length-tension curve under normal resting conditions, heart muscle can exert increased or decreased force in response to changes in venous return (a relationship described by the Starling Law of the Heart). This functions to adjust the cardiac output quickly, on a cycle-by-cycle basis.
7. **(10 points)** People with right heart failure have (1) high blood pressure, as measured in the upper arm, and (2) edema, especially in their legs.
   
   **A. (4 points)** Why do such people have high blood pressure?
   
   Because the stroke volume of the right ventricle is reduced, its stroke volume decreases and the blood builds up in the systemic veins, a build-up that spreads into the systemic capillaries and arteries. This produces an increase in the pressures in all the blood vessels in the systemic system, so the blood pressure measured in the arm is higher. [The blood pressure in the pulmonary vessels is actually lower, because the right ventricle contractions are weak.]
   
   **B. (4 points)** Using the Starling Equation *(aka Starling Hypothesis)*, explain why they have edema.
   
   The increased systemic blood pressure means that the pressure throughout the capillaries is higher; initially, the pressure in the interstitial fluid is essentially 0, so by the equation:
   
   \[ J = k[(P_{cap} + \pi_{int}) - (P_{int} + \pi_{cap})] \]
   
   the balance is in favor of outflow of fluid through the whole capillary (i.e., \( P_{cap} \) is larger than \( \pi_{cap} \) along a greater extent of the capillary).
   
   **C. (2 points)** Why is the edema worse in their legs than in their arms?
   
   The hydrostatic pressure of the fluid in blood vessels adds to the pressure of the fluid at lower levels (that's what "hydrostatic pressure" means). While they are standing, their legs have the highest pressure, so the pressure gradient across the capillaries is higher than in any other part of the body, so the edema is worse in the legs than in any other body part, including the arms.

8. **(12 points total)** You decide to do some Pilates exercises. Before you start, you sit down quietly and measure your heart rate (HR) and blood pressure (BP) in your upper arm, at heart level. Both are normal (BP = 120/70, PR = 70).

   **A. (4 points)** You lie on your back on your Pilates mat. Do you expect there to be any changes in BP and HR compared to when you were sitting up? Briefly explain your answer.
   
   Lying down changes the hydrostatic pressures throughout the body: the pressure in the lower body decreases and the pressure in the upper body (where the carotid baroreceptors are located) increases. This increased pressure increases baroreceptors activity, which decreases the sympathetic activity and increases the parasympathetic activity onto the heart, so the HR decreases. This would lower the BP, to a level near the value in the head while sitting up, because the arm is now at the same level as the baroreceptors.
   
   [Partial credit for trying to explain everything on the basis of the Starling Law.]

   **B. (4 points)** You decide to start your session with leg exercises, so you raise your legs to a vertical position, straight up. Would this change your BP and HR? Briefly explain your answer.
   
   Raising the legs increases the hydrostatic pressure at the baroreceptors, so their activity increases, lowering the sympathetic activity and raising the parasympathetic activity, causing a decrease in HR. If this compensation were perfect, the BP would remain the same because the arm is at the level of the baroreceptors and the decreased HR would
compensate for the increased hydrostatic pressure. In reality, the compensation is never complete, so the BP would go up a small amount.

**C. (4 points)** You start to pump your legs as though you are riding a bicycle. After 60 seconds of this exercise, do you expect additional changes in BP and HR? Briefly explain your answer.

The exercise would generate "local factors" (e.g., CO₂) that would open capillaries in the legs, which would lower the total peripheral resistance, and thereby lower the BP. This would decrease the baroreceptor activity, which would increase sympathetic activity and decrease parasympathetic activity, which would increase the HR.

[In fact, there are additional mechanisms that increase HR in exercise (e.g., there are chemoreceptors that measure CO₂ levels, and there are psychological factors), which would increase the HR and BP. Mentioning these would be fine, but are not required to answer this question because they were not mentioned in lectures or readings.]
9. (5 points) Digitalis is an extract from the foxglove plant that inhibits the Na\(^+\)-K\(^+\) ATPase. In low doses, it is an effective medication for people with weak hearts because of its inotropic effect. Explain how blocking the Na\(^+\)-K\(^+\) ATPase in cardiac muscles can have an inotropic effect.

Although much of the relaxation of cardiac muscle is caused by Ca\(^{++}\) being pumped back into the sarcoplasmic reticulum, a significant percentage of Ca\(^{++}\) is removed from the cytoplasm in exchange for Na\(^+\), by the Na\(^+\)-Ca\(^{++}\) exchanger (Silverthorn calls it the NCX).

Poisoning the Na\(^+\)-K\(^+\) ATPase with digitalis increases the [Na\(^+\)] in the cytoplasm of the cardiac muscle fibers, which lowers the Na\(^+\) gradient across the membrane. This diminished Na\(^+\) gradient provides less drive to the exchanger, so the fibers remove Ca\(^{++}\) more slowly. As a result, the time of increased Ca\(^{++}\) in the muscle fibers is prolonged, increasing the contraction strength of the muscles.

10. (12 points total) For the following three groups of statements, circle every letter that makes a TRUE statement. Note that any number of statements may be true (including none of them), and that not circling a letter indicates that you think that the statement is false. You will receive one point for each correct answer that is circled and each incorrect answer that is not circled. [Note: If any part of the statement is incorrect, the statement is false.]

A. Bones and muscles around joints act as levers and fulcrums:
   a. in most joints, the fulcrum is at one end of the lever, the load is at the other end of the lever, and the muscle is attached between the fulcrum and the load.
   b. the closer the muscle attaches to the fulcrum, the faster the speed of the movement and the less work required of the muscle.
   c. genetic variability in the attachment site of the muscle along the bone affects the force required to move or resist a load.
   d. over a large range, the speed of muscle contraction is independent of the load on the muscle.
   (a,c) (pp. 428-31 in Silverthorn, 5th edition)

B. The contraction of vascular smooth muscle can result from many local factors:
   a. increases in blood pressure stretches vascular smooth muscle cells, which open mechanically-gated Ca\(^{++}\) channels that causes the smooth muscles to contract.
   b. paracrines (including the gases O\(_2\), CO\(_2\), and NO) produced by the vascular epithelialial cells, can cause vasoconstriction and vasodilation.
   c. an increase in tissue blood flow following a period of low blood perfusion to an area is known as active hyperemia.
   d. serotonin, released from platelets from damaged blood vessels causes a strong vasoconstriction that helps slow blood loss.
   (a,b,d) (pp. 523-4, in Silverthorn, 5th edition)

C. Steroid hormones:
   a. are stored in vesicles and released by peptide releasing factors.
   b. are not very soluble in plasma and other body fluids, so they are often bound to protein carrier molecules in the blood.
   c. diffuse across the lipid bilayer of target cells by mass action.
   d. such as estrogens, in addition to their effects on genes, also have membrane receptors that trigger effects on signal transmission pathways that are similar to peptide hormones.
   (b,c,d) (pp. 222-5, in Silverthorn, 5th edition)