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

1. Write your name on every page. (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.
   • 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 to write your answers, but do NOT use RED INK and DO NOT USE WHITE-OUT of any kind. (You cannot request a regrade if you use pencil.)

POTENTIALLY USEFUL EQUATIONS:

\[ \pi = \sigma RT (C_0 - C_i) \quad F = A \eta \frac{\Delta V}{\Delta X} \quad C_s = \frac{[S]_U}{[S]_P} \cdot \frac{V_U}{V} \]

\[ R = \frac{8 \eta l}{\pi r^4} \quad J = k[(P_{\text{cap}} + \pi_{\text{int}}) - (P_{\text{int}} + \pi_{\text{cap}})] \quad V_m = \frac{G_{\text{Na}} E_{\text{Na}}}{\sum G} + \frac{G_{\text{K}} E_{\text{K}}}{\sum G} + \frac{G_{\text{Cl}} E_{\text{Cl}}}{\sum G} \]

\[ I_Y = G_Y (V_m - E_Y) \quad I_{\text{total}} = \sum \{G_j [V_m - E_j]\} \quad J = -PS(C_{\text{out}} - C_{\text{in}}) \quad E = mc^2 \]

\[ \frac{1}{R_{\text{Total}}} = \sum \frac{1}{R_i} \quad E_x = R T \ln \frac{[X^+]_{\text{out}}}{[X^+]_{\text{in}}} \quad \text{concentration} = \frac{\text{quantity}}{\text{volume}} \quad I_X = G_X (V_m - E_X) \]

\[ V = Q/A \quad P = QR \quad R_{\text{Total}} = \sum R_i \quad R_{\text{Total}} = \sum R_i \quad I_X = G_X (V_m - E_X) \quad A = \pi r^2 \quad V = IR \]

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
KEY FOR MULTIPLE CHOICE QUESTIONS:

<table>
<thead>
<tr>
<th>A. MIDTERM #1</th>
<th>B. MIDTERM #2</th>
<th>C. NEW MATERIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1. (c,d)</td>
<td>B1. (b,c)</td>
<td>C1. (b)</td>
</tr>
<tr>
<td>A2. (none are correct)</td>
<td>B2. (d)</td>
<td>C2. (a,c)</td>
</tr>
<tr>
<td>A3. (a)</td>
<td>B3. (a,d)</td>
<td>C3. (a,b,d)</td>
</tr>
<tr>
<td>A4. (none are correct)</td>
<td>B4. (a,b)</td>
<td>C4. (a,c)</td>
</tr>
<tr>
<td>A5. (a)</td>
<td>B5. (a,b)</td>
<td>C5. (a,d)</td>
</tr>
<tr>
<td>A6. (a,b,d)</td>
<td>B6. (a)</td>
<td>C6. (a,b)</td>
</tr>
<tr>
<td>A7. (a,c)</td>
<td>B7. (a,c)</td>
<td>C7. (a)</td>
</tr>
<tr>
<td>A8. (a,b)</td>
<td>B8. (a,c)</td>
<td>C8. (b,c)</td>
</tr>
<tr>
<td>A9. (d)</td>
<td>B9. (b,c,d)</td>
<td></td>
</tr>
<tr>
<td>A10. (a,c)</td>
<td>B10. (none are correct)</td>
<td></td>
</tr>
<tr>
<td>A11. (a)</td>
<td>B11. (a,b)</td>
<td></td>
</tr>
<tr>
<td>A12. (a,c,d)</td>
<td>B12. (b,d)</td>
<td></td>
</tr>
<tr>
<td>A13. (c)</td>
<td>B13. (a,b,c,d)</td>
<td></td>
</tr>
<tr>
<td>A14. (a,b)</td>
<td>B14. (a)</td>
<td></td>
</tr>
<tr>
<td>A15. (c)</td>
<td>B15. (a,b,c,d)</td>
<td></td>
</tr>
</tbody>
</table>
1. (9 points total) You run a 100-yard dash.

A. (3 points) Describe what happens to the magnitude (does it increase, decrease, or remain the same?) and distribution of your cardiac output throughout the body.

Total cardiac output (CO) goes up. The percentage going to your skeletal and cardiac muscles increases greatly. The amount of blood going to your brain remains the same (the percentage of CO decreases), and the amount of going to your other internal organs decreases, so that the CO to them decreases a lot.

B. (2 points) What is the mechanism of the redistribution of the cardiac output to the muscles?

There is a generalized increase of sympathetic vasoconstriction throughout the body, with local factors (e.g., CO2 and metabolites) causing a strong vasodilation in the muscles being used for running.

C. (2 points) How would this change in cardiac output affect your GFR?

The lowered blood flow to the kidneys (due to vasoconstriction in the afferent arterioles) lowers the GFR, because the hydrostatic pressure in the glomerulus decreases.

D. (2 points) Briefly describe an intrinsic mechanism that would help to keep your GFR constant.

The decrease in GFR lowers the flow of tubular fluid in the distal tubule. The macula densa cells in the distal tubule sense the decrease in tubular [Cl-] and exert two effects on renal blood vessels (either one gets full credit):

(i) they stop releasing paracrine vasoconstrictor substances onto smooth muscles of the afferent arterioles, which increases blood flow to the kidney and, therefore, increases GFR; and

(ii) the macula densa cells activate the JGA cells in the afferent arteriole to release renin, which breaks angiotensinogen into angiotensin I (ANG I). Before the ANG I makes it to the efferent arteriole, it is broken down into ANG II, which is a strong vasoconstrictor. The ANG II causes a constriction of the efferent arterioles, which raises the hydrostatic pressure in the glomerulus, which increases the GFR.

2. (8 points total) Mannitol is used as an “osmotic diuretic” because it is freely filtered and not reabsorbed or broken down.

A. (4 points) Explain why these properties make mannitol a diuretic.

The mannitol is filtered into Bowman’s capsule and remains in the tubule as water is progressively removed. The concentration of the mannitol, therefore, progressively increases as water moves along the tubule. In the distal tubule, some amount of water is retained because of the increased osmotic pressure due to the amount of mannitol in the tubular fluid. Depending upon the dose of mannitol taken, this could be a small or very large amount of increased urine production; i.e., at a sufficiently high dose, mannitol can cause diuresis.
B. (4 points) Predict what would happen to the osmotic gradient in the renal medulla in response to a sustained dose of mannitol. Briefly explain the mechanism for your prediction.

At a sufficiently high dose of mannitol to cause diuresis, the fluid would move through the renal medulla so fast that:

(i) the urea cannot reach its equilibrium, and more urea than normal would be washed out in the urine. This means that the part of the gradient in the interstitial fluid caused by urea would decrease.

(ii) not as much Na+ would be pumped out of the thick ascending limb of the loop of Henle or the distal tubule, so the upper half of the gradient would also be reduced.

(EITHER EXPLANATION RECEIVED FULL CREDIT)
3. (15 points total) The graph below is a plot that shows various measures of how our kidneys handle different plasma concentrations of glucose.

![Graph showing various measures of how kidneys handle glucose](image)

A. (3 points) Label the three lines on the graph.

- Left-most 45° line = filtered (or "filtration")
- Horizontal line = reabsorbed (or "reabsorption")
- Right-most 45° line = excreted (or "excretion")

B. (4 points) Define $T_m$ and label it on the graph.

$T_m$ is the tubular maximum: the maximum concentration of glucose that can be reabsorbed by the kidney (in this case, the proximal tubule). It is caused by the saturation of the glucose-Na+ symporter on the mucosal surface of the proximal tubular cells. The label should be at the right end of the "reabsorbed" curve, or pointing to the Y axis at the value where the "reabsorbed" curve goes horizontal.

C. (4 points) Sergliflozin is a drug that selectively blocks the glucose-Na+ symporters in the epithelial cells of the proximal tubule in a dose-dependent manner. A person receives a dose of sergliflozin that knocks out 80% of these symporters. Draw dashed lines on the graph above to indicate how the lines would change in the person receiving this dose of sergliflozin. (If there is no difference, draw nothing.)

The "filtered" curve does not change. The "reabsorbed" curve becomes horizontal at 20% of the value of the current value—just below 100 mg/min. The "excreted" curve is shifted to the left, parallel to the curve shown but crossing the X axis at less than 100 mg%.

D. (4 points) The graph below shows the concentration of inulin in different parts of the nephron of a person with healthy kidneys after receiving an injection of inulin. On the graph, draw a solid line to show the relative concentration of glucose in different regions in an untreated kidney and a dashed line to show how the relative glucose concentrations are different in a person receiving sergliflozin, as described in part C.
Solid line: a straight line from 1.0 on the Y axis that hits the X axis about 2/3 of the way through the proximal tubule.

Dashed line: a straight line with less of a slope, so that it does not hit the X axis. After crossing the line between the proximal tubule and the loop of Henle, this line should parallel the inulin line through the remainder of the nephron. [It, too, is not secreted or reabsorbed through the remainder of the nephron, but its concentration would remain lower than that of inulin.]
4. (9 points total) The results of a person’s kidney function test are:

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺]</td>
<td>150 mM/L</td>
<td>750 mM/L</td>
</tr>
<tr>
<td>[Inulin]</td>
<td>1 mg/ml</td>
<td>150 mg/ml</td>
</tr>
<tr>
<td>[Creatinine]</td>
<td>0.01 mg/ml</td>
<td>1.25 mg/ml</td>
</tr>
<tr>
<td>[PAH]</td>
<td>0.15 mg/ml</td>
<td>60.0 mg/ml</td>
</tr>
</tbody>
</table>

Urine flow = 1 ml/min.
Hematocrit = 0.50

A. (3 points) What is this person’s GFR? Show your calculations.

\[
GFR = C_{\text{inulin}} = \frac{[\text{inulin}]_{\text{urine}}}{[\text{inulin}]_{\text{plasma}}} \times \text{urine flow rate} = \frac{150}{1} \times 1 = 150 \text{ ml/min}
\]

[2 points if creatinine clearance is used, unless the answer says that this is a clinical test.]

B. (3 points) What is this person’s renal blood flow? Show your calculations.

\[
\text{Renal plasma flow (RPF)} = C_{\text{PAH}} = \frac{[\text{PAH}]_{\text{urine}}}{[\text{PAH}]_{\text{plasma}}} \times \text{urine flow rate} = \frac{60}{0.15} \times 1 = 400 \text{ ml/min}
\]

\[
\text{Renal blood flow (RBF)} = \frac{\text{RPF}}{\text{hematocrit}} = \frac{400}{0.5} = 800 \text{ ml/min}
\]

C. (3 points) From just these test results, what can you say about how Na⁺ is handled by this person’s kidneys?

\[
C_{\text{Na⁺}} = \frac{[\text{Na⁺}]_{\text{urine}}}{[\text{Na⁺}]_{\text{plasma}}} \times \text{urine flow rate} = \frac{750}{150} \times 1 = 5 \text{ ml/min}
\]

The net effect is Na⁺ reabsorption, because 

5. (7 points total) While cutting down a Christmas tree, Christopher Cringle is injured and loses a substantial amount of blood.

A. (2 points) What procedure would you perform to determine much blood Mr. Cringle has lost?

Inject a substance like the dye Evans Blue (EB) that distributes evenly in the plasma but does not cross into the interstitial fluid, wait some time (e.g., 10-30 min), remove a sample of blood, and measure the concentration of EB in the plasma. The volume of plasma would be the amount of dye injected divided by the concentration of the dye in the plasma. This value would have to be divided by the hematocrit to determine the blood volume. [This would tell you how much Chris has left, not how much he lost. The “original” volume can be estimated as about 8% of his body weight.]

B. (2 points) You determine that he has lost 25% of his blood volume. What effect would this blood loss have on the volume and the osmolarity of the intracellular fluid? [Assume that the hormonal effects have not yet been activated.]

Initially, the volume lost from the plasma would equilibrate with the interstitial fluid, so some fluid would move from the interstitial compartment into the plasma compartment, but because there is no change in the osmolarity of the interstitial fluid, there would be no movement of either ions or water out of the intracellular compartment. [Later, there will be hormonal effects.]
C. (3 points) How would the changes in volume and osmolarity in Mr. Cringle’s would affect the plasma levels of the following hormones:

a. ADH: increased or no change were accepted; the osmoreceptors would not be activated, so they would not cause a change in ADH levels. If the volume change is sufficiently large [it probably is, in this case], baroreceptor activity would cause the release of ADH, increasing the plasma ADH level.

b. Aldosterone: increased, [by the release of renin by the macula densa cells in the kidney afferent arterioles, which cleaves angiotensin I (ANG I) from angiotensinogen; ANG I is cleaved to ANG II, which acts on cells in the adrenal cortex to release aldosterone.]

c. ANP: decreased [the decrease in the blood volume would turn down the activity of the stretch receptors in the right atrium, which would turn down the release of ANP.]