1. a. Proximal tubule.
   b. Proximal tubule.
   c. Glomerular endothelial fenestrae, filtration slits between podocytes of Bowman's capsule.
   d. Thick ascending limb of the loop of Henle (NaCl transport) and collecting duct (recycling of urea).
   e. Collecting duct (and, indirectly, the loop of Henle).
   f. Collecting duct (and, indirectly, the loop of Henle).
   g. Peritubular capillaries and the vasa recta, then renal venules, renal veins.
   h. Peritubular capillaries, renal venules, renal veins.
   i. Proximal tubule.

2. a. The osmolarity of tubular fluid in Bowman's capsule is identical to its osmolarity the beginning of the descending thin limb of the loop of Henle. [Although a huge amount of solute is reabsorbed in the proximal tubule, its osmotic equivalent amount of water is also reabsorbed, changing the solute content of the tubular fluid, but not its osmotic concentration.]
   b. The inulin concentration in Bowman's capsule would be lower than the inulin concentration at the beginning of the descending thin limb of the loop of Henle, because all of the filtered inulin remains in the tubule, whereas the amount of water is reduced to less than half of the filtered amount by the time the tubular fluid reaches the loop of Henle.
   c. The concentration of glucose in Bowman's capsule would be much higher because all (or most) of the filtered glucose is reabsorbed in the proximal tubule.
   d. In diabetes, some glucose—and maybe a lot—would enter the descending thin limb of the loop of Henle, but since glucose is neither reabsorbed from or secreted into tubular fluid past the proximal tubule, the amount of glucose entering of the distal convoluted tube would be equal to the amount in the loop of Henle.

3. The very high hydrostatic pressure and the high permeability of the endothelial walls in glomerular capillaries causes a much greater volume of fluid to be driven out into the interstitial space than occurs in muscle capillaries. However, proteins are retained inside both types of capillaries. When so much water moves out of the glomerular capillaries, the volume of water is reduced, so the concentration of the proteins (and thus, their oncotic pressure) is increased. In muscle capillaries, relatively little water leaves the capillaries driven by hydrostatic pressure, so the volume of plasma in which the plasma proteins are dissolved changes relatively little and there is little change in plasma oncotic pressure from the arterial end to the venous end of the capillary.

4. If the protein content of the blood were to double, the oncotic pressure of plasma would be doubled. Since the balance between filtration and reabsorption in the glomerular capillaries (and all other capillaries, as well) depends upon the balance between net hydrostatic and plasma osmotic pressures, a doubling of oncotic pressure would shift the balance away from filtration and toward reabsorption. You would have to have exact measurements of the hydrostatic and oncotic pressures in the capillaries and in the interstitial space in order to determine the quantitative shift in net fluid movement. In fact, the normal hydrostatic pressure in the glomerulus is unusually high, so the net movement of fluid across most of the glomerular endothelium would probably still be filtration.
[Not asked in the question, but interesting: Further along the nephron, the hydrostatic pressure in the peritubular capillaries is quite low, so an increase in plasma oncotic pressure could significantly shift the balance between filtration and uptake along these vessels, greatly increasing the efficiency with which fluid was reabsorbed from the interstitial fluid (and indirectly from the lumen of the proximal tubular wall) and returned to the general circulation.]

[Notice that the blood is always our point of reference: "filtration" always means movement out of the plasma and "uptake" or "reuptake" always means movement back into the plasma.]

5. a. In the first 10 minutes, GFR = (127 x 2)/20 = 12.7 ml/min

(Notice that you must be careful of the time units. The urine samples were taken every 10 minutes, so the rate of urine production per minute needs to be calculated.)

The calculated values every 10 minutes ranged from 10.6 ml/min to 12.7 ml/min, with an average value of 11.7 ml/min. Because there was no obvious systematic change in the values with time, the average value is probably the best number to represent the GFR.

b. The first measurement was taken only 10 minutes after infusion began, a time when the inulin would still be equilibrating in the plasma and interstitial fluid compartments, so unusually high or unusually low numbers probably represent inadequate mixing at this time. Furthermore, the tubular fluid within the nephrons at the time when the infusion began did not contain any inulin, nor would much inulin be filtered into the nephrons for several minutes as mixing occurred.

c. This GFR is about 1/10 of the normal expected GFR of about 125 ml/minute filtered. Yes, this person has a problem with their kidney function.

d. The tubular maximum for glucose is about 300 mg/100 ml of glucose, so the amount in excess of 300 that enters the tubules per minutes will be excreted in the urine.

e. Because a large amount of glucose is reabsorbed in the proximal tubules, the clearance of glucose would be lower than the clearance of inulin.

f. Because the clearance of PAH very closely reflects renal plasma flow:

\[
\text{Renal plasma flow} = \text{clearance of PAH} = \frac{([\text{PAH}]_{\text{urine}} \times V_{\text{urine}})}{[\text{PAH}]_{\text{plasma}}} \\
= \frac{((375 \text{ mMoles/liter}) \times 2 \text{ ml/min})}{(15 \text{ mMoles/liter})} \\
= 50 \text{ ml plasma/min},
\]

Correcting for hematocrit, the renal blood flow is approximately 100 ml blood/min.

Normally the kidneys receive 20-25% of the cardiac output, and the heart pumps about 5 liters per minute. So under normal conditions you would expect the kidneys to receive about 1 to 1.25 liters of blood per minute. The value that you just calculated is about one tenth of that. It looks as though there is some blockage in the flow of blood to the kidneys. (You probably would want to check the real cardiac output, but a cardiac output that is reduced to a tenth of normal is probably fatal, so blocked renal blood flow is more likely.)

6. a. When plasma volume decreases, venous return to the heart decreases, reducing the stretch on the right atrial stretch receptors. This drop in right atrial stretch stimulates release of ADH by cells of the hypothalamus that have their endings in the neurohypophysis.

Plasma osmolarity is sensed by cells within the hypothalamus. When plasma osmolarity increases, the ADH cells release their hormone from the neurohypophysis. In the presence of ADH, the collecting ducts are very permeable to water, so urine becomes concentrated under the
influence of the medullary osmotic gradient. [In the absence of ADH, the collecting ducts are impermeable to water, and urine is dilute.]

b. When blood volume drops, venous return to the right heart drops, decreasing the secretion of atrial natriuretic hormone (ANH). The decreased ANH causes more Na\(^+\) reabsorption in the collecting duct, causing more water reabsorption. This hormonal reflex helps to decrease water loss in the urine, thus helping to keep the blood volume from dropping even lower.

c. A drop in either blood volume or blood pressure causes ADH release. (PLEASE NOTE that much less ADH is released in response to changes in blood pressure or blood volume than to a change in plasma osmolarity.) ADH causes vasoconstriction in the systemic circulation, raising peripheral resistance and thus raising blood pressure. ADH also acts on the kidney to increase water retention. Retaining water helps to maintain blood volume, and hence prevents a further drop in blood pressure. The effects of ADH on the blood vessels and the kidneys, therefore, act synergistically to maintain blood pressure.

[IMPORTANT NOTE: The kidneys cannot increase blood volume. The only way that blood volume can increase is by drinking or through an IV drip. The kidneys do respond to emergencies by minimizing fluid loss in the urine.]

7. a. When amiloride blocks the path that Na\(^+\) uses to cross the mucosal membranes of tubule cells, it reduces the Na\(^+\) available to the Na\(^+\)/K\(^+\) ATPase molecules in the serosal membranes so that less Na\(^+\) is reabsorbed from fluid in the proximal nephron and in the thick ascending limb of the loop of Henle and the distal tubule. Enough water will remain in the tubular fluid to keep it iso-osmotic with the interstitial fluid, so the osmolarity of the urine would remain the same.

b. Because Na\(^+\) is by far the most abundant solute in tubular fluid, blocking reabsorption of Na\(^+\) greatly reduces reabsorption of H\(_2\)O in the nephron and therefore increases the amount of fluid lost in the urine.

c. The clearance of Na\(^+\) would go up and become closer to the clearance of inulin.

8. a. After this volume loading, the body fluid volume is expanded and the osmolarity of plasma is lower. There will be at least two major responses in the control systems regulating renal activity:

(1) The increase in the volume of plasma will lead to increased venous return to the right heart and an increase in the secretion of atrial natriuretic hormone. Increased ANH will decrease Na\(^+\) reabsorbed in the collecting duct, which will lead to a mild increase in the volume of urine produced. Notice that this diuresis will be due to the retention of Na\(^+\) in the urine, so this mechanism cannot excrete water at the same time that solute is being saved. [NOTE: Any increase in the amount of sodium in the urine is called "Natriuresis".]

(2) Much more significantly, the decrease in plasma osmolarity will decrease activity of the osmoreceptor cells in the hypothalamus, causing the level of ADH in the blood to drop. The collecting ducts will become relatively impermeable to water, and a large volume of dilute urine will be excreted. As a result, water will be excreted and solute will be retained.

b. Adding an iso-osmotic solution increases the extracellular volume without changing the osmolarity of body fluids. The activity in osmoreceptors within (or projecting to) the hypothalamus will not change significantly. The increased volume will cause at least a transient increase in venous return to the heart and increased right atrial stretch. Increased activity in right atrial stretch receptors causes less ADH secretion from the hypothalamus, so the volume of urine will increase.
The increase in plasma volume can lead to at least a transient increase in blood pressure, which will increase the pressure in the afferent arterioles, reducing the secretion of renin. When less renin is released from the juxtaglomerular apparatus, less angiotensin II and less aldosterone will be present. With less aldosterone present, less Na\(^+\) will be reabsorbed across the epithelial cells of the distal tubule and of the collecting duct, so both salt and water will be lost in the urine.

Finally, increased blood volume stimulates atrial stretch receptors to cause release of more ANH, which inhibits Na\(^+\) uptake by the distal nephron, producing a loss of salt and water in the urine. So this combination of effects has just the right outcome: the loss of both water volume and salt.

c. Drinking sea water is a big mistake. The problem is that you increase volume to your system, but the osmoreceptors read the increase in plasma osmolarity as though it was due to dehydration. The regulatory responses that result have a water-conserving effect: osmoreceptor activity increases, leading to increased ADH levels and a reduction in urine flow. The resulting concentrated urine will contain a higher concentration of salt than normal, but there will be a lot lower volume, so water will be saved and salt will be only very slowly excreted. That will take care of some of the salt problem, but it doesn't help the volume loading. To make matters worse, the thirst center will respond to the increased osmolarity by becoming very active, you will be inclined to drink lots more water, and the result will be further volume loading during the time when the salt is slowly being lost.

To help solve the volume problem takes some time. First, the increased plasma volume will (at least transiently) increase blood pressure somewhat, so renin secretion will be reduced, reducing the level of angiotensin II and promoting the loss of some salt and water in the urine. Second, the increase in blood volume will also increase venous return to the right heart, stimulating the release of ANH, which also reduces the uptake of Na\(^+\) and further promotes the loss of salt and water in the urine. You will, however, have an uncomfortable few days of systemic edema as you slowly wash the salt and water out of your body.

d. Beer is hypo-osmotic to plasma, so the plasma osmolarity goes down and the blood volume goes up when you drink this much beer. As a result of the decreased osmolarity ADH secretion is reduced; and as a result of the increased plasma volume (and hence increased blood pressure) renin secretion is reduced. These two changes cause an increase in the volume of urine produced and a decrease in urine osmolarity. All of these effects so far are the direct result of changes you have made in plasma osmolarity and volume. However, ethanol also directly inhibits the release of ADH, which reduces the amount of circulating ADH even more than volume loading alone would have. This further increases the volume of urinary output. This diuretic effect of ethanol is quite strong, so you would produce more urine even if you had been consuming a small amount of straight Scottish whisky. As a result, drinking alcoholic beverages dehydrates your body.

NOTE: If you were asked this question on an exam, it would be most efficient to state your answer showing effects connected by arrows, e.g:

\[ \text{plasma osmolarity} \Rightarrow \text{ADH secretion} \Rightarrow \text{collecting duct H2O permeability} \Rightarrow \text{etc.} \]

9. a. Spironolactone would inhibit the action of aldosterone by blocking its binding to the target cells. If aldosterone action is blocked, there is less uptake of Na\(^+\) and a shift toward the production of a larger volume of iso-osmotic urine. Salt and water are lost.

b. The mannose in the plasma is filtered into the proximal tubules. Because it is neither reabsorbed nor metabolized, it remains in tubular fluid as it passes along the proximal tubules. Because proximal tubular fluid is iso-osmotic with plasma, the mannose causes an increase in the water retained in the tubule (i.e., a reduction in the amount of the water that is reabsorbed by the
proximal tubule). The amount of mannose that is contained within the tubular fluid will not change during the passage along the nephron, so the amount of water that remains in the fluid will continue to be higher than normal. This increased solute and water will increase the volume of urine excreted at any ADH level in the blood.

c. By blocking the Na/K/2Cl co-transporter, **Furosemide** blocks NaCl reabsorption in the thick ascending limb of the loop of Henle, which causes the reduction or collapse of the concentration gradient in the renal medulla. As a result, much less water can be reabsorbed in the collecting duct, even if ADH is present, and the volume of urine increases.

d. By blocking the Na\(^{+}\)-K\(^{+}\) ATPase, **ouabain** blocks reabsorption of NaCl. The unabsorbed NaCl then holds its osmotic equivalent of water inside the nephron, and the increased salt and water travel through the nephrons, increasing the volume of excreted urine.