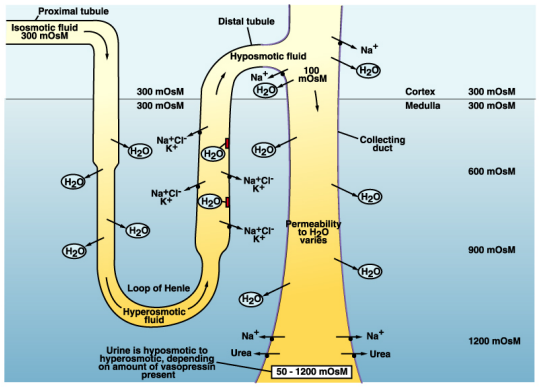
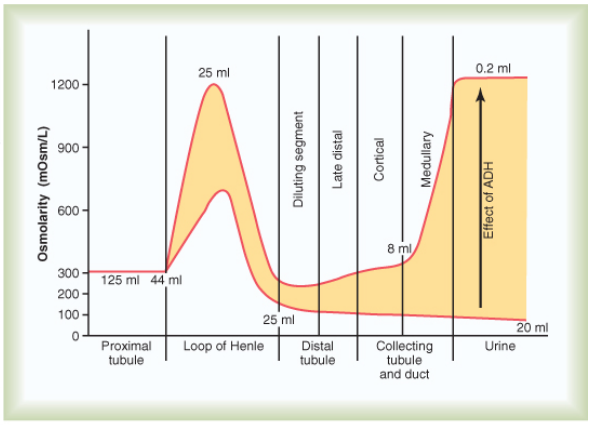
Exam Key

NROSCI/BIOSC 1070 and MSNBIO 2070
Exam # 3
November 20, 2015

Total POINTS: 100 20% of grade in class

1) Draw a schematic of a juxtamedullary nephron and label the major portions of the tubule. Then, assuming this is a normal, juxtamedullary nephron of a typically hydrated individual, note the osmolality of the fluid in each segment and the approximate volume of fluid passing through that segment each minute *(use volumes for the total of all juxtamedullary nephrons, not a single nephron)*. ***(10 points).***





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Note: Ending osmolality for normal individual is ~600 mOsM

Approximate volumes of fluid at beginning of each segment (from slide 27 of Renal lecture 3 pictured above):

Proximal tubule: 125ml/min
Loop of Henle: 25ml/min
Distal Tubule: 25ml/min
Collecting Duct: 8ml/min

2) Loss of either ADH or aldosterone would cause and increase in urine volume. Other than measuring these two hormones, what could you measure in blood or urine that could inform you as to which hormone's function was lost? Explain your answer. ***(10 points).***

One possibility is to measure blood K+; Aldosterone causes K+ secretion, so lack of Aldosterone causes K+ levels in the blood to increase.

Another possibility is to measure urine or plasma osmolarity. Loss of ADH would result in hypoosmotic urine (low urine Na+), and an increase in plasma osmolarity. Loss of Aldosterone would result in loss of Na+ in the urine, but water would follow the solute, so the urine osmolarity would remain fairly constant.

3) A patient is determined to have an inulin clearance of 100 ml/min and a PAH clearance of 400 ml/min. To the extent that these values are not normal, what do you think might be going on in this patient? ***(10 points).***

Given these values, both GFR and PAH clearance are below normal. The filtration fraction is normally 20%, but this patient is experiencing an above average FF of 25%. This patient could be experiencing increased filtration pressure and increased resistance due to the constriction of the efferent arteriole, or the patient could have very low blood pressure AND a breakdown of filtration barriers (which would decrease blood flow and also increase FF).

Exam Key

4) What are the two major stimuli for aldosterone secretion and how do these make sense in the context of the actions of aldosterone? In contrast, what are the two major stimuli for ADH secretion? ***(9 points).***

The primary triggers for Aldosterone secretion are high plasma K+ and high plasma AngII. This makes sense, as aldosterone acts to promote K+ secretion and retention of water and Na+. Since AngII secretion is a result of low blood pressure and low Na+ sensed by macula densa, high Aldosterone plays a key role in restoring plasma Na+ and blood pressure.

ADH is secreted in response to low blood pressure or blood volume sensed by atrial and arterial baroreceptors, as well as increased plasma osmolarity.

Exam Key

5) Mutations of proteins associated with Cl^- transport on the basolateral membrane of the ascending limb of the loop of Henle cause a syndrome of Na^+ loss and hypotension. Why should this happen as a result of changes in Cl^- transport at the basolateral membrane of this segment of the nephron? ***(10 points).***

The mutation of this transporter prevents the transport of Cl- ions out of the cell, and thus increases the concentration of Cl- ions within the cell. This decreases the gradient of Cl- ions across the apical membrane, causing the Na-K-2Cl transporter to not effectively bring Na+ ions into the cell. This lowered reabsorption of Na+ ions also causes more H_2O to be excreted (as water follows high Na+ concentration), leading to hypovolemia and hypotension.

6) A young child comes to the clinic suffering severe and widespread autoimmunity. When further testing is done it is determined that he suffers from IPEX syndrome, which is characterized by a loss of FOXP3. What suppressive immune cells would be detrimentally impacted by the loss of FOXP3? ***(2 points).***

Regulatory T cells or T_{reg}

7) Hematoxylin and Eosin (H&E) staining of a smear of peripheral blood or bone marrow is a common way to differentiate blood cell types and assess for changes indicative of infection and pathology. Name the innate cell indicated by the following physiological and histological descriptions. ***(8 Points)*.**

a) Highly represented leukocytes that contain a multi-lobed nucleus and ample cytoplasm full of reddish-purple granules consisting of anti-microbial substances and enzymes.

Neutrophil

b) Very rare white blood cells with dense blue granules and a bi-lobed nucleus.

Basophil

c) These large white blood cells have significant cytoplasm, but lack pronounced granules and exhibit a bean or horseshoe shaped nucleus. A quick estimate suggests they represent about 10% of the leukocytes.

Monocytes

d) Relatively rare leukocytes (1-3% of white blood cells) with a bi-lobed nucleus and bright red granules containing major basic protein.

Eosinophil

Exam Key

8) Immunoglobulin from one individual B cell comes with a single specificity due to their particular combination of Variable Light (V_L) and Variable Heavy (V_H) regions. Upon activation and appropriate interactions with other immune cells, however, that B cell can generate 5 distinct immunoglobulin isotypes. Each isotype has a distinct function that is shaped by the kinetics of its expression and structure. Identify each isotype described below. ***(8 points).***

a) Which isotype is secreted as a pentamer and is important for agglutination?

IgM

b) Which isotype is often fixed to the surface of mast cells and supports degranulation of mast cells?

IgE

c) Which isotype is driven by B cell exposure to IL-5 and is found on the surface of mucosal surfaces

IgA

d) Which isotype is the first expressed by the B cell after its education in the bone marrow?

IgD

Exam Key

9) While much attention is given to the role of leukocytes in the immune system, protective physical barriers do the bulk of protecting the host from microbes. Describe how the following mechanisms help the barriers of the body prevent infections. ***(8 points).***

a) Lysozymes

Damage bacterial cell walls through hydrolysis of the glycosidic linkages in the peptidoglycan of bacterial cell wall.

b) Commensal microbes

Act as a competitive barrier that prevents the colonization of the skin by pathogenic microbes.

c) Defensins

Defensins act by forming pore like structures that cause bacterial cell walls to become leaky.

d) Mucus

Mucus entraps microbes and particulate matter, which is then swept out by cilia. Mucus also contains IgA to neutralize previously recognized pathogens, as well as anti-microbe enzymes including lysozyme. (Note: only the first point needed for credit).

Exam Key

10) The loading of small peptides onto MHCI takes place in the endoplasmic reticulum (ER) of all nucleated cells of the body. The transporter associated with antigen presentation (TAP) pumps these peptides into the ER. TAP deficiencies limit MHCI loading. ***(4 points).***

a) What subset of T cells would be detrimentally impacted by a TAP deficiency?

CD8+ T cells or CTLs

b) Decreased MHCI on the surface of all cells may open an individual open to a significant pathology mediated by which innate immune cell population?

NK cells

11) Individuals who lack recombination-activating genes (RAG) do not have functional T cells. Why? ***(4 points).***

The RAG1 and RAG2 enzymes are required to carry out the DNA rearrangements required to generate the variable domain of the TCR. The variable domain is required to form a functional TCR. Without this receptor, T cells cannot be saved from positive selection in the thymus.

Exam Key

12) Why is the epitope specificity for an antibody produced by a B cell not altered by isotype switching? ***(4 points).***

In isotype switching, the VDJ domain making up the epitope-binding domain of the remains unchanged, but is moved by different constant genes. These constant genes determine what heavy chain will be produced by the B cell and it is the heavy chains that determine the isotype.

13) Activated lymphocytes routinely use perforin and granzyme to precisely kill target cells. Explain the effector mechanisms of these two proteins. ***(4 points).***

Perforin creates a channel through the target cell membrane, which allows cytolytic proteins to enter the cell. Granzyme is a family of serine proteases that cleave intracellular substrates, including those that trigger many apoptotic pathways to ensure target cells die.

Exam Key

14) Describe the three types of potential transplant rejection responses that could occur after transplantation of a cadaveric heart, and briefly discuss the treatment *(if any)* that can be used to counteract each type of rejection. ***(9 points).***

- Hyperacute rejection occurs minutes after transplantation and results when pre-existing antibodies to donor antigens bind to endothelial cells of the graft. This initiates complement activation and profound thrombosis. This is not a significant concern, as risk for hyperacute rejection can be removed through testing the patient for pre-exisiting antibodies.

- Acute rejection happens months after transplantation and results with alloreactive T cells, and to a lesser extent, antibodies recognize the graft as non-self and initiate and immune response. Acute rejection is a concern, but for the most part, can be addressed by available immunosuppressants.

- Chronic rejection develops over the course of years from a poorly understood immune response involving both T cells and humoral immunity. Chronic rejection is resistant to available immunosuppressant and thus is the most problematic type of rejection in heart transplantation today.