IMMUNOLOGY OF TUMAMOC HILL

By

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With Honors in

Physiology

THE UNIVERSITY OF ARIZONA

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ABSTRACT

The Immunology of Tumamoc provides an overview of the immune system and examines its role in human interactions with Tumamoc Hill, in Tucson, Arizona. In particular, it delves into immunopathologies that might affect people on the hill, such as allergy and asthma, delayed-type hypersensitivity, and medial tibial stress syndrome. Included in the thesis are several helpful resources that might assist those who frequent Tumamoc to avoid the unpleasant consequences of these immunopathologies such as a pollen calendar for the state of Arizona, a list of commonly allergenic species of flora on Tumamoc, a list of flora on Tumamoc that will induce delayed-type hypersensitivity, and an informational brochure. The brochure contains information on all the immunopathologies mentioned above, as well as practical ways that their effects can be avoided. These brochures were passed out at Tumamoc Hill on April 12, 2014 by the student and faculty advisor.

Keywords: immunology, Tumamoc Hill, allergy, delayed-type hypersensitivity, medial tibial stress syndrome

INTRODUCTION

Humans live a world in which every breath and touch brings the inside of the body into contact with millions of outside microorganisms and particulates. These interactions are mediated by the body's security forces – the components of the immune system. Even when mishaps occur within the body, as in the case of cellular injury, the immune system facilitates inflammation and healing. This paper will explore these mechanisms in relation to the environment of Tumamoc Hill, a landmark of Tucson, Arizona. First, a background into immunology will be provided to enhance the understanding of the immunopathologies that occur on Tumamoc. Because this subject is inherently complex, it is beyond the scope of this thesis to afford a comprehensive review of all the aspects of immunology. Rather, the purpose of this thesis is to inform those who visit Tumamoc Hill of enough immunologic background to understand the immunopathologies that are frequently encountered in this location, their risk for experiencing these effects, and how they can avoid them. The topics covered in this paper include: a background on Tumamoc Hill, an introduction to innate and acquired immunity, and allergies, asthma, delayed-type hypersensitivity, and medial tibial stress syndrome as they relate to Tumamoc Hill.

TUMAMOC HILL

Home to the Tohono O'odham people since 1450 and converted to the world's first restoration ecology project in 1906, Tumamoc Hill continues to make history as a United States National Historic Landmark, ecological reservation, and research and education facility of the University of Arizona. The hill is located just west of downtown Tucson, in a populated and easily accessible area. It is no surprise then that it has become one of the most popular hiking

destinations among Tucsonans, offering not only convenience, but also a well-paved path to breathtaking views 760 feet above the city (Rosenzweig). Consequently, Tumamoc experiences medium to heavy traffic each day, as it is traversed by university workers, researchers, and recreational hikers.

These many humans interact closely with the abundant desert wildlife on this ecological reservation. Tumamoc is home to more than three hundred species of native plants and about fifty exotic (and sometimes invasive) species. From timeworn saguaros that stand out along the landscape to the tiny winter annuals that often go unnoticed despite their wispy charm, an incredibly varied array of flora paint the scenery of Tumamoc. This rich diversity is derived from the hill's many habitats and seasons, which provides numerous niches for different specializations to thrive. Certain plant communities also work in symbiosis to aid in the growth of each individual, adding to the variety of flora. For example, small cacti will sometimes grow near more mature plants that provide shade against the harsh desert sun (Rosenzweig).

Kinsey, B. (2014, January 1). Southeastern Arizona Wildflowers. Firefly Forest. Retrieved April 23, 2014, from http://www.fireflyforest.com/flowers/

These thriving flora enrich the ecological system by providing habitats and food sources for the fauna that reside on Tumamoc. Local hikers have spotted a variety of animals, including "deer, javalina, foxes, coyotes, rattlesnakes, roadrunners and cougars" (Barajas et al., 2013). Though some of these species may pose a significant risk to humans, large animals do not often approach the main trail or research facilities. There are of course, smaller animals such as snakes and tarantulas that frequent the trail at night, but they are easily spotted and avoided with a good flashlight as they are very conspicuous against the uniform pavement.

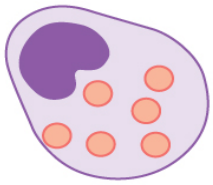
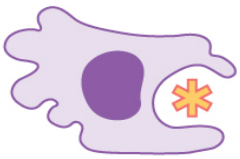
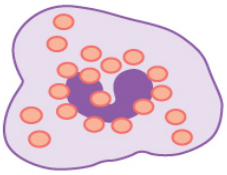
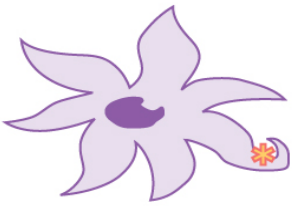
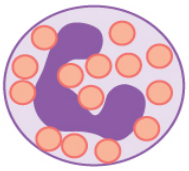
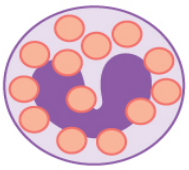
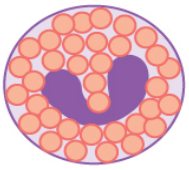
INNATE IMMUNITY

Because Tumamoc has such rich ecology and heavy traffic, it is important to explore the consequences of these interactions with the human immune system. The immune system protects humans from infection through a layered defense system of increasing specificity. The first line of defense includes the skin and the mucous membranes, which act as physical barriers to the outside environment. The skin also produces biochemical agents that work to kill or neutralize foreign pathogens (Z. Cohen, Innate Immunity lecture, September 5, 2013).

The next line of defense is innate immunity, which acts as a nonspecific barrier against common microorganisms and malfunctioning or injured cells. When potentially dangerous stimuli such as damaged cells, irritants, or pathogens are detected by the innate immune system, it triggers acute inflammation in an effort to remove the initial cause of injury and repair the damage. Many specific cells are involved in activating inflammation, as detailed in Table 1.0; their functions in this process are summarized. Neutrophils, basophils, and eosinophils are a subgroup of these called polymorphonuclear leukocytes (PMNs). They have specialized

functions; neutrophils phagocytose the invading agent, basophils release histamine which heightens the inflammatory response, and eosinophils defend against helminthes. Monocytes are precursors for both neutrophils and macrophages. Like neutrophils, macrophages also phagocytose foreign materials. The innate immune system also includes three other types of cells: mast cells, dendritic cells (DC), and natural killer (NK) cells. Mast cells are one of the first cells that are activated after cellular injury is detected. Their function is discussed further in the mast cell degranulation stage of acute inflammation. Dendritic cells phagocytose foreign pathogens like other cells mentioned before, but they are particularly exceptional because they present the antigens of the things that they ingest to the cells of the adaptive immune system, serving as the bridge between these two lines of defense (Janeway et al., 2001). Unlike the previous cells of the innate immune system, natural killer cells mostly work to keep the body's own cells in check. They play an important role in destroying tumors and virally infected cells. NK's contain perforin, which forms pores in the cell membrane of the target cell, causing it to lyse. They also contain granzymes which programs the target to undergo apoptosis. This is important when the cell contains virions, which will be released if the cell is lysed, but destroyed if the cell undergoes apoptosis ("Natural killer cell"). All of these cells work together to mediate nonspecific host-rejection of invading agents and tumors.

Table 1.0 Cells of the Innate Immune System

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

OpenStax College. (2013, June 21). Innate Immune Response. Retrieved from the Connexions Web site: http://cnx.org/content/m44820/1.5/

The innate immune system mediates its defense of the body through acute inflammation. The first stages of acute inflammation are: mast cell degranulation, activation of plasma systems, and release of cellular products. These stages do not occur chronologically, but simultaneously (Z. Cohen, Innate Immunity lecture, September 5, 2013). Immediately after pathogenic antigens or cellular injury has been detected, mast cell degranulation occurs, releasing histamine, neutrophil chemoattractant factor, eosinophil chemoattractant factor, and other chemical mediators into the blood. Histamine causes vasodilation and increases the permeability of the vessels so that leukocytes (white blood cells) can get to the site of injury (Z. Cohen, Innate Immunity lecture, September 5, 2013). Neutrophil and eosinophil chemoattractants draw these leukocytes to the affected site and activate them to induce phagocytosis of bacteria. Mast cells also synthesize leukotrienes, prostaglandins, and platelet activating factor, but these go into effect later than the mediators that are released via degranulation because their production takes time. Like histamine, both leukotrienes and prostaglandins induce vasodilation and increase vessel permeability. Platelet activating factor (PAF) is a bit different from these other mediators, in that it induces not only increased vascular permeability, but also platelet aggregation, inflammation, chemotaxis of leukocytes, and anaphylaxis (Zimmerman, McIntyre, Prescott & Stafforini, 2002). In addition to inflammation, mast cells play an important role in allergy and asthma, as both histamine and PAF cause dermatitis (rash) and airway constriction (Metcalfe, Baram & Mekori, 1997).

Activation of plasma protein systems is also an important part of acute inflammation. There are three cascade systems: complement, coagulation, and kinin. The complement system is activated in a variety of ways, by both the innate and adaptive immune system, and will be discussed further in relation to the adaptive immune system. The clotting cascade stops bleeding

and creates a framework that not only prevents the spread of infection by trapping the pathogen and macrophages so that they are secluded from the rest of the body, but it also creates a foundation for future repair. The end product is fibrin, which is the protein that forms the mesh framework in collaboration with platelets (Z. Cohen, Innate Immunity lecture, September 5, 2013). The kinin cascade produces bradykinin as its end product. The physiological effects of bradykinin are: vasodilation, increased vascular permeability, smooth muscle contraction in the bronchus and gastrointestinal tract, and pain (Parpura et. al, 1994).

While degranulation and activation of plasma systems are occurring, all the cells involved in immunity, both innate and adaptive (specific immunity, which will be discussed later), are secreting cytokines that contribute to the symptoms of acute inflammation. Table 1.2 provides a small sample of common cytokines, their source, and some of their actions. Note that cytokines work to heighten not only the innate immune response, but also the adaptive response.

Table 1.2 Cytokines

Cytokine	Cell source	Target	Actions
Proinflammatory Cytokines			
IL-1	Macrophage Dendritic cell	Lymphocytes Endothelial cell CNS Liver	Enhances responses Activates Fever, sickness behavior Synthesis and release of acute-phase proteins
IL-6	Macrophage Dendritic cell Endothelium Th2 cell	Liver B cell	Synthesis and release of acute-phase proteins Proliferation
TNF-alpha	Macrophage Dendritic cell Th1 cell	Endothelial cell Neutrophil Hypothalamus Liver	Activates vascular endothelium – increased permeability and stimulates adhesion molecules Activates Fever Synthesis and release of acute-phase proteins
Anti-inflammatory Cytokines			
IL-10	Macrophage Th2	Macrophage Dendritic cell	Inhibits IL-12 production Inhibits pro-inflammatory cytokine synthesis
Il-12	Macrophage Dendritic cell	CD4+T helper cell NK cell	Th1 differentiation IFN-gamma synthesis
Cytokines Involved in the Acquired Immune Response			
IL-2	T cell	T cell NK Cell B cell	Proliferation Activation and proliferation Proliferation
IL-4	Th2 cell Mast cell	T cell B cell Macrophage	Th2 cell development/proliferation Isotype switch to IgE Inhibit IFN-gamma activation
IFN-gamma	Th1 cell Cytotoxic T cell NK cell	T cell B cell Macrophage	Th1 cell development Isotype switch to IgG Activation

Marsland, A. (2006, October 23). Cytokines. Retrieved from http://pmbcii.psy.cmu.edu/core_e/cytokines.html

To summarize, there are three major components to acute inflammation: vascular alterations that result in increased blood flow and brings more leukocytes to the site of injury, structural changes in the endothelium lining of the microvasculature that allow leukocytes to leave the circulation and migrate to the tissue, and activation of these cells to eliminate the pathogen. The characteristics of inflammation include redness, fever, swelling, pain, and loss of function in the affected area. Fever is particularly useful because many pathogens cannot tolerate

the rise in body temperature. In general, inflammation is a beneficial process that repairs injuries and incapacitates or kills pathogens (Z. Cohen, Innate Immunity lecture, September 5, 2013).

ADAPTIVE IMMUNITY

Though it nonspecifically targets pathogens, the innate immune response is heavily involved in activating the body's third line of defense: adaptive immunity, which is much more specific. Inflammation increases the lymphatic flow into lymphoid tissue, which contains antigen and antigen-presenting cells (APCs). An "antigen" refers to any substance that the immune system can recognize. There are two classes of antigens: immunogens, which will induce an immune response; and toleragens, which do not induce an immune response. Under physiological conditions, the cells of one's own body are covered in toleragens, as it is not beneficial for the immune system to attack self (NovImmune, 2013). For the purposes of this paper, the term antigen will be used when referring to both antigens and immunogens. APC's include, but are not limited to, dendritic cells, macrophages, and B cells. Their functions are to present ingested antigens to T cells and produce signals necessary for the propagation and differentiation of lymphocytes. All the while complement creates pores in the microbial membrane; opsonizes bacteria, marking them for phagocytosis by macrophages (which will present the antigen to T cells); and acts as a chemotactic agent to call in other lymphocytes from both the innate and adaptive branches. However, the cells that specialize in presenting antigen to T lymphocytes and actually initiating adaptive immunity are dendritic cells (Janeway et al., 2001).

Dendritic cells (DC) are constantly engulfing extracellular material, which allows them to make a broad sweep for viruses or bacteria that may be present in the periphery. This process is known as macropinocytosis (Falcone et al., 2006). The adaptive immune response is triggered when an immature dendritic cell recognizes foreign pathogens, using the many receptors on its surface to distinguish their protein structures, such as those in bacterial cell walls. As with macrophages, when these receptors bind to a foreign antigen, it stimulates the DC to endocytose the pathogen and degrade it within specialized vesicles, which causes the DC to become activated, advancing out of the immature state. However, unlike the macrophages mentioned before, the DC's are not primarily programmed to destroy the invading agent, but to move to peripheral lymphoid organs such as the lymph nodes or the spleen. There, the DC will present the foreign antigen to T cells (Janeway et al., 2001).

T CELLS

So far, six different kinds of T cells have been described. Five of the six T cell types are helper T cells: Th1, Th2, Tfh, Th17, and Treg. The sixth type is the cytotoxic T cell (CTL). All of them arise in the bone marrow and mature in the thymus, and all have CD3 surface markers, as well CD4 or CD8, depending on the type of T cell. When T cell precursors first arrive at the outer cortex of the thymus, they are negative for both CD4 and CD8. They then become positive for both molecules, and as they mature, they become singly positive for either CD4 or CD8 (CD4 for helper T cells and CD8 for killer T cells). To reach the stage of full maturity, T cells must recognize the combination of a foreign antigen peptide combined with self major histocompatibility complex (MHC). MHC is a set of molecules on the surface of cells which mediate the interactions between T cells and other cells of the body, including leukocytes. When

they mature, T helper cells will bind MHC class II and CTLs will bind MHC class I. The selection process for T cells that effectively perform this function is rigorous in order to minimize the possibility of autoimmunity. There are three outcomes of the selection process: negative selection, non-selection, and positive selection. If a T cell binds strongly to self MHC found in the thymus, it undergoes negative selection and dies because this would lead to autoimmunity. The AIRE gene induces thymic cells to express vast variability of self-peptides normally found in other locations in the body to ensure that self-reactive T cells are removed. On the other hand, if the T cell receptor (TCR) has no affinity for MHC, it also undergoes apoptosis, resulting in non-selection. Positive selection occurs when there is "low, but real" affinity for MHC, because there is a good chance that this will result in high affinity for MHC bound to a foreign peptide (Z. Cohen, T cells lecture, October 8, 2013).

Th1 cells control intracellular pathogens such as viruses and some kinds of bacteria through cell-mediated immune responses and the induction of inflammation (Constant & Bottomly, 1997). Interferon gamma (IFN-γ) is the main cytokine released by these T helpers and its functions are: to initiate inflammation, activate macrophages and other leukocytes to phagocytose pathogens, inhibit the Th2 response, and stimulate B cells to produce IgG antibodies which enhance phagocyte connection to the pathogen. Other Th1 secretion products include: IL-2, which activates other Th1 cells, stimulates specific CTL's, and aids in creating T cell memory; IL-10, which auto-regulates Th1 activation; and transforming growth factor (TGF)-β, which enhances the activity of neutrophils (eBioscience, 2013). Th17 functions similarly to Th1. It also facilitates inflammation and aids in destroying extracellular pathogens. More recently, Th17 has also been shown to be an important factor in clearing pathogens (Korn,

Bettelli, Oukka & Kuchroo, 2009). Th1 cells are also responsible for delayed-type hypersensitivity (DTH), or Type IV immunopathology.

While Th1 is very much pro-inflammatory, Th2 reduces inflammation and helps the system heal. The cytokine products of Th2 are IL-3, IL-4, IL-5, IL-10, and IL-13 (eBioscience, 2013). Overall, Th2 cells recruit and activate M2 macrophages to the site of infection (Z. Cohen, T cells lecture, October 8, 2013), which promotes cell division and subsequently tissue repair. These M2 macrophages in turn promote further Th2 response (Mills, 2012). Th2 cells also inhibit the actions of the Th1 response, which is protective when the Th1 response becomes dangerous due to prolonged systemic inflammation (Wynn, 2003).

In contrast to Th1, Th2, and Th17, which mediate the immune response through the activation of macrophages, T follicular helper cells (Tfh) regulate the development of humoral immunity, which is mediated by the antigen action of B cells. They aid in the formation and maintenance of B cell germinal centers, where B cells mature. Here they also regulate B cell differentiation into plasma cells (mature B cells) and class-switching. These actions are accomplished through the secretion of IL-21, the main cytokine product of Tfh, and allow the B cells to be more effective against specific pathogens, a subject that will be discussed more in-depth in regards to B cells. However, Tfh does at times produce undesirable immunologic consequences such as atopy (a genetic disposition to develop allergies) and B cell-mediated autoimmunity. Because it helps B cells class switch, it allows them to produce IgE, which is a main component in allergy. The facilitation of B-cell class switching also heightens other types of B cell mediated autoimmunity. Also, studies have shown that Tfh may provide inappropriate

signals to self-reactive B cells to proliferate in many autoimmune diseases such as lupus and rheumatoid arthritis (King, Tangye, & Mackay, 2008).

The last type of helper T cells is T regulatory cells (Treg). Their effector cytokines are IL-10 and TGF- β which mainly work to suppress the effects of the other T cells in order to prevent immune reactions from getting out of hand. IL-10 works to inhibit Th1 cytokine secretion, is anti-inflammatory, and suppresses hematopoietic cells. It also inhibits APC's from presenting antigen by downregulating expression of MHC II. Similarly, TGF- β inhibits "T cell proliferation, cytokine production, and cytotoxicity". It is worthwhile to note that both of these compounds also have immunostimulatory effects, but this rarely occur in vivo. Since Treg is involved in immunosuppression and regulation, considerable research is being conducted on its future role in cellular therapies for autoimmunity, graft vs. host reactions, and allergy (Roncarolo et al., 2001).

Cytotoxic T lymphocytes (CTL) are unique in that they recognize antigen-bound MHC I, not II. Their main job is to destroy cells that are malfunctioning or producing viral antigen. Since viruses live inside the cell, they are not accessible to antibodies, rendering humoral immunity futile. However, if the cell could be altered or destroyed, the virus would also most likely be destroyed, which is where CTL's come in. These killer T cells destroy infected cells by releasing specialized lytic granules, which contain cytotoxic effector proteins such as perforins and granzymes. Perforin forms pores in the target cell membrane and granzymes are proteases which trigger apoptosis as well as an enzyme cascade which fragments the DNA of the cell and that of the virus. Another mechanism by which CTL's kill infected cells involves Fas ligand, which is

present on the membrane of activated CTL's. When Fas is ligated, caspases are activated, which causes the target cell to undergo apoptosis (Janeway et al., 2001).

Table 2.0 T cell Types

Type	Cytokine Stimulus	Effector(s)	Main Target Cells	Effector Targets/Functions
Helper T cells				
Th1	IL-12 & IL-2	IFN-γ, TGF-β, & IL-2	Macrophages, dendritic cells	Intracellular pathogens
Th2	IL-4	IL-3, IL-4, IL-5, IL-10, & IL-13	Macrophages	Tissue repair
Tfh	IL-2 & others	IL-21 & either IL-4 or IFN-γ	B cells	Class Switch Recombination and Affinity Maturation of antibodies
Th17	TGF-β plus IL-6	IL-17, IL-22 & IL-23	Neutrophils	Extracellular bacteria and fungi mediates inflammation
Treg	TGF-β minus IL-6 Stimulated by retinoic acid and IL-2	IL-10 & TGF-β	All the other types of T cells	Immunosuppression; anti-inflammatory
Killer T cells				
CTL	IL-21	Perforin/Granzymes FasL/ Fas	Infected cells	Destroy self-cells infected by virus

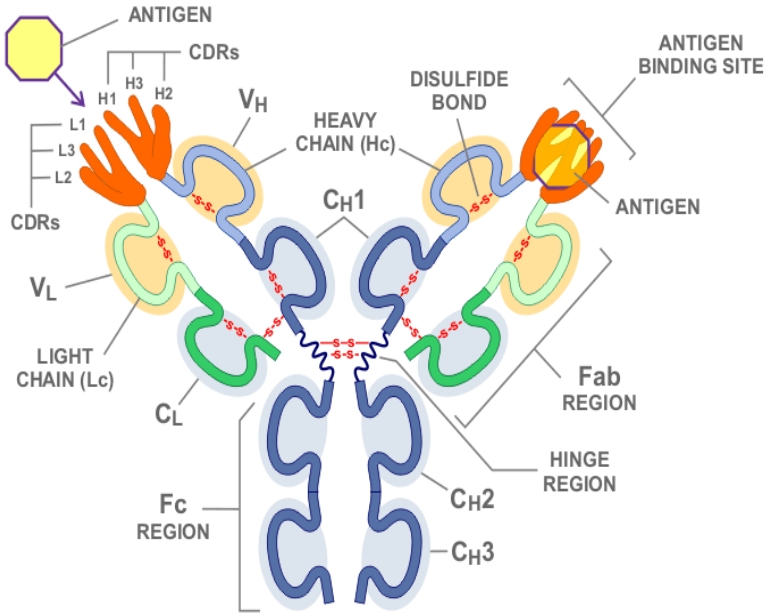
Kimball, J. (2013, August 01). Kimball's biology pages. Retrieved from http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/

B CELLS

Although T cells are among the first components of the adaptive immune system that are activated during contact with a foreign pathogen, the first components of the adaptive immune system to be characterized by scientists were the antibodies secreted by B cells. Scientists estimate that humans have about ten billion different kinds of antibodies that each bind to a particular antigen. The simplest antibodies secreted by B cells are Y-shaped, with a binding site at each tip of the arms of the Y, which results in a total of two antigenic binding sites. The tail of

the Y, or the Fc region, mediates the activation of complement. Each antibody molecule consists of four polypeptide chains linked by covalent and non-covalent disulfide bonds: two duplicate light (L) chains and two duplicate heavy (H) chains. Both light and heavy chains work together to form the antigen binding site. A comprehensive view of antibody structure is shown below (Alberts et al., 2002).

Figure 1.0 Antibody Structure



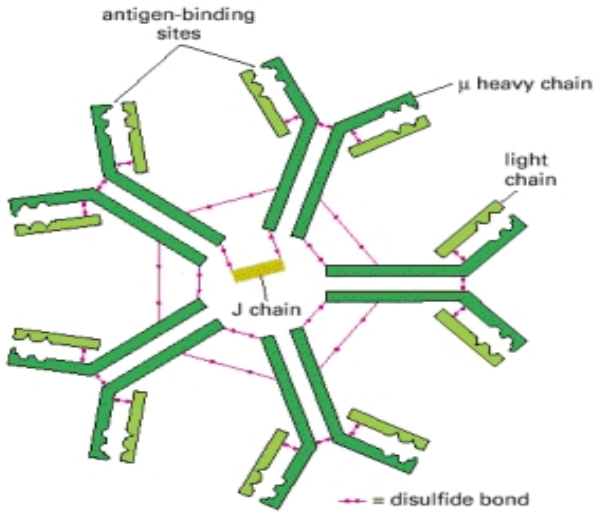
NovImmune. (2013). Science: Antibodies. Retrieved from http://www.novimmune.com/science/antibodies.html

There are five classes of antibodies secreted by B cells: IgM, IgG, IgD, IgA, and IgE, determined by the class of heavy chain: μ, γ, δ, α, and ε, respectively. Each B cell is programmed to make specific antibodies that can be of any class, but only one class is produced at a time. IgM is the first class of antibody created by all immature B cells, though mature B cells will class-switch with assistance from T helper cells as the need arises (Alberts et al., 2002). The μ chain is the first detectable immunoglobulin component in the cytoplasm of a developing B cell, called a

pro-B cell. When complete cytoplasmic IgM is formed (and the light chains are joined with the heavy chain), the B cell has become a pre-B cell. Next, surface IgM appears. When the B cell has completed maturation, both IgM and IgD are found on its surface (Z. Cohen, Ontogeny lecture, September 19, 2013). IgD is only secreted in small amounts and seems to mainly function as a surface antigen receptor.

Unlike IgD, IgM is produced in large quantities and is the first antibody present in the blood during a primary antibody response to first exposure of a novel antigen. When secreted, IgM is a pentamer, composed of five antibody units, giving it a total of ten antigen binding sites. The tail regions of these units are held together by a J (joining) chain (see Figure 1.1). Since the activation of complement requires two adjacent Fc regions, IgM is the best antibody for activating complement, having five adjacent Fc regions at all times. Complement may either opsonize the pathogen, or directly destroy it (Alberts et al., 2002).

Figure 1.1 Structure of IgM

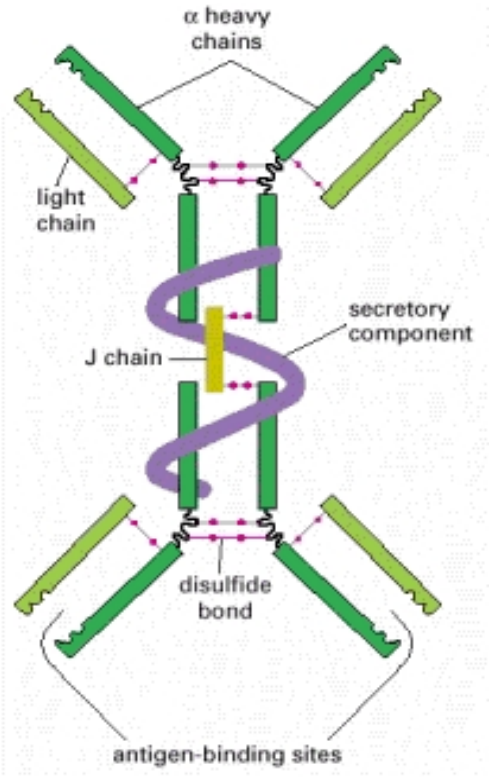


Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. B Cells and Antibodies. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26884/

Though it is great at activating complement in the blood, IgM's structure makes it too large to get into the periphery. IgG has the basic antibody structure shown in Figure 1.0, and this is one of the many reasons why it is the most abundant class of immunoglobulin in the body. Unlike IgM, which is produced in large quantities in response to the first exposure to a foreign pathogen, IgG is most abundant in a secondary exposure, so much so that it overshadows the amount of IgM. IgG can also activate complement, but not with the same efficacy as IgM. However, it is very good at binding its Fc receptors to phagocytic receptors, which then bind, engulf, and terminate bacteria coated with this immunoglobulin. Thanks to these specific Fc receptors and its size, IgG is also the only antibody that can pass through the placenta, giving the fetus passive immunity through its mother. It does this by binding with placental cells that then direct the antibody to the fetus (Alberts et al., 2002). IgG is also found in breast milk and is absorbed into the newborn's blood from its gut. Since the baby does not begin making its own IgG until about three months of age, this passive immunity provides extra protection against infection.

Another antibody found in breast milk, and in most secretions (in the lungs, intestines, saliva, tears, etc.), is IgA. In the blood, IgA has a similar structure to IgG: a monomer. However, in secretions, IgA is a dimer composed of two antibody units held together by a J chain and a secretory component as shown in Figure 1.2. The secretory component protects IgA molecules from degradation, as it is sometimes secreted in harsh environments, such as the acidic environment of the intestine. But how does IgA get from B cells to secreted fluids? Secretory epithelial cells lining these regions have special receptors for the Fc region of IgA, which binds and transports the antibodies from the extracellular fluid to the secreted fluid.

Figure 1.2 Structure of IgA



Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. B Cells and Antibodies. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26884/

Finally, there is IgE, which, like IgG and IgD, is a simple four-chain monomer. IgE is most infamous for its role in Type I immunopathology, or allergy. Unlike most other antibodies which bind to effector cells only after encountering its specific antigen, IgE can link to Fcε-receptor in the absence of bound antigen. This is due to its great compatibility with these receptors on mast cells and basophils; IgE may remain bound for months. When an antigen crosslinks two IgE molecules that are already bound on a mast cell, the mast cell immediately undergoes degranulation, releasing histamine, heparin, and TNF, much like a degranulation event initiated during inflammation. As aforementioned, the mast cell also produces prostaglandins and leukotriennes. These compounds initiate inflammation and

bronchoconstriction, both key components in allergies. Eosinophil chemoattractant factors are also released, causing eosinophils to accumulate at the scene. When these leukocytes become activated, their prolonged presence is a major contributor to tissue damage during chronic allergic inflammation. With more exposure to the allergen, the allergic response will occur more quickly. IgE production is dependent on Tfh (which are needed for class-switching) and IL-4, but developing high enough levels of antibody to cause allergic symptoms takes about seven years (Janeway et al., 2001).

ALLERGY & ASTHMA

All of these antibodies are produced by B cells and they work to protect the extracellular areas of the body. However, like almost all other areas of the immune system, B cells are responsible for some immunopathologies, such as allergies caused by IgE. Allergies are in fact one of the most commonly encountered immunopathologies in the United States, and on Tumamoc Hill. Out of the more than three hundred species of plants on Tumamoc (Rosenzweig), there are approximately twenty-six species of commonly allergenic flora, though there are additional species of uncommon allergens. A list of these species has been compiled and it can be found in the appendix. These plants usually induce symptoms in allergic individuals through the release of pollen, which normally enters the body through inhalation. The antigens in this pollen activate mucosal mast cells located underneath the nasal epithelium. These mast cells release their contents which then diffuse across the mucus membranes in the nose. This results in allergic rhinitis, characterized by local edema that blocks up the nasal passageway, runny nose,

sneezing, itching, and irritation. When pollen gets into the eye, it may cause a similar reaction, known as allergic conjunctivitis. Both of these allergies are seasonal and typically do not cause lasting damage (Janeway et al., 2001).

Allergic asthma is more serious, and occurs when the allergens have reached the lower airways, triggering submucosal mast cells. Within seconds, the bronchial airways are constricted and there is increased secretion of mucus, making it harder to breathe. Thus, asthma attacks may be fatal if not treated. There is also chronic inflammation of the airways, which are caused by Th2 cells and a variety of leukocytes, including eosinophils attracted by IgE. Though asthma is initially triggered by a specific allergen, this chronic inflammation may continue even in the absence of allergen. This often causes the airways to become more sensitive to environmental air pollutants (Janeway et al., 2001). Since Tumamoc has already been said to grow many allergenic species of flora, it is no surprise then that allergic asthma may be triggered by being in this environment. In addition, the popular hike is located only about ten minutes away from downtown Tucson, so one may infer that there are air pollutants there that might aggravate asthmatic symptoms. In order to prevent allergic symptoms, it might be beneficial to learn the specific cause of the allergies through skin or blood tests so that we can avoid encountering the antigen. As it relates to Tumamoc, allergenic plants are generally seasonal so hikers may avoid allergies by hiking during seasons in which these plants are inactive. For this reason, I have created a pollen calendar for the state of Arizona (which will also be relevant on Tumamoc) that can be found in the Appendix. In addition, antihistamines can help combat allergic symptoms should people desire to hike during allergy season.

DELAYED TYPE HYPERSENSITIVITY

In addition to allergies, it has been found that two species of plants on Tumamoc will elicit a Type IV immunopathology, or delayed hypersensitivity, response. These species are the Agave Americana (American Century Plant) and Phacelia Crenulata (Notch-Leaved Phacelia). There are two phases of delayed hypersensitivity: sensitization and elicitation. During the sensitization phase, toxic antigens from the plant penetrate intact skin and may cause itchiness. This is why it is critical to avoid even slight contact with these plant species. In the case of the Agave Americana, it is particularly important to avoid the sharp thorns on the plant, which will break skin and deliver toxin more easily. These antigens bind to MHC of dendritic cells (DC), which lie right beneath the epithelium. These DC's migrate to lymph nodes where they encounter and activate Th1 cells, which then produce memory T cells (Janeway et al., 2001). The memory T cells eventually spread throughout the body.

Left to right: Agave Americana & Phacelia Crenulata.

Kinsey, B. (2014, January 1). Southeastern Arizona Wildflowers. Firefly Forest. Retrieved April 23, 2014, from http://www.fireflyforest.com/flowers/

If the reactive antigen is encountered a second time, the elicitation phase begins as DC cells present the toxin to the memory T cells. These T cells release IFN- γ and IL-17, both inflammatory cytokines, inducing the epidermis to release its own inflammatory chemokines. These chemical factors attract more macrophages and T cells to the area (Black, 1999). This results in localized inflammation of the affected area, which is visible in six to twelve hours, and peaks after one to two days. Unlike allergies, this does not require B cells or antibodies and affects everyone who comes into contact with the antigen. Type IV immunopathology may also occur as a result of contact with microbial antigens, in which case it is advantageous for the host and is called cell-mediated immunity (Z. Cohen, Type IV Immunology lecture, October 24, 2013). Prevention of delayed-type hypersensitivity when walking on Tumamoc is mainly about not coming into contact with the species of plants that have reactive antigens. Since it is a paved hike, and straying from the trail is not allowed, hikers may breathe easy as long as they do not leave the paved walkway.

MEDIAL TIBIAL STRESS SYNDROME

Hikers or runners who frequent Tumamoc may experience another unpleasant side effect of inflammation: medial tibial stress syndrome (MTSS), more commonly known as shin splints. Risk factors for MTSS include exercise that involves repetitive activity, wearing ill-fitting shoes, and bone strain. The specific physiological cause is unknown, but is thought to be related to "an irritation of the tendons and muscles near the shin bones". Overexertion most likely damages the myocytes, and when this cellular injury has been detected by the innate immune system, inflammation is triggered resulting in pain and swelling of the affected area. Walking uphill is a repetitive motion, and when the same myocytes of the posterior tibialis muscle are continuously utilized, overexertion of these cells can occur, leading to damage. This would be seen as micro-

tears in the muscle. The innate immune system senses this cellular injury and acute inflammation is set in motion. This inflammation usually occurs at the periosteum of the bone and the tendons associated with the tibia (Kellicker, 2011). Mast cell degranulation releases chemicals such as histamine that causes vasodilation, leading to increased blood flow and quicker delivery of leukocytes such as neutrophils. Macrophages, DC's, and Th1 cells release TNF-α (tumor necrosis factor – alpha), which increases vascular permeability and stimulates adhesion molecules, which will allow the leukocytes to leave the circulation and facilitate their migration into the tissue. The increased vascular permeability will also result in edema, which is accumulation of fluid in the interstitium. Because of inflammation, the area will present with redness, swelling, pain, and loss of function (Z. Cohen, Innate Immunity lecture, September 5, 2013). However, MTSS can be prevented by: training slowly, spacing out days of exercise, incorporating warm up and stretching exercises prior to running, wearing shoes that fit properly, and changing these shoes out every five hundred miles (Kenner Army Health Clinic, 2012).

CONCLUSION

The varied ways that the human immune system interacts with the outside environment almost always lead to the defense or increased resistance of the host against foreign pathogens. This improved resistance is mediated by both the innate and adaptive immune systems, and the many complex pathways that have specific triggers. However, when things go awry and pathways are mistakenly triggered by erroneous stimuli, it may lead to consequences ranging from mild annoyance and discomfort to death. In the example of Tumamoc hill, immunopathology may result in any combination of allergies and asthma, delayed-type

hypersensitivity, or medial tibial stress syndrome. Fortunately, there are many ways to protect against these unpleasant effects, so that humans can continue to enjoy Tumamoc's rich ecology and majestic views.

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APPENDIX

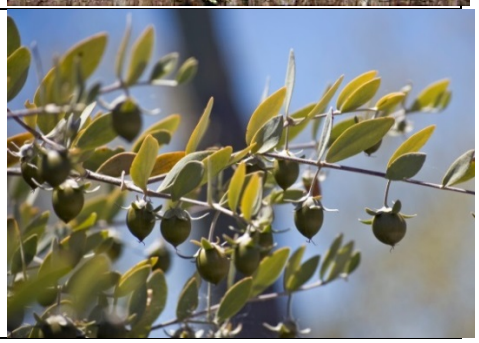
Table 1.0 Allergenic Flora of Tumamoc

Burrobush / White Bursage — Ambrosia Dumosa (Asteraceae)
Sixweeks Threeawn — Aristida Adscensionis (Poaceae)
Blue Threeawn — Aristida Purpurea Nealleyi (Poaceae)
Wheelscale Saltbush — Atriplex Elegans (Chenopodiaceae)
Wild Oat — Avena Fatua (Poaceae)
Needle Grama — Bouteloua Aristidoides (Poaceae)
Sixweeks Grama — Bouteloua Barbata (Poaceae)
Sideoats Grama — Bouteloua Curtipendula (Poaceae)
Rothrock'S Grama — Bouteloua Rothrockii (Poaceae)
Athsmaweed / Wavy-Leaf Fleabane — Conyza Bonariensis (Asteraceae)
Canadian Horseweed — Conyza Canadensis (Asteraceae)
Desert Thorn-Apple — Datura Discolor (Solanaceae)
Brittlebush — Encelia Farinosa (Asteraceae)
Stinkgrass — Eragrostis Cilianensis (Poaceae)
African Lovegrass — Eragrostis Echinochloidea (Poaceae)
Lehmann Lovegrass — Eragrostis Lehmanniana (Poaceae)
Desert Olive — Forestiera Shrevei (Oleaceae)
Blue Paloverde — Parkinsonia Florida (Fabaceae)
Foothill Paloverde — Parkinsonia Microphylla (Fabaceae)
Velvet Mesquite — Prosopis Velutina (Fabaceae)
African Sumac — Rhus Lancea (Anacardiaceae)
Jojoba — Simmondsia Chinensis (Simmondsiaceae)
Johnsongrass — Sorghum Halepense (Poaceae)
Woolly Tidestromia — Tidestromia Lanuginosa (Amaranthaceae)
Bristly Scaleseed — Spermolepis Echinata (Apiaceae)
Crimson Fountaingrass — Pennisetum Setaceum (Poaceae)
Ciliare — Pennisetum Ciliare (Poaceae)

Table 2.0 Flora of Tumamoc that Cause Delayed-Type Hypersensitivity

American Century Plant — Agave Americana (Agavaceae)
Notch-Leaved Phacelia — Phacelia Crenulata (Hydrophyllaceae)

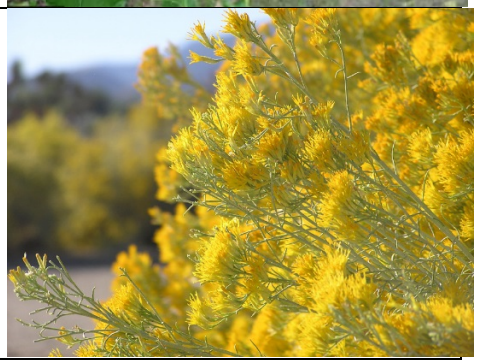
January

Common Name	Scientific Name	Time of the month	Picture
African Sumac	Rhus lancea	All	
Arizona Cypress	Cupressus arizonica	All	
Alligator Juniper	Juniperus deppeana	All	
Jojoba	Simmondsia chinensis	Late	

February

Common Name	Scientific Name	Time of the month	Picture
African Sumac	Rhus lancea	All	
Arizona Cypress	Cupressus arizonica	All	
Alligator Juniper	Juniperus deppeana	All	
Ash Tree	Fraxinus	All	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Cottonwood	Populus fremontii	All	
Triangle Leaf Bursage / Rabbit Bush	Ambrosia deltoidea	Late	

March

Common Name	Scientific Name	Time of the month	Picture
Ash Tree	Fraxinus	All	
Arizona Cypress	Cupressus arizonica	All	
Alligator Juniper	Juniperus deppeana	All	
Cottonwood	Populus fremontii	All	

Pollen Calendar for Arizona

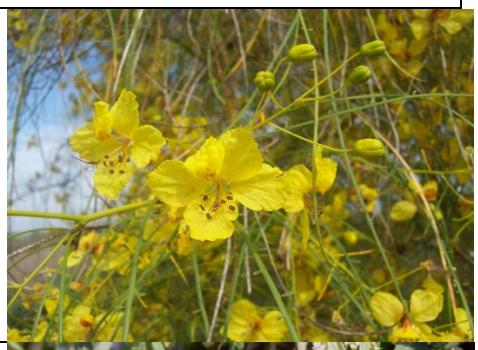
Common Name	Scientific Name	Time of the month	Picture
Mulberry	Morus	All	
Canyon Ragweed	Ambrosia ambrosioides	Late	
Triangle Leaf Bursage / Rabbit Bush	Ambrosia deltoidea	All	

April

Common Name	Scientific Name	Time of the month	Picture
Triangle Leaf Bursage / Rabbit Bush	Ambrosia deltoidea	All	
Canyon Ragweed	Ambrosia ambrosioides	All	
Bermuda Grass	Cynodon dactylon	All	
Mulberry	Morus	All	

Common Name	Scientific Name	Time of the month	Picture
Olive	Olea europaea	Last two weeks	
Mesquite	Prosopis juliflora	Late	
Sweet Acacia (Mimosa)	Acacia farnesiana	Late	

May

Common Name	Scientific Name	Time of the month	Picture
Paloverde	Cercidium	First two weeks	
Olive	Olea europaea	First two weeks	
Canyon Ragweed	Ambrosia ambrosioides	All	
Triangle Leaf Bursage / Rabbit Bush	Ambrosia deltoidea	All	

Common Name	Scientific Name	Time of the month	Picture
Mesquite	Prosopis juliflora	All	
Mulberry	Morus	All	
Ash Tree	Fraxinus	All	
Bermuda Grass	Cynodon dactylon	All	

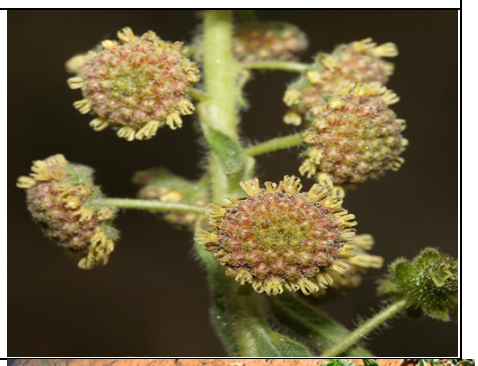
June

Common Name	Scientific Name	Time of the month	Picture
Mesquite	Prosopis juliflora	Early	
California pepper tree	Schinus molle	All	
Privet	Ligustrum lucidum	All	

July

Common Name	Scientific Name	Time of the month	Picture
California pepper tree	Schinus molle	All	
Privet	Ligustrum lucidum	All	

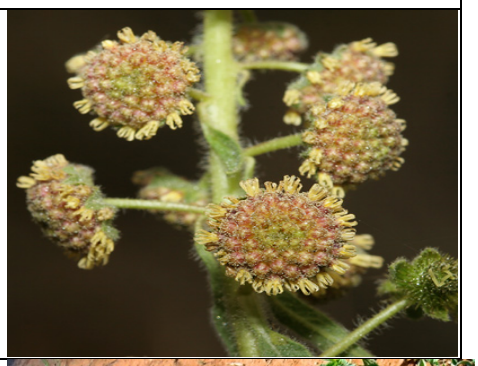
August

Common Name	Scientific Name	Time of the month	Picture
Canyon Ragweed	Ambrosia ambrosioides	Monsoon season	
Carelessweed (Palmer's Amaranth)	Amaranthus palmeri	Monsoon season	
Russian Thistle	Salsola	Monsoon season	
Bermuda Grass	Cynodon dactylon	Monsoon season	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Buffelgrass	Pennisetum ciliare	Monsoon season	

September

Common Name	Scientific Name	Time of the month	Picture
Canyon Ragweed	Ambrosia ambrosioides	All	
Carelessweed (Palmer's Amaranth)	Amaranthus palmeri	All	
Russian Thistle	Salsola	All	
Bermuda Grass	Cynodon dactylon	All	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Buffelgrass	Pennisetum ciliare	All	
Fountain Grass	Pennisetum setaceum	All	
Lehman's Lovegrass	Eragrostis Lehmanniana	All	

October

Common Name	Scientific Name	Time of the month	Picture
Slim Leaf Bursage	Ambrosia confertiflora	All	
Canyon Ragweed	Ambrosia ambrosioides	All	
Russian Thistle	Salsola	All	
Bermuda Grass	Cynodon dactylon	All	

Common Name	Scientific Name	Time of the month	Picture
Carelessweed (Palmer's Amaranth)	Amaranthus palmeri	All	
Buffelgrass	Pennisetum ciliare	All	
Lehman's Lovegrass	Eragrostis Lehmanniana	All	
Purple Threeawn	Aristida purpurea	All	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Fountain Grass	Pennisetum setaceum	All	
Rothrock Grama Grass	Bouteloua rothrockii	All	

November

Common Name	Scientific Name	Time of the month	Picture
Carelessweed (Palmer's Amaranth)	Amaranthus palmeri	All	
Russian Thistle	Salsola	All	
Bermuda Grass	Cynodon dactylon	All	
Desert Broom	Baccharis sarothroides	Late	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Fountain Grass	Pennisetum setaceum	All	
Buffelgrass	Pennisetum ciliare	All	

December

Common Name	Scientific Name	Time of the month	Picture
Carelessweed (Palmer's Amaranth)	Amaranthus palmeri	All	
Russian Thistle	Salsola	All	
Bermuda Grass	Cynodon dactylon	All	
Desert Broom	Baccharis sarothroides	Late	

Pollen Calendar for Arizona

Common Name	Scientific Name	Time of the month	Picture
Fountain Grass	Pennisetum setaceum	All	
Buffelgrass	Pennisetum ciliare	All	

Top to bottom: Lehman's Lovegrass, Sixweeks Threeawn, Foothill Paloverde, and Velvet Mesquite

Allergies

The Facts

Plant products, especially pollen, are sometimes mistakenly identified by the immune system as a threat. To combat this perceived hazard, the body produces allergic symptoms. When IgE antibodies bound on mast cells bind an allergen, the mast cells release histamine and a host of other chemicals. These chemicals cause symptoms ranging from mucus secretion to constriction of the airways. The severity of this reaction varies widely, from runny noses and sneezing to life-threatening asthma attacks (Janeway et al., 2001).

Tumamoc

About the Hill

Home to the Tohono O'odham people since 1450 and converted to the world's first restoration ecology project in 1906, Tumamoc Hill continues to make history as a U.S. National Historic Landmark, ecological reservation, and research facility of the University of Arizona. The hill is one of the most popular hikes in Tucson offering a well-paved path to breathtaking views 760 feet above the city.

Find out more: www.tumamoc.org

About – Naomi Bui

I made this brochure as part of my Honors Thesis for the University of Arizona. I am studying the applications of immunology on Tumamoc hill, one of my favorite hikes and will be graduating with a Bachelor's degree in Physiology in May 2014.

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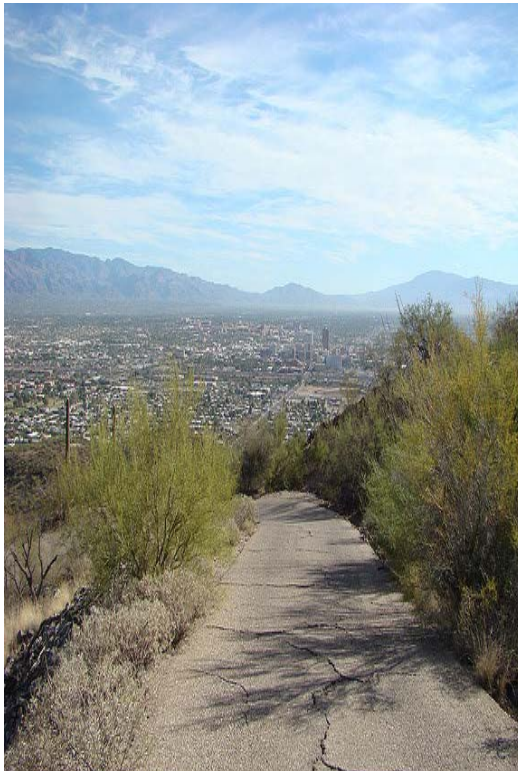


THE IMMUNOLOGY OF TUMAMOC

Staying safe on your hike!

What's the culprit?

Tumamoc is home to at least 27 different species of commonly allergic plants. The worst times to hike if you're allergic are spring, when most flowering plants are releasing their pollen, and shortly after the Tucson monsoon season, when the weeds that had dried out acquire new life. However, there are plants actively producing allergens year round. In addition, since it's located so centrally, the pollution of Tucson is another factor to consider if you suffer from allergies (Rosenzweig).

Solutions for an allergic hiker

- POLICE POLLEN- You can reduce your risk of suffering through those allergic symptoms by monitoring pollen counts at these websites:

  http://www.accuweather.com

  http://allergy.peds.arizona.edu/southwest/calendars.html
- WASH UP- Clean your clothes and your hair, especially if you use sticky hair products, as these might trap pollen
- ANTIHISTAMINES- There are many over the counter antihistamine options that will put a stop to your symptoms. If these don't do the trick, consider asking your doctor about prescription alternatives.
- KEEP YOUR NOSE CLEAN- Pollen might stick to the inner surfaces of your nose and activate the mast cells there. Almost all drug stores sell saline sinus rinses.*

*Information gathered from health.com

Get tested!

Get an allergy test to see what you are specifically allergic to. This can help you determine what time of year it's best to hike, and what times you may need an antihistamine to go without symptoms.
Resources in Tucson:

www.alvernonallergy.com
www.tucsonallergyasthma.com

Tumamoc is home to at least 27 species of allergic plants

Contact Dermatitis

What is it?

This is what happens when skin encounters specific toxins such as those from poison ivy. There are two phases to this reaction. In the first phase, immune cells in the dermis come into contact with the toxin and signal other cells to produce memory T cells. There are not enough yet to produce symptoms. If the toxin is encountered again, the second phase begins, and the memory T cells that are already there release chemicals that causes localized inflammation of the area (Janeway et al., 2001). There are two species of plants on Tumamoc which contain these toxins: the American Century Plant (Agave Americana) and the Notch-Leaved Phacelia

Avoid it

Contact dermatitis is very easy to avoid on Tumamoc because it is a paved hike. Simply stay on the trail to avoid coming into contact with these plants.

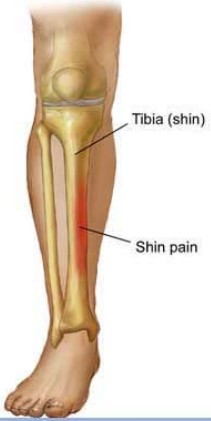
Shin Splints

…Or "Medial Tibial Stress Syndrome"

There's no official explanation for MTSS yet, but most agree that it is an irritation of the tendons and muscles near the shin bones. When a repetitive action and overexertion damage muscle cells, the body responds with inflammation. This causes swelling and pain.

Prevention

- Train slowly, don't overexert yourself
- Space out days of exercise
- Incorporating stretching and warm up exercises prior to rigorous training
- Wearing shoes that fit properly
- Change out shoes every five hundred miles (Kenner Army Health Clinic, 2012)



Immunology of Tumamoc

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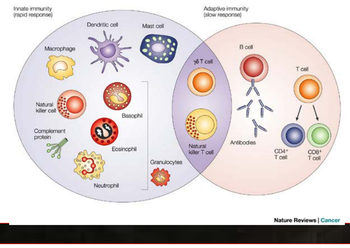
Introduction

This project explored the immunologic reactions associated with interactions with the environment of Tumamoc Hill. I concentrated on allergy, hypersensitivity reactions, and medial tibial stress syndrome (shin-splints). The project includes a literary review, a list of common allergens specific to Tumamoc, a allergy calendar & an educational brochure that was distributed to the hikers on the hill.

The Immune System

Innate Immunity: not specialized. Includes PMN's, macrophages, and mast cells, which mediate inflammation- key in almost all immunopathologies.

Adaptive immunity: specialized. Includes all the classes of T and B cells, as well as the products that they release (chemokines, antibodies, etc.)

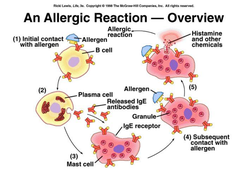


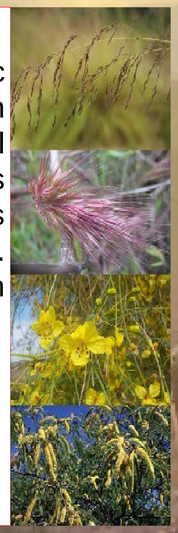
Tumamoc Hill

Home to the Tohono O'odham people since 1450 & converted to the world's first restoration ecology project in 1906, Tumamoc Hill continues to make history as a U.S. National Historic Landmark, ecological reservation, & research and UA education facility. It's also a popular hiking destinations in Tucson- offering breathtaking views 760 ft. above the city.

Allergies

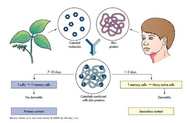
There are 26 species of common allergenic flora on Tumamoc. The Ag's in their pollen activate mucosal mast cells under the nasal epithelium. These cells release their contents which diffuse across the mucus membranes in the nose, resulting in allergic rhinitis. Allergic asthma occurs when allergens reach lower airways.





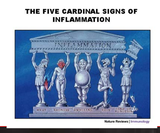
Delayed-Type Hypersensitivity

Two species of Tumamoc flora will elicit hypersensitivity: Agave Americana & Phacella Crenulata. There are two phases: sensitization and elicitation. Sensitization: toxic plant Ag's penetrate skin & bind to MHC of DC's, which migrate to lymph nodes where they encounter and activate Th1 cells, which then produce memory T cells. Elicitation: DC's present antigen to memory T cells, which release inflammatory cytokines..



Medial Tibial Stress Syndrome

(Shin Splints) Hypothesized cause: "an irritation of the tendons and muscles near the shin bones".) – risk factors include repetitive exercise, ill-fitting shoes, & bone strain. The symptoms (pain, swelling, redness, heat) are associated with inflammation.



Conclusions

On April 12, 2014, Dr. Cohen & I hiked Tumamoc & passed out brochures on the immunology of Tumamoc to hikers we passed. Though some seemed confused, everyone was receptive to the info. One lady, upon overhearing us explain the brochure to another couple actually requested to have a brochure! We also gave away brochures to a group of nursing students. We believe that we provided hikers with good information on the types of immunopathology that they might encounter while hiking the hill and ways that they might prevent the unpleasant effects of allergies, hypersensitivity, & shin splints.

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