When your body is invaded by a virus, like the flu, or by bacteria such as on a thorn that pricks your skin, your immune system works to protect you. It tries to identify, kill, and eliminate these foreign invaders that might hurt you. What is the immune system made of? It is a network of cells and tissues throughout the body that work together to fight foreign organisms and substances (called antigens) that enter the body.

White blood cells are the army of the human immune system. Although they make up only about 1 percent of blood, they are the primary mechanism for defending the body against invading bacteria, viruses, fungi, and parasites. Because blood circulates through our entire body, white cells are present everywhere. However, there are places where white blood cells are particularly concentrated – the lymph nodes and the spleen – which are the sites where the immune system launches its attack against an infection. Immune cells also concentrate in parts of the body that come in contact with the outside world through food or air, such as the mouth, nose, lungs and the gut. Many white blood cells are also found in the skin, where they can destroy any germs right where they enter the body.

The cells of the immune system

All immune cells are made in the bones. Bones are very hard, but they have a spongy core called the bone marrow. Blood cells are made from special cells in the bone marrow called hematopoietic cells. Newly made immune cells stream out from the bone marrow into the body via blood vessels. These are the cells that make up the immune system (Figure 1):

Continue on Page 2......
Neutrophil
In the event of injury or infection, the immune system reacts with a response known as inflammation. During inflammation, neutrophils, a group of white blood cells that are always present in the blood, become activated, pass through the walls of the blood vessels, and migrate to the site to destroy the germs.

Macrophage
Another type of white blood cell is the macrophage, which destroys bacteria directly by “eating” them. You will find macrophages in the lungs, liver, skin and gut.

Lymphocytes
Lymphocytes are another type of white blood cell, and they are the smallest members of the family. They can measure less than a 100th of a millimeter, or 10 microns. There are several different types of lymphocytes, each with its own specialized function. B and T lymphocytes are the most abundant. In response to antigenic stimuli, such as a bacterium, virus, parasite or transplanted organs, B lymphocytes produce antibodies, which are proteins that neutralize the antigens by binding specifically to them. After being generated in the bone marrow, T lymphocytes complete maturation in the thymus gland, and orchestrate the immune system’s response to infected or malignant cells, either by secretion of regulatory proteins called cytokines, which moderate further immune response, or by direct killing.

Distinguishing among antigens
The cells of the immune system can tell the difference between mumps virus and measles virus, for example, because they recognize them as two entirely different things. The job of distinguishing among different antigens belongs to the lymphocytes. Both T cells and B cells have special tools on their surfaces that tell antigens apart. These tools are called antigen receptors, but their shapes and functions are a little different between B cells and T cells (Figure 2).

B cell antigen receptors look like the letter “Y” and have a hole at the end of each arm. T cell antigen receptors look like rods and have just one hole at the end. Each of these holes on antigen receptors is shaped to fit only with a specific antigen. This characteristic is called antigen specificity and works like a key in a keyhole. Each lymphocyte has only one type of antigen receptor. The mumps virus will be detected only by lymphocytes with antigen receptors that “recognize” it, while cells that detect other antigens such as the measles virus will ignore it. However, all around us are millions of different germs, so the body needs to have an enormous number of different lymphocytes to protect it. Several studies have shown that there are over 10 billion different kinds of these lymphocytes, and with so many different receptors the immune system can protect the body from a huge variety of antigens.

Immunological memory
Lymphocytes can remember pathogens that they have met before so that if a person was to catch one of these pathogens a second time, they will not fall ill. This is called immunological memory. The first time a B cell meets an antigen, it takes over a week for the cell to produce antibodies against it. During this time the B cell changes itself into a cell that produces antibody. Some B cells – called memory cells – have the job of remembering the new antigen. When a memory B cell meets the same antigen again, it produces an enormous amount of antibodies in just a few days. T cells also make memory cells. T cells normally travel around the body patrolling it. When they come across an antigen, the T cells with matching antigen receptors began to divide rapidly and attack it. This response also takes about one week to build up. During this time some T cells change into memory T cells so that if they meet the same antigen again they are primed to eliminate it immediately. In this way people who have recovered from the mumps, for example, have a large number of memory B and T cells that can recognize just that virus and will protect them from getting sick with it again.
Regulation of the immune response and autoimmunity

The immune system provides the body with an extremely reliable defense system. However, it has to be restrained from reacting to every thing that it comes across, like food or pollen, or from over-reacting and causing more damage than good. The immune system can not only halt a response already underway, it can also prevent an unnecessary one from launching, including an attack against the body itself. The ability to accept the body’s own cells is called self tolerance. Newly-made lymphocytes are tested to see if their antigen receptors match the body’s own cells before they are released into the blood. For B cells this test takes place in the bone marrow, while for T cells it occurs in the thymus. Cells that have dangerous antigen receptors are destroyed on the spot. But sometimes, these dangerous cells manage to survive and reach the blood stream, where other regulatory mechanisms can destroy them. However, if this ability to tolerate itself breaks down, the body ends up under attack as the immune system mistakes the body’s own cells for invaders (Figure 3). This condition is called autoimmune disease.

The National Institutes of Health (NIH) estimates that as many as 23.5 million Americans suffer from autoimmune disease and that the prevalence is rising. Researchers have identified more than 100 different autoimmune diseases. These diseases are chronic and can be life-threatening. In an autoimmune reaction, antibodies or immune cells attack the body’s own healthy tissues. Autoimmune diseases can affect almost any part of the body, including the heart, brain, nerves, muscles, skin, eyes, joints, lungs, kidneys, glands, the digestive tract, and blood vessels.

Scleroderma is an autoimmune disease characterized by excessive production of collagen in the skin and blood vessels. In more severe forms, collagen can build up in the kidneys, lungs, heart, and gastrointestinal tract, leading in some cases to organ failure. The immune system in patients with scleroderma loses its control. Antibodies specific to the nucleus, a structure present in every cell of the body, are found in the blood of these patients and immune cells produce cytokines and other substances that cause inflammation all over the body as well as stimulate collagen production, resulting in excessive fibrosis. It is not yet understood why the body begins to attack itself. In most cases, a combination of factors is probably at work. For example, a person might have a genetic tendency to develop the disease. A virus infection or exposure to chemical substances can also be risk factors that provide the initial tissue injury which activates the immune system.

Most autoimmune diseases, including scleroderma, are treated with drugs that suppress the body’s immune system while trying to help the function of joints and organs that have been weakened by the attack. However, there are people for whom this treatment does not work or for whom the side effects, such as the weakened immune system, increase the risk of infection. Clearly, developing new treatment strategies is important.
WHAT IS THE UV INDEX?

Overexposure to the sun’s ultraviolet (UV) radiation can cause immediate effects, such as sunburn, and long-term problems, such as skin cancer and cataracts.

The UV Index, which was developed by the National Weather Service and the U.S. Environmental Protection Agency (EPA), provides important information to help you plan your outdoor activities to prevent overexposure to the sun’s rays.

The UV Index provides a daily forecast of the expected risk of overexposure to the sun. The Index predicts UV intensity levels on a scale of 1 to 11+, where 1 indicates a low risk of overexposure and 11+ signifies an extreme risk. Calculated on a next-day basis for every ZIP Code across the United States, the UV Index takes into account clouds and other local conditions that affect the amount of UV radiation reaching the ground in different parts of the country. Please visit www.EPA.Gov/sunwise for additional information on UV levels in your area. You can also download an app for your smartphone so you can access the UV levels in your area and be prepared this summer.

<table>
<thead>
<tr>
<th>UV INDEX</th>
<th>RATING</th>
<th>DESCRIPTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or less</td>
<td>LOW</td>
<td>No danger to the average person</td>
<td>You can safely stay outdoors with minimal protection. Wear sunglasses on bright days; use sunscreen if you have particularly fair skin.</td>
</tr>
<tr>
<td>3 to 5</td>
<td>MODERATE</td>
<td>Little risk of harm from unprotected sun exposure</td>
<td>The level of UVR may cause skin damage. Wear sunglasses and use SPF 30+ sunscreen, cover the body with clothing and a hat, and seek shade around midday when the sun is most intense.</td>
</tr>
<tr>
<td>6 to 7</td>
<td>HIGH</td>
<td>High risk of harm from unprotected sun exposure</td>
<td>The level of UVR can cause skin damage. Wear sunglasses and use SPF 30+ sunscreen, cover the body with sun protective clothing and a wide-brim hat, and reduce time in the sun from two hours before to three hours after solar noon (roughly 11:00 AM to 4:00 PM during summer in zones that observe daylight saving time).</td>
</tr>
<tr>
<td>8 to 10</td>
<td>VERY HIGH</td>
<td>Very high risk of harm from unprotected sun exposure</td>
<td>The level of UVR is high and dangerous. Wear SPF 30+ sunscreen, a shirt, sunglasses, and a hat. Do not stay out in the sun for too long. If you must be outside avoid the sun from two hours before to three hours after solar noon (roughly 11:00 AM to 4:00 PM during summer in zones that observe daylight saving time).</td>
</tr>
<tr>
<td>11 or higher</td>
<td>EXTREME</td>
<td>Extreme risk of harm from unprotected sun exposure</td>
<td>The level of UVR is at its highest and most dangerous. Take ALL precautions, including: wear sunglasses and use SPF 30+ sunscreen, cover the body with a long-sleeve shirt and trousers, wear a very broad hat. Avoid the sun from two hours before to three hours after solar noon unless absolutely necessary. ( roughly 11:00 AM to 4:00 PM during summer in zones that observe daylight saving time).</td>
</tr>
</tbody>
</table>
**Walk With Tori 2014**

The fourth annual “Walk with Tori” scleroderma walk in Doubs Woods Park, Hagerstown, Maryland is scheduled for Sunday, September 14, 2014.

Tori Anderson was diagnosed with scleroderma on Valentine’s Day 2008. Along with friends and family, she organizes the walk to bring awareness about the disease and to raise money to support research which hopefully will lead to finding the cause and cure. All monies raised at the event are used for scleroderma research.

*To date, Tori and her team have raised over $100,000!*  

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**CLINICAL TRIAL UPDATE**

The Scleroderma Center continues to recruit for the NIH-sponsored trial examining the use of rituximab in Scleroderma-associated pulmonary arterial hypertension.

Rituximab is an immune suppressing drug currently used by hematologists for certain malignancies such as lymphoma. It is also approved for use in rheumatoid arthritis. Rituximab eliminates B cells from the blood stream. These cells participate in immune responses and may be responsible for some types of immune injury to tissues in patients with rheumatoid arthritis, lupus, and other related diseases, including Scleroderma. It is given by vein twice, two weeks apart. This study is directed at Scleroderma patients who have confirmed pulmonary arterial hypertension (PAH or high blood pressure in the lungs) for less than 5 years, regardless of how much skin thickening they have. Half of the patients will receive rituximab and half placebo. A right heart catheterization both before the study (to determine eligibility) and after 6 months on treatment (or placebo) is required. Other PAH medications can be continued throughout the study. Patients will be followed for 1 year or until the B cells in their blood have returned.

For additional information on this trial, please contact our research coordinator, Dana Ivanco at des2@pitt.edu or 412-648-7040.

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Do you have a question regarding scleroderma that you would like answered by our Scleroderma Center team of experts?

Please send your question to Maureen Laffoon at laffoonm@pitt.edu

If your question is selected, the question and answer will be published in a future issue of the newsletter.
A FAMILY GIVES BACK

Jewel Heald, a junior in high school, appears to lead the life of a typical teenager. She maintains a high GPA and plays for both volleyball and golf teams. On weekends, she breaks from her busy schedule to travel with her parents and three dogs from their hometown of Sheridan, New York, to Peek’n Peak ski resort where she enjoys snowboarding. But, Jewel and her parents have also been living a life of pain and frustration in doctors’ offices.

“Jewel was misdiagnosed for years,” her mother, Shari, said. In 2002, she noticed a thick patch of skin the size of a quarter on Jewel's back and took her to see a dermatologist. The doctor conducted a punch biopsy, a procedure which removes a sample of skin tissue for observation, and reported Jewel as having Connective Tissue Nevus, a skin abnormality.

As the patch continued to grow, Jewel continued to see doctor after doctor. In 2007, a second punch biopsy was done, yielding the same results. Shari remembers her daughter looking up at her and the doctors, asking “Is it going to kill me?” and the doctors devastating reply, “No, but I am sorry there is nothing we can do.”

Thanks to Dr. Torok of the Pittsburgh Scleroderma Center and Jewel's local physician at the Women & Children's Hospital of Buffalo, her scleroderma has stopped spreading and appears to be decreasing in thickness. Jewel says of her experience at the Pittsburgh Scleroderma Center, “Everyone there was so nice and inviting. I'm usually nervous to meet a new doctor, but not this time. Dr. Torok was one of the nicest doctors I have had, and I've been to more than I can count.” At the Center, Jewel felt that the doctors and staff truly cared about her. “I cannot thank Dr. Torok and the Pittsburgh Scleroderma Center enough for the help they have given me,” she said.

Jewel's parents share her sentiments. “We owe a lot to Pittsburgh. They gave us hope,” said Shari, “If only we would have known what she had and gotten to Dr. Torok sooner.” Shari and her husband made a generous gift in support of the work being done at the Pittsburgh Scleroderma Center. “We gave back because it is a disorder that is missed quite frequently. We went to numerous doctors and none could tell us what she had. I would love for them to figure out how to keep this from happening to other children,” Shari said.

Both Jewel and her parents believe that scleroderma deserves as much attention as any other serious disease. They know it is not easy to live with, and hope that others will be as lucky as Jewel was to stop the disease from spreading to her joints. Their greatest hope is that others will have the same heart they did to give back, so that researchers will find a way to be rid of the disease altogether.

Since receiving the diagnosis, Jewel and her family maintain a healthy outlook on life. Jewel is considering medical school after she graduates from high school. “I know I want to be a doctor, possibly a rheumatologist like Dr. Torok,” she says.

“ar of these interactions well, it is still obvious to her mother that she is bothered by them.

Since receiving the diagnosis, Jewel and her family maintain a healthy outlook on life. Jewel is considering medical school after she graduates from high school. “I know I want to be a doctor, possibly a rheumatologist like Dr. Torok,” she says.

In the summer of 2014, Jewel will be attending Envision's National Youth Leadership Forum: Careers in Medicine, in Boston. There she will gain real-world medical career experience and explore professional opportunities in the fields of medicine and healthcare. She hopes to pay it forward, helping others as she was so graciously helped at the Pittsburgh Scleroderma Center.
We would like to thank the following donors for their support of scleroderma research

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