“The body makes its own medicine.”  
— Andrew Taylor Still, 1885

“I don’t know why we’re so worried about the communists, it’s the viruses that are going to get us.”  
— Stacy F. Howell, 1958

“If you’re not smart enough to know that it can’t be done, you may be able to do it.”  
— John E. Upledger, 1975

“Before we try to change nature we should understand her.”  
— John E. Upledger, 1977

“Man’s ego is a major cause of disease.”  
— John E. Upledger, 1977
Upledger Institute International, Inc.
Workshop Admission Policy

Continuing-education workshops conducted by Upledger Institute International (UII) are designed to augment the professional practices or educational programs of healthcare practitioners. Admission requires each participant to hold a current healthcare license or certificate, or be enrolled in an educational program granting licensure or certification. Upon course completion, participants must also assume responsibility for understanding which techniques fall within the scope of their practices.

Special consideration may occasionally be given to laypersons who wish to attend our workshops. In these cases, UII carefully evaluates personal and/or professional circumstances. If granted a waiver of our licensure/certification requirement, the layperson must sign a consent form stating that completion of an Upledger workshop will not, by any means, provide licensure or certification for hands-on bodywork.

The modalities taught in these workshops demand a solid anatomical and physiological working knowledge. Therefore, all participants must assume responsibility for advance preparation.
**Policies, Procedures and Code of Ethics Relating to the CranioSacral Therapy Curriculum**

We are pleased to provide you with this training opportunity. We hope that you benefit greatly from this experience and that you apply the concepts and techniques with success in the future.

It is essential that the purity of this work and the high-quality teaching standards that have been established for this curriculum are maintained. As such, if you wish to present or teach any portion of the copyrighted material from this workshop, you must first undergo the required training and/or obtain written permission from Upledger Institute International.

Upon course completion you are invited to take advantage of the Institute’s many ongoing programs and resources. Information is currently available to help you successfully:

- Submit a press release on your continuing education experience and clinical practice
- Get articles published on techniques, applications, client cases and more
- Form a study group
- Sponsor workshops in your area
- Train to become an instructor or presenter
- Network as a technique demonstrator at trade shows

Please let us know your area(s) of interest. We will gladly assist you in determining the most productive use of your assets, as well as support you in organizing presentations, etc. Working together will ensure that the information presented is current, correct and professionally supported with collateral materials.

As a practitioner using therapies taught through Upledger Institute International, you are expected to adhere to the highest professional standards. Among these are the commitment to provide quality therapy to all persons without discrimination, to seek educational opportunities to enhance therapeutic skills, to respect each client’s right to privacy, and to accept the responsibility to do no harm to the physical, mental and emotional well-being of self, clients and associates.

Insurance reimbursement policies vary for manual therapies. If insurance reimbursement is an integral part of your practice, we encourage you to verify insurance acceptance for your profession in your state/locale.

Finally, attendance at this training is not intended to be used as a hands-on license. You must work within your professional scope of practice and abide by the rules and/or laws that govern healthcare practices in your applicable region (i.e., city, state or province).

If you have any questions about these or other issues, please contact Educational Services at 1-800-233-5880.
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Introduction

The immune system is composed of cells, organs and specialized tissues, all working together to protect its owner from invasions by viruses, bacteria, parasites, fungi, allergens and, hopefully, from our own cells when they run rampant and develop tumors. When your immune system is working properly it helps maintain your good health. Yet occasionally your immune system may become dysfunctional and cause malignant and/or autoimmune diseases.

Recently, we have begun to understand that the immune system communicates along two-way streets with the nervous system, the endocrine system, the psyche and much more. My own clinical experience has shown me that the immune system will communicate in precisely this way with a therapist who has established a trusting relationship. Patients/clients can also learn to respectfully and politely make requests of their immune systems or specific components, and they will be honored. The proof of is in the clinical results.

This workshop is about getting you acquainted with the components of the immune system, as well as the total system in a holistic sense. It’s about learning to palpate and dialogue with the immune system and its components, and helping or facilitating immune functions.

This study guide focuses upon each part of the immune system, describing it in terms we can all understand. You should read the study guide, know the topics presented, and use it as a reference manual in order to better understand patient/client situations as they arise.

We’re on a most exciting adventure together. Imagine the wonderful service you can render when you teach someone to consciously recognize and communicate with his or her own immune system and its components.

Our goal is for every one of you to become that teacher. As the lessons spread, more and more people will become self-reliant in matters of health and resistance to disease.

Enjoy, and be glad this gift has been given to us.

Sincerely,
John E. Upledger, D.O., O.M.M.
Organization of this Study Guide

This study guide is divided into three major sections. The first section contains an overview of the various parts of the immune system, the cells and molecules that make up those parts, and a description of how all those parts work together to protect us from external threat. In addition, this section contains a discussion of some of the things that can happen when something goes wrong.

The second part of this study guide contains a discussion of how to palpate and treat the immune system. The immune system is a part of the body, and can be treated like any other part of the body using the principles of CranioSacral Therapy. Its anatomy differs from most other systems in body, however, in that the immune system does not consist of a dense contained tissue like most other organs. It is instead a network of 10 billion or so loosely connected cells, communicating with each other energetically and via messenger molecules. This network-like structure has a different quality of craniosacral rhythm than does a more solid tissue, and requires some subtle modification of how we engage with it in order to treat effectively.

The third and final part of this manual contains observations that Dr. Upledger made with regard to the immune system and its parts that arose out of his many years of clinical experience treating this system of the body. This section is intended to be used as a reference manual for additional information about each aspect of the immune system.

In addition, there is an appendix that contains other, more ancillary, information that may of use in treating immune issues.
The Immune System
The Immune System
– General Overview

What Is The Immune System?

The immune system is that aspect of the body whose function is to protect us from harm. As such, the immune system is intimately concerned with issues of boundary - Where do I end and where does the rest of the world begin? - and of Self/Nonself - What is me and what is not-me? Is that which is not-me benign, or threatening? Can I live in symbiosis and cooperation with what is out there, or must I constantly defend myself against it?

One way to think of the immune system is as an organ, but unlike any other organ in the body. Rather than being dense and localized, it consists of a distributed network of roughly 10 billion loosely cooperating cells, all communicating with each other physically, energetically, and through chemical messengers. There is enormous intelligence and ingenuity within the immune system, as there is within the body as a whole, and in general it does an amazing job of protecting us throughout our lifetime.

Occasionally, however, a problem can arise. There can be confusion or miscommunication within the immune system, or it may simply require additional resources to do its job. That is where CranioSacral Therapy can help. As we shall see, it is possible to both palpate and treat the immune system very specifically.
Where is the Immune System?

Even though it consists of a distributed communications network of cells and molecules, under ordinary circumstances the immune system is NOT located everywhere in the body. The immune system guards the entry points for infection, thus there are sentinel cells just underneath the epithelial layers of the skin and mucous membranes. These sentinel cells act as garbage collectors, removing any toxins that make it past the surface barrier, but also act as the first line of defense should a bacteria or parasite attempt to enter the body.

Immune cells also patrol the blood and lymph, and occupy certain specialized immune system organs such as the thymus, the spleen, and the lymph nodes. Since all the immune cells are formed in the bone marrow, the immune system extends into the bones as well. Under ordinary circumstances, however, in the absence of inflammation, there are very few immune cells within the tissue in general. They only enter the parenchyma of the tissue when damage has occurred, when there is an infection, or an ongoing inflammatory process.

Isolation of the immune cells to particular pathways is one of the ways the body limits immune activity. These limits build tolerance into the system; that is, the immune system tolerates our own cells and does not attack them. When this tolerance breaks down, the result is autoimmune disease.
Layers of Defense
– Major Divisions of the Immune System

The immune system consists primarily of three layers of defense. The first layer is simply the physical barrier of the skin and mucous membranes. These keep out most of the stuff that needs to be kept out. While you might think that the skin is the more extensive of these two, it is actually the other way around. While we each have about 2 square meters of skin, counting the linings of the respiratory, digestive, urinary, and reproductive tracts, we have over 400 square meters of mucous membrane in our bodies.

The second layer of defense of the immune system is called the innate immune system. The innate immune system consists of a number of cells and molecules that are pre-programmed to attack in certain common scenarios, such as when they encounter proteins that are routinely found on the surface of bacteria or parasites. The response of the innate immune system is very fast and very powerful, however it does not learn from previous encounters. If it encounters a problem a second time, it will respond exactly the same way that it did the first time.

The third layer of the immune system is called the adaptive immune system. As the name suggests, the adaptive immune system is able to learn from previous encounters - it is able to adapt. It is able to create a customized response that is perfectly tailored to deal with a particular individual threat. This customized response takes time, however. Thus the body relies upon the innate immune system to respond initially to a threat and brings in the adaptive immune system if the threat continues over time or if the innate system is not able to deal with the situation by itself.

The adaptive immune system is the basis of adaptive immunity, the process by which vaccinations are able to protect us from disease.
**Actions the Immune System Takes to Defend Us**

The immune cells and molecules, working as a coordinated team, have many actions they can take to deal with a threat. Which actions are taken in any given circumstance depends upon the exact nature of that particular threat.

Immune cells can **examine or test** to see if a particular thing it encounters is or is not a threat. Certain immune cells are able to examine the surface of each of the cells in the body to determine if that cell has been invaded by a virus. Other immune cells can **transport** suspicious proteins elsewhere in the body, then **display** those proteins to still other cells, either to help determine if that protein represents a threat, or to signal that anything exhibiting that protein needs to be attacked and dealt with.

Cells and molecules of the immune system are able to bind with a threat, coating it (**opsonizing**) so that it is neutralized, or flagging it so other immune cells can find it more easily. Specific immune proteins called **antibodies** are made by the adaptive immune system that fit a particular threat protein like a lock and key, neutralizing anything exhibiting that protein and only that protein. Other immune molecules, called complement proteins, have a much more general response, attaching to anything that is non-self.

Some immune cells are able to gobble and digest foreign proteins and bacteria (**phagocytosis**). Others kill by dumping poison in the vicinity of their target (**granulosis**). Still others are able to kill bacteria and parasites by punching a hole in their outer protective membranes. Immune cells that detect that another cell has been invaded by a virus are able to tell that cell to commit suicide, causing the cell to disassemble itself in an orderly manner (**apoptosis**) that does not leave any toxic debris.

Still other cells and molecules act to coordinate and direct the action, ramping up immune activity or toning it down as appropriate.
Immune Cells

Human blood cells are divided into two main categories - red blood cells called *erythrocytes* and white blood cells called *leukocytes*. It is the leukocytes that make up the cells of the immune system. There are many different types of leukocytes. Some are part of the innate immune system; some are part of the adaptive immune system. The leukocytes that are part of the adaptive immune system are often referred to as *lymphocytes*, since many of them can be found in the lymph nodes. All these cells are made inside the bone marrow.
Immune Molecules

There are a large number of molecules produced by the cells of the immune system that serve a myriad of purposes. Molecules are used to communicate between immune cells, to control the activity of immune cells, to either activate and urge them onto the attack (pro-inflammatory molecules), or to moderate their activity and dampen down the immune response (anti-inflammatory molecules). Molecules are also used to neutralize threats. They may be tailored to bind only to a very specific threat (antibodies) or they may be able to coat or opsonize any non-self object (complement). They may kill bacteria or parasites, by poisoning them, for example. Some molecules, when injected into cells that have been invaded by bacteria cause them to commit apoptosis.

Whoever discovers a new molecule gets to name it, so there are as many terms to describe these various molecules as there are labs that discovered them. This can get very confusing at times. For example, molecules that signal between cells in general are called cytokines (from the Greek cyto-, meaning cell; and -kinos, meaning movement). Cytokines that direct immune cell traffic are called chemokines. Cytokines that control the cells of the adaptive immune system are sometimes called lymphokines. Other terms that are often used to describe immune molecules are immunoglobulins (a fancy word for antibody), interleukins (communication and control molecules), interferons (antiviral agents that can also fight tumors), and CD markers (identifying markers found on the surface of cells). And many, many others. All this nomenclature is still in flux and continues to evolve. All you really need to remember is that these are all just names for various molecules that interact with the cells of the immune system in various ways.
Important Concepts
– Antigens and Antibodies

**Antigens** are those molecules that trigger a response from the immune system. These molecules are either themselves dangerous, or are attached to things from outside from which we need to be protected. An antigen may be a simple atom, like a toxic metal ion, an organic compound, a virus, or a complex protein on the surface of a bacteria, parasite, mold, or fungus. Antigens that trigger an allergic reaction in the body are called **allergens**.

One of the ways that the body has of dealing with antigens is to make a custom designed molecule that attaches to the antigen in a very precise way, much like a key fits into a lock. This molecule attaches to the antigen in such a way that it is neutralized and is no longer a threat to the body. Such molecules are called **antibodies**.

A coupled antigen/antibody pair is called an **immune complex**. While an immune complex does not in and of itself trigger an immune reaction, residual immune complexes can cause problems if there are so many of them that the body is unable to eliminate them fast enough. They can clog up the system and contribute to an ongoing inflammatory process.
**Important Concepts**  
– **Antigen Presentation**

Once an antigen gets into the body, or a virus gets into a cell, how does the immune system know it is there? That is where antigen presentation comes in. **Antigen presentation** is the process by which one cell presents a **peptide** (a small snippet of a protein) on its surface and shows it to another cell, typically a patrolling cell of the immune system. The peptide presented may be a snippet of a protein made inside the presenting cell, or it may be part of a protein that was found floating around in the interstitial environment.

When a virus gets into a cell it takes over the protein manufacturing machinery of that cell and starts making viruses. How do patrolling immune cells know what is going on within the cells they encounter? Cells have a quality control system for the proteins being manufactured within them. Each cell routinely takes short snippets of all the proteins that are being made within that cell, transports them to the surface of the cell, and displays those snippets on specialized display molecules called **major histocompatibility complexes** (MCH's). (The term major histocompatibility complex comes about since these are the molecules on the surface of a blood cell that are examined to determine blood type.)

Patrolling immune cells examine the snippets of protein being presented and that is how they recognize what is going on within the cell. This is a very difficult task. A cell may have upwards of 10,000 MHC molecules on its surface, each displaying a small bit of a protein being made in that cell. Once a virus gets in and takes over the cell, 1 or 2 of those snippets might change. Detecting such a small change is a Herculean task that the immune system accomplishes amazingly well.
**Important Concepts**  
- **Major Histocompatibility Complexes**

MHC molecules are like hot dog buns on the surface of cells within which the peptide hot dogs are arranged. There are, in fact, two different types of MHC molecules, MHCI's and MHCII's.

**MHCI** molecules are found on the surface of every cell in the body. MHCI molecules are used by the cell to display snippets of proteins being manufactured within that cell. These molecules inform passing killer T lymphocytes what is going on **INSIDE** that particular cell. Proteins and peptide (small portions of proteins) are made up of building blocks called **amino acids**. MHCI molecules are able to display peptides up to nine amino acids long. In effect, they are like hot dog buns with closed ends that you can only use for hot dogs that are shorter than the bun. Longer hot dogs that would hang out over the ends of the bun will not fit.

**MHCII** molecules, on the other hand, are found only on the surface of certain specialized immune cells called **antigen presenting cells** (APC's). These cells are able to sample peptides floating around in the environment. When they find a peptide that is suspicious, they engulf the peptide, travel to the spleen or to a lymph node, and there present the peptide on the surface in an MHCII molecule for other immune cells to examine. In effect, they are saying to the other immune cells, "Hey, look what I found over there. What do you think?" Thus, MHCII molecules are used to inform other immune cells of what is happening in the interstitial space, **OUTSIDE** the cells. MHCII molecules are able to display slightly longer peptides, up to 15 amino acids long. They are like open ended hotdog buns into which you can put hot dogs that are longer than the bun, hot dogs that hang over the ends.
Important Concepts
– Co-Stimulation

The immune system is so powerful that if it were to get out of hand the results would be disastrous. Thus nature has devised many different strategies to keep it in check. **Pathway induced tolerance**, in which the immune cells lie under the skin and mucous membranes and patrol the blood and lymph, but do not reside within the tissue, is one example. The requirement for co-stimulation is another.

It is usually not sufficient for an immune cell to simply recognize an antigen in order to trigger an immune response. **Co-stimulation**, in which another immune cell comes along and says, "That thing is a threat. Attack it!" is also required. This is much like the system required to open a safety deposit box in a bank. You have one key, but that key alone will not get you into the box. The bank also has a key that will fit all the boxes, but without your key, the bank's key will not get you into your box either. Both keys are required for the box to open.

This requirement for co-stimulation is particularly true of the cells of the adaptive immune system. Without ongoing co-stimulation, the adaptive immune response tapers off and dies out. This safeguard prevents an immune response from going on too long, after all the antigen has been neutralized.
Organs of the Immune System

Primary Lymphoid Organs

The primary lymphoid organs are those organs within which the cells of the immune system are made and in which they mature. There are two primary lymphoid organs - the bone marrow and the thymus.

Bone Marrow

There are two kinds of bone marrow, yellow and red. Yellow or fatty bone marrow, which is found primarily in the long bones, does not produce blood cells. Blood cells are produced in red or hematopoietic (blood cell producing) bone marrow, which is predominantly found in the flat bones of the body, bones such as those of the pelvis, the sternum, the scapula, and bones of the cranial vault.

Blood cells are produced in the red bone marrow by hematopoietic stem cells. One way to think of stem cells is that they have not yet decided what to be when they grow up. They have a couple of interesting properties. They are essentially immortal, in that unlike other cells, they can reproduce over and over without losing their vitality. They are also pluripotent, meaning that they can go anywhere and become any type of cell that is needed. Put a stem cell in the liver and it will become a liver cell. Put it in the brain and it will become a neuron or a glial cell.

This is the idea behind stem cell research. Take an embryological stem cell and inject it into someone else's tissue, hoping that it will turn into the kind of cell necessary to repair that tissue. Since we all have stem cells in our bone marrow, however, one option open to us using CranioSacral Therapy is to invite the client's own stem cells to go to the location where they are needed and affect the repair. Often stem cells are quite happy to do this, they just want to be politely asked.

Cells of the innate immune system are born and mature in the red bone marrow. Once mature, they move out into the blood stream and lymphatic system. Some migrate to the spleen and to the lymph nodes. Some take up station as sentinel cells under the skin or mucous membranes.

The cells of the adaptive immune system are also born within the red bone marrow. Some of them, the B cells (B for bone marrow), also mature within the bone marrow. Other cells of the adaptive immune system, the T cells (T for thymus), travel to the thymus and mature there.
The Thymus

The thymus is a two-lobed gland about 5 cm long that is located just above the heart, just posterior to the sternum. The thymus is where T cells go to mature. For this reason, the thymus is sometimes referred to as the master immune gland. Once the T cells mature, they are required to pass two specific tests before being released out into the rest of the body. Only a small portion of the T cells that are produced are able to pass both these tests. Cells that do not pass these tests commit apoptosis. Maturation of T cells will be discussed in much more detail when we discuss the adaptive immune system.

Each lobe of the thymus consists of an outer capsule enclosing a large number of lobules inside. Each lobule has an outer cortex and an inner medulla. T cells mature in the cortex of each lobule, while mature T cells undergo testing within the medulla.

The thymus has no incoming lymphatic vessels. Like all other organs, it does have both incoming and outgoing blood vessels, as well as outgoing lymphatic vessels. Thus, immune cells are able to pass from the circulatory system into the lymphatic system in the thymus, but not the other way around.
Secondary Lymphoid Organs

Secondary lymphoid organs are those macroscopic parts of the immune system that are not involved in the production and maturation of immune cells. These include the spleen and the lymph nodes, as well as other, non-encapsulated, groupings of lymphatic tissue. Basically, secondary lymphoid organs are filters. The spleen is the primary filter for the blood. The lymph nodes and other groupings of lymphatic tissue are filters for the lymph.

In addition to their basic filtration function, a good way to think of secondary lymphatic organs is as "singles bars" where immune cells can go and meet, and hook up, with antigens. Immune cells that are travelling alone in the blood or lymph encounter relatively few antigens on their travels. They would only be exposed to what is in their immediate vicinity.

Immune cells situated in the spleen or in a lymph node are much more likely to be exposed to any given antigen, since any antigen floating in the blood or lymph will regularly be pumped through the system, passing by all the waiting immune cells as it passes through the filters. Having immune cells that wait in the filters, observing what is passing by, is a much more efficient way to examine the blood and lymph for irregularities than simply having the cells patrol the fluid itself.
The Spleen

The spleen is the body's primary filter for the blood. It removes debris from the blood, as well as old and defective red blood cells. In addition, it is a major site where leukocytes can hang out and observe what is passing by in the blood stream. Like the thymus, it has no incoming lymphatic vessels, but does have incoming and outgoing blood vessels, as well as outgoing lymph. Thus, like the thymus, it can serve as a transfer station for immune cells to travel from the blood stream into the lymphatic system, but not the other way around.

The spleen typically lies in the upper left abdominal quadrant, just posterior to the stomach, up under the left rib cage. It is nominally about 5 inches long, but its size changes depending upon how much blood it holds. In addition to its function as a filter, this ability to engorge and store blood allows the spleen to act as a reservoir, contracting to give the body a sudden infusion of blood in case of catastrophic blood loss.

The inside of the spleen consists of a number of smaller filtration units, each fed by a branch of the splenic artery. Each filter consists of two parts. Incoming blood first encounters a portion of the filter called the white pulp. Within the white pulp reside both T and B cells, which examine the incoming blood for antigens. The blood then passes through the red pulp, a region filled with macrophages which swallow and dismantle old and defective red blood cells. The blood then passes into the splenic vein and back out into the body.
**Lymph Nodes**

The lymphatic system is the "storm drain" of the body. Every cell in the body lies very close (within the thickness of a fingernail) to a capillary bed. Oxygen, fluid, and nutrients transported into the capillary beds by the arteries diffuse out into the tissue where they can be used by the cells. Carbon dioxide, fluid, and waste products diffuse back into the capillary beds where they are transported off by the venous system. Not all the fluid and waste products are able to make it back into the capillary beds, however. A small fraction remains in the interstitial space between the cells. If there was no provision for removing this excess fluid and waste, the tissue would swell up and eventually the function of the circulatory system would be compromised. (This is what happens in lymphedema, a condition where the lymphatic system itself is damaged.) It is the lymphatic system that removes this excess fluid and waste.

Throughout the tissue, small collectors gather up this excess fluid and waste and shunt it into pre-lymphatic vessels which merge to create larger and larger vessels. The fluid and waste is gradually moved along these vessels by peristaltic action of the lymphangiome muscles which surround them, eventually making its way up behind the clavicles, where it is dumped back into the venous system. Situated throughout this network of vessels are small bodies called lymph nodes. These nodes act as filters for the lymph. Since they have lymphatic vessels both coming in and out, as well as blood vessels coming in and out, lymph nodes act as transfer points that allow leukocytes to transit back and forth between the circulatory system to the lymphatic system in both directions.

Like the filter units of the spleen, the lymph nodes act as "singles bars" where leukocytes can hang out and observe any antigens that pass through. The inside of each lymph node is divided into three regions. The outer cortex contains resting and active B cells and antigen presenting cells. The next layer in, the paracortex, contains resting T cells and antigen presenting cells. The most medial layer, the medulla, primarily contains activated T and B cells.
Non-Encapsulated Lymphoid Tissues

In addition to the lymph nodes, the body has several other aggregates of lymphatic tissue. Unlike lymph nodes, these tissues are not enclosed in a capsule. These include the tonsils and the appendix, as well as Peyer's patches - patches of lymphoid tissue that filter nutrients as they transition between the small intestine and the blood stream. In addition, the body contains numerous isolated lymphatic nodules which are formed in response to infection. If a particular area is in need of greater filtration of the lymph, isolated nodules will form as necessary. These are essentially lymph nodes, but without the outer capsule.
The innate immune system is our second line of defense against invaders. It is preprogrammed to detect and respond to certain proteins that commonly appear on the surface of bacteria and parasites. Thus the innate immune system is preprogrammed to attack in many of the common scenarios that our body is exposed to. The response of the innate immune system is very fast and very powerful, however it does not learn from previous encounters. If it encounters a problem a second time, it will respond exactly the same way that it did the first time, and so on.

The innate immune system provides a very powerful deterrent to invasion by bacteria and parasites, and is also able to recognize and attack viruses that are present in the interstitial space, between the cells. However, for the most part it has no way of dealing with viruses that have already made their way into our own host cells. For that, we need the adaptive immune system.

The innate immune system consists of several components. One of the most powerful is a series of proteins called the complement system that act together as a cascade to neutralize anything that is recognized as non-self. The innate immune system also contains a wide variety of leukocytes. There are cells called phagocytes whose primary action is to engulf and digest things, particularly bacteria. There are cells called granulocytes whose primary action is to poison things that are too large to be easily digested, such as parasites. The innate immune system also contains other cells that do not fit easily into these two categories.
The Complement System

The **complement system** is so named because it complements, or helps, the cells of the innate immune system deal with invaders. It does so by opsonizing, or attaching to, or coating, anything that is recognized as non-self. The complement system consists of a group of 20 or so proteins that act very, very quickly in a cascade to attach to any unprotected surface. Once initiated, the cascade proceeds at a geometrically increasing rate until the antigen is fully neutralized. Once complement is activated, it acts as a trigger, signaling to other parts of the immune that the "attack is on."

The complement can neutralize a pathogen simply by opsonizing it sufficiently that it is no longer a threat. Complement can also serve as handles that allow other cells to more easily attach to or neutralize the invader. For example, pathogens are often quite "slimy" and are difficult for phagocytes like macrophages to grab hold of. In effect, the complement prepares the pathogen for phagocytosis. Complement proteins can also act as chemo-attractants, chemicals that recruit other immune cells to the inflammation site.

The complement cascade can be initiated in several different ways. The **classical pathway** (the one that was discovered first) relies on an antibody to first attach to the antigen. This antibody then signals to the complement system for the cascade to begin. The cascade may also occur spontaneously in what is referred to as the **alternate pathway**. In this case, no antibody is needed. Once one complement protein attaches to the antigen, which is enough to initiate the cascade. There is a third way in which the cascade can be initiated called the **lectin pathway**. This pathway utilizes certain proteins, called lectins, which are produced in the liver, which preferentially bind with certain carbohydrate molecules found on the surface of many common pathogens. The lectins act as a bridge that can facilitate attachment of the complement protein to the pathogen.
**Complement Cascade Pathways**

The alternate pathway complement cascade is the easiest to understand. It relies upon an unstable protein called C3. C3 has the property that it spontaneously breaks apart into two halves, C3a and C3b, and then very quickly recombines. The process of recombining after it breaks apart takes about 60 micro seconds. C3b is very reactive and readily attaches to anything that is non-self, so if a C3b encounters a non-self antigen within that 60 micro second window, it attaches to the antigen.

C3b has another interesting property - it facilitates the breakup of other C3 proteins. Thus, once the first C3b is attached to the antigen, it will cause other C3 molecules in the vicinity to break apart and the resulting C3b's will also attach to the antigen. This creates a positive feedback loop and results in a geometrically increasing amount of C3b attaching to the antigen surface. Other molecules in the cascade are then able to attach to the surface as well, neutralizing the surface and acting as chemo-attractants for immune cells.

The other two pathways differ only in the mechanism by which the first C3b molecule attaches to the surface of the antigen. In the antibody pathway, an antibody first attaches to the antigen, then the C3b preferentially attaches to the antibody. In effect, the antibody acts as a bridge between the antigen and the C3b. The lectin pathway is initiated in a similar way, except the lectin protein acts as the bridge. The major difference between the lectin and antibody pathways lies in the specificity of the bridge molecule. Lectin molecules will attach to many common carbohydrate molecules present on commonly encountered bacteria and parasites. Antibodies, on the other hand, are made to react to a specific antigen protein and only that antigen protein. Thus, the antibody pathway is much more targeted than the lectin or alternate pathways.
Cells of the Innate Immune System

The cells that make up the innate immune system fall into three principle categories. There are cells whose primary function is to engulf and digest pathogens. You might think of these cells as the professional phagocytes. Phagocytes are primarily responsible for dealing with bacteria and some smaller parasites. Phagocytosis is a very clean process and does not leave toxic debris. In the process of digestion, pathogens are broken down into their component amino acids that are then available as building blocks for the body to use for other purposes.

Larger parasites that are too big to engulf and digest are dealt with by another group of cells called granulocytes. Granulocytes kill by using poison, which they dump into the interstitial space around their target. This is a much messier process. Both the poison and debris from the parasite end up floating in interstitial space, causing inflammation. Under some circumstances, these toxins may be free to move to other areas of the body, causing inflammation there as well.

There is a third category of cells made up of those cells that don't fit neatly into the first two categories. These include natural killer cells and megakaryocytes.
Phagocytosis

The process of phagocytosis (engulfing and digesting) an antigen involves several steps. The phagocyte initially reaches out, grabs the antigen, engulfs it, and brings it into the cell. Once inside the cell, the antigen is enclosed within a small sack inside the phagocyte called a phagosome. There are other small sacks inside the phagocyte called lysosomes which contain chemicals capable of digesting the antigen. Lysosomes are merged with the phagosome, dumping the digestive chemicals in with the antigen, breaking it down into its component amino acids. Once the antigen is fully broken down, the resulting amino acids are excreted into the surrounding environment where they can be used as building blocks for other cellular activity.
The Professional Phagocytes of the Innate Immune System

There are two professional phagocytes in the innate immune system - monocytes/macrophages and polymorphonuclear leukocytes, often called neutrophils, or simply "polys." A third cell, the dendritic cell, is also phagocytic, but presents the engulfed antigen for other cells to look at rather than digesting it.

Monocytes/Macrophages

The name macrophage means "Big Eater." Macrophages are the largest of the immune cells and are the primary sentinel cells of the body. Monocytes are the smaller, more mobile, travelling form of the macrophage. Monocytes are one of the few cells of the immune system that are able to cross the blood brain barrier. Monocytes and macrophages are very long lived, with life spans of the order of a few months.

Many macrophages migrate (as monocytes) to a place just under the skin or mucous membrane and wait for invasion to occur. While they are waiting they act as garbage collectors, cleaning up any waste products or toxins in the area. Other macrophages migrate to the spleen or lymph nodes where they perform a similar function.

If there is inflammation in the area, macrophages may be activated, or put on alert, by an antigen presenting cell which presents the macrophage with a snippet of protein from the invading antigen. Direct contact with the antigen changes the normally sedate macrophages into vicious killing machines. If more macrophages are necessary to deal with the invasion, in addition to attracting monocytes from elsewhere, macrophages can clone themselves as necessary to build up their numbers.
Neutrophils ("Polys")

Cells are generally invisible under a microscope unless they are dyed to differentiate them from the background. Neutrophils, also called polymorphonuclear leukocytes (or "polys"), are so named because they preferentially take up dyes that have a neutral pH. (From neutro - neutral, phil - like or love.) They make up about 70% of the white blood cells in the blood stream. Neutrophils are much smaller and faster moving than macrophages, and they have a much shorter lifespan. Neutrophils typically live for only 3 or 4 days. They are not able to clone themselves, as macrophages can, but they are produced in great numbers.

Whereas a macrophage can digest things repeatedly, neutrophils can only digest something one time, then they die. They are self-sacrificing. They are like a bee that can only sting once. Neutrophils are particularly adept at digesting bacteria. Most of the pus that is found in a wound is made up of dead neutrophils and the bacteria they have ingested.
Dendritic Cells

Dendritic cells are an unusual variant of the professional phagocyte. They are one of the body's primary antigen presenting cells. Dendritic cells ingest material just like the macrophage and neutrophil, but they do not digest what they take in. Instead they store it, travel to the spleen or to a lymph node, and display the antigen on the MHCII molecules on their surface, alerting other immune cells of the presence of the antigen. As we will see, dendritic cells are one of the major control and activation mechanisms for the adaptive immune system.
The Professional Granulocytes of the Innate Immune System

There are many other cells in the innate immune system whose function is not primarily phagocytic. They use other mechanisms to deal with invaders, especially invaders like parasites that are too large to engulf and digest. In this group are the granulocytes, which kill invading parasites by dumping poison in their vicinity.

Eosinophils

Eosinophils are so named because they preferentially take up eosin, a fluorescent red that is acidic. Normally, eosinophils make up between 1 and 6% of the circulating white blood cells, although their numbers increase dramatically in the presence of a parasitic infection (eosinophilia). Eosinophils typically live for 8 to 12 hours in circulation, but can survive for 8 to 10 days in the tissue if unstimulated.

Eosinophils carry toxic chemicals within small granules distributed within the cell, chemicals such as histamines and proteins like eosinophil peroxidase, ribonulease, and lipase. Once the eosinophil is activated, these chemicals are released by a process called degranulation, and dumped into the surrounding tissue in the neighborhood of the antigen parasite.

While these chemicals are toxic to the parasite, they are unfortunately also toxic to host tissues. As we shall see, eosinophils and their cousins, basophils and mast cells, are the mechanism behind of allergic reactions.
**Basophils and Mast Cells**

Basophils are similar to eosinophils, but they preferentially take up dyes that are basic in pH, rather than acidic. They are the least common granulocyte, making up about 0.01 to 0.3% of the circulating white blood cells. Basophils have a very short lifespan of only 1 to 2 days. Like eosinophils, they contain granules that house toxic chemicals, chemicals which are dumped into the surrounding environment when the basophils are activated.

Mast cells appear similar to basophils, but rather than circulating in the blood they reside in the tissue underneath the skin and mucous membranes. They are the body's primary sentinel cell for dealing with parasitic invasion. They are much longer lived than basophils, with a lifespan typically of 6 months to a year. While it was originally believed that they were basophils that had taken up residence in the tissue, current research shows that they originate from a different precursor cell in the bone marrow than the basophil.

Like the eosinophil, both basophils and mast cells are involved in allergic reactions.
Other Cells of the Innate Immune System

Natural Killer Cells

Natural killer cells (NKs) kill by injecting poison into their target cells, causing them to dissolve. They are relatively poorly understood at the moment. Originally it was thought that they did not need activation, but could decide independently, through some mysterious mechanism, what to attack. It is true that they do not need education like the adaptive immune cells.

Current thinking is that NKs attack any cell that does not display enough MHCI molecules on its surface. They are one of the body's primary defenses against certain tumors (those which affect the density of MCHI molecules), toxic cells, bacteria, and virus infected cells.
Megakaryocytes and Platelets

Megakaryocytes and platelets are responsible for blood clotting. Megakaryocytes are large cells that are the precursors of the platelets. Fragments of the megakaryocyte detach as necessary to form the platelets themselves. Platelets do not have a nucleus. They normally circulate in the blood, but with injury and inflammation start to cling to each other and to the surrounding tissue. As they cling, they form clots, controlling bleeding.
The Inflammation Response

Injury to tissue causes a response from the body to control the trauma and eventually repair the tissue. This response is called inflammation. Typically inflammation occurs in two phases - acute and chronic. Acute inflammation is the immediate response of the body to injury. When the body sustains a wound, for example, the priorities for the body are to clean the wound (through initial bleeding), transport leukocytes into the tissue to kill any invaders that came in with the wound (constrict venules, dilate arterioles, increase permeability of capillary walls), stop bleeding (clotting), begin to repair the tissue (through the action of fibroblasts). Signs of acute inflammation are redness, swelling, heat, pain, and loss of function.

Chronic inflammation can result from an acute inflammation response to non-degradable pathogens, viral infections, toxicity, and autoimmune reactions. Chronic inflammation is characterized by the simultaneous destruction and healing of the tissue and may result in tissue destruction, fibrosis, and ultimately necrosis. It is not uncommon for a small area of chronic inflammation, a sprain that never quite healed due to nerve facilitation, for example, to act a driver for other inflammation responses elsewhere in the body. Finding and treating the initial, low grade injury along with its attendant facilitation can short circuit such a repetitive pattern.
The Adaptive Immune System

The adaptive immune system constitutes our third line of defense and is particularly effective at dealing with viruses. Unlike the innate immune system, the adaptive immune system learns from previous encounters. Whereas the innate immune system will respond exactly the same way each time to a repeated encounter with an antigen, the adaptive immune system develops a customized response. This customized response, however, takes time. Thus, the innate immune system provides our initial defense, buying time for a customized adaptive response to come on line if it is needed.

Once the adaptive immune system has been exposed to a particular antigen, it remembers that encounter, and if the exposure is repeated will respond much more quickly the second time around. This is the basis for adaptive immunity and vaccination.

Cells of the adaptive immune system are called lymphocytes. There are two main kinds of lymphocytes, B cells and T cells, named for where they mature. Like all other leukocytes, lymphocytes are formed in the bone marrow. B cells remain in the bone until they mature. T cells, on the other hand, migrate as immature cells to the thymus and mature there. B cells produce antibodies. An antibody is a customized molecule that neutralizes a particular antigen by bonding with it the way a key fits into a lock. T cells examine host cells to determine if they have been invaded by a virus or other pathogen. Once a T cell discovers such an invaded cell, it will cause that cell to commit apoptosis, effectively destroying the virus within it.
Cytokines

Lymphocytes communicate with each other via molecules called cytokines. There are hundreds of different cytokines, called by many, many different names. Examples are lymphokines, immunoglobulins, interleukins, interferons, and CD markers. There are many others. It is easy to get confused. The thing to remember is that all these cytokines are used to communicate and take action by the adaptive immune system.

Cytokines can be divided roughly into two categories, pro-inflammatory molecules that tend to encourage the inflammatory response, and anti-inflammatory molecules that tend to discourage it and dampen down the inflammation.
B Cells

B cells produce antibodies, molecules programmed to interact with and neutralize specific antigens. Like all immune cells, B cells are produced in the bone marrow. They remain in the marrow until the mature. This maturation process requires several steps. Once mature, the B cell moves outside the bone marrow and typically will take up residence in a lymph node or in the spleen. Inactive B cells wait there looking for the antigen to which they are pre-programmed to respond. Once exposed to that antigen, they activate and begin to produce antibodies. A single activated B cell can make 10 million antibodies per hour.

On the surface of B cells are many B cell receptors (BCRs), Y-shaped molecules that interact with molecules in the environment of the cell. It is the BCR that is programmed to fit a particular antigen. Antibodies produced by an activated B cell are reproductions of this BCR combined in various ways.
DNA Recombination

The process by which B and T cells are programmed to detect a specific antigen is called DNA recombination. Lymphocytes shuffle, or recombine, their DNA to program for a particular BCR, and thus to program for response to a particular antigen. Thus, lymphocytes have slightly different DNA than do the other cells of the body.

It has been calculated that about 100 million different BCRs are needed to cover all the possible antigens that the adaptive immune system may encounter. Since each B cell is programmed to deal with one and only one antigen, that means we need about 100 million different programmed B cells. DNA is like a code that contains information about all the proteins the body may need to make. There is not sufficient memory storage capacity in the DNA if the DNA simply contained instructions for making all 100 million of these different molecules; it would more than use up all the information capacity of the DNA. Instead the DNA in the lymphocytes is programmed by selecting individual sequences from a number of possible alternatives in a number of different categories, altering the DNA in the programmed lymphocyte from the normal DNA of other cells. This random selection process allows for a large number of BCRs to be produced from a very few number of gene segments.

By way of analogy, consider two brothers that each own a sandwich deli. These two brothers have very different business models. One brother decides that he wants to have all the sandwiches premade, so when a customer comes in all they have to do is pull the premade sandwich off the shelf. The other brother decides to make each sandwich from scratch whenever a customer comes in and places a particular order.

Let's assume that the deli has 10 different kinds of bread, 10 different kinds of meat, 10 different kinds of add-ons like lettuce, cheese, onions, etc., and 10 different condiments. How many possible sandwich types are there? That is an easy calculation. There are 10 x 10 x 10 x 10, or 10,000 different possible sandwich combinations. The first brother would have to provide storage for 10,000 different sandwiches, many of which would never be ordered. This would require enormous storage capacity for a deli. The second brother merely has to store the ingredients, a much simpler proposition. DNA recombination works in exactly the same way.
B Cell Activation

BCRs on the surface of B cells can bond with antigen floating along in the blood or lymph. The body has many defenses against overreaction by the immune system, however, and simply encountering its corresponding antigen is not enough to activate a programmed B cell. B cell activation requires clustering of many BCRs on the surface of the B cell. This clustering occurs when an encounter with a sufficient number of antigen molecules all in one place bond to a number of BCRs, causing them all to migrate to one position on the surface of the B cell. If enough bonded BCRs cluster in a small enough area of the surface, the B cell will activate.

It is also possible for B cells to be activated by a combination of clustering and co-stimulation by a helper T cell. This requires a smaller amount of clustered BCRs than does clustering alone. In effect, the helper T cell says to the B cell, "This thing you are being stimulated by, it is important. Go ahead and activate."

There are several other steps required once a B cell is activated before antibodies can be made. The first step is the reproduction of the activated B cell. The B cell clones itself so that there are now many, many activated B cells. There are also a number of different types of antibodies, each consisting of copies of the BCRs combined in various ways. It is necessary for the B cells to decide which type of antibody is most appropriate. Then the antibody must be fine tuned so that it exactly matches the offending antigen. Only then will the B cells begin to make antibodies.

B cells that are actively making antibodies are called plasma cells. Plasma cells are able to make 10 million finely tuned antibodies per hour. They only live for a few days, however. Responding to an infection requires a very fine touch so that the infection is contained with minimal damage to host tissue, and with minimal amount of antigen/antibody pairs produced that all must be detoxified from the system. The relatively short lifespan of an activated B cell is one of the ways the body controls the adaptive immune response to make sure it does not get out of hand.

A few of the activated and fine tuned B cells do not become plasma cells, but instead become memory cells. Memory cells remember the encounter with this particular antigen and hang around for a long time, often years, in case of another encounter. This is the basis of adaptive immunity.
**Types of Antibodies**

Another term for antibody is immunoglobulin. There are a number of different types of antibodies, each consisting of copies of BCRs combined with other molecules in various ways. These different antibodies have different half-lives and different properties.

**IgM Antibody (Immunoglobulin M)**

This is the first antibody produced in an encounter. IgM has a half-life of 1 to 5 days in the body. IgM consists of five copies of the BCR all bonded together, thus each molecule has five chances to bond with the antigen, making it a very powerful antibody. IgM is also very good at fixing complement molecules, making it ideal for initiating a complement cascade.

**IgG Antibody (Immunoglobulin G)**

IgG is the most abundant antibody in the blood. It has a half-life of between 7 and 23 days. The body's IgG response begins to come on line just as the body's IgM response is beginning to die down. IgG consists of only a single copy of the BCR. IgG is also able to fix complement. Unlike the other antibodies, IgG is able to pass through the placenta and is the basis for a lot of the immunity that babies acquire from their mothers.

**IgA Antibody (Immunoglobulin A)**

IgA is overall the most abundant antibody in the body, making up about 75% of all the antibodies produced. It is specifically made to guard mucosal surfaces. IgA has a half life of 1 to 7 days. IgA consists of two copies of BCR attached together. Unlike the other antibodies, IgA is a very poor activator of the complement system and opsonizes only very weakly.

**IgE Antibody (Immunoglobulin E)**

Like IgG, IgE consists of a single copy of the BCR. IgE is particularly focused on dealing with parasites and as such, works closely with the professional granulocytes of the innate immune system. It binds well to receptors on mast cells, basophils, and eosinophils. IgE antibodies are found only in mammals.

IgE plays a strong role in allergic reactions. Early exposures to an allergen create plasma cells which produce IgE antibodies. When these antibodies bind to a mast cell, basophil, or eosinophil they prime that cell to degranulate immediately in the presence of the antigen. This leads to a very fast, and often excessive, reaction by the immune system to the offending allergen.
**T Cells**

Bacteria, parasites, and viruses that are floating around in the blood, lymph, or interstitial fluid are fair game for the cells of the innate immune system, the complement system, and antibodies produced by the B cells. How does the body cope, however, with a virus that is hiding within a cell? Such viruses are not accessible to these mechanisms. In addition, viruses are very good at hiding. Once a virus gets into a cell and takes over the protein manufacturing machinery of that cell, often only one or two of the 10,000 or so protein snippets being displayed on the MHCI markers on the surface of the cell will change. It is very difficult for the immune system to even discover which cells have been invaded and which have not. The body has evolved T cells to deal with this problem.

There are several types of T cells, categorized according to their functions. **Killer T cells** are the cells that cause cells which have been infected by a virus to commit apoptosis. They are also called **cytotoxic T lymphocytes**, or **CTLs**. Other cells called **helper T cells** coordinate T cell activity. **Suppressor T cells** dampen down the adaptive response when it is no longer needed. There are also **memory T cells** that serve the same function as memory B cells, retaining a memory of exposure to certain antigens so that any future exposure can be dealt with more quickly.

A very important distinction between B cells and T cells is that BCRs on the surface of B cells can bind to antigens floating around in the interstitial environment. T cells cannot do this. T cells have similar receptors on their surface called **T cell receptors (TCRs)**. Unlike BCRs, TCRs can only bind to snippets of antigen that are being presented on MHC molecules of other cells. They cannot bind to antigen that is floating free.

Once they are activated, T cells will investigate the snippets of proteins being displayed on the MHCI molecules of cells suspected of harboring a virus. Once it detects the antigen on the surface of such a cell, the T cell will instruct that cell to commit apoptosis. During this process, the cell will dismantle itself in an orderly manner, taking apart its proteins into their component parts. At the same time, it will similarly dismantle any viruses inside the cell, rendering them harmless.
How Do T Cells Mature?

T cells are formed in the bone marrow then move to the thymus. There they are programmed to a specific antigen via DNA recombination in a manner very similar to that experienced by B cells. Being programmed is not enough, however. Before they are released into the blood stream they must pass two very specific tests.

The first test is to see whether or not they can recognize self MHC molecules. Those T cells that cannot recognize them are rejected and commit apoptosis. The second test is to see whether they are able to recognize self peptides. The correct answer to this question is NO. T cells that do recognize self peptides are also rejected and commit apoptosis. If you think about it, this makes sense. The presence of T cells that reacted strongly to self peptides would inevitably lead to autoimmune disease, triggering the adaptive immune system to attack the body's own tissues. Only about 3% of T cells produced are able to pass both tests and reach full maturity.
Antigen Presenting Cells

The T cell adaptive immune response is initiated by antigen presenting cells (APCs) that present antigens to the T cells causing them to activate. The samples of antigen are presented on MHCII molecules located on the surface of the APCs. There are three primary APCs - dendritic cells, activated macrophages, and activated B cells. Of these, the dendritic cell is the most important. Dendritic cells act as the "coach" of the adaptive immune system. Dendritic cells decide which antigens are important enough to warrant an adaptive immune response.

Dendritic cells are an unusual variant of the professional phagocyte. Dendritic cells ingest material just like the macrophage and neutrophil, but they do not digest what they take in. Instead they store it, travel to the spleen or to a lymph node, and display the antigen on the MHCII molecules on their surface, alerting other immune cells of the presence of the antigen. Although dendritic cells are one of the major control and activation mechanisms for the adaptive immune system, they are in fact part of the innate immune system. Thus, the innate immune system controls the adaptive immune response, only triggering an adaptive response if it is needed.
Helper T Cells and T Cell Activation

If the dendritic cell is the "coach" of the adaptive immune system, telling the system which antigens are important and how to respond to them, it is the helper T cell that acts as the "quarterback," directing and coordinating the actual adaptive immune response. Helper T cells must be activated themselves by the APCs before they will go into action. This occurs when an APC presents the helper T with a snippet of the antigen displayed in an MHCII molecule. This, however, is not enough to activate the helper T. The helper T must also be co-stimulated by the APC at the same time. In effect, the co-stimulation says to the helper T cell, "This thing I am showing you, it is really important. Go ahead and activate."

Once the helper T is activated, it fine tunes itself, adjusting the profile of cytokines it produces to suit the situation it is presented with. There are cytokine profiles specific to dealing with viruses, profiles specific to dealing with bacteria, profiles specific to dealing with parasites, etc. Once the helper T has fine tuned itself, it activates killer T cells and periodically re-stimulates them so they maintain the attack.
Killer T Cells

Killer T cells, or cytotoxic T lymphocytes (CTLs), are the active, destructive arm of the T cell adaptive immune response. CTLs must be activated by helper T cells for them to function. Once activated, they must be continually re-stimulated by helper T’s or their response will die down. The body puts many roadblocks in the way of CTL response because it is so powerful. One would not want CTLs running wild and attacking things they should not be attacking.

CTLs typically reside in lymph nodes or in the spleen, waiting to be activated. A CTL is activated when a helper T cell shows it an antigen that matches its preprogrammed response, and simultaneously co-stimulates the CTL. Once activated, the CTL rapidly proliferates, making clones of itself to build up its numbers. The CTLs then leave the lymph node or spleen and search for the invaders. Once they find the site of the infection, the CTLs exit the blood stream and enter the tissue. There they begin to examine the peptides displayed on the MHCI molecules of the tissue cells, looking for the antigen for which they are programmed.

When they find a cell that is infected, they bond with that cell and inject that cell with a vesicle containing two enzymes, granzyme and perforin. Once inside the target cell, the perforin pokes holes in the wall of the vesicle, releasing the granzyme into the cytoplasm of the target cell. The granzyme initiates the chain reaction that causes the cell to commit apoptosis. When the cell commits apoptosis, any DNA inside the cell is disassembled into its component amino acids. This includes any viral DNA.
Suppressor T Cells

Suppressor T cells, also known as regulatory T cells are T cells that act to limit the action of the CTLs, acting to keep the CTLs in check. They down-regulate the immune response, help maintain tolerance to self-antigens, and act to suppress autoimmune responses. This is an important "self-check" built into the immune system to prevent excessive reactions. These T cell variants are not well understood. They may be a version of the helper T cell.
Memory T Cells

Most activated T cells have a limited life span and commit apoptosis after a time. This acts as a further check on their activity. However, like B cells, some of the activated T cells stick around. They do not maintain their activation, but remember their experience with the target antigen, in a manner similar to memory B cells. If they are exposed to the same antigen again, they will be able to mount a much faster and more powerful response the second time around.
When Things Go Wrong

Problems can occur in the immune response in a number of ways. It is possible that the person's vitality is low and the immune system is too weak to deal effectively with an incoming threat. This may be due to diet, stress, or other lifestyle issues. We all know if we push ourselves too hard and do not get enough sleep, we are more likely to come down with a cold. Some viruses and bacteria are very good at fooling the immune system. Other situations can arise that cause the immune system to take inappropriate action, sometimes even causing it to attack the body itself.

Here is a partial list of some conditions that may compromise the immune response.

- Chronic Inflammation
- Chronic Infection
- Inappropriate Normal Immune Response
- Defects in Immune Regulation
- Autoimmune Disease
- Immune Deficiency
- Cancer
Chronic Inflammation

As modern humans we live in an increasingly toxic environment. This has led to an increase in so called "lifestyle diseases," that have as a common denominator low grade chronic inflammation. There are many contributing factors to this pattern, including diet (eating mostly high sugar, high fat, highly processed, low nutrient content foods), food sensitivities (gluten, dairy, etc.), environmental toxicity (heavy metals, organic compounds, pesticides, etc.), sedentary lifestyle, and stress, to name just a few.

Often these lifestyle diseases are treated symptomatically, without any thought given to the underlying cause, with the result that the patient is given a multitude of drugs to treat his multitude of symptoms, further increasing the toxic load on the body. It is no wonder that diabetes and obesity rates are increasing rapidly in our culture and that the cost of medical care continues to climb precipitously.

CST can be a useful part of an overall treatment strategy for chronic inflammation that not only addresses its underlying causes, but focuses on creating health rather than merely combating disease.
Chronic Infection

Low grade chronic infection can play havoc with the body and its defenses. Particularly insidious infections of this type are blood borne diseases transmitted by ticks, fleas, and mosquitoes. Two examples of this are malaria and Lyme.

Malaria is an infection caused by a parasite that is transmitted by the bite of the anopheles mosquito. The parasite invades the red blood cells and can cause fever, vomiting, convulsions, and brain damage, among other symptoms. Malaria is found mostly in the tropics. It is most wide spread in Africa, but is also found in South East Asia and South America. To give you an idea of the enormity of the malaria problem facing Africa, it has been estimated that the difference in gross domestic product between the continent belonging basically to the Third World, and Africa belonging to the First World community of nations is due essentially to the loss of productivity and other costs that malaria places on African economies.

Here in the United States we do not have malaria, but rather Lyme disease. Lyme disease is caused by a spirochete bacteria similar to syphilis that is transmitted by the bite of a tick. Initial infection usually results in severe flu-like symptoms, inconsistently with a bulls-eye pattern rash surrounding the bite. A second stage of infection, sometimes coming years later is often characterized by meningitis and encephalitis. Final stages of the disease can mimic many other illnesses as the bacteria invade many different parts of the body. Symptoms can include arthritis, headaches, fatigue, and peripheral neuropathy, among others. Some doctors have estimated that Lyme disease is the fastest growing epidemic in the United States.

First stage Lyme can often be eradicated successfully with antibiotics. Lyme, however, like malaria is characterized by a dormant cyst phase which is resistant to antibiotics as well as to the efforts of the immune system. In addition, Lyme bacteria can exist in a cell-wall deficient (CWD) form that lacks many of the markers targeted by the immune system. Once the disease is established these alternate forms can make Lyme difficult for conventional medicine to treat. There is some evidence that antibiotics encourage the conversion of the bacteria from the active spirochete form to the CWD and cyst forms.

In many cases chronic stages of these diseases cannot be cured, but must be managed to prevent and minimize flare ups. CST may be of help to support the immune system in targeting these difficult to manage organisms.
Inappropriate Normal Immune Response

Sometimes the normal immune response is inappropriate for the circumstance. Then, even though the immune system is behaving normally, damage to the body may occur because the normal response is not the correct one.

Two examples of this are tuberculosis and methicillin-resistant staphylococcus aureus (MRSA), an antibiotic resistant super-bug often found in hospitals. Both these bacteria are able to interfere with normal macrophage activity. The tuberculosis bacteria is able to prevent fusion of the lysome with the phagosome inside the macrophage. This prevents the digestive chemicals from being dumped in the vicinity of the bacteria. The macrophage tries to destroy the bacteria, but it does not work.

MRSA takes this one step further. It does not prevent fusion, but instead resists the effects of the digestive enzymes in the lysome. Since these enzymes have no effect on the MRSA bacteria, the macrophage dumps more enzymes into the phagosome, then more, then more, until eventually the phagosome boundaries fail, releasing the enzymes into the body of the macrophage, killing it. The MRSA bacteria then continues on its merry way, unaffected by the activity of the now dead macrophage.

Another situation involving inappropriate immune response is sepsis or whole body infection, often referred to as blood poisoning. Technically, sepsis is the combination of bacteremia (bacterial infection of the blood) combined with systemic inflammatory response syndrome (SIRS). In effect, the infection is so widespread that the immune system has trouble coping. The immune system reacts properly, but is overwhelmed and does too much. It over-reacts, pushing the person into septic shock. This can cause multiple organ failure and eventually death.
Defects in Immune Regulation

Sometimes the immune response is too aggressive for a given situation. If an aspect of the immune response is underutilized it will lose the subtlety of its ability to respond. Unexercised, its response will be either too strong, or not strong enough. An example of this is an allergic reaction.

It could be argued that historically the most dangerous disease threat that we have ever faced as human beings are parasites. We were exposed to many, many dangerous parasites over the million years or so we have been around. Many people living in Third World conditions are still exposed to them. In response, the body has developed an extremely powerful response to deal with parasites - the granulocytes of the innate immune system.

Those of us living in First World conditions with good public hygiene and clean water supplies are almost never exposed to these threats. As a result, our body's response to parasites is underdeveloped. The system is untrained if you will, and often lacks sufficient subtlety in its response. When the granulocytes are exposed to a protein that looks like it might come from a parasite, they overreact. Often this protein is on something innocuous to which ideally the body would not react at all, but because the system has had so few encounters with real parasites, it is unable to tell the difference.

If the granulocytes of the innate immune system react to a protein to which the body has been exposed to for a long period of time, like a protein on pollen, mold, or perhaps a food we are eating, the inflammatory response they trigger will also trigger a corresponding response from the adaptive immune system. B cells will start to make IgE antibodies to the protein that triggered the inflammation. These IgE antibodies will bind to mast cells, priming them to react strongly to the next exposure of the antigen. This is an appropriate response if the antigen is a protein on a parasite. It is not appropriate, however, if the antigen is a protein on something that is innocuous. Pre-primed mast cells are like little grenades, waiting to go off at the slightest touch of the innocuous antigen. When they do go off, they wreak havoc on the body, potentially triggering a massive allergic response. If this response is large enough, it can push the patient into life threatening anaphylactic shock.
Autoimmune Disease

Autoimmune disease occurs when the immune system reacts to one of the body's own proteins. It sees the self-protein as an antigen and attacks the body itself. Autoimmune disease may be genetic in origin, or it may be non-genetic. Given how powerful the immune system is, it is not surprising that the body has many layers of defense built in to prevent the body from attacking itself. In genetic autoimmune disease some aspects of these defenses are missing or malfunctioning, breaking down the body's tolerance for itself.

Three conditions are required for non-genetic autoimmune disease to develop. First, MHC II molecules on antigen presenting cells must be able to efficiently display the self-antigen. Second, T and B cells must be able to recognize that antigen when it is presented to them, in violation of the test criteria T cells passed when they were being programmed. Finally, environmental factors must be present that act to break down the body's tolerance for itself.

Tolerance refers to the ability of the immune system to recognize and not attack the proteins made by our own cells. The immune system tolerates our own body, but vigorously attacks anything foreign that is a threat. This tolerance is built into the body in many ways, each of which either prevents the immune system from attacking our own tissue, or limits its ability to do so.

**Tolerance by Training** - T cells must pass a test in the thymus. Those that exhibit a tendency to attack our own proteins are not allowed to mature.

**Tolerance by Ignorance** - Immune cells typically reside as sentinels under the skin or mucous membranes, reside in the lymph nodes and spleen, or circulate in the blood and lymph. They do not invade other tissues of the body unless there is an injury or infection. Thus they are not normally exposed to most of the proteins made by the body. Even if such a protein could theoretically trigger an immune response, the immune system never sees it, and thus remains ignorant of its existence.

**Peripheral Tolerance** - This refers to tolerance that is imposed upon the T and B cells once they are mature and have moved on to the periphery of the body. Many safeguards exist to control and prevent over activation of this system. Chief among them is the requirement for co-stimulation for any substantial adaptive immune response to occur or continue. In the absence of continual co-stimulation activated immune cells will commit apoptosis and the immune response will die down.

**Tolerance by Activation Induced Death** - As mentioned above, continual co-stimulation is required for an adaptive immune response to continue. In its absence, activated immune cells will commit apoptosis and the immune response will die down. In addition, even with continual co-stimulation, activated immune cells have a very limited lifespan and will eventually commit apoptosis even if an ongoing infection is still present, further acting to limit the response of the immune system.
Autoimmune Disease and Molecular Mimicry

It is very common to have an autoimmune disease only develop after some other inflammatory process occurs in the body. The patient does not have autoimmune disease, they get sick, and only later does the autoimmune disease develop. Or perhaps the patient develops autoimmune thyroiditis (Hashimoto's disease) some time after a major car wreck in which they sustained a whiplash injury. This pattern occurs because of a phenomenon called molecular mimicry. The body itself has a protein that looks vaguely similar to a protein that the immune system is programmed to react to. The two molecules mimic each other.

Let us assume that the patient has a particular group of T cells that respond weakly to some self-protein in his body. This self-protein has the potential to become a self-antigen. Normally, the T cells are confined to the blood and lymph and, if the self-protein is primarily to be found out in the parenchyma of the tissue, these T cells never encounter it. Now let us assume that the patient gets an infection. Some protein associated with this infectious agent looks a bit like this self-protein. The infection changes the traffic pattern of the T cells, exposing the T cells not only to the infectious agent, but for the first time to the self-antigen as well. Even though the reaction of the T cells to the self-antigen may be weak, if it is strong enough exposure to the self-antigen can provide re-stimulation. The result will be autoimmune disease.

It does not need to be an infectious process that triggers this reaction. Sometimes a non-infectious inflammatory process will accomplish the same thing. It is very common for patients to develop a hypothyroid condition shortly after a major whiplash injury. This may be purely due to structural tension and guarding in the neck that limits blood flow to the thyroid, but it may be autoimmune in origin as well. Inflammation caused by the whiplash injury may allow T cells that react weakly to a protein in the thyroid to be exposed to that protein for the first time. The resultant reaction triggers an autoimmune disease.
**Immune Deficiency**

Immune Deficiency refers to a situation where the immune system is weakened to the point where it is unable to fight off the normal day-to-day pathogens to which we are all exposed. Immune deficiency may be either genetic in origin, or it may be acquired due to circumstances later in life. Acquired immune deficiency may be the result of malnutrition, immunosuppressive drugs (taken to combat organ transplant rejection or the effects of autoimmune disease, for example), or disease (AIDS).

AIDS (Acquired Immune Deficiency Syndrome) is caused by the HIV virus. This virus is primarily transmitted through blood via transfusions, shared needles, or unprotected sexual contact. HIV lies dormant in the cells until conditions are favorable for it to reproduce.

HIV has proven to be a particularly difficult virus to develop effective treatment strategies against. Initially a diagnosis of HIV was a death sentence. Current drug regimes are now sufficiently effective to allow infected patients to live many years with the disease. Further research offers continued promise.

There are several reasons why HIV is such a difficult problem to treat. The HIV virus mutates often, potentially rendering previously effective treatments ineffective. In addition, HIV acts by specifically targeting the cells of the immune system. When they target antigen presenting cells (T helper cells, macrophages, and dendritic cells), these cells immediately carry the virus into the spleen or into a lymph node, thereby exposing many more immune cells to the virus. Ultimately, the HIV virus invades so many immune cells that the population levels of CTL's collapse and the patient develops full blown AIDS.
Cancer

Cancer refers to a situation where some particular cells in the body start to reproduce inappropriately. The resulting mass of tissue interferes with body function and can ultimately cause death. There are internal cellular mechanisms that prevent a cell from reproducing inappropriately. Sometimes, however, these internal safeguards are overridden and cells begin to reproduce when they shouldn't.

It is not sufficient, however, for a cell to simply begin to reproduce inappropriately for cancer to develop. Cells need oxygen and nutrition. In the absence of an increased blood supply to provide this support, any mass of inappropriately dividing cells will simply wither and die. Occasionally, however, in addition to learning to reproduce inappropriately, a cell will develop a mutation that allows it to encourage the development of its own blood supply in the surrounding tissue. This can allow the tissue to grow into a substantial mass. This is still not cancer, however, but merely a benign tumor. Cancer develops when, in addition to developing a blood supply, cancer cells develop the ability to move, or metastasize, to other parts of the body. At that point, it becomes very difficult to treat.

Typically, the immune system is not much involved in this process. Cancer cells are the body's own cells. They typically display all the appropriate markers on their surface and for the most part the immune system is unable to recognize that anything is amiss. One thing we can do with CST is to dialogue with the immune system and inform it of the threat. Once the immune system is able to recognize the cancer it may be able to assist in its removal.
Palpating and Treating the Immune System
Palpating and Treating the Immune System

On the Nature of CranioSacral Therapy

CranioSacral Therapy (CST) and its relatives are unique among manual modalities. Most approaches to manual medicine are technique-oriented. The function of the therapist is to apply his or her expertise to discover the problem in the tissue. Once that problem is discovered, the therapist applies a technique to attempt to resolve or ameliorate the problem. While the techniques of CST can certainly be applied in this way, doing so is relatively inefficient and does not utilize the full power of the work.

At its core, CST is a process-oriented modality. The core principle on which CST is based is the idea that the body contains an innate wisdom, and that given the proper resources, the body will self-correct if it is able. John Upledger's term for this aspect of ourselves is the Inner Wisdom, or alternatively, the Inner Physician. The Inner Wisdom of a client has infinitely more knowledge and wisdom about what that person needs than the therapist, no matter how much assessment the therapist does. Therefore, rather than acting to try to resolve the situation or "fix" the client, the therapist's role becomes that of a facilitator supporting the Inner Wisdom. This involves being relatively passive, supporting the process, and being a witness, rather than acting on the tissue. CST is much more about "Being Present" than about "Doing To."

Treating the immune system is, in a way, no different than treating any other part of the body. All the same principles apply. We support the Inner Wisdom and the body's process as it self-corrects. We are not really doing anything new here; we are just applying what we know about CST to a new part of the body.
Palpating the CranioSacral Rhythm

The craniosacral rhythm (CSR) is the principle tool that we as CranioSacral therapists use to assess and guide our treatment of the client. As you know, the CSR is produced by the cycling on and off of the production of cerebral spinal fluid (CSF) in the lateral ventricles of the brain, and manifests globally in the body as a slow, rhythmic external and internal rotation of the tissue with a frequency of 6 to 12 cycles per minute (5 to 10 seconds per cycle).

We palpate the CSR using our proprioceptive sense, placing our hands on the tissue and allowing the tissue to move our hands, thus generating proprioceptive input. We feel the client's CSR by feeling our own hands being moved. (While it is possible to palpate the CSR using the pressure sensors of the hand by feeling the tissue move or slide under your hands, this method is much less sensitive than allowing the client's tissue to move your hands directly.)

In order to feel the CSR using proprioception, the therapist must be supremely relaxed. Any tension in the body of the therapist, particularly in the hands, arms, and shoulders, will put a lower limit on what he or she is able to palpate. Any slight movement of the client's tissue that is too subtle to overcome the internal resistance to movement of the therapist will not trigger proprioceptive input. The therapist may tune into this movement energetically, but they will not be able to palpate it physically. Thus it is vital that the CranioSacral therapist be as physically relaxed as possible when treating.

The CSR is useful precisely because it is so easily disrupted by fascial tension, which affects the symmetry, quality, and amplitude of the CSR in the tissue that is tight. In CS1 we focused primarily on using the CSR as a evaluation tool in a very global way - paying attention to the listening stations, feeling how the CSR was manifested in the feet, the legs, the hips, the ribs, etc. However, ideally the CSR manifests fully throughout the body, and all parts of the body move, or should move, in response to the CSR. This is true on a macro scale, like the listening stations, but is true on a micro scale as well.

With practice, you can learn to feel how the CSR is manifesting in very minute and precise areas of the body. You can, for example, palpate how the coronal arteries are moving in response to the CSR, or the synovial fluid of the left knee, or the retina of the left eyeball, or the right amygdale in the brain. The only limits on how precisely you can palpate are your degree of relaxation and the clarity of your intention.


**Tides - Harmonics of the Basic CSR**

Typically we speak of the CSR as a rhythmic motion of the tissue with a frequency of 6 to 12 cycles per minute, or 5 to 10 seconds per cycle. There are, however, harmonics to this movement, much like harmonics on a musical scale, and it is possible to feel similar rhythms that move at twice this speed, at four times this speed, at eight times this speed, etc., as well as rhythms that move at half this speed, and one fourth this speed, one eight this speed, etc. Sutherland was aware of these harmonics which he labeled as "tides." What we call the CSR, Sutherland called the Short Tide. The harmonic that moves at half the speed of the basic CSR (i.e. 3 to 6 cycles per minute, 10 to 20 seconds per cycle) Sutherland called Mid Tide. Long Tide moves at one quarter the speed of the CSR, approximately 1.5 to 3 cycles per minute, 20 to 40 seconds per cycle.

When John Upledger developed CST he was aware of these harmonics. He was, however, unable to demonstrate the existence of any but the basic CSR in the laboratory. He could rig up an experiment that would display the CSR (short tide) on an oscilloscope, but he was unable to externally demonstrate the existence of the other tides. Therefore, he chose not to emphasize them in CST. You may find, however, that on occasion you naturally find yourself palpating one of the harmonics other than the basic CSR.

Some therapists believe that certain tides relate to certain aspects of the body or energy field. One can easily imagine, however, palpating the mid tide simply by picking up every other cycle of the CSR. This is how harmonics in music work. Any general wave form can be broken down into contributions from each of the various harmonics. You can choose to tune into any harmonic of the CSR that you like. All the essential information about fascial tension and significance detector are contained in each of the harmonics. From this point of view, it does not matter which one you pay attention to. Work with the harmonic that you are being presented with.
**Reciprocal Inhibition**

Reciprocal inhibition, as the term is used in osteopathy, refers to the phenomenon that when two areas of restriction in the body are engaged simultaneously, one of them will temporarily release. The restriction that does NOT release is the more significant of the two. Traditionally this principle is applied by physically engaging both restrictions with firm pressure, inhibiting the more significant restriction, thus releasing (temporarily) the other. Reciprocal inhibition is quite useful in determining where to treat in order to have the maximum result for the minimum input. If the place in the body that is tightest is released, tensions in any areas that are strongly connected to that place will be reduced as well.

This concept can be generalized to apply to CST using much lighter palpation pressure. Blending and melding simultaneously with two areas of the body which exhibit reduced amplitude in the CSR will generally cause one of those two areas to begin to temporarily move in the CSR. The area that does not begin to move is a more significant restriction than the one that does. Reciprocal inhibition, combined with palpating the SQAR of the CSR as it is manifested in different areas of the body, allows the therapist to very efficiently determine the location of the cornerstone that is holding any particular restriction pattern.
How is the CSR Manifested in the Immune System?

Ideally the CSR manifests fully throughout the body, and all parts of the body move, or should move, in response to the CSR. This includes the immune system. It is part of the body and, like everything else, should move in the CSR. The immune system, however, is unlike any other tissue in the body. Rather than being dense and localized, it consists of a distributed network of roughly 10 billion loosely cooperating cells, all communicating with each other physically, energetically, and through chemical messengers. What does the CSR as it manifests in such a distributed network feel like?

The basic CSR is the same throughout the body, since all the tissues are being moved in response to the pressure changes occurring within the craniosacral system. The rate will be the same everywhere. The basic pattern of movement will be consistent throughout the body. The cranium widens in flexion and narrows in extension, away from neutral and then back to neutral. The centerline moves caudal in flexion and cephalad in extension, again away from neutral and then back to neutral. On either side of the centerline, the body rotates externally in flexion and rotates internally in extension, again away from neutral and then back to neutral. The thing that does change from one location to another is the amplitude and the quality of the movement.

The CSR manifests in all parts of the body. Not only does this include the immune system, this includes the energy field. If you place your hands on the abdomen, for example, and tune in to the CSR of the tissue there, what is the quality of the movement? Assuming the tissue is moving freely in response to the CSR, you will feel a fairly strong movement with good amplitude and lots of driving force. The tissue, being fairly dense, has a quality of solidity to its movement in the CSR. Now bring your hands slightly off the body and tune in to the CSR as it manifests within the energy field. It will move in the same direction and with the same rate as the tissue below it, but the quality of the movement will be very different. The energy field, being much less dense than the tissue, has a much more ephemeral quality to its movement - the movement feels much less solid than does that of the tissue.

The immune system, being as it is a distributed network of cells, is less dense than the tissue in general. It is, however, more dense than the energy field. This character is reflected in the quality of its movement in the CSR. Movement of the immune system in the CSR will feel less solid than that of the tissue as a whole, but more solid and substantial than the movement of the energy field. This half solid/half ephemeral quality of movement is characteristic of the immune system. Once you are able to reliably palpate it you will be able to accurately place your intention within the immune system. Once you can do that, you can then begin to palpate other characteristics of this distributed system of cells and molecules.

Remember, however, that the immune cells are only located in certain areas. Under ordinary circumstances, they are under the surface of the skin and mucous membranes, within the lymphoid organs, and floating around in the blood and lymph. There are very few immune cells in the tissue in general. This means that if you try to palpate the movement of the immune system’s response to the CSR, again in the abdomen, for instance, you will feel this half solid/half ephemeral quality of movement right under the skin. If you move your intention deeper into the tissue, however, this quality of movement will no longer be palpable, since there are no immune cells deeper in the tissue. If you extend your intention down further into the tissue, however, into the lining of the small intestine, this quality of half solid/half ephemeral movement will reappear.
There is another reason, however, why there may be no perceptible response of the immune system to the CSR in a particular part of the body. There may be immune activity present, but that activity may be dysfunctional. Just as fascial tension or other problems in the tissue can disrupt the CSR in that tissue, problems in the immune response may disrupt the immune system's movement in the CSR. It is very important to be able to distinguish this situation from one where there is no perceptible CSR in the immune system because there are no immune cells in that location. The qualitative feel of the two situations is very different.

When there are no immune cells present in the tissue, the quality of the immune system's response to the CSR has an empty feel. The system feels as if it simply is not there. When, on the other hand, there is immune activity present in the tissue but it is dysfunctional, the immune system's response feels tight and restricted, stuck, even when there is not palpable amplitude to the CSR. The first case describes the normal situation when there is no inflammation present in the tissue, and thus very few immune cells in the area. The second describes a dysfunctional situation where there is lots of inflammation and many immune cells in the tissue, but they are having trouble dealing with whatever is happening. In that case, using CST to encourage the CSR as manifested in the immune system will help the body to effectively deal with the situation, whatever that may be.
Developing Precision in Palpating the CSR

Perceiving the CSR as it is manifested in the immune system requires very subtle and precise palpation skills. It is very important to be able to put your awareness and intention precisely on the thing you are trying to palpate - at the precise physical location, with the correct degree of focus on detail macro to micro, and paying attention to precisely the correct qualitative density. All three of these characteristics exist on continuums.

**Continuums in Palpating the CSR**

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The CSR may be used to feel for fascial restrictions globally, for example, as when paying attention to listening stations. Once a general area of restriction is found, the CSR may be used to localize precisely where that problem is coming from by changing your awareness to a much more detailed focus and paying attention to exactly which depth in the tissue is restricted. You can also vary whether you choose to put your awareness on the tissue itself, the fluid in the tissue, the network of immune cells and molecules, or the energy field. In working your way from one to the next the quality of the CSR will feel progressively less dense and more ephemeral.

The more precisely you can focus your awareness and intention the better you will be able to follow the client's process and their Inner Wisdom, and the better will be the results of your treatment.
Palpating Other Characteristics of the Immune System

We have extended our definition of tissue to include a distributed communication network of cells and molecules like the immune system. The immune system moves in response to the CSR. Therefore, it will exhibit all the characteristics of other tissue in regard to the CSR. For example, one can palpate a significance detector stop within the immune system. One can also induce a stillpoint in the body by inhibiting flexion within the immune system, just as one can in the tissue in general or in the energy field.

Does such a system also exhibit other tissue-like characteristics, like fascial tension, for example? Can the network of the immune system be bent, twisted, or sheared? Stretched or compressed? Can the immune system exhibit facilitated or inhibited communication pathways? Can such a distributed system hold energy cysts? Can it contain more distributed areas of increased entropy, analogous to energy cysts but not localized? The answer to all these questions is yes. Once you are able to easily and reliably palpate into the immune system, you will discover all of these characteristics of this marvelous system and more. All of the techniques of CST that you already know can be applied to the immune system, once you are able to reliably palpate the system and feel how it is moving in response to the CSR.
Treating the Immune System Using CST

How can CST be used to enhance immune function? In a way, treating the immune system is no different than treating any other aspect of the body/mind/spirit/psyche. There is, after all, essentially only one technique in CST. We approach with neutral intent, we blend and meld, we follow and support the process, we offer energy or to be a barrier as appropriate, we dialogue as appropriate, and we follow the significance detector as our guide. The Inner Wisdom will affect the change . . . or not. That is CST in a nutshell. Working with the immune system is no different.

Having said that, there are some common themes that occur when treating the immune system.

1) Removal of structural restrictions to mobility.

Fascial restrictions in the tissue can put stress on the system and inhibit the ability of the immune system to fight disease. Fascial restrictions within the immune system itself can cause communication breakdowns within the network. Anything we can do to release these restrictions and improve the expression and SQAR of the CSR, either in the immune system itself or in the tissue as a whole will potentially be helpful.

2) Enhance fluid, energy, and information flow on all levels.

CST by its very nature improves fluid and energy flow in the body, whether that fluid is CSF, blood, lymph, or by extension, energy or communication within the immune system network. Anytime we can get fluid, energy, and information moving better within the body, the body will generally be better off.

3) Discover the presence of foreign energies and pathogenic microorganisms.

Foreign energies, whether localized like energy cysts, or not localized and more generalized in form, are like splinters. They disrupt the functioning of the body, adversely affecting it on all levels. In addition, they are often the primary generators of dysfunctional patterns and the drivers of chronic disease. Often, the body is on some level unaware of their presence. Similarly, the body may be unaware of the presence of a pathogenic microorganism. CST arcing skills can be used to identify the presence of these factors.

4) Notify the immune system of the presence of foreign energies and pathogenic microorganisms.

The immune system generally functions very well. The 10 billion or so cells that make up the system work together remarkably well in most circumstances. The very complexity of the system, however, means that there is opportunity for miscommunication and lack of awareness. Sometimes there are foreign energies or pathogenic microorganisms disrupting the system and the immune system is unaware of their presence. Simply arcing in and discovering the foreign energies or microorganisms is often enough to allow the immune system become aware of them. Once the Inner Wisdom knows the energies or microorganisms are there, they are often able to be dealt with.

5) Help the immune system locate and correct any foreign energies.
Sometimes it is not enough simply to inform the immune system of the presence of foreign energies. The support and resources provided by the active participation of the therapist may be necessary to affect a release. That is what we do as CranioSacral therapists. The same support and resources may be needed to deal with invading pathogenic microorganisms.

6) Establish rapport between the therapist and the immune system.

Anytime we are present and support the process, we establish rapport with the client. Anytime we act, provided we do so at the request of the Inner Wisdom, we also work to establish rapport. When we act not at the request of the Inner Wisdom, however, we tend to reduce that rapport. Be present in the moment, witness the process, and follow the significance detector as your guide.

Blending and melding with the tissue is the primary way in which we establish rapport. Dialoguing is another. It is important to remember that dialoguing is a tool. Like any tool, sometimes it is the perfect tool. Sometimes, however, it is the wrong tool and only gets in the way. When all you have is a hammer, everything looks like a nail. Used judiciously, with a neutral intent, dialoguing can be a very powerful instrument to facilitate healing.

With dialoguing it is important, however, not to take sides. In particular, DO NOT ally yourself with the part of the client that wants to get better. Doing so necessarily means that you will be allying yourself against the part of the client that does not want to change. Be neutral. Remember, you do not know what healing looks like for this person. Healing may look like sitting in the middle of the conflict and no change occurring whatsoever. Healing may look like dying from the disease.

When dialoguing, think of your role as similar to that of a corporate mediator helping to resolve a dispute between management and labor. In order to function effectively, such a mediator must maintain his or her neutrality. If the mediator were to ally with either side, he or she would immediately lose all credibility with the other side.

7) Help the patient/client gain rapport with his/her own immune system.

Anytime we can educate our clients and help them to be more in tune with their bodies, to be more connected to their own Inner Wisdom and with their process, we are doing them a service. If we can help them to develop a rapport with their own immune system, they can perhaps begin to assist the immune system as it works to protect them or fight off illness.

Helping our clients be more in tune with their own Inner Wisdom and process is, in fact, to a large degree the goal of therapy.
Observations on the Immune System
by John Upledger DO, OMM
The Immune System
– General Responses

When a component of your immune system, probably a cell, recognizes a foreign “something” that it considers “non-self” — or something of its “self” that is judged not healthy or salvageable — several things happen within seconds to minutes.

First, the recognizing cell takes in the image of the non-self or sick-self something, and passes this image to other immune system cells, tissues and organs. The undesirable something is called the antigen. This antigen quickly comes into the awareness of many immune cells and the search for similar antigens begins.

Phagocytes and lymphocytes now “recognize” the antigen. Antibodies to the specific antigen are manufactured by specific immune cells and, a little later, by the liver. Fever may be started by endogenous factors that think fever may kill the invading bacteria.

It’s all hustle and bustle with absolutely brilliant judgment calls being made by organs, tissues, cells and molecules. Brilliant strategies and plans are devised and efficiently executed by these immune system components.

These activities are going on much of the time without our awareness. Imagine what the guardian antibodies and immune cells are coping with every time we eat tainted food or breath impure air. You don’t usually become aware of the work that is going on inside of you to prevent an illness unless the immune system has some difficulty controlling the situation. Then you might not feel so well.

In any case, the general immune response includes phagocytosis, the production of messenger molecules, the production of antibodies, the cloning of millions of cells that have recognition of the antigen whether they’ve seen it or not, the complement system assisting in the destruction of enemy microorganisms, the opening of blood vessels to get more immune cells to the site in question as rapidly as possible, and so on. If calling 911 was one-tenth as efficient as your immune response, we could rest easy.
Notes:
Stem Cells

Stem cells are the progenitors of a wide variety of cells in the human body. They are the source of all of the cells of the hematopoietic system. The cells of this system are called hematopoietic stem cells, or HSCs.

The location of the highest concentration of HSCs in the human body is the bone marrow, where about one cell in 10,000 is an HSC. In adults the concentrations of HSCs in the thymus and spleen run fairly close to the ratio of HSCs to other types of bone marrow cells. In the circulatory blood the ratio of HSCs to other blood cells is about one in a million. This means there is about one HSC in every 10 milliliters of circulatory blood. Since HSCs look so much like lymphocytes, this is a difficult count to make.

In the immune system as in other systems of the body, cell proliferation is carefully balanced between cell death and/or the need for new cells. The need for rapid proliferation of immune cells of all types increases greatly during times of antigenic and/or toxic challenge, as well as during the stresses imposed by traumatic tissue damage and inflammatory responses. Traumatic tissue damage includes surgical intervention as well as toxic challenges, such as anesthetics and various medications or drugs.

In the embryonic bone marrow the stem cells can become anything depending on what signals are received. The same stem cell can reproduce itself at the same time it produces other cell types for other organs and tissues. The embryonic stem cell is a most remarkable creature. It always seems so willing to accommodate requests made by various body systems that communicate with it in a multitude of ways. Many tissue cells that are not necessarily stem cells are capable of self-proliferation, but none come close to the self-proliferation/cloning abilities of the stem cells. As non-stem cells become more specialized, most of them lose their ability to self-perpetuate. Not so with stem cells.

Some embryonic stem cells specialize and become hematopoietic stem cells (HSCs), but this specialization does not compromise their ability to proliferate and produce massive numbers of whatever lineages of blood and immune cells are in demand at any given time. All stem cells, including HSCs, seem to be able to proliferate and produce other cells indefinitely. Stem cells are inherent in all bodily tissues. They continually supply the cells necessary to repair tissue damages that have occurred secondary to daily wear and tear. We often call this healing. If you give an overworked tissue a rest, chances are the stem cells will repair it. If the rate of tissue destruction outweighs or overwhelms the stem cells’ ability to repair and replace, they may receive help from other stem cells — or the tissue may fibrose or die, depending again upon the rate of destruction. Clearly, rest is important. Ask the stem cells.
Hematopoietic Stem Cells (HSCs)

HSCs (hematopoietic stem cells) relate specifically to the blood and immune systems. They are a group of stem cells that have specialized. HSCs are essentially immortal and possess multiple developmental capabilities. In fact, it is not an overstatement to say that the origins of the human immune system as we know it are the HSCs located in the bone marrow, the thymus, the spleen, and perhaps in some lymph nodes and nodules. It is thought that the bone marrow came first but this is more conjecture than fact.

It is also interesting to note that the bone marrow is home to certain stem cells called NSCs. These are neural stem cells. These NSCs form neuronal cells for the brain, while other related yet somewhat different stem cells produce the astrocytes and oligodendrocytes that perform multiple functions for the nervous system, but are not neurons.

Following is a model that represents the known activities of the HSCs. I do not pretend it is totally complete — new information is coming in daily. However, I believe that, in working with the immune system as a therapist, you will find it functional and effective.
Diagrammatic Representation of HSCs’ Known Potentials and Activities

Quiescent HSCs

Activated HSCs

Self Perpetuation
Exact Clones

Vascular
Specialized
HSCs

Erythrocytes (RBCs)
Megakaryocytes
(become platelets)
Macrophages

Other Specialized HSCs

Lymphoid Specialized HSCs

Myeloid Specialized HSCs

Acquired Immunity
Lymphoid Cells
T-Lymphocytes
Killer
Helpers
Suppressors
B-Lymphocytes
Plasma Cells
Natural Killer Cells

Innate Immunity
Myeloid Cells
Polymorphonuclear
Leukocytes
Monocytes
Macrophages
Eosinophils
Basophils
Mast Cells
Dendrocytes
In viewing the previous diagram, let’s first look at the potential activators that move the HSCs from quiescent to active. Most of the stem cell stimulators are relatively low weight protein or even lower weight polypeptide molecules combined with carbohydrate molecules. They are thus glycoproteins or glycopeptides. There are a wide variety of these molecules, which are known as the cytokines.

A subdivision of cytokines that is particularly effective in moving the HSC from the quiescent to the active state is the group known as interleukins. Interleukin-8 (IL-8) is especially effective. On the other hand some interleukins — IL-1 and IL-3 — have the reverse effect. They will move the active HSC into quiescence. This is why arrows are pointing in both directions between these two states, quiescent and activated.

If we go back to embryonic stem cells before differentiation has occurred, a molecule called telomerase, which has been used in the laboratory, can prevent the embryonic stem cells from specializing or differentiating. It would almost seem that these cells could be kept alive in an undifferentiated state forever. When they are treated with the appropriate cytokines or interleukins, they can be activated and then guided into specific specialization by the use of specific molecules, or exposure to specific cells, and/or placing them in certain tissues. For example, if these embryonic stem cells are placed in bone marrow they will usually produce blood cells. On the other hand, if marrow stem cells that are as yet undifferentiated are placed in brain tissue they will produce neurons. Or if they are placed in the liver they will produce liver cells, and so on.

When HSCs are activated they can then specialize in one of several directions. They can produce cells related to the vascular system, to the myeloid division of the innate immune system, to the lymphoid division of the acquired immune system, or to other specialized areas. Certain molecules called chemokines can get HSCs to change their specialization to another area, or even to focus only upon self-renewal.

Chemokines are a subdivision of cytokines, with at least two sulfur-containing cysteine molecules in the protein molecule. To date, at least 50 different chemokine molecules have been identified. Besides the effect of changing the specializations of the HSCs, chemokines provide the chemotactic effect that attracts phagocytes to the sites of injury, infection, inflammation, etc. They also somehow regulate the genesis of new blood vessels (angiogenesis) when more blood is needed to an area. Or when it is appropriate to cut off a blood supply, chemokines can close down existing blood vessels. In the latter instance, chemokines can be considered anti-tumor molecules, because tumors require increased blood supply. Something from a successful tumor causes new blood vessels to develop. Certain chemokines will work against this development. Chemokines also, in as yet unknown ways, exercise regulatory effects upon the immune system in general. They have been used with some success in the suppression of HIV activity in infected patients.

Other molecules in the physiological environment of HSCs, and all stem cells for that matter, greatly influence HSC activity. It is thought these molecules have a lot to do with the rate at which blood cells are allowed to leave the bone marrow and enter the general circulation. The connective tissue cells of the bone marrow are thought to secrete these control molecules, which are most likely in the cytokine-chemokine family.

All the cells named in the diagram will be considered in detail later in this text, as will the communication and control molecules that have been mentioned thus far. Just a few more observations about the HSCs and other stem cells before we take a closer look at the bone marrow as a home for these hematopoietic stem cells (HSCs).
The movement of various stem cells into specialization is naturally stimulated by physiological and biochemical factors. For example, when implanted in a heart, undifferentiated stem cells will produce heart muscle cells (cardiocytes). When implanted in the brain they will produce brain cells, both neurons and glial cells. When undifferentiated stem cells are in the marrow and when they activate for unknown reasons, they will often become neurons or cardiocytes in the marrow.

It is also interesting to note that, when bone is compressed, osteoblasts are produced, forming new bone. On the other hand, stretching the matrix of the marrow causes tendon to form. When for some reason stem cells become clumped together in the marrow, chondrocytes are produced and cartilage is formed.

Go figure.
A true appreciation of the importance of stem cells really came to the fore in the 1960s. Marshall R. Urist at UCLA noted that powdered bone implants injected into animals often resulted in the development of whole bones in the animal body where no bone had been before. Subsequently, it was seen that a protein in the ground bone was responsible for this new bone growth. The protein was then named Bone Morphogenetic Protein (BMP).

As technology advanced, genetic researchers learned to produce BMP using DNA sequencing techniques. Soon BMP was used in research settings to grow new bone at long-term, non-union fracture sites, first in animals and then in humans. Presently BMP is used clinically in this way, and also to restore eroded bone that is secondary to periodontal disease. So it is proving to be quite useful in both orthopedics and dentistry.

As investigations into the possibilities of new tissue growth from proteins and stem cells progressed, it became apparent that developing tissue required new vascular development to service the new tissues. Research into new vascular development (angiogenesis) is now coupled with research into the inhibition of angiogenesis as a treatment for various tumors. Tumors require more blood vessels to survive. Regulatory proteins were found that would promote angiogenesis, and other proteins were found that would stop angiogenesis. Beyond that, some proteins were found that would destroy an existing vascular system.

Many of the proteins that exerted controlling influences over the blood vascular delivery system were seen to be products of blood cells that looked a lot like lymphocytes but weren’t. This recognition as non-lymphocytes earned them another name: stem cells.

It was soon realized that a single stem cell could not only replace itself but also multiply logarithmically. Beyond self-replacement, they could create huge colonies of themselves — colonies of clones. So in a way the stem cell can be immortal if it chooses.

In addition to self-replication at an amazing speed, the stem cell can concurrently produce specialized tissue cells such as liver, heart, neurons, etc., depending on the physiological environment it’s placed in and/or the various messenger or communication molecules with which it comes in contact. So stem cells placed in a liver can not only reproduce themselves, they can also replenish liver cells as needed. This is true of many other tissues and organs of the body. Stem cells can replenish almost any needy tissues. This alone certainly makes it worthwhile to learn to communicate/dialogue with stem cells.

The most versatile stem cells are embryonic stem cells (ESCs) taken from the blastocyst formed in the uterus shortly after implantation of the fertilized egg. ESCs taken from the embryo can be kept alive almost indefinitely in test tubes. Using various specialized molecules in the test tubes along with the ESCs, specialization can be achieved under laboratory conditions. The created specialized stem cells can then be implanted in the heart, brain, liver, etc. The implanted stem cells will then multiply and replenish the needy organ with healthy functioning cells.
The Bone Marrow

The bone marrow has the highest concentration of hematopoietic stem cells (HSCs) — 100 for every million of any other type of bone marrow cell. The bone marrow tissue is a soft, rather fatty material that can be either yellow or red. The yellow marrow, which has a higher concentration of fat cells, makes up the majority of the marrow substance in the long, essentially straight bones of the body. The ends of these long bones, however, have red marrow. During conditions that involve significant anemia, the yellow marrow turns red and produces erythrocytes to help correct the anemia. Red marrow is the dominant type in the bones of the skull, the vertebrae, the ribs, the sternum, and any other short or flat bones. The red marrow is involved in the constant high-level production of all types and lineages of blood cells, both red and white.

Both yellow and red bone marrows have a framework that consists of fat cells, fibroblasts and other types of blood cells. The framework has a nutrient delivery function in addition to forming a connective tissue framework that is interwoven with the marrow’s vascular system. This system has in its construction a great many sinusoidal structures that collect the maturing progenitor blood cells from the marrow’s stroma. These sinusoidals then coalesce to form the venous drainage system.

The total architecture of the bone marrow is designed to meet the requirements of hematopoiesis. The hematopoietic cells are required to have side-to-side contact with one another. All types of cells, including stem cells, are also required to have easy exit from the stroma and easy entry into the vascular system. The ease of passage relies largely upon the deformability of the cell that is moving from stroma into sinusoidal structure. These moving cells actually pass through the sinusoidal epithelial cell bodies. These precursor cells get narrower and longer as they pass through the epithelial cells. Immature progenitor cells are less deformable. Therefore, the more immature cells are unable to enter the sinusoids before the time is right.

Bone marrow cells have antigenic protein molecules attached to their surfaces. These antigenic molecules hold blood cells attached to the marrow cells until a biochemical signal tells the marrow cells to release the blood cells so they can pass into the sinusoidal structures, then through the tiny venous structures and into the vascular system. (In this study guide, the term “white cells” encompasses all cells of the immune system.)

The sinusoidal endothelial cells also have a remarkable ability to clear debris from all the fluids that occupy the sinusoid, even very briefly. These endothelial cells also produce biochemical growth factors that stimulate the maturation of hematopoietic cells.

The stem cells in the marrow cannot be morphologically differentiated in regard to what their products will be until they begin to demonstrate the function of their progeny. These stem cells are called pluripotent. That is, they seem to be able to do anything. They can differentiate, they can proliferate any kind of blood/immune cell, and they can renew themselves. Stem cells will sometimes leave the marrow and travel to areas of depleted blood cells, especially the spleen or lymph nodes. Upon arrival, the stem cells replenish whatever kinds of cells are in short supply. The stem cells repopulate areas that have suffered loss of cell population for any reason.

I have long felt that, as CranioSacral Therapy (CST) enhances sutural motion, it probably enhances the ease of blood cell movement through the haversian canals from the marrow into the sutural vascular
I would hypothesize that the constant, natural opening and closing motion of the sutures helps move blood out of these sutures and into their (sutural) drainage systems. In doing so, it reduces any back pressure that might be hampering the exodus of the blood cells from the marrow. So CST facilitates to some extent the immune response by helping to move the immune system cells more quickly from marrow to somatic vasculature.
The Thymus Gland

Development of the Thymus Gland in Utero

During the 4th to 6th week of gestation, when the embryo is about 1 centimeter long (10 millimeters) — a little less than half an inch — the thymus gland begins to develop as two outgrowths, one on each side of the third pharyngeal pouch of the embryo. Some authorities say the thymic origins come from both the third and the fourth pharyngeal pouches of the embryo. In either case the two thymic growths are destined to mature into the two lobes of the thymus gland.

It is of interest to note that, at the same time the thymus beginnings make their appearance, the inferior parathyroid glands develop, one from each side of the posterior aspect of the third laryngeal pouch of the embryo. When something interferes with the development of the third laryngeal pouch in the developing embryo, both the thymus and the parathyroids are unable to develop normally. This may result in the DiGeorge Syndrome. Normally, the thymus gland ends up in the lower neck and upper thorax, and the parathyroids migrate to the thyroid gland where they are found in the normal adult.

The DiGeorge Syndrome is manifested by several factors. The child’s physical appearance is very suggestive at the time of delivery. There is no philtrum present. The philtrum is the vertical groove on the midline between the upper lip and the nose. There is a small, fish-like mouth. It looks like someone imitating a goldfish. Hypertelorism is present. This is an excessively wide distance between the eyes. The eyes have a slant that is the opposite of the typical Down’s syndrome child. The ears are set very low and either notched or folded.

Clinically, the child will present with low blood calcium (hypocalcemia) and secondary intractable tetany. There may be weakness or failure of the cardiovascular system due to developmental problems with both the heart and the aorta. The heart will often manifest the tetralogy of Fallot, which is pulmonic stenosis, interventricular septal defect, hypertrophy of the right ventricle, and dextroposition of the aorta. The aorta may show a defect in its arch, as well as atruncus arteriosis, wherein the aorta connects to both the right and the left ventricles. Since the left ventricle is stronger than the right, when this occurs there is often an increased pressure or even a back flow of arterial blood into the right ventricle. This compromises the child’s cardiopulmonary function. The DiGeorge child also manifests subnormal T-lymphocyte counts, which result in compromise of immune system function. Commonly, these children are afflicted with a wide array of infectious processes, from resistant candidiasis to uncontrollable diarrhea. This child is missing both a healthy thymus gland and functional parathyroid glands. The child’s prognosis is very poor.

The thymus gland’s origins from the third (and fourth) pharyngeal pouch(es) are from epithelial cells. These epithelial cells actually arise from endoderm tissue. The lymphoid cells that soon show up in the developing thymus are derived from embryonic mesoderm tissue.
The thymus gland begins as two hollow endodermal elongations which, by the end of the 8th week of gestation, have descended into the embryonic thorax. These two elongations then pass in front of the developing great blood vessels (aorta, pulmonary vessels and their major branches). At this time the inferior parathyroid glands separate from the thymus and come to rest upon the posterior surface of the thyroid gland. Occasionally, this separation does not occur and the parathyroids mature inside of the thymus substance in the anterior thorax/media sternum.

A fusion of the two thymic diverticula occurs, which involves only the mesenchymal connective tissue into which the thymic tissue has grown. The thymic parenchyma does not connect between the two fusing diverticula. During this time of fusion, the open connections between the pharyngeal pouches and the thymic diverticula close. This is called “closure of the thymopharyngeal duct.” The thymopharyngeal stalk may persist for an indefinite time. At this time lymphoid cells appear in rather large numbers in the thymic epithelial tissue. Thus, the thymus gland becomes a lymphoepithelial organ. Any failure in the caudal migration of the thymic diverticula may result in thymic dysplasia, which shows up in the newborn as an immune deficiency disease.

By the 10th week the medulla and cortex of the thymus are developing. The medulla is epithelial in nature. Its compact epithelial structure is interlaced with fibrous reticular network. The epithelial cells are secretory. They produce thymic hormones that strongly influence T-cell behavior, both within the thymus and throughout the peripheral body. The thymic cortex is more peripheral in the gland while the medulla is more central. During this time, the cortex is being infiltrated by precursor cells (stem cells) that will become lymphocytes in the near future. The cortex is predominately lymphocytes. These lymphocyte precursor cells come from the yolk sac, the liver and the spleen. In postpartum life through adulthood, the lymphocyte precursor (stem) cells come exclusively from the bone marrow.
Histogenesis of the Thymus Gland

The differentiation of the cells in the developing thymus gland begins when solid cords of endodermal epithelial cells grow caudally into the mesenchyme. As this growth occurs, blood vessels penetrate these cords of cells. The endodermal epithelial cells take on a stellate shape. The stellate-shaped cells remain connected to each other by the extension of cellular processes. These cells thus form a mesh called the cytoreticular meshwork. Some of the cells of the mesh work begin to change shape so they form concentrically positioned globes or clusters. These clusters are called thymic corpuscles or Hassall’s bodies. These corpuscles become the manufacturing centers for thymic hormones. The centers of the corpuscles degenerate so that cysts are formed. The hormone is stored in the cyst until it is time to be released or secreted.

During the 8th week of gestation lymphocytes begin to appear in the developing cytoreticular mesh work. These lymphocytes fill in the interstitial spaces between the endodermal epithelial cells. The lymphocytes are derived from stem cells that are delivered to the thymus via the blood stream. These stem cells come from the embryonic yolk sac, liver and (perhaps) spleen. There is some controversy about the spleen as a stem cell source in the embryo. After birth, all stem cells delivered to the thymus gland come from the bone marrow. Once the stem cells get into the thymus gland they are called thymocytes. When they become known as lymphocytes is rather arbitrary. Thymocyte proliferation in the gland is very high. In fact, at the time of birth, thymocyte proliferation is thought to be the highest rate of proliferation seen in any organ or gland of the body.

These thymocytes, once produced, leave the thymus and travel to all parts of the body. The maturation time from stem cell entry into the thymus gland to lymphocyte departing the thymus is only two or three days. These young lymphocytes pass through the walls of the thymic venules and enter the blood stream. Some of these lymphocytes remain in the blood but a majority enters the lymphatic system and travel to the lymph nodes, Peyer’s patches on the intestines, the appendix, the tonsils and the adenoids.

Within the thymus gland this rapid and massive proliferation of thymocytes is not driven by antigen stimulation as lymphocyte proliferation is in the lymph nodes. It is apparently driven by genetic code and/or molecular messengers, perhaps by the thymic hormones per se.

As it matures, the thymus develops into a cortex and a medulla. Immature thymocytes become lymphocytes in the cortex and then move into the thymic medulla for differentiation into helper or suppressor T-lymphocytes. During their maturation process, T-lymphocytes are also given the ability to recognize non-self antigens. This is known as gaining immunocompetency.

The discussion of the cortex and medulla within the thymus gland is presented in the two sections entitled Gross Anatomy of the Thymus Gland and Microscopic Structure of the Thymus.
Gross Anatomy of the Thymus Gland

At the time of obstetrical delivery, the average thymus gland weighs about 12-14 grams. At about 2 years of age, the thymus gland reaches its maximum size of about 35 grams. This size is retained until thymus involution begins shortly after puberty. These weights are extrapolated from studies on children who have died. I wonder how accurately this reflects the weight of the living thymus gland in a healthy person? How do you weigh a thymus gland in a healthy, living human being?

The mature thymus gland consists of two lateral lobes held together by a bridge of connective tissue. Frequently, the right lobe is larger. It often crosses the midline and overlaps the left lobe, with the overlap from the right lobe being superficial to the left lobe. The two lobes/total thymus is encapsulated by a distinct connective tissue layer. This capsule encloses the whole gland and has various attachments to adjacent fascias.

The fully developed thymus gland extends from the lower border of the thyroid gland in the lower neck to the level of the fourth costochondral cartilages in the upper thorax. In the neck the thymus gland is anterior and lateral to the trachea, and deep to the origins of the sternohyoideus and sternothyroideus muscles. In the thorax the thymus gland is in the upper mediastinum anterior to the pericardium, the aorta, its branches and the pulmonary vessels in that region.

The thymus gland is usually a pinkish-gray color. It is on the order of 5 centimeters long, 4 centimeters wide, and a little over half of a centimeter in thickness.

The aforementioned connective tissue capsule that covers the whole gland (both lobes) presents extensions of its connective tissues that enter the glandular tissue and form septa. These septa serve to partially subdivide the two major lobes into lobules. The peripheral portions of the lobules are heavily infiltrated with lymphocytes. These peripheral areas are called the cortex of the thymus gland. The more central portions of the lobules are known as the medulla. The medulla of the thymus gland contains fewer lymphocytes and more endodermally derived epithelial cells. This is where the thymic hormones are produced.

Within the thymus there are also thymic corpuscles (Hassall’s bodies). These corpuscles are cystic and contain hormones and keratin in their centers. Keratin is a rather insoluble protein that may be considered under these circumstances as a source of sulfur and some of the major amino acid ingredients for thymic hormones.
Microscopic Structure of the Thymus

The two major lobes of the thymus gland are subdivided by connective tissue septa into many smaller lobes that are between 0.5 to 2 millimeters in diameter. The parenchymal cells (cells involved in glandular function compared to connective tissue stroma) within the lobules are often interconnected by cytoplasmic projections. These interconnections afford communications not only between the cells in a given lobule, but also between the parenchymal cells of adjacent lobules.

The cortical parts of the thymus and its lobules are composed primarily of a network of stellate reticular cells that are embryonically derived from endodermal endothelial cells, and of numerous tightly packed aggregations of thymocytes (young lymphocytes). These aggregations occupy the interstitial spaces within the cytoreticulum.

The medullary portions of the thymic lobules contain mostly reticular cells of varying shapes, and an abundance of thymic corpuscles (Hassall’s bodies). The presence of thymocytes (young lymphocytes) is much less prominent in the medulla than in the cortex of the thymus gland and its lobules. (Remember, the medulla produces mostly thymic hormones while the cortex produces lymphocytes.) The lobules of the thymus seem to replicate the total gland in terms of cortex and medulla. In the gland the cortex is more peripheral and the medulla more central. This is also true in each lobule, so one might think of each lobule as a gland within a gland.
Blood and Nerve Supply to the Thymus Gland

The septa that divide the gland into its lobules carry blood vessels and nerves into the gland and its lobules. Grossly, the arteries of the thymus gland are branches of the internal thoracic arteries and the inferior thyroid arteries. These arteries are derived from the mediastinal arteries that have branched off of the aorta. The small branches of the thymic arteries travel through the interlobular septa. They enter the depths of lobular parenchyma by traveling along the corticomedullary border. From this vantage location very small arteries form capillary systems that penetrate the cortex. Small arteries enter the medulla before they form capillary systems. The difference is that capillary systems are formed before entering the cortex. Capillary systems are formed within the medulla from arteries that have entered this tissue. I don’t know why this is so, but it is how nature designed it. It may have something to do with making it easier for the thymocytes to get into the cortex as compared to the medulla.

The venous return from the thymic tissue follows the rule that veins accompany arteries and the blood flows in a reverse direction. Once out of the glandular tissue, the thymic veins drain into the left brachiocephalic, the internal thoracic and the inferior thyroid veins. Lymphatic vessels from the thymus gland drain into the parasternal, anterior mediastinal and tracheobronchial lymph nodes.

The thymus gland is innervated by small branches from the sympathetic nerve ganglia and chain in the neck and thorax, and from the vagus nerve as it passes by. The phrenic and the ansa cervicalis nerves give branches only to the capsule of the thymus gland. These branches do not penetrate the glandular tissue. Clearly, from this innervation the functioning balance between the sympathetic and parasympathetic nervous systems have an effect upon thymic function, and hence upon the effectiveness of the total immune system. This ties in very nicely with the observations that stress of any kind reduces effective function of the immune system. Certainly, the thymus occupies a key position in immune system function.
Functions of the Thymus Gland

I consider the thymus gland to be the Immune University. (IU, if you will, not UI.) IU has functions analogous to classrooms, laboratories and libraries. In the thymus, T-lymphocytes learn to recognize self from non-self markers on cells. It is also here that some T-lymphocytes learn to be killers, others learn to be helpers, some learn to be messengers, and still others learn to be suppressors. This is the classroom aspect of the thymic university.

In the thymus, experiments are carried out on how to decide whether or not borderline self/nonself cells should be allowed to survive. How these experiments are carried out is still a puzzle but they are, and decisions are made based on the results. Let your imagination run free with this one, and dialogue with the thymus to help you understand how these decisions are made.

The library aspect of the thymus is quite straightforward. This is where all of the information is kept that offers recognition of non-self antigenic markers that have been brought to the thymus since the first trimester of gestation. It is also the place where information about suspicious yet self markers is catalogued so that a mistake will not be made. A failure in this system may well result in an autoimmune disease.

In addition to these functions, the thymus gland is responsible for the development of all T lymphocytes of all specialty types that are involved in the cellular aspect of the immune response. The thymus is the master gland for the immune response. It orchestrates that response throughout life. Nature has designed this gland in a most remarkable way, and placed it in a very well-protected area of the body.

Initially, pluripotential stem cells infiltrate the thymus gland. These stem cells come from the embryonic/fetal liver, spleen and yolk sac. These cells then acquire surface antigens that are part of the thymus library. They correlate with, or perhaps even dictate, the cell’s new specialized functions. As these cells mature and specialize they migrate from thymic cortex to medulla. The specialization is dictated in some way by the thymic hormones according to need. There also seems to be some influence by direct cell contact.

It is interesting to note that the thymus has the highest cell production, not only of all of the lymphoid tissues but of essentially all the organs of the body. However, the number of T lymphocytes that leave the thymus is estimated to be significantly lower than the number produced within the gland.

Another interesting factor is that the thymus, as stated earlier, is the place where information on all antigens is stored for future reference and educational purposes. Yet it is extremely well protected from exposure to foreign antigens. It gathers its information about antigenic material from messenger lymphocytes that present antigenic samples taken from the periphery for evaluation by the thymic “intelligence.” It is then decided whether or not the cells bearing these antigenic markers shall live or die.

In summary, the thymus produces millions of well-educated T-lymphocytes that are specialized in the various ways discussed in the lymphocyte section. The thymus also produces hormone substances that greatly influence and guide the immune response in terms of antibody formation by lymphocytes, both within the gland tissue and throughout the periphery of the body. Further, these hormones influence the production of antibodies by both lymphocytes and plasma cells.
Development of T-lymphocytes
Within the Thymus Gland

Undifferentiated Thymocyte

Differentiated Thymocyte

Differentiated Thymocyte

Suppressor T-Lymphocyte

Killer T-Lymphocyte

Helper T-Lymphocyte
Involution of the Thymus Gland

Shortly after puberty the full-grown thymus gland begins to involute. The reason is not known. It is interesting to note that the thymic capsule does not usually change its size. The glandular tissue inside of the capsule atrophies and is replaced by adipose tissue. The involution occurs as the cortical lymphocytes disappear and the reticulum appears to become compressed. Untimely or accidental involution of the thymus gland can result from starvation, excessive stress, exposure to radiation, and/or acute disease at any age.

Why thymic involution occurs is not known. Perhaps this question can be explored in this class. We should also consider that there are healthy disease-resistant and immunocompetent senior citizens in our midst. Perhaps their thymuses have not involuted, or perhaps as other lymphoid organs become more competent, the thymus is less essential for the maintenance of a strong and effective immune system. It may not necessarily be the case that age begets disease vulnerability because the thymus is supposed to involute.
The spleen is difficult to describe in terms of size because it is so variable. It is located in the upper left quadrant of the abdomen between the fundus of the stomach and the respiratory diaphragm. In the average adult the spleen is about 12 centimeters long, 7 centimeters wide, and 3 or 4 centimeters deep. During the first year of life the spleen is much smaller, weighing about 15-20 grams, with a small but extremely flexible shape. By about age 20 the normal spleen weighs about 170 to 180 grams. It gradually gets smaller with the passing years, losing 25 to 35% of its total weight by the seventh decade of life.

These estimates of spleen size and weight are inexact in that men’s spleens usually weigh more than women’s spleens. The size of the spleen increases significantly after a meal when the digestive process is active. When a person is well-fed, his or her spleen is larger. During caloric and/or total nutritional deficit, the spleen reduces significantly in size. Adult cadaveric spleens have presented weights ranging from 50 to 400 grams, depending upon the person’s general health and nutritional status at the time of death. In one case of malarial death, the spleen weight was recorded at 9 kilograms (9,000 grams).

The long axis of the relatively normal spleen is parallel to the axis of the 10th rib as it leaves its vertebral articulation and runs to the midaxillary line. The usual upper and lower boundaries of the spleen are parallel to the upper boundary of the 9th rib and the lower boundary of the 11th rib, respectively. The medial side of the spleen is usually about 4 centimeters left of the midline. Laterally, the spleen will often extend to the midaxillary line. In a standing, well nourished adult, it is not uncommon for the spleen to extend downward as far as the level of the 3rd lumbar vertebrae. As you can see, to assign specific anatomical boundaries to the spleen is pure folly. You have to learn the “feel” of the spleen to be able to effectively evaluate its condition. It is a soft and friable organ that feels somewhat like a balloon full of a viscous fluid, perhaps about as thick as room-temperature honey or molasses. During surgery the living spleen is usually a dark purplish color. What it looks like without the surgical invasion is anybody’s guess. Since the spleen is so responsive to immune and autonomic changes, its natural appearance cannot be reliably predicted.

The relationships the spleen has with other structures are:

1. Its diaphragmatic surface is rather sharp and notched. The respiratory diaphragm separates the spleen from the left 9th, 10th and 11th ribs, as well as the left lung and pleura. The diaphragm and the spleen enjoy significant independent movement from each other. If this were not so, every time you stood up your left diaphragm would be pulled down by the spleen. Diaphragmatic adhesions to the spleen can cause difficulty in breathing.

2. The spleen and the dorsal aspect of the stomach are rather firmly connected by the gastrosplenic ligament. This means that stomach activity broadcasts to the spleen.

3. The spleen and the left kidney are connected by the lienorenal ligament. This ligament may also involve the left adrenal gland. Problems originating in either of these connected organs may broadcast via these connections to the other organ(s).

4. The spleen rests upon but is not necessarily attached to the splenic flexure of the colon and to the phrenicocolic ligament that connects the diaphragm and the colon in a suspensory fashion.
5. The spleen is frequently in contact with the tail of the pancreas, but it is seldom firmly attached to it.

6. The capsule of the spleen is covered by closely adherent visceral peritoneum, except at the hilus of the spleen. This peritoneal connection attaches the spleen to the posterior part of the abdominal cavity. The blood vessels and nerves to the spleen pass through the peritoneal layers to reach the spleen via the hilus.

There are many variants in splenic ligaments and suspension systems. You will have to evaluate each patient with an open mind to understand his or her particular system.
Development of the Spleen

During the 5th week of gestation, multiple clusters of mesenchymal cells appear in the dorsal aspect of the mesogastrium near the tail of the pancreas. The mesogastrium is the beginning of the embryonic stomach and its omentum. Soon these mesenchymal cell clusters, or aggregates, become vascularized and begin fusing together to form a lobulated structure that becomes the spleen. The adult spleen often presents evidence of its lobulated origin in the form of the notches that are seen, especially along the superior margin of the mature spleen.

As the embryonic stomach develops it rotates toward the left, carrying the embryonic spleen with it. Ultimately, the spleen comes to rest behind the stomach and in contact with the left kidney. The part of the mesogastrium that ends up between the spleen and the left kidney becomes the lienorenal ligament, and the mesogastrium part between the greater curvature of the stomach and the spleen becomes the gastrosplenic ligament.

Some of the things that can go astray during development of the spleen include agenesis (no spleen develops), polysplenia (many spleens develop, all of significant size), accessory small spleens (they develop in addition to a relatively normal spleen), and splenicgonadal fusion (spleen tissue in the scrotum descends with the gonads). These are just some of the atypical formations. All are surgically correctable but surgery may not be required. The scrotal spleen may not adapt to the cooler temperature and simply atrophy. All the other anomalous situations may be quite functional unless their mass is not able to be accommodated in the space available.
Microarchitecture of the Spleen

The spleen is an encapsulated lymphatic organ that filters blood through its sinuses. In this respect it differs from lymph nodes that filter lymph through their sinuses.

Within the peritoneal tissue covering described in the General Information about the spleen, there is a specialized capsule that is derived from the embryonic splenic tissue. The peritoneal outer coat is known as the external serous coat, and the inner covering of the spleen is simply known as the splenic capsule. Both coverings of the spleen are markedly elastic, as are the numerous fibroelastic bands, called trabeculae, that are given off from the internal surface of the capsule and from the sheathes that are derived from the inner capsule. These sheathes follow the blood vessels that enter the spleen via the hilus. The tissues that form the capsule and the trabeculae also contain a significant number of smooth muscle fibers. Thus, the spleen is able to contract when called upon to do so, as well as to expand. Contraction occurs when there is a need for blood cells, red or white, to be released for any reason.

The trabeculae are flattened strands of connective tissue that divide the spleen into innumerable smaller compartments, each being (+) or (-) 10 millimeters in diameter. These compartments maintain intercommunication structures and pathways. Also, keep in mind that the trabecular walls of these compartments contain a higher proportion of elastic tissues than do the capsule and the sheathes that follow the blood vessels into the splenic parenchyma. The sheathes branch with all of the blood vessels within the spleen and continue to give off trabeculae until they, the sheathes, are quite small.

Besides the blood vessels, the spleen also has a system of lymphatic vessels that are principally formed from the capsule and the trabeculae. These vessels deliver lymph to the splenic lymphnodes that are located between the layers of the gastrospenic ligaments, and to the pancreaticosplenic lymph nodes that are located along the superior border of the tail of the pancreas.

Microscopically small whitish areas about 1 millimeter in diameter are scattered throughout the larger and more predominant reddish-brown tissue. The former is called the white pulp and the latter is called the red pulp. Individually, the white pulp regions are known as lymphatic nodules or malphagian nodules. Lymphocytes are concentrated in the white pulp, especially in those areas that surround the central arterioles, areas known as the per arteriolar sheathes. The cells found in these areas are mostly T-lymphocytes. They are concentrated more closely to the center of the sheath. B-lymphocytes are seen more in the periphery of these per arteriolar sheathes. Both types of lymphocytes enter and leave the sheathes via the capillaries related to the central arterioles. These capillary networks are located in the marginal zones that separate the white from the red pulp. After giving off capillary branches, the remaining main stem arteries/arterioles penetrate the red pulp. As these arteries and arterioles pass into the red pulp they continue to give off capillary networks that form white pulp nodules within the red pulp.

The red pulp is the main substance of the spleen. It is composed of rich plexuses of tortuous venous sinuses. Between the sinuses there are connecting cords that contain lymphatic cells of all kinds, and many macrophages and other phagocytic cells, as well as many red blood cells. These cells are all enmeshed in the reticulum formed by the splenic stellate cells. The macrophages serve as a clean-up crew, removing debris from red blood cells that were defective, and any other waste products delivered from infectious, toxic or other necrotizing sites around the body.
Blood Vessels of the Spleen

Arteries
The splenic artery is a branch of the celiac trunk that comes off of the aorta just below the aortic hiatus of the respiratory diaphragm. The splenic artery is the largest branch of the celiac trunk. It has a rather tortuous path with loops and coils as it travels along the border of the pancreas to reach the spleen. Prior to entering the spleen, the splenic artery first divides into superior and inferior branches. Each of these two major branches divides into four or five smaller branches before reaching the splenic hilus where they all make entry. Thus, we may have up to 10 splenic artery branches that enter the spleen. I suspect the extreme tortuosity of the splenic artery is to allow for the constantly increasing and decreasing size of the spleen. I also suspect that the arterial branches that enter the spleen are designed that way in order to offer more sheathing around which the white pulp gathers, as well as to offer a greater vascular wall surface area for the transference of all types of white blood cells to move from blood to splenic pulp and back as needed.

After entry, the arteries all go in separate directions to their respective zones. Each then further subdivides into smaller trabecular arteries. These smaller arteries travel in the trabecular tissues. As they leave the trabecular structures they lose their connective tissue sheath, which is called the tunica adventitia. The tunica was blended with the trabecular tissues as the arteries passed through these trabecular tissues. When these smaller arteries exit the trabecular structures/walls, they leave their tunics behind. They become surrounded by lymphocytes enmeshed in reticular fibers. This is how the white pulp is formed. These small arteries surrounded by reticular enmeshed lymphocytes are now called central arteries. When smaller arteries leave the trabecular tissues they are not accompanied by veins. Until this time they traveled with veins. These central arteries then branch and, of course, become smaller as they do so. When the branches of the central arteries get very small, about 50 microns in diameter, they then further divide, producing up to six branches at the same time. These branches are called penicillar arteries.

Lymphocytes continue to surround all of these branches since the artery left the trabecular structure. The penicillar arteries are now surrounded by a single or double layer of lymphocytes. These penicillar arteries now enter the red pulp. Each penicillar artery now within the red pulp divides into two or three capillaries. These capillaries have endothelial cell linings. They have no muscle in their walls. They immediately acquire a thick sheath of concentrically arranged macrophages and reticular fibers. They are now called sheathed capillaries. Their diameter is about 6 to 8 microns. In a short distance after forming and sheathing, these capillaries branch into non-sheathed capillaries. This is more the usual case. Most capillaries in other parts of the body do not have sheathing. Finally, the blood traveling through the aforementioned system reaches the venous sinuses from the unsheathed capillaries. We are not sure exactly how the blood gets into the venous sinuses, but we do know that the rate of blood flow through the spleen is controlled by arteriolar muscular contraction and relaxation.
**Splenic Venous Sinuses and the Drainage System**

The venous sinuses are the end point for the capillaries of the pulp of the spleen. These sinuses are tortuous channels measuring 10 to 50 microns in diameter. Their walls are made up of long, narrow endothelial cells that are longitudinally oriented. Some authorities have stated that these endothelial cells were actually macrophages that cleared the blood of unwanted debris and defective cells as they passed by. This is a rather romantic fancy against which there is a lot of scientist opposition. Personally, I like the idea, and since we make our own reality, why not? These endothelial cells (macrophages?) are held in position by reticular fibers that are ultimately connected to the collagen fibers of the trabecular structures. The reticular fibers that surround the venous sinuses form rings around them, and thus offer significant support to these rather weak walled sinuses.

The venous sinuses then drain into the rather delicate veins of the splenic pulp. These veins merge to form the trabecular veins, which in turn merge to form the larger veins that ultimately become the several tributaries that emerge from the splenic hilus and become known as splenic veins. These five or six veins that exit the spleen via its hilus unite to form a single vein. It travels across the abdomen from the patient’s left to his or her right. It joins the superior mesenteric vein. This union is then known as the portal vein, which goes to the liver. Thus, splenic blood is passed through the liver, most likely for purposes of purification, but it may also carry information molecules that tell the liver which antibodies and serum globulins to produce. From the liver, blood is drained via the hepatic veins into the inferior vena cava.

**Lymphatic Vessels of the Spleen**

Very few, if any, lymphatic vessels are to be found in the pulp of the human spleen. Lymphatic vessels are seen in the splenic capsule and along some of the larger trabeculae. These lymphatic vessels emerge from the spleen at its hilus along with the veins. They then go into the pancreaticosplenic lymph nodes located along the superior border of the pancreas. What happens there is discussed under the heading Lymph Nodes.

**Nerves of the Spleen**

The nerves that go to the spleen are derived from the celiac plexus. These nerve fibers are mostly unmyelinated and are part of the sympathetic division of the autonomic system. They follow the splenic artery from their celiac origin into the spleen. They are vasomotor in function, causing the blood vessels in the spleen to contract, thus reducing blood flow into the spleen during times of stress. There are also fibers from the vagus nerve that enter the spleen. They are parasympathetic and serve to balance the sympathetic effect.

Since the spleen is seen to enlarge during digestion, it seems reasonable that increased vagus activity at that time also increases splenic blood supply. This may help to purify blood that has received some undesirable pseudonutritional molecules from some of our giant food corporations, or smaller fast-food delivery systems.
Functions of the Spleen

The information regarding splenic function is, in my opinion, sadly lacking. It is considered that the removal of the spleen has minimal effect upon body physiology, and so it seems. Many people have lived reasonably “normal” lives after splenectomy. On the other hand, we don’t know what their lives would have been like had they not lost their spleens. I suspect that follow-up on post-splenectomy patients is poor. I also suspect that problems that occur months or years after the loss of the spleen are seldom thought to be related to the absence of whatever spleens do.

At present we know that, during fetal life and in early infant life, the spleen does produce lots of new red blood cells (erythrocytes). It seems that this production of red blood cells stops when we are very young. However, we do know that throughout life the spleen serves as a reservoir for red blood cells. It has contractibility and stretchability. When it contracts it may indeed give you an infusion of red blood cells when you are in need. This would almost be like a natural blood transfusion.

We also know that red blood cells pass through the spleen. During their splenic tour they must pass “inspection” by these macrophages. If a red blood cell is sickly or unacceptable for any reason, the macrophage devours and digests it. Some of the raw materials may be recycled. I mentioned the record for splenic enlargement was almost 20 pounds (9 kilograms) in the introductory section on the spleen. This person died from malaria. The plasmodium organism infects the red blood cells. In this case I suspect that the macrophages were overwhelmed and the spleen collected all of these infected red blood cells, which caused it to expand so much.

The spleen also seems to have the ability to help certain lymphocytes learn to produce antibodies. The spleen seems to “skim” some lymphocytes from the blood vascular system and transfer them to the lymphatic system. They are then delivered to the lymph nodes where they may share certain intelligence regarding destructive activities that are going on in the body.

The spleen also stores a great number of platelets. Since the spleen possesses contractibility, it may be reasonable to assume that, when an emergency supply of platelets is needed to control a hemorrhage, it may be the spleen that helps with this task.

Practicing clinicians have long known that an enlargement of the spleen during an (pathogenic) infection is considered an ominous sign. This enlargement may well be an indicator that the spleen’s powers to cleanse the blood are being overwhelmed, and debris, infected cells, and perhaps foreign pathogens are accumulating within the splenic tissue.

Folks, investigate the spleen and see what it has to say. I do not believe that it is a second class citizen.
Notes:
The Lymphatic System

The lymphatic system is a vascular network of thin-walled capillaries and larger vessels. It drains lymph from tissue spaces either within organs or in other tissues. The lymphatic system then returns this fluid to the venous system for recirculation. The major lymph vessels empty into the junctures between the jugular and subclavian veins on both sides of the neck. The endothelial lining of the veins and the lymphatic vessels that empty into them is continuous.

Lymphatic fluid is a filtrate of blood. It passes through various lymphatic tissues, nodes, etc. on its way to rejoin the blood. The lymphoid tissues through which it passes on its way back to the venous blood system are lined with macrophages and other phagocytes that remove foreign matter, debris, damaged cells, etc. Many lymphocytes enter the lymphatic fluid as it passes through lymph nodes and other lymphoid tissues. Also, as the fluid passes through the nodes, antibodies (immunoglobulins) that were synthesized in these lymph nodes are deposited in the lymphatic fluid. Lymph draining from various organs varies a great deal in its consistency. When it has drained from the liver it may be high in protein, when it drains from the intestines it may have a high fat level if the recent meal has been high in fat content, and so on.

In general, the lymphatic system consists of an extensive capillary network that collects lymphatic fluid from various organs and tissues. There is an elaborate system of vessels that collects the lymphatic fluid from the capillary network and deposits it in the venous system. This system of lymph vessels is valved so that backward flow cannot normally occur. Along the pathways of the lymph vessels are numerous lymph nodes that serve to filter the lymphatic fluid as it passes through them. These lymph nodes are firm, rounded or oval encapsulated bodies that vary in size, perhaps up to 1 to 2 centimeters in longitudinal diameter, depending on how much filtering they have been called upon to do. Normally, they are less than a half centimeter in diameter. Primary lymph nodes begin development in the latter part of the first trimester of pregnancy.

Other concentrations of lymphatic fluid-filtering tissues are the tonsils, the adenoids, and Peyer’s patches along the intestine. Lymph nodules are essentially lymph nodes that have developed upon demand to assist in the control of infectious and toxic states. Lymph nodules are not encapsulated. They feel more like matted tissue as compared to lymph nodes, which are much more clearly defined as you palpate them. The node’s definition is due to its firm capsular walls.
Lymph Nodes

The lymph node is usually an oval shaped structure with a depression, the hilus, on one side where blood vessels enter and leave. However, the hilus does not have exclusive rights to all vessels. The incoming (afferent) lymphatic vessels enter through a wide variety of sites in the lymph node’s periphery. Most often the outgoing (efferent) lymphatic vessels exit with the blood vessels, but there are a significant number of exceptions to this “rule.”

Trabecular partitions/walls extend into the lymph node’s parenchyma from the capsule and the hilus. A network of reticular fibers extends into the spaces between the trabecular walls. This network provides a supporting meshwork for the lymphocytes that are inside of the node. There is a space beneath the capsule called the subcapsular or marginal space. This space is lined with endothelial cells and macrophages. The lymphatic fluid that enters around the periphery of the node is cleared of unwanted substances and/or organisms by the macrophages. It is when the macrophages are overwhelmed that the lymph node enlarges. Other radially oriented sinuses arise from the subcapsular space. These sinuses follow the trabecular walls. The afferent lymphatic vessels deposit lymphatic fluid into the subcapsular space. The fluid then follows the sinuses from the outer cortical region of the lymph node into the medullary region from which it is drained by the efferent lymphatic vessels. The sinuses are crosshatched by a multitude of reticular fibers that slow the rate of lymphatic fluid flow significantly so that the various lymphocytes, macrophages, antibodies, etc., have time to police the lymphatic fluid and eradicate pathogenic/infectious organisms that have entered the lymphatic system. It is as though everything that passes through this system of sinuses must pass inspection.

Within the lymph node’s sinus system there is also a tremendous production of lymphocytes. It is estimated that about 50 times more lymphocytes exit the sinus than enter it. Some of the extra lymphocytes come into the lymph node via the blood stream, but a great many come from proliferation within the sinus. Most of the blood lymphocytes are T-lymphocytes (T-cells). They enter via the post capillary venules that are in the deep cortical region of the lymph node. Many of these T-lymphocytes manage to wander through the cortex into the medulla and exit the lymph node via the efferent lymphatic vessels.

A few B-lymphocytes enter via the blood stream. These B-lymphocytes (B-cells) migrate to germinal centers in the cortical area of the lymph node. Here they wait for an antigen to arrive. When this happens the B-lymphocytes do two things. They multiply very rapidly and they make lots of specific antibody molecules to neutralize the foreign antigen. The great increase in B-lymphocytes causes the cortical areas of the lymph node to enlarge greatly, which causes the total lymph node to enlarge. During all of this B-lymphocyte activity, they also find time to present the antigen to the T-lymphocytes so that they will recognize and kill the antigen carriers. These T-lymphocytes also multiply and leave the lymph node in great numbers to go out and find the antigens. They then destroy the antigen carriers.

Lymph nodes are compartmentalized. They have germinal centers where relatively immobile B-lymphocytes reside. These are paracortical areas through which traveling T-lymphocytes rapidly pass. They include the sinuses that are chock full of reticular network, macrophages and dendritic cells that participate in delaying antigens as they pass through so the immune cells can learn to recognize them. This allows B-lymphocytes to make appropriate antibodies and T lymphocytes to kill the carrier.
Other Lymphoid Tissues

As mentioned earlier, other lymphoid tissue exists throughout the body. Much of it is improvised as part of the immune response to serious infections and toxic conditions. There are nonencapsulated lymphoid cell aggregations with improvised designs that offer the same services as the lymph nodes.

Almost all, if not all, mucous membranes have specialized tissues that offer protection against invaders. Particularly, the gastrointestinal tract has its Peyer’s patches, which are aggregates of macrophages, lymphocytes and dendritic cells. These cells are in the “patches” that are in the lining of the intestinal wall. These patches are oval in shape. They may be about 1 centimeter wide and between 3 and 5 centimeters long. They are the largest and most frequent in the distal ileum. They are only a single-cell layer thick.

Similar mucosa-related lymphoid tissues are seen in the respiratory tract and the genitourinary tract. Each is somewhat specialized in order to be most effective against the most common invaders.
The Cellular Division of the Immune Response

The cellular division of the immune response refers to those immune activities carried out by immune cells that are directly cytotoxic to the non-self cells. This aspect of the immune response is further subdivided into phagocytic and nonphagocytic cells. Those cells which indulge in phagocytosis are considered first.
Phagocytosis and Phagocytes

Phagocytosis is the process whereby a particle or one-celled organism is ingested by a cell. It is usually a four-step process. The first step is attachment. There are a variety of means by which attachment may be achieved, and each phagocyte “species” seems to have its own somewhat unique set of attachment techniques. Regardless of the individualized attachment method, the “prey” must be attached by the phagocyte in order for the second step to begin.

Step two is ingestion. Ingestion is engulfment. First, a cavity or phagosome is formed into which the material that has been attached by the phagocyte is placed. The material can be bacteria, antigenic particles of any kind, or just plain debris. The phagosome closes to form the phagosomic vacuole, which now contains the ingested material.

Next comes the third step, digestion. The vacuole is then approached by one or more of the phagocytes’ lysosomes, which are one type of its cytoplasmic inclusion bodies. The lysosome membrane attaches to and blends with the vacuole membrane, which then opens so that the contents of the lysosome can be “squirted” into the phagosomic vacuole. These contents include digestive enzymes, bacteriocidal agents such as lysozyme, as well as acid, because the enzymes require an acid environment in which to do their work. The contents of the vacuole are then digested. After digestion has been completed the vacuole moves to the phagocytic cell membrane.

The fourth step is excretion. The membranes of the vacuole and the cell blend, an opening is formed, and the contents of the vacuole are discharged from the cell. In some cases these contents are at least partly reusable amino acids that are picked up for use by neighboring cells. Some of the contents may simply be waste that is carried by the surrounding fluid systems to organs of elimination, such as the kidneys and the liver. In other cases the contents may be taken by the phagocyte to an organ of the lymphatic system and presented as antigens for recognition by lymphocytes. In other words, the contents may be used for educational purposes.

Bacteria taken into the phagosomal vacuole are usually killed initially by myeloperoxidase (MPO), which is a halide complex with hydrogen peroxide (H₂O₂). This chemical kills aerobic (oxygen-dependent) bacteria. Anaerobic bacteria, those that do not require oxygen, are killed by the lysozyme, the acid and/or granular cationic proteins that are present within the vacuole and that bind to the bacterial membranes causing bacterial death.

All is not peaches and cream, however. There are some bacteria that do not succumb to phagocytosis. For example, the resistant staphylococcus aureus has a capsule that resists all of the chemical attacks that are aimed at it within the phagosomic vacuole. Frequently, the attacks continue and the quantities of attacking chemicals, acid and enzymes especially, continue to increase until the vacuole ruptures. The discharged acid and enzymes enter the surrounding cytoplasm and destroy the host phagocyte. In this case the bacterium won the battle.

There are also bacteria whose capsules resist attachment by the phagocyte. In these cases step one is thwarted. Some of the pneumococcus bacteria are very good at this evasive maneuvering. When this occurs, complements and antibodies are usually tried by the immune system. (Complements are immune molecules that attach to the resistant bacteria cells and aid their destruction.) Sometimes this latter approach is successful and sometimes not. It is an ongoing chess game. The players are the bacteria and the immune cells (system).
**Phagocytes**

Phagocytes include monocytes, macrophages, neutrophiles (polymorphonuclear leukocytes), and perhaps basophils and eosinophils. There is some evidence that the latter two cell groups may do some phagocytic activity but the jury is still out. Dendritic cells perform a modified phagocytosis. They ingest but do not focus on the digestion of ingested materials. Rather they deliver antigens to lymph nodes, thymus and spleen. The antigens are then used as display materials for other immune cells.
Diagrammatic Representation of Phagocytosis Showing Ingestion Process and Intracellular Digestion
Dendritic Cells

Dendritic cells are sentinels who are on the lookout for antigenic non-self materials. There are mobile dendritic cells that roam through the blood, the lymph and all of the interstitial fluids. Functionally, these cells resemble monocytes in their mobility. There are also stationary dendritic cells that are more like macrophages in that they are imbedded in tissues and have tendrils that reach out and snare non-self antigenic material. This behavior is more like the macrophages. As an aside, monocytes roam and convert to macrophages at appropriate times.

All dendritic cells arise from stem cells, particularly hematopoietic stem cells (HSCs), in the bone marrow. They then migrate through the various fluids. After migrating a while, some of them decide to settle in tissues and wait for antigens to pass by and be snared. Other dendritic cells continue moving and searching through body fluids for antigens.

When a dendritic cell snares an antigen, it engulfs it and carries it to a lymph node where the antigenic material is presented to waiting and ready lymphocytes of both the T and B varieties. The presentation of these antigenic materials to the lymphocytes is done in order to enable them (the lymphocytes) to develop recognition when similar antigens are encountered. In other words, the lymphocytes are now alerted for and able to identify specific targets for destruction. Like macrophages, dendritic cells are “presenting cells,” but they are more precise and specific than macrophages. Both dendritic cells and macrophages are very efficient triggers for the immune response.

When dendritic cells ambush or snare an antigen, they “squirt” a chemical called Interleuken-12 before they migrate with their “catch” to the lymph node. The Interleuken-12 serves to mark the area and attract other immune cells to the vicinity so that no time is lost. Once in the lymph node the presentation process by the dendritic cell is essentially a regurgitation of the antigen so that the lymphocytes can view it and recognize its antigenic kin.

Dendritic cells are found in every tissue of the body except the brain and spinal cord. They are also extremely rare in cerebrospinal fluid. They are mononuclear. They extend tendrils from their cytoplasm. These tendrils are ever changing, scanning and searching. Dendritic cells are slightly larger than lymphocytes. They have no true phagocytic ability. That is, they cannot ingest a whole bacterium and destroy it. They only take the identifying antigens from its surface for presentation to lymphocytes. Presenting cells other than dendritic cells only present to memory T-lymphocytes. Dendritic cells present to all types of T and B-lymphocytes.

Recent research suggests that dendritic cells only mature upon contact with an antigen. It also suggests that, when exposed to specific triggers, monocytes can become dendritic cells. Why and/or how this occurs is not yet understood.
Monocytes

Monocytes are single nucleus phagocytes that are derived from stem cells. The stem cell produces the monoblast, which is the first differentiation. The monoblast quickly matures into the promonocyte, which then becomes the full-fledged monocyte. The process from stem cell to monocyte takes about one or two days.

Monocytes are seen in the circulating blood. Their job is to find and remove any antigenic materials that they may encounter as they patrol the vascular system. When there is an injury to tissue or an antigenic presence, the monocytes quickly respond to biochemical signals produced by complement, and lymphocytes go there. When monocytes receive these signals, they then transform into macrophages (usually).

The transition from monocyte to macrophage involves changes in cell morphology, biochemistry and function. In order to make the transformation, the monocyte enlarges and develops more internal organelles, such as mitochondria, Golgi apparatuses, liposomes and lipid droplets, so that it can better destroy invading bacteria. Monocytes do not always become macrophages. However, our knowledge of the unchanged monocyte’s role in fighting bacteria is sketchy at best. We do know that they have myeloperoxidase that will kill aerobic but not anaerobic bacteria. We also know that the ability of monocytes to reproduce is impaired by radiation and several chemical toxins. Their effectiveness in aged persons is reduced. It has also been observed that monocytes will join forces with eosinophils to fight candida albicans and parasitic infections.

In a normal blood count, monocytes account for 3% to 8% of the WBCs (white blood cells). Monocytes are larger than lymphocytes and have more cytoplasm. The monocytic nucleus is usually eccentrically placed and is either oval or kidney-shaped. The monocytic cytoplasm contains a large number of liposome-filled vacuoles.

In general, one can say that monocytes usually circulate and become macrophages when they settle into tissue. The monocytes are phagocytic, ingesting both bacteria and debris. Sometimes (more often than not), when the monocyte encounters invading bacteria it becomes a macrophage. In general, a macrophage can ingest a bacterium in about 1/100th of a second.
**Macrophages**

Macrophages are the largest of the immune cells. They are very aggressive. I might call them “street brawlers.” If anything seems at all suspicious the macrophage will attempt to destroy it. In this respect they differ from Killer T-lymphocytes, which are very specific. They are the “professional boxers.” They won’t attack something unless there is a recognized non-self antigen, usually on the surface of the prey. Because of their non-specifically directed aggressive behavior, the macrophages are often the first to trigger the total immune response.

Most often monocytes are roaming around doing “patrol” duty in both blood and lymph. When they site a problem they immediately become macrophages. Their transition has been described in more detail earlier in the section on monocytes. However, there is flexibility in this system. Macrophages may come directly from stem cells or they may come from monocytes. Although macrophages seem to prefer to hang out in tissues rather than perform as roaming patrol participants, some macrophages are seen traveling around looking for prey. Most often, however, macrophages lie in wait and snare possible antigens as they pass by. They seem to enjoy being the ambush cells.

Regardless of their developmental origins, macrophages do a beautiful job of cleaning up the debris from wound/injury areas. They are very nondiscriminating. They will devour anything in the area. A macrophage has been clocked in a laboratory setting as devouring a bacterium in about 1/100th of a second. It would seem that the macrophage reputation has spread into the viral and bacterial communities. These organisms have been seen under laboratory circumstances to literally run the other way when they sense a macrophage in the vicinity.

At the site of a bacterial or viral invasion, macrophages secrete a substance called lymphocyte activating factor (LAF), which triggers the on-site proliferation of all types of T-lymphocytes (killer, memory and suppressor types). At the same time that the macrophages are secreting LAF, they are cloning themselves and phagocytizing the bacteria/viruses/debris or any other entity that suggests it has an antigenic quality. As soon as an antigenic material is ingested by the macrophage the digestion process begins. At the same time, the macrophage will most likely head for a nearby lymph node to present some of the ingested antigen to the local lymphocytes so that recognition studies can be carried out. After recognition is completed, many lymphocytes are cloned that recognize the antigen that has just been presented to them by the macrophage. The lymphocytes then go out and search for that specific antigen. The killer T-lymphocytes destroy the antigenic carrier, whatever it may be.

It is amazing how a macrophage will reach out like an octopus with a cytoplasm tentacle and attach to a virus or bacterium (or any other foreign or irregular-appearing object), bring it in and engulf it in its “stomach” (phagosome) within a small fraction of a second. Once in the macrophage’s phagosome, the enzymes of the macrophage go to work chopping up the ingested proteins into peptides. Biochemicals and enzymes are used to kill the ingested bacterium or virus. Then these same enzymes digest the protein of the bacterium or virus. Some of the enzymes that have been identified include acid phosphatase, beta glucuronidase, cathepsin, lysozyme, aryl sulfatase and cytochrome oxidase. Hydrogen peroxide is also secreted by the macrophage as a “killer” substance. Peptide “snippets” of the digested protein are then presented by special macrocytic molecules (if they feel it is appropriate) called MHC-II molecules on the surface of the macrophage membranes. Helper T-lymphocytes then evaluate these snippets to see whether or not they represent a danger. If they feel the presented material is representative of something the person would do better without, the helper T-lymphocytes secrete molecules that summon other lymphocytes, especially the killer T-lymphocytes, to view, recognize and
remember the snippet, which is now considered a non-self antigen. The lymphocytes then clone by the millions and go out in search of similar non-self antigens/snippets. Whatever structure carries the snippet will then be destroyed.

Similar activities are carried out in the thymus gland. Some of the macrophages present their snippets there. Also, some of the memory lymphocytes, especially the B-lymphocytes, will go to the thymus gland and the spleen to add this new, non-self information to the library of antigens that are to be watched for. Millions of phagocytes and lymphocytes are educated in the thymus gland regarding the recognition of non-self.

It has also been seen that messenger cytokine molecules are released at injury and infection sites. When these cytokine releases occur, macrophages are drawn to the area. These giant immune cells (macrophages) also have specialized receptors for antibody and complement on their membrane surfaces. These receptors help them recognize organisms that have been coated by antibody complement. The receptors receive the immune globulins known as IgG and IgE as well as CR, which is a complement receptor. Opsonin is the term used to describe the principle used in coating a bacteria, etc., with antibody complement to attract macrophages and other phagocytes.

A couple other molecules that have been discovered but not fully understood yet are macrophage activating factor (MAF) and macrophage migration inhibiting factor (MMIF). The first increases macrophage activity and the second somehow keeps them where they are rather than letting them leave, even after having phagocytized a non-self something.

Another interesting fact about macrophages is that they can change in seconds. They are very individualistic. Many of these differences relate to locales and activities. Their changes in shape and function are strongly influenced by the various molecules of cytokine subgroups. For example, macrophages in the lung get smaller, phagocytize less and move indiscriminately. They may even serve as response-suppressor cells to avoid severe allergic responses to inhaled antigens, etc. All in all, I would say that the monocyte-macrophage duo is of extremely powerful awareness, of high IQ, and totally dedicated to its owners.

Of late we have seen that certain bacteria have developed resistance to macrophages. Some of these bacteria have developed a slippery coat so the cytoplasmic tentacle with its sticky end cannot grasp the bacteria and reel it in to its stomach/phagosome for digestion. You might call this passive resistance.

The notorious “hospital staph,” a strain of staphylococcus aureus, is not only resistant but aggressive. It kills macrophages. When a macrophage ambushes a resistant staph aureus with its tentacle and reels it in to its stomach, this particular bacterium has a protective coat that the macrophage does not know about. The macrophage secretes its killer biochemicals and enzymes but the staph bacterium doesn’t die. It is protected by its coat. Further, the staph aureus secretes its own substance that causes the macrophage’s stomach/phagosome to lose its ability to contain its own killer biochemicals and digestant enzymes. The macrophage continues to secrete in its attempt to kill the staph aureus and, in the process, kills itself. The staph aureus goes free and awaits another macrophage that will reel it in and die.

Here’s a little “hot off the press” addition about interactions between macrophages and T lymphocytes. When a macrophage ingests an antigen that is then presented by MHC-II, proteins on the macrophage cell surface and the antigen is only recognized by a few T lymphocytes. When one of those few T-lymphocytes attaches to the macrophage, there is an interaction between the attached lymphocyte and the macrophage that sparks a tremendously large and immediate proliferation of T-lymphocytes by the
attached one. This produces many, many T-lymphocytes that recognize this antigen without the parent T-lymphocyte even detaching itself from the macrophage surface.

Also, it is now clear that macrophages are big producers of Interleukin-12 and Interferon gamma.
Polymorphonuclear Leukocytes

Polymorphonuclear leukocytes are also known as neutrophils, neutrophilic granulocytes, or simply polys. They have multiple nuclei that appear to be connected by threads. They were known as neutrophilic granulocytes more often in the past in order to differentiate them from the other granulocytic cells. The granules to which I refer are cytoplasmic. During the staining process (Wright’s stain), the polys’ granules do not turn a color. In basophils and eosinophils the cytoplasmic granules turn blue and red, respectively, when stained. (This is how cell groups are differentiated from each other.)

Polys are significantly smaller than macrophages and they are much faster moving than their big brothers, the macrophages. However, they do slow down when they have secreted lysosomal enzymes from one-third or more of their granules. This does not slow their phagocytic activity. Polys are phagocytes. They clean up the bacterial cadavers left by killer T-lymphocytes and other debris, as well as being very active phagocytes against living bacteria and viruses. Their bacteriocidal enzymes are not as powerful as the macrophage enzymes. However, they usually get the job done.

Polys are also very self-sacrificing. When a poly ingests/phagocytizes a live bacterium, it kills the bacteria and then dies itself. You might think of polys as “kamikaze” phagocytes. The pus that is present at infection sites, etc., is in significant proportion composed of dead polys.

Unlike macrophages, polys do not clone themselves, but stem cells create great numbers of polys when the demand is present. Estimates are that 100 billion polys per day are created by the stem cells of a healthy body when a crisis occurs. Stem cells create myeloblasts that quickly mature through the stages of promyelocytes to metamyelocytes to band cells and, finally, to mature polymorphonuclear leukocytes (polys). The ratio of immature to mature polys in peripheral blood as seen under the microscope offers an idea about how the body is responding to an infection or injury. There are also large numbers of mature polys stored in the bone marrow and the spleen. They are armed and ready to go when the alarm is given.

Under normal circumstances, the polys constitute about 60 to 70% of the total white blood cell count. The next highest percentage is the lymphocytes, which are usually about 30%. The balance of the white blood cell count is made up of small percentages of basophils, eosinophils, monocytes, mast cells, an occasional macrophage, and so on.

Usually, the polys circulate in the blood for about 12 hours after leaving the bone marrow or the spleen. Then they enter a tissue where they remain until they die. Once in tissue, polys do not return to the blood or move to other tissues as do lymphocytes and macrophages. In the tissues the average poly may live up to 48 hours, usually less.

Polys, once summoned to a site of injury or pathogenic invasion, are very avid and effective phagocytizers. They work closely with the complement and antibody systems to destroy invading pathogens.
The granules that are located in the polys’ cytoplasm carry degradation enzymes and small proteins that, if released into tissues, induce inflammation, which enhances blood supply to the area. The result is that an ever-increasing number of polys come to the area to fight the infection. As the number of pathogenic bacteria is controlled and reduced, fewer “kamikaze” polys die, less of their granular-contained enzymes and proteins are released, and the inflammation dies down. You have all seen this happen in your own cuts and infections. This is truly an ingenious system.

The primary granules of the polys are called lysosomes. They are about 0.4 microns in diameter. They are very electron-dense and contain a variety of hydrolases (enzymes that digest water containing proteins, etc.), methyl peroxidase, arginine-rich protein, acid phosphatase, and sulfated mucopolysaccharides. There are also some secondary granules that are about 0.3 microns in diameter. These granules are rich in alkaline phosphatase, lysozyme and amino peptidase. Both types of granules are important for the killing of ingested bacteria and the break down of non-living ingested materials. The production of cytoplasmic granules is ongoing in polys as well as in other granulocytic cells. Its processes are not as yet understood, but each cell seems to control its own rate of granule production.

It might be of interest to know that lysozyme, which is a powerful antibiotic and is used by almost all of our human immune cells, is also found in tears of humans and many other species. It protects the eyes from infection. It is also plentiful in egg whites. It protects the fertilized yolk from bacterial invaders. For a short time during the ’40s and ’50s there were a few studies done wherein lysozyme was isolated from egg white and rather successfully used to treat strep throat in humans. Lysozyme can’t be patented because it occurs naturally. Therefore, there is not much profit to be made selling lysozyme. Perhaps when you cry you could bottle and refrigerate your tears and drink them when you have an infection.
Eosinophils

Eosinophils are phagocytic granulocytes. They are called eosinophils because their granules absorb eosin dye, which turns them red. Their granules are larger than those of the neutrophilic granulocytes (polys). Eosinophilic granules are located in the cytoplasm of the cell. They are rich in acid phosphatase and peroxidase. The eosinophilic granules have a crystalloid substructure, the core of which contains a unique protein that weighs about 11,000 daltons. This protein is toxic to certain parasites such as schistosoma, etc. It is also toxic to the eosinophil itself should it be released into its cytoplasm. Unlike other phagocytic granules, the eosinophilic granules do not contain lysozyme, which is bacteriocidal. Therefore, they are not as effective against bacteria and/or viruses, and in their wisdom they do not phagocytize these organisms.

The normal eosinophil count is about 1 to 3% of the total white blood cell count (WBC). In parasitic infections the eosinophil count may elevate to between 25 and 50% of the WBC. Eosinophil counts also elevate during allergic responses. These elevations are usually accompanied by elevations of immune globulin E (IgE), which often contribute to allergic hyper-reactions. In some way eosinophils seem to be able to modulate the excessive responses to allergens that, at least in part, are due to IgE. On the other hand, eosinophils contain and may secrete large amounts of histamine that, in turn, can produce excessive tissue response to allergens.

In addition to the aggregation of eosinophils at the sites of parasitic infestations and allergic responses, eosinophils also collect at the sites of any antigen-antibody responses. It would seem that T-lymphocytes call for eosinophils to come to the sites where they are working. These T-lymphocytes also regulate to some degree the activities of the eosinophils once they have arrived on site. Eosinophilic activities are also influenced by a variety of complement proteins and many other cell products.

When foreign protein enters the body by any pathway, the eosinophil count significantly elevates. These pathways of foreign protein entry would include the mucous membrane linings of the intestinal tract, the respiratory system (especially the alveolae of the lungs), and by injection or traumatic injury through the skin. When the entry of protein into the body is recognized as non-self, the eosinophils serve to neutralize these proteins. Clearly, inadequacies of the protein digestion of foods keep the eosinophils busy. At times, eosinophilic activity may become excessive and tissue damage may result. I suggest this may be the case in some ulcerative bowel conditions, as well as in some chronic lung problems. These tissue damages may be due to release of the aforementioned toxic proteins that the eosinophilic granules carry, which are probably intended for parasites. It may also be due to excessive histamine release, as well as other factors as yet unidentified.

Eosinophils arise directly from bone marrow stem cells and they complete their maturation process in the marrow. This is in contrast to neutrophils that mature in the blood stream. Eosinophil maturation in the bone marrow takes between three and six days, after which they are released into the blood stream. They have a relatively short stay in the blood with a half-life of about 30 minutes if they do not land in an appropriate tissue. If they land in a tissue, their half-life is about 12 days. Once in tissues, eosinophils do not return to the blood stream.
Rather, they are eliminated through the mucosal surfaces of the respiratory and gastrointestinal tracts, which are the areas where they usually find “dockage.” In other cases they are biodegraded by enzymes, and their components are either recycled for use by other cells or they are excreted as waste.

We have a lot to learn about eosinophils and their pluses and minuses for the total body. They can be either extremely helpful or quite damaging, depending upon the situation and the messages they receive that influence their activities.
Basophils

The major contribution of basophils is to serve as mediator cells. By this I mean that their major function is the liberation of “messenger molecules” to the cells and tissues of the body under specific circumstances.

Basophils and mast cells are very similar in morphology and function. In fact, some authorities suspect that basophils may become mast cells under certain circumstances. Both basophils and mast cells release histamine, serotonin and heparin selectively and under (hopefully) appropriate circumstances. Platelets are also mediators for the immune response, but they only release histamine and serotonin. They do not release heparin.

Histamine, when released, serves to dilate blood vessels so that blood flow to specific areas is increased. This call for increased blood flow usually comes from an area that has been injured or is under attack by pathogenic bacteria, viruses, etc. The increased blood flow provides for the transport of increased numbers of phagocytic cells to the area. Too much histamine can often occur, as with colds and allergic reactions. Under these conditions we usually take antihistamine medications.

The actions of serotonin are more variable than those of histamine and heparin. Serotonin may increase or decrease voluntary and sensory nerve activity to given tissues, depending upon the locale in which it is released. Serotonin may also increase or decrease autonomic nerve activity. Quite often serotonin reduces pain conduction by peripheral nerves that are not autonomic. In the brain, serotonin deficiencies often result in emotional “flatness” or depression. There is a lot to be learned about why basophils, mast cells and platelets all have the ability to release serotonin.

Heparin is released by basophils and mast cells under specific conditions. It is not released by platelets. Heparin is an anticlotting molecule and the advantages of its release at sites of compromised blood flow, as in the case of strokes and heart attacks, are easy to understand. Platelets participate in the clotting activities of blood, as well as in the immune response. It would be self-defeating for platelets to produce clots and concurrently release heparin, which dissolves clots and prevents the further clotting of blood.

In the normal total white blood cell count (WBC), there are usually about four basophils per 1,000 white blood cells (0.4% basophils). The basophil count goes up during inflammation related to any cause. In chronic inflammation the red blood cells have a tendency to clump together. Basophils have been seen to counter this clumping by the release of histamine and heparin.

Basophils have large, multilobular nuclei, one nucleus per cell. Yet most cells (except polys) have unilobular nuclei, again one nucleus per cell. Both basophils and mast cells have cytoplasmic granules.

Despite their similarities and the possibility that basophils may become mast cells, both types are derived from different precursors. Basophilic granules are large and they stain dark blue to purple using Wright stain. These granules are electron dense and they contain acid mucopolysaccharides, such as heparin. It is not clear whether or not histamine and serotonin are from these same granules or perhaps are synthesized and stored separately from heparin-containing granules. Most authorities seem to favor the concept that all three mediators are from the same granules. And there is some evidence that these basophilic granules also contain hyaluronic acid, which is an essential component for collagen and cartilaginous ground substance.
It has been observed that antigen contact directly with the basophil and/or an antigen reaction with another cell’s membrane-bound IgE near the basophil stimulates it to release histamine. It has also been seen that adenosine monophosphate, when present, will reduce the release of histamine by the basophil. It may be that supplementary adenosine could be helpful in persons suffering from allergies such as hay fever, allergic asthma, etc.
Mast Cells

Mast cells are white blood cells with a granular cytoplasm. Their granules contain histamine, serotonin and heparin, which they secrete in response to specific signals. Mast cells also secrete chemotactic factors that attract eosinophils and polymorphonuclear neutrophilic phagocytes (polys). At times the over-secretion of eosinophilic chemotactic factor results in an overabundance of eosinophils at the site. This situation is often seen in anaphylactic shock. As the mast cells release their various molecular substances, their granules are seen to disappear. Along with basophils, mast cells secrete histamine during allergic responses. Both types of cells also synthesize prostaglandins and leukotrienes at the allergic response sites.

It is often seen that mast cells are unable to determine when enough is enough, or too much. By their lack of “judgment” they over-secrete and actually create or worsen allergic responses, even into life-threatening anaphylaxis. There is much to be learned about the mast cell.

Mast cells are plentifully located in lung tissue, the mucosa of the nose, and the intestines, the skin and the tongue. Within these tissues mast cells aggregate, particularly around blood vessels. A lot of their effect is upon the vasculature of these tissues, causing an increased blood flow and, with it, an increase in all kinds of white blood cells to the area.

Immune globulin E (IgE) often attaches to the mast cells (and basophils) in the tissues. This IgE attachment to these cell membranes may also induce allergic response for reasons unknown to us at the time of this writing. It would seem that the IgE binding to the membranes of both mast cells and basophils readies them for the almost instant release of histamine, serotonin and heparin when a suspected allergen is recognized. This is a hair-trigger response in some people, and it causes the vascular changes seen in the inflammation that is part of the allergic response that is inappropriate for them.

It is thought by some authorities that, although mast cells are derived from stem cells in the bone marrow, basophils often convert to mast cells when they arrive at specific tissue sites. Whether or not mast cells have such a dual origin is still under discussion, and it probably will be for some time.

Mast cell membranes have a wide variety of leukotrienes attached to them. Among them the following have been identified and studied. They don’t have fancy names as yet, only letters and numbers.

1. Leukotriene B4 is a powerful chemotactic agent that attracts other immune cells to the area in which it is activated.

2. Leukotrienes C4 and D4 are powerful, smooth muscle contractants when activated.

3. Leukotriene PGD4 is a powerful vasodilator. Obviously, this enhances blood flow to the area when activated, so it works in conjunction with B4.

4. Leukotriene PGI2 causes platelet disaggregation, thus discouraging the clotting mechanism that, if active, would interfere with both B4 and PGD4.
In addition to the impact that mast cells have upon sites of allergic reactions, etc., they have an influence upon both benign and malignant tumors. In very high concentrations, the mast cells may be tumor-toxic. They seem to be able to interfere somehow with tumor-cell proliferation, at least in the laboratory. In the body, high concentrations of mast cells have been seen to kill tumors. Ironically, x-rays kill mast cells as well as tumor cells, so they cancel out some of the body’s natural defenses against tumors.

On the other side of the coin, low concentrations of mast cells in the area of tumor growth seem to promote that growth. Very little is known about how this occurs, but there is strong suspicion that heparin, secreted by both mast cells and basophils, encourages tumor growth. This may occur because heparin inhibits the blood-clotting mechanism and, since tumors require increased blood supply, heparin may assist somewhat.

It is also seen that mast cells stimulate tissue-graft rejection, fibrosis and inflammatory arthritis. So, with our present level of understanding, mast cells would appear to be a mixed blessing.
Non-Phagocytic Cells

Lymphocytes

General Information
Functionally, lymphocytes differ from phagocytic cells in that they react to specific antigens to which they have been sensitized. Phagocytes are much less specific. Lymphocytes also manufacture and secrete very specific molecules, some of which serve to communicate with other cells and some of which are antibodies that will be used against identified foreign (nonself) antigen carriers, whether they are viruses, bacteria or other unwelcome foreign molecules.

The category called lymphocytic includes the plasma cells, which are derived from the B lymphocytes. When lymphocytes and plasma cells are introduced to and then sensitized to a given antigen, they will recognize that antigen in the future. Once sensitized, they maintain long-term memory for that specific antigen, and will attack the recognized antigen carrier immediately.

The development of vaccines as preventive medicine relies in large part upon the use of vaccines that possess specific antigens related to specific disease organisms. These antigens are injected into the patient as samples that sensitize the recognition mechanisms of the lymphatic cells, and then rely upon the long-term memories of these cells to attack anything that presents the same antigen at a later date. Booster vaccinations are given at intervals that are intended to refresh the lymphatic cells’ memories of the antigens in question before that memory is lost. The time periods between booster vaccine administrations are, in truth, “best guesses.” The problems that we have seen with untoward vaccine reactions are most probably related to the sources and/or selection of the antigens to be injected into the patient, although we must keep in mind the possibility of errors in the manufacturing and/or preservative processes.

Once a lymphocyte or plasma cell has put the recognition of alien/enemy (non-self) antigen into its memory bank, it becomes known as an immunocyte. An immunocyte is defined as any cell of the lymphoid family that is programmed to attack a specific antigen at first sight. Some activated lymphocytes immediately begin to produce specific antibodies that will neutralize the antigenic substances. Some alerted lymphocytes will also send out messenger molecules that alert and summon all other cell types of the immune system, such as the phagocytes, etc., to come and support the immune response/defense against the “invaders.” Some lymphocytes will attack and kill the invading antigen carriers directly. The latter type is commonly known as killer T-cells or killer T-lymphocytes.

Lymphocytes and plasma cells are easily differentiated under the microscope from other immune cells in that all cells of the lymphoid division are single-nucleus cells. Their cytoplasm is devoid of granulations, and it is clear and somewhat basophilic in nature (it stains somewhat bluish). Lymphocytic cytoplasm contains free ribosomes that are deeply involved in protein synthesis. The focus of this protein synthesis may be related to the production of antibodies, as well as to transmembrane-channel and neurotransmitter-guidance-system proteins.
T and B Category Lymphocytes

Functionally, lymphocytes are divided into two major categories: T and B-lymphocytes. The T-lymphocytes are so named because they pass from their bone marrow site of origin to the thymus for maturation and education before going to the peripheral lymphoid system. B-lymphocytes bypass the thymus (and the spleen), going directly from bone marrow to the peripheral lymphoid system, which consists of lymph nodes, nodules, etc. (These are discussed in the section that describes lymphoid tissues and organs.) Once the B-lymphocyte has been activated by confrontation with an alien (non-self) antigen, it gets its name changed to plasma cell.

In the human fetus, stem cells that produce the cells of the immune system are found first in the yolk sac and then in the liver and bone marrow. In the adult, the primary site for these stem cells is in the bone marrow. However, these immune-system-related stem cells are also found in various places in the adult body as need is present. They are most commonly found in the thymus, the peripheral lymphatic tissues, the spleen, and at or near “battle sites” between immune defenses and pathogenic and/or alien (non-self) invaders.

Stem cells are extremely versatile, as we have discussed in the stem cell section. The same stem cell can become the precursor for any type of lymphoid cell prior to making its firm commitment to the production of any one type of lymphocyte. T-lymphocytes that are produced in the bone marrow go directly to the thymus for what we might call orientation and instruction. Here they are introduced to unacceptable antigens. These recognition patterns are put into their memory banks. The antigenic information in the thymus has been brought in by other lymphocytes. The mechanisms of this “saga” are discussed below.

Once the new T-lymphocyte has been educated in the “thymus university,” it is classified by immunologists as an immunocompetent T-lymphocyte. (T-cell is often used in conversation.) The T-lymphocyte educational process in the thymus gland usually takes about two or three days, after which the immunocompetent T-cell (perhaps with diploma in cytoplasmic hand) travels by way of the blood stream to the peripheral lymphatic system. During their travels these immunocompetent T-cells are looking for the antigens that they have been trained to recognize as unwelcome. Should they meet any of these non-self antigens along the way, they will sound the alarm to start the total immune response and, as T-cells of one kind or another, do their thing against the non-self alien antigen carrier.

The bone marrow T-stem cells also produce, by some mysterious method, a number of T lymphocytes that are immunocompetent at birth. These cells will remain in the bone marrow as protection for that very rich substance that would make wonderful nourishment for some hungry pathogens. These bone marrow T-cells may also respond to emergency situations that are outside of their marrow home and leave at a moment’s notice. Subdivisions of functional T-cell types are described below.

B-lymphocytes are also produced in the bone marrow by B stem cells. These B-lymphocytes may remain in the marrow or they may go directly to the peripheral lymphoid organs. They skip the thymic university of alien/non-self antigenic materials. They receive their education either at birth from their B-stem cell parent or from other immune cells at the time of an immune response.

Both T and B-lymphocytes that are immunocompetent are allowed to return to the bone marrow for what almost might seem a rejuvenation period. They do this in small, not massive, numbers.
Another path that is available to and followed by all lymphocytes, whether T or B, involves a sort of recirculation from blood to lymph to blood to lymph, etc. The transition from blood to lymph and vice-versa is done in the peripheral lymph nodes for both T and B-lymphocytes. The transfer may also be done in the spleen but only for T-lymphocytes. B-lymphocytes seem not to transfer in the spleen, although they do visit it without transferring between blood and lymph in either direction.

When transferring from blood to lymph or vice-versa in the spleen, the process takes the T-lymphocytes about 5-6 hours. In the lymph nodes the same process takes 15-20 hours. B-cells accomplishing the same blood-lymph transfer in either direction spend about 30 hours, and this is only done in the peripheral lymph nodes. All of these times are approximations. You will find variations in the literature. The aforementioned times are “in the ballpark.”

When something is wrong inside of a cell, i.e., a virus has taken over or a toxic stress is severe, a “distress” antigen is placed on the surface of that cell. When this antigen is recognized by the lymph cells, the immune response begins and that cell is destroyed. In order for the lymphocyte to recognize the distress antigen molecule as a signal for cell destruction, this antigenic molecule must be taken to the cell surface and held in place by two MHC (major histocompatibility complex) molecules. If the MHC molecules are not present, the lymphocyte will not sound the alarm that starts the immune response. The lymphocyte will simply assume that the cell is in good health and go on about its business. When a lymphocyte does recognize an antigen and interacts with it, that lymphocyte begins to proliferate and to differentiate into the various subgroups. Each time that lymphocyte or any of its progeny sees that antigenic form again, it recognizes it and begins its proliferation and differentiation once again. By differentiation I mean that some of its progeny will become memory cells, some will become T-killer lymphocytes, some will become T-helpers and some will become T-suppressors. It will also produce B-lymphocytes that become plasma cells and produce antibodies.

As you can see, each lymphocyte, no matter what its type or subgroup, is extremely versatile. Each can proliferate and produce all types of lymphocytes. It took true genius to design this system.
There are two major categories of specialized lymphocytes: T and B. The T-lymphocyte category has to do with the killing of unwanted cells. The target cells may be host (self) cells that have been successfully invaded by a virus, a bacterium, a fungus or a parasite. T lymphocytes may also recognize tumor cells, and cells that are toxic and/or damaged by any of the aforementioned agents. These cells are marked for destruction by the antigenic markers that are placed on their exterior membrane surfaces. Each of these antigenic markers is held in place by two MHC (major histocompatibility complex) molecules, much as a hot dog is held in a bun. The antigenic markers are actually snippets of cellular protein, about nine amino acids long. They are sampled from the intracellular proteins by the MHC (protein) molecules and delivered to the cellular surface by the reticular delivery system that runs through the cytoplasm and serves as a transit system for the cell. This T-lymphocyte category is further subdivided into killer T-lymphocytes, helper T-lymphocytes and suppressor T-lymphocytes.

The second major category of lymphocytes is the B-lymphocyte. I’m sure that by the time you read this, the B-lymphocytes will also be subdivided, but at present this is not the case. B-lymphocytes are primarily involved in the production of antibodies, the secretion of communication molecules, and the rapid production of more lymphocytes. Once the B-lymphocyte has become activated into the immune response and is making antibodies, it becomes a plasma cell.

Let’s go back to the T-cells. If macrophages are the “street brawlers,” killer T-lymphocytes are the “expert boxers.” The killer T-lymphocyte needs only to brush against an antigen and it begins a well-organized program to destroy the antigen and its carrier. The killer T-lymphocyte begins producing clones immediately. Very soon thousands of these cloned killer T-lymphocytes are circulating, looking for the same antigen that triggered parent killer T-lymphocyte’s response. All of these killer T-lymphocytes will remember, via their progeny, this particular antigen (as an enemy) for many cell generations. Some of these sensitized clones will deliver the antigen information to the thymus, nearby lymph nodes and spleen, where the antigen becomes a part of the immune-system records. Whenever the antigen is again spotted, it and its carrier are destroyed. Killer T-lymphocytes can change their appearances as they patrol in search of deviant cells, bacteria, viruses, etc., that carry that antigenic material. Often viruses and bacteria learn what the killer T-lymphocyte looks like and try to avoid these known patrol cells. The disguises adopted by the patrolling killer T-lymphocytes are apparently meant to fool the wary antigen-carrying intruders.

A killer T-lymphocyte recognizes a non-self/alien or toxic-produced antigen or tumor cell by brushing against it. You might say that they evaluate the “feel” of the cell surface. As soon as the antigen is recognized, concurrently with the production of clones, the killer T-lymphocyte begins perforating holes in the membranes of the antigen carrier. The holes become abnormal pores or passageways through which unwanted fluids and other substances enter. Usually, in a matter of a few minutes, the antigen carrier swells up and bursts. Hence, the name: killer T-lymphocyte. There is also some evidence that the killer T-lymphocytes inject a toxin into the target cell. This is under investigation.

A second subcategory of T-lymphocytes is the helper T-lymphocyte. Upon recognition of an antigen that is alien, the helper T-lymphocyte sends out several types of messenger molecules that alert the total immune system. These messenger molecules are a wide variety of cytokines and interleukins. They excite killer T-lymphocytes to action. We might think of them as “adrenalizing” these killers. They also stimulate B-lymphocytes to begin immediate, appropriate and specific antibody production. In addition, these molecules serve to pass information to the thymus and other lymphoid organs, and they stimulate...
the cloning process for all lymph cells. They also communicate with phagocytes and recruit their assistance.

The third and last (at this writing) subcategory of T-lymphocyte is the suppressor cell. There are two major functions of the suppressor T-lymphocytes. They prevent killer T-lymphocytes from going into a state of killing frenzy as occurs in anaphylactic shock, milder allergic reactions and autoimmune diseases. Secondly, they modulate the number of antibody molecules produced by the B-lymphocyte so that the body fluids do not become supersaturated and hyperviscous.

**B-Lymphocytes and Plasma Cells**

This is the second major category of lymphocytes. These cells do not go through the thymus gland for briefing/educational purposes. They go directly from bone marrow to the peripheral system. When B-lymphocytes encounter an alien antigen, the message goes directly to the B-lymphocyte’s nucleus. The cell then enlarges and becomes a plasma cell. When this occurs the B-lymphocyte loses its ability to clone/proliferate. It develops an extensive endoplasmic reticular system that has a lot of cisterns in it. The antibodies that the plasma cell manufactures are stored in these cisterns. Plasma cells can also form directly from reticulocytes (immature red blood cells). When large amounts of antibodies are being produced, the number of plasma cells increases markedly. The sources of the increased plasma cell count are both the B-lymphocytes (which can clone/proliferate themselves) and the reticulocytes.

B-lymphocytes are created by stem cells in the bone marrow. They are also educated in the bone marrow. There are estimates that one B-lymphocyte leaves the bone marrow with the ability to produce over 1 million different antibody molecules, and when stimulated it can turn out over 10 million specific antibody molecules in an hour. Helper T-lymphocytes are necessary to activate the B-lymphocytes, which then turn into plasma cells and produce the 10 million molecules per hour of the correct antibody. Actually, the term plasma cell is losing popularity. It is easier if we simply say that the B-lymphocyte undergoes some morphologic changes when it is activated. (The changes being overall enlargement, some basophilic changes in the cytoplasm, and the formation of vesicles for the storage of manufactured antibodies.) B-lymphocytes, once exposed to antigen, carry the memories with them for several years.

B-lymphocytes are obviously present shortly after birth. They are already educated at that time. They sample protein scraps as they pass by. If a scrap of protein fits into an idioype receptor, the alarm goes off and the B-lymphocyte (plasma cell) starts producing antibodies that are specific to the antigenic trigger protein sample that set off the alarm.

Large numbers of B-lymphocytes are found in mucosal tissues and related lymphoid tissues. It is at these locations that many foreign invaders try to enter the host body. B-lymphocytes are often the first encounter that these antigenic carriers experience. The B-lymphocyte sounds the alarm and begins to manufacture (hopefully) appropriate antibodies. The other immune cells hear the alarm and rush to the site of invasion.
Natural Killer Cells

Natural killer cells (NK cells) are sometimes considered a subpopulation of lymphocytes. However, they don’t have the CD-3 surface marker that all lymphocytes have. NK cells also have a different/unique functional role in the immune response that differentiates them from their lymphocytic brethren. Other lymphocytes rely upon the memory of previously recognized markers to decide when a marker is a non-self antigen, and thus attack it or warn against it, etc. NK cells do not need to have had previous exposure to recognize an antigen as non-self. Nor do they remember the antigen after having encountered it. In short, the NK cell attack is not induced by the antigen, nor does it remember the antigen after it has attacked the antigenic carrier. By some method as yet unknown, it does select appropriate target cells and destroy them. We do know that the recognition of the target cell by the NK cell requires cell-to-cell contact without which the attack will not occur.

More recently, research by Thomas Spies at the Hutchinson Cancer Research Center in Seattle suggests that a protein marker named MICA on the target cell may help the NK cell identify the encountered cell as target. This is a protein that appears upon self cells that are in trouble. These cells may be tumor cells or toxic cells, etc., that are essentially asking to be destroyed by NK cells or other killer cell types. MICA has not as yet been identified upon the surfaces of bacteria or viruses that, nonetheless, are targeted by NK cells.

NK cells arise from stem cells in the bone marrow. Their numbers have been seen to decline when the bone marrow becomes dysfunctional for any reason. NK cell activity is most significant in the early development of the infant when more specifically focused cytotoxic/killer cells are in the developmental stages in terms of the antigen, non-self educational process. NK cells do not seem to require education in order to decide which cells are targets.

When fully developed, NK cells are very similar to large granular lymphocytes (LGLs), which make up about 5% of the peripheral lymphocyte population. The differentiation between the two cell types is based upon the surface protein markers of the NK cell as compared to the markers on the LGLs. The surface of the NK cell typically has CD2, CD8, but no CD-3, as do all lymphocytes.

Prior to full development, NK cells are not cytotoxic to target cells. Some of the factors that encourage NK cell maturation from the pre NK cell phase into the full cytotoxic power state of the NK cell include the cytokines, Interleukin-1 and 2, and Interferon a and b. In the presence of Interleukin-2, it has been seen that large granular lymphocytes become NK cells. The activity of mature NK cells is inhibited by prostaglandin secretion, suppressor cells, and certain developmental impairments.

NK cells patrol the body constantly checking for targets in the form of abnormal body cells, bacteria and viruses. They are a significant fraction of the immune police force. Once a target is recognized by contact, the NK cell binds to the target cell and activates its killer (lytic) machinery, which destroys the target. Granules within the NK cellular cytoplasm seem to inject lethal substances into the target cells. One unique protein that NK cells use to poison targets has a molecular weight of 18-36,000. Not much more is known about it as this writing. What is known is that target cells dissolve during the NK cell attack. It is also known that NK cells release cytokines and participate in the regulation of the total immune response. We also know that NK cells are followed by phagocytic feeder cells (WBCs and macrophages) that clean up the debris left in the NK cell’s “wake.”
NK cells are a very important and “impulsive” first line of defense in killing tumor cells, toxic cells, bacteria and viruses. They buy time while the rest of the immune response is activated. Recently, it’s been seen that NK cells also produce Interferon gamma, which helps the immune response.
Megakaryocytes and Platelets

Megakaryocytes are the precursors of platelets. Found in the bone marrow, they are giant cells containing large, lobulated nuclei. The platelets, also known as thrombocytes, are actually fragments of the megakaryocyte that have detached. Platelets do not take any of the megakaryocytic nuclei with them as they detach. The circulating platelets are not nucleated, but their cytoplasm is granular. Under normal conditions there are between 200,000 and 500,000 platelets per cubic millimeter of blood. Under normal conditions they circulate without adhering to the blood vessel walls or to each other. However, when a tissue injury occurs they immediately cling to each other, forming a sort of dam that begins to curtail blood loss. At the same time the platelets secrete biochemical factors that initiate the blood-clotting mechanism. This contribution to the control of blood loss due to injury and clotting is what platelets were first known for. More recently, we see that they have other functions besides damage control.

Platelets are involved in the immune response in that they have on their surfaces receptors for IgG and IgE gamma globulins. They also have receptors for MHC Class I molecules.

IgG is an immune-response protein that coats invading microorganisms, and thus identifies them for recognition and destruction by macrophages and other phagocytic cells, as well as by killer T-lymphocytes2. IgE is a protein that defends us against invading parasites. It identifies these organisms for destruction by the appropriate immune cells. Eosinophiles are key in the control of parasitic infestations. MHC Class I molecules help killer T-lymphocytes identify invading organisms by presenting parts of the protein of an invader that has entered a host cell onto the surface of that host cell. The lymphocyte easily recognizes that an invader, probably a virus, has successfully occupied the cell. The lymphocyte then takes action. It usually destroys the host cell in order to rid the organism of the invader. How the MHC molecules are able to do their work is a mystery.

The part that platelets play in protecting against invading organisms is not limited to the aforementioned relationship with the gamma globulins. As the platelets adhere to and aggregate on the damaged endothelium of the vascular system, they release molecular attractants that guide leukocytes to the area along with other molecules that increase the capillary permeability so that, once attracted, the leukocytes have more ease of entry into the area wherein the danger of bacterial invasion is present.

There is a cytokine named Platelet Derived Growth Factor (PDGF) that is secreted by platelets at appropriate times. PDGF is a glycoprotein consisting of two smaller peptide chains. The molecular weight of each chain is between 14,000 and 17,000. PDGF is stored in the platelet granules. It has several functions related to the cellular reactions that are observed during wound healing. When released from the platelets it attracts monocytes and neutrophils that, in turn, release more PDGF. The PDGF attracts fibroblasts and vascular smooth muscle cells, both of which are required for the repair job.

PDGF, when out of control, may cause over activities of fibroblasts and attract too many smooth muscle cells. In these cases atherosclerosis may result. There is also some suspicion that platelet production of PDGF gone awry may be an underlying cause of idiopathic pulmonary fibrosis, or neoplastic (tumor) growth.
Molecules of the Immune System: Antigens and Antibodies

An antigen is any substance capable of eliciting an immune response by reacting with an immune cell and ultimately resulting in the production of antibody.

Antibodies are a heterogeneous group of proteins that are called immunoglobulins. There are five major classes of immunoglobulins identified thus far in human blood serum: gamma globulin that has four subgroups, alpha globulin that has two subgroups, globulin M, globulin D and globulin E. They are all released by B-lymphocytes.
Antigens

Proteins are almost universally antigenic. There is also a wide range of other nonprotein molecules or protein-fat and protein-carbohydrate complexes that are antigenic. These are called lipoproteins and glycoproteins, respectively. Carbohydrate fat (glycolipid) complexes can also be antigenic. Clearly, we are surrounded and bathed internally by antigenic molecules all the time. In abnormal situations your own body can become antigenic to your own immune system. This is an autoimmune condition/disease. It is fair to say that most antigens are very large molecules (macromolecules), although some are small.

Haptens are smaller molecules that alone are not antigenic, but when combined with a nonantigenic protein or polypeptide, the combination becomes an antigen. Very often these polypeptides are synthetic molecules. As an example, penicillin is a hapten. Sometimes penicillin molecules combine with serum proteins that are self molecules. The result is an allergic reaction to penicillin. I’ll vouch for that one. I had about five penicillin shots before I developed hives over most of my body. Then when I got a polio vaccination that had just a hint of penicillin in it about three and a half years after the allergy developed, I produced significant hives just from the vaccine. Once a hapten finds a way to chemically combine with one of your own self proteins, the die is cast. You will be allergic to that hapten for the rest of your life unless the protein that the hapten has learned to attach to ceases to exist in your body. Haptens can be metallic, poison ivy, oak or sumac, or a laundry detergent. It makes little difference — the reaction will occur once the hapten has found a protein carrier. In diseases such as Systemic Lupus Erythematosus, Crohn’s, Amyotrophic Lateral Sclerosis and many others, the haptens are often fragments of the patient’s own DNA or RNA that have broken off and then combined with self proteins.

Adjuvants are substances that are capable of increasing the immune sensitivity to antigens. Adjuvants include aluminum salts, bacterial endotoxins, the pertussis (whooping cough) organism (Bordetella pertussis), certain bacilli like the Bacillus Calmette-Guérin (BCG) and many others. Adjuvants are the reason that some people react more strongly than others to heavy metal toxicity and certain infections. Usually, when the adjuvants combine with the antigens, they form aggregates that serve as depots that produce prolonged immune stimulation and response. These prolonged reactions can wear out your immune system. There are also adjuvants that can and do activate non-antigenic specific factors and enhance the immune response. How they do this is still a bit of a mystery, but adjuvant substances that do this include such things as oil and water emulsions and liposomes. A liposome is a particle of lipid (fatty) material that is held emulsified in non-fatty tissue. Liposomes are sometimes called invisible fat when they are in your body.

The body’s response to antigens is influenced by the path of entry of the antigenic material. Intravenous antigen usually goes directly to the spleen where appropriate antibodies are very quickly produced by the lymphocytes that are hanging out in that organ. But the ability of antibody manufacture and release may be overwhelmed by the rapid entry of a large antigenic dose directly into the blood stream that circulates through wide regions of the body. This rapid entry is a danger when using the intravenous route of entry. Anaphylactic shock is common when antigens are administered intravenously. Subcutaneous and intradermal injections of antigen usually go to the local lymph nodes where cell-mediated immune response combined with antibody production have a much better chance of control or at least delaying the hypersensitivity reaction. This also offers a better chance of control. Intramuscular antigen injection responses depend a great deal upon the proximity to blood vessels, lymph vessels, etc. So it is less predictable, but the response will be somewhere between intravenous and subcutaneous administration, depending upon the body’s ability to control the distribution at the injection site.
Inhaled antigens produce local sensitization and immediate hypersensitivity. They can be quite dangerous depending upon the antigen and the level of the immune response. Quite often the inhaled antigen provokes an excessive immune response that results in serious difficulties in breathing. These occurrences require the prompt administration of antihistamines, steroids or other pharmaceutical agents in order to reverse or suppress the immune response and restore breathing capacity.
Antibodies

Helper T-lymphocytes enable B-lymphocytes to make antibody molecules. The helper T lymphocytes bind to the antigen MHC-II complex on the surface of the antigen-presenting cell. MHC stands for Major Histocompatibility Complex. The helper T-lymphocyte then gives the necessary information to the B-lymphocyte so that a fitting and specific antibody can be made. A third cell is necessary for this to work. That is the antigen-presenting cell (APC). This is the cell upon whose surface the MHC-II molecules are presenting the antigenic molecule.

The macrophage is perhaps the most common antigen-presenting cell (APC). It ingests the total antigen and inside of its “stomach” breaks it into antigenic fragments. These fragments are then picked up by the MHC-II molecules and taken to the macrophage’s membrane surface via the endoreticular system. Once presented on the macrophage surface, it is usually not long before helper T-lymphocytes recognize and bind to the antigen-MHC-II molecular complex. Once attached, the helper T-lymphocyte sends out the communication to other lymphocytes, both killer T-lymphocytes and antibody-producing B-lymphocytes. The controlling immune response is now underway.

Let’s look now at the various classes of antibodies that are made by the B-lymphocytes. IgM immunoglobulin is usually the first class of antibody that appears in response to an antigenic presence. IgM levels begin to rise almost immediately. They peak at about seven days after the appearance of the antigen. IgM is a five-pointed, star-shaped molecule. It is found mainly in the serum and, under normal conditions, it makes up about 10% of the total serum globulins.

During bacterial infection, serum levels of IgM rise markedly. It usually does not enter tissue spaces but remains in the serum. It is very effective against bacteria. Taking advantage of its star shape, it attaches crab-like to the bacterial cell. It attracts complement proteins that, in turn, assist in the destruction of the bacteria by facilitating the piercing of holes in the bacterial membranes. These perforations cause ionic inflow and burst the bacterial cells. IgM is thought to be about 1,000 times more bacteriocidal than IgG. It is the first immunoglobulin to respond to bacterial invasion, but it has no memory. Each antigenic encounter is like the first meeting. IgM is also considered about 20 times more effective at agglutinating bacteria than IgG. Most B-lymphocytes have some IgM and some IgD on their surfaces at all times. As serum IgM begins to wane after peaking at about 75 days, IgG begins to rise. The IgG elevations in serum levels that are noticeable appear at about 6-7 days after antigenic stimulation. They peak at about 10 to 14 days post-antigenic stimulation.

IgG production is not indefinite. If it were there would be a tendency to overwhelm the body with antibody. The production of IgG by B-lymphocytes is controlled by suppressor T-lymphocytes and by a feedback loop that lets the suppressor T-lymphocytes know when the levels of IgG are adequate. Further reduction of IgG is accomplished by neutralizing of antigen molecules by the IgG molecules without replenishing those that have been used up in the neutralization process.

Immunoglobulin G (IgG) is a major antibody. It exists both in blood serum and in tissue spaces. It exists as a monomer, which is a relatively simple molecule. It often combines with other monomers to form polymers that are much more complex and of much higher molecular weight. Although IgG is not as potent as IgM, it is the main antibody used by the immune system against antigenic challenge. It interlocks with toxins to neutralize them. It coats microorganisms with its molecules. This molecular coating attracts all types of phagocytes that then destroy the antigenic carrier. This coating is called opsonization. IgG combines with antigens and facilitates the unleashing of complement protein which
has bacteriocidal enzymes. IgG is also able to protect cells from viral entry. IgG (gamma globulin is its much-used name) has a half-life of about 20-25 days in blood serum.

There are four subclasses of IgG. They are IgG 1, 2, 3 and 4. Each subclass has a different structure and different biological functions. IgG is most effective against the pneumococcus that has lipopolysaccharide in its capsular membrane.

Immunoglobulin IgA is a dimer molecule, which are two identical molecules combined chemically. This dimer is combined with a polypeptide molecule that is produced by epithelial cells when it is located in various mucous membranes. The combination of IgA with the polypeptide gives it resistance to proteolytic digestion in these membranes, especially in the gastrointestinal tract. Serum IgA is not combined with the polypeptide because it is not in danger of being digested in the blood serum.

The dimer IgA is produced by plasma cells. It travels via the serum to various membranes where it becomes part of body fluids such as saliva, tears, gastrointestinal secretions, vaginal secretions and prostatic secretions.

The combined IgA-polypeptide complex can cross mucosal epithelium by actively passing directly through the epithelial cells. This is called endocytosis. In this position IgA plays a major defense role in blocking infections by viruses and bacteria by preventing them from adhering to and passing through the mucosal tissues. IgA does not bind to complement protein but it does help complement molecules to opsonize the invading organisms. IgA protects us against food poisoning, inhaled pathogens, some sexually transmitted diseases, conjunctivitis, and anything else that involves membranes and secretions. There are two subcategories of IgA, namely 1 and 2, but clinical differences have not been evaluated as yet.

Immunoglobulin IgD is a monomer that occurs in the blood serum in trace amounts. It is found almost exclusively inserted within the membrane capsules of B-lymphocytes in adults. In obstetrical situations it has been seen to be highly concentrated in umbilical cord blood.

IgD in postpartum humans helps to regulate B-lymphocyte activity. Plasma cells that produce IgD are plentiful in tonsils and adenoids. They are rare in other lymphoid tissues. There is much to be learned about the role of IgD in the immune system and its functions. The B lymphocytes that have IgD in their cell membranes also have IgM on the same membranes.

Immunoglobulin IgE is normally present in trace amounts in blood serum. It is known to bind tightly to both B- and T-lymphocytes, as well as to mast cells and basophils. When IgE-coated cells react to antigens we frequently see histamine release, hypersensitivity reactions (allergic), and sometimes anaphylactic shock. IgE is a factor in hay fever, asthma, wheal, and flare reactions like hives and so on.

The plasma cells that produce IgE are found mostly in tonsils, adenoids, and mucous membranes of both the respiratory and gastrointestinal systems. IgE is a chemotactic factor for eosinophils. It elevates in parasite infections. It is probably a protective factor in parasitic exposure.
Lymphokines are a group of protein molecules that are synthesized and secreted by lymphocytes. They are not immunoglobulins. They are soluble in body fluids and use these fluid systems to travel to their specific receptor cells or to combine with other molecules to become activator or inhibitor complexes. Some lymphokines play an essential role in the cellular aspects of immunity while others participate in the antibody responses and the inflammatory process, as well as the growth, proliferation and differentiation of hematopoietic cells. Some lymphokines have more than one function and others do only one specific thing.

Most lymphokines are synthesized and secreted by activated T-lymphocytes. The lymphokine molecules are not preformed and stored. They are formed at the time of demand/request and are fresh when they are released from the lymphocyte.

The lymphokines are a subgroup of a broader cytokine heading. Cytokines can be manufactured and released by any cell. Interleukins are a subgroup of lymphokines and are identified by numbers, i.e., IL-1, 2, etc.
Lymphokines That Affect Cell-Mediated Immunity

There are three different lymphokines that influence macrophage activity:

1. Monocyte Chemotactic Factor (Lymphokine)
   These molecules attract monocytes to the site of antigen-lymphocyte interaction. As soon as they arrive, the monocytes become macrophages. Specific lymphokines of this chemotactic factor group also attract neutrophils, eosinophils and basophils. Which cells are attracted is a “judgment call” by the on-site lymphocyte(s). Other chemotactic signals come from the bacteria themselves and from the complement system.

2. Migration Inhibitory Factor (Lymphokine)
   These molecules prevent macrophages from leaving the site to which they have been drawn. The process is not well understood but the molecules of migration inhibitory factor seem to interact with some of the glycolipid (carbohydrate-fat complex) molecules located in the macrophage membrane.

3. Macrophage Activating Factor (Lymphokine)
   These molecules enhance the killing ability of the macrophages. They induce morphologic, metabolic and functional changes in the macrophages so that they become more specifically effective against bacteria or viruses or tumor cells, whichever may be undesirables at the site to which the macrophages have been summoned.

Interferon gamma is a subcategory of the macrophage activating factor lymphokines. This is the only known interferon that is produced by lymphocytes. In addition to its macrophage activating properties, interferon gamma is a B-lymphocyte differentiating factor. Its production is stimulated by the presence of bacteria, viruses, plant mitogens (a mitogen is a substance that stimulates mitotic cell division), polynucleotides and some synthetic polymers. Interferons do not attack viruses; they render host cells more resistant to viral invasion.
Interleukins

The interleukins are a large category, some of which are lymphokines. They are known by numbers following the IL abbreviation. As of this writing there are at least 16 known interleukins. Some of them fit into the cell-mediating lymphokine family and others are more concerned with B-lymphocytes and antibody production. I believe that the name interleukin derives from the concept that these molecules are used for communication between white cells (leukocytes). The number sequence is patchy. When some of the interleukins received their numbers, it was discovered that one molecule sometimes had two or more different numbers. That’s because it was discovered by different researchers who each thought he or she was the exclusive discoverer and gave it a number.

Interleukin-2 (IL-2) was formerly known as T-cell (T-lymphocyte) Growth Factor. It is a glycoprotein produced by activated T-lymphocytes and is therefore a lymphokine. IL-2 causes proliferation of both helper (CD4) and killer/suppressor (CD4 and CD8) T-lymphocytes. In order to be activated, IL-2 requires the presence of IL-1. The latter is a product of stimulated macrophages and possibly some other cells as yet unknown. It is known that glucocorticoid hormones (from the cortex of the adrenal gland) inhibit IL-2 activity. Secretion of IL-2 by T lymphocytes requires 10-15 hours after the activating stimulus has been received. IL-2, since it is such a powerful turn on for killer T-lymphocyte activity, has been tried as a treatment for cancer. It often kills the tumor but the side effects can be devastating. For example, IL-2 can increase the porosity of the vasculature to the extent that weight gain of several pounds per day may occur due to leakage of blood plasma into the interstitial spaces. The resultant edema can be very painful as well as a powerful heart stressor.

Cytotoxic Factors (Lymphokines)
There are several lymphocytic types that produce cytotoxic factors. They have become known as lymphotoxins. To date they are all proteins and they require active synthesis by the lymphocyte. There are cytotoxic-factor lymphokines that inhibit antigenic carrier growth, that block their proliferation and colony growth, and that stop DNA synthesis. There are also some lymphotoxins that directly kill the antigenic carriers by mechanisms unknown at this writing.

Procoagulant Activity Factor (Lymphokine)
In this group of lymphokines, the stimulated lymphocytes are seen to release a factor that delays the clotting mechanisms of blood. This process is seen to occur mostly in hypersensitivity reactions and allergies.

Leukocyte Inhibitory Factor (Lymphokine)
This lymphokine inhibits the migration of leukocytes/neutrophiles, but not monocytes. It seems to inhibit the chemotactic effect, but how is not yet understood.

Colony Stimulating Factors (Lymphokines)
There are many different types of colony-stimulating factors but there is not a lot known about most of them. One of these factors is known by the letters GM-CSF. This one is produced by T-lymphocytes. It stimulates the differentiation of granulocytes (neutrophils, basophils and eosinophils) and monocytes. It activates macrophages to selectively kill certain microorganisms and/or tumor cells. It stimulates eosinophils to become more aggressive killers of specific antigen carrier cells. Interleukin-3 (IL-3) is another colony-stimulating factor that affects macrophages, granulocytes and mast cells to proliferate in colonies.
Lymphokines that Regulate B-Lymphocytes and Antibody Production

Transforming Growth Factor B (TGF-B) is a lymphokine that is produced not only by lymphocytes but also by blood platelets and monocytes. It has the ability to block the differentiation and production of specialized cells by multipotential progenitor cells. It induces the expression of the gene structure that produces Interleukin-2. It has the ability to deactivate macrophages. The reason it is presented in this section is that it enhances the production of immunoglobulin IgA by B-lymphocytes. It also inhibits the production of IgM, IgG1 and IgG3 by these same cells.

IgA plays an important role in the protection against viruses and bacteria through the various mucous membranes. Its role in immunoglobulin enhancement and inhibition production suggests the possibility of a limited amount of bioenergy being available in the immunoglobulin production reservoir. TGF-B plays a role in the distribution of this energy as it perceives the most pressing needs.
Interleukins and Antibodies

Interleukins 4, 5, 6 and 7 all have roles that influence antibody production either directly or indirectly.

Interleukin-4 (IL-4) is a glycoprotein that affects many cells, but its main effect is on B-lymphocytes. It also, to a lesser extent, stimulates the maturation of T-lymphocytes and megakaryocytes. It causes B-lymphocytes to continue the production of IgM rather than switching to IgG2. It also inhibits the switching of the production of IgE to IgG1. In addition, IL-4 causes B-lymphocytes to express MHC-II molecules that are used for the presentation of antigen.

Interleukin-5 (IL-5) strongly supports B-lymphocyte proliferation and growth. It also induces the differentiation and colony growth of eosinophils. Since eosinophils are often called upon in parasitic infections, it would seem that the combination of effects of IL-5 upon B-lymphocytes and eosinophils suggests that IL-5 is released when the word is passed that parasites are invading.

Interleukin-6 (IL-6) is produced by T-lymphocytes. It has several functions relating to the regulation of immune responses. It matures B-lymphocytes and stimulates their production of antibodies. It also activates T-lymphocytes and, in combination with IL-2, induces the development of killer T-lymphocytes from immature thymocytes.

Interleukin-7 (IL-7) is produced by lymphocytes. It induces the proliferation of young B-lymphocytes as well as young T-lymphocytes. It also seems to accept some of the responsibility that lymphocytes have the proper CD markers on their surfaces. All lymphocytes have CD-4, and T-lymphocytes have CD-4 and CD-8.

Interleukin-12 (IL-12) is thought to be the most powerful immune molecule yet discovered. It is presently being tested as treatment for everything from parasites to cancer. It is being considered as an almost universal vaccine. It recruits T-lymphocytes to the scene. The major problem is a dose of IL-12 from an external source can be physiologically overwhelming. At present, fibroblasts have been genetically engineered to produce IL-12. These fibroblasts are then injected into cancer in hopes that the IL-12 will result in a cure. So far it is rather unpredictable — some successes and some failures.
CD markers are unchanging marker molecules affixed to the cellular membranes of immune system cells. The letters CD stand for Cluster of Differentiation. The CD markers on cells remain the same and identify their specialties. Non-CD markers are constantly changing. They reflect conditions and happenings inside of the cell upon which they are found.

All lymphocytes have CD-3 markers. The CD-3 marker is made up of a cluster of six distinct polypeptides. Killer T-lymphocytes have CD-3 and CD-8 markers. Helper T-lymphocytes have CD-3 and CD-4 markers. These markers tell you that they secrete IL-2 (Interleukin-2). Natural killer cells do not have CD-3 markers. Therefore, they are not classified as lymphocytes. They do have CD-56. (Perhaps you can’t tell a book by its cover, but it would seem you can tell a cell by its markers.)
Major Histocompatibility Complex (MHC) Molecules

In the case of self cells that have antigen on their membranes, these antigens are presented on the cell surface by two major histocompatibility complex (MHC) molecules. The antigenic material is collected from inside of the cell by these two MHC molecules that then escort the antigenic material to the cell surface via the endoreticular system. Once on the surface, the two MHC molecules present the antigenic material rather like a hot dog on an open bun. Both CD-4 and CD-8 markers (helper and killer T-lymphocytes, respectively) recognize the MHC-antigen combination and are able to adhere to the MHC-antigen presentation.

Signals are then elicited by the binding of the T-lymphocyte to the MHC-antigen complex and the maturation of both helper and killer T-lymphocytes is begun. These cells are developed from thymic precursor cells.
Immune complexes are clusters of interlocking antigens and antibodies. These clusters travel in the bloodstream and are rapidly removed by macrophages (mostly in the spleen) and by Kupffer cells in the liver. If these immune clusters are not cleared by these macrophages and Kupffer cells and continue to circulate, the clusters become trapped in kidneys, lungs, joints, arterial bifurcations and the deep skin. When this occurs the areas of cluster entrapment become inflamed, producing anything from kidney failure to arthritis, depending upon the location of the aggregated clusters.

Constant exposure to antigens may overload the body with immune complexes that overwhelm its abilities to clear them. It is this mechanism whereby farmers constantly exposed to moldy hay contract lung disease and so on. Use your imagination.
The monoclonal antibody is a very specific cell marker on the surface of the immune cell. This marker is very specific to a given antigen. The genes in the cell can change the marker when information comes in that suggests a different marker would be more appropriate for changing external conditions. This is a most remarkable system. It certainly verifies the existence of cellular and molecular intelligence. The monoclonal antibody markers seem to be constantly changing in response to gene instructions. Each specific receptor on the cell membrane is a monoclonal antibody. The term monoclonal is used because each antibody that is specific arises from a single gene source.

At present experiments are going on at Stanford in the attempt to manipulate the genes and get monoclonal antibodies that would be specific in response to antigens presented by cancer cells.
Notes:
Defense Molecules (Defensins)

The production of antimicrobial peptides and proteins is a most important means of host defense against microbial invasion. Larger antimicrobial proteins are often enzymes that digest the microbe, beginning at its most vulnerable part. They may be nutrient-binding proteins that starve the microbe, or they may simply be proteins that have sites that combine with specific macromolecules of the microbe and thus disrupt its functional integrity.

Smaller antimicrobial peptides (considered to have 100 or less amino acids) act in large part by disrupting the structure or function of the microbial membrane. In humans many of these peptide defense molecules contain disulfides. These are bridges formed where two sulfur atoms connect. These peptides are now called defensins.

Defensins, like many other antimicrobial peptides, are cationic or polar molecules. They have space between their two ends. One end is hydrophobic. That is, it dislikes water so it inserts itself into the fatty (phospholipid) capsule of the microorganism. This hydrophobic end really likes the oily interior of the membrane so it stays there. The other end of the defensin molecule is a cation. It carries a positive electrical charge. It draws negatively charged anions to it. Many of the phospholipids on the more external surface are negatively charged anions. The result of this defensin implantation is disruption of the microbial membrane. Often several defensins group together to form a pore in the bacterial membrane. This results in sudden death for the bacteria or fungus, depending upon which type of microbe is targeted.

Defensins are among the most abundant polypeptides that are secreted by phagocytic white cells. They are particularly prominent in the defenses against microbes that are seeking entry through the walls of the gastrointestinal tract.
Notes:
The Complement System

The complement system is composed of 20 or more specific and interacting proteins that are critical to host defense. These proteins are found in the blood.

The best-known sources of complement protein are the macrophages. These first-line-of defense cells secrete the proteins of the complement system as well as several of the regulatory molecules that activate, deactivate and guide the complement system. To further enhance your respect for these wonderful macrophages, they decide which regulatory agents and complement proteins to secrete as they evaluate the situation and the environment. In order to do their work as it relates to the complement system, the macrophages must be mature. Neutrophils also secrete substances that activate the complement system but they do not, according to current wisdom, produce complement proteins.
Functions of the Complement System

The functions of the complement system are rather wide in scope. This system provides a very early line of natural defense against invading microorganisms. In order to do this it sends out messenger molecules that stimulate the antibody system and other humoral responses that aid in the defense effort. It generates several of its own non-specific mediators that stimulate the immune response. It also sends out signals that induce mast cells to release/secrete histamine. Histamine increases blood supply and vascular permeability so that more immune cells are brought to the area and can get out of the blood vessels and into the involved tissues more quickly and easily. When this mechanism goes awry we get too much histamine. This causes the typical allergic response for which we may use antihistamine drugs for relief.

At the same time the complement system is promoting chemotactic attraction that draws monocytes (which will convert to macrophages in seconds), neutrophils (polymorphonuclear leukocytes, often referred to as polys), both T and B-lymphocytes, mast cells, basophils and eosinophils. As the invitations to these cells are being sent out, complement secretions are widening the roads to the site and opening the exit ramps wider so that the immune cells can get there in the shortest possible time.

The complement system also sends out molecules that cause smooth muscle contraction. I’m not sure why. Perhaps as the smooth muscle contractions continue they inhibit peristalsis and several other parasympathetic factors so that available energy can be focused upon the problem. We’ll see how that turns out as we are better acquainted with the complement system.

The protein molecules of the complement system have the ability to adhere to the cell membranes of invading bacteria, viruses, and even cells of the self that have become dysfunctional or turned malignant. The process that the complement proteins go through to attain adherence to the undesirable cell are not fully understood at present. By adherence the complement protein may mark the unwanted cell for the phagocyte so that it can be ingested and thus destroyed. I’m sure the macrophages and neutrophils appreciate this assistance from the complement proteins.

On occasion the complement proteins can accumulate on the unwanted cell’s membrane and puncture it. The puncture allows the ionic balance across the membrane to be disrupted and cell death usually follows. In this way complement alone may destroy invading viruses and bacteria. However, the complement proteins do not seem to be searching for self-aggrandizement. They don’t need to be heroes. They seem happy to turn over the execution process to the phagocytes.

In summary, the complement system functions as opsinons. It provides vasodilation and, using chemotactic agents, attracts a wide array of immune cells to the site. Complement can and does singularly kill bacteria and viruses when it seems appropriate.
Complement System Pathways

There are two pathways used by the complement system: the classical pathway and the alternative pathway. Both pathways end up in the formation of enzymes that activate the critical protein component known as C3. After C3 the pathways are the same. An antigen antibody reaction is required to activate the complement system’s classical pathway. The activation of the alternative pathway does not require an antigen-antibody reaction. Dysfunctions in the classical pathway are associated with immune-complex mediated diseases. Problems with the function of the alternative pathway are associated with poor resistance to bacterial infections.

Before describing the two pathways, it will be helpful to acquaint you with some of the nomenclature related to the complementary system.

Complement protein components that are part of the classical pathway that is activated by antibody-antibody complex are numbered C-1 through C-9. The C stands for complement. Protein components of the alternative pathway, which does not require antigen-antibody reaction to activate, are given letters rather than numbers. Since C-3 is where the two pathways merge, only two alternative letters are necessary: C-P and C-B. P is for Properdin and B is for Factor B.

A bar over a component, C-1 for example, means that that component is activated. Cleavage products are given lowercase letters. For example, when protein C-3 is cleaved by an enzyme into two parts, these parts are designated as C-3a and C-3b. When a component of the complementary system has been inactivated, a lowercase “i” is placed in front of it. For example, if our previous example of C-3b were inactivated, it would become iC-3b. When a protein such as C-3 is cleaved into C-3a and C-3b, the “a” is used to designate the smaller fragment and the “b” indicates a larger fragment.

Triggers for the classical pathway include antigens bound to immunoglobulins IgM, IgG1, IgG2 and IgG3. IgM is a pentamer. (This is not a poem. In biochemistry it refers to a molecule that has five binding sites.) A single IgM molecule is enough to activate the first classical pathway component. In contrast, two adjacent IgG molecules with only one binding site each are required to activate the C-1 protein component of the classical pathway. The alternative pathway is not nearly so demanding. It can be activated by almost any microorganism.
Classical Pathway

The triggers for the classical pathway are antigen-antibody reactions that involve IgM and the three IgGs (IgG, IgG2, IgG3) previously mentioned. The first protein in this pathway is C-1. It is composed of three subunits called C-1q, C-1r2 and C-1s2. C-1q is made up of 18 connected polypeptide chains. C-1q binds directly to the immunoglobulins (IgM and the three IgGs). C-1r2 does not bind to the immunoglobulin directly. Rather, it activates C-1s2 after C-1q has connected to immunoglobulin. Once C-1s2 has been activated, it activates C-4 protein, which oversees the reactions and prevents overreaction of the complementary system.

The activated C-1 (remember, the bar indicates activation) cleaves C-4 into a C-4a (a small fragment) and C-4b (a large fragment). C-4b then binds to the membranes of the unwanted bacteria, virus or dysfunctioning self cell. At the same time, C-4a sends out messenger molecules that give mast cells the signal to secrete histamine, which causes vasodilation and increases vascular permeability, allowing an easier entree into the site of the unwanted bacteria, etc.

C-1 (bar means it is activated) also cleaves C-2 into C-2a and C-2b. In the presence of magnesium ion, C-2a binds to C-4b to form an enzyme called convertase. Convertase C-3 cleaves C-3 into C-3a (the small fragment) and C-3b (the large fragment). C-3a further stimulates mast cells to release more mediators of inflammation besides histamine. We don’t have good identification of them as yet. C-3b binds to the unwanted cell/viral membranes next to C-4b and together they form another enzyme known as convertase C-5. C-3b also induces immune adherence to the antigen, thus assisting the phagocytes that are tuned in to C-3b (have C-3b receptors) in locating their intended prey.

Convertase C-5 then cleaves protein C-5 into C-5a (small fragment) and C-5b (large fragment). C-5a also stimulates mast cells to release mediators (as does C-3a), as well as to provide chemotaxis for neutrophilic phagocytes (polys). C-5b binds with C-6 to form C-5b6, which then binds to C-7 to form C-5b67. This C-5b67 molecule then detaches from convertase C-5 and either attaches to a new site on the same cell or attaches to another cell that has not yet been sensitized, thus extending the cytolytic effects to the other cells and sometimes to “innocent bystanders.” This C-5b67 molecule seems to be very discriminating. If C-5b67 does not attach to anything, it becomes inactive iC-5b67.

When C-5b67 does enter a cell membrane, it binds with a complementary protein molecule C-8. Together they damage the cell membrane. Ions flow in. Next the C-5b678 complex binds six molecules of C-9, and this kills the unwanted cell very rapidly.

This combination of C-5b678 with six C-9 molecules is known as the Membrane Attack Complex (MAC).
Alternative Pathway

The alternative pathway does not require antibody. Therefore, it plays a critical role in nonspecific defense against infection. The cleavage of complement protein C-3 occurs in this alternative pathway just as it does in the classical pathway, but it does so without antibody as a stimulus. Complement proteins C-1, C-2 and C-4 are also not required in this alternative pathway as they are in the classical pathway.

The activators of the alternative pathway are furnished by a variety of microorganisms and mammalian cells. These activators include:

1. Polysaccharides as found in bacterial-cell membranes
2. Zymosan as found in yeast-cell membranes
3. Bacterial endotoxins
4. Agarose, a carbohydrate substance found in agar
5. Rabbit erythrocytes
6. Virus-infected cells
7. Some transformed cell lines, as in tumors, etc.
8. Aggregated IgA, which is an immunoglobulin primarily found in secretions
9. Parasites of many types

We should also realize that the alternative pathway may also be activated by the precipitates (particles) of antigen-antibody reactions.

In the alternative pathway only the beginning is different. Both the classical and alternative pathways use C-3 through C-9 complement proteins as a final common pathway. Only the initial steps are modified, so the term “alternative” may be somewhat misleading. It is actually an alternative entry to a final common pathway.

The alternative entry is as follows: when one of the aforementioned activators is present in serum that contains magnesium ion, activation of C-3 complement protein occurs. Several other proteins must also be concurrently present. They are P (properdin), B (a protein similar to C-2), D (an enzyme that cleaves B producing C-3 and Bb), and C-3 complement protein.

In this alternative entry two types of C-3 convertase are formed. One is a primary type and the second is an amplification type. The primary type of C-3 convertase is to supply C-3b in order to produce the amplification type. Primary convertase is generated from C-3. C-3 undergoes some hydrolysis that enables it to bond with B (the protein similar to C-2). This bonding requires the presence of magnesium ion. The bonded B is then cleaved by D (an enzyme) to form C-3, Bb. C-3, Bb are combined to form C-3 convertase. This enzyme splits C-3 molecules into C-3a and C-3b fragments, and this leads us into the common pathway described previously.

I know that this is all very complicated. But trust me, this is the simplified version. Please do not be intimidated or feel overwhelmed. In essence we simply have two entryways into a common path by which the complement system participates as a valuable part of the immune system.
Appendices

These appendices should be read along with the text of this study guide. They contain information that will help your general context when doing this work.
A few miscellaneous observations about the complement system:

1. Lysozyme is an enzyme that is present in blood serum. It is effective against gram (+) bacteria by itself, but it requires complement to kill gram (-) bacteria.

2. C-reactive protein in blood increases during infection. It binds to phosphorylcholine and activates the classical complement system pathway.

3. Protein malnutrition manifests as a reduction in complement protein, which increases vulnerability to infectious agents.

4. C-3 receptors on the cell membranes of phagocytes move around on the membrane rather like the magnets are movable on your refrigerator door. This enables the C-3 receptors to reposition themselves advantageously when the phagocyte process requires that the membrane wrap around the prey and perhaps involute. Thus, C-3 complement can attach to the phagocyte, whatever it is doing.

5. A full-term fetus has 50-100% of the C-3 complement protein present in an adult.

6. There is no transplacental transport of complement protein. The fetus makes it all.

7. Complement is found as early as 28 days gestation.

8. Total complement declines in the elderly, thus the increased susceptibility to flu bugs and so on.

9. Neutrophils, monocytes, macrophages, T and B-lymphocytes, basophils, mast cells and eosinophils all have very specific receptors for specific complement messenger molecules. This allows the complement system to regulate which immune cells respond to which infections, traumas, allergens and so on.
In this section I have arranged alphabetically some of the words that represent other topics you will encounter.

**Chemotaxis**
Chemotaxis is the process whereby messages are sent out that cause target cells to be drawn to specific areas or sites in the body. One of the most common chemotactic events occurs when a localized infection by bacteria releases specific identifying peptide molecules. These molecules serve as attractants. Leukocytes cruising in the bloodstream sense the attractants and follow the increasing concentrations until they arrive at the site where they go into phagocytic action, as well as releasing their own brand of messenger molecules that summon the desired array of other immune cells to the site.

The array of chemoattractant agents is wide. However, at present there is conjecture that an enzyme called phosphoinositide-3-OH kinase is perhaps universally necessary. The chemoattractant agents are derived from some bacteria, from the complement system and from lymphocytes. The cells attracted by chemotaxis are mostly macrophages and leukocytes. Recall that monocytes convert to macrophages when stimulated, so it will most likely be more macrophages than monocytes that arrive at the scene, since the chemoattractant stimulation is often enough to cause the conversion. There are also specific chemoattractants that summon either eosinophils or basophils. The eosinophils come to parasitic infections and the basophils to allergic problems.

Presently, the immunology community is becoming convinced that all neutrophilic attractants are leukotrienes. Also, there is some research that suggests that some tumor tissues produce antichemotatic factors.

**Cytokine**
The clue about what it means is in the word that was created to identify the molecule. Cyto means cell, kine refers to energy. A cytokine is an action molecule that is secreted by a cell. Cytokine has come to refer to any of a large group of proteins that are released by mammalian cells. These protein molecules (cytokines) serve as highly potent messengers for other cells. They may cause a wide variety of responses in their target cells. A cytokine may be the activator that induces the target cell to specialize (differentiate). It may cause it to clone or proliferate. It may cause the target cell to secrete hormones, enzymes, other cytokines or immunoglobulin molecules. It may also activate or inhibit the killer instinct in a macrophage or other cell with the killer potential, and on and on as far as your imagination can reach.

Some years ago, cytokine was the word for all of these messenger molecules. Since then, many subdivisions have occurred. Today cytokine is a catchall term that includes leukokines (leuko indicates that the origin of the molecule is the leukocyte), lymphokine (origin is the lymphocyte), interleukin (communicates between leukocytes), interferon (these molecules interfere with viral invasions of cells), tumor necrosis factor (causes tumors to die by interfering with the blood supply — we think), and so on. **Interferon**
Interferons are a family of glycoproteins (carbohydrate molecules attached to protein molecules). They are subdivided into alpha, beta and gamma types. Leukocytes (polymorphonuclear leukocytes, better known as polys) produce alpha interferon. Beta interferon is produced by fibroblasts, and gamma interferon is produced by both T-lymphocytes and natural killer (NK) cells. It is now thought that leukocytes produce 13 different forms of interferon. Gamma interferon plays an early role in body defense against viruses. It strengthens the self cells’ resistance to the viruses. It does not (as of this writing) seem to damage the virus directly.

As of 1996, the FDA had approved alpha interferon for treatment of hepatitis, genital warts, Kaposi’s sarcoma, hang cell leukemia and malignant melanoma. Approval was in process for myelogenous leukemia. Also, beta interferon was under consideration by the FDA as treatment for multiple sclerosis. Unfortunately, the side effects experienced from the external administration of interferon of any type can be devastating and life-threatening.

Interferons were discovered in the 1950s as factors released by viral infected cells. The molecules secreted seemed to protect the neighboring cells from the virus.

A few abbreviations in relationship to interferons that you may encounter are:

IFN = Interferon
IPC = Interferon producing cell – has short life span
PDC2s = Precursor dendrite cells – thought to produce up to 1000 times more IFN than other IPCs

**Major Histocompatibility Complex (MHC)**

Major Histocompatibility Complex (MHC) molecules are present inside of every living human cell. They are divided into two subgroups: MHC-I and MHC-II. The class I Major Histocompatibility Complex (MHC-I) molecules are displayed on the surface of the cell with a snippet of protein taken as a sample from within the cell. The MHC-I molecules are rather like display racks showing the snippet for all to see. Without the display rack presentation, somewhat like a hot dog on an open bun, the snippet would not be seen by passing immune cells. The presentation is very specific. The class II Major Histocompatibility Complex (MHC-II) molecules are rather more specific. The displays put forth by these MHC-II molecules are only of antigenic substances and are “seen” only by T-lymphocytes, having CD-4 markers and specializing as helper T-lymphocytes.

The class-I Major Histocompatibility Complex (MHC-I) molecules simply display snippets of every class of protein made within their cells of origin. MHC-I molecules are present as protein is being manufactured inside of the cell. They take samples from each type of protein periodically, much as inspectors evaluate every 100th batch of pharmaceutical agents that come off of the production line. The snippets/samples taken are usually about nine amino acids long. Normal and abnormal snippets are displayed by the MHC-I proteins without prejudice. They do not judge. There are about 10,000 molecules on display at any one time. Twenty or more abnormal snippets will cause the inspecting immune cell to send out alarm messenger molecules and destroy the cell in question at the same time if killer skills (cytotoxicity) are within the discoverer’s repertoire. At the same time, other immune cells are being attracted to further inspect and gain information about the abnormalities. That information is then sent to the thymus, probably to the spleen and to lymph nodes, so that all manner of immune cells will recognize similar snippet abnormalities, even though they have not seen them. Within the cell the MHC molecules use the cytoskeletal reticular system to move the snippets from the inner cell to its surface. Tumors can stop making recognizable proteins so that they will not attract the immune cells.
Antibodies do not require the Major Histocompatibility Complex system. They simply attach to a doomed cell and the immune cells then destroy the cell. How the antibodies know where to attach is not fully understood. (Perhaps we can find out.) However, the MHC display increases efficiency tremendously. Remember, MHC-I molecules display snippets of protein that is self. These snippets are judged by passing immune cells for quality. MHC-II molecules fix and display antigenic molecules. The MHC-II displays are recognized by T-lymphocytes having the CD-4 receptor. These are helper cells. This is the latest wisdom. I'm not sure helper T-lymphocytes are the only cells that recognize MHC-II antigen displays.

**Monokines**

A monokine is a cytokine that is produced by a monocyte and, some authorities say, also possibly by a macrophage. Since monocytes are precursors of macrophages, it would seem that the answer to this question depends upon when the observer makes his/her observation. Known monokines include Interleukin-1 (IL-1) and Macrophage Inflammatory Protein (MIPs). There are MIP subdivisions into MIP-1a, MIP-1b and MIP-2.

Interleukin-1 (IL-1) is a regulatory monokine (within the larger category called cytokines). It is an endogenous pyrogen. This means that it is a factor that is released from within you that causes fever. Fever is thought to be part of the body’s defense against pathogenic microbes that do not survive higher temperatures. Interleukin-1 (IL-1) also stimulates glucocorticoid synthesis and secretion by the adrenal cortex. It induces the release of prostaglandins, collagenase and acute phase proteins into the blood stream. The acute phase proteins refer to those proteins that are released during the acute phases of stress. They include opsinons, fibrinogen, haptoglobin and ceruloplasmin. Interleukin-1 (IL-1) also stimulates the growth of fibroblasts, synovial cells and endothelial cells. It also stimulates muscle wasting and bone resorption in order to get more available energy.

Interleukin-1 (IL-1) also stimulates chemotaxis, drawing neutrophils, macrophages, lymphocytes and natural killer cells to an area of infection or acute injury. T-lymphocytes require the presence of an antigen or lectin plus Interleukin-1 before they can synthesize and secrete Interkeukin-2 (IL-2). The activity of Interleukin-1 is antagonized by the presence of viral infection, malignant tumor and overwhelming inflammation. Interleuken-2 (IL-2) has a positive effect upon natural killer cells and T-lymphocytes as killers.

**Macrophage Inflammatory Proteins (MIP-1a, MIP-1b and MIP-2)**

Macrophage Inflammatory Proteins (MIP-1a, MIP-1b and MIP-2) can aggregate and bind heparin, which is released by basophils. This binding of heparin enhances the clotting mechanism, which may or may not be beneficial at the time. They also bind the endogenous mediators of inflammation induced by endotoxins. They are also chemotactic agents, attracting neutrophils and granulocytes to the site.
Natural Killer Cell Stimulating Factor
Natural Killer Cell Stimulating Factor (NKSF) is also known as Cytotoxic Lymphocyte Maturation Factor (CLMF). It is secreted by macrophages and becoming more popularly known as Interleukin-12. Not much is known about it yet except that it does exactly what its NKSF name suggests.

Opsinon
Here’s another widely defined word that started out with a precise definition. Today an opsinon is any of various proteins that bind to microorganisms or other foreign materials to enhance their susceptibility to engulfment by any phagocyte, i.e., macrophage, polymorphonuclear leukocyte, etc. They give a message to the phagocytic cells. The message is to attack. The main types of opsinons are the immunoglobulin gamma (IgG) antibodies.

Phage
Phage is another word for phagocytic cell. A phagocytic cell or phage engulfs its prey and (hopefully) digests it for recycling or excretion. A macrophage is a very big phagocyte.

Tumor Necrosis Factor
Tumor Necrosis Factor (TNF) is a cytokine, which has also been known as lymphotoxin. Now we have Tumor Necrosis Factor-a and b. Tumor Necrosis Factor-a is now also known as cachectin. Tumor Necrosis Factor-b is known as lymphotoxin.

Tumor Necrosis Factor-a (cachectin) produces cachexia in patients with malignancies. It also contributes to septicemic shock (which can be fatal). It enhances antibody dependent eosinophil killer (cytotoxic) abilities. It enhances neutrophilic adhesion to endothelial cells, especially in arteries. It seems to play a central causative role in the brain inflammation that accompanies malaria and AIDS.

Tumor Necrosis Factor-b (lymphotoxin) causes macrophages to be formed from monocytes. It seems to liquify tumors. It attacks and shuts down the tumor vasculature causing a liquefying necrosis. Tumor Necrosis Factor-b does not seem to affect the vasculature to normal/nonmalignant tissues. As the endothelial cells of the blood vessels are attacked they secrete cytokine molecules that attract macrophages and neutrophils to the site, often within 15 minutes. Then by some mechanism of communication unknown as of this writing, the T and B-lymphocytes arrive “en masse.” They now recognize the tumor and set about collaborating with the phagocytic cells to destroy it. This seems a potential miracle treatment for malignancy. Unfortunately, externally given doses of lymphotoxin can kill patients. (Perhaps dialogue could enhance the endogenous production of Tumor Necrosis Factor-b in the correct doses.)

Presently, Tumor Necrosis Factor-b is used in cases where the molecules can be injected into the tumor and the tumor kept isolated from the rest of the body, as in a bone sarcoma of the leg, etc. When used, Tumor Necrosis Factor-b makes tumor cells hemorrhage and die. In so doing the tumor may be gone in two or three days. But as the tumor cells hemorrhage and die, the normal cells go into shock and die.
A Science of Consciousness?

Consciousness: Paradigms, Craniosacral Rhythms and Therapeutic Applications

by John E. Upledger, DO, OMM

It seems to me that it is virtually impossible to investigate consciousness within the confines of scientific method and experimental design, because the subject of the investigation is in a very real sense investigating itself. This does not allow for any type of objective investigation. In the final analysis the consciousness of the investigator(s) must interpret the data. One might argue that one consciousness might interpret the data of another, but if the energies of consciousness interact on a more or less universal level, this argument becomes invalid and the investigation of consciousness is subjective. It cannot be objective.

This being the case, the investigation and study of consciousness must rely almost entirely upon observations, experiences and outcomes that are largely subjective and/or serendipitous. The very definition of consciousness is variable between authorities and is subjective because it requires consciousness to define consciousness. It is obvious to most if not all of us that we are the subjects of experiences that we are the recipients of sensations and perceptions, that we think and act in response to that which we receive, and we create both in thought and by action. This is called being conscious, and yet one of our greatest mysteries is how physical bodies such as ours have these abilities to appreciate, think and act beyond pure neurosynaptic responses. If this is mysterious, consider the possibility that molecules of DNA have consciousness, that the smallest subatomic particles may have consciousness, and that there is perhaps a universal or cosmic consciousness. Consider, too, the possibility that all things between the sizes of subatomic particles and the cosmos have consciousness, and that all of these consciousnesses are interconnected and blended so that they all affect and influence one another.

Lessons in Consciousness

Based upon my own subjective experiences and observations, I have developed a model of consciousness with which I am quite comfortable. Perhaps it would be more correct to say that the model has developed in my consciousness in response to these experiential and observed inputs. The model states that all things exist in an energy field which, at present, we describe as electromagnetic. All things also create energies that interact with the energetic milieu in which they are located. Therefore, their energy fields are influenced by their energetic environments, just as they influence their own larger environments. As we go up the size scale in stages, we see that the very smallest of particles has some influence upon the condition of the cosmic whole, just as the effected cosmic energy field, which I see as consciousness, has effect upon the smallest particles, as well as every cell and every living creature.

I have been privileged to have participated in several experiences and to have observed several events that have yielded this model. I shall now recount a few of them so that you may better understand how it came about. I should be very clear in stating that my own understanding of consciousness is not something I strived to develop. Rather, the experiences and observations were laid out before me and the model autonomously created itself.
My lessons in consciousness began in my early teens when I started working as a jazz pianist at night clubs, etc. It became very clear to me early on that most jazz players had some sort of “magic.” Quite often, without a word being spoken, we would begin a song all at the same time and all in harmony and synchrony. This occurrence was very common if we knew each other. This could be explained in terms of familiarity. On the other hand, it frequently happened between jazz musicians who had just been introduced to each other a few minutes before the music began. This was much harder to explain in terms of familiarity. I worked as a jazz pianist for over 25 years, and was repeatedly amazed at this rather common happening. This sort of shared consciousness was more effective when the players had a little alcohol, but not a lot. It seemed to have a relaxing effect. Perhaps it quieted the skepticism that was rationally warning them how difficult it could be to play improvised jazz music for four hours without knowing the other musicians prior to the start of the job. I was in this position many times. Once I quieted my skepticism, which often was done before I even met the other musicians; we worked together as though we had done so for years. We shared a common (musical) consciousness.

Another contribution to my consciousness model occurred during my time as an osteopathic medical student. I had been awarded a fellowship in the department of biochemistry. This involved supervising the laboratory, as well as presenting about one-third of the lectures. We had one experiment that was presented each year to the students in order to demonstrate the effect of insulin on blood glucose in rabbits. The rabbits were given the insulin subcutaneously, and blood was drawn from the rabbit’s ear veins every 15 minutes for an hour. The blood samples were analyzed for glucose levels as the students watched. I found that projecting kindness to the rabbits facilitated the success of the phlebotomies. My mentor, Dr. S.F. Howell, taught me this. At the end of the first semester, I was ordered to terminate the rabbits. I had fed them daily for several weeks and was quite attached to them. The idea of terminating them was quite saddening. On the day I was to do this, I entered the laboratory through a door about three feet from the rabbits’ cages. Upon my entry, they began to cry like human babies. I am sure they could consciously feel my sadness and my intent to end their lives. We shared my conscious state.

I entered private practice of general medicine and surgery in 1964 in Clearwater Beach in Florida. This was a rather acute practice. My patient load was about 50% tourists. Quite often I began to know what was wrong with these new patients before I entered the treatment room. Frequently, while I was in the hall approaching the room, I sensed the patients’ emotional status as well as their diagnosis. I began to understand that, in addition to sharing a consciousness through a closed door, there was something in the patients that knew their diagnosis and put that information out into their field of consciousness energy. For some reason, I was allowing this information to enter my own consciousness. I suspect that I was a willing recipient because I had learned this openness as a jazz musician. In order to confirm my ideas about the patient’s consciousness knowing the diagnosis, I used hypnosis the night before surgery on two very puzzling cases. Under hypnotic trance, the patient was able to tell me what we would find during the surgery. The first was a ruptured ovarian cyst rather than appendicitis. The second was a Meckel’s diverticulum high on the ascending colon. In both of these cases, the patient under hypnosis was able to accurately describe the pathologic anatomy that we found the next day. Another interesting case was that of a woman with all the digestive symptoms of gall bladder disease. However, her physical examination revealed that the pain was in the upper left quadrant of the abdomen rather than on the right side where the gall bladder is located. Also, the referred pain to the 10th rib and scapula was on the left side rather than on the right where it is typically found. These findings contraindicated gall bladder disease as the diagnosis. I used hypnosis and asked what the problem was. Under hypnosis the patient informed me that her gall bladder was on the left side instead of the right. Later that day we confirmed this transposition of the gall bladder on X-ray. These experiences further confirmed my suspicion that there is an intelligence inside a patient that knows the problem. This intelligence is usually operating beneath
the conscious awareness of a skilled healthcare practitioner. Also, it is projected into the patient’s field of consciousness energy and is there for the taking by the open-minded recipient.

Another very interesting lesson in consciousness came from a man who presented with a blood filled cyst overlying his right olecranon process. I drained the cyst and sent the blood to the laboratory. The findings were unremarkable. He had just returned from a vacation in Mexico with his best friend and both their wives. Four weeks later the blood cyst reoccurred. I drained it of blood and I took tissue samples from the walls of the cyst. We also took urine and stool samples. We did the standard tests for venous blood, urine and stool tests for parasites. All were essentially normal. This problem reoccurred at four-week intervals two more times. Each recurrence was more extensive and severe than the last. At the time of the fourth recurrence I spoke at length with the pathologist, Dr. Osatin. I had, by now, obtained a history from the patient in which he stated that he had started an adulterous affair with his friend’s wife during the Mexican vacation. He denied guilt. Dr. Osatin mentioned a condition called “menses sympatico” as a possibility. It was a rather disrepected diagnosis that suggested that a male could have a sympathetic menstrual cycle on/in some part of his body in synchrony with the menstrual cycle of a lover when emotional issues were involved. Upon later questioning, the patient confirmed his elbow cysts were synchronous with his best friend’s wife’s menstrual flow. I informed him of the possibility of guilt but he strongly denied any emotional upset. However, his olecranon blood cysts never reoccurred. Another lesson in the potential of consciousness was presented.

**CranioSacral Therapy and Consciousness**

It was in 1971 that I became acquainted with the craniosacral system quite by accident. I had no previous knowledge of such a system and, in fact, we gave it this name about five years later when I was working in the Michigan State University, Department of Biomechanics as a clinician researcher. I was assisting at a surgical procedure that involved the removal of a round calcified plaque about 1.5 cm in diameter. It was almost symmetrically located at the midline on the posterior external surface of the dura mater layer of the meningeal membranes at the level of the third cervical vertebra. We had removed the posterior aspects of the third and fourth cervical vertebra in order to obtain a satisfactory operative field. Since the plaque was located entirely on the external surface of the dural membrane, we planned to scrape the plaque away without incising the membrane. The dural membrane system would be maintained intact. In surgeries involving the brain, the spinal cord and/or the dural meningeal system, the integrity of the dural system is usually, if not always, interrupted. This was one of the few times that this system’s integrity was maintained.

It was my responsibility to hold the exposed dural membrane still while the neurosurgeon scraped the plaque from the membrane. A slip might incise the membrane and open an avenue for infection, and so on. I was unable to maintain the dural membrane in a still state. It kept rhythmically bulging out from and retracting into the operative site. These cycles of bulging and retracting were repeating at about 10 cycles per minute. They were not in synchrony with the patient’s breathing, nor with his heart rate. No one in the operating room could recall ever having seen this phenomenon before. This is because most often the dural membrane is incised during surgical procedures when it is exposed. The bulging and retracting activity was a reflection of the rhythmical rise and fall of both volume and pressure of the cerebrospinal fluid held within an intact dural membrane system. With some thought and some study, it evolved that the dural membrane forms the boundary system of semi-closed hydraulic system into which the inflow and outflow of cerebrospinal fluid is controlled by multiple homeostatic mechanisms. The surgery was a success and the patient did very well.
In 1975 I joined the Biomechanics Department at Michigan State University as a clinician researcher with the purposes of studying this craniosacral system (as it was soon to be called), investigating acupuncture, and evaluating the uses of Kirlian photography as both a research tool and a clinical adjunct. All of these works contributed powerfully to the development of my consciousness model.

I teamed up and worked intensively with two biophysicists, a neurophysiologist, an anatomist and a designer during my eight-and-a-half-year tenure at MSU. We developed a basic science model that functioned very well as an aid to the understanding of the clinical effects of craniosacral system dysfunctions, and for the development of a therapeutic approach. Our treatment process developed into a very gentle, hands-on approach that used the system’s own self-corrective hydraulic activity as its therapeutic mainstay. Soon we began to realize that inherent energies as well as foreign energies were present. The inherent energies were often used to obtain positive therapeutic effect by the use of the therapist’s hand placement coupled with focused intention. More often than not, the foreign energies were identified as obstructions to function and were released by body position and/or manual direction of energy using strong intention by the therapist. One of the biophysicists (Zvi Karni) made measurements of whole-body electrical potential during these treatment sessions. It was seen that patient body position and/or therapist intention were capable of producing recorded patterns of electrical potential changes, which we came to regard as indicative of positive change in the function of the craniosacral system.

It soon became clear that CranioSacral Therapy facilitated access to levels of consciousness that were previously in the patient’s “unawareness.” Over and over again we had patients image their various suppressed experiences. The facilitating factors seemed to be that the therapist offered permission and support for whatever the inner wisdom of the patient chose to bring forth, no matter what it might be. This offering by the therapist often was not verbal. It only had to be an unspoken message transferred by touch. As we developed these processes several things became clear. First, that an intentioned touch was a powerful method of helping the patient to liberate suppressed emotions, memories and experiences. It also became clear that, more often than not, the therapist got the image before the patient. It soon became a rule that the therapist would never speak of any images, etc., before the patient did. We want, at all costs, to avoid suggestion to the patient. Working with Dr. Karni and monitoring the whole body potential, it was soon observed that, when a significant word was spoken, a significant thought was brought forward, or a significant body position was obtained, the level of activity of the patient’s electrical potential dropped, as did its baseline. Concurrently, we saw that the craniosacral system’s activity, which by now we were easily monitoring by hand, also was stopped. When the “energy” of the problem was released, the baseline potential usually came up somewhat as the palpable craniosacral rhythm resumed. Dr. Karni and I measured the energy releases with a thermograph and we saw that these releases were localized in specific areas. We ultimately called these heat releases “energy cyst” releases. And we called the stopping and starting of the craniosacral rhythm the significance detector.

During this time both biophysicists (Zvi Karni and Richard Roppel) and I began formulating concepts of consciousness energy fields that are easily shared by the patient and the therapist. We realized that the patient’s body will go to the position of release if the therapist establishes trust between him/herself and the patient, if the therapist’s hands are used to counterbalance gravity, and if the therapist will offer a generic kind of energy to the patient that has no strings attached and can be readily qualitatively manipulated by the patient’s inner intelligence or wisdom. By this time, we were using the term inner physician for this patient consciousness level, which seems all-knowing regarding problems. That the patient’s body would often go to a position of injury when assisted became very apparent. We called this tissue memory. And when the patient released emotional blocks as they obtained significance detector stops in specific body positions, we called it SomatoEmotional Release®. We developed this terminology
to differentiate these events from psychosomatic medicine. In our work the body released the emotion. As things developed, patients were encouraged to describe the images as they presented, and we began to dialogue with the image through the patient.

A teaching model, which emerged from our discussions and which I have frequently used, is shown in Figure 1 on the following page.

I will not belabor the details of this approach to healthcare, only to say that it is a process of self-healing by the patient that is facilitated by the therapist. CranioSacral Therapy and its progeny have expanded our use of consciousness energy into a functional realm, which is far beyond anything I had foreseen. I can best give you an understanding of this model of consciousness by offering a few examples of its uses and some brief case descriptions.

**Therapeutic Blending**

We have found that when the touch is intentioned, the craniosacral system is accessed, and the consciousness energy fields of patient and therapist are blended, almost any kind of healing can occur. For example, a patient with rather advanced breast cancer came in on a Thursday. She was scheduled for a radical mastectomy on the following Tuesday. We blended our consciousness energy fields very quickly and her inner wisdom disclosed the reason for her breast cancer. In brief, it was a dissatisfaction with being female because of the restrictions this placed upon her in the business world. She was vice president of an architectural firm at the time the cancer developed. I reasoned with her inner wisdom that removing the breast would further defeminize her. She agreed to soften her personality and allow her femaleness to express itself. Her consciousness agreed to allow the axillary nodes to disappear and her breast cancer to reduce in size so that a simple lumpectomy could be done. I put energy into her breast as I felt directed. In a period of 45 minutes the tumor shrunk to less than half its previous size. A lumpectomy was done and she remained fine for about four years. Then she had a tumor recurrence, which her inner wisdom related to the return of her “masculine aggressiveness.” Once again, the tumor shrunk as she pledged to return to being a female. To my knowledge she is presently in good health.

Another breast cancer patient who is a CranioSacral Therapy practitioner had a similar experience regarding her femaleness. She had a biopsy one week before seeing me. The biopsy was highly malignant in the breast, as were biopsied axillary lymph nodes. We had three treatment sessions during which the reasons for the cancer were explored and the problems resolved. She requested of her consciousness that all malignancies disappear. She returned to her home state and, since the tumors did not reduce in size, the surgeon and her husband convinced her to have the radical mastectomy. All pathology reports indicated only benign tumors. I have copies of the reports before and after surgery in her file.

Another case was very simple. This was a 70-year-old woman with pancreatic cancer. I simply blended with her consciousness energy field. She seemed to have no reason to have cancer so she let it go. I only saw her once as I was passing through. Either the diagnosis was incorrect or she healed her pancreas, because there is still no evidence of malignancy two years later. I believe that these are examples of what can be accomplished with trust, blending with the patient’s consciousness, and facilitating healing rather than making therapeutic decisions on your own. The patient’s consciousness knows what it needs and will usually trust you if you are sincere.
Post-Traumatic Stress Disorder and the Energy of Consciousness

Another area wherein this work has proven remarkably beneficial is in Post-Traumatic Stress Disorder (PTSD). We have worked with all types of victims of violent crimes, from rape to attempted murder. We also have worked with children who have been abused and/or been victims of satanic cult rituals. We have worked intensively with PTSD disabled Vietnam war veterans. They have all done well. The factor that all of these cases seem to have in common is residuum of consciousness energy from the perpetrators of the violent acts, or simply from the energy fields of the location, such as were present on some of the battlefields. When the therapist blends with the PTSD patient, the practitioner can locate this destructive area within the consciousness energy field and help the individual identify it also. Working together, it seems that the constructive energies of patient and therapist are able to expel the destructive energy. During the time of being expelled, the unwanted consciousness energy field often is visible to the therapists and to the patient. We often use multiple (two, three or four) therapists for one patient during this process. Once the destructive consciousness energy has been expelled, the patient can respond very quickly to counseling and/or other therapies to which they have been previously unresponsive.

Images and Consciousness Energy

It is also very common for the therapist to receive a detailed image of a diseased organ once he or she has blended with the patient. I feel that this image is presented by the patient’s consciousness. We also often smell anesthetic agents when patients are reliving surgical operations and the like. I have had the privilege of dialoguing with a floppy baby and getting the answers for the floppiness through the stops and starts of the craniosacral rhythm. We went back into the womb to a time that preceded an episode wherein the mother had inhaled toxic organic solvents for several hours. Once I had this information I talked the baby through a normal intrauterine development and delivery by verbally creating a dynamic
image. When we were finished, the baby’s motor system was no longer impaired. The floppy baby syndrome of six months duration was no longer present. It is very interesting to note that this occurred in France (before a class of 40 French students who served as witnesses), and that the family of the baby only spoke French. I dialogued in English as I do not speak French. It amazed me, too, that this child was born with a severe motor deficit and corrected it in less than an hour. I am sure that the consciousness of all the French students were assisting the baby’s recovery. The child is now six years old and functions normally.

This latter experience was the beginning of what we have named Completion of Biological Processes. In this technique, we feel that if we regress in the experience to the time before a traumatic incident occurred, we can pick it up and bring it forward through an imagined and guided normal process. Often this eliminates the disability or dysfunction. We also use this to complete pregnancies in the field of the conscious energy when there has been an abortion. I suspect that, when a conception or an implantation occurs, a series of events is set in motion.

When an abnormal interruption occurs, such as an abortion, the series of events does not go to conclusion, which in this case is term delivery. This incompleteness leaves a physiological confusion in the expectant mother’s body that can be returned to order by guiding the patient through a normal term pregnancy and delivery. This is another use of the consciousness to relieve the body of physiological confusion. Also, it would seem that the consciousness is multilingual or alingual, depending upon your point of view. In this case, I use the word alingual to indicate that words are not essential to comprehension.

**Dolphins and Consciousness**

My initial contact with dolphins was in 1954 while I was serving in the United States Coast Guard aboard an air-sea rescue ship. Quite often, a little before sundown, about 100 miles offshore in the Gulf of Mexico, our ship’s captain would announce a “swim call” over the loud speaker system. The first time he did this I was quite fearful because I had seen sharks as we were cruising. However, most of the crew were diving into the water. So I screwed up my courage and did the same. I was afraid. There were several dolphins around as we entered the water. I was immediately approached by a dolphin upon my entry into the water. I noted that my fear was immediately relieved. That dolphin remained near me all during the time I remained in the water, which I’m sure was more than half of an hour.

I served on this ship for two years. We were at sea about 50% of that time. We had a lot of swim calls far away from shore. I noticed that, as soon as the captain announced swim call, the dolphins were present. Quite often they formed a sort of circle around the swimmers. I felt their protective consciousness; I was never afraid again.

It was not until 1964, eight years later, that I again came in touch with dolphins. I lived in Clearwater Beach on the west coast of Florida. I had a rather busy practice, which I alluded to previously. During this time I became a fanatic about sailing very small boats. I bought a sailfish boat, which is about 11-feet long, has no cockpit, and is driven by a lateen sail. I spent many happy hours relaxing out in the Gulf of Mexico on my boat. I can hardly remember a time when I was not under the watchful eye of some dolphins. I felt totally safe in their company. I began to believe that they were extremely evolved and kind. Our consciousness energies felt like they blended together.
In 1996, staff members of The Upledger Institute HealthPlex Clinical Services had the opportunity to work in the water with patients in conjunction with dolphins. This took place for about four months at the Dolphin Research Center in the Florida Keys. We had patients come from all over the United States and from Europe. We put each patient on minimal flotation tubes under the chest and behind the knees. Each patient had three therapists working with him/her, standing in about four feet of water. There was a therapist on the head, on the feet, and one on the pelvis. This left one whole side of the patient free for dolphins to join in the therapy.

Usually a dolphin would circle our group and sort of scan. Then perhaps another dolphin would do the same. We always had at least two patients in the water at the same time, and ultimately we reached a situation wherein the dolphins would decide which treatment group to join. Initially, the trainers tried to make these decisions for the dolphins, but soon with our collective consciousnesses urging the dolphins to make their own decisions, it came to be that way. After some manifestations of disobedience, the trainers relinquished most of their control in this area.

Soon the dolphins were putting energy into therapists and patients alike. Their energetic input was often by a prolonged touch to a body part by the dolphin’s nose (rostrum). Sometimes these wonderful creatures touched the back of a therapist between the shoulder blades and treated the patient through the therapist’s body. Sometimes they touched the patient in a very specific place repeatedly. Sometimes they came alongside a therapist and suddenly that therapist knew how to do something new, and did it.

The dolphins have a craniosacral rhythm that stops and starts as a significance detector, so we can monitor their rhythm as we think about certain things. When we are thinking something significant, their rhythm stops. Soon you realize that this formality is not necessary. When a dolphin comes around you simply know something you did not know before. A little girl, age 10, used an arm that she had never used before after two sessions with the dolphins and us. A pelvic contracture relaxed and a short leg lengthened by about 1 inch after the dolphin and our treatment group worked together. All patients improved and all therapists got smarter.

How do you communicate with dolphins? You simply share consciousness energy fields with them. They have much to tell us about so many things. I know deep in my consciousness that this is the beginning of an interspecies communication on their terms, which puts it on a much higher plane than we are used to.

**Music and Tissue Consciousness**

As a musician I became aware, at a very early age, that certain parts of my body would resonate to certain notes. I was always especially responsive to lower notes, such as those played on a bass fiddle. My epigastrium especially seemed to like these notes. About six years ago in Amsterdam, a cardiologist friend and I were talking about the potential of tissue resonance. He told me that he had been a concert cellist several years prior. He was persuaded to take out his cello and play scales. There were four of us who were not playing. We all laid on the floor and paid attention to which notes felt good and which did not — I became clear that a single note might give me a pain but relieve a pain that one of the others had. All of us had our own best and worst notes.

Upon my return I began looking for a cellist who would like to experiment with patients while I was treating them. Through fate, a new conductor came to the local Pops orchestra. He had back problems. I saw my chance so I suggested that if he could come with one of his orchestra’s cellists, I would try to
help him find which notes were best for his back. I could do this by palpating the changes in muscle
tension in the affected areas as the cellist played different notes. It did not take long to discover that an
open string “G” gave him muscle relaxation and relief from pain. It also became apparent that concert
“A” 440, the note to which the orchestra routinely tunes, caused his back muscles to contract and
produced discomfort. He now avoids the stage when the orchestra is tuning, and he has a cellist play his
“G” when he needs relief.

The cellist herself became quite interested and began working with us on a weekly basis with the
patients we have in our intensive treatment programs for one or two weeks. We have found that, when
we find the note to which the tissue in question resonates, we can then entice it to follow the cello into
simple melodic lines. As this progresses we can feel an increased relaxation, vitality and energy flow in
the tissue. It seems to be very effective therapeutically. I am somewhat convinced that individual organs,
muscles and nerves not only have their own consciousness energies, but also have their own musical
likes and dislikes. Our previous director of intensive treatment programs (a physical therapist) and I are
both piano players. We usually heard the same melody line in our consciousness that was appropriate for
a given tissue once the note of initial resonance was found. Could this be the tissue consciousness letting
us know the melodic lines that would be therapeutic?

Conclusions
All of these experiences, and many more, have led me to believe that matter is dense energy, that energy
is very thin matter, and that every stage of density or thinness between the two exists. I also believe that
things are in a constant state of density flux between the two extremes.

I also have a visceral knowing that all things have a consciousness and that the energy fields of this
infinite number of consciousnesses are constantly blending and interacting. Therefore, the feelings that
you experience at any time, or the ideas that enter your head, may be due to the effects of the changing
consciousness energy fields, either in your close proximity or at a distance. An exact description of
consciousness energy’s condition or state of being at any given time or location is not possible. A
qualitative understanding, which is less rigorous, is possible and probably much more useful than
attempting a quantitative description, which would of necessity be less than accurate and therefore
misleading. The fact that exactitudes are impossible is a fact of life to which we simply must adjust and
with which we must live. Once this adjustment is made, life becomes much less strenuous.

If we consider that energy is information and that dolphins put out energy, as do cellos and a multitude
of other things — in fact, all things — it seems reasonable that, when we humans open our “minds”
widely, we can gain wisdom from any and all things. I suspect that all energy contains information. The
consciousness energy environment in which we are located at any given instant is the composite of all
the influences upon it and of all of its constituents. We, as singular units of consciousness, give to and
take from this consciousness energy environment. Since all fields are constantly interacting, the
consciousness energy that you project has an effect, diluted though it may be, on distant consciousness
energy fields, and perhaps a more powerful effect upon the closer fields. And since these fields have no
boundaries, it becomes conceivable that a powerful intention to project information, carrying
consciousness energy to distant places, is doable — once we learn how to do it.

In any case, all of our consciousness energies are influencing the whole universe, as well as those
consciousness energies in our immediate vicinity. The effect at a distance may be less dramatic but it is
present. Perhaps if we all keep our consciousness energies in constructive and loving modes, something good may come of it.
Cerebrospinal Fluid: What It Is and Where to Find It
by John E. Upledger, DO, OMM

The brain is about 80% water, and about 20% is extracellular. In addition to the water, the cranial cavity contains blood and cerebrospinal fluid. Each of these fluids serves specific needs related to functions of the brain, the spinal cord and all other intracranial structures.

Cerebrospinal fluid is secreted into the craniosacral system by the choroid plexuses, which are located primarily in the lateral ventricles of the brain. Inconsistently, small patches of choroid plexus tissue is seen in the third and fourth brain ventricles and, on rarer occasions, in other areas of the meningeal membrane system.

The structure of the choroid plexus is rather similar to the distal and collecting tubules of the kidney. It consists of minute tufts of blood vessels, mostly capillaries, although there are some arterioles and venules present. These tufts are part of the pia mater, which projects as a sort of mat into the ventricular spaces. All the tufts are covered by ependymal epithelial cells. The blood supply to the choroid plexuses is from the choroidal branches of the internal carotid arteries. Clearly, carotid artery insufficiency can result in a reduction of cerebrospinal fluid production. This may be compensated by reducing outflow from the craniosacral system, but a degree of stasis is inevitable when this compensatory mechanism is active.

The choroid plexus not only secretes cerebrospinal fluid into the craniosacral system, it also helps maintain the chemical stability of the cerebrospinal fluid. In this stabilizing role it conducts various biochemical substances into the craniosacral system. It also, by specific active conduction, removes some biochemical ions and molecules from the cerebrospinal fluid and deposits them into the venous drainage of the choroid plexus structures. Most of what is removed from the cerebrospinal fluid by this reverse action of the choroid plexus consists of metabolic by-products, or waste and toxic materials that somehow gained entry into the craniosacral system.

Once secreted into the craniosacral system, the cerebrospinal fluid flows from the lateral ventricles of the brain through the interventricular foramina (of Monro) into the third ventricle, where the few choroid plexuses located there may add more cerebrospinal fluid. From the brain’s third ventricle, the cerebrospinal fluid then flows through the cerebral aqueduct (of Sylvius) into the brain’s fourth ventricle. (In congenital hydrocephalus, it is usually this cerebral aqueduct that is not competent. In that case, the surgical placement of a shunt is usually mandatory.)

From the fourth ventricle, the cerebrospinal fluid then passes through the foramina of Luschka, which are paired, and Magendie, of which there is only one. The latter foramen (Magendie) is located on the midline in the roof of the fourth ventricle. The former two foramina (Luschka) are located bilaterally in the lateral aspects of this fourth ventricle. The existence of choroid plexus structures in this fourth ventricle is much more sparse than even in the third ventricle. From the fourth ventricle, the cerebrospinal fluid empties into the subarachnoid space through these three foramina and directly into the central canal of the spinal cord. The cerebrospinal fluid that enters this subarachnoid space then
bathes the brain, the spinal cord and the spinal nerve roots, only as far distally as dural sleeves extend on these nerves. In the spinal area these dural sleeves end at the intervertebral foramina.

This latter situation continues to be somewhat controversial. From its time of origin, the Osteopathic Cranial Academy taught that cerebrospinal fluid followed all the nerves out of the spinal cord to their destinations in the periphery. Indeed, this is how they explained the perceptible cranial motion they felt all over the body. It’s a nice, easy explanation, but it is simply not true. It is true that the olfactory and optic cranial nerves (known as nerves I and II) are bathed in cerebrospinal fluid to their end points. However, these first two cranial nerves are not really nerves. They are extensions of brain tissue, because they are not synaptically separated from brain tissue. Thus, we might say that these brain extensions, throughout their length, maintain their relationship with the dura mater and the cerebrospinal fluid that flows within this tough watertight sheath. The other cranial nerves, III through XII, have the luxury of the cerebrospinal fluid bath only as far as they have the luxury of the sheath of dura mater, which is not throughout their entire course.

How can I be so sure of this when some “authorities” still maintain the idea that cerebrospinal fluid follows all nerves to their destinations? Over 20 years ago, while I was in the biomechanics department at Michigan State University, a good friend and colleague, Irvin M. Korr, Ph.D. (physiology), was researching this very question. We had neighboring offices and we shared many hours of conversation. Dr. Korr was interested in the trophic (vitalizing) influence of nerves upon their end organs. As most of you know, when a nerve becomes dysfunctional for any reason, whether from disease, being cut, entrapment, etc., its end organ begins to atrophy or become dystrophic. Dr. Korr was the creator of the facilitated segment concept. He had observed mild dystrophic changes related to the end organs of the nerves from facilitated segments, and his research was leading him into the investigation of the cause of these dystrophic-end-organ responses.

Dr. Korr injected radioactive tracers into the glossopharyngeal nerve nuclei of guinea pigs. The glossopharyngeal nerve is cranial nerve IX. It goes to the tongue in both guinea pigs and humans. He found that the radioactive tracers took about two days to travel from the glossopharyngeal nucleus to the guinea pigs’ tongue. He also found that the radioactive tracers were attached to protein molecules that were traveling through the glossopharyngeal axons to the tongues of the guinea pigs. The rate of motion was between 1 and 2 millimeters per hour. He reasoned that the trophic influence of the nerve, which he observed in his work with facilitated segments, was quite possibly related to the protein substances that we now know are manufactured in the nerve cell body and transported via the reticulum tubes and the vesicular systems that travel throughout the length of each axon to its end organ. When there is an intervening synapse en route, it seems that the presynaptic protein somehow signals the postsynaptic neuron to manufacture and send similar if not identical proteins to its (the postsynaptic neuron’s) axonal destination.

As a part of this same work, Dr. Korr injected radioactive tracers into the guinea pigs’ brain ventricles. He allowed me to join him in this work because of my interest in what was later called the craniosacral system. We monitored nerve trunks beyond the end of the dural sleeves, and not once did we find radioactivity distal to these dural sleeve terminal points. We did, however, find radioactivity throughout the length of the spinal cord, the dural tube, and out the dural sleeves as far as the intervertebral foramina. At this same time I was preparing my first research proposal to the National Institutes of Health in Washington, DC. I made a thorough search of the literature at that time and found several confirmatory
pieces of research that used both intraventricular dye injection and the injection of radioactive tracers. No one found either the dye or the radioactive tracers beyond the dural compartment.

This, of course, left the question of what makes the whole body reflect the craniosacral rhythm. I believe this whole-body response is probably due to the pumping effect of the cerebrospinal fluid upon the motor system, which causes a rhythmical tonification and detonification of the myofascial system in response to rhythmically fluctuating nerve signals. This concept seems supported by more recent research that has traced the flow of cerebrospinal fluid in response to its pressure fluctuations deep into the brain’s sulci and into the depths of the cerebral cortex through the Virchow-Robin spaces. These are perivascular spaces that carry the cerebrospinal fluid (all within the dural envelope) into the interstitial spaces of the brain. An apparent free diffusion of small molecule solutes occurs in these spaces. This obviously facilitates the removal of metabolic by-products, as well as delivery of those substances that the cerebrospinal fluid carries. I feel reasonably safe when I say that this fluid fluctuation would have an effect upon the motor cortex.

Now let’s look at what happens to the cerebrospinal fluid if it doesn’t exit the craniosacral system via all the post-root nerve trunks. Incidentally, if it were ultimately found that cerebrospinal fluid goes throughout the body with the nerves, this would not contradict the Pressurestat Model, which explains the mechanics of the craniosacral system. It only offers an expansion of the controlled outflow of cerebrospinal fluid from the craniosacral system. However, in my eyes the evidence supports the arachnoid system as the one that returns cerebrospinal fluid to the blood vascular system. The major absorption of cerebrospinal fluid from within the dural envelope is through the arachnoid villi and, to a lesser extent, through the arachnoid granulation bodies (also called pacchionian granulations).

The arachnoid structures are typically found in clusters encased in a sac of arachnoid membrane that protrudes through “pores” in the dural membrane and into the lumina of the venous sinuses of the brain. The sinus that has the greatest density of arachnoid granulations is the superior sagittal sinus. The arachnoid granulation bodies that we refer to are concentrated at and near the anterior end of the straight venous sinus. We know these latter granulation bodies have the ability to raise or lower venous sinus back pressure, thereby changing the rate of cerebrospinal fluid outflow from within the dural envelope (which forms the boundary of the craniosacral system) into the venous blood.

It is not yet totally clear how the arachnoid granulation system works to return cerebrospinal fluid into the venous blood of the brain’s sinus systems. My own preferred idea is that the membranes of the arachnoid granulations, which separate the cerebrospinal fluid from the venous blood, are selective because of the size of pores they have. Thus, these membranes would reject the passage of the larger molecules and cells into the craniosacral system from the blood. Therefore, the blood remains more dense or concentrated because it has many more cells and large molecules than does cerebrospinal fluid. Influenced by osmotic pressure and the forces of diffusion, the cerebrospinal fluid attempts to dilute the blood. In this attempt, cerebrospinal fluid passes through the membrane over to the blood side as it seeks equilibrium. Since more concentrated blood is continually moving into the regions of the arachnoid villi, the constant quest for equilibrium produces a dominant flow of cerebrospinal fluid into the venous blood.

Other possibilities yet to be confirmed or rejected include a system of tubules or channels that might cross the barrier between the cerebrospinal fluid and the venous blood. Similar to the tubule concept but less open and requiring more energy is the possibility of vacuoles filling with cerebrospinal fluid on one side of the cellular barriers and emptying into the venous blood on the other side. This latter possibility
would be an active transport system requiring a well designed and rather complex control system, as well as a lot of available energy. In as much as Mother Nature usually has multiple back-up systems, it would not be surprising to see any or all of these three systems operative, as well as some yet undiscovered systems.

The composition of cerebrospinal fluid is in a “steady state” with the extracellular/interstitial fluids of the brain. In fact, from the point of view of fluid composition, they are the same fluid. They are named differently according to location, but I feel quite safe in saying that cerebrospinal fluid is the extracellular/interstitial fluid of the brain and spinal cord. Incidentally, the fluid between the dural and arachnoid membranes is, according to composition, also cerebrospinal fluid. I believe both of these mythical, man-made divisions of fluids will soon be gone.

Because of its singular and continuous fluid system, in order to bathe the neurons and glial cells of the brain, it is essential that cerebrospinal fluid flow not be impaired. If an area of brain tissue is even partially deprived of optimally effective cerebrospinal/extracellular/interstitial fluid motion and flow that brain area will be forced into some degree of functional compromise.

This cerebrospinal fluid circulation removes metabolic waste products as well as toxic substances from brain tissue. In this way it serves a function similar to the extradural lymphatic system, yet these two fluids (cerebrospinal and lymphatic) are different. The cerebrospinal fluid also floats the brain, thus countering the forces of gravity. An in situ brain floating in cerebrospinal fluid weighs about 50 grams under normal circumstances. A brain taken out of the body and not floating weighs about 1 to 1.5 kilograms. Remember, it takes a thousand grams to make a kilogram, so the extracorporal brain weighs 20 to 30 times more.

In addition, cerebrospinal fluid serves as a shock absorber in head jolts. It also serves as a vehicle for the transport of all kinds of hormones and peptides. The pH of cerebrospinal fluid has marked effects on the breathing control centers of the brain, thus influencing rate and depth of pulmonary respiration. Through its pH it also influences cerebral blood flow. As you can see, cerebrospinal fluid has several important known roles. How much is yet to be discovered?

If we compare some of the components of cerebrospinal fluid and blood serum, we can see the importance of the choroid plexuses and the arachnoid villi and granulation bodies. These differentials in components and pH are necessary because brain tissue has qualitatively and quantitatively different requirements than other body tissues.

Here are a few of the differences between cerebrospinal fluid and blood serum:

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<th>Cerebrospinal Fluid</th>
<th>Blood Serum</th>
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<tbody>
<tr>
<td>Water</td>
<td>99%</td>
<td>93%</td>
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<tr>
<td>Protein mg/dl</td>
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<tr>
<td>Chloride mg/l</td>
<td>119</td>
<td>102</td>
</tr>
<tr>
<td>pH</td>
<td>7.33</td>
<td>7.41</td>
</tr>
</tbody>
</table>

mg = milligram        dl = deciliter    l = liter
Before concluding, it seems appropriate to briefly describe blood plasma, blood serum and lymph, and what makes them differ. Blood plasma differs from whole blood in that plasma is blood with the cells removed. This makes plasma a much less rejected substance to give to a person who requires additional blood in a hurry when there is no compatible whole blood available. It restores blood volume, contains many nutrients and vitamins, as well as proteins, lipids, hormones, peptides, etc., but no cells. This means needy patients who receive plasma may remain anemic and low on white blood cells, but they won’t die in hypovolemic shock.

Blood serum has all the stuff of plasma except the fibrin and other factors involved in clotting. The cells have been removed just as in plasma. Blood serum is the fluid upon which most blood chemistry analyses are performed. Of course, whole blood is required for the blood cell count procedures. Since both whole blood and plasma have clotting ability, anti-clotting substances are added to them when the clot is unwanted.

Lymph is a colorless fluid found within the lymphatic system. It is derived from extracellular/interstitial fluid by lymph capillary absorption. The size of the pores in the lymph capillary walls is significantly larger than the pores in blood vascular system capillaries. Therefore, larger molecules that are rejected by the blood vascular capillaries are found in lymph.

The composition of lymph includes water, a variety of dissolved salts and proteins, and a variety of fat molecules, all of which are in suspension rather than in solution. Lymph also contains a potpourri of metabolic by-products, toxic substances, infectious by-products, etc. These substances end up in lymph because, in essence, lymph is the vacuum cleaner of the intercellular spaces of the body, excluding the brain and spinal cord. The lymph capillaries either drain into lymph nodes or become tributaries to tubular vessels that may then drain into lymph nodes.

The lymph nodes serve as filtration stations. After they have done their purification work, they send the cleansed lymph into lymph vessels, which form a system of tributaries that ultimately returns the lymph to the venous side of the blood vascular system. The whole lymphatic system has its own rhythmical pumping action, which aids in its fluid transport. When infectious or toxic materials, whether live or by-products, are too much for the lymphatic system, you may see painful swelling of overburdened lymph nodes. Often these swollen nodes become fibrous and may ultimately be excluded from the lymphatic system.

The chemical composition of lymph is extremely variable because of its clean-up duties. Therefore, it is not often used for chemical assessments. It is influenced almost moment to moment by what is going on in the body. It is influenced by digestive processes, infectious processes, toxic processes and so on. It is called interstitial or extracellular fluid until it enters the lymphatic system. It is then called lymph because of its location rather than its composition.

In addition to the aforementioned aspects of the mechanisms that keep cerebrospinal fluid separate and distinct from other body fluids, we have a brain protector call the blood-brain barrier. Paul Erlich was the creator of the concept. He injected dyes into blood that attached to serum albumen molecules. He found that most internal organs were stained by the dyes, except the brain. Further study has confirmed that the blood-brain barrier is another system of protection for the brain. It is located in specialized endothelial cells of the cerebrovascular system’s capillaries. These specialized cells are contacted by astrocyte projections from the brain side of the system. Somehow these astrocytes let the capillary
endothelial cells know which molecules in the blood are allowed to cross over into the cerebrospinal fluid and the brain tissue, and which are not.

The entire system is quite ingenious and rather strict about the enforcement of its immigration laws. Who made the laws? Who trained the enforcers? Somebody a lot smarter than me.
The Expanding Role of Cerebrospinal Fluid in Health and Disease

by John E. Upledger, DO, OMM

It was 1971 when I first witnessed the rhythmical activity of cerebrospinal fluid as its hydraulic forces affected the patch of dura mater I was watching. At the time I had no inkling of the incredible journey that was in store for me.

That small section of dura mater was only about 1½ inches long and 2 inches wide. We had exposed it to remove a dime-sized calcium plaque from the outer surface of the dura. The operative site was the posterior aspect of the mid-cervical region of the patient.

My assignment was to hold the dura very still with a pair of tissue forceps while the neurosurgeon delicately removed the calcium plaque without incising the dural membrane. Yet in spite of my attempts, the exposed dural membrane repeatedly protruded and receded at about 10 cycles per minute.

That particular rhythm was a surprise to everyone in the operating room. It didn’t synchronize with the anesthetist’s breathing apparatus nor the cardiac monitor — both were in my view. The only thing I could think of that could create this force was the pumping of cerebrospinal fluid inside the dura mater.

Yet the very subject of cerebrospinal fluid was quite contentious at the time. When I was in osteopathic college back in the early ’60s, cerebrospinal fluid was considered mainly a shock absorber for the jelly-like brain during swift starting and stopping movements. There was also some debate about cerebrospinal fluid being a transport system to deliver nutrients and remove waste, yet no one was certain. Some cranial osteopaths even made vague references to cerebrospinal fluid following nerve fibers to every cell of the body and delivering some kind of “mystical” energy.

Despite the theories, scientific knowledge at that time stated quite firmly that cerebrospinal fluid did not penetrate the brain’s surface, nor leave the compartment formed by the dura mater. The fluid did appear to follow nerve roots peripherally from the brain and spinal cord, but only as far as the dura mater provided a sheath for the roots. This, it was thought, was to bathe the nerve roots as well as the surface of the brain.

Yet controversy even existed over whether the fluid in the subdural space should even be considered cerebrospinal fluid. There was evidence to support the concept that the arachnoid membrane was impermeable to cerebrospinal fluid and, therefore, the fluid outside the arachnoid membrane but inside the dura mater was not cerebrospinal fluid, even though they were biochemically identical. This, of course, raised yet another question. Should a fluid be named by its biochemical characteristics or by the compartment in which it resides?
It was against this backdrop that I observed the pumping activity of cerebrospinal fluid in 1971. And it was in this environment that I went on to develop CranioSacral Therapy.

My initial focus with CranioSacral Therapy was to mobilize the meningeal membranes that related to the entire central nervous system and the proximal aspects of its major nerve roots. I used the bones that attach to these membranes, either directly or indirectly, to manipulate the meningeal membranes and release any mobility restrictions.

Yet I found CranioSacral Therapy also released restrictions in membrane mobility and in the sutures between bones of the skull vault by effectively using the hydraulic forces provided by the pumping of cerebrospinal fluid. The therapist simply drew those forces into restricted areas by gently inhibiting the areas of maximum (compensatory) compliance to the rhythmical rises of hydraulic forces. By continuing this gentle manual pressure, the fluctuating hydraulic forces helped naturally release those restrictions.

My colleagues and I were fascinated by the wide variety of patient improvements we witnessed using these new techniques and theories. Most positive responses came in cases of pain that were attributable to meningeal restrictions, in cases of painful sutural restrictions, and with learning disabilities that could be related to specific dysfunctions in this craniosacral system. Yet what was truly difficult to explain were the positive results seen with diseases like Parkinson’s, multiple sclerosis, chronic fatigue syndrome, and acute and chronic infections, including resistant staphylococcus and cytomegalovirus.

Indeed, there were many, many positive results from CranioSacral Therapy in areas that seemed untouchable based on concepts held about cerebrospinal fluid at that time. Even now, as scientific research continues to uncover the secrets of cerebrospinal fluid, we see more and more how CranioSacral Therapy helps in so many surprising ways.

Several research projects over the past few years have demonstrated that, contrary to previously held ideas, cerebrospinal fluid is the interstitial fluid of the brain and spinal cord. That means it permeates the spaces between all the nervous and glial cells of the brain and spinal cord. In this way it carries nutrients; removes metabolic byproducts, waste and toxic molecules; strongly influences pH (acidity); and is now thought to influence the electromagnetic environment of the neurons and other cells of the central nervous system. [For a complete overview of these research projects, see Science News, January, 1999.]

In The New York Academy of Science Annals, Volume 854, an article entitled “Towards the Prolongation of a Healthy Life Span” reported that cerebrospinal fluid contains low-molecular weight chelating agents that remove metal atoms from the interstitial spaces of the brain and spinal cord, as well as from the neuronal and glial cell membranes. According to the article, cerebrospinal fluid also protects against oxidation and toxic accumulations of nonmetallic toxins. This is especially enlightening in the cases of recent studies that have shown both Parkinson’s and Alzheimer’s diseases may be induced by toxic build-ups of heavy metals — within the basal ganglia in the case of Parkinson’s, and in the cortical and subcortical regions in the case of Alzheimer’s disease. So enhancing cerebrospinal fluid circulation may well help prevent these two diseases, along with many other types of senility and deterioration problems.

In my own clinical practice I’ve been able to break fevers, alleviate chronic viral infections, prevent flu… the list goes on and on. All these results suggest an enhancement of immune function, which is exactly what I believe CranioSacral Therapy does. It moves cerebrospinal fluid and every other body
fluid, especially the interstitial fluids. By whatever name, the fluids between cells must move in order to deliver molecules that not only nurture cells but also transport messages and patrol for antigens — all vital to strong immune function. Physicians at Stanford University have also discovered that the exchange of cerebrospinal fluid slows with age. While there is a complete turnover of cerebrospinal fluid about four or five times a day in healthy middle-aged people, in the elderly that rate may be cut in half.

In fact, the Stanford folks became so convinced that cerebrospinal fluid turnover is important that they’ve placed shunts in a sample of nine patients with reduced turnover to see whether the drainage of stagnant cerebrospinal fluid enhances production and reduces certain substances in the cerebrospinal fluid — and hence the central nervous system — that are believed to contribute to brain deterioration and Alzheimer’s disease.

I firmly believe CranioSacral Therapy can effectively help maintain or regain the normal production and reabsorption of cerebrospinal fluid so that a normal daily turnover of fluids can be maintained with all of its attendant health benefits.

**Note:**

I can’t resist presenting this new information that came forth in one of The Upledger Institute’s recent “The Brain Speaks” seminars. A practitioner was dialoguing with the cerebellum of a fellow classmate when the cerebellum “reported” that it had many crystals within it that had to be kept clean by cerebrospinal fluid washing. When these crystals get dirty, cerebellar function deteriorates in terms of motor, balance, memory, hearing association, and many other areas that generally go with old age. Yet in this case, old age would not be old age — just dirty crystals. Through continuing dialogue, the practitioner discovered these crystals could be kept clean by the same treatment that helps cerebrospinal fluid circulate.

Now comes the fun part. In 1992, Joseph L. Kirshvink et al from Cal Tech in Pasadena published an article entitled “Magnetite Biomineralization in Human Brain” in the Proceedings of the National Academy of Science, USA, Volume 89, biophysics section, pg. 7683-87. In it, Dr. Kirshvink stated that he found over 5 million single-domain magnetite (Fe₃O₄) crystals per gram of human brain tissue. He also found over 100 million of the same type of crystals per gram of pia mater and dura mater. Even allowing for a 25% error in counting such large numbers, that’s a lot of crystals to wash.

The message is clear: Pump those craniosacral systems.
Continuing Education and Complementary Care

Upledger Institute International (UII) is a health resource center dedicated to the advancement of innovative techniques that complement conventional care. It’s recognized worldwide for its groundbreaking continuing-education programs, clinical research and therapeutic services.

Founded in 1985 by John E. Upledger, DO, OMM, UII has trained more than 80,000 practitioners worldwide in CranioSacral Therapy and other gentle healthcare modalities. Today it conducts hundreds of workshops each year educating healthcare professionals of diverse disciplines.

The cornerstone of our educational training is CranioSacral Therapy, a gentle, hands-on, whole-body method of releasing restrictions around the brain and spinal cord to enhance central nervous system performance and allow the body to self-correct.

Developed by Dr. John E. Upledger after eight years of clinical research and testing at Michigan State University, CranioSacral Therapy has proven effective in aiding individuals with a wide range of medical challenges, including migraines, neck and back pain, fibromyalgia, chronic fatigue, TMJ syndrome, motor-coordination impairments, autism, central nervous system disorders, colic, learning disabilities, brain and spinal cord injuries, emotional difficulties, stress-related problems, neuro-vascular or immune disorders, post-traumatic stress disorder and post-surgical dysfunction.

Just as with CranioSacral Therapy, every modality practiced or taught through UII is designed to relieve health problems at their source to offer a wealth of benefits, from pain relief to whole-body wellness. And because each UII course curriculum is personally designed by its modality developer, your education comes straight from the source.
CranioSacral Therapy
Developed by John E. Upledger, DO, OMM

CranioSacral Therapy (CST) is a gentle, light-touch method of evaluating and enhancing the cranio-sacral system, the environment in which the brain and spinal cord function. An imbalance or dysfunction in the craniosacral system can cause sensory, motor or neurological disabilities. These problems may include chronic pain, eye difficulties, scoliosis, motor-coordination impairments and learning disabilities, as well as other physical and psychological problems.

The CranioSacral Therapy curriculum begins with the entry-level workshop CranioSacral Therapy I, which provides the critical foundation necessary to understand the functioning of the craniosacral system. Using palpatory skills to detect subtle biological movements, and fascial and soft-tissue release techniques in a 10-Step Protocol, participants learn to evaluate and work with the entire body.

CranioSacral Therapy Certification
Upledger Institute International offers certification in CranioSacral Therapy at two levels: a CST Techniques certification for those who have completed CS2, and a more advanced Diplomate level for Advanced CST alumni. Examination for certification at each level is a multi-tasked project including written, oral and hands-on testing.

CranioSacral Therapy Courses

- CranioSacral Therapy 1
- CranioSacral Therapy 2
- Clinical Application of CranioSacral Therapy
- CranioSacral Dissection
- Therapeutic Imagery & Dialogue 1
- SomatoEmotional Release 1
- Clinical Application of SomatoEmotional Release
- SomatoEmotional Release 2
- The Brain Speaks
- CranioSacral Therapy for Pediatrics 1
- CranioSacral Therapy for Pediatrics 2
- Unwinding Meridians: Applying Acupuncture Principles to CranioSacral Therapy

- CranioSacral Therapy and the Immune Response
- CranioSacral Applications to Obstetrics 1
- Advanced 1 CranioSacral Therapy
- Clinical Application of Advanced CranioSacral Therapy
- BioAquatic Explorations
- Advanced 2 CranioSacral Therapy
- Advanced Preceptorship
- Advanced 2 Preceptorship
- CranioSacral Techniques for Estheticians
- ShareCare®
- Clinical Application of Cranio-Sacral and SomatoEmotional Release for Pediatrics
- CranioSacral Techniques and the Reversal of Pathogenic Processes
- Clinical Application of Advanced CranioSacral Therapy for Pediatrics
The International Alliance of Healthcare Educators (IAHE) is a cooperative of Continuing Education providers who offer other workshops in alternative healthcare modalities. The current modalities available through IAHE include:

- **CranioSacral Therapy/ SomatoEmotional Release**  
  John E. Upledger, DO, OMM

- **Visceral Manipulation**  
  Jean-Pierre Barral, DO, MRO(F), PT

- **Neural Manipulation/Manual Articular Approach**  
  Jean-Pierre Barral, DO, MRO(F), PT  
  & Alain Croibier, DO, MRO(F)

- **Heart Centered Therapy**  
  Alaya Chikly, LMT

- **Lymph Drainage Therapy**  
  Bruno Chikly, MD, DO

- **Healing From the Core**  
  Suzanne Scurlock-Durana, CMT, CST-D

- **Therapeutic Systems**  
  Kerry D’Ambrogio, DOM, AP, BSc, PT

- **Equine CranioSacral Therapy**  
  Gail Wetzler, RPT, CVMI, BI-D, EDO

- **NeuroMuscular Therapy**  
  Judith (Walker) Delany, LMT

- **Mechanical Link**  
  Paul Chauffour, DO

- **Zero Balancing**  
  Fritz Smith, MD

- **Process Acupressure**  
  Aminah Raheem, PhD

- **The Feldenkrais Method**  
  Ann Harman, DO

- **Qigong T’chings**  
  Cloe S. Couturier LMT/CO, CST-D

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SUBMITTING YOUR NEWS RELEASE TO LOCAL PUBLICATIONS

• Type the news release sample from the following page onto your letterhead, filling in the blanks as indicated. Be sure to include your name and a telephone number where you can be reached during business hours.

• Develop a mailing list of publications — daily and weekly newspapers as well as local magazines. Telephone these sources and ask for the name of the news editor. Your press release should be addressed by name to these individuals at their respective media outlets.

• Don’t forget to mail releases to any local professional organizations that publish newsletters, as well as to your school if you studied locally. Be sure to mention that you are an alumnus of that school.

• Include a 5x7 black and white photograph, if available, with your release. Be sure to put your name on the back and include a sturdy piece of cardboard in the envelope to keep the photograph from bending. It’s a good idea to print “Do Not Bend” on the envelope, too. Photographs often will not be returned.
FOR IMMEDIATE RELEASE:  
(insert today’s date)  
CONTACT:  
(Your name, phone number, e-mail address)  

THERAPIST BRINGS ENERGIZING NEW TECHNIQUES TO  
[INSERT YOUR HOMETOWN]  

[YOUR CITY, state] – [Your name and professional title] recently participated in the CranioSacral Therapy 1 workshop offered by Upledger Institute International, an innovative organization that offers continuing education courses to healthcare professionals worldwide.

The course is designed by osteopathic physician John E. Upledger, who developed CranioSacral Therapy and has taught the technique internationally.

CranioSacral Therapy is used to detect and correct imbalances in the craniosacral system, which may be the cause of sensory, motor or neurological dysfunction. The craniosacral system consists of the membranes and cerebrospinal fluid that surround and protect the brain and spinal cord. It extends from the bones of the skull, face and mouth — which make up the cranium — down to the sacrum, or tailbone area.

The therapy has been successfully used to treat headaches, neck and back pain, TMJ, chronic fatigue, motor coordination difficulties, eye problems and central nervous system disorders.

For information on CranioSacral Therapy or Upledger Institute International, please call 1-800-233-5880.

###
MODEL FOR RESEARCH CASE STUDY
OR SINGLE-SUBJECT DESIGN

Introduction

Following are suggestions for a simple yet concise research case study or single-subject design. You can utilize sections 5 and 7 to expand on philosophy or constructs. Sections may even be omitted as appropriate. When most of this information is incorporated on an intake evaluation and discharge form, then only minimal effort is needed to make a publishable single subject design or case study format.

The submitted report will:
• Support the effectiveness of the therapy that was used in the study.
• Open opportunities to validate concepts and techniques within various professional forums.
• Reinforce the depth of your knowledge and skill as a published practitioner.

Report Format

A report could be divided into the following sections:

1. **Introduction**: What is the problem/diagnosis?
2. **Review of Literature**: Past medical history, etiology of the problem, date of onset, social history, previous treatment including surgeries for this problem (and results), and any diagnostics done.
3. **Procedure/Treatment**: Include all treatment procedures, modalities, exercise (home and office) treatment time per session, plus total treatment span (including frequency). If modalities were used, be specific as to any particulars. Mention specific treatment positions if appropriate for further classification.
4. **Outcomes/Analysis of Results**: Both functional and structural outcomes should be listed here, i.e., pre- and post-tests if applicable. (Try to get 2-3 measurements each pre-and post-test as it improves reliability and validity of treatment.) Measure outcomes functionally, also. (Most clinics/practitioners are obtaining this information from patients as well as the “objective” data.) Include patient’s self-assessment as well as therapist’s patient assessment. Rate a percentage of improvement (usually a scalar measurement).
5. **Discussion**: What do your findings mean? How do they add to the established body of knowledge? Where do you go with your results? Make recommendations for change for further analysis of the same subject.
6. **Summary**: An abstract. Summarize points 1-4 (for potential publication).
7. **Conclusions and Recommendations for Further Study**: Was the treatment successful? If so, how did you measure success? If not, what would you do differently with this individual?
8. **Appendices**: May include subject consent form (if appropriate), technical data, date of birth, treatment dates. (If no-name submission, use an identification process other than abbreviations or initials.)
9. **References**: If appropriate or beneficial for further research. Format as:
UII-Approved Study Groups

Following the completion of your class, you will be eligible to participate in an Upledger Institute International-sanctioned study group that corresponds to the coursework you studied. Study groups offer a small-group environment where you can network, reinforce your skills and discuss case histories with similarly trained colleagues.

Study-group leaders may charge members a nominal fee; these generally range from $5-$10 per meeting.

**To locate a study group in your area:**

- See your class facilitator. A list of active study groups is available at the product tables at all workshops.
- Call Educational Services at 1-800-233-5880.
- Log on www.upledger.com. Go to “work with us” and click on the “study groups” tab on the left or cut and paste this url: www.upledger.com/content.asp?id=16 into your web browser.

“Study groups are worth their weight in gold. They build practitioners’ confidence and help them remember the technical details. They’re invaluable in terms of providing good, guided practice time. And practice is what really makes a good practitioner into an excellent one.”

– Suzanne Scurlock-Durana, CMT, CST-D
Welcome...

to the Upledger Institute
International - Alumni Association! We are the world's largest network for CranioSacral Therapy.

Alumni Benefits:
- As an alumnus of any Upledger CST course, you are part of the most respected group of CranioSacral Therapy-trained practitioners in the World
- Strength and support from being part of the World's largest CranioSacral Therapy global network, with practitioners trained in over 100 countries
- Complimentary listing on the World's largest CranioSacral Therapy practitioner referral and networking site
- Support through legislative efforts to increase awareness, recognition, insurance reimbursement and protect the right to practice
- Professional Liability insurance available at a discount
- Continued efforts to support recognition through various research projects

Medallion Benefits:
- A level of membership designed to further growth and continued learning
- Your listing ranked higher than basic alumni
- On-Line Profile for referrals and networking
- On-Line course review for most core classes
- Special offers on products and classes
- On-Line access to articles on subjects important to you and your business, to further your knowledge or to share with clients
- On-Line exclusive interviews with Institute instructors

For more information, please speak with your instructor or facilitator.

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