A L P S

NIH

Autoimmune Lymphoproliferative Syndrome

An Introduction for ALPS Patients and Their Families

INTRODUCTION

ALPS (autoimmune lymphoproliferative syndrome) is a rare disease discovered by a team of doctors and scientists at the National Institutes of Health (NIH). The National Institute of Allergy and Infectious Diseases (NIAID) and the National Human Genome Research Institute (NHGRI) are components of the NIH working on ALPS. Our team of doctors and scientists is continuing to search for better ways to diagnose and treat ALPS. This brochure is designed to answer questions that many ALPS patients and their families have asked.

ALPS

YOU OR ONE OF YOUR RELATIVES has been invited to visit doctors at the National Institutes of Health (NIH) because of health problems related to the immune system. We first began to study these problems in 1990, when we saw a child who had immune system symptoms that did not fit any previously known disorders. Since then, dozens of other children and adults with similar problems have been identified and followed at the NIH.

In 1995, we gave this newly identified condition a name—ALPS. By August 1999, we diagnosed ALPS in 58 individuals from 35 families. These families come from all over the country and are of many different racial backgrounds.

We hope that this brochure will help answer some of your questions about ALPS. Share it with your family, physicians, members of your community, and your children's teachers so that they can understand ALPS better, too.

ALPS-WHAT IS IT? ALPS is a rare disease that affects both children and adults. ALPS stands for **A**utoimmune **L**ympho**P**roliferative (lim-fo-pro-lif'-er-a-tive) **S**yndrome. Each of these three words helps describe the main features of this condition. The word *autoimmune (self-immune)* identifies ALPS as a disease of the immune system. The tools used to fight germs turn against our own cells and cause problems. The word *lymphoproliferative* describes the unusually large numbers of white blood cells (called lymphocytes (lim'-fo-sites)) stored in the lymph nodes and spleens of people with ALPS. The word *syndrome* refers to the many common symptoms shared by ALPS patients.

CLINICAL FEATURES OF ALPS *Some signs of ALPS are ones that people can feel or see, and some of them can be detected only by laboratory tests. Not all people with ALPS will have all of its possible symptoms. Some people have only a few. Some things that are seen most often in people with ALPS include:*

- *an enlarged spleen*
- *enlarged lymph nodes, especially in the neck and underarms*
- *an enlarged liver*
- *skin rashes*
- *frequent nose bleeds*
- *anemia (low blood counts)*
- *an increase in certain types of white blood cells (including double-negative T cells)*
- *an increased life-span of some white blood cells that are no longer needed*
- *an alteration in a gene.*

WHAT WE'VE FOUND OUT SO FAR AT THE NIH At this time we are still learning about ALPS. Based on our experience, we believe the following to be true:

- ALPS is a disorder that develops in early childhood.
- ALPS is not cancer; it is not contagious; it is not AIDS.
- There is a wide spectrum of illness in ALPS. For some, it is very mild; for others, it is more severe.
- Once a person has ALPS, he or she does not become sicker and sicker over time. In fact, the problems seem to improve as children get to be teenagers and young adults.
- Most people with ALPS have episodes of autoimmune problems. These can happen at any age, but they appear worse in childhood.

Types of Autoimmune Problems Common autoimmune problems in ALPS include:

- Very low red blood cell counts (hemolytic anemia) that can make one weak.
- Very low platelet counts (*immune-mediated thrombocytopenia*, or *ITP*) that cause bruises and nose bleeds, and may pose a risk for hemorrhage (excessive bleeding). Little spots called petechiae (pet-eek'-ia) may also show up on the skin when platelets are low.
- Very low white blood cell counts (autoimmune neutropenia), creating a risk for bacterial infection.
- Less often, other autoimmune problems can occur in almost any organ—skin, liver, kidney and nerves are examples.

A BRIEF INTRODUCTION TO IMMUNOLOGY You may wonder what the connection is between the findings in ALPS and the immune system. To understand what happens in ALPS, we would like to review some basic information about the immune system. It is the immune system that defends our bodies against germs. There are many components of the immune system. Two major components are the spleen and white blood cells. The spleen is a

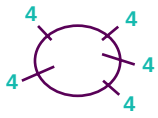
fist-sized organ found to the left of your stomach. It has a special job of filtering the blood, by cleaning out dead blood cells that aren't needed any more. The blood contains many types of cells:

- *red blood cells* help transport oxygen to your tissues
- *platelets* help to form blood clots
- *white blood cells* are the soldiers in your immune system.

One major class of white blood cells is called *lymphocytes.* There are many kinds of lymphocytes to combat the variety of germs in the world. *B cells* and *T cells* are two major kinds of lymphocytes.

There are many kinds of T cells. Some of these direct our immune response to infections, and others kill infected cells. Each T cell is named for the markers found on its surface. There are over 100 different markers. For example, some T cells are called CD4 cells because they have the type 4 chemical marker coating their surfaces. Other T cells are named CD8 cells because they are coated by the type 8 marker. Almost all T cells of healthy people have either the type 4 or the type 8 marker. Those with neither type 4 nor type 8 markers are called *double-negative T cells.* People with ALPS often have increased numbers of double-negative T cells.

CD4 T cell



CD8 T cell

double-negative T cell

People with ALPS often have extra B cells, too. The B cells produce *immunoglobulins* (*Ig's*, also called antibodies). The antibodies are custom-fit to stick to specific germs. There are thousands of different antibodies in the body. Each is molded for a specific germ. Because ALPS patients have more B cells than normal, they produce more antibodies, including ones that cause autoimmune problems.

WHAT HAPPENS IN ALPS To better understand how ALPS works, imagine that you have a respiratory infection, perhaps the flu. The cells in the nose and throat send out a message to the immune system to start making more lymphocytes to fight the flu. New troops of lymphocytes come to the nose and throat to seek out and destroy the cells infected with the flu virus. Once the virus is conquered, the lymphocytes get a message that their job is done and they are no longer needed. At this point, it is normal for most of the fighter cells to disintegrate through a process called *apoptosis* (a-pop-to'-sis).

The immune systems of people with ALPS are efficient in fighting germs. The problem in ALPS happens after an infection is gone. In ALPS, apoptosis does not work as well as it should. In other words, the troops (lymphocytes) don't hear the message that the war is over. As a result, excess T and B cells gather in the lymph glands, liver and spleen. We can detect the extra cells in people with ALPS by looking for high numbers of double-negative T cells. In general, these extra T cells don't cause a problem.

Sometimes in ALPS, the B cells make a mistake. Instead of making antibodies to be custom-designed against germs, the B cells make antibodies against platelets, red blood cells, or other cells. This causes autoimmune problems. The antibodies become stuck to the platelets and red blood cells, which then get stuck in the spleen. The spleen has to work extra hard to filter out the sticky cells. This is another reason why the spleen gets so big.

MANAGEMENT OF ALPS There is no cure for ALPS. However, we can treat and prevent *most* of its complications. Management of ALPS involves:

- *Diagnosis*. You probably know from experience that this may take months or years until you find a doctor who recognizes the features of ALPS.
- *Counseling and education*. The more you know about ALPS and how to recognize its symptoms and signs, the better you will be able to manage it.
- *Knowing what's treatable.* Unfortunately, we have not found

ways to permanently make the swelling of lymph nodes go down or to fix the problem with apoptosis (see **WHAT HAPPENS IN ALPS**).

- *Therapies.* Complications of ALPS, including the many different autoimmune problems, can be treated successfully. ALPS can be managed through close communication with doctors as symptoms and signs arise.

WAYS TO MANAGE ENLARGED SPLEENS IN ALPS Virtually all people with ALPS have an oversized spleen. Usually, it is not necessary to remove the spleen unless there are severe problems like anemia. However, removing a spleen carries both risks and benefits, which doctors and patients must carefully consider before deciding what to do.

BENEFITS OF SPLENECTOMY

- It will be easier to regulate and control blood counts.
- You will feel less discomfort.
- There is no longer a risk of spleen rupture, a very serious problem, should it occur.

RISKS OF SPLENECTOMY

- You will be missing an organ which helps protect against infection. Your chances of getting certain bacterial infections increase. You must get some vaccines to avoid these infections.
- After your spleen is removed, you may need to take antibiotics for many years to help prevent specific bacterial infections.

WAYS TO MANAGE AUTOIMMUNE PROBLEMS IN ALPS

Steroids are the first line of treatment for autoimmune episodes, like hemolytic anemia and *ITP*. One common steroid is prednisone. It is often given for a short time, but sometimes it is needed for longer periods. When prednisone is not enough to treat the episode, other drugs, such as Imuran and cyclosporin, may also be prescribed. Steroids have saved lives and have

dramatically reduced the complications in some people with ALPS. However, like all treatments, steroids have some disadvantages, so they should not be used too much or for too long.

POSSIBLE LONG-TERM SIDE EFFECTS OF STEROIDS

- Thinning of bones
- Poor wound healing
- Difficulty in fighting infection
- Diabetes
- Cataracts of the eyes
- Mood swings
- Weight gain
- The body starts to rely on the steroids and the amount has to be slowly reduced.

TREATMENTS

- *Blood Transfusions* are useful to replace red blood cells when anemia is severe.
- *Vaccines* are important to help prevent infections. The fewer infections you have, the less often you will need to "call in the troops." In addition to all the childhood vaccinations, it is important to get a yearly flu shot and boosters as needed. People with allergies to eggs should discuss this with their doctor prior to receiving a flu shot.
- *Gene Therapy* is unfortunately not likely to work for ALPS.

DOES ALPS RUN IN FAMILIES? Children can inherit ALPS from one of their parents. The process of apoptosis is controlled by several genes. Most people with ALPS have an altered gene that plays a major role in apoptosis. The altered gene may be passed from one generation to the next. Before discussing what this gene does, we need to describe some basic information about genes and how they work.

A BRIEF INTRODUCTION TO GENETICS *Genes,* which are made of DNA, are located on chromosomes in the cells of our

body. We have two copies of each gene, except for the genes on the sex chromosomes. Genes act as the blueprint for the development and operation of our bodies. Each gene contains the instructions for making one of the building blocks of a cell. We each have around 100,000 genes that determine who we are, what we look like, and how our bodies work. By chance, every person has approximately 10-12 genes that don't work as well as they should or don't work at all. These genes are mutated. That is, the DNA is slightly different in mutated genes. Not all changes, or mutations, are harmful. Sometimes these changes cause no problems at all, but sometimes they cause human disease. Sometimes it takes alterations in several genes to cause problems. Other times the genetic mutation interacts with the environment to cause health problems.

THE FAS GENE We have found genetic changes or *mutations* that seem to be factors in the development of ALPS. In over 83% of the ALPS patients, we have found an alteration in a gene that encodes a cell component, or protein, called *Fas.* This alteration causes the gene to produce abnormal *Fas* protein. We do not completely understand how abnormal *Fas* protein leads to ALPS, but it clearly does. We still need to identify other genetic and non-genetic factors that contribute to the development of ALPS.

The *Fas* protein is one of several proteins that are important for apoptosis, the normal process through which cells die. *Fas* controls the life span of certain cells, particularly the lymphocytes. Like people, cells have a normal life span in which they grow, do their job, and then die. The mutated *Fas* protein does not work well, and can't give the cells the message that it is time to die. Although most ALPS patients have one normal and one altered copy of the *Fas* gene, the altered protein is able to interfere with the function of the normal one.

However, *Fas* mutations do not explain all cases of ALPS. About 17% of people with ALPS do not have a *Fas* mutation. In some of them there are alterations in other proteins known as Fas-ligand and Caspase-10. In some ALPS patients a genetic alteration has not yet been found. Also, there are many relatives of ALPS patients who have a *Fas* mutation and *do not* have ALPS. We believe that other genes and environmental factors also play a role determining which people get ALPS.

ARE MY CHILDREN AT RISK IF I HAVE A FAS GENE MUTATION? There are many people who have no signs of ALPS, yet have a *Fas* mutation. Individuals with a *Fas* mutation have a 50/50 chance of passing the *Fas* mutation on to their children. That means that each child has a 50% chance of inheriting the unaffected gene and a 50% chance of inheriting the altered gene. This chance is the same for each child. In other words, if you have 5 children and they have each inherited the *Fas* mutation, the sixth child still has the same 50/50 risk of inheriting the *Fas* mutation. Of the children who inherit the *Fas* mutation, approximately half of them will develop some features of ALPS. This figure is based on the 98 people we have studied so far at NIH who have a *Fas* gene mutation. Of these 98 people with the *Fas* gene mutation, 48 have enough symptoms to be diagnosed with ALPS and additional persons have some features of ALPS. Children who have inherited the unaltered *Fas* gene have almost no chance of developing ALPS.

HOW TO EXPLAIN ALPS TO YOUR KIDS It may seem easier not to tell your children anything about ALPS, but children, like adults, often want to know "why?" and don't like to be left in the dark. The more children understand about ALPS, the fewer fears and misunderstandings they may have. The following is one way we have explained ALPS to a child. You may find these ideas helpful for your family.

ALPS IS A PROBLEM WITH THE IMMUNE SYSTEM.
Usually, the immune system attacks germs, as an army would attack its enemy. The soldiers are called lymphocytes. They go around the blood stream and find germs. After the soldiers kill the germs, their job is done and it is time for them to go away and die. In ALPS, the soldiers don't hear the message to die. They stay and hang out in places like your spleen and the lymph nodes found under your cheeks, making them really big. Sometimes, the soldiers become confused and they attack members of their own side, such as the red blood cells and platelets in your body. Without enough red blood cells, you may feel tired. Without enough platelets, you may get nosebleeds, red spots on your skin and bruises. Sometimes you may need to take medicine or get a

transfusion of new blood. Sometimes you have to be extra careful not to bump your belly because your spleen is fragile.

Even though living with ALPS can be hard, all kids still go to school, and most adults work. All have responsibilities, contribute to their communities in many ways, have friends, and have fun.

SOME COMMON QUESTIONS AND PROBLEMS PEOPLE WITH ALPS FACE

Do you have the mumps? No! People with mumps have a very different condition, even though both involve swelling of the sides of your face. Some people who ask questions are well-meaning, some are curious, and some are just plain rude. You don't have to answer if you don't want to. You can just ignore the question. A simple answer, such as "I was born this way" or "God made me this way" is often enough to satisfy curiosity. People tend to say different things depending on their mood. The important thing is to find an answer that feels comfortable to you.

Why is your face so round? If you are taking steroids, you may gain weight quickly. Some parents talk to teachers about the side effects of steroids in advance, so that the class knows what to expect. Try to remember that the swelling is temporary. It goes away once you stop taking the medicine.

Are you contagious? People often worry that ALPS is catching. It is important that people understand that ALPS is not infectious.

Stares from strangers: It's a fact of life that people will stare at people who look different. Often there are good days when stares don't seem to matter, and bad days when you feel like crawling under the bed. Parents of children with ALPS have to work extra hard to develop their child's self-confidence and sense of security. The important thing is to let them know that you love them no matter how they look. Children and adults with ALPS need to be reminded that they have many positive characteristics.

Spleens and sports: Sometimes doctors recommend that people with enlarged spleens not play contact sports. When the

spleen is large, it is fragile and there is a risk of rupture. This can be hard for many to accept. We at the NIH encourage people with large spleens to wear spleen guards. A spleen guard is a piece of fiberglass that is molded to a person's stomach. It is easily wrapped around your stomach and held in place under your shirt. In general, the spleen guard is worn whenever someone is involved in an activity at high risk for stomach injury, such as contact sports. Other people choose different sports, such as swimming, track, or bicycling.

Relatives who do not have ALPS: Brothers and sisters or other relatives who don't have ALPS are still affected by the condition. Some worry that their brother or sister will die. Some think they will develop ALPS because they look or act like their brother or sister. Some children struggle with how much of their parents' time is spent with their sick brother or sister. Relatives who have a *Fas* mutation but do not have ALPS may feel guilty that they are not sick. It is important for families to talk openly about ALPS so that any misconceptions can be explained and feelings can be expressed. Family counseling is often helpful.

The positive side: Many families say that ALPS has brought them closer together. Family members learn that they can rely on each other for support. Children learn from their parents' open and honest communication, and the experience teaches them how to solve problems.

A L P S

A T T H E N I H

THE ALPS TEAM AT THE NIH The team at the NIH is composed of doctors, scientists, nurses, genetic counselors, and several students and scientists in training. Physicians from around the country refer families suspected of having ALPS to us. We study their blood for specific laboratory findings related to ALPS. After reviewing the medical records and lab results, the team invites those who we think have ALPS to NIH for evaluation and follow-up. With the many referrals we have been getting recently, we are beginning to think that ALPS is more common than once thought.

WHAT'S THE PURPOSE OF OUR STUDY AT THE NIH? We are trying to better understand this rare disease, to find the cause and hopefully to find improved ways to treat ALPS. Of course, the ultimate hope is to find a cure.

WHY WE WANT TO INVOLVE OTHER MEMBERS OF YOUR FAMILY IN OUR STUDY We know there is a genetic component to ALPS. However, the development of ALPS in families with mutations in apoptosis genes is not straightforward. For example, we want to know why some family members have an alteration in *Fas* and no sign of ALPS. Therefore, we would like to study this gene, and other genes, in your family. We have other research questions that may be helped by studying other members of your family. Therefore, we are inviting your family members to join our study by providing us with a small sample of their blood in order to help us answer our research questions.

PARTICIPATING IN OUR STUDY Each person who is interested in participating will have a chance to discuss study details with the investigators. We will ask each person to read and sign a consent form. *All* of the tests, evaluations and treatments at the NIH are free. Family members who participate will be helping us better understand ALPS.

We hope that you found this information helpful. Since 1990, we have moved from identifying and treating one child to dozens of families. We look forward to learning more about ALPS so that we can learn better ways to manage the condition.
Please call either,
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